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# Studies towards the Total Synthesis of Disorazole C<sub>1</sub> and its Analogues

**Kevin John Ralston**



A thesis submitted for the degree of  
Doctor of Philosophy

The University of Edinburgh

2014

## **Declaration**

This thesis is submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at The University of Edinburgh. Unless otherwise stated, the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualification at this or any other university. In accordance with the dissertation regulations as specified by the University of Edinburgh, this thesis does not exceed 100,000 words in length.

Kevin Ralston

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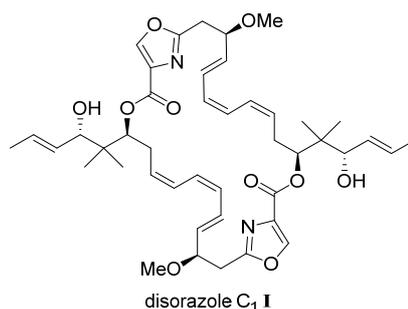
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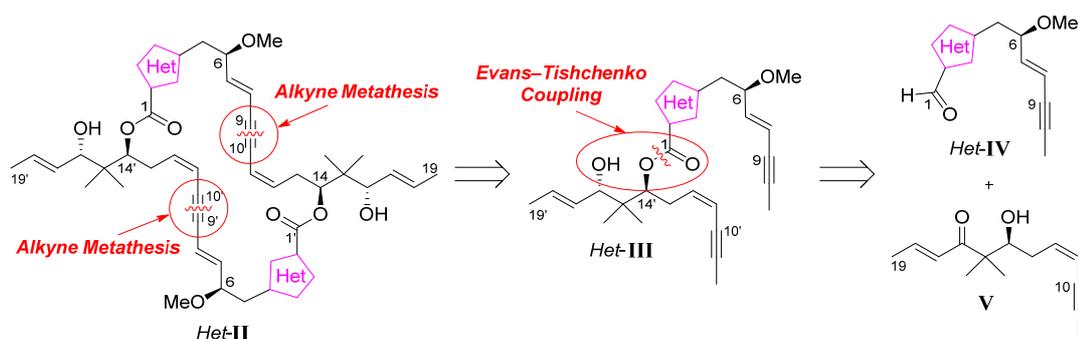
*“...the dream shall never die...”*

## Abstract

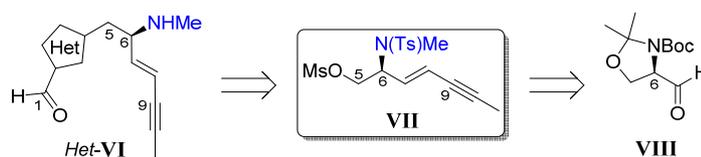
Structure–activity relationships (SARs) in the disorazole family have been revealed through the biological testing of natural disorazoles and their synthetic analogues, but little is known about the contribution of the oxazole to the anti-tubulin activity of disorazole C<sub>1</sub> **I**. The development of a novel Evans–Tishchenko/alkyne metathesis (ET–AM) route towards the synthesis of disorazole C<sub>1</sub> will provide straightforward access to disorazole C<sub>1</sub> and its heterocyclic analogues, thus allowing the contribution of the oxazole to the natural product’s bioactivity to be elucidated.



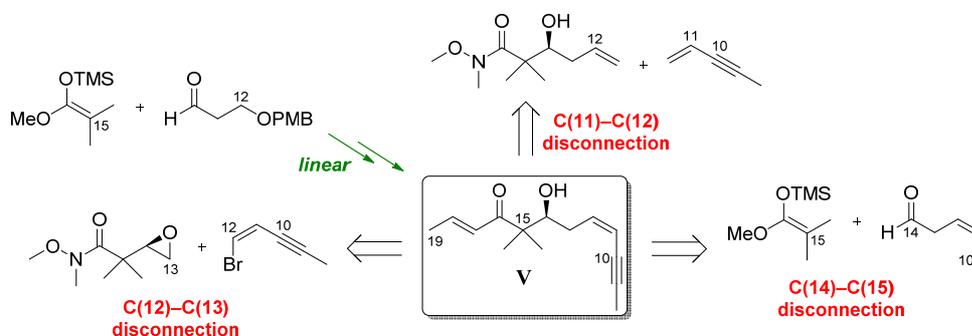
Our ET–AM approach offers a highly diastereoselective and convergent means of constructing heterocyclic analogues of the disorazole C<sub>1</sub> scaffold *Het-II*. It is envisaged that ET coupling of C(1)–C(9) aldehydes *Het-IV* to the C(10)–C(19) β-hydroxyketone **V** will give the key, requisite, 1,3-*anti* diol monoester bis-alkynes *Het-III* for dimerisation *via* an alkyne cross-metathesis/ring-closing alkyne metathesis (ACM–RCAM) reaction.



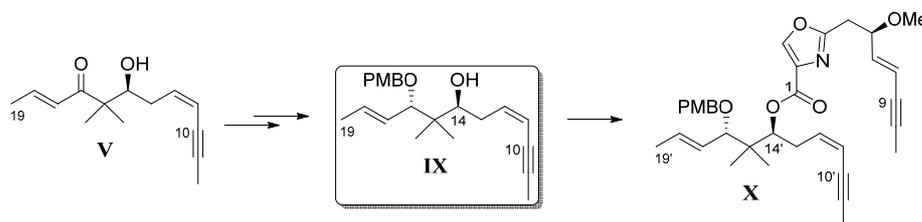
Further diversification may be achieved through the synthesis of C(6)-heteroatom analogues of the C(1)–C(9) fragment *Het-IV*. **Chapter 2** outlines efforts towards the synthesis of C(6)-amino analogues *Het-VI* of the C(1)–C(9) fragment **IV**. Elaboration of Garner’s aldehyde **VIII** allowed the synthesis of the *N*-protected C(5)–C(9) mesylate **VII**; an analogue of an advanced C(1)–C(9) fragment intermediate.



A scalable route towards the synthesis of the C(10)–C(19) fragment **V** and investigations into its reactivity under ET coupling conditions are critical to the success of our ET–AM approach. **Chapter 3** details convergent approaches towards the synthesis of the C(10)–C(19)  $\beta$ -hydroxyketone **V**, which centred around: (i) an olefin cross-metathesis reaction [C(11)–C(12) disconnection]; (ii) an epoxide ring-opening reaction [C(12)–C(13) disconnection]; and (iii) a Mukaiyama aldol reaction [C(14)–C(15) disconnection]. **Chapter 4** describes our successful linear synthesis of the  $\beta$ -hydroxyketone **V**.



Gram-scale preparation of the C(10)–C(19) fragment **V** permitted investigation into the viability of the ET reaction as a fragment coupling strategy, the results of which are reported in **Chapter 5**. Although many (hetero)aryl aldehydes failed to react, the successful coupling of electron-deficient substrates allowed a contingency strategy to be explored through preparation of the mono-protected diol **IX**. Esterification of **IX** with the carboxylic acid derivative of the C(1)–C(9) oxazole has allowed generation of the C(1)–C(9)/C(10')–C(19') bis-alkyne **X** required for future AM investigations.



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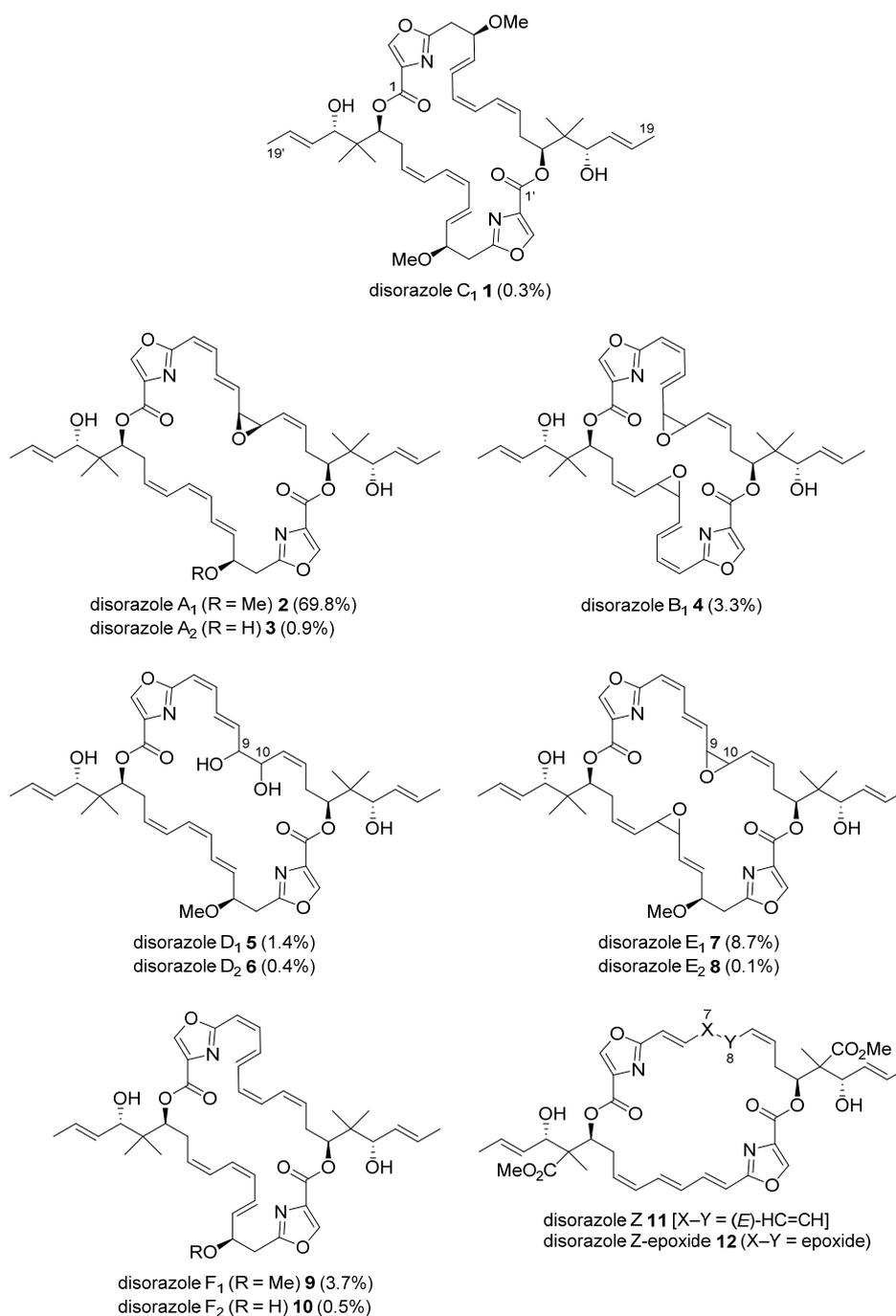
## 1.1 The Disorazoles: Background

### 1.1.1 Discovery and Isolation

The disorazoles<sup>1</sup> are a class of 31 polyketide natural products, 29 of which were isolated from a portion of the neutral extracts of a fermentation broth of the myxobacterium *Sorangium cellulosum* in 1994;<sup>2a</sup> while the final disorazoles – disorazole Z and disorazole Z-epoxide – were discovered 13 years later.<sup>2b</sup> **Figure 1.1** shows the structure of 12 of the 31 disorazoles and their relative abundance with respect to their isolated mass. As can be ascribed from **Figure 1.1**, all disorazoles are (pseudo)dimeric large-ring (28 to 32 atom) macrocyclic dilactones that each contain the oxazole heterocycle; a number of double bonds, many of which are conjugated and sometimes have internal vinylic epoxides, alcohols or ethers; and a number of stereogenic alcohol (or derivative) groups. Disorazole variants are typically distinguished by the presence (or absence) of epoxides and hydroxyl groups, and differences in their double bond stereochemistry.

Of their relative isolation mass, disorazole A<sub>1</sub> **2** is by far the most abundant component, accounting for 69.8% of the isolated (disorazole) mass from the neutral extracts; followed by disorazoles E<sub>1</sub> **7** (8.7%), F<sub>1</sub> **9** (3.7%) and B<sub>1</sub> **4** (3.3%). The remaining mass accounts for a total of 14.5%, with disorazole C<sub>1</sub> **1** representing only 0.3% of the mass of the metabolites. However, the soluble organic extracts from which the majority of the disorazole family were discovered represents only a small fraction of the isolates: further disorazole A<sub>1</sub> and E<sub>1</sub> (ratio 3:1) were obtained from other sources of the broth and therefore the percentage by mass for these metabolites, in reality, represents more than 69.8% and 8.7%.

Interest in the disorazoles stems from their pronounced cytotoxic activity, whereby all tested disorazoles (A<sub>1</sub>, C<sub>1</sub>, D<sub>1</sub>, E<sub>1</sub> and Z) have shown at least nanomolar activity, with some displaying cytotoxicity at picomolar levels.<sup>2b,3-5</sup> Studies examining the mechanism of action of the disorazoles have concluded that their cytotoxicity stems from their ability to act as tubulin inhibitors.<sup>3,4</sup> Because tubulin is essential during the cell cycle, their anti-tubulin activity makes the disorazoles strong candidates for development as anti-cancer agents.

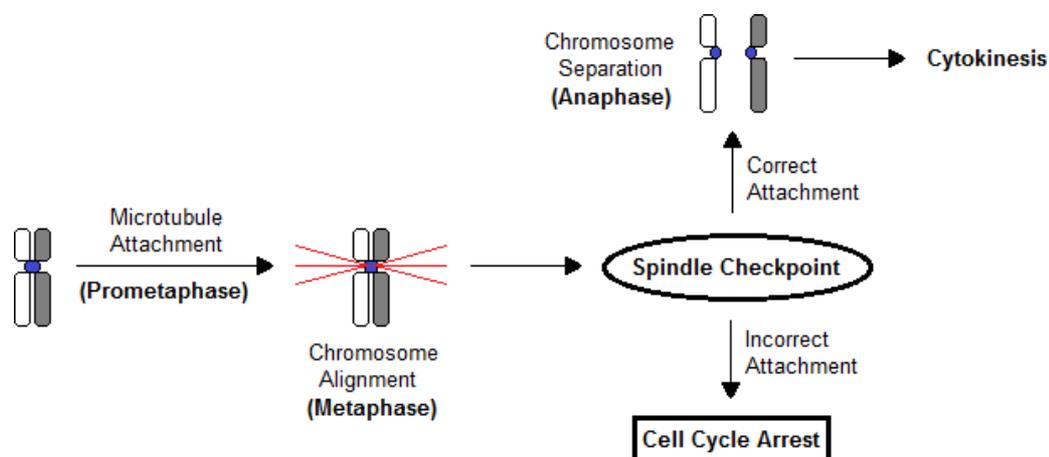


**Figure 1.1** Selected members of the disorazole family of natural products and their relative abundance from the initial *Sorangium cellulosum* fermentation broth. Note 1: no data was reported for the disorazole Z variants **11/12** in the initial isolation study<sup>2a</sup> and so their abundance is not indicated). Note 2: not all stereocentres have been assigned in the literature, and disorazole D<sub>1</sub> and D<sub>2</sub>, and disorazole E<sub>1</sub> and E<sub>2</sub> differ in the relative stereochemistry at C(9)–C(10) (and their transposes in the case of the disorazole E class) but the absolute stereochemistry is yet to be defined. Other variants (not shown), typically show differences from those above in double bond stereochemistry or have diols as opposed to epoxides (and *vice versa*).

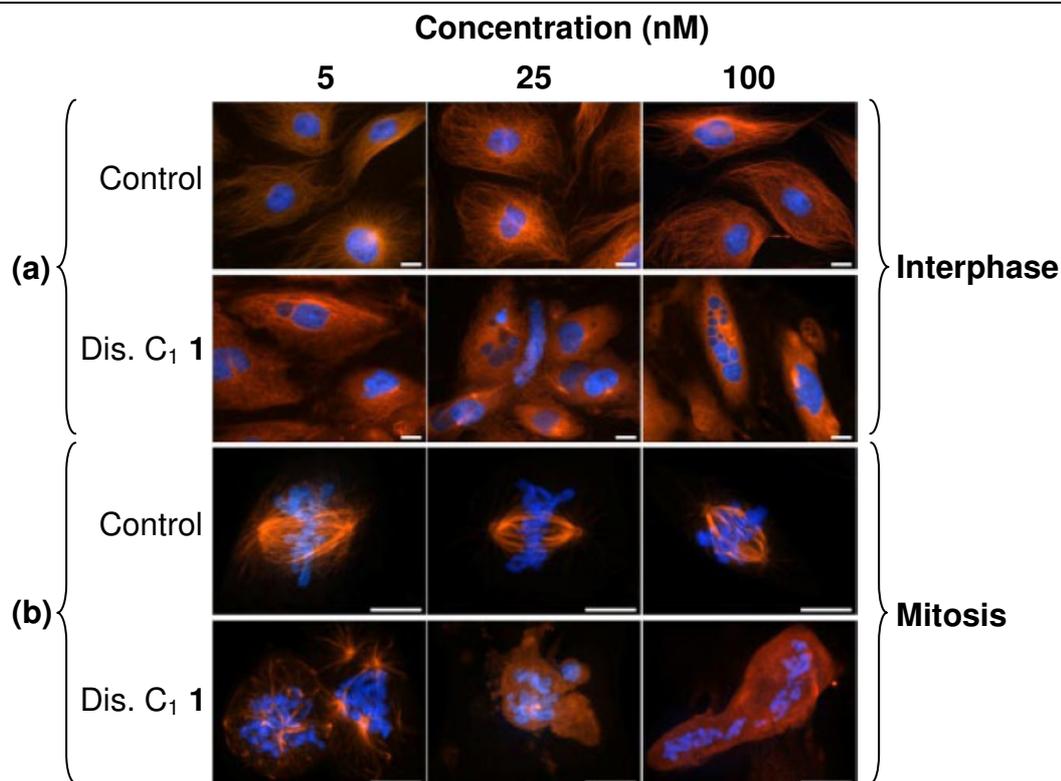
### 1.1.2 Biological Activity

Tubulin is important during a number of stages of cell development and therefore makes an excellent target for cancer therapy.<sup>6</sup> Tubulin is essential for attachment of microtubules from the mitotic spindle to sister chromatids (at their kinetochores) during the mitosis phase of the cell cycle. Mitosis is the process of forming two new daughter cells that each contain a copy of the parent chromosomes during cell replication. During metaphase and anaphase, sister chromatids attached to the mitotic spindle *via* microtubules are ‘lined up’ (metaphase) and are then ‘pulled apart’ (anaphase), resulting in a copy of each parent chromatid, which is incorporated into the daughter cell during the latter stage (cytokinesis) of the cell cycle. However, as illustrated in **Figure 1.2**, in order for this process to take place, proper attachment between the kinetochore of the chromosomes and correctly structured microtubules must occur. Incorrectly attached or mis-structured tubulin can lead to the onset of cell cycle arrest *via* spindle checkpointing mechanisms,<sup>7</sup> which are responsible for terminating a cell’s development in the event that errors in microtubule binding or structural integrity are discovered.

The disorazoles are believed to induce cell cycle arrest by disrupting microtubule dynamic instability,<sup>8</sup> which refers to polymerisation (stabilisation) and depolymerisation (destabilisation) of tubulin at the microtubule ends; and is essential for attachment of microtubules to the kinetochore of chromosomes, spindle assembly and the generation of mechanical force during chromosome separation. The disorazoles are believed to inhibit polymerisation (and cause depolymerisation) of



**Figure 1.2** Simplified representation of the spindle checkpointing mechanism.



**Figure 1.3\*** Microtubule disruption by an inactive control and disorazole  $C_1$  **1** at the (a) interphase; and (b) mitosis stages of the cell cycle. Microtubules are shown in orange-red, and chromosomes in blue.<sup>4a</sup>

microtubules,<sup>3,4</sup> and indeed *in silico* docking studies<sup>9</sup> have shown an affinity of the disorazoles for the (microtubule destabilising) vinblastine binding site; although the same study identified some affinity of the disorazoles for the (microtubule stabilising) paclitaxel binding site, and so it is possible that the disorazoles have further, unknown modes of action.<sup>9</sup> Regardless, as can be seen from **Figure 1.3**, disorazole  $C_1$  disrupts microtubules at both the interphase (**Figure 1.3a**) and mitosis (**Figure 1.3b**) stages of the cell cycle at nanomolar concentrations in the range of 5 to 100 nM.<sup>4a</sup> This is particularly clear on comparison of the images obtained for the differentially treated cells during mitosis, whereby the classically depicted structure of the mitotic spindle connected to the aligned chromosomes at the spindle equator (clearly shown in the *control* conditions) is greatly perturbed as a result of the presence of the active agent (*Dis. C<sub>1</sub>* conditions). As a result, the division event is

\***Figure 1.3** is adapted from ‘Fig. 4’ of: “Microtubule Binding and Disruption and Induction of Premature Senescence by Disorazole  $C_1$ ”, *The Journal of Pharmacology and Experimental Therapeutics*, Tierno *et al.* (2009),<sup>4a</sup> and is included with the authors’ and publisher’s kind permission.

believed to fail spindle checkpointing and the cell enters controlled senescence,<sup>4a</sup> thus impeding cell replication and proliferation. Disorazole A<sub>1</sub> and other disorazoles are believed to act in a similar manner and inhibit cells *via* the same mechanism of action.<sup>2b,3-5</sup> A number of medically approved anti-cancer drugs such as vinblastine<sup>10</sup> and taxol<sup>11</sup> are also believed to inhibit cell growth by causing microtubule disruption, and therefore it is plausible that the disorazoles could also be developed as anti-cancer agents, because they show a similar level of cytotoxic activity.

Most studies that have examined the anti-proliferative activity of the disorazoles have focussed on disorazole A<sub>1</sub> and C<sub>1</sub>, with some data available regarding the activity of disorazoles D<sub>1</sub>, E<sub>1</sub> and Z. Against cancer cell lines, disorazole A<sub>1</sub> was exhibited a mean IC<sub>50</sub> of 0.012 nM (number of cell lines  $N = 10$ ),<sup>3</sup> while disorazole C<sub>1</sub> displayed a mean IC<sub>50</sub> of 1.66 nM ( $N = 12$ ).<sup>4a</sup> Disorazoles D<sub>1</sub>, E<sub>1</sub> and Z showed cytotoxicity against cancer cell lines in the picogram range, with measured activities of 19 and 7 pg/cm<sup>3</sup> (EC<sub>50</sub>;  $N = 5$ );<sup>5</sup> and 30 pg/cm<sup>3</sup> (IC<sub>50</sub>;  $N = 1$ ),<sup>2b</sup> respectively.

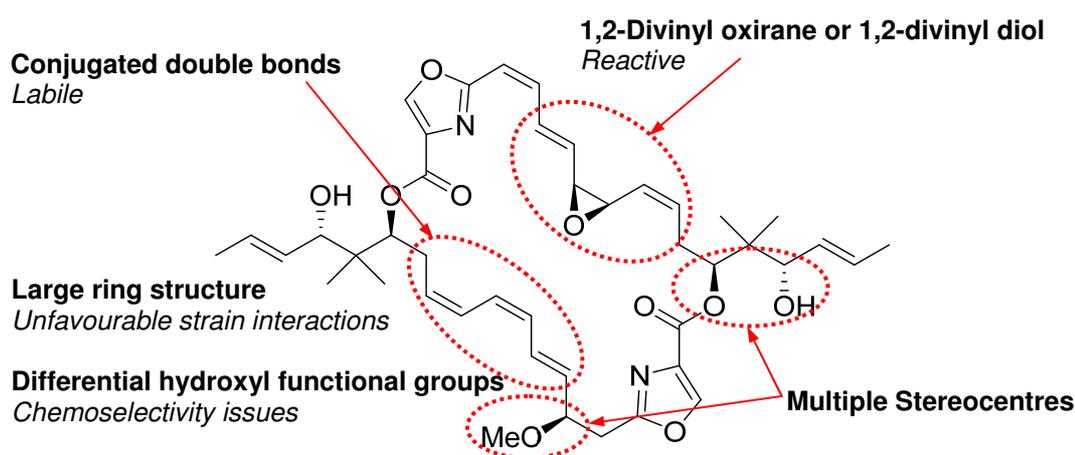
These data are further discussed with respect to structure–activity relationships (SARs) in **Section 1.4**, but there are a number of noteworthy points that centre around these studies in relation to the potential for development of the disorazoles as anti-cancer agents. Firstly, disorazoles A<sub>1</sub> and C<sub>1</sub> displayed comparable or higher *in vitro* potency to the clinically approved anti-cancer drug vinblastine,<sup>3,4a</sup> implying that the natural products are sufficiently active for development as anti-cancer drugs. Secondly, disorazole C<sub>1</sub> exhibited some selectivity for cancer cells, with wild-type confluent fibroblasts displaying an IC<sub>50</sub> some 15 to 384 times greater than the cancer cell lines, which is promising given that poor malignant-cell selectivity is a major problem associated with chemotherapy.<sup>4a</sup> Finally, disorazole A<sub>1</sub> was shown to be active against a multidrug resistant (KB-V1) cell line,<sup>3</sup> which again, is promising, because drug resistance is also a problem in chemotherapy.<sup>12</sup> However, this activity implies that cancers may not possess (or have developed) mechanisms to cope with the drug's mode of action, and may also imply (albeit speculatively) that the disorazoles have the capability to act against cellular mechanisms of drug resistance. Indeed, the generation of cells resistant to the disorazoles has been met with great difficulty,<sup>13</sup> suggesting that they could be highly robust therapeutic agents.

### 1.1.3 Key Challenges in the Synthesis of the Disorazoles

In order to establish SARs in the disorazoles, a route towards their laboratory syntheses would be highly desirable. On the basis of biological activity, the synthesis of disorazole A<sub>1</sub>, D<sub>1</sub>, E<sub>1</sub> or Z would perhaps appear to be most attractive owing to their increased potency over disorazole C<sub>1</sub>. However, it has been suggested that the picomolar cytotoxicity displayed by disorazole A<sub>1</sub> would be too potent for clinical use as an anti-cancer agent;<sup>14a</sup> and disorazole A<sub>1</sub> accounts for over 70% of the mass of the isolated disorazoles, and therefore could perhaps be obtained more economically through use of the organism's fermentation broth.<sup>15</sup> Conversely, disorazole C<sub>1</sub> is a minor component, and therefore obtaining this disorazole in appreciable quantity would be more suited to laboratory synthesis.

The synthesis of all disorazole variants is highly demanding owing to the size of their structures, the multiple stereocentres present, and the known lability of conjugated double bond systems. In addition, divinyl epoxides and divinyl diols are reactive functional groups, and therefore the syntheses of disorazole variants containing these moieties would be especially difficult, from both a preparation and handling perspective (**Figure 1.4**).

Aside from possessing an acceptable level of cytotoxicity (and some selectivity for cancer cells), the symmetrical, homodimeric structure of disorazole C<sub>1</sub> lends itself to a modular approach towards its synthesis, and the installation of potentially labile



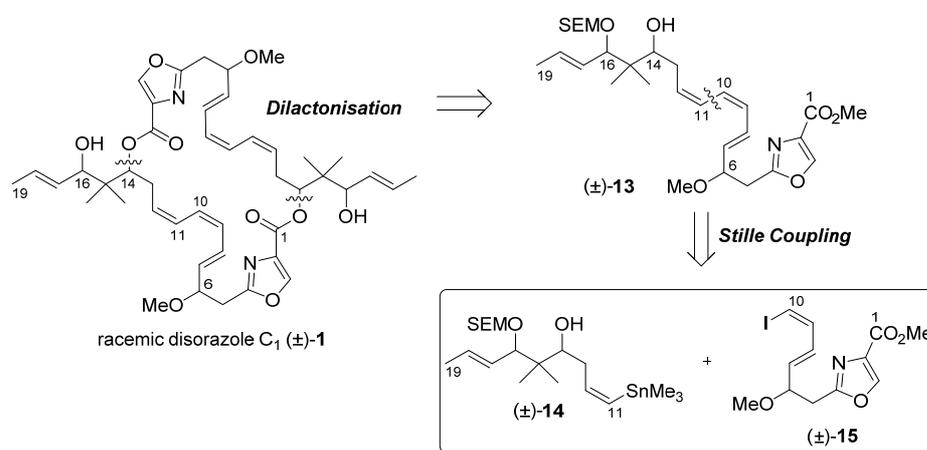
**Figure 1.4** Key challenges in the synthesis of the disorazoles.

divinyl epoxides need not be carried out. In addition, the disorazole C<sub>1</sub> monomer is present in 17 of the 31 disorazoles, and therefore successful synthesis of this subunit provides access to other members of the series. Finally, the synthesis of disorazole C<sub>1</sub> will assist in establishing strategies for synthesising other disorazoles.

The following section outlines the efforts towards the synthesis of the disorazoles. For reasons of brevity, this section will focus primarily on methods used to assemble the macrocyclic framework of the disorazoles; more comprehensive reviews that address the various fragment syntheses are available in the literature.<sup>1,16</sup>

## 1.2 Synthesis of the Disorazoles

### 1.2.1 C(1)–C(19) Monomer Synthesis (Meyers, 2000)

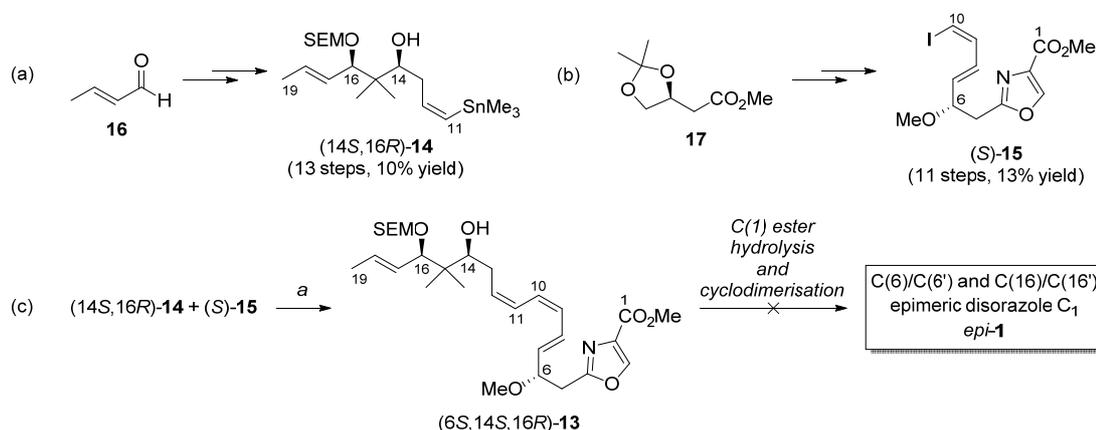


**Scheme 1.1** Meyers' first generation strategy towards the synthesis of disorazole C<sub>1</sub>, as exemplified for racemic disorazole C<sub>1</sub> (±)-1.<sup>17</sup>

The first attempted synthesis<sup>17</sup> of disorazole C<sub>1</sub> aimed to both construct the macrocycle, and to elucidate the stereochemistry of each chiral centre [at C(6), C(14) and C(16) and their transposes, which were unknown at the time] through application of conditions used according to a test-route with fragments of different, known stereochemistry. If successful, this approach was predicted to produce a library of stereochemically distinct disorazoles through which the optical rotation of the synthetic products could be compared to that of the literature value for the natural product as a means of identifying the correct stereochemistry. In addition, the synthesis would provide a monomer **13** which would give access to 16 other

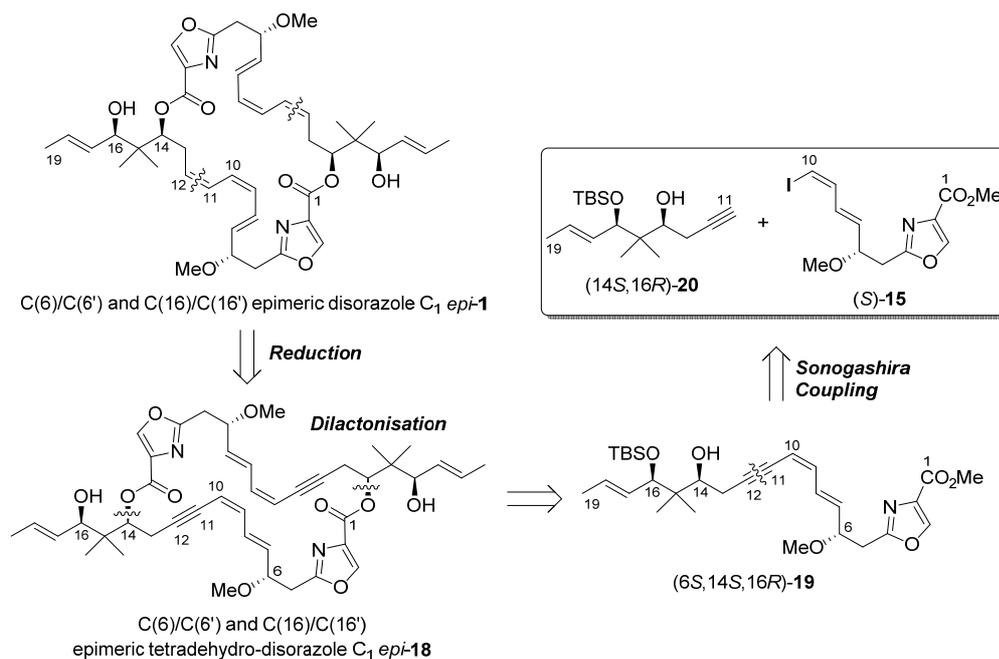
disorazoles owing to the presence of this monomer in 17 of the natural disorazoles.

Meyers' retrosynthesis (**Scheme 1.1**) targeted the C(1)–C(19) monomer **13**, which it was believed would give access to disorazole C<sub>1</sub> by a cyclodimerisation at C(1) and C(14); with a Stille coupling<sup>18</sup> reaction between the C(11)–C(19) stannane **14** and the C(1)–C(10) vinyl iodide **15** used to construct the monomer at C(10)–C(11) (**Scheme 1.1**). The C(11)–C(19) stannane **14** was prepared in 13 steps and 10% yield from (*E*)-crotonaldehyde **16** (**Scheme 1.2a**), while the C(1)–C(10) vinyl iodide **15** was synthesised in 11 steps and 13% yield from the readily prepared ester **17** (**Scheme 1.2b**). Monomer **13** completion was achieved using a Stille coupling reaction between the stannane **14** and the vinyl iodide **15**, which proceeded in very good yield (76%; **Scheme 1.2c**). However, successful cyclodimerisation was not reported, and it was stated in a follow-up study that the triene system was too unstable to undergo the required double lactonisation reaction following saponification of the C(1) ester on monomer **13**.<sup>19</sup> In addition, the monomer was reported<sup>17</sup> to have undergone gradual decomposition (by double-bond isomerisation) under standard low-temperature storage conditions (–20 °C), and thus implied that a route that uses a protected triene would perhaps be required for reasons of both lability and storage. The use of a protected triene would prove to be an important strategy in all subsequent disorazole C<sub>1</sub> syntheses.



**Reagents and conditions:** (a) PdCl<sub>2</sub>(MeCN)<sub>2</sub>, DMF, rt, 76%.

**Scheme 1.2** Synthesis of the (a) C(11)–C(19) stannane **14**; and (b) C(1)–C(10) vinyl iodide **15** fragments. (c) Synthesis of the C(1)–C(19) disorazole C<sub>1</sub> monomer **13** by Stille coupling between the C(1)–C(10) vinyl iodide **15** and the C(11)–C(19) stannane **14**; and attempted macrocycle completion.<sup>17</sup>

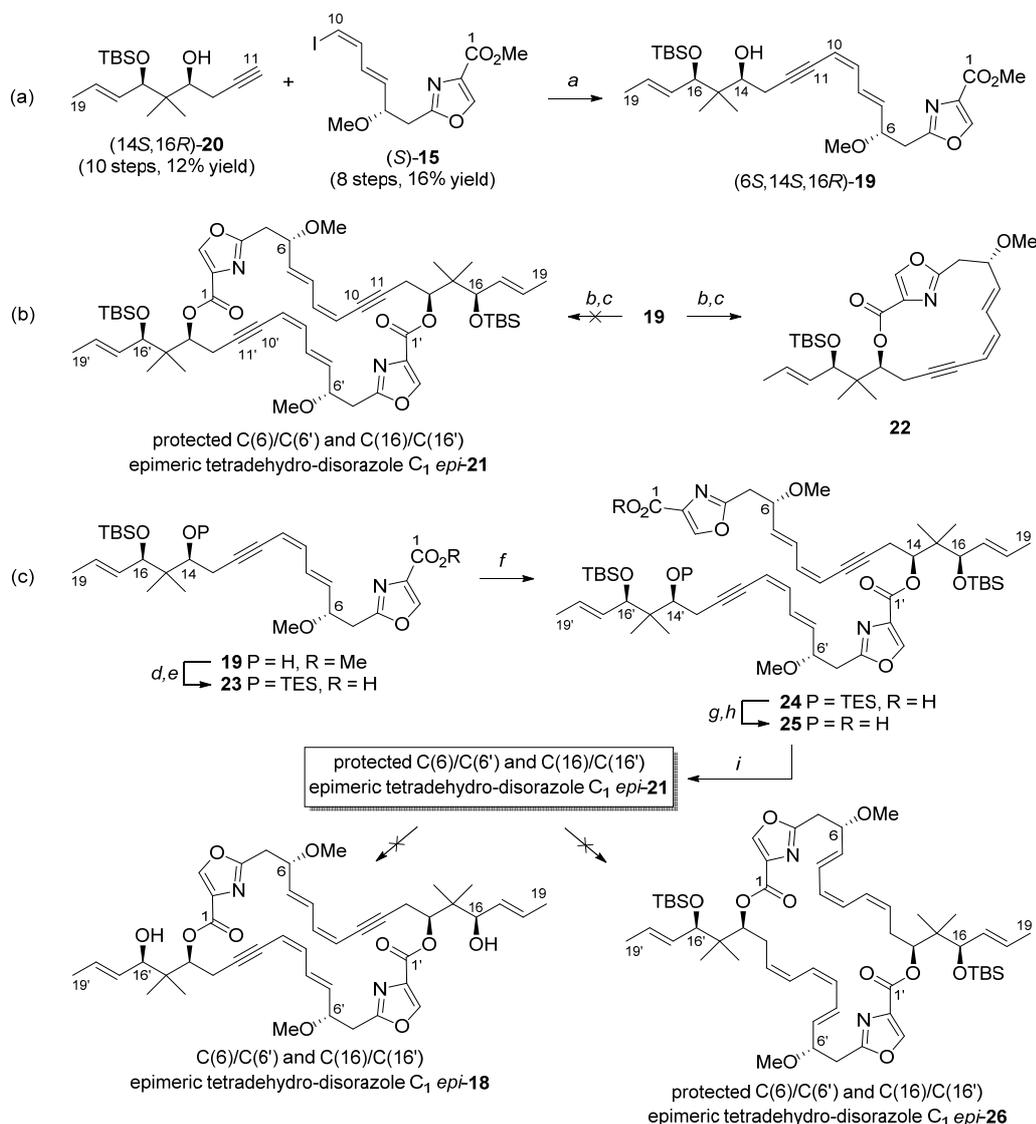
1.2.2 C(11)–C(12) Tetrahydro-Disorazole C<sub>1</sub> (Meyers, 2001)

**Scheme 1.3** Meyers' second generation approach towards the synthesis of disorazole C<sub>1</sub>.<sup>19</sup>

Meyers' second generation<sup>19</sup> synthesis of disorazole C<sub>1</sub> (**Scheme 1.3**) envisaged masking the C(11)–C(12) alkene unit as an alkyne before performing a dilactonisation between two C(1)–C(19) monomers **19**. The assembly of the monomer **19** would be carried out using Sonogashira coupling<sup>20</sup> between the C(10)–C(19) alkyne **20** and the C(1)–C(10) vinyl iodide **15**, and like its predecessor, this synthesis also aimed to reveal disorazole stereochemistry; therefore the di-epimeric disorazole C<sub>1</sub> *epi-1* was targeted arbitrarily as a proof of concept.

The C(11)–C(19) alkyne **20** and C(1)–C(10) vinyl iodide **15** were synthesised in 8 and 10 steps in 16 and 12% overall yield, respectively, and coupled *via* a Sonogashira reaction to give the protected monomer **19** (**Scheme 1.4a**). Unfortunately, ester hydrolysis and attempted dilactonisation (DPTC)<sup>21</sup> led only to intramolecular reaction and thus the isolation of the cyclised monomer **22** in 46% yield, with none of the dimer **21** detected spectroscopically (**Scheme 1.4b**).

Fortunately however, an obvious linear contingency strategy was devised that involved esterification of the C(16)-mono-protected diol **19** with a doubly protected diol (carboxylic acid **23**) followed by selective C(14) hydroxyl deprotection, ester



**Reagents and conditions:** (a) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, Et<sub>3</sub>N, MeCN, -20 °C to rt, 2 h, 87%; (b) LiOH, THF/H<sub>2</sub>O, rt, 7 h; (c) DPTC, DMAP, PhMe, reflux, 12 h, *epi*-**21** 0%, **22** 46% (2 steps); (d) TESOTf, 2,6-lutidine, DCM, 0 °C to rt, 4.5 h, 69%; (e) LiOH, THF/H<sub>2</sub>O, rt, 2 h; (f) **19**, DPTC, DMAP, PhMe, reflux, 48 h, 65% (2 steps); (g) TFA, THF/H<sub>2</sub>O, rt, 1 h, 65%; (h) LiOH, THF/H<sub>2</sub>O, rt, 48 h; (i) 2,4,6-TCBC, Et<sub>3</sub>N, DMAP, 48 h, rt, 24% (2 steps).

**Scheme 1.4** (a) Synthesis of the C(1)–C(19) monomer **19** by Sonogashira coupling; and (b) attempted C(1)–C(14) dilactonisation. (c) Successful linear strategy towards the generation of the protected tetrahydro-disorazole C<sub>1</sub> dimer *epi*-**21**, and attempted silyl deprotection or alkyne semi-reduction.<sup>19</sup>

hydrolysis and a lactonisation reaction to generate the desired protected dimer *epi*-**21** (**Scheme 1.4c**). Accordingly, the C(14) hydroxyl group of the monomer **19** was protected as its TES-ether, and the C(1) ester was hydrolysed to give the carboxylic acid **23** which was then esterified with the C(14) hydroxyl group of fragment **19** to afford the open chain dimer **24**. Selective TES deprotection and hydrolysis of the methyl ester **24** gave the requisite *seco*-acid **25**, with a final Yamaguchi

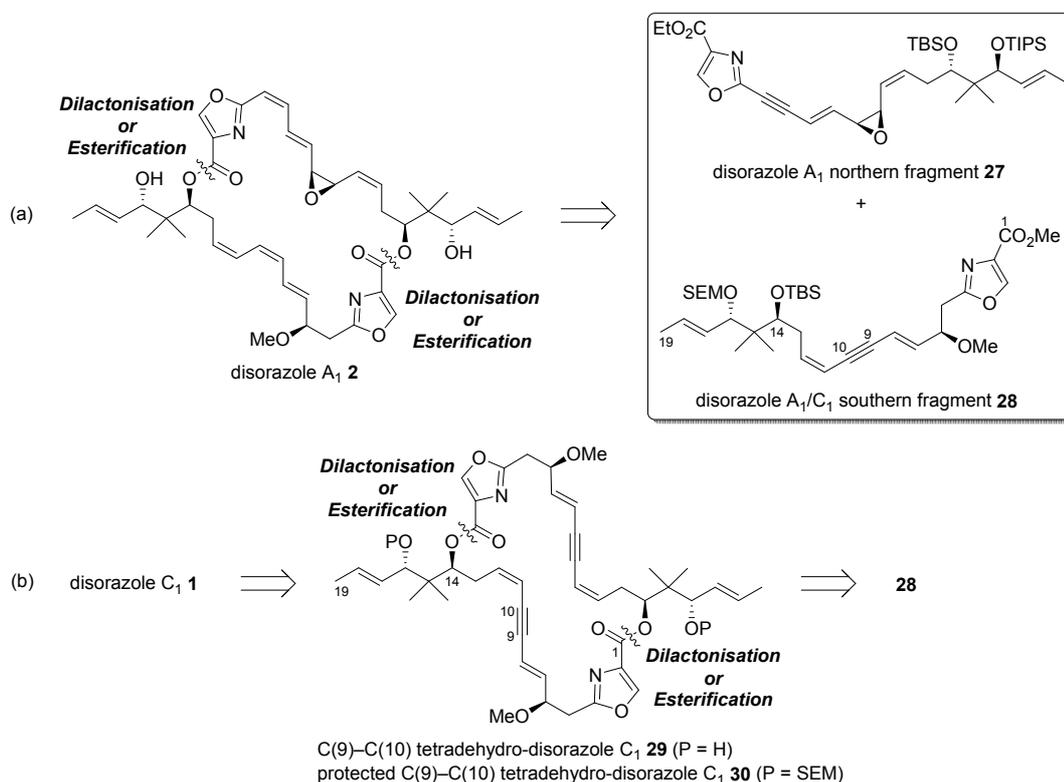
lactonisation<sup>22</sup> step affording the desired protected tetrahydro-disorazole C<sub>1</sub> scaffold *epi-21* in 24% yield (**Scheme 1.4c**).

Despite this promising result, early attempts to either deprotect the TBS-ethers to give the tetrahydro-disorazole *epi-18*; or to selectively reduce the alkyne bonds to their corresponding (*E*)-alkenes, and hence generate the bis-silyl-protected disorazole *epi-26* (**Scheme 1.4c**), were unsuccessful; and unfortunately no further work towards the synthesis of disorazole C<sub>1</sub> was conducted by the Meyers group in order to find suitable conditions. In spite of these disappointing results, the synthesis of the protected tetrahydro-disorazole C<sub>1</sub> scaffold **21** identified an important strategy through use of stable, dienynyl fragments as protected trienes. The study was also a large step towards the synthesis of disorazole C<sub>1</sub>, because this was, at the time, the only published example of the synthesis of a disorazole-like macrocyclic framework.

### 1.2.3 C(9)–C(10) Tetrahydro-Disorazole C<sub>1</sub> (Hoffmann, 2002–2006)

In their early studies (2002/2003),<sup>14,23</sup> the Hoffmann group focussed their efforts towards the synthesis of the northern and southern fragments of disorazole A<sub>1</sub> **27/28**; the latter of which would also allow the total synthesis of disorazole C<sub>1</sub>, because the southern fragment of disorazole A<sub>1</sub> is the disorazole C<sub>1</sub> C(1)–C(19) monomer (and is present in 15 other disorazoles, and would therefore potentially have further synthetic value).<sup>24</sup> Like Meyers' second generation approach, Hoffmann chose to mask one olefin in the triene system as an alkyne for each of the fragments. However, on the basis of computational studies,<sup>14</sup> the central C(9)–C(10) alkene unit in the disorazole C<sub>1</sub> monomer was chosen as the site of the alkyne, as opposed to the C(11)–C(12) unit as carried out previously.<sup>19</sup>

To achieve the synthesis of disorazoles, it was hoped that a two-step esterification and lactonisation sequence (for disorazoles A<sub>1</sub> and C<sub>1</sub>, **Scheme 1.5a**) – in a procedure akin to that eventually utilised by Meyers in their synthesis of the C(11)–C(12) tetrahydro-disorazole C<sub>1</sub> derivative *epi-21* – could be adopted to synthesise the C(9)–C(10) isomer **29** (or the protected derivative **30**); or alternatively, for disorazole C<sub>1</sub>, a direct, single-step dilactonisation of (the carboxylic

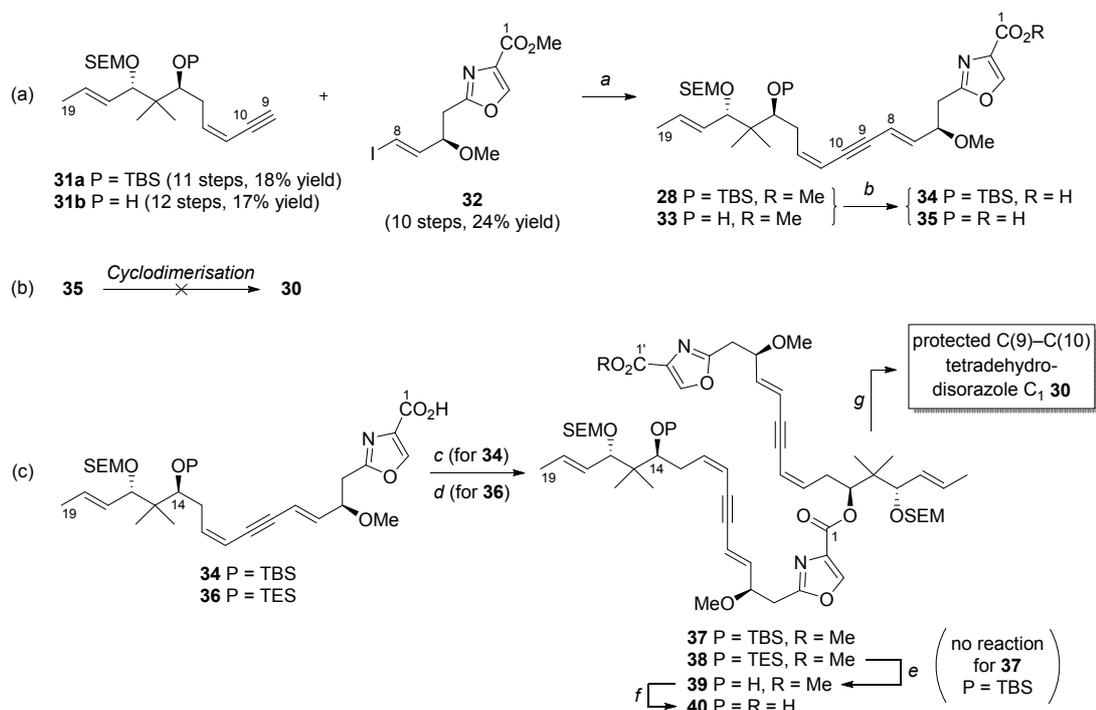


**Scheme 1.5** Hoffmann's retrosyntheses of (a) disorazole A<sub>1</sub> and (b) disorazole C<sub>1</sub>.<sup>14,23,25</sup>

acid derivative) of the southern disorazole monomer **28** could be utilised (**Scheme 1.5b**).

The total synthesis of disorazole A<sub>1</sub> was never reported by the Hoffmann group, but, in 2006, the synthesis of a protected C(9)–C(10) tetrahydro-disorazole C<sub>1</sub> **30** was described.<sup>25</sup> In order to pursue their retrosynthetic analysis (**Scheme 1.5b**) in a forward sense, the southern fragment **28** and a free alcohol derivative **33**, were synthesised using a Sonogashira coupling reaction between the C(1)–C(8) vinyl iodide **32** and the appropriate C(9)–C(19) alkyne **31** (**Scheme 1.6a**). For the purposes of esterification or lactonisation, the fragment was further derivatised by saponification of the methyl esters **28/33** with aqueous LiOH in THF.

The monomeric C(1)–C(19) fragment **35** was initially subjected to attempted cyclodimerisation under a range of standard lactonisation conditions (**Scheme 1.6b**), but this was to no avail with respect to the preparation of protected tetrahydro-disorazole C<sub>1</sub> **30** and consistently led to only the isolation of unreacted starting material. A stepwise approach was then pursued: an initial esterification



**Reagents and conditions:** *Synthesis of the C(1)–C(19) monomers 34 and 35:* (a) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Cul, Et<sub>3</sub>N, DMF, rt, 6 h, **28** 77%, **33** 89%; (b) LiOH, THF/H<sub>2</sub>O, rt, 4 h, quant; *Completion of protected C(1)–C(9) tetrahydro-disorazole C<sub>1</sub> 30:* (c) **33**, DPTC, DMAP, PhMe, reflux, 36 h, 45%; (d) (i) **36** (20% of total mass to be used), 2,4,6-TCBC, Et<sub>3</sub>N, PhMe, rt, 45 min; (ii) Addition of mixture from (i) over 45 min to **33**, DMAP, PhMe, 40 °C; (iii) 4 further iterations of steps (i) and (ii); (iv) 40 °C, 2 h, 69%; (e) TBAF, AcOH, H<sub>2</sub>O, THF, rt, 3 d, 87%; (f) Ba(OH)<sub>2</sub>, THF/MeOH/H<sub>2</sub>O, 0 °C to rt, 3 h, quant; (g) (i) 2,4,6-TCBC, Et<sub>3</sub>N, PhMe, rt, 1 h; (ii) Addition of mixture from (i) over 5 h to DMAP, 40 °C; (iii) 40 °C, 24 h, 31%.

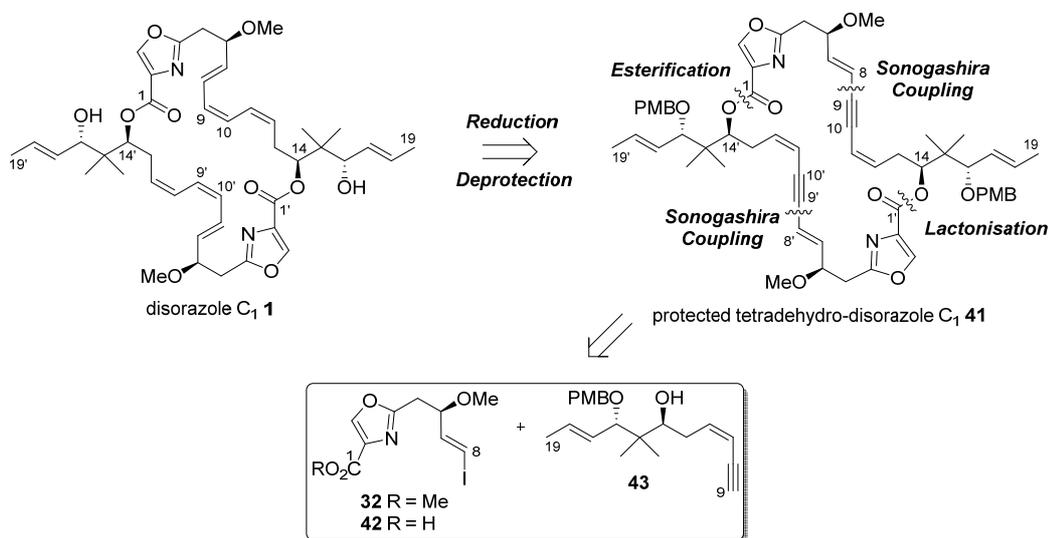
**Scheme 1.6** Hoffmann's synthesis of the protected C(9)–C(10) tetrahydro-disorazole C<sub>1</sub> **30**.<sup>14,23,25</sup>

reaction between the C(1) carboxylic acid **34** with the free alcohol **33** would be followed by C(14) silyl deprotection, C(1') ester hydrolysis and a lactonisation reaction between the alcohol and carboxylic acid moieties thus revealed to give the protected tetrahydro-disorazole C<sub>1</sub> **30** (Scheme 1.6c) in a procedure to that akin to Meyers' synthetic efforts.<sup>19</sup>

Although the initial esterification between alcohol **33** and the carboxylic acid **34** to generate the open-chain dimer **37** was successful, silyl deprotection of the TBS-protected *seco*-ester **37** could not be achieved, and therefore the route could not be pursued further. To overcome this problematic deprotection step, the sequence was repeated using the analogous TES-protected monomer **36**, and this proved to be a successful means of generating the desired macrocycle. Esterification of the alcohol **33** with the monomer **36** proceeded in 69% yield under carefully

implemented Yamaguchi esterification conditions. Silyl cleavage of the more labile TES-ether **38** and selective methyl ester hydrolysis of **39** revealed the C(14) hydroxyl and C(1') carboxylic acid moieties, respectively, to give the *seco*-acid **40** in excellent yield (87%, 2 steps). This *seco*-acid **40** underwent lactonisation in 31% yield to give the target protected tetrahydro-disorazole C<sub>1</sub> **30** (Scheme 1.6c). No further work was done to complete the natural product, because the preparation of this tetrahydro-disorazole C<sub>1</sub> **30** would represent a formal total synthesis of disorazole C<sub>1</sub>; the Wipf group had since published the synthesis of a similar protected variant during their total synthesis of disorazole C<sub>1</sub>, and this synthesis is detailed in the following section.

### 1.2.4 The First Total Synthesis of Disorazole C<sub>1</sub> (Wipf, 2004)



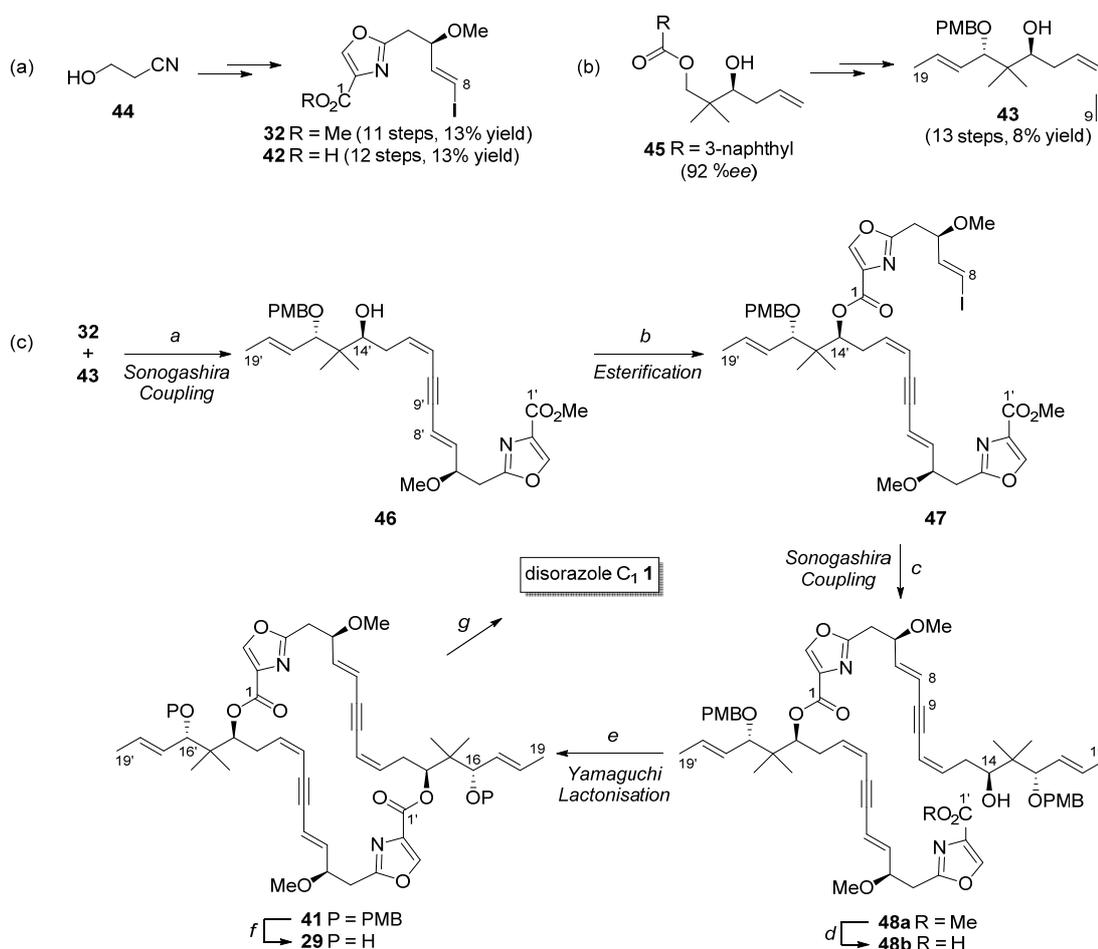
**Scheme 1.7** Wipf retrosynthesis of disorazole C<sub>1</sub>.<sup>26</sup>

The first total synthesis of disorazole C<sub>1</sub> was achieved in 2004 by Wipf and Graham,<sup>26</sup> and this approach took advantage of discoveries relating to stability and macrocycle construction from previous attempted syntheses. Firstly, given that the triene unit was unstable, Wipf chose to adopt the somewhat successful alkyne-masking approach as investigated previously (and independently) by Meyers and Hoffmann. Secondly, since Meyers had reported difficulty in reducing the triple bond on masking of the C(11)–C(12) olefin as an alkyne; and because Hoffmann had suggested that the central C(9)–C(10) alkene unit was more energetically favourable

in terms of steric strain,<sup>14</sup> Hoffmann's approach to the masking of the triene unit was adopted. However, in order to completely negate issues of monomer formation, the lactone ring system would be formed in two distinct esterification steps in a similar fashion to that which led to successful completion of the disorazole derivative macrocycles *epi*-**21** in Meyers' efforts<sup>19</sup> and **30** in Hoffmann's efforts.<sup>25</sup> The use of silyl groups to protect the C(16) hydroxyl group was also avoided in favour of PMB-ethers owing to previous failures in Meyers' approach to achieve desilylation without concomitant product decomposition.<sup>19</sup>

Wipf's approach anticipated preparation of the natural product **1** using a deprotection and selective alkyne reduction of the alkyne-masked and C(16)/C(16') bis-*O*-protected macrocyclic disorazole C<sub>1</sub> derivative **41**. To assemble the macrocycle **41**, four distinct disconnections in the macrodiolide's retrosynthesis were envisaged, as opposed to targeting a monomer representative of half of the structure and assembling the dimeric macrocycle **41** through direct dilactonisation (**Scheme 1.7**). Each of the C(9)–C(10) alkyne units would be introduced using a Sonogashira coupling reaction between the terminal alkyne of the protected diol **43** and the vinyl iodide moiety of the oxazole fragment **32**. Separate esterification and lactonisation reactions involving the C(14) hydroxyl group of the C(16)-protected diol **43** and oxazolyl carboxylic acids and would allow construction of the dilactone.

Although slightly less direct than previous approaches, the route had two key advantages: (1) despite the four-step nature of the synthesis, only three fragments were required, one of which (acid **42**) was easily derived from another (ester **32**) in a single step; and (2) the use of a potentially unselective, capricious, and inefficient dilactonisation was avoided in favour of using predictable, well-precedented, reactions. The C(1)–C(9) oxazole fragments **32/42** were synthesised in 11/12 steps and 13% overall yield from 3-hydroxypropionitrile **44**; synthesis of the C(9)–C(19) alkyne fragment **43** was achieved in 8% yield, 13 steps and 92 %*ee* from the homoallylic alcohol **45** (**Scheme 1.8a** and **b**, respectively). Construction of the macrolactone (**Scheme 1.8c**) commenced with a Sonogashira coupling reaction between the vinyl iodide **32** and the alkyne **43** to give the tetrahydro-disorazole monomer **46**. Steglich esterification<sup>27</sup> of the monomer's C(14) hydroxyl group with



**Reagents and conditions:** (a)  $\text{PdCl}_2(\text{PPh}_3)_2$ , CuI,  $\text{Et}_3\text{N}$ , MeCN,  $-20^\circ\text{C}$  to rt, 75 min, 94%; (b) **42**, DCC, DMAP, DCM,  $0^\circ\text{C}$  to rt, 14 h, 80%; (c) **43**,  $\text{PdCl}_2(\text{PPh}_3)_2$ , CuI,  $\text{Et}_3\text{N}$ , DCM,  $-20^\circ\text{C}$  to rt, 75 min, 94%; (d) LiOH, THF/ $\text{H}_2\text{O}$ , rt, 13.5 h, 98%; (e) (i) 2,4,6-TCBC,  $\text{Et}_3\text{N}$ , THF, rt, 2 h; (ii) DMAP, PhMe, rt, 16 h, 79%; (f) DDQ, phosphate buffer, DCM, rt, 15 min, 61%; (g)  $\text{H}_2$ , Lindlar's catalyst, quinoline, EtOAc, rt, 1 h, 57%.

**Scheme 1.8** Synthesis of the (a) C(1)–C(8) vinyl iodide fragments **32/42**; and (b) C(9)–C(19) alkyne **43**. (c) Endgame strategy of Wipf and Graham's total synthesis of disorazole C<sub>1</sub>.<sup>26</sup>

the oxazole carboxylic acid **42** gave the 'three-quarter' disorazole **47**. A second Sonogashira reaction (with **43**), selective hydrolysis of the methyl ester **48a** and Yamaguchi lactonisation of the *seco*-acid **48b** allowed completion of the synthesis of the protected tetrahydro-disorazole C<sub>1</sub> derivative **41**. The synthesis of the natural product **1** was concluded by deprotection of the C(16)/C(16') PMB-ethers to give tetrahydro-disorazole C<sub>1</sub> **29**, and Lindlar hydrogenation of the alkynes; the endgame sequence thus furnishing disorazole C<sub>1</sub> **1** in a respectable 19% yield over the 7 key steps (**Scheme 1.8c**). Overall, Wipf and Graham's approach allowed access to disorazole C<sub>1</sub> **1** in 20 steps and 1.5% overall yield for the longest linear sequence of reactions.

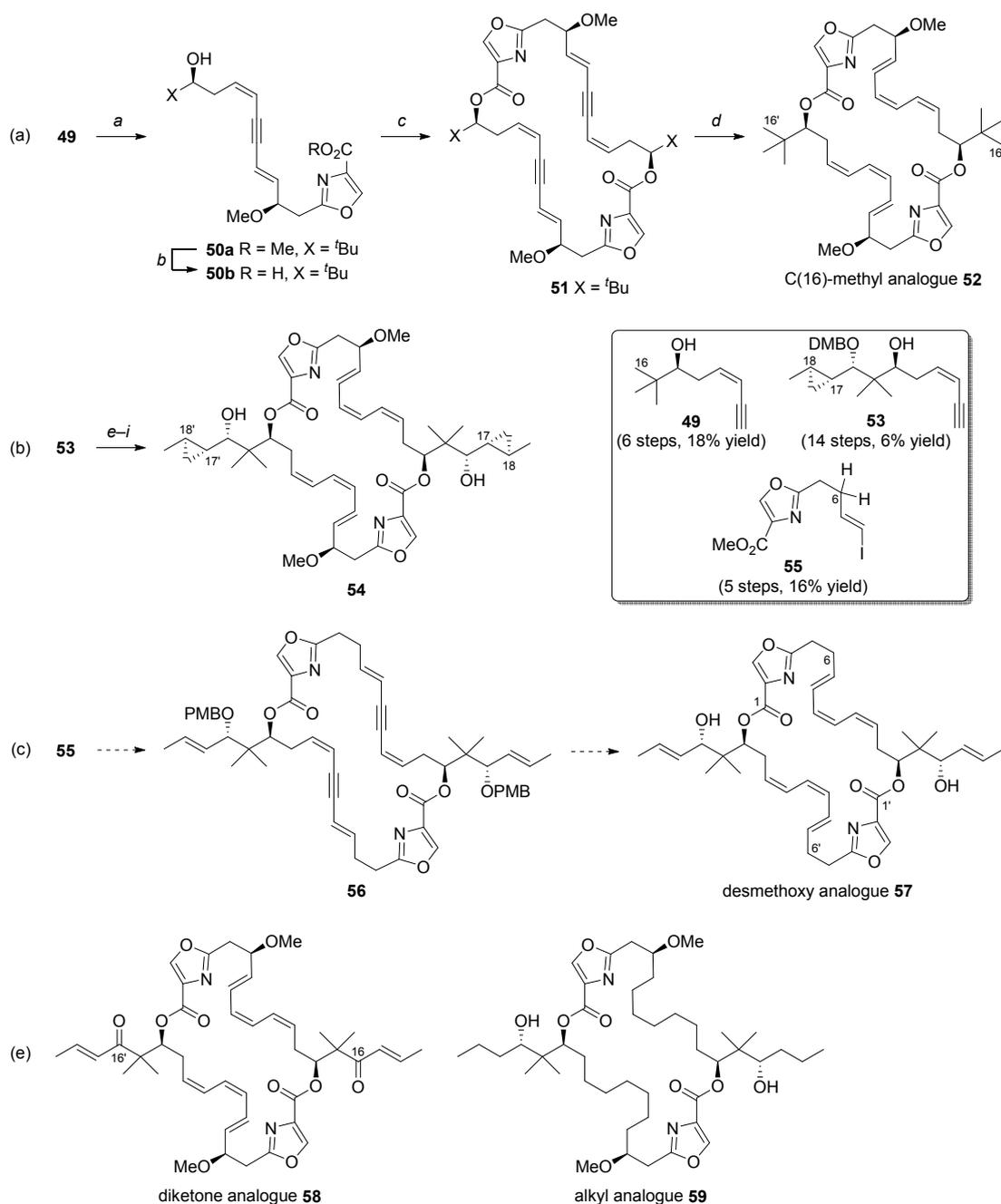
## 1.3 Synthesis of Disorazole Analogues

### 1.3.1 Disorazole C<sub>1</sub> Analogues (Graham, 2006)

In addition to describing the synthesis of natural disorazole C<sub>1</sub>, in his thesis,<sup>26b</sup> Graham reports – for reasons of investigating SARs – the synthesis of a number of analogues. Analogues included both those that were synthesised according to multistep procedures, and straightforward derivatisations of disorazole C<sub>1</sub>. Unlike the synthesis of the natural product, the analogues were assembled using a dilactonisation from a C(1)-carboxylic acid/C(14)-hydroxy monomer. Graham did not speculate on the reasons for this deviation from the highly successful stepwise approach; however, from a biological testing point of view, it was presumably carried out for increased expediency; and from a synthetic perspective, it would allow a comparison between the direct dimerisation and stepwise metal coupling/esterification approaches towards the disorazole C<sub>1</sub> scaffold to be made.

To synthesise the C(16)-methyl analogue **52**, homoenynyl alcohol **49** (obtained in 6 steps and 18% yield from pivaldehyde) was subjected to Sonogashira coupling with the C(1)–C(8) vinyl iodide **32** to give the monomer **50a**. Methyl ester hydrolysis and cyclodimerisation under Yamaguchi conditions gave the dimer **51** in 26% yield; and from this, subsequent Lindlar hydrogenation afforded the desired C(16)-methyl analogue **52** in 43% yield. The C(17)–C(18) cyclopropane analogue **54** was synthesised in an analogous fashion from the hydroxyalkyne **53** in 5% yield over 5 steps. Unfortunately, routes investigated towards the synthesis of the desmethoxy analogue **57** from vinyl iodide **55** were unsuccessful. Both direct cyclodimerisation (of the **55**→**43** Sonogashira coupled monomer, not shown), and stepwise macrocycle construction (*cf.* disorazole C<sub>1</sub>, **Section 1.2.4, Scheme 1.8**), led to a poor isolation (11 to 20%) of the dimeric product **56** in unsatisfactory purity, and therefore attempts to synthesise the analogue **57** were abandoned due to a lack of material.

The final disorazole C<sub>1</sub> analogues synthesised by Graham were more straightforwardly obtained: the C(16)-didehydro “diketone” analogue **58** was prepared in 91% yield using Dess–Martin oxidation<sup>28</sup> of disorazole C<sub>1</sub> **1**, while the hexadecahydro “alkyl” analogue **59** was obtained by hydrogenation of an over-reduced side-product mixture obtained from the Lindlar hydrogenation step in

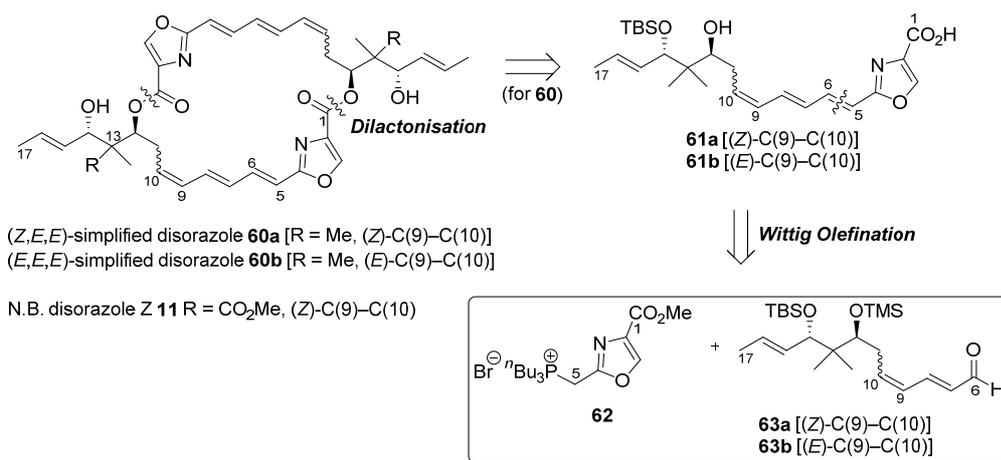


**Reagents and conditions:** *Synthesis of the C(16)–C(19) methyl analogue 52:* (a) **32**, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, Et<sub>3</sub>N, MeCN, 0 °C, 2 h, 94%; (b) LiOH, THF/H<sub>2</sub>O, 20 h, rt, 97%; (c) (i) 2,4,6-TCBC, Et<sub>3</sub>N, THF, rt, 2 h; (ii) DMAP, PhMe, rt, 2 h, 26%; (d) H<sub>2</sub>, 5% Pd/BaSO<sub>4</sub>, quinoline, EtOAc, rt, 30 min, 43%; *Synthesis of the C(17)–C(18) cyclopropane analogue 54:* (e) **32**, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, Et<sub>3</sub>N, MeCN, 0 °C to rt, 1.5 h, 94%; (f) LiOH, THF/H<sub>2</sub>O, rt, 12 h, quant; (g) (i) 2,4,6-TCBC, Et<sub>3</sub>N, THF, rt, 1 h; (ii) DMAP, PhMe, rt, 4 h, 27%; (h) DDQ, phosphate buffer, DCM, 0 °C to rt, 30 min, 91%; (i) H<sub>2</sub>, 5% Pd/BaSO<sub>4</sub>, quinoline, EtOAc, rt, 1.5 h, 22%.

**Scheme 1.9** Graham's disorazole C<sub>1</sub> analogues.<sup>26b</sup>

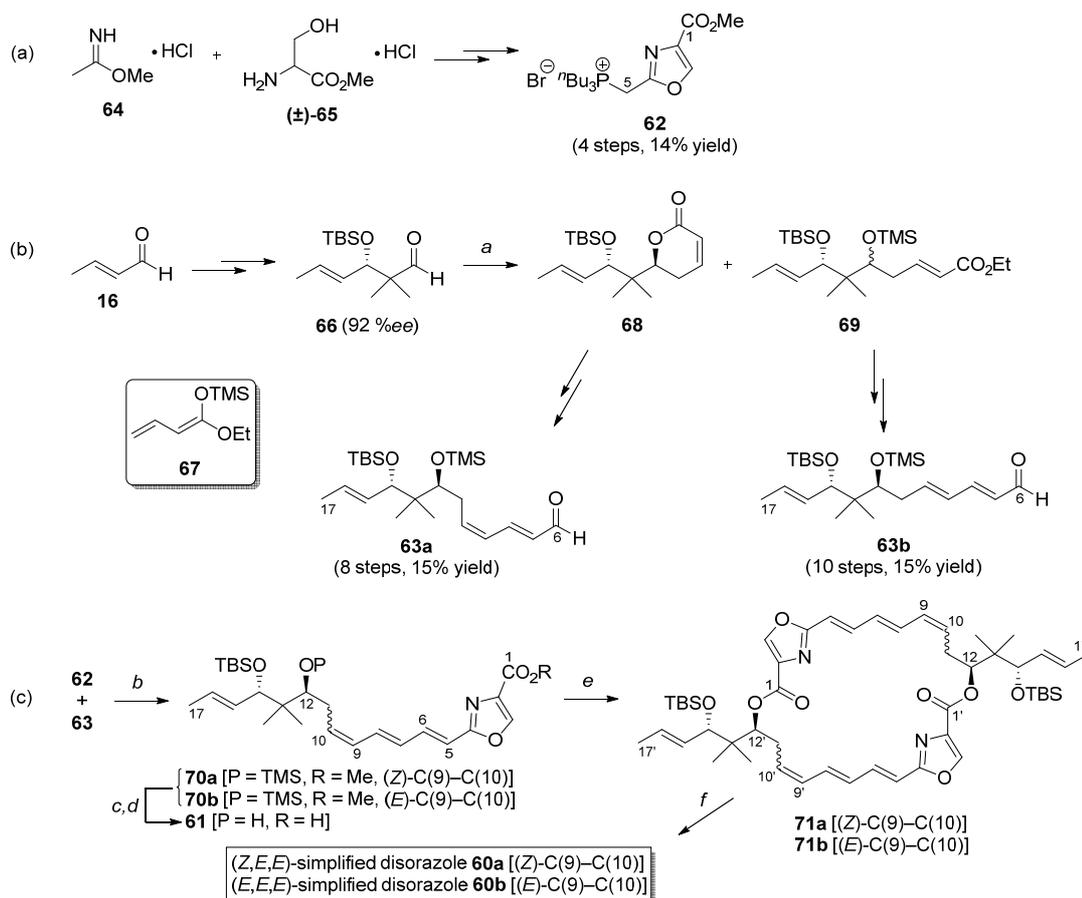
disorazole C<sub>1</sub>'s total synthesis. All of the newly synthesised disorazoles were later tested for their activity against a range of cell lines and would provide important structure–activity relationship information (see: **Section 1.4**).

## 1.3.2 The Simplified Disorazoles (Kalesse, 2010)

Scheme 1.10 Retrosynthesis of Kalesse's simplified disorazoles **60**.<sup>29</sup>

The Kalesse group synthesised so-called “simplified” disorazoles<sup>29</sup> whereby the disorazoles were smaller – lacking a CH<sub>2</sub>CHOMe unit in each monomer and hence two stereocentres – when compared to the structure of disorazole C<sub>1</sub>; and where the C(13) methyl ester group is absent in comparison to disorazole Z (which their structures most closely represent). The synthetic process was also simplified: Wipf's total synthesis employed a multistep process of consecutive palladium coupling and esterification reactions between three fragments to construct the macrocycle and required 21 steps for the longest linear sequence. Kalesse regressed somewhat (Scheme 1.10), and anticipated the preparation of both simplified disorazole stereoisomers **60** by a dilactonisation reaction between C(1)–C(17) monomers **61**, which were to be prepared *via* a Wittig reaction<sup>30</sup> between the C(1)–C(5) oxazole Wittig reagent **62**, and the C(6)–C(17) aldehydes **63**. It was hoped that a route could be established that would provide access to disorazole frameworks that were more rapidly synthesised (*cf.* Wipf's approach) but were equipotent as cytotoxic agents.

Synthesis of the C(1)–C(5) oxazole Wittig reagent **62** was achieved in 14% yield over 4 steps *via* an initial condensation reaction between methyl acetimidate **64** and serine methyl ester ( $\pm$ )-**65** (commencing from their hydrochloride salts; Scheme 1.11a), while the (*Z*)-C(6)–C(17) aldehyde **63a** and its (*E*)-stereoisomer **63b** were synthesised in 15% yield over 8 and 10 steps, respectively. It is worth noting that the formation of two products at a key (vinologous Mukaiyama aldol reaction)<sup>31</sup> step



**Reagents and conditions:** *Synthesis of the C(6)–C(17) aldehydes 63:* (a) (i)  $\text{Cu}(\text{OTf})_2$ , (S)-Tol-BINAP, THF rt, 20 min; (ii) TBAT, 20 min; (iii) **66**, **67**, 24 h, **68** 30% yield, 5:1 *dr* (separable), **69** 25% yield, 3:1 *dr* (separable at a later step); *Synthesis of the simplified disorazoles 60:* (b) (i) **62**,  $t\text{-BuOK}$ , THF,  $-78$  to  $0$   $^\circ\text{C}$ , 1 h; (ii) **63**,  $-78$  to  $0$   $^\circ\text{C}$ , 3 h, **70a** 85%, **70b** 75%; (c) HF·Py, Py, THF,  $0$   $^\circ\text{C}$  to rt, 20 min; (d) LiOH, THF/ $\text{H}_2\text{O}$ ,  $0$   $^\circ\text{C}$  to rt, 15 h, absence of light, **61a** 75%, **61b** 60%; (e) MNBA, DMAP,  $4$  Å MS, absence of light, **71a** PhMe, 6 d, 26%; **71b** PhMe/THF, 3 d, 18%; (f) HF, MeCN/ $\text{H}_2\text{O}$ ,  $-20$   $^\circ\text{C}$ , 3 d, absence of light, **60a** 22%, **60b** 34%.

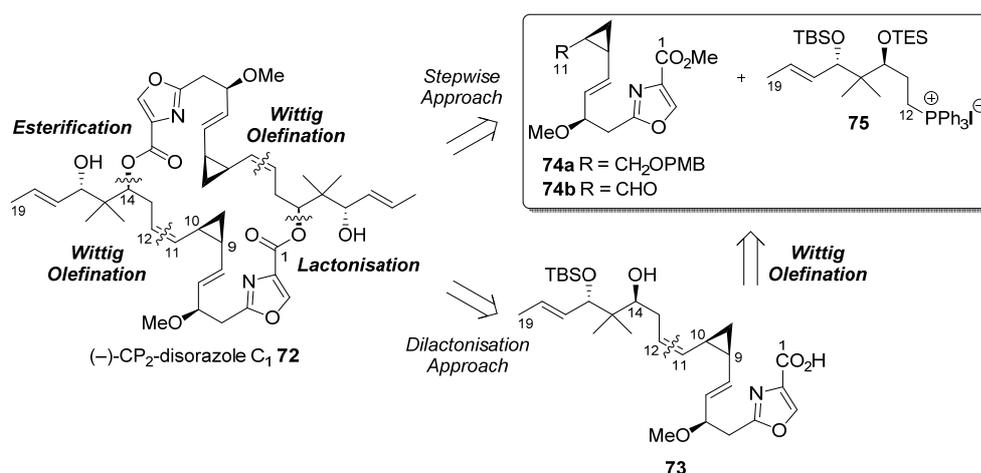
**Scheme 1.11** Synthesis of the (a) C(1)–C(5) oxazole Wittig reagent fragment **62**; and (b) C(6)–C(17) aldehyde fragments **63**. (c) Endgame strategy towards the synthesis of the simplified disorazoles **60**.<sup>29</sup>

allowed the synthesis of both (*E*)- and (*Z*)-stereoisomers of the aldehydes **63** (**Scheme 1.11b**) from aldehyde **66**. Lactone **68** (a precursor of aldehyde **63a**) was obtained in 30% yield and 5:1 *dr*, with the desired *anti*-isomer separable chromatographically. Vinylic ester **69** (a precursor of aldehyde **63b**) was obtained in 25% yield as a 3:1 mixture of *anti:syn* diastereomers, which were separable following TMS-ether hydrolysis at a later stage in the synthesis of **63b**.

The structural similarity of the aldehyde isomers **63** allowed pursuit of an identical endgame strategy for completion of the simplified disorazoles **60** (**Scheme 1.11c**). Generation of the C(1)–C(17) protected monomers **70** from the C(1)–C(5) and the

C(6)–C(17) fragments **62/63** was accomplished using a Wittig olefination, which proceeded in high yield (>75%) for both aldehyde precursors. Selective TMS deprotection followed by ester hydrolysis gave the hydroxyacids **61** in good yield. Cyclodimerisation of the fragments **61** with MNBA<sup>32</sup> proceeded in manageable yields of 18 and 26%. Completion of the disorazoles **60** was achieved by treatment of the TBS-protected derivatives **71** with HF in MeCN.

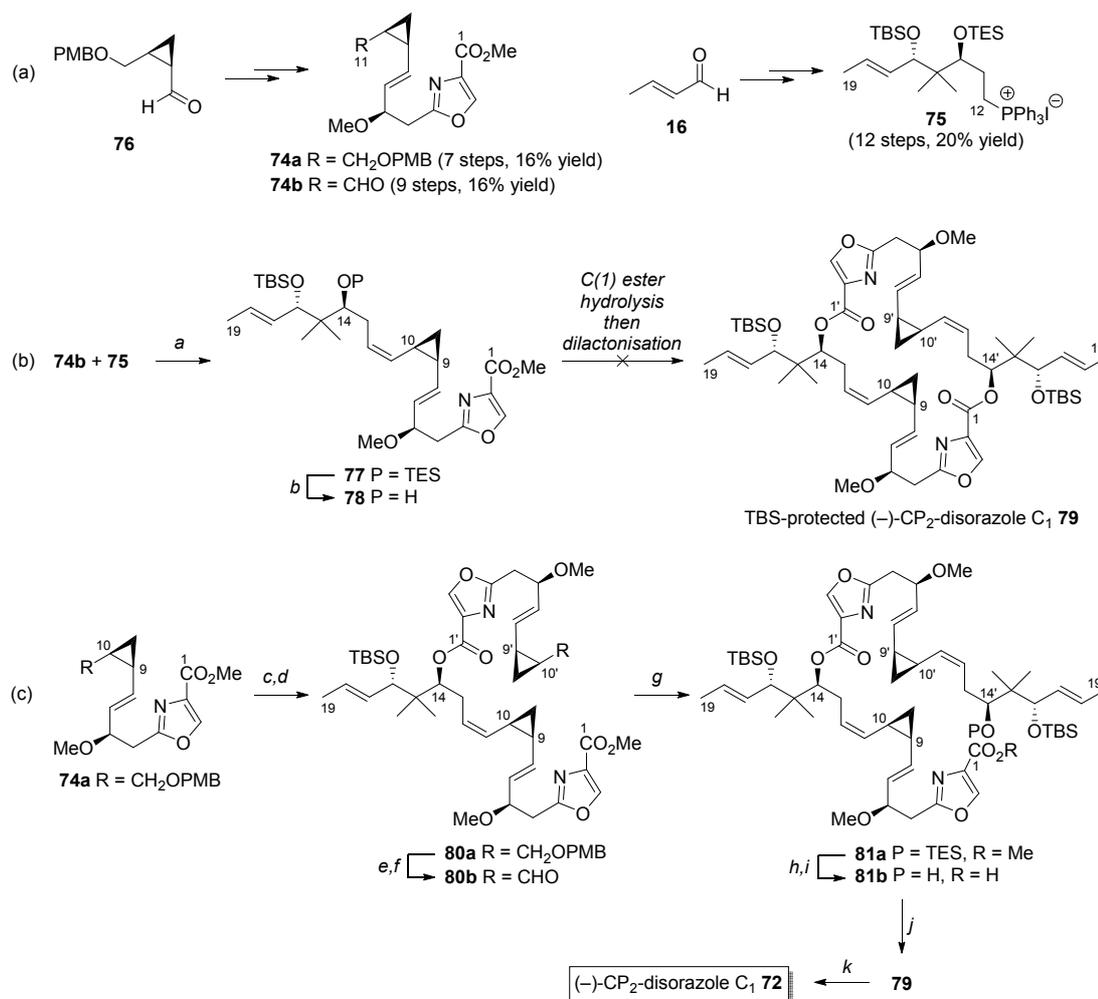
### 1.3.3 (–)-CP<sub>2</sub>-Disorazole C<sub>1</sub> (Wipf, 2011)



**Scheme 1.12** Retrosynthesis of (–)-CP<sub>2</sub>-disorazole C<sub>1</sub> **72**.<sup>33</sup>

The Wipf group followed up their total synthesis of disorazole C<sub>1</sub> with the synthesis of a disorazole C<sub>1</sub> analogue **72**, in which the central C(9)–C(10) alkene unit of disorazole C<sub>1</sub> was replaced with a cyclopropane moiety.<sup>33</sup> Aside from the cyclopropane group being a common isostere of the double bond,<sup>34</sup> this moiety was intended to mimic the shape of the epoxide functionality present in disorazole A<sub>1</sub> and other epoxide-containing analogues and probe for reactivity of the epoxide in the binding site. For this reason, the stereochemistry of the cyclopropane group was chosen such that it matched that present in disorazole A<sub>1</sub>.

The retrosynthesis of (–)-CP<sub>2</sub>-disorazole C<sub>1</sub> **72** (**Scheme 1.12**) was not far removed from that used by Wipf in the synthesis of disorazole C<sub>1</sub>, in that it involved four key retrosynthetic disconnections that centred around two important and reliable types of reaction. Esterification/lactonisation was anticipated for formation of the C(1)–C(14) ester moieties; however, a Wittig olefination was used to generate the C(10)–C(11)



**Reagents and conditions:** *Synthesis of the monomer 78 and attempted dilactonisation:* (a) (i) **75**, KHMDS, THF, -78 °C, 30 min; (ii) **74b**, 0 °C, 24 h, 84%; (b) PPTS, MeOH, 0 °C, 23 h, 65%; *Synthesis of (-)-CP<sub>2</sub>-disorazole C<sub>1</sub> 72:* (c) LiOH, THF/H<sub>2</sub>O, rt, 20 h, quant; (d) **78**, DCC, DMAP, rt, 22 h, 89%; (e) DDQ, DCM/phosphate buffer, 1.5 h, 81%; (f) Dess–Martin periodinane, NaHCO<sub>3</sub>, DCM, 0 °C, 6.5 h, 99%; (g) (i) **75**, KHMDS, THF, -78 °C, 30 min; (ii) **80b**, -78 to 0 °C, 17 h, 74%; (h) PPTS, MeOH, 23.5 h, 63%; (i) Ba(OH)<sub>2</sub>, THF/H<sub>2</sub>O, rt, 26 h; (j) MNBA, Et<sub>3</sub>N, DMAP, PhMe, rt, 29 h, 55%; (k) HF•Py, THF, 0 °C to rt, 22 h, 64%.

**Scheme 1.13** Endgame strategy towards the synthesis of (-)-CP<sub>2</sub>-disorazole C<sub>1</sub>.

double bonds, as opposed to reliance on transition metal catalysis which understandably could not be so predictably relied upon given the alkyl substitution at C(11)–C(12). Initially, a dilactonisation was anticipated with the monomer **73**, although this was later revised to a stepwise approach akin to that used for the synthesis of the natural product. The fragments required for both of these routes included the C(1)–C(11) oxazole **74** and the C(12)–C(19) Wittig reagent **75**.

The C(1)–C(11) oxazole PMB-ether **74a** and its aldehyde derivative **74b** were synthesised in 7 and 9 steps (respectively) and 16% yield longest linear sequence

from the easily accessed aldehyde **76** (**Scheme 1.13a**). A Wittig olefination of the aldehyde **74b** with the C(12)–C(19) fragment Wittig reagent **75** [which was synthesised from (*E*)-crotonaldehyde **16** in 20% yield over 12 steps; **Scheme 1.13a**] proceeded in good yield to give the C(1)–C(19) monomer **78**. Unfortunately, attempted dimerisation [with the C(1)-carboxylic acid derivative of **78**, monomer **73**] to give the protected disorazole C<sub>1</sub> analogue **79** failed, and therefore a stepwise approach was investigated.

The stepwise route was performed in the vein of that seen in Wipf's disorazole C<sub>1</sub> total synthesis: the monomer **78** was esterified with the C(1)-carboxylic acid derivative of **74a** to give the 'three-quarter' disorazole **80a**. Two-stage conversion of the PMB-ether **80a** to the aldehyde **80b** followed by a second Wittig reaction furnished the protected disorazole C<sub>1</sub> *seco*-ester **81a**. Selective TES deprotection followed by ester hydrolysis, and lactonisation of the *seco*-acid **81b** thus obtained gave the protected disorazole C<sub>1</sub> analogue **79**. A final TBS deprotection with HF•pyridine completed the synthesis of (–)-CP<sub>2</sub>-disorazole C<sub>1</sub> **72** in 1.1% yield and 23 steps longest linear sequence.

It is worth noting that the final deprotection step was remarkably efficient, giving the product **72** in 64% yield. This stands up very well against previous efforts whereby comparably diminished yields were typical, and shows the effect of removing the conjugation associated with the unsaturated C(7)–C(12) unit can have over the success of silyl deprotection steps (*cf.* Meyers' and Kalesse's syntheses, **Section 1.2.2, Scheme 1.4** and **Section 1.3.2, Scheme 1.11**, respectively). It also implies that greater than expected success might be obtained in (silyl) deprotection of C(11)–C(12)-epoxide-based natural product derivatives, should a suitably mild set of conditions compatible with epoxides be found for generation of the required macrocycle. This is because the epoxide functionality interferes with the conjugation associated with the triene unit, and the unconjugated diene **79** was found to survive fluoride-mediated deprotection.

## 1.4 Structure–Activity Relationships in the Disorazoles

All studies carried out towards the synthesis of disorazole C<sub>1</sub> and related analogues were followed up with biological testing, and an examination of the cytotoxic potency of the various disorazoles allows determination of the SARs that may be present within the family of natural products. **Table 1.1** indicates the level of cytotoxicity (IC<sub>50</sub> or EC<sub>50</sub>) of a range of disorazoles (in descending order of potency) against cancer cell lines, along with a broad statement describing the difference in chemical structure on comparison to the structure of disorazole C<sub>1</sub>. The disorazoles in **Figure 1.5** (to which **Table 1.1** refers) were either naturally obtained, are synthetic analogues or (in the case of disorazoles **82** and **83**) were obtained by methanolysis of disorazole A<sub>1</sub>.<sup>35</sup>

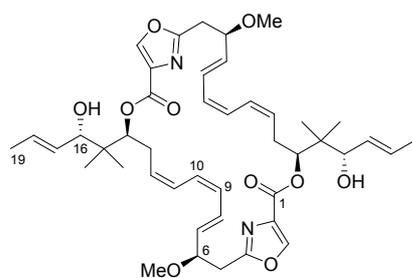
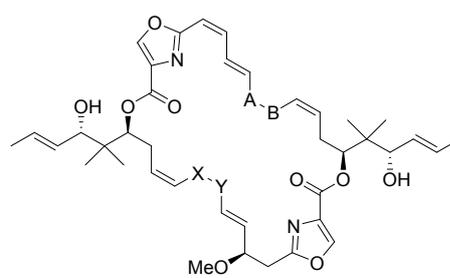
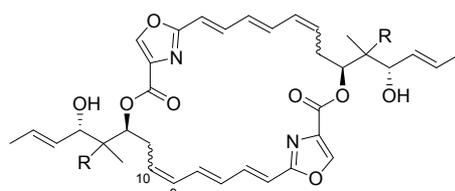
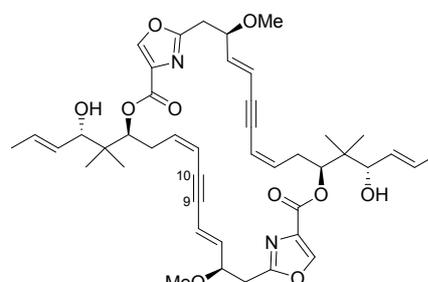
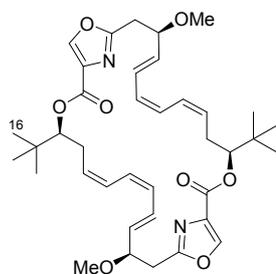
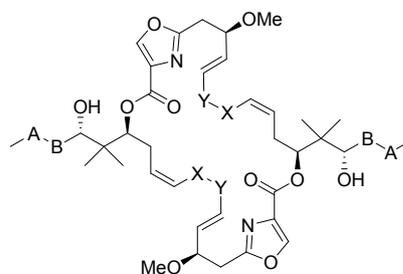
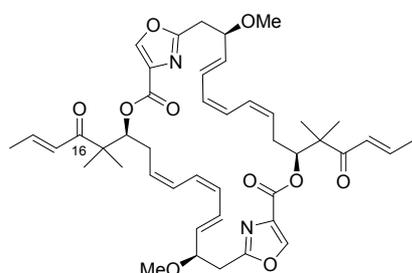
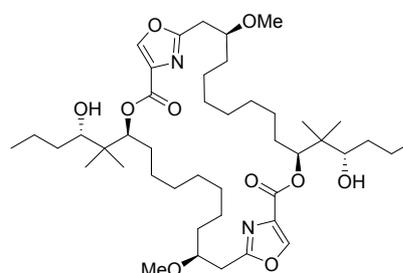
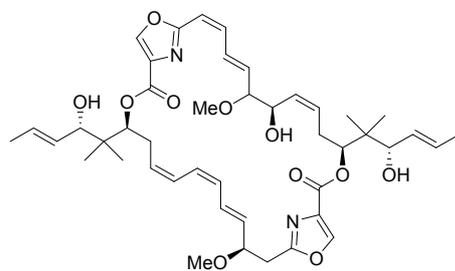
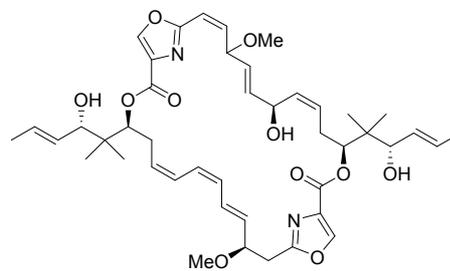
As can be seen from **Table 1.1** Entry 1, the most potent variant is disorazole E<sub>1</sub> **7**, followed by disorazoles D<sub>1</sub> **5** and A<sub>1</sub> **2** (**Table 1.1**, Entries 2 and 3).<sup>3,5</sup> All three structures contain the divinyl epoxide (or -diol) moiety, which suggests that these isosteres give the most potent cytotoxicity. However, given that disorazoles D<sub>1</sub> and A<sub>1</sub> show almost equipotent activity, a diol at the C(9)–C(10) position may be sufficient for high potency; and indeed the methanolysis product KOS 1903 **82** (**Table 1.1**, Entry 5) – which is effectively a monomethylated disorazole D<sub>1</sub> analogue – still shows activity at sub-nanomolar concentrations.<sup>35</sup>

After the C(9)–C(10) epoxide and diol containing disorazoles, disorazole Z **11** is the most potent analogue (**Table 1.1**, Entry 4).<sup>2b</sup> This is particularly interesting, because it lacks both a C(9)–C(10) epoxide/diol and a C(5)–C(6) methylenemethoxy group; although like the most potent disorazoles, at least one triene framework exists in conjugation with the oxazole. Kalesse's (*Z,E,E*)-simplified disorazole **60a** is also highly potent (**Table 1.1**, Entry 6),<sup>29</sup> however, the stereochemistry at C(9)–C(10) is important, because the (*E,E,E*)-triene configured simplified disorazole **60b** (**Table 1.1**, Entry 10) is some 46 times less potent than this analogue.<sup>29</sup> These data imply that high activity can be achieved without the epoxide or diol moiety, but that the double bond configurations in the triene are very important. The increased activity of disorazole Z **11** over disorazole **60a** probably relates to the presence of the C(13) methyl ester, which would appear to make the natural product **11** 2.4 times more

**Table 1.1** Mean IC<sub>50</sub> and EC<sub>50</sub> values for a range of disorazoles listed in descending order of potency.

Entry	Disorazole <sup>a</sup>	Mean IC <sub>50</sub> (nM) <sup>b-e</sup>	Mean EC <sub>50</sub> (nM) <sup>b-e</sup>	Notes	Refs.
1	E <sub>1</sub> <b>7</b>	—	0.09 (5)	Two C(9)–C(10) epoxides; one C(6) OCH <sub>3</sub> group absent.	5
2	D <sub>1</sub> <b>5</b>	—	0.24 (5)	C(9)–C(10) diol; one C(6) OCH <sub>3</sub> group absent.	5
3	A <sub>1</sub> <b>2</b>	0.012 (12)	0.27 (5)	C(9)–C(10) epoxide; one C(6) OCH <sub>3</sub> group absent.	3, 5
4	Z <b>11</b>	0.40 (1)	—	No C(5)–C(6) CH <sub>2</sub> OCH <sub>3</sub> groups. Has an ester at C(15) and C(15').	2b
5	KOS 1903 <b>82</b>	0.73 (5)	—	Epoxide replaced with a C(9)–C(10) monomethylated 1,2-diol.	35
6	(Z,E,E) <b>60a</b>	0.96 (5)	—	No C(5)–C(6) CH <sub>2</sub> OCH <sub>3</sub> group; (Z)-C(9)–C(10) olefin.	29
7	C <sub>1</sub> <b>1</b>	1.66 (10)	14.6 (1)	Dimeric. No epoxides or diols within the double bond framework.	4
8	KOS 2296 <b>83</b>	6.20 (5)	—	One triene disrupted; OCH <sub>3</sub> at C(7), and OH group at C(10).	35
9	(–)-CP <sub>2</sub> <b>72</b>	35.27 (3)	—	The C(9)–C(10) olefin is replaced by a cyclopropane group.	33
10	(E,E,E) <b>60b</b>	44.2 (5)	—	Lacks C(5)–C(6) CH <sub>2</sub> OCH <sub>3</sub> group; (E)-C(9)–C(10) olefin.	29
11	Tetradehydro <b>29</b>	—	3912 (1)	C(9)–C(10) olefin replaced with an alkyne; conformation altered.	4a, 26b
12	Alkyl <b>59</b>	—	>5000 (1)	All double bonds absent; conformation markedly altered.	26b
13	Cyclopropyl <b>54</b>	—	>5000 (1)	C(17)–C(18) olefin replaced by a cyclopropane group.	26b
14	Diketone <b>58</b>	—	>5000 (1)	C(16) OH groups replaced with carbonyl (ketone) groups.	26b
15	C(16)-Methyl <b>52</b>	—	>5000 (1)	C(16)–C(19) propenyl alcohol removed and replaced with a CH <sub>3</sub> group.	26b

<sup>a</sup>Structures are shown in **Figure 1.5**; <sup>b</sup>Refers to the average IC<sub>50</sub> or EC<sub>50</sub> obtained when tested over a number of cancer cell lines (non-cancer cell line values have been omitted from calculation). <sup>c</sup>IC<sub>50</sub> and EC<sub>50</sub> measure the drug concentrations at which 50% cell growth inhibition is achieved, and the concentration of the drug required to cause 50% cell death, respectively; <sup>d</sup>The number of cell lines to which the IC<sub>50</sub> or EC<sub>50</sub> value refers is indicated in parentheses; <sup>e</sup>In some cases, nanomolar concentrations (nmol/dm<sup>3</sup>) were calculated from the corresponding drug activities as measured in micro- (μ) or pico- (p) grams *per* cm<sup>3</sup>; <sup>f</sup>Where relevant, displayed as IC<sub>50</sub>, [EC<sub>50</sub>].

disorazole C<sub>1</sub> **1** (1.66, 14.6 nM)disorazole A<sub>1</sub> **2** [A-B = epoxide, X-Y = (Z)-HC=CH] (0.012, 0.27 nM)disorazole D<sub>1</sub> **5** [A-B = 1,2-diol, X-Y = (Z)-HC=CH] (0.24 nM)disorazole E<sub>1</sub> **7** [A-B = X-Y = epoxide] (0.09 nM)disorazole Z **11** [R = CO<sub>2</sub>Me, (Z)-C(9)-C(10)] (0.04 nM)(Z,E,E)-simplified disorazole **60a** [R = Me, (Z)-C(9)-C(10)] (0.96 nM)(E,E,E)-simplified disorazole **60b** [R = Me, (E)-C(9)-C(10)] (44.2 nM)C(9)-C(10) tetrahydro-disorazole C<sub>1</sub> **29** (3912 nM)C(16)-methyl **52** (>5000 nM)cyclopropyl **54** [A-B = cyclopropyl, X-Y = (Z)-HC=CH] (>5000 nM)(–)-CP<sub>2</sub>-disorazole C<sub>1</sub> **72** [A-B = (E)-HC=CH, X-Y = cyclopropyl] (35.27 nM)diketone **58** (>5000 nM)alkyl disorazole C<sub>1</sub> **59** (>5000 nM)KOS 1903 **82** (0.73 nM)KOS 2296 **83** (6.20 nM)

**Figure 1.5** Biologically tested disorazole structural variants and analogues (potencies are reported as IC<sub>50</sub>, EC<sub>50</sub>).

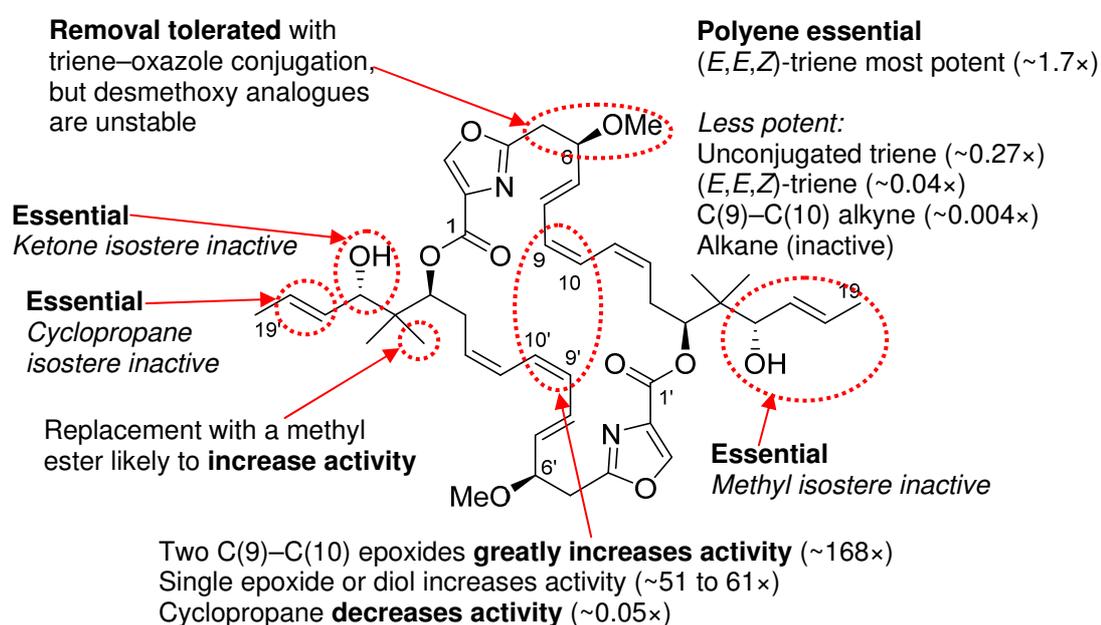
potent than its synthetic analogue.

Disorazole C<sub>1</sub> (**Table 1.1**, Entry 7) is the next most potent disorazole, displaying an IC<sub>50</sub> of 1.66 nM<sup>4a</sup> and an EC<sub>50</sub> of 14.6 nM.<sup>4b</sup> Compared to most of the more potent variants, disorazole C<sub>1</sub> lacks oxygen functionality within its two triene systems, and has methoxy groups at C(6). Conjugation of the olefin system with the heterocycle is no longer present, and it could be argued that this to some extent decreases activity and therefore the removal of the methoxy group in favour of conjugation with the oxazole is likely to augment activity. However, it should be noted that the methoxy group probably reduces triene lability, because Graham's efforts to synthesise the desmethoxy analogue **57** were met with great difficulty;<sup>26b</sup> and therefore the group may be required to maintain structural stability.

After disorazole C<sub>1</sub>, the methanolysis product KOS 2296 **83** is the most potent (**Table 1.1**, Entry 8).<sup>35</sup> Notably, the conjugation within one 'half' of the disorazole has been completely abolished, and this perhaps has implications for binding activity to the natural product's target. Wipf's (-)-CP<sub>2</sub>-disorazole C<sub>1</sub> analogue **72** (which, incidentally, also lacks triene conjugation) is approximately 21 times less potent than disorazole C<sub>1</sub> (**Table 1.1**, Entry 9),<sup>33</sup> and therefore this information indicates that a cyclopropane group at C(9)–C(10) is not a good isostere for the olefin or the epoxide.

After the (*E,E,E*)-simplified disorazole **60b** (**Table 1.1**, Entry 10),<sup>29</sup> cytotoxicity rapidly declines towards micromolar levels of potency: tetrahydro-disorazole C<sub>1</sub> **29** (**Table 1.1**, Entry 11) displays an EC<sub>50</sub> of approximately 4 μM, whilst the saturated alkyl analogue **59** (**Table 1.1**, Entry 12) has an even higher EC<sub>50</sub> value (>5 μM).<sup>26b</sup> These two changes in particular are representative of large changes in disorazole conformation,<sup>4b</sup> and therefore highlight the importance of the three-dimensional structure on the activity of the disorazoles. The remaining disorazoles (**Table 1.1**, Entries 13 to 15) also showed potency greater than 5 μM.<sup>26b</sup> These data are important, because they identify moieties of the disorazoles which are of critical importance with respect to bioactivity: the C(17)–C(18) olefin of disorazole C<sub>1</sub>, the C(16) hydroxyl groups, and the C(16)–C(19) hydroxypropene group.

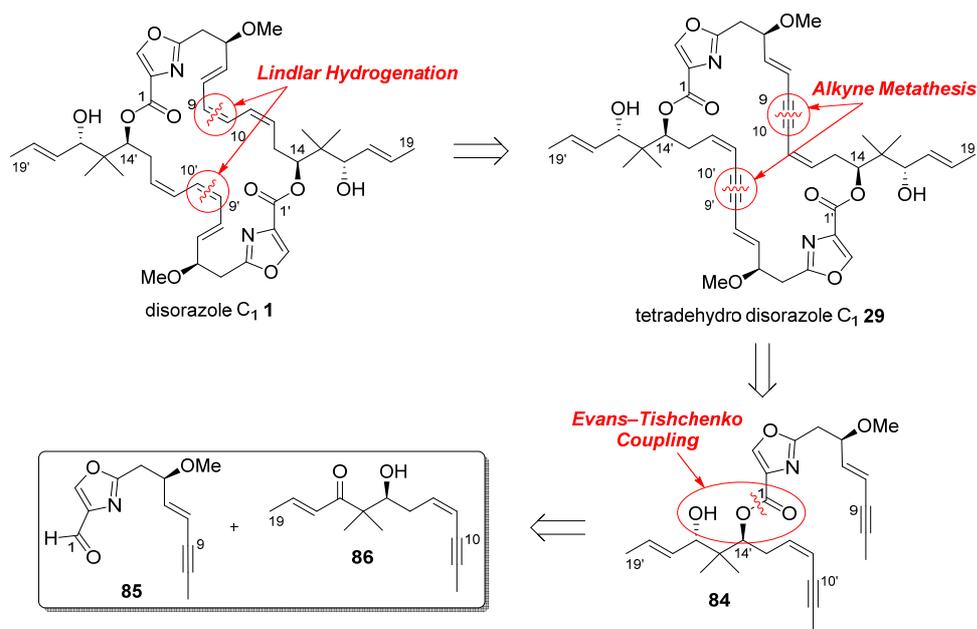
A summary of the above discussion is shown in **Figure 1.6**. As can be seen from **Figure 1.6**, variations in structure with respect to disorazole C<sub>1</sub> mainly include modifications to the polyene system and changes to the C(15)–C(19) group, while removal of the C(5)–C(6) methylenemethoxy group and the C(15) methyl group are apparent in a range of the natural disorazoles and disorazole Z. A change to the identity of the C(2)–C(4) heterocycle has never been explored, and it is the modification of this group that the Hulme group wishes to achieve. In addition, replacement of the methoxy group with an alternative functionality, save for its removal, has never been investigated. These modifications have been reflected in our retrosynthesis of the natural product.



**Figure 1.6** Summary of SARs in the disorazole family. Numerical values refer to the increase or decrease in cytotoxic potency observed when compared to disorazole C<sub>1</sub>.

### 1.5 The Hulme Group Strategy towards the Synthesis of Disorazole C<sub>1</sub>

Although the synthesis of disorazole C<sub>1</sub> **1** and a variety of analogues has been achieved previously, the most direct route – which requires a dilactonisation reaction – has often been unsuccessful, low yielding (typically less than 30% yield) and in some cases lacks chemoselectivity. Furthermore, the synthetic sequences are generally long (~20 steps longest linear sequence) and the approach relies on protecting group strategies owing to the multiple hydroxyl groups present in the synthetic intermediates. Our strategy towards the synthesis of disorazole C<sub>1</sub> **1** focuses

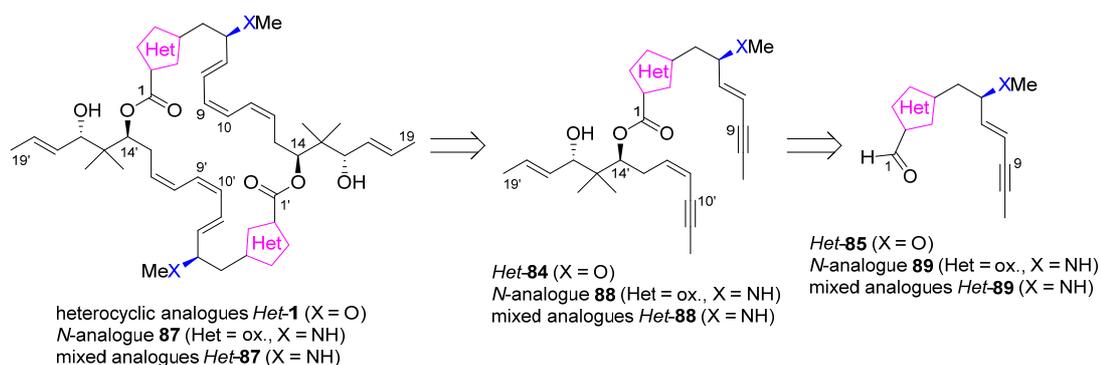


**Scheme 1.14** The Hulme group strategy towards the synthesis of disorazole C<sub>1</sub>.

on a novel Evans–Tishchenko/alkyne metathesis<sup>36,37</sup> (ET–AM) approach towards the synthesis of the large-ring dilactone (**Scheme 1.14**). We believe that this methodology will be higher yielding, and more atom-economical than previous efforts due to reduced reliance on protecting groups; and more chemoselective because of the avoidance of lactonisation protocols. We also believe that this will allow access to a number of disorazole C<sub>1</sub> heterocyclic analogues *Het-1*, which have not as yet been synthesised.

Our retrosynthesis of disorazole C<sub>1</sub> 1 (**Scheme 1.14**) requires the synthesis of the C(9)–C(10)/C(9′)–C(10′) dialkynyl macrocyclic dilactone 29, from which it is already known that the natural product can be derived.<sup>26</sup> The synthesis of the disorazole precursor 29 will be achieved through use of an alkyne cross-metathesis/ring-closing alkyne metathesis dimerisation<sup>38</sup> (ACM–RCAM) reaction between two C(1)–C(9)/C(10′)–C(19′) 1,3-*anti* diol monoesters 84 to generate the C(9)–C(10)/C(9′)–C(10′) alkyne bonds. An ET reaction between the C(1)–C(9) oxazolyl aldehyde 85 and the C(10)–C(19) β-hydroxyketone 86, will permit the generation of the key C(1)–C(9)/C(10′)–C(19′) bis-alkyne intermediate 84 in a highly diastereoselective fashion (**Scheme 1.14**).

Application of this methodology to the synthesis of heterocyclic analogues *Het-1* will



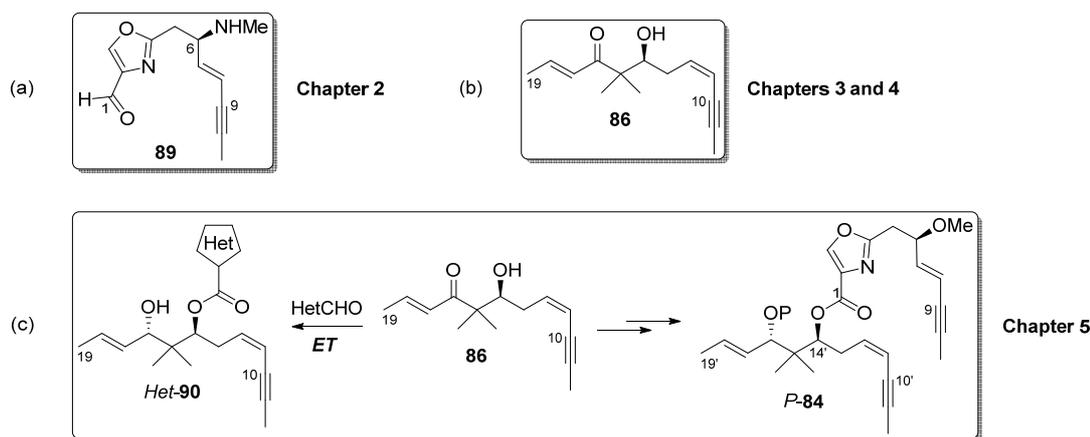
**Scheme 1.15** Adaptation of the ET–AM approach towards the synthesis of heterocyclic analogues *Het-1*, C(6)-amino ('*N*') analogue **87** and 'mixed' C(6)-amino/heterocyclic analogues *Het-87* (ox. = 2,5-oxazole *cf.* structures from **Scheme 1.14**).

be achieved through synthesis of C(1)–C(9) aldehydes *Het-85* derived from alternative heterocycles, thus providing novel heterocyclic disorazole C<sub>1</sub> analogues for future SAR studies (**Scheme 1.15**). Similarly, elaboration the C(6)-amino C(1)–C(9) analogue **89** will permit the synthesis of a C(6)-amino disorazole analogue **87**, and mixed C(6)-amino/heterocyclic variants *Het-87* thereof (**Scheme 1.15**). In order to investigate our ET–AM approach, the syntheses of the aldehyde **85** and  $\beta$ -hydroxyketone **86** fragments, is required.

## 1.6 Thesis Overview and Research Aims

The Hulme group approach towards the total synthesis of disorazole C<sub>1</sub> and its analogues revolves around the implementation of an ET–AM sequence to generate the disorazole C<sub>1</sub> macrocyclic scaffold **29**, from which it is known that the natural product can be accessed. As was also alluded to, it is likely that this method may be readily applied to the synthesis of C(6) analogues whereby the C(6) methoxy group is replaced by an alternative methylated heteroatom; and heterocyclic analogues whereby the C(2)–C(4) oxazole is replaced with an alternative heterocycle.

So far in our efforts towards the synthesis of disorazole C<sub>1</sub>, the Hulme group has successfully developed a reliable route towards the preparation of the C(1)–C(9) fragment **85**, and therefore an obvious step forward would be to assess the viability of synthesising analogues. Towards this end, the first research chapter (**Chapter 2**) discusses efforts towards the synthesis of a C(1)–C(9) fragment analogue **89** which



**Scheme 1.16** Overview of the work described in **Chapters 2** to **5** (Results and Discussion).

bears a methylamino group at the C(6) position as opposed to the methoxy group present in the natural product (**Scheme 1.16a**).

Perhaps more important than achieving analogue syntheses, however, is the synthesis of the C(10)–C(19)  $\beta$ -hydroxyketone fragment of disorazole C<sub>1</sub> **86**. A route to the synthesis of **86** has so far remained elusive, and it is critical that a reliable means of preparing this key intermediate is devised. Accordingly, the two subsequent chapters address research efforts towards the synthesis of the C(10)–C(19) fragment **86** in both a convergent (**Chapter 3**) and linear (**Chapter 4**) sense (**Scheme 1.16b**).

Following on from the synthesis of the C(10)–C(19) fragment **86**, it was predicted that an ET reaction between this fragment and various C(1)–C(9) heterocyclic aldehydes *Het-85* would permit the synthesis of C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkynes *Het-84* for investigations into the generation of the alkyne-masked disorazole macrocycle **29** via an ACM–RCAM dimerisation reaction. **Chapter 5** discusses the synthesis of a number of model heterocyclic aldehydes, and their reactivity under ET coupling conditions with the C(10)–C(19) fragment; and presents the strategy that was used towards the synthesis of (an *O*-protected variant *P-84* of) the key C(1)–C(9)/C(10')–C(19') bis-alkyne **84**.

**Chapter 6** presents the results of some preliminary ACM–RCAM reactions (as performed by other members of the Hulme group) along with concluding remarks and a brief discussion of the future direction required to be explored towards the synthesis of disorazole C<sub>1</sub> and its analogues.

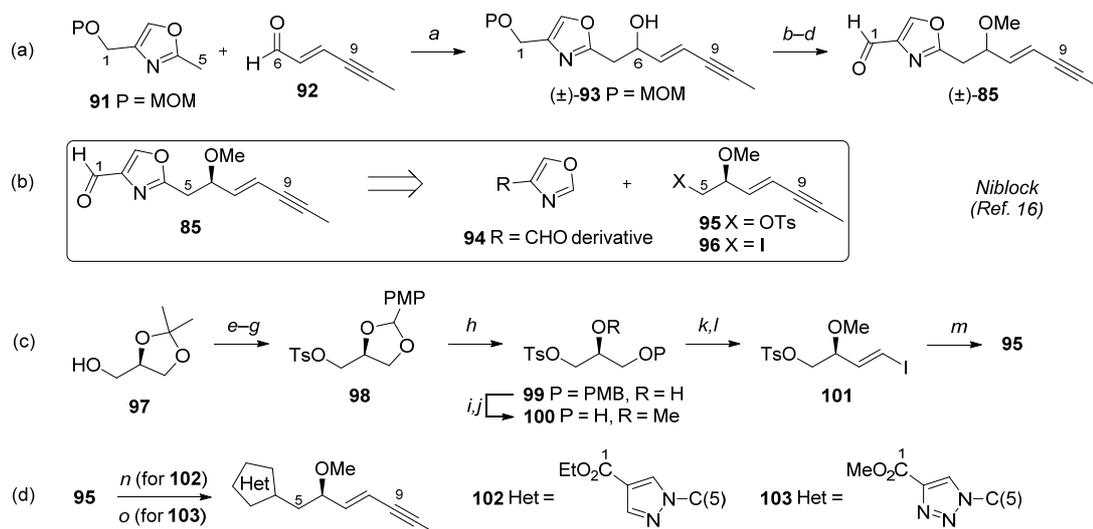
## Studies towards the Synthesis of a C(6)-Amino Analogue of the C(1)–C(9) Fragment of Disorazole C<sub>1</sub>

### 2.1 Overview, Previous Work and Retrosynthesis

Although removal of the C(6) methoxy group from synthetic intermediates led to difficulty in synthesising a C(6)-desmethoxy analogue (see: **Chapter 1, Section 1.3.1**), no studies exist that explore the synthesis or biological activity of other C(6)-heteroatom analogues. The most obvious modification involves exchange of the methoxy group with an alternative functionality, such a methylamino group; and replacement of the methoxy group with this functionality was the basis of the synthesis discussed in the current chapter.

It is important, prior to a discussion of the synthesis of potential analogues, to discuss previous syntheses of the ‘natural’ disorazole C<sub>1</sub> C(1)–C(9) aldehyde fragment **85**. The foundations for the synthesis of this fragment were laid by Niblock, a former PhD student in the Hulme group.<sup>16</sup> Although a route to the optically pure fragment **85** was not established in her studies, the racemic C(1)–C(9) fragment (±)-**85** was successfully synthesised *via* a highly convergent approach which centred around a lateral lithiation<sup>39</sup> of the 2-methyloxazole **91**, followed by reaction with aldehyde **92** in order to generate the C(1)–C(9) alcohol (±)-**93** (**Scheme 2.1a**). The proposed lithiation/carbonyl addition reaction was achieved in 40% yield (**Scheme 2.1a**), and elaboration of the alcohol (±)-**93** thus obtained to the desired fragment (±)-**85** was then accomplished in three steps: alcohol (±)-**93** was C(6)-*O*-methylated, the C(1) MOM group was cleaved under acidic conditions, and the free alcohol thus revealed was oxidised using Dess–Martin periodinane (**Scheme 2.1a**). The overall sequence furnished the fragment (±)-**85** in 9 steps longest linear sequence and 1.6% yield (**Scheme 2.1a**). Unfortunately, problems associated with poor overall yield and the difficulties associated with handling the volatile aldehyde **92** discouraged the development of an asymmetric variant of a route commencing from **92**, and instead an alternative approach was pursued.

Niblock’s most promising route to the enantiopure C(1)–C(9) fragment **85** revolved around activation of the oxazole **94** 2-position followed by reaction with the



**Reagents and conditions:** *Synthesis of the racemic C(1)–C(9) fragment (±)-85:* (a) (i)  $91$   $^n\text{BuLi}$ , THF,  $-78$  °C, 45 min; (ii)  $\text{Et}_2\text{NH}$ , 45 min; (iii)  $92$ , 45 min, 40%; (b)  $\text{MeI}$ ,  $\text{NaH}$ , THF,  $0$  °C to rt, 18 h, 29%; (c)  $\text{HCl}$ ,  $\text{MeOH}$ , rt, 18 h, 74%; (d) Dess–Martin periodinane,  $\text{NaHCO}_3$ ,  $\text{DCM}$ ,  $0$  °C, 2 h, 43%; *Synthesis of the C(5)–C(9) tosylate 95:* (e)  $\text{TsCl}$ ,  $\text{Py}$ ,  $0$  °C to rt, quant; (f)  $\text{DOWEX-H}^+$ ,  $\text{MeOH}$ , rt, 18 h, 87%; (g) 4-methoxybenzaldehyde dimethyl acetal,  $\text{TsOH}\cdot\text{H}_2\text{O}$ ,  $\text{DMF}$ , rt, 18 h, 80%; (h)  $\text{DIBAL}$ ,  $\text{DCM}$ ,  $-78$  °C, 1 h, quant; (i)  $\text{MeI}$ ,  $\text{Ag}_2\text{O}$ ,  $\text{MeCN}$ ,  $60$  °C, 18 h, 85%; (j)  $\text{DDQ}$ ,  $\text{DCM}/\text{H}_2\text{O}$ , 30 min, rt, 79%; (k) Dess–Martin periodinane,  $\text{NaHCO}_3$ ,  $\text{DCM}$ , rt, 2 h; (l)  $\text{CrCl}_2$ ,  $\text{CHCl}_3$ , dioxane/THF, rt, 18 h, 45% (2 steps), 5:1 *E:Z*; (m) (i) 1-propynylmagnesium bromide,  $\text{ZnCl}_2$ ,  $\text{PhMe}$ , rt, 15 min; (ii)  $101$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$ , rt, 18 h, 85%; *Synthesis of heterocyclic C(1)–C(9) analogues 102/103:* (n) Ethyl pyrazole-4-carboxylate,  $\text{K}_2\text{CO}_3$ ,  $\text{DMF}$ , rt, 48 h, 58%; (o) (i)  $\text{NaN}_3$ ,  $\text{DMSO}$ , reflux, 2 h; (ii) Methyl propiolate,  $\text{CuSO}_4$ , sodium ascorbate,  $\text{TBTA}$ ,  $^t\text{BuOH}/\text{H}_2\text{O}$ , rt, 18 h, 58% (2 steps).

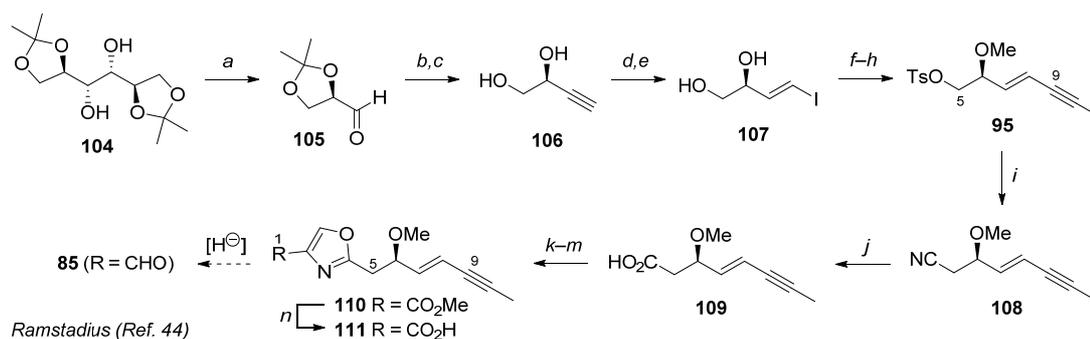
**Scheme 2.1** Niblock's work on the synthesis of the C(1)–C(9) fragment and analogues: (a) synthesis of the racemic C(1)–C(9) fragment (±)-85; (b) retrosynthesis of the enantiopure fragment 85; and synthesis of (c) tosylate 95; and (d) pyrazole 102 and triazole 103 ester analogues.<sup>16</sup>

C(5)–C(9) tosylate 95 or iodide 96 (**Scheme 2.1b**). Synthesis of the key tosylate 95 (**Scheme 2.1c**) commenced with *O*-tosylation of the commercially available alcohol 97 followed by acetonide hydrolysis and reprotection of the diol as its PMP-acetal 98.  $\text{DIBAL}$  reduction selectively (and somewhat surprisingly) gave the secondary alcohol 99, which was *O*-methylated, and the primary alcohol deprotected to yield alcohol 100. Dess–Martin oxidation, Takai olefination<sup>40</sup> and Negishi coupling<sup>41</sup> completed the synthesis of the tosylate 95 as a 5:1 mixture of *E:Z* stereoisomers in 9 steps and 18% yield overall (**Scheme 2.1c**). Although all attempts to achieve coupling between the oxazole 94 and tosylate 95 (or its iodide derivative 96) under lithiation/nucleophilic substitution or C–H activation/C–C cross-coupling<sup>42</sup> conditions were unsuccessful, tosylate 95 would allow the synthesis of two analogues 102/103 as their C(1) ester derivatives by nucleophilic substitution

(pyrazole **102**), and two-stage elaboration *via* the CuAAC reaction<sup>43</sup> (triazole **103**; **Scheme 2.1d**).

Concurrent with the work described herein, Ramstadius, a former postdoctoral researcher in the Hulme group, completed the synthesis of the C(1)–C(9) oxazole ester **110** (**Scheme 2.2**).<sup>44</sup> A revised preparation of tosylate **95** was devised from *D*-mannitol bis-acetonide **104**, which was converted to aldehyde **105** using a sodium periodate-mediated diol cleavage. Seyferth–Gilbert alkylation of **105** with the Ohira–Bestmann reagent<sup>45</sup> and acidic hydrolysis of the volatile product gave alkynyl diol **106**. Hydrostannylation of the alkyne, followed by iododestannylation<sup>46</sup> then gave vinyl iodide **107** as a single (*E*)-stereoisomer (>40:1 *E:Z*). Negishi coupling, selective tosylation of the primary alcohol with TsCl in the presence of Et<sub>3</sub>N and catalytic <sup>n</sup>Bu<sub>2</sub>SnO,<sup>47</sup> and a final *O*-methylation completed the synthesis of tosylate **95** in 8 steps and 14% yield overall (**Scheme 2.2**).

From this key intermediate **95**, a standard cyanide displacement afforded the nitrile **108**, which was hydrolysed to give carboxylic acid **109**. Synthesis of the oxazole was completed by condensation of acid **109** with serine methyl ester and subsequent cyclodehydration, giving oxazole methyl ester **110** in 5 steps and 39% yield from tosylate **95** (**Scheme 2.2**). From ester **110**, aldehyde **85** (for ET coupling) and acid **111** (for esterification) can be derived; semi-reduction of ester **110** to aldehyde **85** has yet to be accomplished, but synthesis of acid **111** was achieved by base



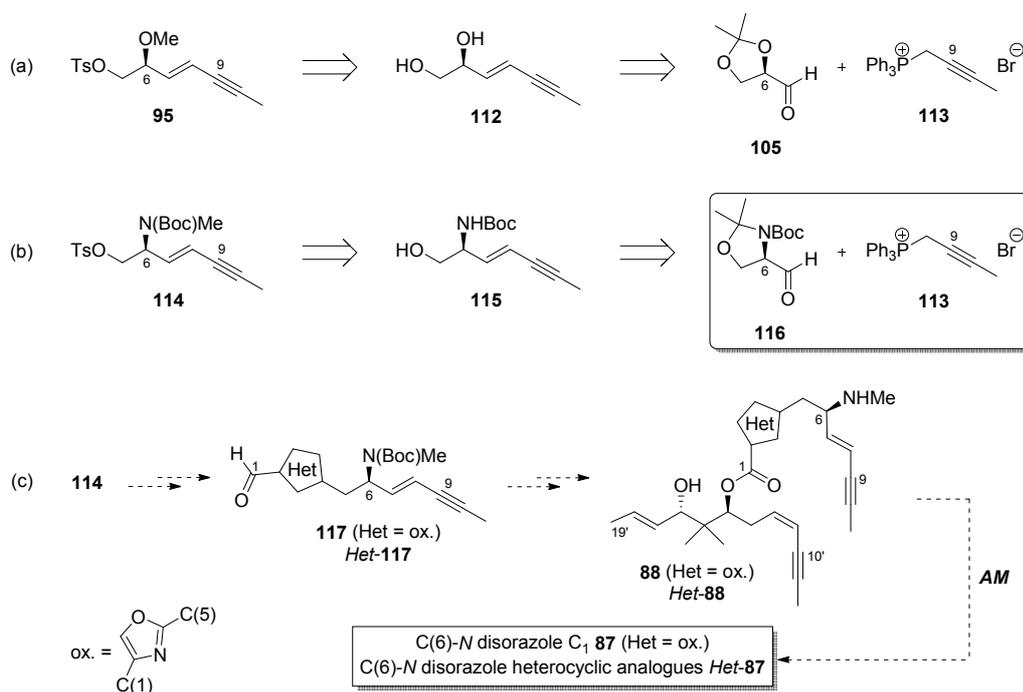
**Reagents and conditions:** (a) (i) NaIO<sub>4</sub>, NaHCO<sub>3</sub>, DCM/H<sub>2</sub>O, 0 °C, 2.5 h; (ii) MgSO<sub>4</sub>, 40 min, 87%; (b) Ohira–Bestmann reagent, K<sub>2</sub>CO<sub>3</sub>, MeOH, 0 °C to rt, 17 h; (c) HCl, Et<sub>2</sub>O/MeOH/THF, rt, 6.25 h, 66% (2 steps); (d) <sup>n</sup>Bu<sub>3</sub>SnH, PhCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Et<sub>2</sub>O, –30 °C, 30 min, 60%; (e) I<sub>2</sub>, Et<sub>2</sub>O, 0 °C, 5 min, 92%; (f) (i) 1-propynylmagnesium bromide, ZnCl<sub>2</sub>, THF, 0 °C 15 min; (ii) **107**, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 25 h; (g) TsCl, <sup>n</sup>Bu<sub>2</sub>SnO, Et<sub>3</sub>N, DCM, 0 °C, absence of light, 60% (2 steps); (h) Me<sub>3</sub>OBF<sub>4</sub>, proton sponge, DCM, rt, 140 min, 76%; (i) KCN, NaHCO<sub>3</sub>, TBAI, 60 to 70 °C, 4 h, 83%; (j) H<sub>2</sub>O<sub>2</sub>, LiOH, EtOH/H<sub>2</sub>O, rt, 34 h, 75%; (k) *L*-serine methyl ester hydrochloride, HBTU, DIPEA, MeCN, 0 °C to rt, 82%; (l) (i) XtalFluor, DCM, –78 °C, 30 min; (ii) K<sub>2</sub>CO<sub>3</sub>, –78 to 0 °C, 40 min; (m) BrCCl<sub>3</sub>, DBU, DCM, –15 °C to rt, 5 h, 76% (2 steps); (n) LiOH, THF/H<sub>2</sub>O, rt, 8 h, 96%.

**Scheme 2.2** Ramstadius' route towards the synthesis of the C(1)–C(9) oxazole ester **110**.<sup>44</sup>

hydrolysis of **110** (Scheme 2.2).

Ramstadius achieved the synthesis of the C(5)–C(9) tosylate **95** using a seven-step sequence, but he had initially anticipated the synthesis of this fragment *via* a more direct means (Scheme 2.3a).<sup>44</sup> His retrosynthesis had envisaged that a Wittig reaction between the aldehyde **105** and the phosphonium ylide generated from the propargylic phosphonium salt **113**, followed by acetonide deprotection would furnish the key diol **112**; selective tosylation and methylation of **112** would then afford the C(1)–C(9) tosylate **95** (Scheme 2.3a). For the synthesis of a C(6)-amino analogue **114** of the C(5)–C(9) tosylate **95**, it was anticipated that a similar set of transformations could be carried out with Garner's aldehyde **116**,<sup>48</sup> which bears obvious structural similarities to glyceraldehyde acetonide **105**.

Thus, our retrosynthesis for the preparation of C(6)-amino C(1)–C(9) fragments of disorazole C<sub>1</sub> is as follows: a Wittig reaction with Garner's aldehyde **116** and subsequent oxazolidine deprotection would be used to install the C(7)–C(9) enyne and furnish the key amino alcohol **115**; *O*-tosylation and *N*-methylation of **115** would



**Scheme 2.3** (a) Ramstadius' early retrosynthesis of the C(5)–C(9) tosylate **95** for synthesis of the natural [C(6)-methoxy] disorazole C(1)–C(9) fragment and heterocyclic analogues. (b) Retrosynthesis of a C(6)-methylamino C(5)–C(9) tosylate analogue **114**; and (c) synthesis of C(6)-amino C(1)–C(9) analogues **117**/*Het-117* and the synthesis of disorazole C<sub>1</sub> analogues **87**/*Het-87*.

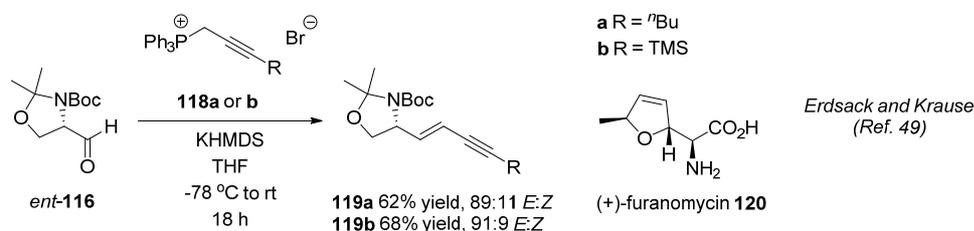
then complete the synthesis of the *N*-protected C(6)-amino C(5)–C(9) fragment analogue **114** (Scheme 2.3b). Elaboration of this structure to heterocyclic derivatives using similar methodologies to those used with the ‘natural’ C(5)–C(9) tosylate **95** (Schemes 2.1d and 2.2)<sup>16,44</sup> would then permit the synthesis of *N*-protected C(6)-amino C(1)–C(9) fragment analogues **117/Het-117**. Subsequent application of our ET–AM methodology gives access to C(6)-amino disorazole analogues **87** or *Het-87* (Scheme 2.3c).

## 2.2 Synthesis of the 1,3-Enyne Garner Aldehyde Derivative (126)

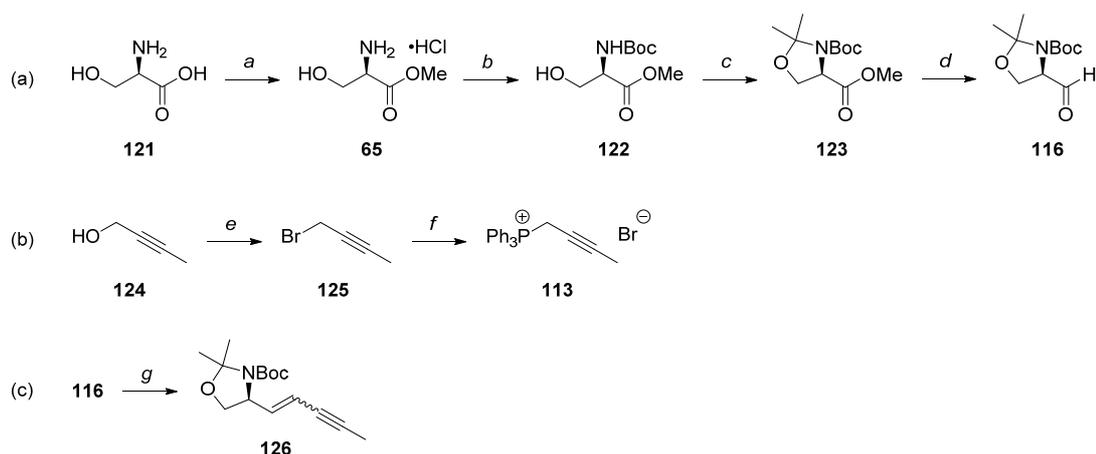
### 2.2.1 Direct Synthesis Using a Propargylic Phosphonium Salt

Our retrosynthesis (Scheme 2.3b) relied upon the synthesis of a 1,3-enyne derivative of Garner’s aldehyde **116**, and it was anticipated that this could be synthesised directly using a Wittig reaction between Garner’s aldehyde and a Wittig reagent derived from a propargylic phosphonium salt **113**. Erdsack and Krause<sup>49</sup> used Garner’s aldehyde *ent*-**116** as a substrate for an enyne-forming Wittig reaction in their efforts towards the synthesis of (+)-furanomycin **120** derivatives, and successfully generated (*E*)-enynyl Garner aldehyde derivatives **119** in good yield (62 to 68%) and with good (*E*)-selectivity (~9:1 *E*:*Z*, Scheme 2.4). Their protocol involved reaction of the propargylphosphonium salts **118** with KHMDS in THF, followed by reaction of the phosphorane thus generated with aldehyde *ent*-**116** at –78 °C; this protocol would provide the basis for our synthesis of the enyne **126**.

The (*S*)-enantiomer of Garner’s aldehyde **116** was synthesised in 4 steps and 64% yield overall from *D*-serine, according to literature procedure (Scheme 2.5a).<sup>50</sup> Phosphonium salt **113** was prepared from 2-butyne-1-ol **124** by bromination<sup>51</sup> and



**Scheme 2.4** Reaction of Garner’s aldehyde *ent*-**116** with propargyl Wittig reagents **118** in the presence of KHMDS.<sup>49</sup>



**Reagents and conditions:** (a)  $\text{SOCl}_2$  (1.3 eq), MeOH, 0 °C to rt, 18 h, 94%; (b)  $\text{Boc}_2\text{O}$  (1.2 eq),  $\text{Et}_3\text{N}$  (2.5 eq), DCM, 0 °C to rt, 16 h, 76%; (c) 2,2-dimethoxypropane (15 eq),  $\text{TsOH}\cdot\text{H}_2\text{O}$  (10 mol%), DCM, 0 °C to rt, 16 h, 95%; (d) DIBAL (1.7 eq), PhMe/hexane (~2:1),  $-78$  °C, 3h, 94%; (e)  $\text{PBr}_3$  (0.4 eq), Py (0.1 eq),  $\text{Et}_2\text{O}$ ,  $-30$  °C to reflux, 2.5 h, 73%; (f)  $\text{PPh}_3$  (1.0 eq), PhMe, 70 °C, 24 h, 90%; (g) **113** (2.5 eq), NaHMDS (2.5 eq), THF,  $-78$  °C, 4 h, 49%, ~5:1 *E:Z*

**Scheme 2.5** Preparation of (a) Garner's aldehyde **116**; and (b) propargyl phosphonium salt **113**. (c) Reaction of Garner's aldehyde **116** with the phosphonium ylide derived from phosphonium salt **113** to generate 1,3-enyne Garner aldehyde derivative **126**.

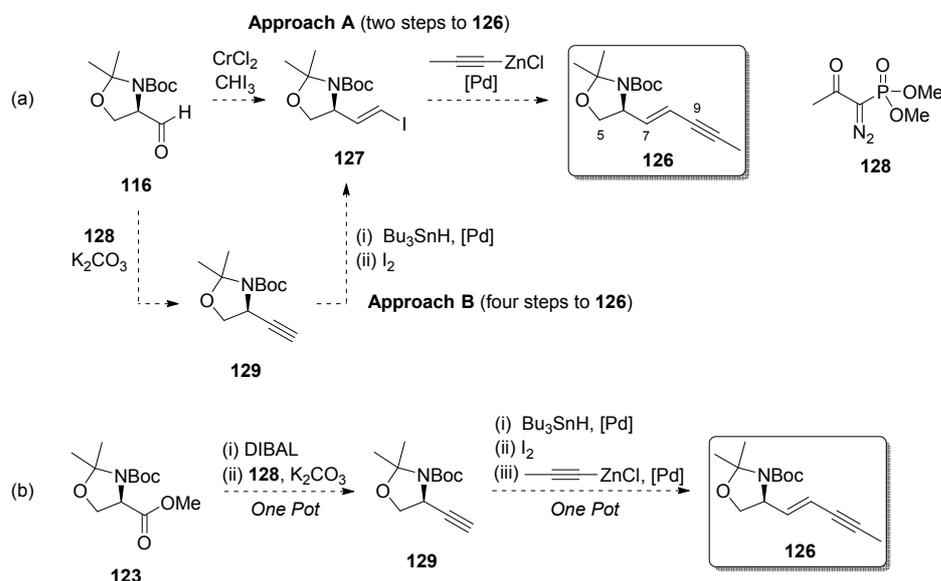
subsequent reaction of the volatile propargylic bromide **125** thus obtained with  $\text{PPh}_3$  (**Scheme 2.5b**).<sup>16</sup> KHMDS was then added to the phosphonium salt **113** to generate the required phosphonium ylide, and a THF solution of the aldehyde **116** was added at  $-78$  °C, according to conditions reported by Erdsack and Krause.<sup>49</sup> After 6 h at the same temperature, aqueous workup and flash chromatography gave, disappointingly, only a 5:1 ratio of inseparable (*E/Z*)-stereoisomers **126** in poor yield (37%).

In an attempt to increase the yield and stereoselectivity, the use of an alternative base was investigated. NaHMDS seemed to be a good choice because a previous study had reported only the isolation of (*E*)-enynes on use of this base,<sup>52</sup> and the use of an HMDS base does not deviate far from that used in the successful enyne syntheses from Garner's aldehyde as reported previously.<sup>49</sup> Unfortunately, NaHMDS gave the same level of stereoselectivity (~5:1 *E:Z*), albeit with a marginal improvement in isolated yield (49%, **Scheme 2.5c**). Although perhaps premature given the narrow range of conditions screened, the one-step route to the synthesis of the product **126** was abandoned because yields were poor and more importantly, the stereoisomers were not readily separable by flash chromatography which implied that even modest stereoselectivity improvements would lead to an impure product. This decision was also in-part a consequence of comparative advancement in an

alternative two-step methodology (discussed *vide infra*); and because the results obtained with Wittig salt **113** were consistently poor in both Ramstadius' work towards the synthesis of the C(1)–C(9) fragment,<sup>44</sup> and work described herein towards the synthesis of the C(10)–C(19) fragment (see: **Chapter 4, Section 4.3.1**).

## 2.2.2 Indirect Synthesis

Having quickly identified problems using a direct Wittig approach, we embarked upon a two-stage route towards the incorporation of the C(7)–C(9) (*E*)-enyne through generation of a vinyl iodide derivative of Garner's aldehyde, followed by Negishi coupling. Fortunately, literature preparations exist for the vinyl iodide **127**, which either require a single step from Garner's aldehyde using the Takai olefination (**Approach A, Scheme 2.6a**);<sup>53</sup> or hydrostannylation and iododestannylation<sup>54</sup> of the known alkyne **129**,<sup>54–56</sup> potentially generating the iodide in three steps (**Approach B, Scheme 2.6a**). Although the latter approach, on inspection, would appear to be appreciably more laborious (requiring four steps overall), synthesis of alkynes using the Ohira–Bestmann reagent **128** can be carried out in one pot from esters,<sup>56</sup> and the same is true of hydrometallation/iododemetalation procedures proceeding from



**Scheme 2.6** Proposed synthesis of the 1,3-enyne **126**, commencing from aldehyde **116**, using (a) a two-stage Takai olefination/Negishi coupling sequence (**Approach A**); or a hydrostannylation/iododestannylation of alkyne **129** followed by Negishi coupling (**Approach B**). (b) Potential streamlining of **Approach B** using a one-pot route to alkyne **129** from ester **123** followed by one-pot hydrostannylation/iododestannylation/Negishi coupling.

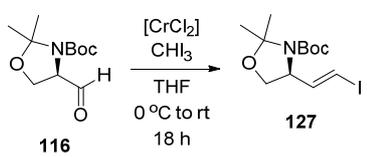
alkynes.<sup>26,57</sup> Furthermore, alkyne hydrometallation procedures (or analogous organoreductive processes) can be performed in one pot with palladium-mediated cross-coupling<sup>58</sup> and so the transformation might be achieved with same number of purification steps as the Takai olefination, would avoid the use of toxic CrCl<sub>2</sub>, and would provide an interesting entry into multistep one-pot syntheses (**Scheme 2.6b**).

### 2.2.2.1 Approach A: Takai Olefination

The synthesis of the antipode of the vinyl iodide **127** using anhydrous CrCl<sub>2</sub> is reported by Taylor *et al.*,<sup>53b</sup> but a detailed procedure is not described. Thus, screening was commenced by the reaction of aldehyde **116** with a large excess<sup>59</sup> of CHI<sub>3</sub> and CrCl<sub>2</sub> in THF.<sup>60</sup> These conditions led to a 37% isolated yield of **127** as a single (*E*)-stereoisomer after chromatography, which improved marginally (to 45%) on scale-up (~1.5 g; **Table 2.1**, Entry 1). It is worth noting that flame drying of the CrCl<sub>2</sub> was essential, because failure to do so led to complete inhibition of reaction under otherwise air- and moisture-free conditions. Given that the yield was somewhat low, it would perhaps be worth investigating changes in temperature, solvent, or reagent stoichiometry, but for reasons described below, a more rigorous optimisation using commercially obtained CrCl<sub>2</sub> was not performed.

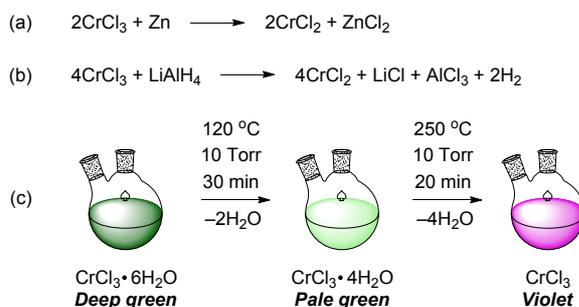
For reasons of cost, we wished to adapt the procedure in order to generate the active species from the comparatively inexpensive CrCl<sub>3</sub>. Two protocols were investigated towards this end, and these involved generation of CrCl<sub>2</sub> by the *in situ* reduction of anhydrous CrCl<sub>3</sub> with (i) zinc<sup>53a</sup> (**Scheme 2.7a**); and (ii) LiAlH<sub>4</sub><sup>61</sup> (**Scheme 2.7b**).

**Table 2.1** Attempted Takai olefination of Garner's aldehyde **116**.



Entry	CrCl <sub>2</sub> Source <sup>a</sup>	Eq [Cr]	Additive	Eq Additive	Eq CHI <sub>3</sub>	Yield (%) <sup>b</sup>	<i>E:Z</i> Ratio <sup>c</sup>
1	CrCl <sub>2</sub>	18	—	—	6	45	>99:1
2	CrCl <sub>3</sub>	10	Zn	6	6	0	—
3	CrCl <sub>3</sub> ·6H <sub>2</sub> O	20	LiAlH <sub>4</sub>	8	6	33	>99:1

<sup>a</sup>All CrCl<sub>2</sub> sources were dried and, where relevant, dehydrated *in vacuo* prior to experiment; <sup>b</sup>Isolated yield; <sup>c</sup>As determined by <sup>1</sup>H NMR analysis of the purified product.



**Scheme 2.7** Reduction of anhydrous  $\text{CrCl}_3$  with (a) zinc; and (b)  $\text{LiAlH}_4$ . (c) Thermal dehydration of  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  *in vacuo*.<sup>53a</sup>

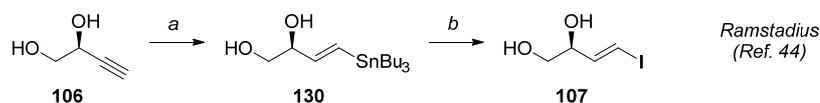
Attempted Takai olefination by way of using zinc for the generation of  $\text{CrCl}_2$  (by pre-heating of anhydrous  $\text{CrCl}_3$  *in vacuo* at 100 °C with zinc powder),<sup>53a</sup> followed by addition of the aldehyde **116** and  $\text{CHI}_3$  in THF proved to be unsuccessful, and none of the desired product was isolated following flash chromatography (**Table 2.1**, Entry 2). This was surprising considering Augé *et al.*<sup>53a</sup> employed this method with Garner's aldehyde, albeit obtaining only moderate yield (56%) and stereoselectivity (4:1 *E:Z*). In retrospect, the most likely explanation probably relates to the purity of the zinc powder, which may have partially oxidised and despite using an excess [relative to the  $\text{CrCl}_3$ ] to account for this possibility, no attempts were made to activate it.<sup>62</sup> It is therefore possible that repetition of the reaction with pre-activation of the zinc may give positive results.

The alternative and ultimately most cost-effective Takai olefination for the synthesis of the vinyl iodide **127** involved using  $\text{CrCl}_2$  generated from  $\text{CrCl}_3$  by reduction with  $\text{LiAlH}_4$  (**Table 2.1**, Entry 3).<sup>61</sup>  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  was first dehydrated by heating under high-vacuum (~10 Torr, 120 to 250 °C, ~1 h), with the course of the reaction easily followed according to the colour of the solid (**Scheme 2.7c**).<sup>53a</sup> The  $\text{CrCl}_3$  thus obtained was cooled (0 °C), suspended in THF, and reacted with  $\text{LiAlH}_4$  (~2 h). After addition of  $\text{CHI}_3$  and Garner's aldehyde **116** and overnight stirring in the absence of light, aqueous workup and flash chromatography gave the product **127** in 33% yield as a single (*E*)-stereoisomer (**Table 2.1**, Entry 3).

Although poor yielding, the main advantage of this protocol is that the most inexpensive form of the chromium chlorides is used alongside the cheap  $\text{LiAlH}_4$  reductant. The scale of the reaction is however, limited: large excesses are used,

requiring large solvent volumes and additional safety precautions, and the reaction mixture can coagulate at the reduction stage, thus necessitating brief mechanical stirring. Purification also occasionally required a second chromatographic step to remove residual  $\text{CHI}_3$ . Nevertheless, the yield was reproducible and only slightly diminished compared to that obtained using commercially purchased anhydrous  $\text{CrCl}_2$  with no loss of stereoselectivity, and thus represented the best option for the synthesis of the vinyl iodide **127** *via* the Takai reaction.

### 2.2.2.2 Approach B: Hydrostannylation/Iododestannylation

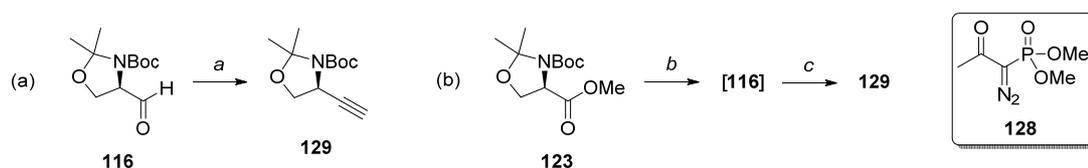


**Reagents and conditions:** (a)  $\text{Bu}_3\text{SnH}$  (1.3 eq),  $\text{PdCl}_2(\text{PPh}_3)_2$  (5 mol%),  $\text{Et}_2\text{O}$ ,  $-30\text{ }^\circ\text{C}$ , 30 min, 60%; (b)  $\text{I}_2$  (1.3 eq),  $\text{Et}_2\text{O}$ , ultrasound, 5 min, 92%.

**Scheme 2.8** Hydrostannylation/iododestannylation of alkyne **106** in Ramstadius' synthesis of the C(1)–C(9) fragment of disorazole  $\text{C}_1$ .<sup>44</sup>

Despite successfully obtaining the vinyl iodide **127**, the disadvantages outlined above merited an investigation into alternative olefination procedures. In parallel with the studies discussed herein, marked progress was being made towards the synthesis of vinyl iodide **107** – a key intermediate in the synthesis of the *natural* disorazole  $\text{C}_1$  C(1)–C(9) fragment; and the optimal conditions for generating this compound called for the hydrostannylation/iododestannylation an alkyne precursor **106** (**Scheme 2.8**).<sup>44</sup> Thus, to potentially improve the protocol for the synthesis of vinyl iodide **127**, and, furthermore, for reasons of complementarity between the two synthetic routes, it seemed sensible to briefly investigate hydrostannylation/iododestannylation.

To prepare the alkyne **129**, Garner's aldehyde **116** was reacted overnight with the Ohira–Bestmann reagent (1.4 eq) in MeOH using  $\text{K}_2\text{CO}_3$  (2.0 eq) as the base.<sup>55</sup> Unfortunately, these conditions gave only a 45% yield of the product, and an increase in the stoichiometry of the reagents led to only a marginal improvement (50% yield; **Scheme 2.9a**). An alternative approach from Garner's ester **123** was therefore investigated according to work by Hinkle *et al.*,<sup>56</sup> who successfully synthesised alkyne **129** in 71% yield in a one-pot procedure using a DIBAL

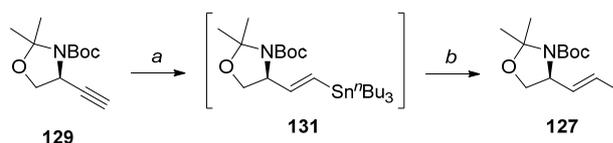


**Reagents and conditions:** (a) **128** (4.1 eq),  $\text{K}_2\text{CO}_3$  (10 eq), MeOH, 18 h, 50%; (b) (i) DIBAL (1.7 eq), PhMe/Hexane (1:1),  $-78\text{ }^\circ\text{C}$ , 3 h; (ii) MeOH (124 eq),  $-78$  to  $0\text{ }^\circ\text{C}$ ; (c) **128** (2.7 eq),  $\text{K}_2\text{CO}_3$  (6.0 eq), PhMe/Hexane/MeOH (~1:1:5),  $0\text{ }^\circ\text{C}$  to rt, 18 h, 32% (2 steps, one pot).

**Scheme 2.9** (a) Reaction of Garner's aldehyde **116** with the Ohira–Bestmann Reagent **128**; (b) attempted one-pot DIBAL reduction/alkynylation of Garner's ester **123**.

reduction/Seyferth–Gilbert homologation. In hope of improving the yield in the current study, the one-pot method was attempted; that is, Garner's ester **123** was treated with DIBAL at  $-78\text{ }^\circ\text{C}$ , followed by quenching and dilution with MeOH and addition of the Ohira–Bestmann reagent **128** and  $\text{K}_2\text{CO}_3$  at  $0\text{ }^\circ\text{C}$ . However, after overnight stirring; quenching, workup and flash chromatography indicated that this modified Seyferth–Gilbert alkynylation protocol had also been poorly efficient, because only a 32% yield of the alkyne **129** was obtained. The reason for this diminished yield in comparison to the literature value could perhaps be attributed to inefficient quenching of the ester–DIBAL complex generated *in situ* leading to poor conversion of the ester to the intermediate aldehyde **116**, the latter of which is required for formation of the alkyne. Alternatively, the result (and indeed the previous, single-step results) may have been detrimentally influenced by the low purity of the Ohira–Bestmann reagent **128**, which was later determined by  $^1\text{H}$  NMR to be only of 67% purity and contaminated with residual tosyl azide and dimethyl 2-oxopropylphosphonate and from preparation; future experiments should aim to ensure that a higher purity reagent is used.<sup>63</sup>

Nevertheless, these reactions provided sufficient quantities of material to progress to the next stage of the synthetic route towards vinyl iodide **127**, and alkyne **129** was submitted to hydrostannylation/iododestannylation conditions. Reaction of alkyne **129** with  $^n\text{Bu}_3\text{SnH}$  under  $\text{PdCl}_2(\text{PPh}_3)_2$  catalysis (1 mol%) at  $-30\text{ }^\circ\text{C}$  (to form the intermediate stannane **131**), followed by the addition of  $\text{I}_2$  to the reaction mixture (**Scheme 2.10**) gave the desired vinyl iodide **127** as a single (*E*)-stereoisomer in 39% yield. Although not far removed from that obtained by Ramstadius (55%, 2 steps),<sup>44</sup> this yield was somewhat disappointing; and because the yield for the route towards vinyl iodide **127** from the alkyne **129** was comparable to that obtained for the direct



**Reagents and conditions:** (a)  $n\text{Bu}_3\text{SnH}$  (2.0 eq),  $\text{PdCl}_2(\text{PPh}_3)_2$  (1 mol%), THF,  $-30\text{ }^\circ\text{C}$ , 1 h; (b)  $\text{I}_2$  (2.2 eq), THF,  $-30\text{ }^\circ\text{C}$  to rt, 1 h, 39% (2 steps, one-pot),  $E:Z > 99:1$ .

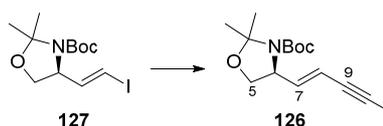
**Scheme 2.10** One-pot hydrostannylation/iododestannylation of Garner alkyne **129**.

Takai iodo-olefination of aldehyde **116**, and offered no advantage with respect to the number of steps, no further efforts to optimise the reaction sequence were taken. As such, the single-step Takai olefination was deemed the best route towards the synthesis of vinyl iodide **127**, and a Negishi coupling would complete the installation of the key (*E*)-enyne moiety of the C(1)–C(9) fragment analogue.

### 2.2.2.3 Completion of the C(7)–C(9) (*E*)-Enyne Moiety

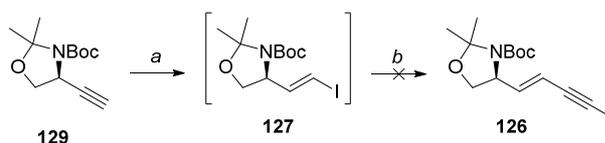
Negishi coupling of the vinyl iodide **127** to generate the enyne **126** (**Scheme 2.11**) was performed according to the established procedure,<sup>41</sup> which involves transmetalation of an organomagnesium or -lithium reagent with a zinc dihalide followed by reaction of the organozinc reagent thus generated with the organohalide substrate in the presence of catalytic palladium. Thus, freshly vacuum-dried  $\text{ZnCl}_2$  was reacted with 1-propynylmagnesium bromide at  $0\text{ }^\circ\text{C}$  in THF with subsequent addition of the vinyl iodide **127** and  $\text{PdCl}_2(\text{PPh}_3)_2$ . Reaction at room temperature for 2 h gave an 89% yield of the product **126**, and concluded the installation of the C(7)–C(9) (*E*)-enyne and thus the synthesis of the required C(5)–C(9) 1,3-enyne Garner aldehyde derivative **126**.

A one-pot iodination/Negishi coupling from alkyne **129** was also investigated, as previously alluded to (see: **Section 2.2.2**). Initially, iodination conditions from **Scheme 2.10** were applied with an increased catalyst loading (5 mol%) to ensure



**Reagents and conditions:** (i) 1-propynylmagnesium bromide (4.0 eq),  $\text{ZnCl}_2$  (4.4 eq), THF,  $0\text{ }^\circ\text{C}$ , 30 min; (ii) **127**,  $\text{PdCl}_2(\text{PPh}_3)_2$  (5 mol%),  $0\text{ }^\circ\text{C}$  to rt, 2 h, 89%.

**Scheme 2.11** Negishi coupling of vinyl iodide **127** to generate the enyne **126**.



**Reagents and conditions:** (a) (i)  $n\text{Bu}_3\text{SnH}$  (2.0 eq),  $\text{PdCl}_2(\text{PPh}_3)_2$  (1 mol%), THF,  $-30\text{ }^\circ\text{C}$ , 1 h; (ii)  $\text{I}_2$  (2.2 eq),  $-30\text{ }^\circ\text{C}$  to rt, 1 h; (iii)  $\text{Na}_2\text{S}_2\text{O}_3$  (6.0 eq),  $0\text{ }^\circ\text{C}$ , 20 min; (b) 1-propynylzinc chloride (5.0 eq),  $\text{PdCl}_2(\text{PPh}_3)_2$  (5 mol%), THF,  $0\text{ }^\circ\text{C}$  to rt, 18 h, **126** 0%, **127** 50%.

**Scheme 2.12** Attempted one-pot hydrostannylation/iododestannylation/Negishi coupling.

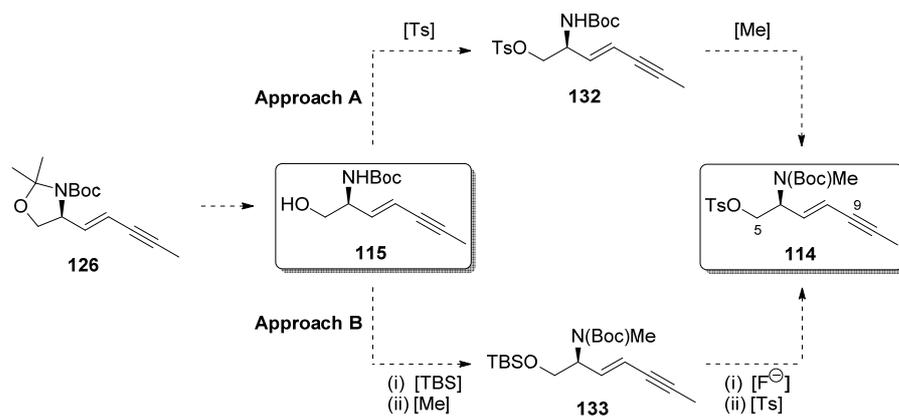
active palladium (0) species remained for cross-coupling. Freshly prepared 1-propynylzinc chloride was then added and the mixture was stirred overnight. Unfortunately, none of the product **126** was detected by  $^1\text{H}$  NMR of the crude material. Speculating that residual  $\text{I}_2$  in the reaction mixture had poisoned the active catalyst,<sup>64</sup> solid  $\text{Na}_2\text{S}_2\text{O}_3$  was added in an attempt to quench residual  $\text{I}_2$  after iododestannylation; and the addition of the catalyst was staggered (1 mol% for hydrostannylation, 5 mol% for Negishi coupling) to account for any loss of activity. However, these modifications had no influence over the results, and iodide **127** was the only product isolated (50%) on purification (**Scheme 2.12**). No further work was done to optimise this one-pot procedure, and instead efforts were focussed towards completion of the fragment.

## 2.3 Oxazolidine Deprotection and *O*-Tosylation

### 2.3.1 Overview, Deprotection and Approach A: Direct *O*-Tosylation

With the best route towards the synthesis of the (*E*)-enynone **126** identified as a Takai olefination and Negishi coupling, steps towards the completion of the tosylate **114** could be taken. This was anticipated to be straightforward: deprotection of the oxazolidine would reveal the key amino alcohol **115**, which would undergo *O*-tosylation and *N*-methylation to complete the C(5)–C(9) analogue tosylate **114** (**Approach A, Scheme 2.13**). Any problems relating to reactivity of the amine with the leaving group during *N*-alkylation could be alleviated by protection of the hydroxyl group (to give, for example, TBS-ether **133**) followed by *N*-methylation, deprotection, and *O*-tosylation (**Approach B, Scheme 2.13**).

Deprotection of the oxazolidine initially invoked the use of the sulfonic acid-based



**Scheme 2.13** Proposed protecting group-free synthesis of tosylate **114** (**Approach A**); and alternative route involving a hydroxyl protection (**Approach B**).

resin Amberlyst-15<sup>65</sup> according to the protocol reported by Bittmann,<sup>66</sup> which seemed an attractive option because the procedure is operationally simple and purification involves only filtration, removal of the solvent, and chromatography. However, use of this reagent (**Table 2.2**, Entry 1) led to only a 23% yield of the product **115**. Unfortunately, the fate of the remainder of the material is not clear, because no starting material was recovered, and a crude NMR spectrum was not recorded. It is very likely however that concomitant Boc deprotection occurred, leading to either irreversible substrate–resin (amine–sulfonic acid) binding; or the isolation of an ammonium salt that was too polar to elute on silica gel.<sup>67</sup>

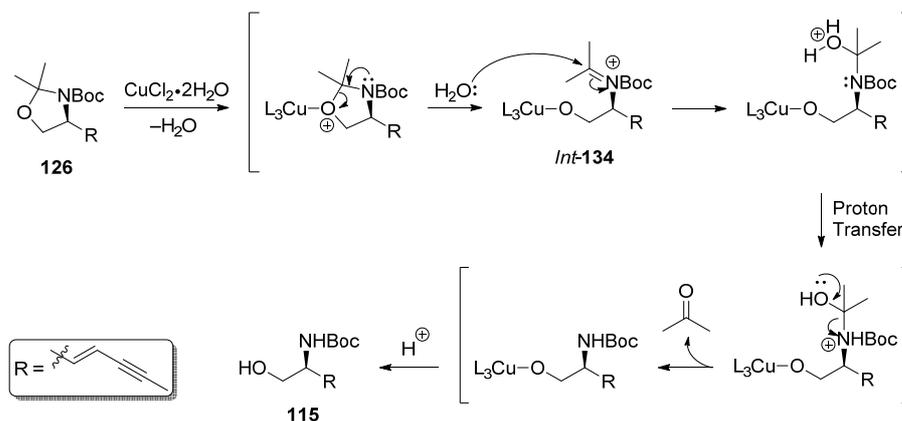
Deprotection using the more standard reagent PPTS (20 mol%) in MeOH at reflux led to an improved but only moderate yield (52%; **Table 2.2**, Entry 2). Increasing the

**Table 2.2** Deprotection of oxazolidine **126** to give amino alcohol **115**.

The reaction shows oxazolidine **126** being converted to amino alcohol **115** through a deprotection step. The reagents used are Deprotection Reagent, Solvent, Temperature, and Time.

Entry	Deprotection Reagent	Eq Deprotection Reagent	Solvent	Temp (°C)	Time (h)	Yield (%) <sup>a,b</sup>
1 <sup>c</sup>	Amberlyst-15	— <sup>d</sup>	MeOH	25	48	23
2	PPTS	0.2	MeOH	70	18	52 <sup>e</sup>
3	PPTS	0.5	MeOH	70	18	63
4	PPTS	0.5	EtOH	83	48	<i>nd</i>
5	CuCl <sub>2</sub> ·2H <sub>2</sub> O	1.6	MeCN	25	1	(100) 87 <sup>f</sup>

<sup>a</sup>Isolated yield unless otherwise stated; <sup>b</sup>Yields determined by <sup>1</sup>H NMR of the crude material are indicated in parentheses; <sup>c</sup>Run was performed using a 5:1 *E:Z* mixture of **126** stereoisomers; <sup>d</sup>1 g per 100 mg **126** was used *cf.* Ref. 66; <sup>e</sup>74% BORSM (30% recovery of **126**); <sup>f</sup>Isolated yield obtained on scale-up.

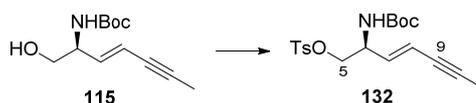


**Scheme 2.14** Mechanism of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ -mediated deprotection of the oxazolidine moiety.

loading of PPTS gave only 63% yield (**Table 2.2**, Entry 3), while changing the solvent to EtOH and heating to a higher temperature also led to incomplete reaction according to TLC (**Table 2.2**, Entry 4, yield not determined). However, a third change of reagent to  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ <sup>68</sup> led to quantitative conversion to the desired amino alcohol **115** and would prove to be the procedure of choice for scaling up (~2 g), where an 87% isolated yield was realised (**Table 2.2**, Entry 5).

The mechanism of the reaction (**Scheme 2.14**)<sup>69</sup> is likely to involve  $\text{CuCl}_2$  acting as a Lewis acid and coordinating to the oxygen atom of **126**. Displacement of an  $\text{H}_2\text{O}$  ligand by the oxazolidine oxygen atom is followed by hydrolysis of the intermediate iminium ion *Int-134* and proton transfer, thus generating the product **115** and acetone as a byproduct. The liberation of acetone would mean that the reverse reaction is less facile, and explains the inferior yields obtained with PPTS, whereby MeOH is the primary nucleophile (as opposed to  $\text{H}_2\text{O}$ ) and dimethoxypropane – which is more reactive than acetone in condensation reactions – would be the side product.

Having revealed the free alcohol and carbamate nitrogen atom, an *O*-tosylation followed by *N*-methylation would complete the key C(5)–C(9) analogue fragment **114**. Tosylation was initially attempted by the reaction of the alcohol **115** with TsCl (1.05 eq) and pyridine (2.00 eq) in DCM at room temperature, but this led to only a 13% conversion to the product **132** by <sup>1</sup>H NMR, which was identified in the crude spectrum according to the appearance of a (-n additional)  $\text{CH}_3$  peak at  $\delta = 2.48$  ppm and aryl *CH* peaks at  $\delta = 7.82$ – $7.79$  and  $7.39$ – $7.36$  ppm. However, a slight increase in TsCl stoichiometry and the use of pyridine as the solvent led to 63% conversion



**Reagents and conditions:** TsCl (1.2 eq), Py (25 eq), 0 °C to rt, 18 h, 47%.

**Scheme 2.15** *O*-Tosylation of amino alcohol **115**.

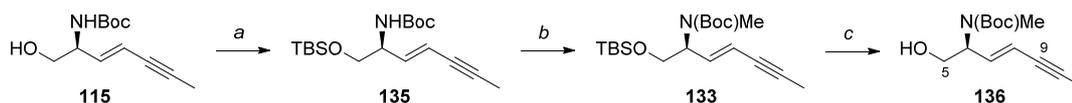
and represented a marked improvement.

Unfortunately, although the tosylate product **135** was subsequently isolated in 47% yield (**Scheme 2.15**), it underwent rapid decomposition,<sup>70</sup> which precluded a full characterisation. This instability rendered the direct approach (**Approach A**) towards the synthesis of the C(5)–C(9) fragment analogue **114** impractical on the basis of the storage and handling difficulties associated with its precursor **132**; and probably impossible, given that tosylate **132** would most likely be unstable to the basic conditions required for *N*-methylation. As a result, efforts were focussed towards our alternative approach (**Approach B, Scheme 2.13**), which would involve the installation of a C(5) hydroxyl protecting group followed by *N*-methylation, hydroxyl deprotection and C(5) *O*-tosylation.

### 2.3.2 Approach B: Protected Alcohol Approach

In order to investigate **Approach B**, the free alcohol (which could be used either chromatographically pure or telescoped directly from the previous deprotection step) was first protected as its TBS-ether under standard TBSCl protection conditions (imidazole, DMF) which gave the product in 96% yield following overnight stirring (**Scheme 2.16**). The choice of solvent proved to be an important factor in the success of the reaction, because the use of DCM led to a sluggish and capricious conversion to the desired product **135**.<sup>71</sup>

*N*-Methylation of **135** was effected using large excesses of NaH and MeI in a 10:1



**Reagents and conditions:** (a) TBSCl (1.5 eq), Im (3.0 eq), DMF, rt, 18 h, 96%; (b) MeI (20 eq), NaH (6.0 eq), THF/DMF (10:1), 35 °C, 18 h, quant; (c) TBAF (1.5 eq), THF, rt, 30 min, 93%.

**Scheme 2.16** Synthesis of the C(5)–C(9) alcohol **136** via *O*-TBS protection, *N*-methylation and silyl deprotection.

mixture of THF/DMF<sup>72</sup> at 35 °C to give, after 18 h, the product **133** in quantitative yield (**Scheme 2.16**). The conditions, although somewhat harsh, were found to be a requirement, because reaction under the same conditions of solvent and reagent loading at room temperature led to incomplete reaction, even after two days (68% conversion by <sup>1</sup>H NMR); while reaction at room temperature with reduced reagent stoichiometry (NaH, 1.3 eq; MeI, 10 eq) in the absence of the DMF co-solvent led only to 7% conversion. It is worth noting that achieving a high conversion was particularly important in this step, because the product and starting material have close TLC R<sub>f</sub> values on silica, and so purification is simplified. Following *N*-methylation, the free alcohol was revealed by silyl deprotection with TBAF in THF, which proceeded rapidly (30 min) in 93% yield and concluded the synthesis of the key precursor **136** for the generation of the C(5)–C(9) tosylate (**Scheme 2.16**).

### 2.3.3 Attempted Tosylation of the C(5)–C(9) Alcohol (136)

Reaction of the primary alcohol **136** to give the C(5)–C(9) analogue tosylate **114** was expected to proceed smoothly using standard tosylation conditions, which typically involve the use of TsCl and (usually) an auxiliary amine base. Unfortunately and – at the time – rather unexpectedly, after investigating a number of conditions, the only product identified was oxazolidinone **137**, which was generally obtained in modest to quantitative yield (as determined by <sup>1</sup>H NMR spectroscopy; **Table 2.3**). Believing at the time that a competing intramolecular cyclisation by attack of the alcohol on the carbonyl group was occurring (later refuted *vide infra*), in an attempt to force the intermolecular reaction, screening conditions were carried out which involved using large and modest excesses of pyridine (**Table 2.3**, Entries 1 to 3); pre-generation of the active pyridinium sulfonylating species prior addition of the alcohol **136** (**Table 2.3**, Entry 4); the use of a vast excess of TsCl and a second base (DMAP; which it was thought may force addition rather than cyclisation, **Table 2.3**, Entry 5); and use of the alternative bases Et<sub>3</sub>N, and imidazole (**Table 2.3**, Entries 7 and 8). Application of conditions involving the use of 4-pyrrolidinopyridine (4-PPy) – which was used in the only published example of tosylation of a β-*N*-Boc-*N*-methylamino alcohol<sup>73a</sup> – was also attempted; but this too proved futile, and led only to the conversion of the

**Table 2.3** Attempted tosylation of alcohol **136**.

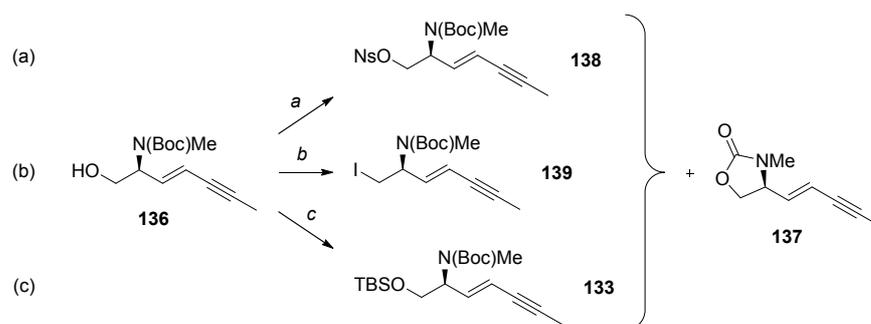
Entry	Eq TsCl	Base	Eq Base	Addt.	Eq Addt.	Solv. <sup>a</sup>	Time (h)	Conv. (%) <sup>b</sup>	Ratio 114:137 <sup>b</sup>
1	1.1	Py	120	—	—	Base	18	0	—
2	2.0	Py	120	—	—	Base	18	23	0:100
3	1.5	Py	12	—	—	Base	18	100	0:100
4 <sup>c</sup>	1.1	Py	12	—	—	Base	48	Trace	nd
5	10	Py	120	DMAP	1.0	Base	1.5	55	0:100
6	10	Py	120	DMAP	2.0	Base	1.5	100	0:100
7 <sup>d</sup>	3.0	Et <sub>3</sub> N	6.0	—	—	DCM	22	100	0:100
8 <sup>d</sup>	6.0	Im	12	—	—	DMF	72	Trace	nd
9	1.1	Py	9.1	4-PPy	0.1	DCM	18	17	0:100

<sup>a</sup>"Base" indicates that the base used in the reaction was also the solvent; <sup>b</sup>As determined by <sup>1</sup>H NMR of the crude material; <sup>c</sup>TsCl was pre-activated by addition to boiling pyridine and cooling to 0 °C; <sup>d</sup>Reagent quantities started with up to 50% of the stated value but were increased after 18 h due to a lack of reactivity (TLC analysis)

starting material **136** to the cyclised product **137** in poor yield (**Table 2.3**, Entry 9).

Because the synthesis of the tosylate ester **114** was not possible under the conditions screened, the use of alternative leaving groups was briefly investigated. Attempted conversion of the alcohol **136** to the 2-nitrobenzenesulfonate ester was initially chosen because the reagent sulfonyl chloride (NsCl) was expected to be more electrophilic than TsCl (and hence more reactive with the alcohol **136**), but at least equally effective as a substrate for subsequent nucleophilic substitution reactions. Hence, synthesis of the nosylate ester **138** was attempted using similar conditions as shown in **Table 2.3**, Entry 6 (with NsCl in place of TsCl); but like attempted generation of the tosylate **114**, these conditions led only to the formation of the oxazolidine **137** product as determined by examination of the crude <sup>1</sup>H NMR spectrum (**Scheme 2.17a**). Conversion of the alcohol **136** under Appel conditions<sup>74</sup> to the iodide **139** was also investigated, but as with the tosylate and nosylate esters, this gave quantitative conversion (NMR) to the cyclised product **137**, with an isolated yield of 70% (**Scheme 2.17b**).

Before investigating the use of alternative leaving groups any further, we felt it was necessary to examine the viability of installing any group at this position under basic

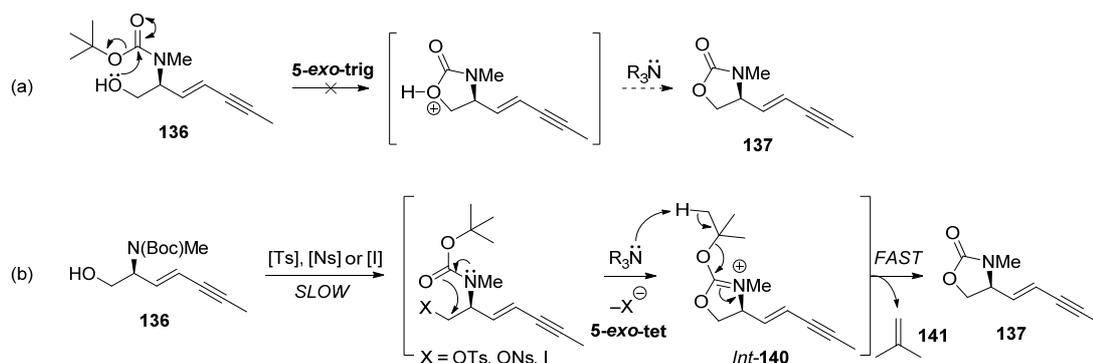


**Reagents and conditions:** (a) NsCl (10 eq), DMAP (2.0 eq), Py (120 eq), 0 °C to rt, 18 h, **138** 0%, **137** quant conv.; (b) I<sub>2</sub> (6.0 eq), PPh<sub>3</sub> (6.0 eq), Im (12 eq), MeCN, 0 °C to reflux, 18 h, absence of light, **139** 0%, **137** 70%; (c) TBSCl (1.5 eq), Im (3.0 eq), DMF, rt, 18 h, **133** 89%, **137** 0%.

**Scheme 2.17** Attempted (a) nosylation; (b) iodination; and (c) silylation of alcohol **136**.

conditions, because it was unclear whether the failure to install the leaving group was due to: (i) preferential reaction of the alcohol with the neighbouring (Boc) carbonyl group in a 5-*exo*-trig type cyclisation, rather than intermolecular reaction with the somewhat sterically hindered electrophiles; or (ii) formation of the product tosylate, nosylate or iodide, which reacts further to form the oxazolidinone **137** in a 5-*exo*-tet fashion. To investigate this, we attempted to reprotect the alcohol **136** as its TBS-ether using conditions as previously employed in the synthesis of its demethylated precursor **135** (see: **Scheme 2.16**). Remarkably, TBS protection of this alcohol **136** was achieved in excellent yield (89%, **Scheme 2.17c**) with no side product observed.

On the basis of these results, rather than proceeding *via* the 5-*exo*-trig type cyclisation (**Scheme 2.18a**) as initially speculated, the mechanism of the reaction<sup>75</sup> (**Scheme 2.18b**) is likely to involve initial formation of the tosylate, nosylate or iodide, followed by cyclisation by displacement of the leaving group by the carbamate oxygen atom in a 5-*exo*-tet manner. Base abstraction of a proton from the *tert*-butyl group of the cationic intermediate *Int-140* would then liberate the oxazolidinone **137** and the byproduct isobutylene **141**. The rate determining step in the reaction must be the formation of the leaving group, with the cyclisation comparatively rapid, because none of the desired products were observed by NMR spectroscopy, even in reactions which did not proceed to completion. The product sulfonate ester or iodide must therefore be consumed immediately after formation, making isolation of the desired synthetic intermediate impossible in this study.



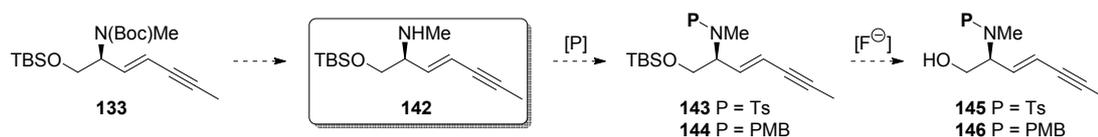
**Scheme 2.18** (a) Single-step; and (b) two-step<sup>75</sup> mechanisms for the formation of the oxazolidinone **137** from the alcohol **136**.

It is unfortunate that the conversion of the alcohol **136** to a suitable C(5)–C(9) analogue electrophile could not be achieved. In hindsight it is perhaps unsurprising, because although a small number of studies indicate that installation of a leaving group at an oxygen atom which neighbours an *N*-alkylated-*N*-Boc amine is plausible,<sup>73</sup> there also exists literature precedent for similar cyclisations of 2-*N*-Boc-amino tosylates on treatment with amine bases;<sup>75</sup> and indeed Lee *et al.*<sup>75a</sup> took advantage of this reaction in a one-pot synthesis of oxazolidinones from alcohols using TsCl and MsCl. Therefore conditions which involve the use of the free alcohol as an alkylating agent, such as the Mitsunobu reaction,<sup>76</sup> could be performed, and may provide some success in the synthesis of C(1)–C(9) heterocyclic analogues.<sup>77</sup> However, to keep the synthetic route concordant with the synthesis of the natural disorazole C<sub>1</sub> C(5)–C(9) side chain, attention was instead focussed on the use of an alternative nitrogen protecting group.

## 2.4. Alteration of the C(6) *N*-Protecting Group

### 2.4.1 Synthesis of the *N*-Protected C(5)–C(9) Amino Alcohols

Owing to its high electron-withdrawing capacity and inert nature, we believed that *N*-tosylation would provide a means of stifling (or at least slowing down) deleterious side reactions of the nitrogen atom (*cf.* **Section 2.3.1**) or the protecting group (*cf.* **Section 2.3.3**) with a newly installed leaving group.<sup>78</sup> However, since our endgame strategy may require deprotection of a PMB-ether following RCAM cyclisation (see: **Chapter 5, Section 5.1.4** for a full synopsis, or **Section 2.5.1** for a brief summary), it



**Scheme 2.19** Strategy for replacing the Boc group with alternative *N*-protecting groups.

was preferred that the Boc group be exchanged for a PMB group, because this would allow global deprotection at the latter stages of the natural product synthesis, thus shortening the synthetic sequence and simplifying deprotection. Therefore, although perhaps somewhat ambitious given the previous problems of leaving group lability, PMB protection was investigated as a primary objective.

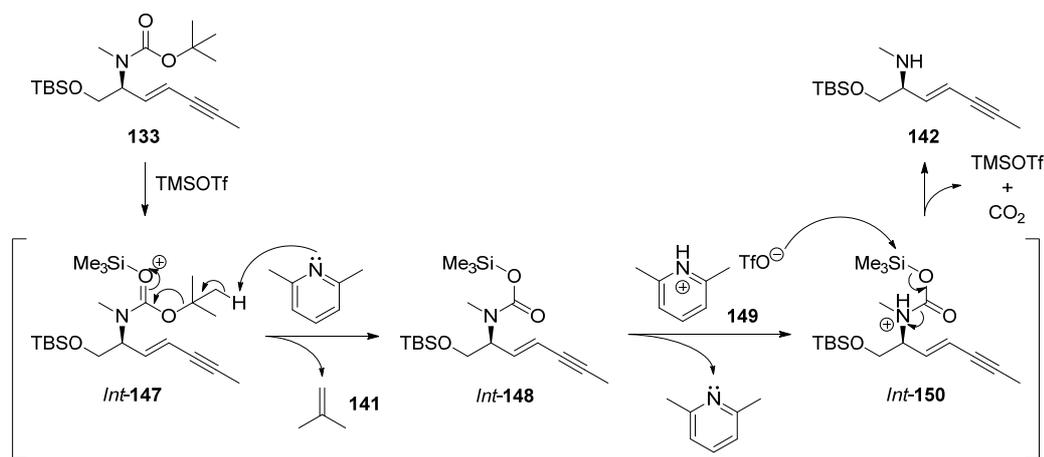
Rather than attempt to repeat the synthesis of the new C(6)-*N*-protected C(5)–C(9) alcohols from the appropriate *N*-protected analogue of Garner's aldehyde, it was decided that the best strategy would be to alter the protecting group from an advanced synthetic intermediate already available. A suitable substrate for this purpose was carbamate **133**, from which amine **142** could be derived by selective deprotection of the Boc group and subsequent submission of the product to various *N*-protection conditions. Silyl deprotection would then yield *N*-protected amino alcohols **145/146** whereby the alcohol could be converted to a leaving group (**Scheme 2.19**).

Because standard acidic Boc deprotection conditions could diminish the yield of the desired amine owing to the potential for the concomitant silyl cleavage, deprotection was attempted using TMSOTf/2,6-lutidine.<sup>79</sup> To our delight, amine **142** was obtained in 92% yield under these conditions (**Scheme 2.20**). This transformation is highly favourable because it is entropically driven as a result of gas formation. The mechanism (**Scheme 2.21**) involves a transesterification of the *tert*-butyl group with with the TMS group, which is initiated by reaction of the carbonyl oxygen with the TMSOTf followed by abstraction of a proton from the cationic intermediate *Int-147* by 2,6-lutidine. To generate the final product **142**, the nitrogen atom of *Int-148* is



**Reagents and conditions:** TMSOTf (3.0 eq), 2,6-lutidine (3.5 eq), DCM, 0 °C, 45 min, 92%.

**Scheme 2.20** Boc deprotection of the carbamate **133** to form amine **142**.



**Scheme 2.21** Mechanism of the TMSOTf/2,6-lutidine-mediated Boc deprotection of **133**.<sup>80</sup>

protonated by the 2,6-lutidinium triflate **149** thus generated, and the cation **Int-150** undergoes decarboxylation with concomitant regeneration of TMSOTf.<sup>80</sup>

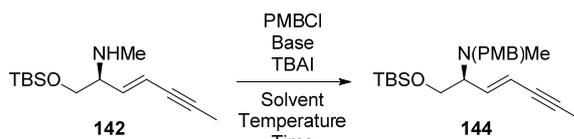
It is worth noting that removal of residual 2,6-lutidine by evaporation is essential to obtain the product in high purity, because the product amine co-elutes with the auxiliary base on silica using both EtOAc/hexane and DCM/MeOH eluents. In hindsight 2,6-lutidine was a poor (albeit standard) choice of base, and should this procedure be repeated, an alternative base should be sought which is either of lower boiling point and thus more easily removed (*e.g.* Et<sub>3</sub>N), or more polar such that purity of the product is less easily compromised by coelution on silica gel (*e.g.* imidazole).

Subsequent steps required *N*-Ts and *N*-PMB protection. Tosylation was achieved straightforwardly by reaction of the amine **142** with TsCl, Et<sub>3</sub>N and catalytic DMAP in DCM to give the product sulfonamide **143** in 85% yield (**Scheme 2.22**). *N*-PMB protection by use of NaH in conjunction with catalytic TBAI was initially attempted at room temperature with a modest (**Table 2.4**, Entry 1) and large (**Table 2.4**, Entry 2) excess of PMBCl, but both conditions led to unsatisfactory yields of the desired



**Reagents and conditions:** TsCl (1.5 eq), Et<sub>3</sub>N (3.0 eq), DMAP (11 mol%), DCM, rt, 18 h, 85%.

**Scheme 2.22** Tosylation of the amine **142**.

**Table 2.4** Attempted PMB protection of amine **142**.

Entry	Eq PMBCl	Base	Eq Base	mol% TBAI	Solvent	Temp (°C) <sup>a</sup>	Time (h)	Yield (%) <sup>b</sup>
1	1.2	NaH	1.1	20	DMF	25	48	29
2	5.0	NaH	2.0	20	DMF	25	18	Trace
3	2.0	NaH	2.0	20	THF/DMF (10:1)	72	18	22
4	1.2	K <sub>2</sub> CO <sub>3</sub>	2.2	20	THF	72	18	68
5	1.4	K <sub>2</sub> CO <sub>3</sub>	2.5	23	THF	72	48	91

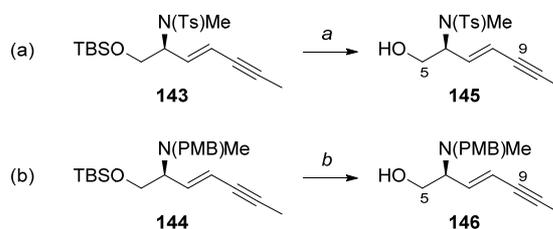
<sup>a</sup>In Entries 1 to 3, the amine **142** was reacted for 1 h at 0 °C to rt with the base prior to addition of PMBCl;

<sup>b</sup>Isolated yield.

product **144**; while elevated temperature also gave poor results (**Table 2.4**, Entry 3).

Since all three conditions (**Table 2.4**, Entries 1 to 3) involved pre-generation of a sodium amide (by stirring of the amine **142** with NaH for 1 h at 0 °C before addition of PMBCl), it was speculated that this intermediate formed on reaction at room temperature was unstable, and so NaH was replaced with K<sub>2</sub>CO<sub>3</sub> and the mixture was heated to reflux in THF (**Table 2.4**, Entries 4 and 5). Gratifyingly, the yield of the product **144** greatly increased, albeit requiring 2 days of reaction for isolated yields close to quantitative levels (**Table 2.4**, Entry 5).

With both *O*-TBS-protected *N*-Ts- and *N*-PMB-derived C(5)–C(9) analogue frameworks **143/144** synthesised, the final step toward the alcohols required for the installation of a leaving group would involve deprotection of the silyl groups. This was easily achieved in both cases by reaction of the silyl ethers **143/144** with TBAF in THF, followed by quenching with aqueous NH<sub>4</sub>Cl (**Scheme 2.23**), which concluded the synthesis of the required alcohols **145/146**.



**Reagents and conditions:** (a) TBAF (6.0 eq), 0 °C, 1 h; 94%; (b) TBAF (6.0 eq), 0 °C to rt, 1 h, quant.

**Scheme 2.23** Silyl deprotection of (a) β-*N*-Ts silyl ether **143** and (b) β-*N*-PMB silyl ether **144**.

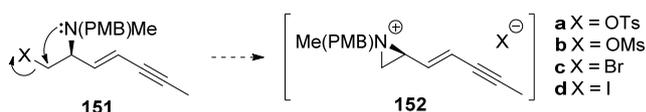
### 2.4.2 Completion of the C(6)-Amino C(5)–C(9) Fragment Analogue

Having successfully achieved the synthesis of both the *N*-Ts- and *N*-PMB-derived amino alcohols **145/146**, the final step involved conversion of the primary alcohol to a leaving group. Because the macrocyclic dialkynyl dilactone disorazole precursor **41** has been shown previously to be stable to standard PMB deprotection<sup>26</sup> (see: **Chapter 1, Section 1.2.4**), the preferred outcome involved the installation of a C(5) leaving group on the *N*-PMB-protected amino alcohol **146**. Unfortunately, efforts to convert alcohol **146** to a C(5)–C(9) electrophile **151** with this substrate were on the whole, unsuccessful, and are summarised in **Table 2.5**. Tosylation of the primary alcohol **146** using Et<sub>3</sub>N (with or without DMAP) or pyridine/DMAP led to no reaction of the substrate with the TsCl and the recovery of the starting material (**Table 2.5**, Entries 1 to 3). The only exception was in the case whereby heating was applied, where a complex mixture of components (as observed by <sup>1</sup>H NMR) was obtained after aqueous workup (**Table 2.5**, Entry 4). Results were similar on attempted mesylation of the alcohol **146** with MsCl in DCM (**Table 2.5**, Entries 5 to 9), or upon utilising Appel conditions to convert the primary alcohol **146** to an alkyl

**Table 2.5** Attempted leaving group installation onto *N*-PMB-protected amino alcohol **146**.

Entry	X	Eq [X] <sup>a</sup>	Base	Eq Base	mol% DMAP	Solvent <sup>b</sup>	Temp (°C)	Time (h)	Rslt. <sup>c</sup>
1	OTs	1.2	Et <sub>3</sub> N	14.3	0	Base	0 to 25	18	NR
2	OTs	2.0	Et <sub>3</sub> N	14.3	20	Base	0 to 25	18	NR
3	OTs	2.0	Py	11.0	100	Base	0 to 25	18	NR
4	OTs	2.0	Et <sub>3</sub> N	14.3	20	Base	95	1	cm
5	OMs	4.0	DIPEA	10.0	0	DCM	25	4	NR
6	OMs	4.0	Et <sub>3</sub> N	10.0	0	DCM	25	4	NR
7	OMs	10	Et <sub>3</sub> N	35.8	20	DCM	0 to 25	18	cm
8	OMs	4.0	Et <sub>3</sub> N	35.8	20	DCM	0 to 25	2.5	cm
9	OMs	2.0	Et <sub>3</sub> N	35.8	20	DCM	0 to 25	3	cm
10	Br	1.3	—	—	0	DCM	0 to 25	18	cm
11	I	3.0	Im	6.0	0	THF/MeCN <sup>d</sup>	0 to 25	18	cm

<sup>a</sup>Values in parentheses indicate the reagent used for the generation of group X: OTs (TsCl), OMs (MsCl), Br (CBr<sub>4</sub>/PPh<sub>3</sub>, 1:1), I (I<sub>2</sub>/PPh<sub>3</sub>, 1:1); <sup>b</sup>“Base” indicates that the base used in the reaction was also the solvent; <sup>c</sup>As determined by <sup>1</sup>H NMR of the crude material; <sup>d</sup>Ratio THF:MeCN, 3:1.

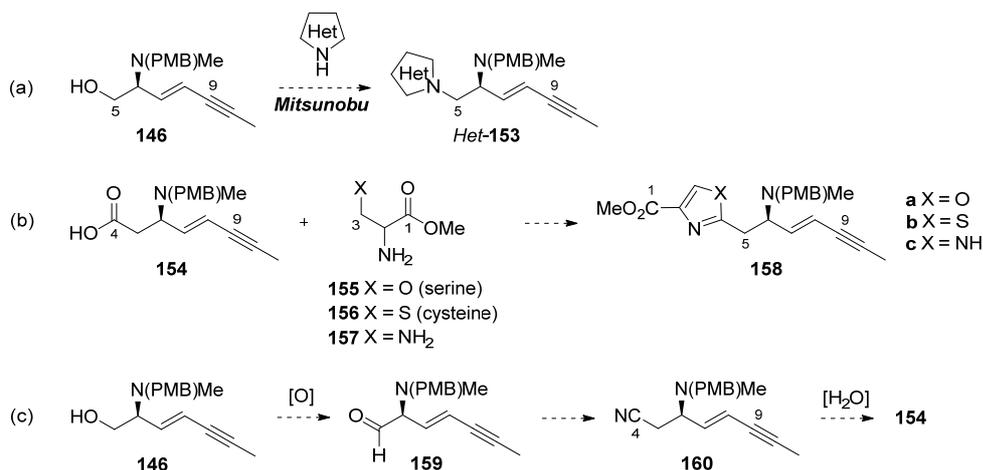


**Scheme 2.24** Mechanism for potential formation of aziridinium salts **152** from PMB-protected amino alcohol derivatives **151**.

bromide (**Table 2.5**, Entry 10) or iodide (**Table 2.5**, Entry 11). In these cases, the substrate either failed to react (**Table 2.5**, Entries 5 and 6), or led only to the formation of a complex mixture of products (**Table 2.5**, Entries 7 to 11) after aqueous workup and subsequent analysis of the crude  $^1\text{H}$  NMR spectrum.

Although purification of the material would perhaps provide insight into the reasons for the failure of the reaction, this was not attempted for number of reasons. Firstly, it was hoped and expected that such a reaction, in particular tosylation and mesylation would proceed unperturbed and therefore failure to do so cleanly in at least moderate conversion (~40%) was deemed unacceptable for such a theoretically straightforward transformation. Secondly, the reactions were typically performed with only a small quantity of material (typically ~20 mg) which would make isolation and characterisation of the multiple products in the mixtures particularly difficult. The most likely reason for failure of the reactions attempted in **Table 2.5**, on the basis of precedent,<sup>81</sup> would involve the nucleophilic substitution of the leaving group thus formed by the adjacent nitrogen atom, giving rise to the aziridinium salts **152** (**Scheme 2.24**). However, since the reactions consistently gave complex mixtures whereby identification of a single product was too difficult, the presence of the products **152** (or decomposition derivatives) was never confirmed. Such a process could perhaps be validated by addition of a nucleophile to the reaction mixture, but unfortunately this was never attempted, and efforts to install a leaving group on the *N*-PMB-protected C(5)–C(9) analogue **146** were discontinued. However, before the installation of a leaving group on the *N*-Ts-protected derivative **145** was carried out, two final, alternative uses of the alcohol as a precursor for heterocyclic C(1)–C(9) fragments were briefly explored.

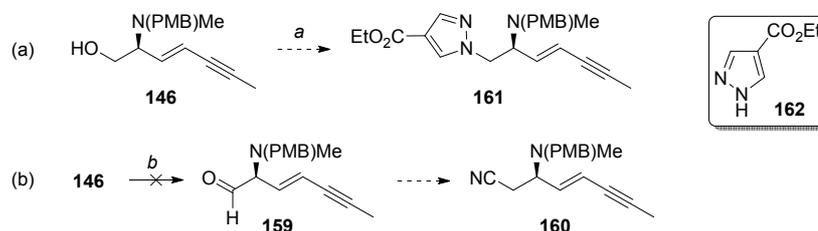
It was suggested in **Section 2.3.3** that a Mitsunobu reaction with a heterocycle and a C(5)–C(9) alcohol could potentially bypass the requirement for derivatisation of the alcohol as a tosylate (or other) leaving group, and the *N*-PMB protected C(5)–C(9)



**Scheme 2.25** Proposed (a) Mitsunobu; and (b) condensation approaches towards the synthesis of the C(6)-amino disorazole C<sub>1</sub> C(1)–C(9) analogues; and (c) synthesis of the carboxylic acid intermediate **154** required for the condensation approach.

alcohol **146** probably represented the best substrate for testing this theory (**Scheme 2.25a**). Another less convergent use of the alcohol **146** towards the synthesis of heterocycles would involve conversion to the carboxylic acid **154** and subsequent generation of the heterocycle by condensation with the methyl ester derivatives of serine **155** or cysteine **156**, or diamine analogue **157** (or their hydrochloride salts; **Scheme 2.25b**). Synthesis of the carboxylic acid **154** would be achieved by oxidation of the alcohol **146** to the aldehyde **159** followed by conversion to the nitrile **160**<sup>82</sup> with subsequent hydrolysis to the carboxylic acid (**Scheme 2.25c**).

However, in a forward sense, both approaches were unsuccessful, because a Mitsunobu reaction between the alcohol **146** and the pyrazole **162** (**Scheme 2.26a**) under mild conditions (0 °C) and more forcing conditions (ultrasonic vibration)<sup>83</sup> gave only trace conversion (<sup>1</sup>H NMR) to the desired product **161**; while attempted



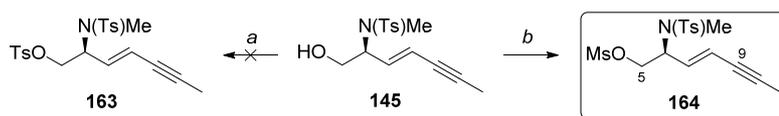
**Reagents and conditions:** (a) **162** (1.2 eq), PPh<sub>3</sub> (1.3 eq), DIAD (1.3 eq), THF, 0 °C or ultrasonic vibration, 4 h, trace conv.; (b) Dess–Martin periodinane (1.3 eq), NaHCO<sub>3</sub> (10 eq), DCM, 0 °C to rt, 3 h, 0%;

**Scheme 2.26** Attempted (a) Mitsunobu reaction between alcohol **146** and pyrazole **162**; and (b) synthesis of aldehyde **159** by Dess–Martin oxidation of alcohol **146**.

Dess–Martin oxidation of the alcohol to the aldehyde **159** gave only unreacted starting material and therefore the synthesis of nitrile **160** could not be pursued further (**Scheme 2.26b**). Unfortunately, further investigation into the optimisation of the Mitsunobu reaction, or use of alternative oxidation conditions optimisation of the Mitsunobu reaction, or use of alternative oxidation conditions could not be performed for reasons of time, and instead we opted to examine the use of the safer *N*-Ts-protected alcohol **145** as precursor for the synthesis of a C(5)–C(9) analogue side chain donor.

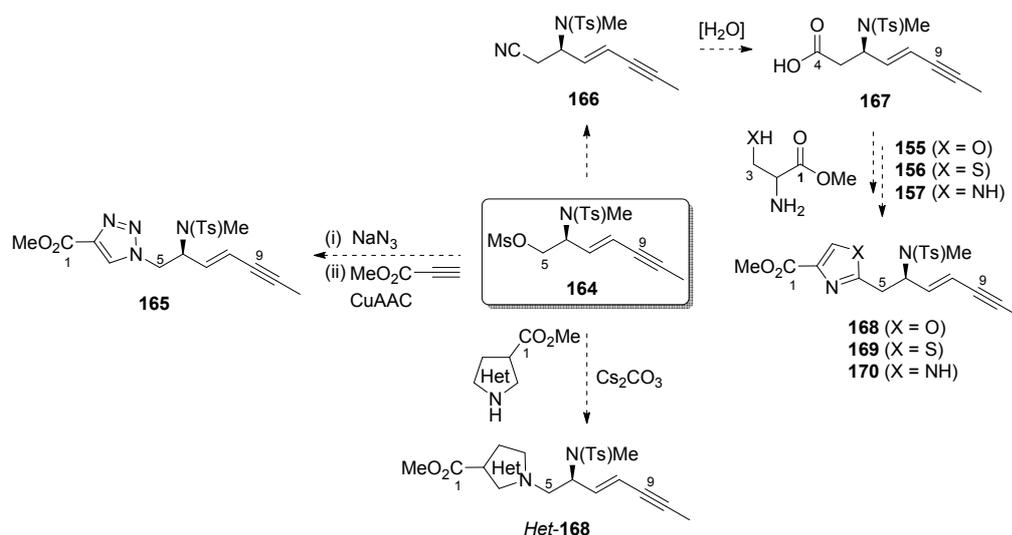
Conversion of the hydroxyl group to a leaving group on the *N*-Ts-protected amino alcohol **145** was predicted to be far more straightforward than with the *N*-PMB-protected amino alcohol **146**, because the electron-withdrawing effect of the sulfonamide would reduce the propensity for reaction of the nitrogen atom with the leaving group; and indeed this proved to be the case, to at least some extent. Attempted tosylation of alcohol **145** with TsCl and pyridine/DMAP (to give tosylate **163**; **Scheme 2.27**) was however, unsuccessful, and can probably be attributed to the energetic demands of placing the large tosyl group in the vicinity of the sterically crowded  $\beta$ -nitrogen atom. Fortunately, conversion of the alcohol **145** to the methanesulfonate ester **164** (**Scheme 2.27**) was achieved almost quantitatively (95%) by treatment of the alcohol **145** in DCM with MsCl in the presence of Et<sub>3</sub>N and catalytic DMAP, and concluded the synthesis of a C(6)-amino C(5)–C(9) fragment analogue of disorazole C<sub>1</sub>.

Time constraints and a lack of material prevented derivatisation of the mesylate ester **164** to fully elaborated, heterocyclic C(1)–C(9) fragment analogues; however, a number of derivatives of the C(6)-amino C(5)–C(9) mesylate may be envisaged (**Scheme 2.28**). Azide displacement (NaN<sub>3</sub>) followed by application of the CuAAC reaction with a suitable alkyne (*e.g.* methyl propiolate), would allow the synthesis of



**Reagents and conditions:** (a) TsCl (2.0 eq), Py (124 eq), DMAP (20 mol%), rt, 18 h, 0%; (b) MsCl (4.0 eq), Et<sub>3</sub>N (35.8 eq), DMAP (20 mol%), DCM, 0 °C to rt, 3.5 h, 95%.

**Scheme 2.27** Attempted C(5) *O*-tosylation and -mesylation of *N*-tosyl amino alcohol **145**.

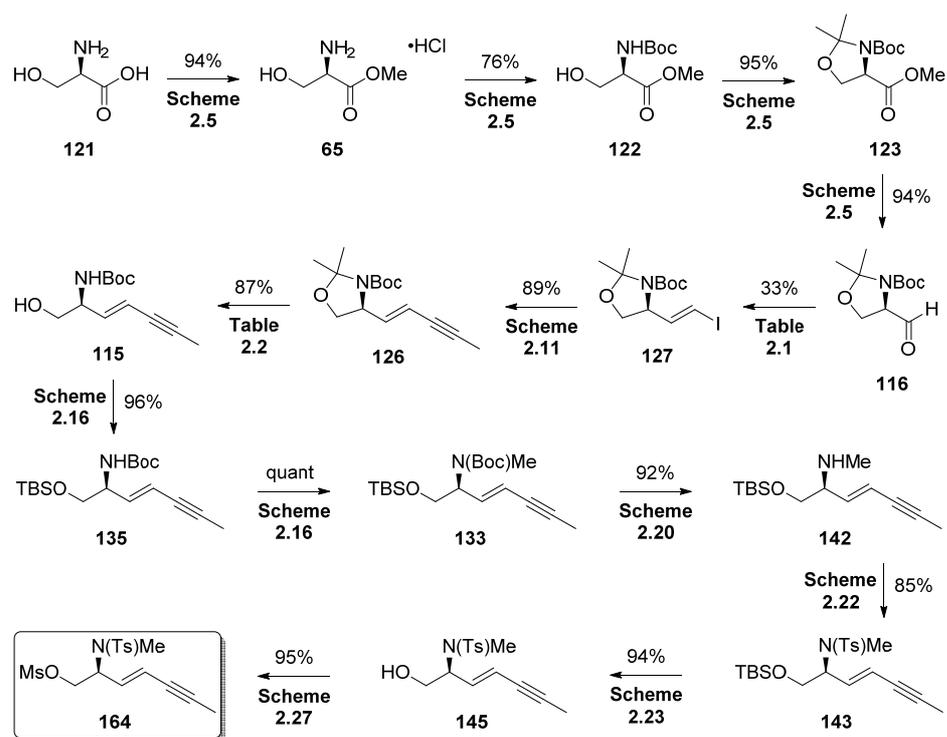


**Scheme 2.28** Proposed syntheses of C(6)-amino C(1)–C(9) fragment analogues using the C(5)–C(9) mesylate **164**.

a C(1)–C(9) triazole analogue **165**.<sup>16</sup> Synthesis of the oxazole analogue **168** would be achieved by cyanide substitution of the mesylate, followed by hydrolysis of the nitrile **166**, and a final three-stage cyclodehydration of the acid **167** thus obtained with serine methyl ester **155**;<sup>44</sup> with thiazole **169** and imidazole **170** analogues made available through replacement of serine methyl ester in this sequence with its appropriate analogue **156/157**. Finally, C(6)-amino C(1)–C(9) *N*-heterocyclic analogues *Het-168* of oxazole **168** would be generated by application of our established *N*-alkylation conditions, which involve nucleophilic substitution of the leaving group with 1*H*-*N*-heterocycles in the presence of  $\text{Cs}_2\text{CO}_3$  (see: **Chapter 5, Section 5.2.5**).

## 2.5 Conclusions and Future Work

Although the synthesis of a full C(6)-amino C(1)–C(9) analogue fragment was unsuccessful, we were able to generate the key C(5)–C(9) intermediate **164**, which was achieved in 11% yield in 13 steps from *D*-serine; and a summary of the relevant synthetic transformations is shown in **Scheme 2.29**. Despite the low overall yield and long synthetic sequence, in the face of the numerous problems encountered, the synthesis can be considered a success and will provide access to C(6)-amino analogues of disorazole C<sub>1</sub> and heterocyclic analogues thereof. The main weaknesses



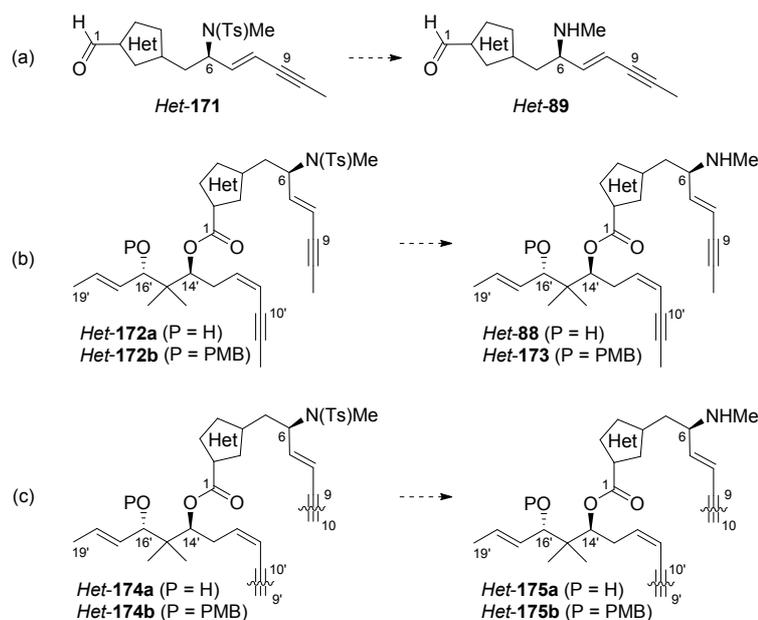
**Scheme 2.29** Overall synthesis of the C(6)-amino C(5)-C(9) fragment analogue **164** of disorazole C<sub>1</sub>.

of the synthetic route primarily revolve around: (1) the use of a low-yielding, inefficient Takai olefination in the stereoselective, two-stage synthesis of the C(5)-C(9) (*E*)-1,3-enyne **126**; (2) the use of an *N*-tosyl protecting group, which will present difficulties at the deprotection stage; and (3) the rather large number of steps required for the synthesis of such a small fragment. Fortunately, being only a first generation synthesis of a C(6)-amino C(1)-C(9) fragment analogue, there remains great scope for enhancing the synthetic route. Improving the yield of the (*E*)-vinyl iodide **127** could probably be achieved by careful optimisation of the Takai conditions, or through use of an alternative iodo-olefination protocol, and therefore for reasons of brevity this aspect of the synthetic route will not be discussed in depth. However, the remaining two points will be addressed in the following section, along with other suggestions for future work towards the synthesis of alternative C(1)-C(9) fragment analogues.

### 2.5.1 The *N*-Protecting Group

It became apparent during the key stage of installing the leaving group at the C(5) position of C(6)-amino C(5)–C(9) alcohols such as **136** and **146** that the nature of the C(6) *N*-protecting group was particularly important. Findings indicated that the group had to be sufficiently electron withdrawing to inhibit reactions of the nitrogen lone pair with the leaving group, but must not contain a reactive functional group which could eliminate the leaving group by acting as a nucleophile. On these bases, the most obvious remedy involved protection of the amine as a toluenesulfonamide, and indeed this proved to be the only successful *N*-protecting group used in our studies.

Aside from potential global PMB deprotection\* that may have been carried out in the event that use of the *N*-PMB protecting group was successful, so far in our discussion nothing has been mentioned about deprotection of the *N*-tosyl (or *N*-Boc) group to reveal the free amine. It is (was) anticipated that this step would be carried out at one

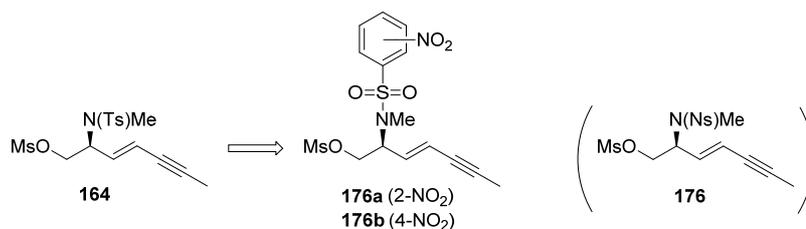


**Scheme 2.30** Potential *N*-Ts deprotection stages.

\*The PMB-protected compounds **172b** to **175b** are encompassed in our strategy towards the C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkynes, as discussed in **Chapter 5, Section 5.1.4**. In brief, it was anticipated that ET coupling of *e.g.* **Het-171** with the C(10)–C(19) fragment **86** would give the bis-alkyne (*e.g.* **172a**), but that if ET coupling failed, C(1)→C(14') esterification of C(1)–C(9) carboxylic acids with a C(10)–C(19) C(16)-*O*-protected diol fragment would provide contingency. C(16) *O*-protection may also be required to overcome incompatibilities of the AM catalyst with the free hydroxyl group; a PMB protecting group was chosen on the basis of precedent.<sup>26</sup>

of three stages: (1) following incorporation of the alkyl group into a full length, C(1)–C(9) heterocyclic fragment *Het-171* (**Scheme 2.30a**); (2) following generation of the AM precursor bis-alkynes *Het-172* by reaction of the C(1)–C(9) fragment with the C(10)–C(19) fragment (**Scheme 2.30b**); (3) following AM (**Scheme 2.30c**), to negate any problems associated with interaction of free amino group with the catalyst used during this reaction. Unfortunately, the disadvantage of using the tosyl group is the difficulty associated with its deprotection, which is normally performed by treatment of the substrate with reducing agents such as  $\text{SmI}_2$ ,<sup>84a</sup>  $\text{Mg/MeOH}$ ,<sup>84b</sup>  $\text{Na/NH}_3$ ,<sup>84c</sup>  $\text{Na/naphthalene}$ ;<sup>84d</sup> or by thermal cleavage under harshly acidic conditions ( $\text{phenol/AcOH/HBr}$ );<sup>84e</sup> and all of these modes of deprotection have some potential for damaging one or all of: (1) ester/lactone frameworks; (2) conjugated enyne systems; or (3) the integrity of heterocycles. Perhaps the most practical method of deprotection would involve the use of  $\text{TMSCl/NaI}$  in  $\text{MeCN}$ ,<sup>84f</sup> but it would be preferable not to rely on a single deprotection protocol because if this was unsuccessful, removal of the tosyl group would present a significant problem.

Given the restrictions in the method of deprotection, the choice of the tosyl group was perhaps an aberration, but was nonetheless useful as it indicated that the sulfonamide group would allow the neighbouring alcohol to be successfully converted to a leaving group. However, to improve the fragment synthesis, an alternative sulfonamide should be chosen which would be more easily deprotected. The best alternatives would be the 2- or 4-nitrobenzenesulfonyl groups (**Figure 2.1**; henceforth in this chapter,  $\text{Ns}$  = 2- or 4-nitrobenzenesulfonyl), which are installed as straightforwardly as the tosyl group ( $\text{NsCl}$ , amine base), but are rapidly and selectively deprotected under mild conditions with the thiolate anion derived from reagents such as  $\text{PhSH}$  and mercaptoacetic acid.<sup>85</sup> As such, on repetition of the C(5)–C(9) analogue synthesis, it would be worthwhile investigating these sulfonamide groups as alternative *N*-protecting groups.

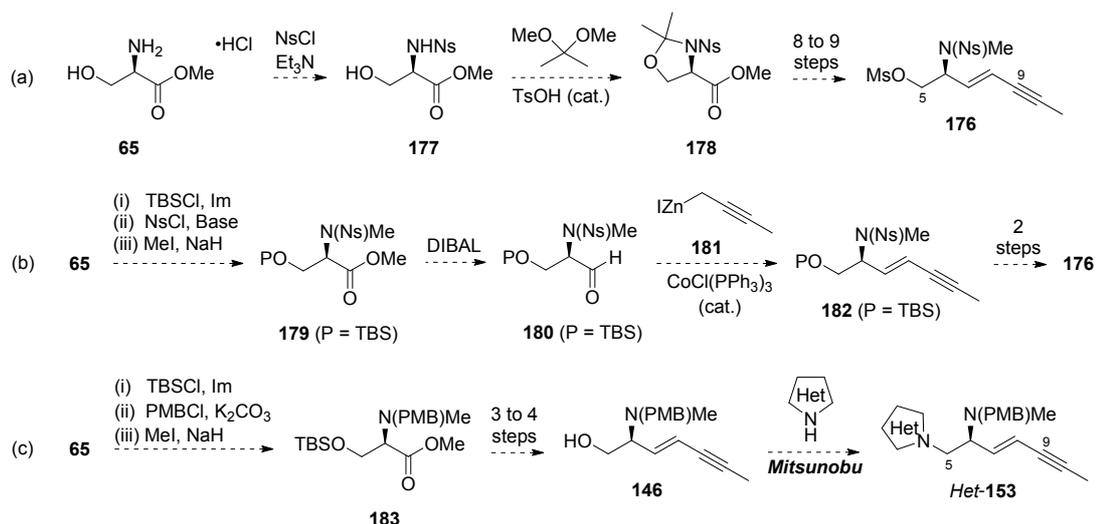


**Figure 2.1** The nosyl group as a more labile alternative to the tosyl group.

## 2.5.2 Streamlining the Synthetic Pathway

Another issue that requires to be addressed is the length of the synthetic route to the C(5)–C(9) analogue fragment **164**, which currently stands at 13 steps and is therefore very atom inefficient. On examination of the points noted above in regards to modification of the *N*-protecting group, one potential method of shortening the sequence would be to use an *N*-nosyl Garner aldehyde derivative **178**,<sup>86</sup> which would be synthesised by installation of the group at the methyl ester **65** stage (**Scheme 2.31a**) and would negate the requirement for Boc protection and deprotection, thus shortening the sequence by two synthetic steps. However, the use of the isopropylidene group may be unnecessary, which would shorten the sequence by a further two (protection/deprotection) steps (**Scheme 2.31b**).

The hydroxyl group in serine methyl ester hydrochloride **65** would be protected as its TBS-ether, and the free amine subsequently nosyl-protected and methylated (**Scheme 2.31b**). DIBAL reduction of the resulting functionalised serine methyl ester derivative **179** to the aldehyde **180**<sup>87</sup> would give a product suitable for subsequent conversion to the enyne **182** *via* the Takai/Negishi coupling protocol; or preferably, a single-step method, for example (and as shown) a cobalt-mediated synthesis<sup>88a</sup> from the zinc reagent **181** derived from 1-butyne iodide.<sup>88b–d</sup> Subsequent silyl deprotection and mesylation would give the C(5)–C(9) fragment analogue **176** in 8

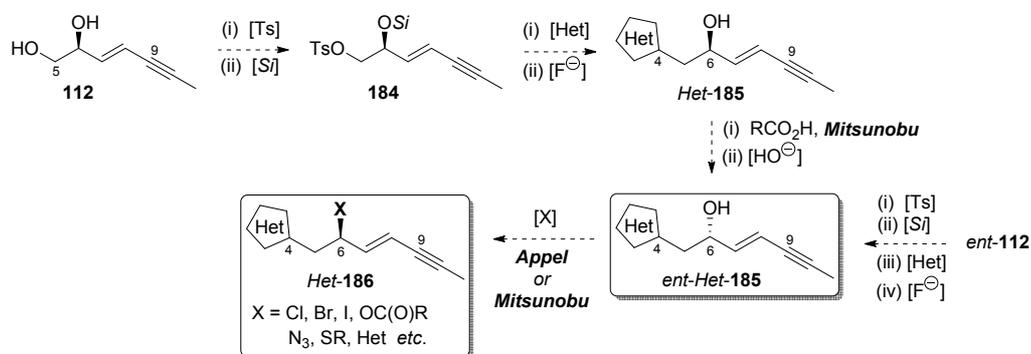


**Scheme 2.31** Alternative strategies towards the synthesis of a C(5)–C(9) fragment analogue *via* (a) the use of an *N*-nosyl Garner aldehyde analogue **178**; and (b) avoidance of installation of the acetonide protecting group. (c) Alternative approach towards the synthesis of the *N*-PMB-protected fragment **146** for use in Mitsunobu reactions.

steps (**Scheme 2.31b**), which would represent a marked improvement over the protocol reported herein. Of course, conversion of C(6)-*N*-protected C(5)–C(9) alcohols (such as **145**) to their mesylate esters could be avoided should useful Mitsunobu conditions be found for reaction of a C(5)–C(9) alcohol with *N*-heterocycles (or derivative functional groups), and optimisation of Mitsunobu conditions to levels of conversion beyond trace quantities would certainly be worthy of further investigation. This would be preferably carried out with the *N*-PMB-protected amino alcohol **146** and so the synthesis of this alcohol could commence from *N*-PMB-*O*-TBS-protected serine methyl ester **183**<sup>89</sup> (**Scheme 2.31c**).

### 2.5.3 Further C(6) C(1)–C(9) Fragment Analogues

Once routes to fully elaborated C(6)-amino C(1)–C(9) fragment analogues are established, the synthesis of alternative C(6) analogues could be investigated. Perhaps the most straightforward route to such analogues would involve the use of an intermediate for which a synthetic route is already well established, and which would be readily converted to a number of functional groups at a late stage of the fragment synthesis; Ramstadius' C(5)–C(9) diol intermediate **112** perhaps represents the best substrate for this purpose. The diol **112** would be converted to its C(5) tosylate ester (*cf.* **Scheme 2.2**) and the secondary alcohol would be silyl protected to give tosylate **184** (**Scheme 2.32**). The heterocyclic portion of the molecule would then be introduced and the silyl protecting group would be cleaved to afford the secondary alcohol *Het*-**185**, the stereochemistry of which would be inverted using a Mitsunobu



**Scheme 2.32** Synthesis of C(6)-functional-group analogues of the C(1)–C(9) fragment of disorazole C<sub>1</sub> *Het*-**186** from Ramstadius' C(5)–C(9) diol intermediate **112** or *ent*-**112**.

reaction with a sacrificial carboxylic acid, followed by ester hydrolysis (**Scheme 2.32**). With the key alcohol *ent*-**Het-185**, a Mitsunobu reaction or an alternative reaction that proceeds with inversion of stereochemistry such as the Appel reaction would provide access to a range of C(6) heteroatom or functional group analogues **Het-186** of the C(1)–C(9) fragment (**Scheme 2.32**). Alternatively, this sequence could be performed with the antipode of Ramstadius' diol **112**, *ent*-**112**, and would negate the requirement for the use of the two-stage (Mitsunobu/hydrolysis) alcohol inversion step. Application of this Mitsunobu/Appel reaction-based methodology will permit expansion of the scope of the disorazole C<sub>1</sub> analogue family.

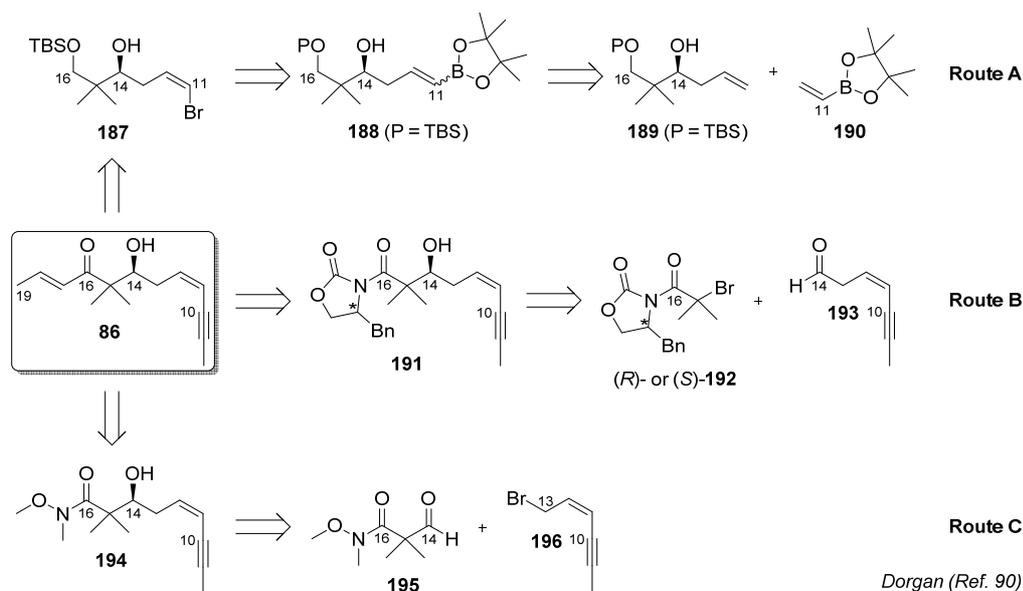
## 2.6 Summary

The synthesis of a C(6)-amino C(5)–C(9) fragment analogue of disorazole C<sub>1</sub> **164** was achieved in 13 steps and 11% yield from commercially available *D*-serine. The key steps involved a Takai olefination, starting from an inexpensive chromium source (CrCl<sub>3</sub>•6H<sub>2</sub>O), to selectively (>99:1 *E*:*Z*) synthesise an (*E*)-vinyl iodide derivative of Garner's aldehyde **127**; with a subsequent Negishi coupling used to complete the installation of the C(7)–C(9) enyne. The main problems encountered during the synthesis were concerned with the installation of the required C(5) leaving group to the C(5)–C(9) alcohol in the presence of the neighbouring C(6) nitrogen atom. A survey of C(6) *N*-protecting groups identified the tosyl group as the most viable option, and although *N*-tosyl protection did not permit the installation of our preferred *O*-tosyl leaving group, installation of an *O*-mesyl group proceeded successfully. Use of mesylate **164** will allow the synthesis of C(6)-amino C(1)–C(9) fragment analogues and if used successfully as part of our ET–AM methodology, will greatly expand the family of disorazole analogues. Aside from the completion of heterocyclic analogues, future work should involve identification of a more labile *N*-protecting group, optimisation of key steps and shortening of the synthetic sequence. As a longer-term target, synthesis of further C(6)-modified C(5)–C(9) analogues could be performed, and this will expand the family of disorazole C<sub>1</sub> analogues upon elaboration to full C(1)–C(9) analogues and use as intermediates as part of our ET–AM approach.

## Convergent Approaches towards the Synthesis of the C(10)–C(19) Fragment of Disorazole C<sub>1</sub>

### 3.1 Overview, Previous Work and Retrosynthesis

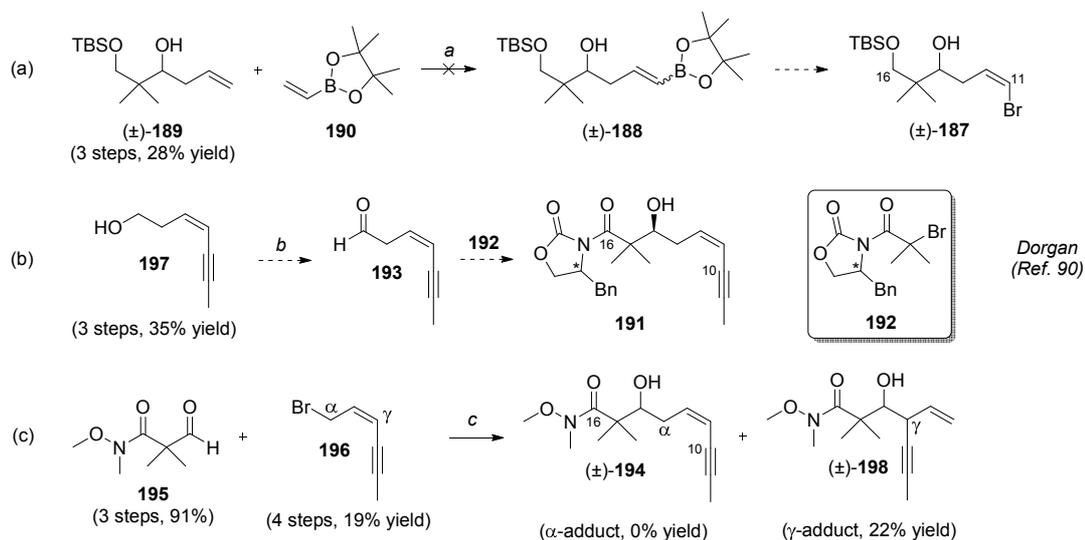
Unlike the synthesis of the C(1)–C(9) fragment, whereby both the racemate and optically pure forms have been synthesised in either their C(1)-formyl or C(1)-carboxylic acid form (see: **Chapter 2, Section 2.1**), a reliable route to either the C(10)–C(19)  $\beta$ -hydroxyketone fragment **86** itself or a suitable advanced derivative has yet to be established. Previous work towards the synthesis of the C(10)–C(19) fragment **86** was carried out by Dorgan,<sup>90</sup> who, during his PhD studies within the Hulme group, investigated three routes towards the synthesis of this key intermediate (**Scheme 3.1**). The first route (**Route A**) relied on the generation of bromide **187** from the boronate **188** following an olefin cross-metathesis (CM)<sup>91</sup> reaction between the homoallylic alcohol **189** and vinyl boronic acid pinacol ester **190**. The second route (**Route B**) required a Reformatsky reaction<sup>92</sup> between bromoacyl oxazolidinone **192**<sup>93</sup> and aldehyde **193**. The third route (**Route C**) was predicted to give the product **86** after Grignard addition to the Weinreb amide **194**, which would be obtained *via* a Barbier reaction<sup>94</sup> between aldehyde **195** and allylic bromide **196**. In the case of **Route A** and **Route C**, the C(14) stereocentre would be introduced by use of an asymmetric allylation and an asymmetric Barbier addition protocol,



**Scheme 3.1** Dorgan's retrosynthetic analysis of the C(10)–C(19) fragment **86**.<sup>90</sup>

respectively; whilst **Route B** would take advantage of the diastereoselectivity provided by the use of an enantiopure amino acid-derived bromoacyl oxazolidinone **192**.

Unfortunately, in a forward sense, all three of these approaches were unsuccessful (**Scheme 3.2**). Despite achieving the synthesis of the homoallylic alcohol ( $\pm$ )-**189** required for the investigation of **Route A**, CM with vinyl boronic acid pinacol ester **190** was unsuccessful and therefore no product ( $\pm$ )-**188** could be obtained for elaboration to the bromide derivative ( $\pm$ )-**187** for transformation to the desired fragment ( $\pm$ )-**86**.<sup>90</sup> **Route B** was unsuccessful owing to difficulties in handling and synthesising the aldehyde **193**, which was volatile and difficult to obtain in high purity despite observing quantitative conversion (from alcohol **197**) by <sup>1</sup>H NMR spectroscopy. As such, this precluded attempted reaction of aldehyde **193** with either enantiomer of the oxazolidinone **192**, thus preventing synthesis of the key C(10)–C(16) intermediate **191**.<sup>90</sup> Finally, although both coupling partners for the Barbier addition reaction were synthesised successfully,<sup>90</sup> **Route C** failed owing to problems of regioselectivity in their combination using a Barbier addition.<sup>95</sup> The desired  $\alpha$ -adduct Barbier addition product ( $\pm$ )-**194** – required for Grignard addition in order to complete the fragment **86** – was not obtained, and instead the  $\gamma$ -adduct ( $\pm$ )-**198** was favoured across a range of conditions for the Barbier addition between

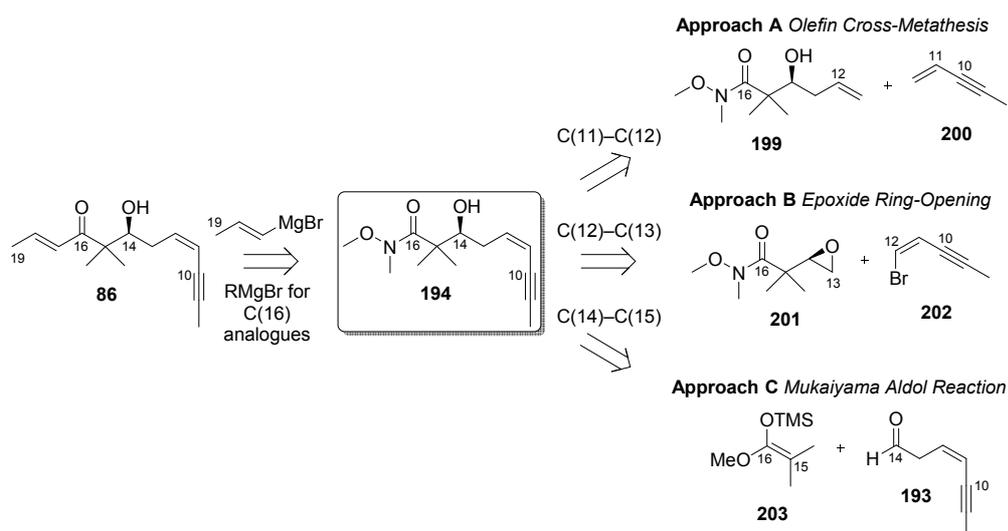


**Reagents and conditions:** (a) Grubbs II, DCM, reflux, 12 h, 0%; (b) Dess–Martin periodinane, DCM, rt, 3 h, 99% conv.; (c) **195**, **196**, In, H<sub>2</sub>O, rt, 48 h, ( $\pm$ )-**194** 0%, ( $\pm$ )-**198** 22%.

**Scheme 3.2** Unsuccessful previous attempted syntheses of the C(10)–C(19) fragment.<sup>90,95</sup>

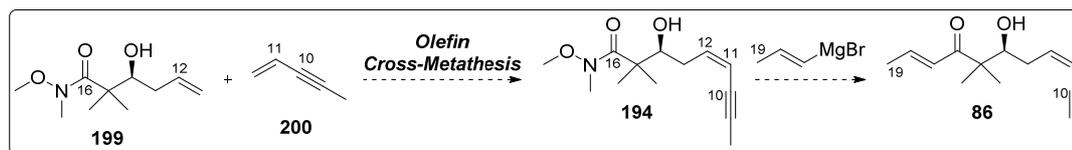
the aldehyde **195** and the allylic bromide **196**.<sup>95</sup> As such, no advanced synthetic intermediate could be obtained from any of the three **Routes A to C** for completion of the C(10)–C(19) fragment **86**, and a novel protocol for its generation is therefore still required.

**Route C** in Dorgan's retrosynthesis (**Scheme 3.1**) identified a potentially useful strategy for introducing the C(17)–C(19) propene group, which was anticipated to involve a Grignard addition reaction between the C(10)–C(16) Weinreb amide **194** and 1-propenylmagnesium bromide (**Scheme 3.3**).<sup>90</sup> Not only would this strategy permit the installation of the C(17)–C(19) propene group in our C(10)–(19) fragment **86**, but reaction of **194** with alternative organometallic reagents would allow access to a number of C(16) analogues of **86**; targeting of the C(10)–C(16) Weinreb amide **194** was therefore performed in our retrosynthetic analysis (**Scheme 3.3**). Synthetic routes to Weinreb amide **194** and thus  $\beta$ -hydroxyketone **86** were designed to encompass a range of bond disconnections, and these included: (1) an olefin cross-metathesis reaction between homoallylic alcohol **199** and enyne **200** [C(11)–C(12) disconnection, **Approach A**]; (2) an epoxide ring-opening route which would involve metallation of the vinyl bromide **202** and addition onto the epoxide **201** [C(12)–C(13) disconnection, **Approach B**]; and (3) a Mukaiyama aldol reaction between the silyl ketene acetal **203** and the aldehyde **193** [C(14)–C(15) disconnection, **Approach C**].



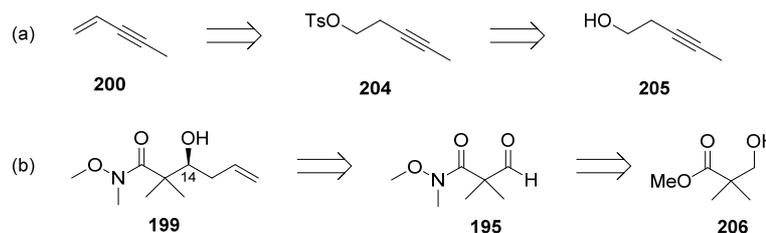
**Scheme 3.3** Retrosynthetic analysis of the C(10)–C(19)  $\beta$ -hydroxyketone **86**.

## 3.2 Approach A: Cross-Metathesis



**Scheme 3.4** Cross-metathesis approach towards the synthesis of the C(10)–C(19) fragment **86**.

The first approach towards the synthesis of key Weinreb amide **194** focussed on an olefin cross-metathesis (CM) reaction between the C(12)–C(16) alkene **199** and the C(10)–C(11) enyne **200** (Scheme 3.4). Although CM with a similar homoallylic alcohol substrate was previously unsuccessful (See: Scheme 3.2),<sup>90</sup> we were nonetheless interested in investigating the route owing to the perceived simplicity involved in synthesising the CM partners, and due to the recent advances in enyne–olefin CM which have indicated a preference for (*Z*)-selectivity in such reactions.<sup>96</sup> Both enyne **200** and olefin ( $\pm$ )-**199** had been synthesised previously, and therefore their retrosyntheses are straightforward: enyne **200** was to be synthesised from 3-pentyn-1-ol **205** through base elimination from tosylate **204** (Scheme 3.5a);<sup>16,97</sup> while alkene ( $\pm$ )-**199** was to be synthesised from aldehyde **195**,<sup>90</sup> which may be derived from methyl hydroxypivalate **206** (Scheme 3.5b). The required (*S*)-stereochemistry at C(14) would be introduced using one of a multitude of the asymmetric allylation methods available for the enantioselective synthesis of homoallylic alcohols from aldehydes.<sup>98</sup>



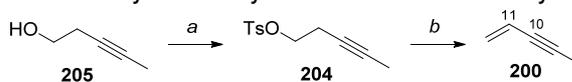
**Scheme 3.5** Retrosynthesis of the (a) C(10)–C(11) enyne **200**; and (b) C(12)–C(16) olefin **199** for implementation of the cross-metathesis approach towards the synthesis of the C(10)–C(19) fragment **86**.

### 3.2.1 Synthesis of the C(10)–C(11) Enyne (200)

Synthesis of the enyne **200** has been achieved previously<sup>16,97a</sup> using base hydrolysis of the precursor tosylate **204** and subsequent fractional distillation of the volatile product. Thus, tosylate **204** was synthesised from 3-pentyn-1-ol **205** in excellent yield by reaction with TsCl in pyridine (94%; see Scheme in **Table 3.1**). Subsequently, tosylate **204** was treated with KOH (1.2 eq) in EtOH in the presence of a trace of detergent (as a solubilising agent) and the volatile product **200** (boiling point 57–59 °C)<sup>97</sup> was collected over a period of 2 h. Unfortunately, use of these conditions (**Table 3.1**, Entry 1) led to a poor yield (trace), and co-elution of EtOH and H<sub>2</sub>O with the product as indicated by <sup>1</sup>H NMR. The poor result was probably both a consequence of using a standard Vigreux distillation apparatus as opposed to a spinning-band<sup>97a</sup> or fractioning<sup>16</sup> column as described previously, and the restriction placed on the maximum reaction temperature by the use of EtOH, which boils at only 18 to 21 °C higher than the product enyne **200**.

To prevent solvent co-distillation, the use of higher-boiling-point solvents was investigated, along with the use of a larger base stoichiometry (to drive the apparently sluggish reaction to completion). Disappointingly, the use of <sup>n</sup>BuOH (**Table 3.1**, Entry 2) gave similar results to that for EtOH, whereby the distillate was contaminated with the reaction solvent and H<sub>2</sub>O. The use of a <sup>t</sup>BuOK/DMSO base and solvent system – which has also been shown to be useful in the generation of conjugated olefins<sup>99</sup> – led to decomposition of the starting material as indicated by the formation of a black tarry residue and no formation of a distillate. However, more

**Table 3.1** Synthesis of enyne **200** by base elimination of tosylate **204**.



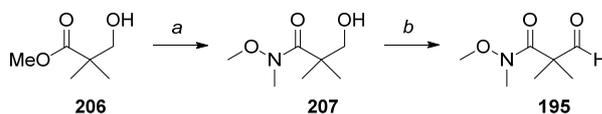
**Reagents and conditions:** (a) (i) TsCl (1.1 eq), Py (1.3 eq), 120 to 0 °C; (ii) **205**, 0 °C to rt, 18 h, 94%; (b) See Table.

Entry <sup>a</sup>	Base	Eq Base	Solvent	Solvent bp (°C) <sup>b</sup>	Temp (°C)	Time (h) <sup>c</sup>	Yield (%) <sup>d</sup>
1	KOH	1.2	EtOH	78	65	2	Trace
2	KOH	2.0	<sup>n</sup> BuOH	117	90	4	<i>nd</i>
3	<sup>t</sup> BuOK	2.0	DMSO	189	120	2	0
4	KOH	6.0	1-Octanol	195	135	4	65

<sup>a</sup>A trace of detergent (~2 μL per mmol **204**) was added to all reactions with the exception of Entry 3; <sup>b</sup>As specified by the manufacturer; <sup>c</sup>Reaction was conducted until the product ceased to distil, or for 2 h in cases where no product was readily collected; <sup>d</sup>Isolated yield.

positive results were achieved through use of KOH in 1-octanol, giving the C(10)–C(11) enyne **200** in good yield (65%) without problems of solvent co-distillation (**Table 3.1**, Entry 4).

### 3.2.2 Synthesis of the C(12)–C(16) Olefin [(±)-**199**]



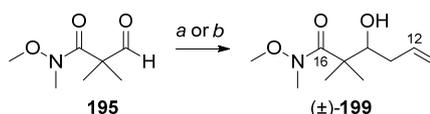
**Reagents and conditions:** (a) (i)  $^n\text{BuLi}$  (6.0 eq),  $\text{HNMe(OMe)}\cdot\text{HCl}$  (3.0 eq),  $-78\text{ }^\circ\text{C}$  to rt, THF/hexane (1:1), 1 h; (ii) **206**,  $-78\text{ }^\circ\text{C}$  to rt, 2 h, 95%; (b) (i)  $(\text{COCl})_2$  (1.5 eq), DMSO (4.5 eq), DCM,  $-78\text{ }^\circ\text{C}$ , (ii) **207**, 1 h; (iii)  $\text{Et}_3\text{N}$  (6.0 eq),  $-78\text{ }^\circ\text{C}$  to rt, 0.5 h, 95%.

**Scheme 3.6** Synthesis of aldehyde **195** from methyl hydroxypivalate **206**.

It was envisaged that asymmetric allylation of aldehyde **195** would give the required enantiopure olefin **199** for CM. However, for the purpose of screening CM reactions, the racemate (±)-**199** would be sufficient; and its precursor aldehyde **195** was synthesised in two steps from methyl hydroxypivalate (**Scheme 3.6**). Conversion of ester **206** to its Weinreb amide **207** was achieved in 95% yield using 3 equivalents<sup>100</sup> of the lithium amide generated by the reaction of  $^n\text{BuLi}$  with hydrochloride salt of *N,O*-dimethylhydroxylamine in THF. Subsequent Swern oxidation<sup>101</sup> gave the target aldehyde **195** in 95% yield on a gram scale (**Scheme 3.6**).

Our initial efforts towards the synthesis of (known)<sup>90</sup> homoallylic alcohol (±)-**199** focussed on the use of a Barbier reaction using indium as the metal catalyst, as we believed that this may be easily adapted towards an enantioselective synthesis<sup>102</sup> of the (*S*)-enantiomer should CM be successful. Thus, aldehyde **195** was allowed to react with allyl bromide in the presence of indium powder in THF. We were delighted to discover that the reaction proceeded to give the product (±)-**199** in near quantitative yield (97%, **Scheme 3.7**).

Because indium is somewhat expensive, use of an alternative metal in this reaction was investigated for reasons of cost. Malvestiti *et al.*<sup>103</sup> report the use of tin powder (activated by HCl) in Barbier addition reactions, which proceed quickly (<1 h), and are environmentally friendly owing to the use of an (acidic or basic) aqueous solvent.

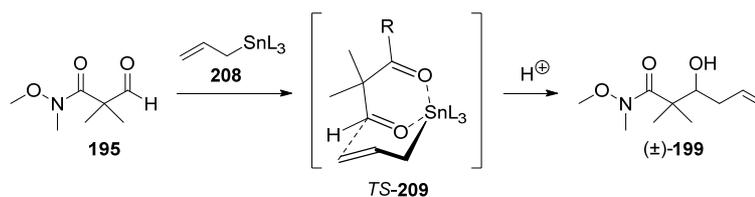


**Reagents and conditions:** (a) Allyl bromide (6.0 eq), In (2.0 eq), THF, rt, 24 h, 97%; (b) (i) Sn (2.5 eq), HCl (16 eq), H<sub>2</sub>O, rt, 45 min; (ii) **195**, allyl bromide (3.7 eq), 2.5 h, 85%.

**Scheme 3.7** Alternative Barbier syntheses of the cross-metathesis precursor (±)-**199**.

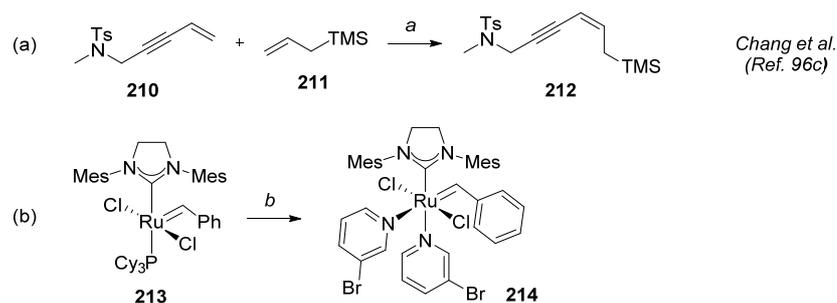
Thus, aldehyde **195** was added to a solution of allyl bromide and tin powder in HCl (1.0 M aq), which had been pre-stirred for 5 to 10 minutes. Purification of the crude product thus obtained gave a good yield (67%) of the C(12)–C(16) homoallylic alcohol (±)-**199** after only 15 minutes. On scaling up (50 mg to 1 g), an improved yield was obtained (85%; **Scheme 3.7**), albeit after a reaction time of 2.5 h; probably as a result of the tin powder – now used in gram quantities – requiring a longer time period (45 min) to undergo dissolution.

The mechanism of the reaction is likely, by analogy to that proposed by Malvestiti *et al.*<sup>103</sup> for the crotylation of *ortho*-substituted benzaldehydes, to proceed *via* a [6,6]-cyclic transition state owing to the presence of the neighbouring β-amide oxygen atom in aldehyde **195** (**Scheme 3.8**). Coordination of the *in situ* generated allyltin species **208** to both oxygen atoms is followed by transfer of the allyl group to the aldehyde carbonyl group *via* transition state *TS-209* (**Scheme 3.8**). Protonation of the oxygen atom – which would be rapid because the reaction is performed in acidic media – then yields the homoallylic alcohol product (±)-**199**.



**Scheme 3.8** Proposed mechanism for the tin-mediated Barbier allylation of aldehyde **195**.

## 3.2.3 Cross-Metathesis Reactions



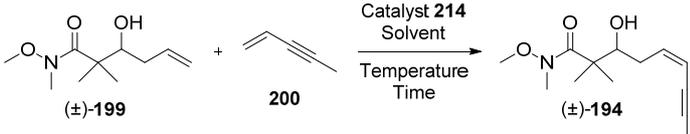
**Reagents and conditions:** (a) **210** (1.0 eq), **211** (3.0 eq), **214** (5 mol%), PhH, 10 h, 50% yield, >25:1 *Z:E*; (b) (i) 3-Bromopyridine (10 eq), 5 min; (ii) Pentane, 4 °C, 18 h, 88%.

**Scheme 3.9** (a) Exemplar enyne–olefin cross-metathesis reaction with catalyst **214**,<sup>96c</sup> (b) synthesis of modified Grubbs' second generation catalyst **214**.

We had envisaged the use of a modified Grubbs' II catalyst **214**, which has been shown to be an exceptional catalyst for the CM of alkenes with enynes, has excellent functional group tolerance, and, crucially, is predominantly (*Z*)-selective.<sup>96a,c;105</sup> For example, Chang *et al.*<sup>96c</sup> demonstrated that enyne **210** and olefin **211** may undergo CM to give enyne **212** as the product with excellent (*Z*)-selectivity (>25:1 *Z:E*; **Scheme 3.9a**). To perform CM reactions in the current study, the catalyst **214** was prepared by treatment of Grubbs' II **213** with an excess of 3-bromopyridine followed by trituration of the crude residue with pentane and filtration of the insoluble green solid, according to literature procedure<sup>104</sup> (**Scheme 3.9b**).

With the required catalyst in hand, the CM reaction between alkene ( $\pm$ )-**199** and enyne **200** was attempted in an effort to synthesise the product ( $\pm$ )-**194** (**Table 3.2**, Entries 1 to 4). Disappointingly, regardless of catalyst loading (5 to 20 mol%), solvent (DCM, toluene, or no solvent), or temperature (room temperature, or 45 to 55 °C), only unreacted starting material was observed in the crude <sup>1</sup>H NMR spectrum, or isolated after flash chromatography. A change of catalyst to the standard, unmodified Grubbs' II **213** was also unsuccessful under our conditions, and led to no reaction in both cases (**Table 3.2**, Entries 5 and 6), although in the case of Entry 5, this may have been a consequence of substrate **200** evaporation.

In order to investigate the compatibility of the homoallylic alcohol ( $\pm$ )-**199** in CM, reaction of the olefin with 1-hexene<sup>106</sup> in the presence of the modified Grubbs' II catalyst **214** (5 mol%) was attempted. This reaction led to no conversion to the CM

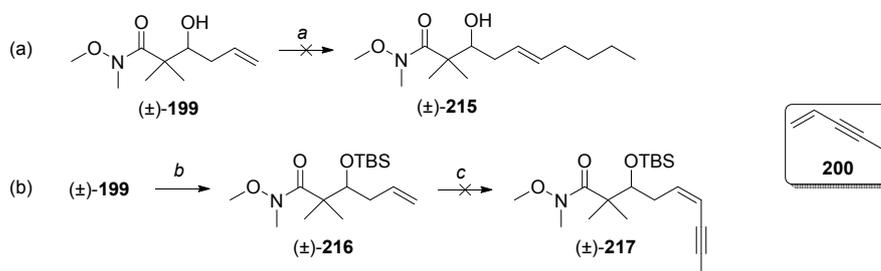
**Table 3.2** Attempted CM between olefin ( $\pm$ )-**199** and enyne **200**


Entry	Eq ( $\pm$ )- <b>199</b>	Eq <b>200</b>	mol% <b>214</b>	Solvent	Temp (°C)	Time (h)	Yield (%) <sup>a</sup>
1	1	6	20	DCM	45	72	0
2	1	6	20	PhMe	25	60	(0)
3	1	6	10	PhMe	55	50	(0)
4	1	3	5	None	25	48	0
5 <sup>b</sup>	2.8	1	28	PhMe	70	18	0
6 <sup>b</sup>	1	3	10	DCM	45	20	(0)

<sup>a</sup>Isolated yield unless otherwise stated; <sup>b</sup>Yields determined by <sup>1</sup>H NMR of the crude material are indicated in parentheses; <sup>b</sup>Grubbs' II **213** as opposed to the modified Grubbs' catalyst **214** was used in these reactions.

product ( $\pm$ )-**215** as indicated by <sup>1</sup>H NMR of the crude material (**Scheme 3.10a**). CM was then attempted using the TBS-protected homoallylic alcohol ( $\pm$ )-**216**, which was synthesised by reaction of the alcohol ( $\pm$ )-**199** with TBSOTf in the presence of 2,6-lutidine in DCM at 0 °C (**Scheme 3.10b**). Unfortunately, this olefin ( $\pm$ )-**216** also failed to react with the enyne **200** under our CM conditions. On the basis of these results, it was concluded that the synthesis of the key intermediate ( $\pm$ )-**194** would not be possible using a CM approach. This is because both the homoallylic alcohol ( $\pm$ )-**199**, and its TBS-protected derivative ( $\pm$ )-**216**, failed to react with either the enyne **200** or a standard, unfunctionalised olefin; and therefore these substrates were deemed incompatible in the reaction.

The failure of the CM reaction between the enyne **200** and either the homoallylic alcohol ( $\pm$ )-**199** or its TBS-protected derivative ( $\pm$ )-**216** in the current study is



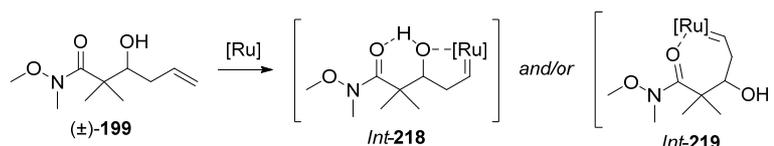
**Reagents and conditions:** (a) 1-Hexene (3.0 eq), **214** (5 mol%), DCM, 45 °C, 24 h, 0%; (b) TBSOTf (1.5 eq), 2,6-lutidine (2.0 eq), DCM, 0 °C, 2 h, 97%; (c) Enyne **200** (3.0 eq), **214** (5 mol%), DCM, rt, 24 h, 0%.

**Scheme 3.10** Attempted cross-metathesis of (a) the homoallylic alcohol ( $\pm$ )-**199** with 1-hexene; (b) the TBS-protected homoallylic alcohol ( $\pm$ )-**216** with the enyne **200**.

perhaps unsurprising. Grubbs previously outlined an empirical model for selectivity<sup>107</sup> in olefin CM on the basis of rate of homodimerisation, which aids in predicting the probability of any two substrates to undergo CM and whether or not the CM reaction is likely to be efficient. Olefins were either classified as Type 1 (fast homodimerisation), Type 2 (slow homodimerisation), Type 3 (no homodimerisation) or Type 4 (no reaction under CM). Type 1 olefins are the most reactive and selective in CM with other classes of olefins because they are the least sterically hindered, are the most electron rich, and their homodimers are readily consumed. By contrast, Type 2 to Type 4 olefins are more sterically hindered, less electron rich, and their homodimers are not as readily consumed and are thus (progressively) poorer CM substrates. Olefins of the same type were less likely to undergo selective CM.<sup>107</sup>

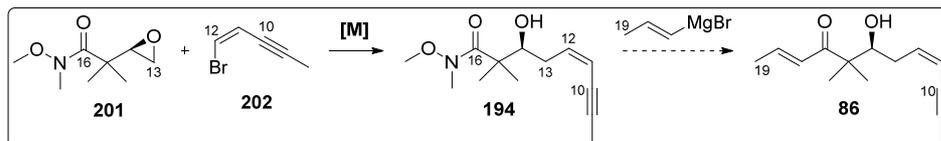
Grubbs' study<sup>107</sup> would go some way to explaining the difficulty in achieving CM with enyne **200** and homoallylic alcohol ( $\pm$ )-**199**. In previous enyne–olefin CM, the enynes (unclassified by Grubbs, but likely to be Type 2) were most often reacted with a Type 1 olefin (such as allyl silane **211**) and therefore the success of the reaction is greatly increased. By contrast, both enyne **200** and olefins [( $\pm$ )-] **199/216** would be predicted to be Type 2 olefins, and therefore do not readily undergo CM.

It is also plausible that the failure of the reaction may have been caused by catalyst deactivation. Although both the homoallylic alcohol and Weinreb amide moieties have been shown to be compatible functionalities in CM,<sup>108</sup> it has been shown that, if chelation is particularly stable, for example through formation of a 5- to 7-membered ring chelate *Int-218* or *Int-219* [which is plausible with our substrate ( $\pm$ )-**199**; **Scheme 3.11**], successful metathesis may be inhibited.<sup>109</sup> Such a process may be overcome through use of additives such as  $\text{Ti}(\text{O}^i\text{Pr})_4$ ,<sup>109</sup> which compete with the metathesis catalyst for heteroatom binding,<sup>109</sup> but unfortunately this was not investigated, and instead the CM approach was abandoned in favour of **Approach B**: epoxide ring-opening.



**Scheme 3.11** Formation of 5- and 7-membered-ring O→Ru chelates *Int-218/Int-219* on attempted olefin CM using the Weinreb amide-containing homoallylic alcohol ( $\pm$ )-**199**.

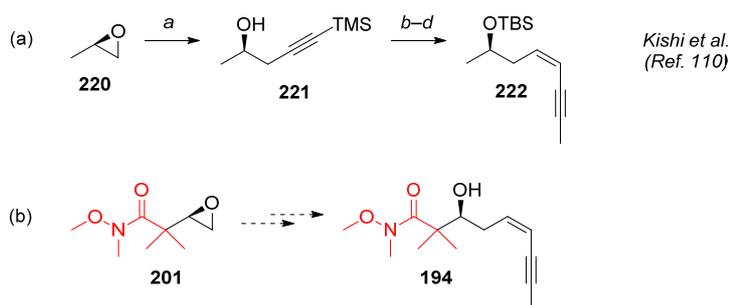
## 3.3 Approach B: Epoxide Ring-Opening



**Scheme 3.12** Epoxide ring-opening approach towards the synthesis of the C(10)–C(19) fragment **86**.

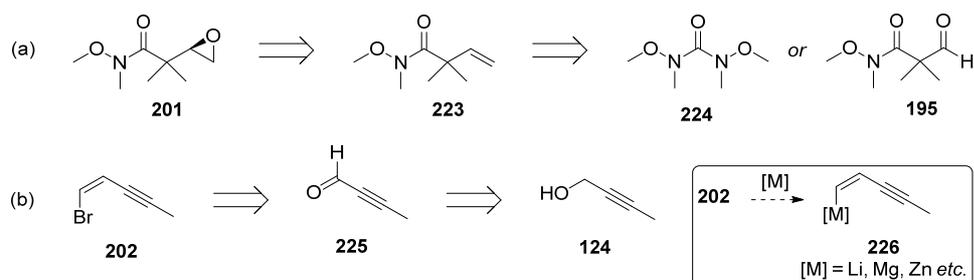
The failure of the cross-metathesis approach necessitated the investigation of an alternative method (**Scheme 3.12**) for generating the key Weinreb amide **194**. Inspired by the work of Kishi,<sup>110</sup> who generated a TBS-protected homo-1,3-enynyl alcohol **222** from (*S*)-propylene oxide **220** (**Scheme 3.13a**), we decided to explore an epoxide ring-opening approach towards our more elaborate fragment **194** (**Scheme 3.13b**). However, instead of the stepwise approach adopted by Kishi,<sup>110</sup> we embarked upon a direct route towards the generation of the enyne **194**.

Our approach would require the synthesis of the C(13)–C(16) epoxide **201** and the C(10)–C(12) vinyl bromide **202** (**Scheme 3.12**). It was anticipated that epoxide **201** could be synthesised from the alkene **223**, which in turn could be prepared from the urea **224**, or the previously synthesised aldehyde **195** (**Scheme 3.14a**). Vinyl bromide **202** was to be synthesised using a variant of the Wittig olefination from the aldehyde **225**, which would be generated from the commercially available alcohol 2-butyn-1-ol **124** (**Scheme 3.14b**). Epoxide ring-opening using a metallated derivative **226** of bromide **202**,<sup>111</sup> it was predicted, would give the C(10)–C(16)



**Reagents and conditions:** (a) (i) TMS-ethyne, <sup>t</sup>BuLi, Et<sub>2</sub>O, –78 °C, 40 min; (ii) **220**, 10 min; (iii) BF<sub>3</sub>·OEt<sub>2</sub>, –78 °C, 1 h; (b) TBSCl, Im, DMF, rt, 48 h; (c) (i) NIS, AgNO<sub>3</sub>, DMF, rt, 5 h; (ii) Cy<sub>2</sub>BH, THF, 0 °C, 3 h; (iii) AcOH, 5 °C, 12 h, 95% (4 steps); (d) Propyne, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, Et<sub>2</sub>NH, rt, 3 h, 96%.

**Scheme 3.13** (a) Synthesis of an enantiopure homo-1,3-enynyl alcohol from an epoxide;<sup>110</sup> and (b) application of this approach towards the synthesis of C(10)–C(16) fragment **194**.



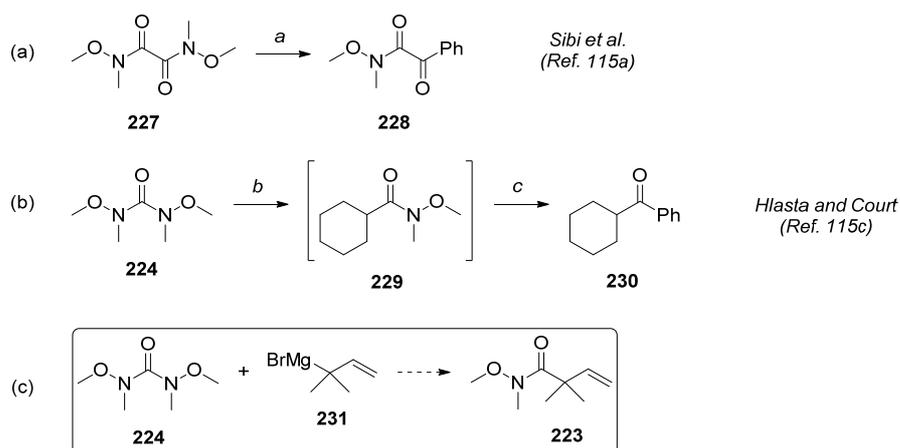
**Scheme 3.14** Retrosynthesis of (a) epoxide **201**; and (b) vinyl bromide **202**.

Weinreb amide **194**, which should give access to the desired C(10)–C(19) fragment **86** after Grignard addition. Stereoselective generation of the epoxide **201** would be achieved through the use of either an asymmetric epoxidation<sup>112</sup> or through hydrolytic kinetic resolution of the racemic epoxide.<sup>113</sup>

### 3.3.1 Synthesis of the C(13)–C(16) Epoxide [(±)-201]

Our preferred route to the alkene **223** relied upon a single-step synthesis *via* reaction of a Grignard reagent with a Weinreb amide **224**. The synthetic importance of Weinreb amides in carbon–carbon bond formation is well documented<sup>114</sup> and indeed our overall synthetic plan relies upon the use of the functionality for the preparation of the C(10)–C(19) fragment **86**. The Weinreb ketone synthesis has also been performed using amide substrates bearing more than one hydroxamic acid moiety<sup>115</sup> to give substituted, mono-Weinreb amides as the products; or indeed to give hetero-disubstituted ketones by sequential, two-step alkyl- and/or arylation. For example, the diamide **227**<sup>115a</sup> and the urea **224**<sup>115b,c</sup> may be transformed to alkyl- or arylated carbonyl compounds **228/230** through (sequential) addition of organomagnesium or -lithium reagents (**Scheme 3.15a** and **b**). Accordingly, we aimed to generate the required Weinreb amide **223** by reaction of urea **224** with an appropriate Grignard reagent **231** (**Scheme 3.15c**).

Urea **224** was synthesised according to literature procedure<sup>116</sup> by condensation of CDI and *N,O*-dimethylhydroxylamine hydrochloride in the presence of pyridine in DCM at reflux (**Table 3.3**). In the absence of the required Grignard reagent **231** (the bromide precursor of which is not commercially available and would require preparation), to establish plausible addition conditions, we initially investigated the



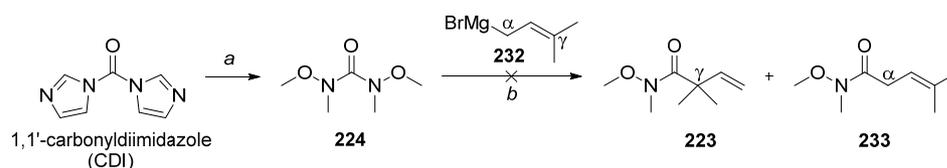
**Reagents and conditions:** (a) PhMgBr (1.5 eq), THF, 0 °C, 1 h, 95%; (b) CyMgCl (1.0 eq), THF, -78 to 0 °C, 3 h; (c) PhLi (1.1 eq), 0 °C to rt, 1.5 h, 41% (2 steps, one-pot).

**Scheme 3.15** (a) and (b) use of bis-Weinreb amides as carbonyl synthons;<sup>115a,c</sup> (c) proposed route to the alkenyl Weinreb amide **223** from urea **224**.

use of prenylmagnesium bromide **232** as a model substrate owing to its isomerism with Grignard reagent **231**. Furthermore, this reagent often reacts in Grignard reactions to give the  $\gamma$ -addition product (*cf.* **223**),<sup>117</sup> as opposed to the  $\alpha$ -adduct (*cf.* **233**), and so we were also conscious of a potentially desirable serendipitous discovery.

Unfortunately, reaction of the urea **224** with freshly prepared prenylmagnesium

**Table 3.3** Attempted preparation of alkene **223** via a Grignard reaction with urea **224**



**Reagents and conditions:** (a) HNMe(OMe)·HCl (2.5 eq), Py (3.0 eq), DCM, 45 °C, 18 h, 91%; (b) **224**, **232**, Et<sub>2</sub>O/THF (1:1); see Table for additional conditions.

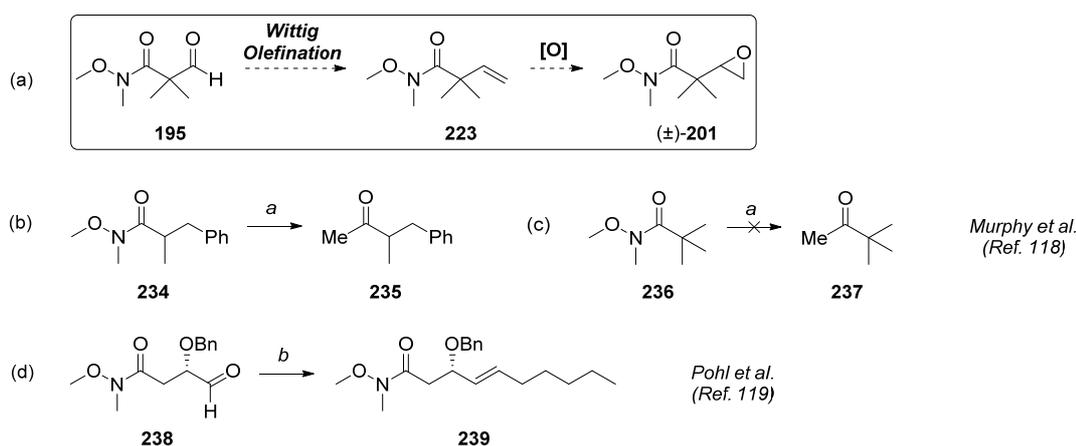
Entry	Eq 232	Temp (°C)	Time (h)	Conv. <b>223</b> (%) <sup>a</sup>	Conv. <b>233</b> (%) <sup>a</sup>
1	1.5	0	2	0	0
2	2.0	0	2	0	Trace
3	3.0	0	2	0	Trace
4	1.5	0 to 25	2	0	Trace
5	1.5	35	2	0	0
6	4.0	-78	3	0	Trace
7	2.0	-78 to 25	5	0	Trace

<sup>a</sup>As determined by <sup>1</sup>H NMR of crude material.

bromide **232** across a number of conditions of temperature and Grignard reagent stoichiometry (**Table 3.3**) was unsuccessful, and resulted in only trace quantities of an alkenyl product (assumed to be  $\alpha$ -adduct **233**) or unreacted starting material in all cases. Given that the bromide required to react with the urea **224** is more sterically hindered and therefore likely to be further inert, no further work was done towards this approach. Instead, an overall three-step route to the alkene **223** from the previously synthesised aldehyde **195** was investigated.

A Wittig olefination to generate the alkene **223** followed by an epoxidation to generate the racemic epoxide ( $\pm$ )-**201** was the first route to be examined that commenced from aldehyde **195** (**Scheme 3.16a**). Although Weinreb amides are known to react with Wittig reagents,<sup>118</sup> reaction times for the transformations according to the described protocol are long (overnight, *e.g.* **Scheme 3.16b**) and pivaloyl Weinreb amide **236** – which bears trisubstitution at the  $\alpha$ -carbon and therefore has obvious structural similarities to our Weinreb amide **195** – failed to react<sup>118</sup> (**Scheme 3.16c**). Therefore it was thought that the comparably shorter reaction times for rudimentary aldehyde-to-alkene Wittig reactions ( $\sim$ 1 h) would allow the reaction to take place selectively at the aldehyde, and indeed such reactions are preceded in the literature (*e.g.* **Scheme 3.16d**).<sup>119</sup>

To synthesise alkene **223**, aldehyde **195** was added to a stirred solution of the

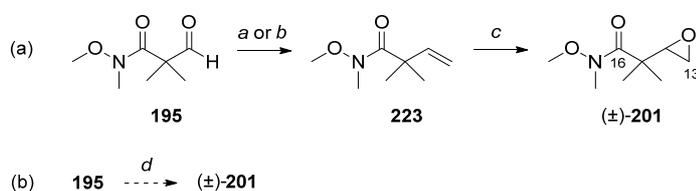


**Reagents and conditions:** (a)  $[\text{Ph}_3\text{PMe}]^+\text{Br}^-$ ,  $n\text{BuLi}$ ,  $-78$  to rt, 20 h, **235** 75%, **237** 0%; (b)  $[\text{Ph}_3\text{P}^n\text{Hex}]^+\text{I}^-$ , KHMDS,  $-78$  °C, 1 h, 86%.

**Scheme 3.16** (a) Proposed synthesis of epoxide ( $\pm$ )-**201** from Weinreb amide aldehyde **195**; Wittig reactions to generate (b) and (c) ketones **235/237** from Weinreb amides **234/236**,<sup>118</sup> and (d) an olefin **239** from an aldehyde **238** in a compound containing a Weinreb amide.<sup>119</sup>

methyltriphenylphosphonium ylide – prepared by the addition of <sup>n</sup>BuLi to methyltriphenylphosphonium iodide and heating to reflux in THF for 15 minutes<sup>120</sup> – and reactions were monitored by TLC (**Scheme 3.17a**). Stirring for 30 min (3 eq of the phosphonium ylide) or 3 h (1.1 eq) at 0 °C indicated completion, but gave the desired product **223** in only 19 and 37% yields respectively. In an attempt to improve the yield, NaHMDS was used as the base, with ylide preparation and reaction at 0 °C, but unfortunately, after 2 h of reaction, these conditions also gave a low yield (37%) of alkene **223**. Further efforts to optimise the yield were at this stage not performed, and synthesis of the epoxide (±)-**201** from olefin **223** was investigated.

In contrast to olefination, epoxidation was achieved straightforwardly using a standard oxone-mediated protocol,<sup>121</sup> which gave a 61% yield of the product and concluded the synthesis of the C(13)–C(16) epoxide (±)-**201** (**Scheme 3.17a**). It is worth noting that a direct approach to the epoxide from aldehyde **195** *via* the Corey–Chaykovski epoxidation<sup>122</sup> was also investigated. Although the reaction of aldehyde with the trimethylsulfonium ylide seemed promising because a quantitative conversion to the epoxide (±)-**201** was observed (<sup>1</sup>H NMR) under our initial screening conditions (**Scheme 3.17b**), attempts to obtain the product (±)-**201** on a preparative scale (~1 g) led to its decomposition on chromatographic purification. It was initially thought that this could be attributed to the lower quality of silica gel<sup>123</sup> used in purification when compared to that used in the oxone-mediated epoxidation described above. However, attempts to repeat the procedure using higher-quality silica gel at the purification stage were unsuccessful, and it was later found that the problem overall was probably an issue of reproducibility, because attempts to obtain

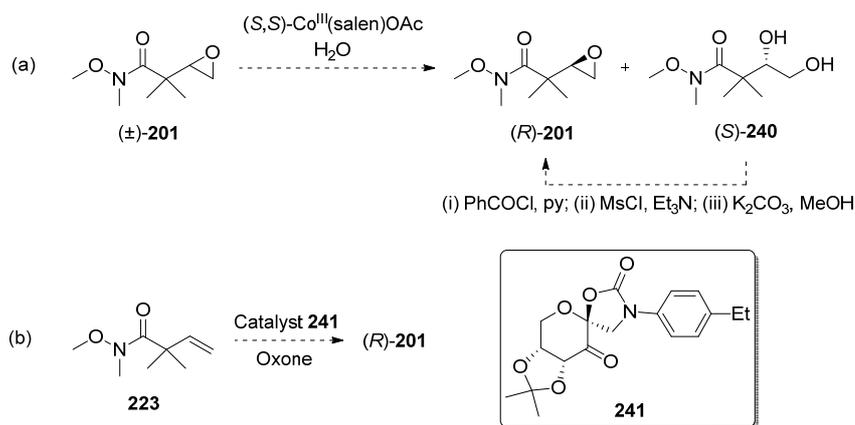


**Reagents and conditions:** (a) (i) [Ph<sub>3</sub>PMe]<sup>+</sup>I<sup>-</sup> (1.1 eq), <sup>n</sup>BuLi (1.1 eq), THF, 0 °C to reflux, 15 min; (ii) **195**, 0 °C, 3 h, 37%; *or* (b) (i) [Ph<sub>3</sub>PMe]<sup>+</sup>I<sup>-</sup> (3.1 eq), NaHMDS (3.0 eq), THF, 0 °C, 30 min; (ii) **195**, 2 h, 37%; (c) Oxone (6.0 eq), NaHCO<sub>3</sub> (14 eq), EDTA (0.9 mol%), acetone/H<sub>2</sub>O (1:1), 0 °C to rt, 6 h, 61%. (d) (i) [Me<sub>3</sub>S]<sup>+</sup>I<sup>-</sup> (1.5 eq), <sup>n</sup>BuLi (1.4 eq), THF, 0 °C, 15 min; (ii) **195**, 0 °C to rt, 2 h, quant conv.

**Scheme 3.17** Synthesis of the C(13)–C(16) epoxide (±)-**201** from aldehyde **195** *via* (a) a two-stage Wittig olefination/oxidation sequence; and (b) a Corey–Chaykovski epoxidation.

even a crude product in high yield were unsuccessful and typically gave epoxide/aldehyde mixtures.

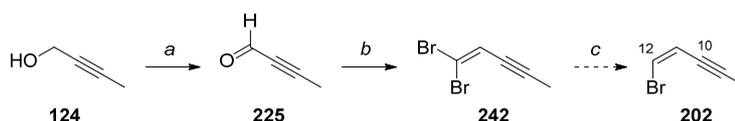
The route to the racemic epoxide ( $\pm$ )-**201** *via* the alkene **223** therefore remains the most promising, and although this would require later optimisation at the key olefination step, we were satisfied that this could be returned to later once a reliable route to the vinyl bromide **202** had been established. In terms of an asymmetric synthesis, this would be achieved *via* a Jacobsen hydrolytic kinetic resolution<sup>113</sup> of racemic ( $\pm$ )-**201**, which would afford the epoxide (*R*)-**201** and a diol (*S*)-**240** in the opposite sense; the latter of which could be later transformed to the desired enantiomer by conversion of the secondary (stereogenic) hydroxyl functionality to a leaving group (**Scheme 3.18a**).<sup>121</sup> Alternatively, a Shi epoxidation<sup>124</sup> – which uses a sugar-derived chiral ketone (*e.g.* **241**) in conjunction with oxone to convert olefins to epoxides – may permit generation of the epoxide (*R*)-**201** from alkene **223** enantioselectively and thus without the requirement for hydrolytic kinetic resolution (**Scheme 3.18b**).



**Scheme 3.18** Proposed generation of the enantiopure epoxide (*S*)-**201** from (a) the racemate ( $\pm$ )-**201** using hydrolytic kinetic resolution; and (b) a Shi epoxidation of alkene **223**.

### 3.3.2 Synthesis of the C(10)–C(12) Vinyl Bromide (**202**)

Towards the synthesis of the C(10)–C(12) vinyl bromide **202**, we hoped to take advantage of Uenishi's protocol<sup>125a</sup> for the synthesis of (*Z*)-1,3-haloenynes, which involves Ramirez–Corey–Fuchs olefination<sup>126</sup> to form the vicinal dihalide from an aldehyde, followed by regioselective palladium-catalysed reductive dehalogenation. This protocol was successfully exploited by Buchwald<sup>125b</sup> in the synthesis of



**Reagents and conditions:** (a)  $\text{MnO}_2$  (10 eq),  $\text{Et}_2\text{O}$ , 0 °C to rt, 18 h, 65%; (b) (i)  $\text{CBr}_4$  (2.0 eq),  $\text{PPh}_3$  (2.0 eq),  $\text{Zn}$  (2.0 eq),  $\text{DCM}$ , 0 °C to rt, 30 min; (ii) **225**, 0 °C to rt, 18 h, 85%; (c)  $^t\text{Bu}_3\text{SnH}$  (1.05 eq),  $\text{Pd}(\text{PPh}_3)_4$  (5 mol%),  $\text{DCM}$ , rt, 2 h, quant conv.

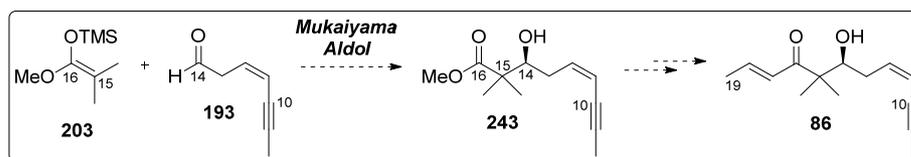
**Scheme 3.19** Synthesis of the (*Z*)-vinyl bromide **202**.

analogous haloenynes and so we were hopeful that these conditions could be applied in our own efforts towards the (*Z*)-1,3-bromoene structural motif. Thus, in our attempts to access enyne **202** (Scheme 3.19), 2-but-yn-1-ol **124** was oxidised ( $\text{MnO}_2$ ) to the corresponding aldehyde **225** in 65% yield,<sup>127</sup> and converted to the vicinal 1,1-dibromo-1,3-enyne **242** in 85% yield according to the Ramirez–Corey–Fuchs protocol.<sup>125b,126</sup> The final reductive dehalogenation step was then attempted through reaction of **242** with  $^t\text{Bu}_3\text{SnH}$  (1.05 to 1.1 eq) catalysed by  $\text{Pd}(\text{PPh}_3)_4$  (5 mol%) in  $\text{DCM}$ . Over a number of runs, consumption of starting material was complete after 1 to 2 h at room temperature, and  $^1\text{H}$  NMR of the crude material showed only the presence of the (*Z*)-isomer of bromoalkene **202**, as indicated by the olefinic coupling constant ( $J = 7.4$  Hz) present between the alkene protons in the  $^1\text{H}$  NMR spectrum.

Unfortunately, bromide **202** was too volatile to isolate in useful quantities by chromatography and was accompanied by residual stannane-byproduct contaminants. Attempts to eliminate the contaminants by stirring the crude product mixture in aqueous  $\text{KF}$ ,<sup>128</sup> resulted in product decomposition; while multiple chromatographic separations did facilitate byproduct removal, but removal of the solvent after each purification resulted in concomitant loss of the product through evaporation. Due to a lack of remaining precursor material **242**, distillation, or alternative routes towards the synthesis of the C(10)–C(12) bromoene **202** were not investigated, and this approach was abandoned to focus on **Approach C**: the Mukaiyama aldol reaction.

### 3.4 Approach C: Mukaiyama Aldol Reaction

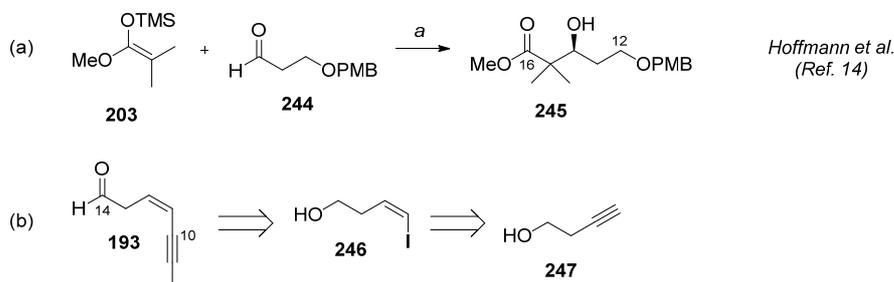
The Mukaiyama aldol reaction<sup>129</sup> is the Lewis acid-catalysed synthesis of  $\beta$ -hydroxyesters through reaction of a silyl enol ether with an aldehyde. Various asymmetric variations of this reaction exist which offer excellent yields and



**Scheme 3.20** Mukaiyama aldol approach towards the synthesis of the C(10)–C(19) fragment **86**.

enantioselectivity;<sup>129</sup> and it has been used extensively in natural product synthesis,<sup>127d</sup> including most synthetic efforts towards the disorazoles.<sup>14,17,19,23–25,29,33</sup> Perhaps most notable in the context of the current study is the reaction performed by Hoffmann<sup>14</sup> to generate the  $\beta$ -hydroxyester **245** (**Scheme 3.21a**) according to the Kiyooka protocol,<sup>130</sup> which involved reaction of the silyl ketene acetal **203** with the aldehyde **244** in the presence of an enantiopure, amino acid-derived organoborane promoter; and gave the product **245** in excellent yield and enantioselectivity. On the basis of Hoffmann's success on using **203** to access the required  $\beta$ -hydroxyketone scaffold directly, and because the use of the Mukaiyama reaction has proven a highly effective means of selectively imparting asymmetry in intermediates during other syntheses of the disorazoles, we felt it would be prudent to investigate this methodology in our own efforts. However, we preferred, in the first instance, to explore a more direct synthesis towards the C(10)–C(16) scaffold, as shown in **Scheme 3.20**.

Synthesis of the C(10)–C(16)  $\beta$ -hydroxyester **243** *via* the Mukaiyama protocol requires the synthesis of the C(10)–C(14) aldehyde **193**, which can be prepared from 3-butyn-1-ol **247**<sup>90</sup> *via* the vinyl iodide **246** (**Scheme 3.21b**). Conscious of the knowledge that aldehyde **193** is highly volatile,<sup>90</sup> the aldehyde derivative of vinyl iodide **246** was also considered for investigation, as it was predicted to be easier to



**Reagents and conditions:** (a) (i)  $\text{BH}_3 \cdot \text{THF}$ , *N*-Ts-*D*-Valine, DCM,  $-78^\circ\text{C}$ ; (ii)  $\text{K}_2\text{CO}_3$ , MeOH, 96% yield, 88% ee.

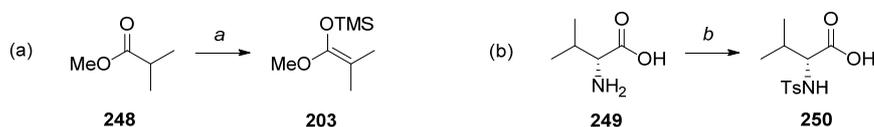
**Scheme 3.21** (a) Hoffmann's use of the Mukaiyama aldol reaction to generate the C(12)–C(16)  $\beta$ -hydroxyester **245**;<sup>14</sup> (b) retrosynthesis of the C(10)–C(14) aldehyde **193**.

handle than the enyne **193** owing to its higher molecular weight. In addition to the aldehyde **193**, the silyl ketene acetal **203** and a source of asymmetry were also required, and the synthesis of these components is discussed in the following section.

### 3.4.1 Synthesis of the Silyl Ketene Acetal (**203**) and *N*-Ts-*D*-Valine (**250**)

Silyl ketene acetal **203** was prepared in 72% yield on a 4 gram scale from methyl isobutyrate **248** by reaction of the (enolisable) ester with LDA and subsequent trapping of the *in situ* generated lithium enolate with freshly distilled TMSCl<sup>131</sup> (Scheme 3.22a). It is worth noting that filtration and distillation was not always completely effective in removing residual solids, and distilled samples occasionally appeared cloudy owing to the presence of the byproduct LiCl. However, an additional distillation step, or – more straightforwardly – filtration of the product through cotton wool or an HPLC filter immediately prior to use, was sufficient to fully remove the solid and give clear samples.

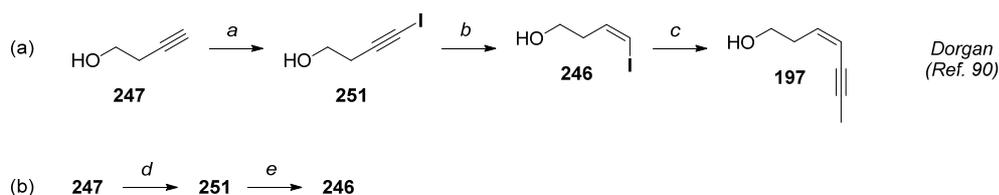
The organoborane Lewis acidic source of asymmetry in Mukaiyama aldol reaction (according to the Kiyooka protocol) is derived by reaction of an *N*-protected amino acid with BH<sub>3</sub>•THF,<sup>130</sup> with the *N*-tosyl derivative of *D*-valine perhaps being the most common ligand for this purpose, and certainly is so amongst the synthetic efforts towards the disorazoles.<sup>14,17,19,23–25,29,33</sup> The most effective means of generating *N*-Ts-*D*-valine **250** involved the reaction of equimolar quantities of *D*-valine **249** and TsCl at 70 °C in aqueous K<sub>2</sub>CO<sub>3</sub>,<sup>132</sup> followed by slow cooling (~1 h) to 0 °C. Acidification of the mixture with concentrated (37%) HCl and filtration of precipitate gave *N*-Ts-*D*-valine **250** in good yield (75%) on a 30 gram scale, and concluded the synthesis of the reagents for the Mukaiyama aldol reaction.



**Reagents and conditions:** (a) (i) <sup>t</sup>BuLi (1.2 eq), <sup>i</sup>Pr<sub>2</sub>NH (1.3 eq), THF, 0 °C, 30 min; (ii) **248** (1.0 eq), 0 °C, 1 h; (iii) TMSCl (2.0 eq), 0 °C, 1 h, 72%; (b) (i) TsCl (1.0 eq), K<sub>2</sub>CO<sub>3</sub> (1.5 eq), H<sub>2</sub>O, rt to 70 °C, 30 min; (ii) 70 °C, 1 h; (iii) 70 to 0 °C, 1 h, 75%.

**Scheme 3.22** Synthesis of (a) the silyl ketene acetal **203**; and (b) *N*-Ts-*D*-valine **250**.

## 3.4.2 Synthesis of the C(10)–C(14) Alcohol (197)



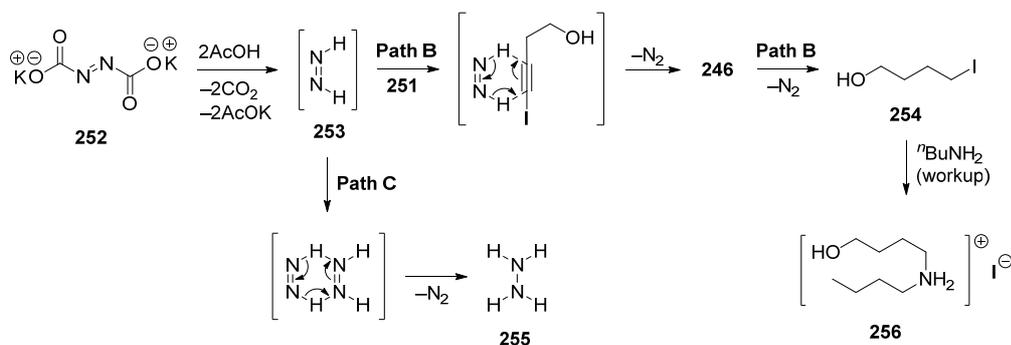
**Reagents and conditions:** (a)  $I_2$  (1.3 eq), KOH (2.0 eq),  $H_2O$ , 0 °C to rt, 3 h, 52%; (b) PADA (6.0 eq), AcOH (6.0 eq), Py (6.0 eq), MeOH, rt, 16 h; (ii)  $nBuNH_2$  (1.0 eq), rt, 6 h, 83%; (c) (i)  $ZnCl_2$  (5.0 eq), 1-propynylmagnesium bromide (5.0 eq), THF, 0 °C, 30 min; (ii) **246**,  $PdCl_2(PPh_3)_2$  (10 mol%), 0 °C to rt, 16 h, 81%; (d) (i)  $I_2$  (1.0 eq), morpholine (3.0 eq), PhMe, 45 °C, 30 min; (ii) **247**, 45 °C, 24 h, 97%; (e) PADA (3.0 eq), AcOH (6.3 eq), Py (6.0 eq), MeOH, rt, 24 h; (ii)  $nBuNH_2$  (10 eq), rt, 7 h, 69%.

**Scheme 3.23** (a) Dorgan's synthesis of enyne **197**,<sup>90</sup> and (b) synthesis of vinyl iodide **246**.

The synthesis of both vinyl iodide **246** and enyne **197** have been achieved previously within the Hulme group<sup>90</sup> in moderate overall yield (43 and 35% respectively) using initial KOH-mediated iodination of 3-butyn-1-ol **247** and subsequent (*Z*)-selective reduction of the iodide **251** thus obtained with dipotassium azodicarboxylate (PADA);<sup>133</sup> with a Negishi coupling used to introduce the propyne moiety in the case of the enyne **197** (**Scheme 3.23a**). As such, this approach was used in the current study; however, in order to improve the overall yield, an alternative synthesis of iodide **251** was used, which was previously obtained in only moderate yield (52%).<sup>90</sup>

Isobe<sup>134</sup> reported a quantitative yield of the iodoacetylene **251** through reaction of 3-but-yn-1-ol **247** with the morpholine–iodine complex, and so **247** was added to a toluene solution of the pre-formed complex and the reaction was stirred overnight at 45 °C. As reported, this method led to the successful synthesis of iodoacetylene **251** in near-quantitative yield (97%; **Scheme 3.23b**). Subsequent reduction of the alkyne **251** with a threefold excess of the diazene progenitor PADA gave a 69% yield of the vinyl iodide **246** exclusively as its (*Z*)-stereoisomer (**Scheme 3.23b**)<sup>134</sup> and concluded the synthesis of one alcohol required for oxidation and aldolisation.

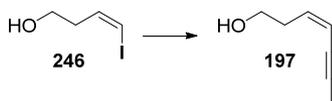
The mechanism of the reaction<sup>133</sup> (**Scheme 3.24**) involves a group transfer reaction during formal addition of  $H_2$  by diazene **253** (generated *in situ* from PADA **252**) and accounts for the observed (*Z*)-selectivity in the product vinyl iodide **246** while stirring of the crude product mixture in an excess (10 eq) of  $nBuNH_2$  removes any over-reduction species **254** (formed *via* a second reduction step, **Path B**) through salt **256** formation. Disproportionation of diazene **253** to form hydrazine **255**<sup>133</sup> (**Path C**;



**Scheme 3.24** Mechanism of the diazene reduction of alkyne **251**.<sup>133</sup>

**Scheme 3.24**) necessitates an excess of PADA (and therefore this over-reduction pathway cannot be easily avoided), but the complete consumption of the starting material and high yield confirmed that close to an optimal quantity was used.

Enyne **197** was prepared in 77% yield by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-catalysed (10 mol%) Negishi coupling of the vinyl iodide **246** with 1-propynylzinc chloride, generated *in situ* by transmetalation of the corresponding organomagnesium reagent with ZnCl<sub>2</sub> (**Scheme 3.25**), according to the procedure reported by Dorgan.<sup>90</sup> It is worth noting that, despite the high yield, two chromatographic separations (or distillation) were required to satisfactorily remove residual palladium-black from the product oil for use in the next step. Nevertheless, the reaction provided sufficient material (*ca.* 4 g) for the aldol reaction and an encouraging overall yield (52%) for the first three steps.



**Reagents and conditions:** (i) ZnCl<sub>2</sub> (3.5 eq), 1-propynylmagnesium bromide (3.0 eq), THF, 0 °C, 30 min; (ii) **246**, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (10 mol%), 0 °C to rt, 24 h, 77%.

**Scheme 3.25** Negishi coupling of vinyl iodide **246** to generate enyne **195**.

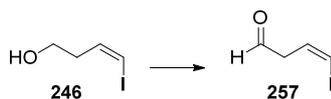
### 3.4.3 The Mukaiyama Aldol Reaction: C(11)–C(14) Vinyl iodide (257)

The remaining step required to perform the aldol reactions involved oxidation of the alcohol **197** and **246** to their corresponding aldehydes. As the homoenynyl aldehyde **193** was previously found to be too volatile and prone to decomposition for straightforward isolation, a two-step reaction which required minimal purification and solvent removal was foreseen. On the other hand, in the case of iodide **257**, which had not been synthesised previously, we believed that isolation would be

simplified owing to the likelihood of a reduced volatility because of the presence of the (high molecular weight) iodine atom in the structure. Although using this route would result in a loss of convergence in the synthetic pathway, it was believed that it would provide suitable contingency should difficulties in substrate handling arise upon oxidation of alcohol **197**. Since Dess–Martin periodinane had been applied successfully in the synthesis of both homoenynyl aldehyde **193**<sup>90</sup> and an analogous (*Z*)-vinyl silane<sup>135</sup> in the literature, this was used as a starting point for oxidation of both substrates.

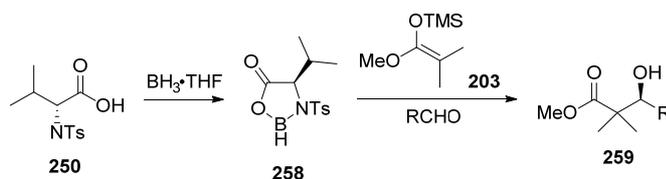
Dess–Martin periodinane and NaHCO<sub>3</sub> were added to a solution of alcohol **246** in DCM and stirred at ambient temperature. After aqueous work-up, an orange-yellow oil was obtained (**Scheme 3.26**). Unfortunately, as indicated by gradual violet colouration, this oil began decomposing both during workup and in air almost immediately (<30 min) which precluded a full spectroscopic analysis of the resulting compound. However, the crude <sup>1</sup>H NMR spectrum of **257** – although containing residual Dess–Martin periodinane and other minor peaks probably associated with decomposition – showed the presence of a major peak in the aldehyde region ( $\delta = 9.77$  ppm) with accompanying olefinic ( $\delta = 6.62$  and  $6.55$  ppm) and methylene ( $\delta = 3.38$  ppm) peaks and therefore we were satisfied that oxidation was successful. Furthermore, significant peaks indicative of olefin migration were not apparent, and therefore we were convinced that this compound could be of use in the Mukaiyama reaction. However, given that rapid decomposition could be problematic, it was obvious that this compound would have to be used immediately.

The standard Mukaiyama aldol reaction under Kiyooka's conditions<sup>130</sup> involves the initial generation of an oxazaborolidine **258** from a *N*-Ts-*D*-valine **250**, followed by either cooling of the resulting solution and addition of the aldehyde and silyl ketene acetal, or by addition of the oxazaborolidine solution to a cooled solution of the aldehyde (**Scheme 3.27**). Fortunately, DCM is often the solvent of choice in such



**Reagents and conditions:** (a) Dess–Martin periodinane (1.2 eq), NaHCO<sub>3</sub> (2.0 eq), DCM, rt, 75 min, quant conv.

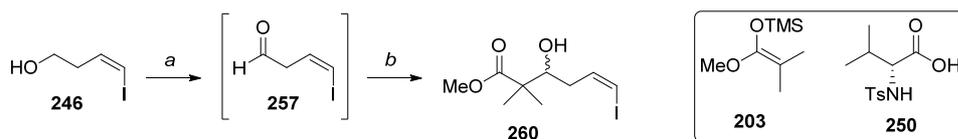
**Scheme 3.26** Oxidation of alcohol **246** to aldehyde **257**.



**Scheme 3.27** General organoborane-mediated Kiyooka aldol reaction using *N*-Ts-*D*-valine **250** derived oxazaborolidine **258**.

reactions, and therefore addition of a DCM solution of the aldehyde **257** – which would simply be concentrated and used immediately after workup to minimise the timeframe for decomposition – would not affect the resulting reaction.

Thus, the oxidation procedure as above was repeated and the aqueous workup was performed. Concurrently, oxazaborolidine **258** was prepared by dropwise addition of a 1.0 M solution of  $\text{BH}_3 \cdot \text{THF}$  to *N*-Ts-*D*-valine **250** at room temperature and stirred for 30 min before cooling to  $-78\text{ }^\circ\text{C}$ . After addition of the crude aldehyde **257** and the silyl ketene acetal **203** and reaction for 4 h in the presence of the organoborane promoter, we were pleased to discover that this procedure gave a 37% yield of the desired product **260** (%*ee* not determined; **Scheme 3.28**). Although low yielding, the knowledge that the desired  $\beta$ -hydroxyester motif could be generated using this method was encouraging, and we were convinced that the relatively low yield could be ascribed to the instability of the aldehyde **257**. As such, and in the interests of convergency, we decided to abandon this approach in favour of using the enyne **193** as our aldehyde substrate.

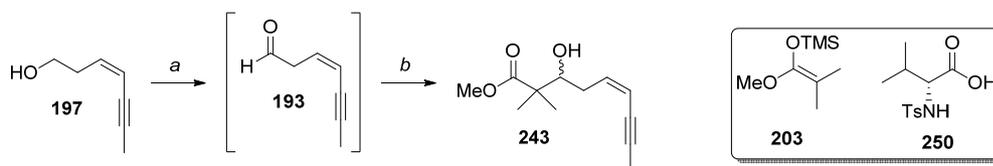


**Reagents and conditions:** (a) Conditions as **Scheme 3.26**; (b) (i) *N*-Ts-*D*-valine **250** (1.0 eq),  $\text{BH}_3 \cdot \text{THF}$  (1.0 eq), DCM, rt, 30 min; (ii) **257** (crude), **203** (1.5 eq)  $-78\text{ }^\circ\text{C}$ , 4 h, 37% (2 steps), %*ee* not determined.

**Scheme 3.28** Mukaiyama aldol reaction with the aldehyde derived from vinyl iodide **246**.

### 3.4.4 The Mukaiyama Aldol Reaction: C(10)–C(14) Enyne (**193**)

In a survey of a number of oxidation protocols, Dorgan<sup>90</sup> found that the Dess–Martin oxidation provided the best results for the oxidation of alcohol **197** to the corresponding aldehyde **193**. However, the product was found to be difficult to



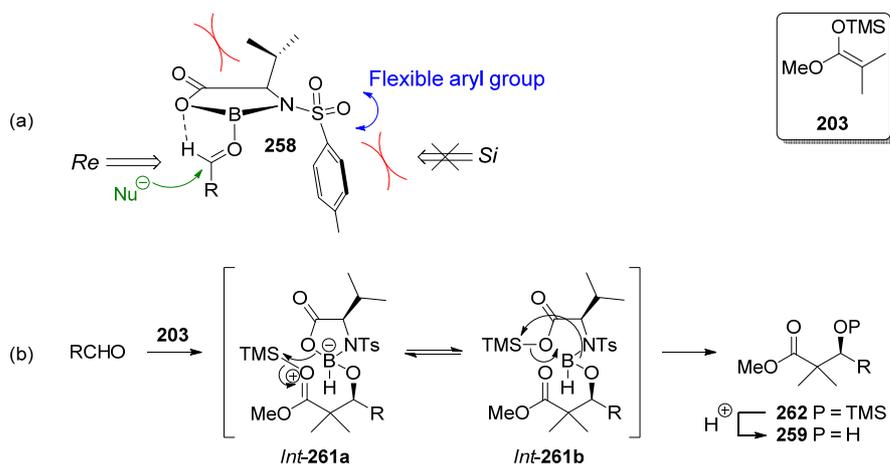
**Reagents and conditions:** (a) Dess–Martin periodinane (1.2 eq), NaHCO<sub>3</sub> (2.0 eq), DCM, rt, 1.5 h; (b) (i) *N*-Ts-*D*-valine **250** (1.2 eq), BH<sub>3</sub>•THF (1.2 eq), DCM, rt, 30 min; (ii) 4 Å MS, **193** (crude), **203** (1.5 eq), –78 °C, 6 h, 48% (2 steps), %*ee* not determined.

**Scheme 3.29** Synthesis of aldol product **243** from alcohol **197**.

handle as a consequence of its volatility, and so, in a similar protocol to that carried out with vinyl iodide **257**, use of the crude aldehyde **193** in the Mukaiyama aldol reaction was anticipated. Oxidation of the alcohol **197** was carried out using Dess–Martin periodinane in the presence of NaHCO<sub>3</sub> in DCM, followed by aqueous workup and careful concentration under reduced pressure to give a solution of the aldehyde **193** (**Scheme 3.29**). Addition of the crude product to the pre-prepared oxazaborolidinone in DCM, followed by the silyl ketene acetal **203** at –78 °C gave the  $\beta$ -hydroxyester **243** in moderate yield (48% over 2 steps; **Scheme 3.29**).

Mechanistically,<sup>129g,130a,b</sup> the Mukaiyama reaction according to the Kiyooka protocol involves association of the aldehyde with the organoborane catalyst *via* both an oxygen–boron bond, and a formyl hydrogen bond<sup>136</sup> between the formyl CH and the oxygen atom of the oxazaborolidinone ring (**Scheme 3.30a**).<sup>130a,b</sup> Nucleophilic attack of the silyl ketene acetal **203** on the carbonyl group leads to generation of the intermediates *Int*-**261**, intramolecular *O*→*O'* silyl migration forms the TMS derivative **262** and regenerates the catalyst; and silyl ether hydrolysis gives the product **259** (**Scheme 3.30b**). The stereochemical outcome of the reaction is controlled by the isopropyl and tosyl substituents. The rigid isopropyl group shields the upper face of the oxazaborolidinone ring, and therefore the steric bulk of the incoming aldehyde is orientated towards the opposite (lower) face, where the comparably flexible tosyl group is able to accommodate the aldehyde and its substituents.<sup>129g</sup> The aryl group obstructs the *si* face of the aldehyde, thus directing the incoming nucleophile to the *re* face and the product is generated enantioselectively (**Scheme 3.30a**).

Unfortunately efforts to replicate the results of the Mukaiyama protocol led to poor



**Scheme 3.30** (a) Selectivity in; and (b) mechanism of the organoborane-mediated Mukaiyama aldol reaction.<sup>129g,130a,b;136</sup>

product **243** yields, which were typically less than 20%; and this precluded further optimisation and measurement of the level of enantioselectivity of the reaction. The reasons for the poor, capricious product yields were unclear, but were initially suspected to be due to varying levels of water<sup>137</sup> within the reaction mixture from the aqueous workup performed after Dess–Martin oxidation of the alcohol **197**. Efforts to counteract this through purification of the aldehyde (by chromatography or distillation) were ultimately unsuccessful, because the aldehyde was highly volatile, unstable, and prone to olefin migration.

Aside from water-induced deactivation, it is possible that the borane did not fully react with the ligand **250**, or that reduction of the aldehyde by the borane–amino acid complex took place in competition with the desired aldol addition.<sup>138</sup> The basis for this conjecture centres around the discovery that, on some runs, varying quantities (up to 32%) of alcohol starting material **197** were recovered following chromatography. Although this could have been a consequence of incomplete oxidation, TLC monitoring of the oxidation typically indicated only trace levels of unreacted starting material after the 1.5 h timeframe, which would predict only trace recovery of the alcohol following the aldol reaction.

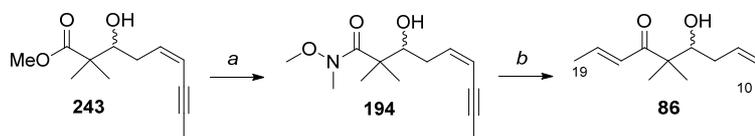
As a result of these difficulties, efforts towards the synthesis of the  $\beta$ -hydroxyketone **243** via the Mukaiyama aldol approach – or indeed by any convergent means – were abandoned in favour of investigating a linear approach. However, sufficient material was obtained from the Mukaiyama protocol for investigation into the final steps of

the fragment synthesis, which would at least confirm that a linear approach that targets the Weinreb amide **194** would be worthwhile.

### 3.5 Fragment Completion from the C(10)–C(16) $\beta$ -Hydroxyester (**243**)

The final steps required to access fragment **86** completion involved conversion of the C(10)–C(19) ester **243** to its Weinreb amide **194** derivative and subsequent Grignard addition with 1-propenylmagnesium bromide. Investigations into the synthesis of the Weinreb amide **194** commenced with the use of *N,O*-dimethylhydroxylamine hydrochloride in conjunction with  $\text{AlMe}_3$  as the coupling reagent for introducing the amide moiety,<sup>139</sup> but this reagent system gave no conversion ( $^1\text{H}$  NMR) to the desired product after 2 h at 0 °C. Fortunately, improved results were achieved through the use of  $^n\text{BuLi}$ : although reaction of the ester **243** with a modest excess (3 eq) of the lithium amide of Weinreb's amine gave a poor isolated yield (23%) on reaction at  $-78$  °C, use of a large excess (9 eq) at the same temperature gave the product Weinreb amide **194** in excellent yield (88%, **Scheme 3.31**).

Reaction of the Weinreb amide **194** with 20 equivalents of the Grignard reagent 1-propenylmagnesium bromide for 4.5 h at 0 °C led to only a 34% yield of the enone **86**, albeit cleanly and with recovery of unreacted starting material. Reducing the temperature to  $-10$  or  $-78$  °C was ineffectual, and led to negligible conversion (TLC) and isolation. However, treatment of the Weinreb amide **194** with 10 equivalents of the Grignard reagent under ultrasonic vibration<sup>140</sup> for 1.5 h led to a respectable 66% yield of the product, and concluded our first generation, convergent synthesis of the C(10)–C(19) fragment of disorazole C<sub>1</sub> **86** (**Scheme 3.31**).



**Reagents and conditions:** (a) (i)  $\text{HNMe(OMe)}\cdot\text{HCl}$  (9.0 eq),  $^n\text{BuLi}$  (18 eq), THF,  $-78$  °C to rt, 30 min; (ii) **243**,  $-78$  °C, 2.5 h, 88%; (b) 1-propenylmagnesium bromide (10 eq), THF, ultrasound, 1.5 h, 66%.

**Scheme 3.31** Completion of the C(10)–C(19)  $\beta$ -hydroxyketone fragment **86** of disorazole C<sub>1</sub> from  $\beta$ -hydroxyester **243**.

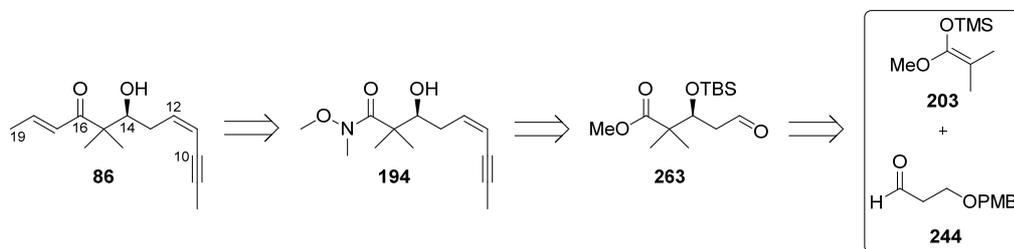
### 3.6 Summary

Three convergent approaches were investigated towards the synthesis of the C(10)–C(19) fragment of disorazole C<sub>1</sub>, which relied on the synthesis of a key Weinreb amide. Routes towards the Weinreb amide included a cross-metathesis approach between an enyne and a homoallylic alcohol [C(11)–C(12) disconnection, **Approach A**]; an epoxide ring-opening approach between an epoxide and a (metallated) vinyl bromide [C(12)–C(13) disconnection, **Approach B**]; and a Mukaiyama aldol approach between a silyl ketene acetal and an aldehyde [C(14)–C(15) disconnection, **Approach C**]. **Approach A** was unsuccessful owing to incompatibility of the substrates in the cross-metathesis reaction. Despite an unoptimised but nonetheless successful synthesis of the racemic epoxide, **Approach B** suffered from difficulties in substrate purification and handling with respect to the vinyl bromide, and therefore was discontinued as a route towards the required fragment. The most successful of the approaches was **Approach C**, and this allowed the generation of a derivative of our key Weinreb amide, from which the fragment could be derived. The Mukaiyama aldol route gave the desired fragment in 14% yield (7 steps), albeit without determination of %*ee*; but unfortunately the capricious nature of the key aldol step prevented an optimisation of the reaction in terms of its yield and enantioselectivity, and therefore the use of this route was ultimately deemed non-viable. Despite this, we were able to validate the use of the Weinreb amide as a means of installing the C(19)–C(17) propene group, and therefore the route provided a synthetic target for a linear synthesis of the C(10)–C(19) fragment.

In general all three approaches suffered somewhat from inherent difficulties in the handling of small, volatile and/or unstable intermediates. This is understandable: the C(10)–C(19) fragment is only a twelve-carbon chain containing a large degree of unsaturation and conjugation, and therefore the various retrosynthetic disconnections will yield small and potentially volatile and reactive fragments. On this basis, it was believed that future work towards the synthesis of the C(10)–C(19) fragment may be more successful with – or indeed necessitate – a linear synthesis. This alternative route is discussed in the following chapter.

## Linear Approaches towards the Synthesis of the C(10)–C(19) Fragment of Disorazole C<sub>1</sub>

### 4.1 Overview, Previous Work and Retrosynthesis

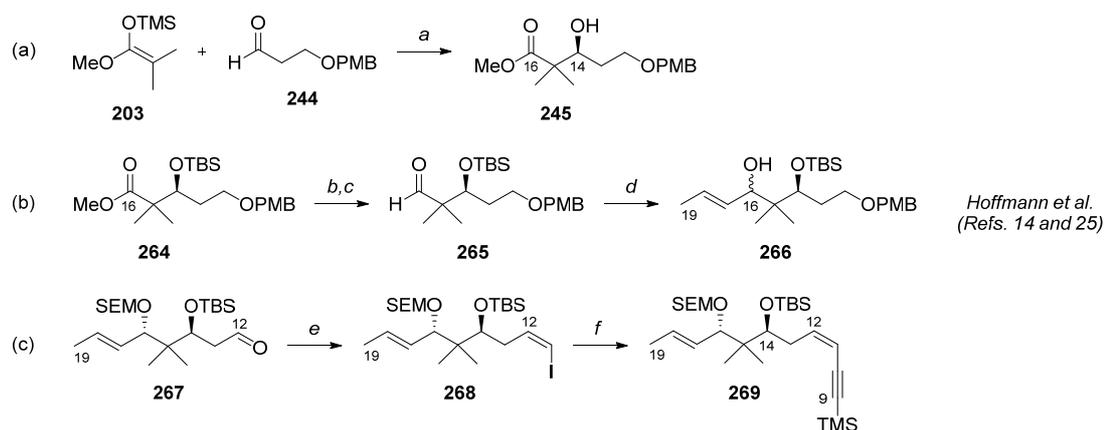


**Scheme 4.1** Retrosynthesis of the C(10)–C(19) fragment **86** using a linear approach.

As outlined in **Chapter 3**, convergent approaches towards the C(10)–C(19) fragment were unsuccessful; thus, a linear approach was explored (**Scheme 4.1**). It can be considered that there are three major challenges associated with the synthesis of the desired fragment **86**: (1) induction of (*S*)-stereochemistry at C(14) whereby a *gem*-dimethyl  $\beta$ -hydroxyketone (or derivative) is formed simultaneously; (2) introduction of the (*E*)-propene group at C(16)–C(19); and (3) generation of a (*Z*)-1,3-enyne at C(10)–C(12).

In their work towards the synthesis of the C(1)–C(19) disorazole C<sub>1</sub> monomer, Hoffmann<sup>14,25</sup> successfully overcame these challenges and used a Mukaiyama aldol reaction with aldehyde **244** to introduce the required (*S*)-stereochemistry at C(14), generating the key  $\beta$ -hydroxyester **245**<sup>14</sup> (**Scheme 4.2a**). This intermediate was later elaborated to the C(9)-protected C(9)–C(19) alkyne **269** and later to the C(1)–C(19) disorazole C<sub>1</sub> monomer **28**<sup>25</sup> (for structure, see: **Chapter 1, Section 1.2.3, Scheme 1.5**). Although a high overall yield (42%, 6 steps), was obtained for the steps of their fragment synthesis relevant to our own, we believed that there were a number of modifications to the route that could be applied in our synthesis that may improve yields, and reduce the number of steps required for completion of the fragment.

The excellent 88 %*ee* that was achieved in the aldol step of Hoffmann's synthesis (**Scheme 4.2a**) was suitable for the current study because we were confident that if the  $\beta$ -hydroxyketone **86** was synthesised, the step could be revisited later, if required, to obtain the fragment in enhanced optical purity while otherwise using the same



**Reagents and conditions:** (a) See Chapter 3, Section 3.4, Scheme 3.21a; (b) DIBAL, PhMe,  $-78\text{ }^{\circ}\text{C}$ , 1.5 h, 94%; (c) Dess–Martin periodinane, DCM,  $0\text{ }^{\circ}\text{C}$  to rt, 3 h, 83%; (d) (i) (*E*)-1-bromopropene,  $t\text{BuLi}$ ,  $\text{Et}_2\text{O}/\text{THF}$ , 3 h,  $-95\text{ }^{\circ}\text{C}$ ; (ii) **265**,  $-78$  to  $-65\text{ }^{\circ}\text{C}$ , 2 h, 84% yield, *anti:syn*-**266** 1:1.2; (e) (i)  $[\text{Ph}_3\text{PCH}_2\text{I}]^+\text{I}^-$ , NaHMDS, THF, rt, 30 min; (ii) **267**, HMPA,  $-78\text{ }^{\circ}\text{C}$ , 45 min, 82%; (f) TMS-acetylene,  $\text{PdCl}_2(\text{PPh}_3)_2$ , CuI,  $\text{Et}_3\text{N}$ , MeCN, 5 h, rt, 81%.

**Scheme 4.2** Relevant steps in Hoffmann's fragment synthesis.<sup>14,25</sup>

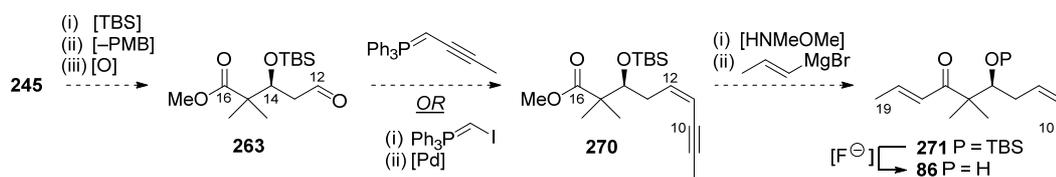
forward synthesis. This approach would allow us to focus on the important problem of finding conditions that would lead us to the skeletal framework of fragment **86**.

The introduction of the C(17)–C(19) propene group was a particular sequence for which it was believed improvements could be made over Hoffmann's previous efforts (**Scheme 4.2b**). Aside from the desire to avoid the use of the particularly hazardous reagent  $t\text{BuLi}$ , if Hoffmann's sequence was used, a three-step route to install the C(17)–C(19) propene group and a final alcohol oxidation to generate the ketone at C(16) would be required to complete the C(16)–C(19) portion of the molecule. This four-step sequence was deemed unnecessary in light of the success obtained using the Weinreb amide functionality as a means of introducing the olefin to our target fragment (see: **Chapter 3, Section 3.5**). As such, we chose to retain the use of the Weinreb amide in the current study, which would make the synthesis more convergent.

The Hoffmann group was successful in carrying out a two-step synthesis of the (*Z*)-enyne functionality from an aldehyde **267** using a stereoselective Stork–Zhao modified Wittig reaction followed by palladium-mediated cross-coupling onto the resultant vinyl iodide **268** (**Scheme 4.2c**). Since high stereoselectivity was obtained (>99:1 *Z:E*) in the Wittig reaction, we felt it would be prudent and straightforward to transfer this two-step methodology to our studies. However, we were interested in

discovering whether or not a Wittig reaction by itself could potentially generate the C(10)–C(12) enyne group through use of a propargylic Wittig reagent.

**Scheme 4.3** shows our proposed forward synthesis of the C(10)–C(19) fragment of disorazole C<sub>1</sub> **86** based on the above discussions. The sequence would commence with an enantioselective aldol reaction to introduce (*S*)-stereochemistry at C(14) and provide the β-hydroxyester scaffold **245**. Following protection of the free alcohol, the enyne and propene groups would then be installed in what could be considered separate key stages of the fragment synthesis. Construction of the C(10)–C(12) enyne would commence with cleavage of the PMB-ether followed by oxidation of the alcohol to give the aldehyde **263**. A Wittig reaction followed by – if required – palladium-mediated cross-coupling would introduce the C(10)–C(12) (*Z*)-enyne and give the protected β-hydroxyester **270**. To introduce the C(16) (*E*)-propene group, a Weinreb amide would be generated from the C(16) methyl ester **270** and subsequently treated with an appropriate Grignard reagent as carried out in **Chapter 3, Section 3.5**. Deprotection of the protected C(10)–C(19) fragment **271** would complete the fragment **86** in 7 or 8 steps from the aldol product **245**.

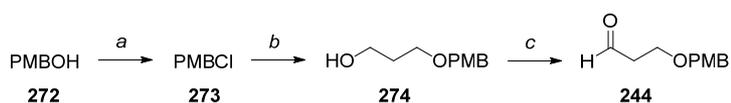


**Scheme 4.3** Simplified forward synthesis of the C(10)–C(19) fragment **86** using linear approaches.

## 4.2 Synthesis of the C(12)–C(16) β-Hydroxyester Scaffold

### 4.2.1 Synthesis of the C(12)–C(14) Aldehyde (**244**)

The first step in the proposed synthesis of fragment **86** requires generation of the 2,2-dimethyl-β-hydroxyester **245** from aldehyde **244** (**Scheme 4.2a**). Aldehyde **244** was synthesised on a multi-gram scale (~30 g; **Scheme 4.4**) in two steps from freshly prepared PMBCl **273**, which was synthesised by treatment of molten PMBOH **272** with ultrasonic vibration in concentrated HCl.<sup>141</sup> Base-mediated (KOH) reaction of the crude (>90% purity) PMBCl with an excess of 1,3-propanediol in DMSO



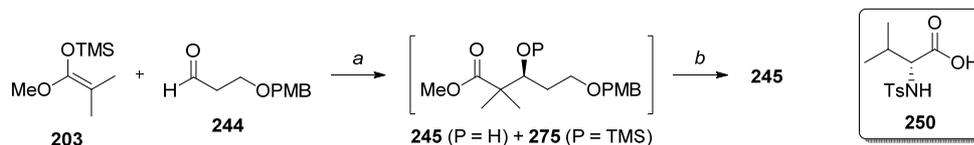
**Reagents and conditions:** (a) HCl (12 eq), H<sub>2</sub>O, ultrasound, 1 to 2 h, quant; (b) 1,3-propanediol (4.0 eq), KOH (4.0 eq), DMSO, 0 °C to rt, 3 h, 78%; (c) (i) (COCl)<sub>2</sub> (1.5 eq), DMSO (4.5 eq), DCM, -78 °C, 10 min; (ii) **272**, 1 h; (iii) Et<sub>3</sub>N (6.0 eq), -78 °C to rt, 1 h, 85%; or NaOCl (1.2 eq), TEMPO (5 mol%), KBr (10 mol%), NaHCO<sub>3</sub> (2.1 eq), DCM/H<sub>2</sub>O (1:2), 0 °C, 45 min, quant.

#### Scheme 4.4 Synthesis of aldehyde **244**.

generated the mono-protected diol **274** in good yield (78%), while subsequent Swern oxidation gave the aldehyde **244** in 85% yield (66% over 3 steps) reproducibly, and on a large scale (>30 g).<sup>142</sup> It is worth noting that the Swern oxidation can be replaced with a TEMPO-mediated protocol,<sup>143</sup> which gave a quantitative yield of the aldehyde **244** (2 g scale); and avoids the requirement for anhydrous conditions, distillation of reagents and reduction of temperature below that of an ice-bath (0 °C). Importantly, it also simplifies the workup procedure because special precautions need not be taken to cope with the presence of the malodorous byproduct Me<sub>2</sub>S.

### 4.2.2 The Mukaiyama Aldol Reaction

The aldol reaction required for generation of the β-hydroxyester **245** was performed according to Hoffmann's procedure.<sup>14</sup> An *in situ* generated organoborane Lewis acid catalyst was prepared by addition of BH<sub>3</sub>•THF to *N*-Ts-*D*-Valine in DCM with stirring for 1.5 h, followed by cooling to -78 °C. Aldehyde **244** and silyl ketene acetal **203** were then added and allowed to react for 5 h at -78 °C. Following aqueous workup, the product β-hydroxyester **245** and its TMS-protected derivative **275** were obtained in an approximate 1:1 ratio (**Scheme 4.5**). However, treatment of the crude material with aqueous HCl in THF gave the product **245** in 85% yield and 89 %*ee*. This result was consistent on scales up to 100 mmol (~20 g **244**) both with



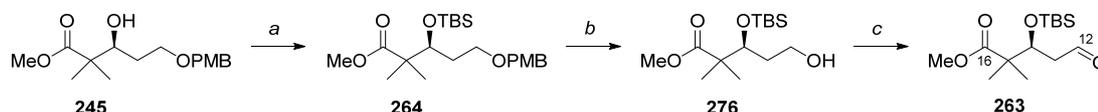
**Reagents and conditions:** (a) (i) BH<sub>3</sub>•THF (1.1 eq), *N*-Ts-*D*-valine **250** (1.1 eq), DCM, rt, 1.5 h; (ii) **244**, **203** (1.8 eq), DCM, -78 °C, 5 h; (b) HCl (5.0 eq), THF/H<sub>2</sub>O (1:1), 3 h, 85%, 89 %*ee*; 60% recovered *N*-Ts-*D*-valine.

#### Scheme 4.5 Synthesis of the C(12)–C(16) β-hydroxyester **245** (100 mmol scale).

respect to the yield (>80%), and enantioselectivity (typically 88 to 89 %*ee*; measured by HPLC on comparison with the trace obtained for the same reaction performed with racemic *N*-Ts-valine), and therefore represented a highly reproducible and efficient means of generating our desired C(12)–C(16)  $\beta$ -hydroxyester scaffold.

It should be noted that although large-scale preparation required multigram quantities of the stoichiometric ligand **250**, it is easily synthesised (see: **Chapter 3, Section 3.4.1**) and may be recovered (typically 60 to 80%) on each run through acidification of the aqueous extracts obtained during each workup and subsequent recrystallisation of the solid thus obtained. However, by contrast, it was found that for large-scale preparations of  $\beta$ -hydroxyketone **245**, commercial acquisition of the silyl ketene acetal **203** was a preferred option owing to the difficulties of reproducibility encountered during its large-scale (~30 g) synthesis. The source of the solvent is also worthy of note: one should ensure that amylene-free DCM (obtained from a purification system or by distillation over CaH<sub>2</sub>) is used, because the use of commercially obtained, stabilised DCM led to diminished enantioselection.

#### 4.2.3 Synthesis of the C(12)–C(16) Aldehyde (**263**)



**Reagents and conditions:** (a) TBSOTf (1.5 eq), 2,6-lutidine (2.0 eq), DCM,  $-78$  °C, 2.5 h, 94%; (b) DDQ (1.5 eq), DCM/H<sub>2</sub>O (18:1), 1.5 h, quant; (c) (i) (COCl)<sub>2</sub> (2.0 eq), DMSO (6.0 eq), DCM,  $-78$  °C, 15 min; (ii) **276**, 1.5 h; (iii) Et<sub>3</sub>N (8.0 eq),  $-78$  °C to rt, 1.25 h, 95%.

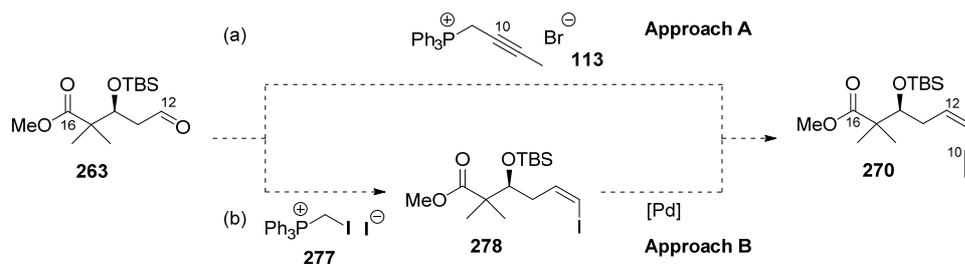
**Scheme 4.6** Preparation of the key C(12)–C(16) aldehyde **263**.

Having successfully synthesised the  $\beta$ -hydroxyketone scaffold, synthesis of the key aldehyde **263** could be commenced (**Scheme 4.6**). A TBS group was chosen as the protecting group for our reaction sequence owing to its stability to organometallic reagents and most standard oxidation and reduction conditions; and its anticipated ease of removal,<sup>144</sup> which would not compromise other functionalities in the protected C(10)–C(19) fragment. Thus, alcohol **245** was treated with TBSOTf in DCM in the presence of 2,6-lutidine at  $-78$  °C to give the silyl ether **264** in 94% yield. DDQ-mediated cleavage of the PMB group from PMB-ether **264** (which may

be telescoped directly from the previous step) followed by Swern oxidation of the free alcohol **276** thus obtained afforded the key aldehyde **263** in 95% yield over 2 steps (**Scheme 4.6**).

This sequence of reactions presented few problems, although it should be noted that the workup used to obtain crude alcohol **276** can be problematic – particularly on a large scale – because the reaction mixture obtained after quenching has a tendency to emulsify. This was overcome by high dilution of the mixture with H<sub>2</sub>O and exhaustive aqueous extraction, and indeed this is a requirement to obtain the product in high yield because yields may diminish if dilution is not sufficient to allow a clean phase separation. It is also advisable that aldehyde **263** be used promptly, because decomposition was thought to occur (TLC) after 1 to 2 weeks at –18 °C.

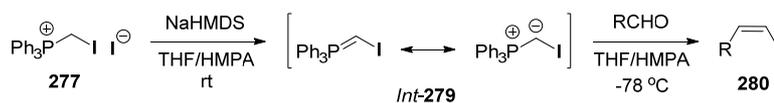
### 4.3 Installation of the C(10)–C(12) (*Z*)-Enyne



**Scheme 4.7** (a) Direct Wittig; and (b) iodo-olefination/Negishi coupling approaches towards the synthesis of the enyne **270**.

The next stage of our proposed fragment synthesis involved introduction of the (*Z*)-enyne moiety to our C(12)–C(16) β-hydroxyester scaffold, and two routes were considered, both of which centred around the use of a Wittig reaction: either (1) a direct Wittig reaction using propargylic phosphonium salt **113** (**Approach A**, **Scheme 4.7**); or (2) generation of vinyl iodide **278** followed by Negishi coupling would be used to generate the C(10)–C(12) enyne group (**Approach B**, **Scheme 4.7**).

Clearly, both routes in our proposed synthesis require a highly (*Z*)-selective olefination, and such a transformation may be achieved through use of the Stork–Zhao reaction.<sup>145</sup> The Stork–Zhao reaction (**Scheme 4.8**) involves generation of a methylene iodide ylide *Int-279* by treatment of phosphonium salt **277** with

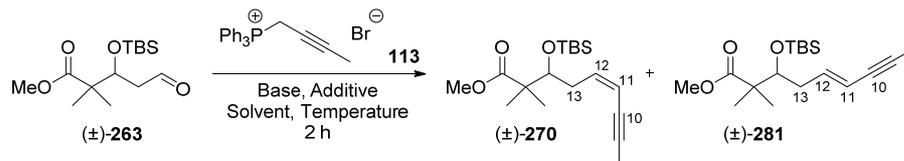


**Scheme 4.8** General Stork–Zhao olefination reaction.

NaHMDS, followed by addition of HMPA and the aldehyde to give the (*Z*)-vinyl iodide **280**. The role of HMPA in the reactions is unclear, but it has been suggested that it is involved in increasing phosphorane solubility<sup>146a</sup> and preventing unwanted side reactions;<sup>146</sup> and it may have a role in chelation of the sodium ion, thus destabilising the phosphonium ylide and promoting (*Z*)-selectivity.<sup>147</sup> According to the Stork–Zhao procedure, we were confident that we could generate a vinyl iodide from our C(12)–C(16) aldehyde **263**, but we were also curious to discover whether or not the addition of HMPA would lead aid in promoting a (*Z*)-selective Wittig olefination using a propargylic phosphonium salt.

#### 4.3.1 Approach A: Direct Synthesis Using a Wittig Olefination

Our initial screening conditions for the Wittig olefination using the propargylic phosphonium salt **113** involved treatment of a THF suspension of phosphonium salt with NaHMDS at room temperature, followed by cooling, subsequent addition of HMPA and finally the aldehyde ( $\pm$ )-**263** at  $-78^\circ\text{C}$ . Reaction for 2 h under these conditions led to completion of the reaction, but unfortunately an approximate 3:2 to 1:1 ratio of *E*:*Z* stereoisomers [ $\pm$ ]-**281:270** was observed on analysis of the crude  $^1\text{H}$  NMR spectrum (**Table 4.1**, Entry 1). The formation of the two products was immediately recognised by the presence of two resonances of approximately equal integral intensity at  $\delta = 5.98$  [1H, dt,  $J = 15.3, 7.5$  Hz; (*E*)-isomer] and  $\delta = 5.88$  [1H, dt,  $J = 10.6, 7.4$  Hz; (*Z*)-isomer] which correspond to the C(12) olefinic protons of each stereoisomer. The expected coupling constants for coupling to C(11) in an (*E*)- and (*Z*)-geometry were observed, while the doublet-of-triplet pattern occurred as a consequence of coupling to the neighbouring C(13)  $\text{CH}_2$  protons [which, importantly, indicated the formation of the C(12)–C(13) bond]. The formation of two enyne products was confirmed by the presence of two ( $\text{CH}_3$ ) resonances at  $\delta = 2.01$  [3H, d,  $J = 2.2$  Hz; (*Z*)-isomer] and  $\delta = 1.98$  [3H, d,  $J = 2.1$  Hz; (*E*)-isomer]; and

**Table 4.1** Screening of the Wittig olefination reaction with aldehyde ( $\pm$ )-**263** and Wittig reagent **113**.

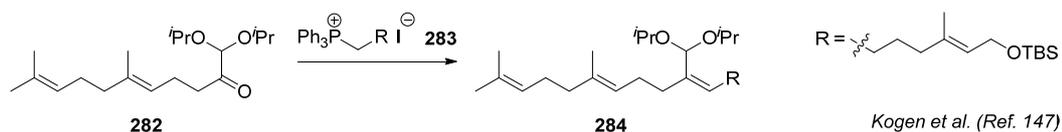
Entry <sup>a</sup>	Solvent	Base <sup>b</sup>	Additive <sup>c</sup>	Temp (°C)	Time (h)	Ratio <sup>d</sup> 270:281	Yield (%) <sup>e,f</sup>
1	THF	NaHMDS	HMPA	-78	2	42:58	100
2	THF	NaHMDS	HMPA	0	2	<i>nd</i>	<i>nd</i> [99]
3	THF	NaHMDS	HMPA	25	2	<i>nd</i>	<i>nd</i> [99]
4	Pentane	NaHMDS	HMPA	-78	2	<i>nd</i>	<i>nd</i> [99]
5	THF/DMF <sup>g</sup>	NaHMDS	HMPA	-78	2	45:55	94
6	THF	NaHMDS	HMPA <sup>h</sup>	-78	2	44:56	63
7	THF	NaHMDS	None	-78	2	42:58	99
8	THF	<sup>t</sup> BuOK	18-crown-6	-78	2	47:53	62

<sup>a</sup>Screening was performed using the racemic form of aldehyde **263** on the basis of substrate availability; <sup>b</sup>1.25 eq of base and phosphonium salt **113** was used in all cases; <sup>c</sup>2.2 eq was used unless otherwise stated; <sup>d</sup>As determined by <sup>1</sup>H NMR of the crude material; <sup>e</sup>Combined NMR yield of both stereoisomers; <sup>f</sup>Where relevant, values in brackets refer to the extent of consumption of the aldehyde starting material; <sup>g</sup>Ratio THF:DMF = 10:1; <sup>h</sup>21.5 eq of HMPA was used on this run.

the C(11) proton resonances for each stereoisomer at  $\delta = 5.47$  [1H, dqt,  $J = 10.6, 2.4, 1.4$  Hz, (*Z*)-isomer] and  $\delta = 5.44$  [1H, dqt,  $J = 15.4, 2.1, 1.7$  Hz, (*E*)-isomer]. As a result of these observations, a range of alternative conditions were screened.

Although Stork and Zhao found that increased temperature was shown to decrease selectivity,<sup>145</sup> increased temperatures (0 and 25 °C, **Table 4.1**, Entries 2 and 3) under the same conditions of phosphonium salt and HMPA quantity were nonetheless screened. Perhaps unsurprisingly, both conditions led to a decrease in conversion to the desired product and generation of a number of byproducts which were not identified – an observation that was tentatively ascribed to instability of the resulting phosphorane or reactive intermediates at higher temperatures. As such, subsequent reactions were conducted at -78 °C.

Reducing the solvent polarity (**Table 4.1**, Entry 4) by conducting the reaction in pentane led to reduced conversion and byproduct formation (*cf.* high temperature conditions), presumably as a consequence of decreased stabilisation of the intermediate phosphorane or betaine in the absence of a chelating solvent. Increasing the solvent polarity through addition of DMF<sup>148</sup> (**Table 4.1**, Entry 5) was also



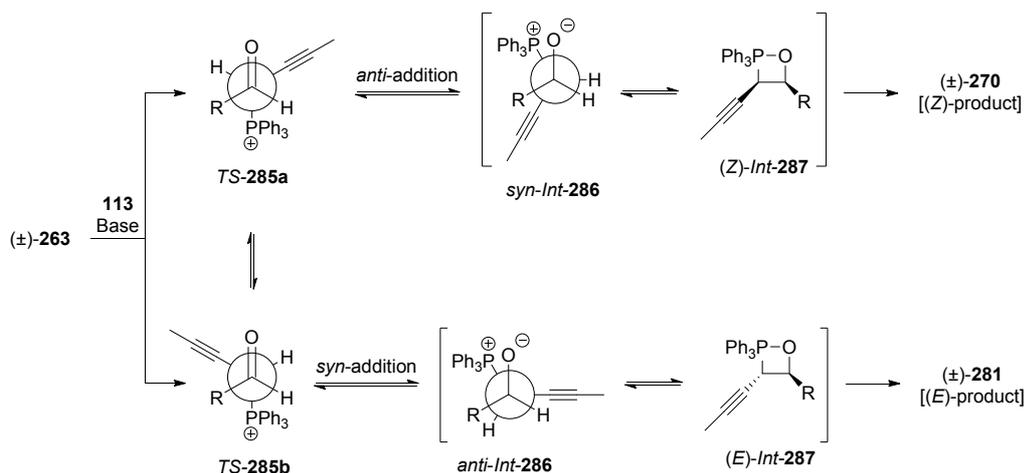
**Reagents and conditions:** (i) **283** (1.5 eq),  $t\text{BuOK}$  (1.5 eq), 18-crown-6 (1.8 eq), THF, rt, 1 h; (ii) **282**,  $-78\text{ }^{\circ}\text{C}$  to rt, 70%, >99:1 *Z:E*.

**Scheme 4.9** Representative example of a  $t\text{BuOK}/18\text{-crown-6}$ -mediated Wittig reaction.<sup>147</sup>

ineffectual in improving selectivity, and had no influence over the results relative to our initial conditions, giving quantitative conversion with an approximately equal *Z:E* ratio. The quantity of the HMPA co-solvent was also investigated; unfortunately, a tenfold increase (**Table 4.1**, Entry 6) did not improve *Z:E* selectivity and in fact hindered the extent of conversion. Interestingly, the absence of HMPA (**Table 4.1**, Entry 7) proved to have no influence on the reaction, indicating that the Stork–Zhao modification was not effective in reactions involving alkynylphosphoranes.

In a final effort to find (*Z*)-selective conditions, an alternative procedure was chosen to establish whether or not the reaction of our aldehyde ( $\pm$ )-**263** with the phosphonium salt **113** was worthy of further investigation. Kogen<sup>147</sup> reported excellent (*Z*)-selectivity (83:17 to >99:1 *Z:E*) in low temperature ( $-78\text{ }^{\circ}\text{C}$ ) Wittig reactions of  $\alpha$ -acetal ketone substrates (*e.g.* **282**) mediated by  $t\text{BuOK}$  and 18-crown-6 (**Scheme 4.9**), whereby the crown ether was thought to influence selectivity by chelating and sequestering the potassium ion, thus destabilising the phosphonium ylide. These conditions of base and additive were applied to our reaction, but unfortunately, this method also proved futile and led to a decrease in yield with no improvement in stereoselectivity (**Table 4.1**, Entry 8), and therefore direct efforts towards the synthesis of the (*Z*)-enyne were discontinued.

The reaction conditions screened consistently led to an approximate 1:1 mixture of *E:Z* isomers, the reasons for which are not entirely clear and are difficult to speculate upon given the debate that surrounds the mechanism of the Wittig reaction;<sup>30a,c</sup> and since the selectivity with alkynylphosphoranes in particular is poorly understood. However, it is plausible that the observed results may be attributed to one or more of the following factors (represented in **Scheme 4.10**):<sup>149</sup> (i) the difference in steric demands between *anti*- and *syn*-addition (*TS-285a* and *TS-285b*, respectively) at the



**Scheme 4.10** Proposed mechanism for the Wittig reaction with aldehyde (±)-263.<sup>149</sup> Note that *syn/anti*- and (*E/Z*)-descriptors in **286/287** refer to the relationship between the R-group and the alkynyl group.

carbonyl group were negligible and thus the  $\text{Ph}_3\text{PO}$  elimination step could occur *via* both the (*Z*)- or (*E*)-oxaphosphetanes [(*Z*)-**Int-287** and (*E*)-**Int-287**, respectively]; (ii) the phosphonium ylide is highly stabilised and the carbon–carbon bond forming step is slow and reversible, resulting in scrambling of the stereochemistry *via* **Int-286**→**TS-285** reversion followed by addition at the alternative face of the aldehyde; or (iii) the resulting eclipsed-betaine intermediate *syn-Int-286* resulting from *anti*-addition (*via* **TS-285a**) is very sterically hindered as a result of a steric clash between the enyne group and the (large) ‘R’-group, which promotes reversion to the starting materials. Of these three options, (i) seems unlikely, because the large R-group – which contains a TBS-ether and *gem*-dimethyl substituents – would place strain on the *syn*-addition transition state **TS-285b** which perhaps explains why (*Z*)-selectivity was actually relatively high compared to many other Wittig reactions involving propargyl halide derived phosphoranes.<sup>150</sup> However, (ii) and (iii) are plausible, and provide a means of improving the reaction conditions.

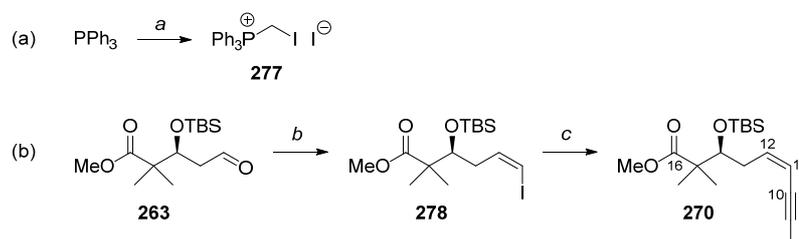
It is likely that the use of a different Wittig reagent will be required to increase (*Z*)-selectivity, such that *anti*-addition is fast and irreversible. Potential options, without deviating from the use of a propargylic salt, include alteration of the phosphonium counterion (*e.g.* tetrafluoroborate);<sup>151a</sup> or use of alternative phosphine ligands (*e.g.* pyridyl<sup>151b</sup> or substituted phenyl).<sup>151c</sup> Yamaguchi *et al.*<sup>149</sup> demonstrated moderate (*Z*)-selectivity (~7:1 *Z:E*) on using trimethylgallium as the base in the

Wittig reaction with propargylphosphonium salts. Although this would involve the use of a highly expensive and reactive reagent, instead, addition of a cationic ligand or Lewis acid to chelate the aldehyde/betaine oxygen [as was speculated as the reason for high (*Z*)-selectivity]<sup>149</sup> could increase the proportion of the desired product. Should these methods fail, a Julia olefination<sup>152a</sup> with a propargylic sulfone<sup>152b</sup> could be used instead of relying on organophosphorus chemistry. Nonetheless, these modifications are a matter for future investigation, and instead the single-step method of generating the (*Z*)-enyne was abandoned in favour of a two-step route *via* the vinyl iodide.

### 4.3.2 Approach B: Synthesis *via* Iodo-olefination/Negishi Coupling

The lack of success in the direct Wittig reaction (**Approach A**) was disappointing, but nonetheless we were confident that the Stork–Zhao reaction would lead to a (*Z*)-vinyl iodide which could be transformed using palladium-mediated cross-coupling to generate the enyne. Towards this end, Wittig reagent **277** was synthesised by reaction of PPh<sub>3</sub> with CH<sub>2</sub>I<sub>2</sub> at 70 °C in the absence of light (**Scheme 4.11a**) according to literature procedure.<sup>153</sup> It should be noted that use of the correct concentration and temperature in this protocol is very important: high concentration (4 M) was required to achieve high product yields (~80 to 90%), while overheating (>100 °C) led to partial decomposition as indicated by a yellowing of the solid.

Addition of the aldehyde **263** at –78 °C to a twofold excess of the phosphorane generated by the addition of NaHMDS to the freshly prepared phosphonium salt **277**

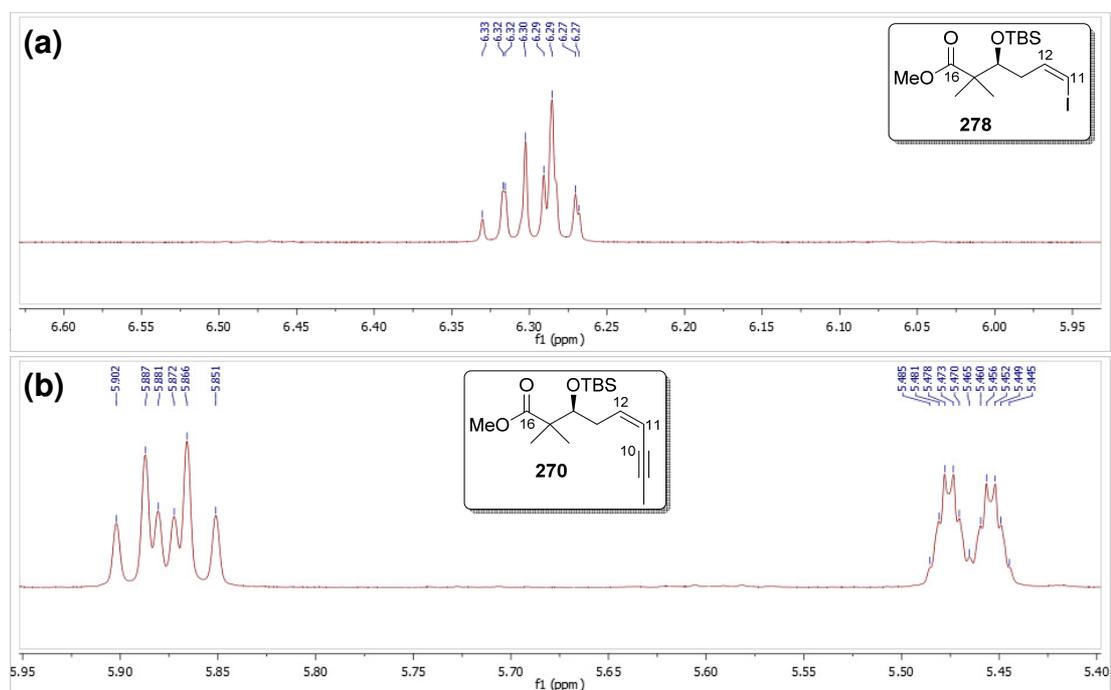


**Reagents and conditions:** (a) CH<sub>2</sub>I<sub>2</sub> (1.4 eq), PhMe (4 M), 24 h, absence of light, 91%; (b) (i) [Ph<sub>3</sub>PCH<sub>2</sub>]<sup>+</sup>Γ<sup>-</sup> **277** (2.0 eq), NaHMDS (2.0 eq), THF, rt, 5 min; (ii) HMPA (4.0 eq), –78 °C, 5 min; (iii) **263**, 2 h, –78 °C, 75% yield, >99:1 *Z*:*E*; (c) (i) 1-propynylmagnesium bromide (3.0 eq), ZnCl<sub>2</sub> (3.6 eq), THF, 0 °C, 30 min; (ii) **278**, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%), 0 °C to rt, 16 h, 92%.

**Scheme 4.11** (a) Preparation of the iodomethyl Wittig reagent **277**;<sup>153</sup> and (b) installation of the C(10)–C(12) (*Z*)-enyne moiety using a Wittig olefination/Negishi coupling approach.

at room temperature in THF/HMPA led to complete conversion of the starting material to the vinyl iodide product **278** (Scheme 4.11b). Gratifyingly, a single stereoisomer was obtained after chromatography in good yield (75%); although owing to the overlapping multiplet for the olefinic protons in the  $^1\text{H}$  NMR spectrum, (*Z*)-stereochemistry could only be tentatively assigned for the double bond (Figure 4.1a). Fortunately, having previously synthesised the TBS-protected form of the target enyne **270** (see: Chapter 3, Section 3.4.4), we were confident that the double bond geometry could be confirmed if a successful Negishi coupling could be carried out with the vinyl iodide product **278**.

Pleasingly, addition of vinyl iodide **278** and  $\text{PdCl}_2(\text{PPh}_3)_2$  (5 mol%) to freshly prepared 1-propynylzinc bromide and stirring of the reaction mixture overnight at room temperature gave the product **270** in 92% yield (Scheme 4.11b) and concluded the synthesis of the C(10)–C(16) enyne. Furthermore, the (*Z*)-geometry of the double bond was confirmed (Figure 4.1b), because two distinct proton resonances were now observed in the  $^1\text{H}$  NMR spectrum of the product with coupling constants consistent with (*Z*)-geometry: C(11)  $\delta = 5.47$  ppm; C(12)  $\delta = 5.88$  ppm;  $J_{11,12} = 10.7$  Hz. The spectroscopic data that pertains to the double bond geometry also closely matched

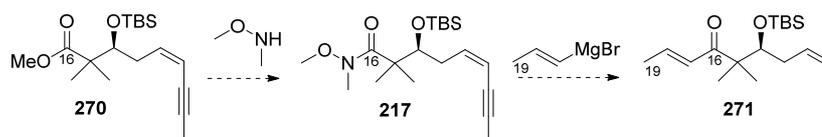


**Figure 4.1** Comparison between the olefinic regions of the 500 MHz  $^1\text{H}$  NMR spectra for (a) vinyl iodide **278**; and (b) enyne **270**. In Figure (b), proton assignments are as follows: right-most peaks: C(11); left-most peaks: C(12).

that obtained for the previously synthesised TBS-free  $\beta$ -hydroxyketone **243**, and indeed deprotection of silyl ether **270** would later confirm that the correct geometry had been obtained (see: **Section 4.4.3**). Confirmation of the successful synthesis of the C(10)–C(12) (*Z*)-enyne allowed the latter stages of the fragment synthesis to be investigated.

## 4.4 Fragment Completion

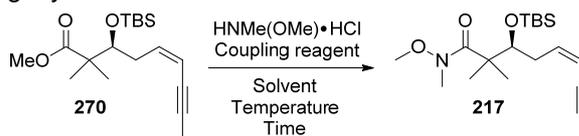
### 4.4.1 Weinreb Amide Synthesis



**Scheme 4.12** Proposed synthesis of the enone **271** from ester **270**.

The remaining steps of the fragment synthesis involved the introduction of the C(17)–C(19) (*E*)-propene group to generate the enone **271** – the TBS-protected form of our target fragment **86**. This would involve conversion of the C(16) methyl ester to its corresponding Weinreb amide **217**, and subsequent reaction of this key intermediate with an appropriate Grignard reagent (**Scheme 4.12**). As a starting point in the synthesis of the Weinreb amide **217**, ester **270** was added to a THF/hexane solution of 6 equivalents of *in situ* generated lithium *N,O*-dimethylhydroxylamide (prepared by treatment of *N,O*-dimethylhydroxylamine hydrochloride with a two-fold excess of <sup>*n*</sup>BuLi) at  $-78$  °C followed by warming of the reaction to room temperature. Application of these conditions (**Table 4.2**, Entry 1) to two runs led to incomplete conversion as judged by TLC, and only a 58 and 55% isolated yield was obtained, albeit with some recovery (26%) of the reactant ester **270** on the second run. Purification was also complicated by column streaking, possibly due to residual lithium salts in the crude mixture, unidentified side reactions of the reactant ester **270**, or decomposition or further reaction of the product Weinreb amide **217**.

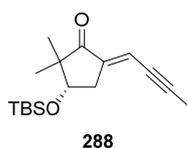
Although column streaking was inconvenient, results were promising at this stage and it was thought that insufficient reagent quantities were used in the reaction and therefore the quantities of <sup>*n*</sup>BuLi and *N,O*-dimethylhydroxylamine hydrochloride

**Table 4.2** Screening: synthesis of Weinreb amide **217** from ester **270**.

Entry	Eq Amine <sup>a</sup>	C. R. <sup>b</sup>	Eq C. R.	Solvent <sup>c</sup>	Temp (°C)	Time (h)	Conv. (%) <sup>d</sup>
1	3	<sup>n</sup> BuLi	6	THF	-78 to 25	1.5 to 2.5	34 to 67 <sup>e</sup>
2	6	<sup>n</sup> BuLi	12	THF	-78 to 25	0.75	68
3	9	<sup>n</sup> BuLi	18	THF	-78 to 25	0.75	~100
4	6	<sup>n</sup> BuLi	12	THF	-78	4	0
5	9	<sup>n</sup> BuLi	18	THF	-78	4 and 5 <sup>f</sup>	0
6 <sup>g</sup>	2.5	<sup>n</sup> BuLi	2	THF	-78 to 25	1	0
7 <sup>g</sup>	3.3	<sup>n</sup> BuLi	3	THF	-78 to 25	1	Trace
8 <sup>g</sup>	12	<sup>n</sup> BuLi	10	THF	-78 to 25	1	54
9	3	<sup>i</sup> PrMgBr	6	THF	0 to 25	2	0
10	3	<sup>i</sup> PrMgBr	6	THF	72	4	0
11	3.3	<sup>i</sup> PrMgCl	6	THF	-78	4	0
12	3.3	<sup>i</sup> PrMgCl	6	THF	0 to 25	24	0
13	3	<sup>i</sup> PrMgCl	6	THF	40	4	0
14	3.3	<sup>i</sup> PrMgCl	6	THF	72	20	0
15	3	AlMe <sub>3</sub>	3	THF	25 to 72	24	0
16	3	AlMe <sub>3</sub>	6	THF	72	18	0
17	3	AlMe <sub>3</sub>	3	PhMe	110	18	0
18	3	LiHMDS	6	THF	25 to 72	24	0
19 <sup>h</sup>	2	<sup>t</sup> BuOK	4	THF/H <sub>2</sub> O <sup>i</sup>	25	6.5	0

<sup>a</sup>HNMe(OMe)•HCl unless otherwise stated; <sup>b</sup>Coupling reagent; <sup>c</sup>Organometallic reagent carrier solvents were also present and typically accounted for 10 to 33% of the solvent mixture. The carrier solvents for each reagent are as follows (indicated in parentheses): <sup>n</sup>BuLi (Hexane), <sup>i</sup>PrMgBr (2-MeTHF), AlMe<sub>3</sub> (Entry 16: Hexane, Entry 18: Heptane); <sup>d</sup>As determined by <sup>1</sup>H NMR of the crude material unless otherwise stated; <sup>e</sup>Isolated yields over six runs; <sup>f</sup>Two runs under these conditions of reagent loading and temperature were attempted; <sup>g</sup>Reaction was performed with the free amine as opposed to the hydrochloride salt; <sup>h</sup>Performed under an air atmosphere; <sup>i</sup>Ratio THF:H<sub>2</sub>O = 5000:1.

were increased (**Table 4.2**, Entries 2 and 3). In accordance with these predictions, the use of a large excess of the Weinreb lithium amide (9 eq) gave quantitative conversion to the desired product when performed on a small scale (0.1 mmol **270**; **Table 4.2**, Entry 3). Unfortunately, attempts to scale up this reaction (~20 mmol) led to a very poor isolated yield (13%) of the desired product; distinctly worse than our initial conditions. Furthermore, on chromatographic purification, the recovered ester **270** co-eluted with a side product (**Figure 4.2**), which was identified by NMR spectroscopy as enone **288**. This indicates that either the starting material **270** or

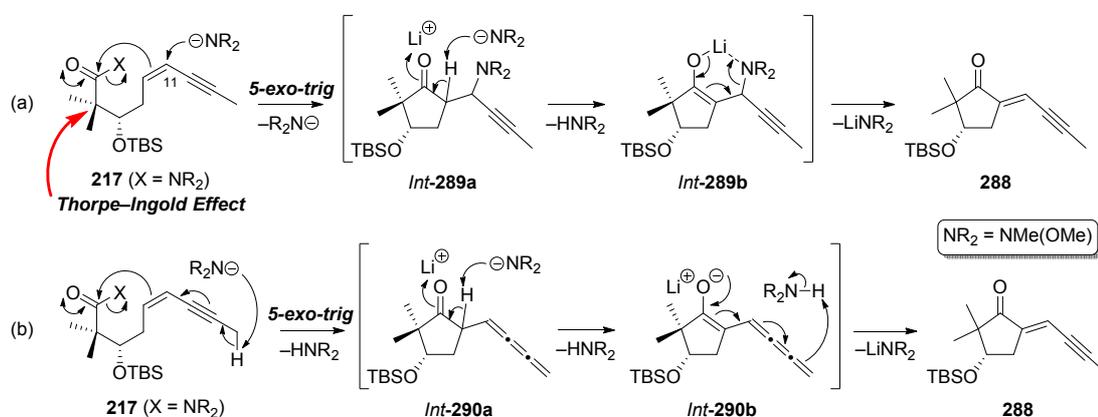


**Figure 4.2** Enone side product **288** obtained from attempted amidation.

(more likely) the product **217** cyclises under the harshly basic conditions.

This cyclisation can be explained by both the Thorpe–Ingold effect<sup>154</sup> – which describes kinetically favoured cyclisation of a sterically hindered molecule containing *gem*-dimethyl substituents – and the thermodynamic stability associated with the highly conjugated  $\pi$ -system which would be formed on elimination of the leaving group. It is possible that the formation of enone **288** occurs as a result of the amide base acting as a nucleophile and a leaving group, by analogy with amines used to mediate the Baylis–Hillman reaction.<sup>155</sup> Nucleophilic attack on the C(11) position of **217** leads to attack by the olefin on the carbonyl group and formation of the ring *Int-289a* in a 5-*exo-trig* fashion (**Scheme 4.13a**). Deprotonation of the ketone to generate the lithium enolate *Int-289b* followed by expulsion of the amino group as its lithium amide gives the product enone **288**. Alternatively, the reaction may proceed by deprotonation of the propargylic methyl group under the harshly basic reaction conditions to generate the intermediate allene *Int-290a*. Deprotonation of the ketone  $\alpha$ -proton to afford the lithium enolate *Int-290b*, followed by regeneration of the ketone and enyne moieties *via* proton transfer gives the product enone **288**.

The scale would be of importance due to the increased time required for the reaction mixture to reach room temperature. As a result, any product formed during the



process of raising the temperature would, with a larger volume, have a longer time-frame to undergo cyclisation or an alternative pathway of decomposition. Unfortunately, use of a higher temperature was a necessity, because the substrate **270** failed to react when the temperature was maintained at  $-78\text{ }^{\circ}\text{C}$  (**Table 4.2**, Entries 4 and 5) and appeared incomplete by TLC below room temperature. This implied that procedures involving the use of  $n\text{BuLi}$  were perhaps not suitable for large-scale preparation because the harsh conditions required for complete conversion were counteracted by the increased time required to warm the mixture to temperatures suitable for formation of the Weinreb amide, and this led to product decomposition

It was speculated that LiCl formed in the reaction of  $n\text{BuLi}$  with the hydrochloride salt may promote side reactions;<sup>156</sup> and as described above, the procedure suffered from difficulties during purification, possibly related to the large stoichiometry of the lithium amide. In an attempt to remedy these problems simultaneously, the reaction was performed using freebase *N,O*-dimethylhydroxylamine, which would require only 1 equivalent of  $n\text{BuLi}$  to form the lithium amide and would not liberate LiCl as a byproduct (**Table 4.2**, Entries 6 to 8). Unfortunately, a large excess of the lithium amide (12 eq) was required for only 54% formation product **217**, and therefore this means of amidation was not further investigated. Interestingly, the diminished reactivity in the absence of the byproduct LiCl indicates that the efficiency of the ester-to-amide transformation must be increased by the salt's presence. This could be a consequence of the ability of LiCl to separate organometallic aggregates,<sup>157</sup> thereby liberating monomeric lithium amide to react with the substrate.

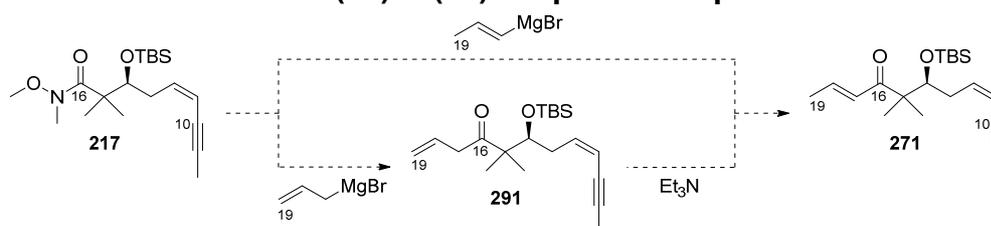
Given the disappointing results obtained on using  $n\text{BuLi}$ , alternative organometallic coupling reagents were briefly investigated. Isopropylmagnesium bromide and chloride are often used for ester-to-amide transformations<sup>158</sup> and therefore represented obvious alternatives. Disappointingly however, use of these organometallic coupling reagents led to no reaction with our methyl ester **270** over a range of temperatures (**Table 4.2**, Entries 9 to 14). Lewis acidic  $\text{AlMe}_3$  was also ineffective (**Table 4.2**, Entries 15 to 17), even under harsh conditions ( $110\text{ }^{\circ}\text{C}$ ). Finally, less orthodox transfer reagents, for example  $\text{LiHMDS}$ <sup>159</sup> and  $t\text{BuOK}$ <sup>160</sup> (**Table 4.2**, Entries 18 and 19) were also investigated, but both showed the presence

of only unreacted starting material on examination of the crude  $^1\text{H}$  NMR spectrum.

Since a successful optimisation of the reaction conditions did not seem to be forthcoming, the initial conditions – which involved 6 equivalents of  $n\text{BuLi}$  and 3 equivalents of the Weinreb amine hydrochloride salt – were deemed the best for completion of the fragment. Unfortunately, this set of conditions also proved to be problematic on repetition, because capricious yields of Weinreb amide **217** – which ranged between a very poor 34% and a more respectable 67% – were obtained over a number of runs on a range of reaction scales.

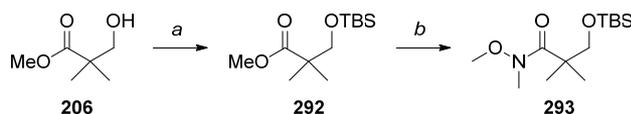
Given that quantitative conversion was achieved on reaction of the ester **270** with 9 equivalents of the lithium amide on a small scale, it is possible that high yields may be achieved on conducting the reaction using a flow reactor.<sup>161</sup> Under flow conditions, the inherently small scale of the reaction would allow the continuous generation of small quantities of the product, as opposed preparing the product in a large-scale (batch) process, the latter of which was found in the current study to be problematic. However, a microreactor for conducting a flow reaction was not available, and so an alternative route to the Weinreb amide **217** was required to be investigated. Fortunately, sufficient quantities of **217** were isolated from the reactions described to allow an investigation into the Grignard reaction, which was required for completion of the C(10)–C(19) fragment.

#### 4.4.2 Installation of the C(16)–C(19) Propene Group



**Scheme 4.14** Proposed routes towards the installation of the C(16)–C(19) propene group in the synthesis of the C(10)–C(19) fragment.

The penultimate step of the fragment synthesis involved Grignard addition with the Weinreb amide **217** to generate the corresponding enone **271**, either through direct formation of the enone with 1-propenylmagnesium bromide, or by use of allylmagnesium bromide followed by double bond isomerisation of allyl derivative



**Reagents and conditions:** (a) TBSOTf (1.3 eq), 2,6-lutidine (2.0 eq), DCM,  $-78\text{ }^{\circ}\text{C}$ , 1.5 h, 99%; (b) (i) HNMe(OMe)·HCl (1.5 eq),  $t\text{BuLi}$  (3.0 eq),  $-78\text{ }^{\circ}\text{C}$  to rt, 20 min; (ii) **292**, THF/hexane (1:1),  $-78\text{ }^{\circ}\text{C}$  to rt, 1.5 h, 73%.

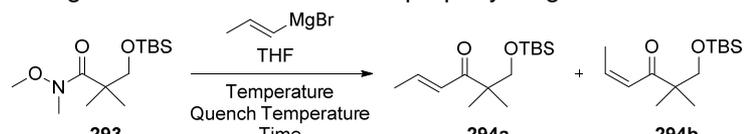
**Scheme 4.15** Synthesis of the model Weinreb amide **293** for Grignard addition screening.

**291** with a non-nucleophilic base (e.g.  $\text{Et}_3\text{N}$ , **Scheme 4.14**). However, due to the difficulties encountered on attempted synthesis of Weinreb amide **217**, and the large degree of steric crowding in the molecule, this addition was not considered to be a formality.

A model system **293** was therefore synthesised by TBS protection of alcohol **206** and subsequent conversion of the ester **292** to the Weinreb amide;<sup>162</sup> a two-step sequence which proceeded in 72% yield overall (**Scheme 4.15**). Interestingly, the amidation step proceeded cleanly, with only a slight excess (1.5 eq) of the lithium amide required to provide product **293** in good yield. Although cyclisation is unlikely to be an issue with **293**, this result highlights the influence of the enyne group on the rate and success of the amidation reaction, because harsh conditions were required with our substrate **217** to achieve quantitative conversion. Regardless, this model system used in conjunction with our fragment Weinreb amide **217**, would allow the correct Grignard reagent for introduction of the propene group to be identified.

#### 4.4.2.1 Reaction with 1-Propenylmagnesium Bromide

The most direct route towards the introduction of the propene group to our fragment would involve the use of 1-propenylmagnesium bromide, because a successful reaction with this reagent with high (*E*)-selectivity would negate the need for a subsequent isomerisation step. Our initial screening studies (**Table 4.3**, Entries 1 to 3) involved treatment of Weinreb amide **293** with an excess of this reagent in THF at  $0\text{ }^{\circ}\text{C}$  and quenching with an aqueous solution of  $\text{NH}_4\text{Cl}$ . After a reaction time of 2.5 h, treatment with two-, three- and fivefold excesses under these conditions led to only moderate conversion (30 to 58% by  $^1\text{H}$  NMR) of the starting material to enone products **294**; these results easily determined by  $^1\text{H}$  NMR through the comparison in

**Table 4.3** Grignard addition to **293** with 1-propenylmagnesium bromide.


Entry	Eq RMgBr <sup>a</sup>	Temp. (°C)	Quench Temp. (°C)	Time (h)	Ratio 294 a:b <sup>b</sup>	Conv. (%) <sup>b,c</sup>
1	2	0	0	2.5	71:29	30
2	3	0	0	2.5	77:23	55
3	5	0	0	2.5	83:17	58
4 <sup>d</sup>	3	25	25	2.5	<i>nd</i>	Trace
5	3	25	0	2.5	—	0
6	3	25	0	24	—	0
7	3	-10	-10	2.5	70:30	10
8	3	-78	-78	2.5	—	0
9	3	0	-78	5	83:17	17
10	3	0	0	5	85:15	32
11	3	0	0	0.25	88:12	17

<sup>a</sup>RMgBr = 1-propenylmagnesium bromide; <sup>b</sup>As determined by <sup>1</sup>H NMR of the crude material;

<sup>c</sup>Combined yield of both stereoisomers; <sup>d</sup>Reaction mixture was treated with ultrasonic vibration.

magnitude of the integrals of the Weinreb amide **293** NCH<sub>3</sub> peak ( $\delta = 3.20$  ppm), with the sum of the product **294** C=CCH<sub>3</sub> peaks ( $\delta_{\text{trans}} = 1.91$  ppm,  $\delta_{\text{cis}} = 2.07$  ppm). It also became apparent that the crude material contained a marked proportion (up to 19%) of the undesired (*Z*)-isomer **294b** in all cases; the stereochemistry and product ratio identified through comparison of the olefinic coupling constants ( $J_{\text{cis}} = 11.7$  Hz,  $J_{\text{trans}} = 15.1$  Hz) in the product alkenes and their relative integral intensities, respectively. Because a mixture was obtained, this indicated immediately that an additional isomerisation step to obtain the (*E*)-isomer **294a** exclusively would be a likely requirement following Grignard addition, but this was predicted to be easily effected through treatment of the isomeric mixture **294** with a non-nucleophilic base and consequently conversion to both isomers was deemed acceptable – even if inconvenient – in this reaction sequence.

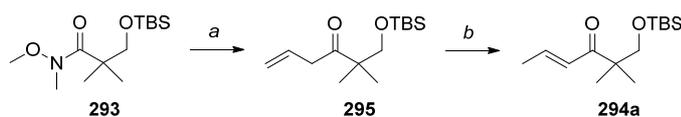
At this stage it was unclear whether the unsatisfactory conversion was due to a straightforward lack of reactivity at the hindered carbonyl centre; or poor quenching, resulting in disruption of the reagent complexation to the Weinreb amide<sup>163</sup> on addition of the aqueous solution.<sup>164</sup> To investigate this supposition, the reaction was performed using ultrasonic vibration; and at both increased and decreased

temperature relative to our initial conditions (**Table 4.3**, Entries 4 to 6). Since the difference in the extent of conversion observed in Entries 2 and 3 was only marginal, 3 equivalents of the Grignard reagent were used in each reaction.

Use of ultrasound, as performed somewhat successfully with Weinreb amide **194** in our convergent route to the C(10)–C(19) fragment (see: **Chapter 3**, **Section 3.5**), was attempted; but this was ineffectual, leading to only trace conversion (**Table 4.3**, Entry 4). On conducting the reaction over a range of temperatures (25, –10 or –78 °C; **Table 4.3**, Entries 5 to 8), only reaction at –10 °C gave any conversion to the desired enones **294**, and in poor yield, implying that 0 °C was the optimum temperature for the reaction from the conditions screened. Using this temperature (0 °C) but reducing the quench temperature to –78 °C (**Table 4.3**, Entry 9) did not improve the yield, nor did shortening or lengthening the reaction time (**Table 4.3**, Entries 10 and 11); it was therefore concluded that the modifications made to the conditions offered no advantages over our initial protocol (**Table 4.3**, Entry 2).

Because these results were disappointing and indicated that reaction with 1-propenylmagnesium bromide was particularly disfavoured, the use of this Grignard reagent – which was expensive, and in any case was supplied as a mixture of isomers – was abandoned in favour of using an allylation/isomerisation approach.

#### 4.4.2.2 Reaction with Allylmagnesium Bromide



**Reagents and conditions:** (a) AllylMgBr (6.0 eq), Et<sub>2</sub>O, –20 to –78 °C, 1.5 h; (b) Et<sub>3</sub>N, 60 h, rt, 91%, 96:4 E:Z.

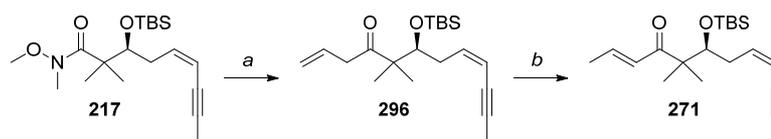
**Scheme 4.16** Model Grignard addition with allylmagnesium bromide.

Attention was focussed on a two-step procedure involving initial Grignard addition of allylmagnesium bromide to the Weinreb amide followed by isomerisation with a non-nucleophilic base. Use of such a protocol would carry cost advantages, and the additional step was deemed inconsequential owing to the likely requirement for an additional (isomerisation) step in the direct route with 1-propenylmagnesium bromide. Thus, freshly prepared allylmagnesium bromide (6 eq) was added to the

model Weinreb amide **293** at  $-20\text{ }^{\circ}\text{C}$ . After 1.5 h followed by quenching at  $-78\text{ }^{\circ}\text{C}$ ,<sup>165</sup> excellent conversion (91%) to the ketone product **295** was observed by  $^1\text{H}$  NMR, while stirring of the crude product for 60 h at room temperature in  $\text{Et}_3\text{N}$  led to almost exclusive (96:4 *E:Z*) formation of the (*E*)-enone product **294a** (Scheme 4.16).

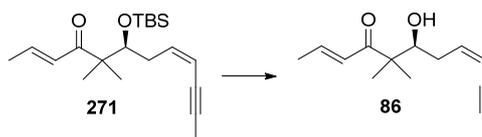
The success in obtaining useful conditions for Grignard addition with the model system **293** would go on to provide an excellent basis for the reaction of allylmagnesium bromide with our fragment Weinreb amide **217** (Scheme 4.17), although a slight increase in reagent quantity was used to ensure quantitative conversion and to account for additional steric hindrance present in the fragment Weinreb amide **217**. Thus, treatment of **217** with 8 equivalents of freshly prepared allylmagnesium bromide at  $-20\text{ }^{\circ}\text{C}$  followed by quenching at  $-78\text{ }^{\circ}\text{C}$  with saturated aqueous  $\text{NH}_4\text{Cl}$  gave, gratifyingly, quantitative conversion to the ketone product **296** after 2 h. Unfortunately, isomerisation with  $\text{Et}_3\text{N}$  according to the conditions used for the model system did not lead to satisfactory stereoselectivity in the resulting enone ( $\sim 1:1$  *E:Z*). However, this proved to be a minor problem and was easily remedied through the addition of DBU<sup>24</sup> and heating ( $50\text{ }^{\circ}\text{C}$ ) of the  $\text{Et}_3\text{N}$  solution of **296**; and these conditions, upon repetition of the experiment, gave the product TBS-protected  $\beta$ -hydroxyenone **271** in 81% yield with excellent stereoselectivity (98:2 *E:Z*).

The final step of the reaction sequence involved removal of the silyl protecting group, and it was envisaged that acidic conditions or a fluoride source would lead to successful silyl cleavage and generation of the free alcohol **86**. Reaction of TBS-ether **271** with TFA in THF led only to moderate yield (48%) of the deprotected product **86**, and rather discouragingly required a large reagent excess (60 eq) and stirring overnight of the reaction mixture. Similarly, attempted fluoride-mediated deprotection with TBAF at reflux in THF was unsatisfactory and led to a complex mixture of products, with  $\beta$ -hydroxyketone **86** not detected by  $^1\text{H}$  NMR of the crude



**Reagents and conditions:** (a)  $\text{AllylMgBr}$  (8.0 eq),  $\text{Et}_2\text{O}$ ,  $-20$  to  $-78\text{ }^{\circ}\text{C}$ , 2 h; (b) DBU (4.0 eq),  $\text{Et}_3\text{N}$  (20 eq),  $50\text{ }^{\circ}\text{C}$ , 18 h, 81% (2 steps), 98:2 *E:Z*.

**Scheme 4.17** Grignard addition to synthesise protected C(10)–C(19) fragment **271**.

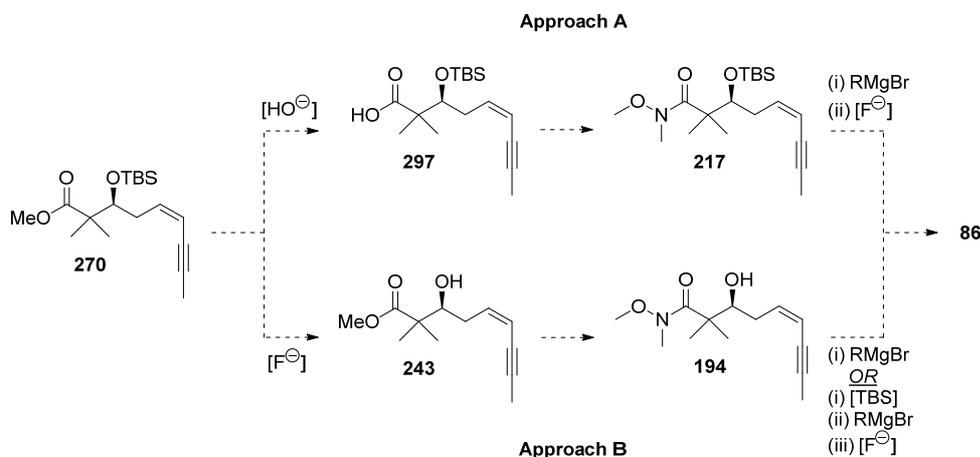


**Reagents and conditions:** HF (30 eq), MeCN/H<sub>2</sub>O (~5:1), 0 °C to rt, 45 min, 85%.

**Scheme 4.18** Silyl deprotection to complete the synthesis of the C(10)–C(19) fragment **86**.

material; although this could possibly be ascribed to the use of poor quality reagent or reagent decomposition owing to the use of elevated temperature. Pleasingly however, use of 48% aqueous HF led to clean, quantitative deprotection of the silyl ether **271** and required a reaction time of only 1 h at room temperature; and, on scale-up (~6 g), an excellent yield (85%) of the alcohol product **86** was obtained after cautious aqueous workup and flash chromatography **Scheme 4.18**). It is worth noting that the addition–isomerisation–deprotection sequence may be telescoped to give the β-hydroxyketone in up to 68% yield, which is almost identical to the yield obtained with purification at each step (69%). These steps concluded the synthesis of the C(10)–C(19) fragment **86** of disorazole C<sub>1</sub>, but given the capricious yield obtained for the Weinreb amide **217** synthesis from ester **270**, work still remained to be done to establish whether or not the route could be made more reliable.

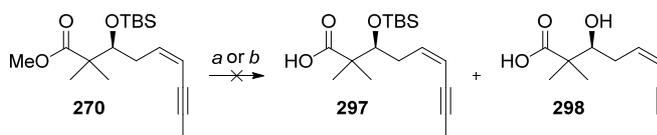
The alternative options (**Scheme 4.19**) without deviating from the use of the Weinreb amide as a means of introducing the propene group can be reduced to either: (i) base hydrolysis and conversion of the resulting acid **297** to Weinreb amide **217** using one of the multitude of acid or peptide coupling reagents available<sup>166</sup> (**Approach A**, **Scheme 4.19**); or (ii) carrying out an early-stage silyl deprotection and completing



**Scheme 4.19** Alternative routes towards the fragment **86**.

the fragment by Grignard addition with the Weinreb amide **194** (**Approach B**, **Scheme 4.19**) which we already knew from previous work (see: **Chapter 3, Section 3.5**) would be successful, at least when it came to conversion of the ester **243** to the amide **194**. The resulting Weinreb amide **194** could either be reacted directly with a Grignard reagent to complete the fragment in an identical number of steps, or if unsuccessful, reprotected and reacted with the Grignard reagent with a second, final deprotection completing the target C(10)–C(19) fragment.

#### 4.4.3 Early-Stage Deprotection and Grignard Reaction

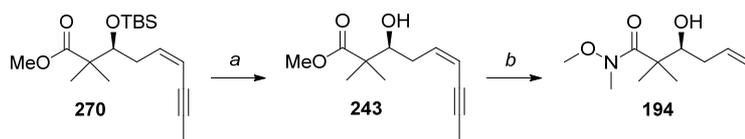


**Reagents and conditions:** (a) NaOH (10 eq), H<sub>2</sub>O, reflux, 18 h; (b) KOH (50 eq), H<sub>2</sub>O, reflux, 18 h.

**Scheme 4.20** Attempted base hydrolysis of ester **270**.

On investigating **Approach A**, alkaline hydrolysis of the methyl ester (which it was thought may also deprotect the TBS-ether concomitantly given the high temperature, **Scheme 4.20**) was found, surprisingly, to be unsuccessful even under forcing conditions (heating, large base excesses) and gave only unreacted starting material. This route was therefore ruled out immediately; and hence, without using the unreliable set of conditions described above, the only remaining option proceeding from ester **270** involved using an early stage deprotection approach (**Approach B**, **Scheme 4.19**) as the method of obtaining a useful Weinreb amide.

To perform the silyl deprotection, TBS-ether **270** was treated with 48% aqueous HF in MeCN to give the product alcohol **243** in quantitative yield (99%; **Scheme 4.21**). Reaction of **243** with 4 equivalents of the Weinreb lithium amide at  $-78$  °C and warming of the reaction to room temperature gave the product amide **194** in 82% yield on a large scale (~7 g; **Scheme 4.21**); which was comparable to the excellent yield (88%) obtained when performed on a smaller scale (~0.5 g) during our earlier convergent efforts towards the generation of Weinreb amide **194** (see: **Chapter 3, Section 3.5**). The final question that remained to be answered in our fragment synthesis was whether this Weinreb amide **194** could be converted directly to the



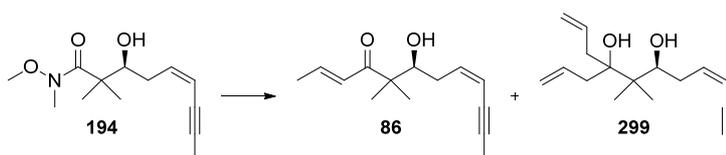
**Reagents and conditions:** (a) HF (30 eq), MeCN/H<sub>2</sub>O (~5:1), 0 °C to rt, 1 h, 99%; (b) (i) HNMe(OMe)·HCl (4.0 eq), <sup>n</sup>BuLi (8.0 eq), -78 °C to rt, 30 min; (ii) **243**, THF/hexane (1:1), -78 °C to rt, 1.5 h, 82%.

**Scheme 4.21** Silyl deprotection and Weinreb amide **194** synthesis.

$\beta$ -hydroxyketone **86** using allylmagnesium bromide and isomerisation to the (*E*)-enone, or whether a reprotection of the alcohol **194** and subjection of the product **217** to the conditions outlined in the previous section was required.

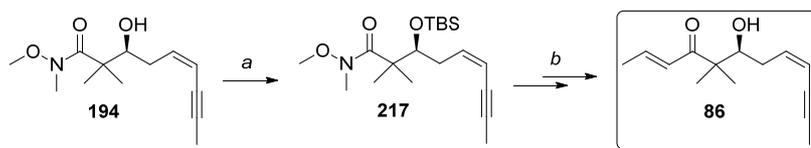
In order to gain clarity into which of these was the preferred option, Weinreb amide **194** was subjected to the Grignard addition conditions which were found to be successful for its TBS-protected derivative **217**, but this still left some 35% of the starting material unreacted (<sup>1</sup>H NMR). Doubling the quantity of Grignard reagent (from 8 to 16 eq) led to >90% consumption of the starting material, assumed to be complete conversion to the desired ketone product **86**. Unfortunately, the product  $\beta$ -hydroxyketone **86** was accompanied by the di-addition product **299**, with these compounds obtained in 22 and 34% isolated yields, respectively (**Scheme 4.22**). On closer inspection of the crude <sup>1</sup>H NMR spectrum, this undesired di-addition at the carbonyl group should have been identified during screening due to the presence of the allylic CH (2H,  $\delta$  = 6.04–5.93 ppm) and CH<sub>2</sub> (4H,  $\delta$  = 5.18–5.11 ppm) resonances, but was missed because of the complex overlapping peaks in this region.

The remainder of the mass balance in this reaction was unaccounted for, but was presumably lost owing to the multiple chromatographic purifications that were used to separate the two products which had very similar polarity in a number of solvent systems and appeared as a homogenous, single product by TLC under the hexane/EtOAc conditions normally used in purification. Fortunately, the valuable



**Reagents and conditions:** (i) AllylMgBr (16 eq), Et<sub>2</sub>O, -20 to -78 °C, 1 h; (ii) DBU (5.0 eq), Et<sub>3</sub>N (20 eq), 50 °C, 18 h, **86** 22%, >99:1 *E:Z*, **299** 34%.

**Scheme 4.22** Reaction between allylmagnesium bromide with Weinreb amide **194**.



**Reagents and conditions:** (a) TBSOTf (1.3 eq), 2,6-lutidine (2.0 eq),  $-78\text{ }^{\circ}\text{C}$  to rt, 2 h, 96%; (b) See: **Scheme 4.17**, and **Scheme 4.18**.

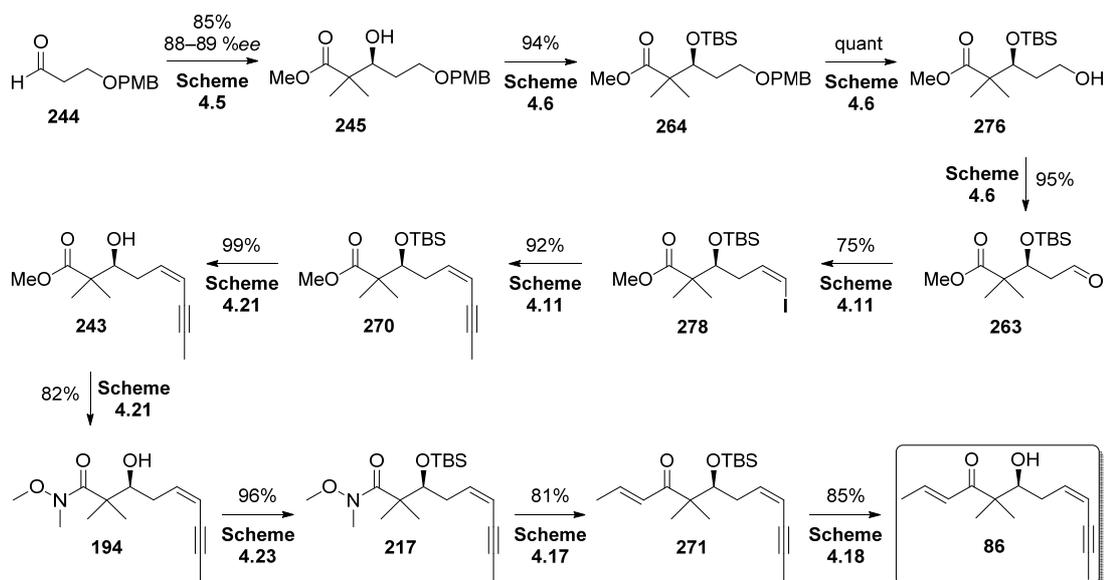
**Scheme 4.23** TBS protection of  $\beta$ -hydroxy-Weinreb amide **194** and fragment **86** completion.

$\beta$ -hydroxyketone **86** was recovered after careful separation using a DCM/Et<sub>2</sub>O eluent, but time constraints prevented a more complete optimisation of the reaction to limit the formation this unwanted side product; so in light of these results, the best route from TBS-protected  $\beta$ -hydroxyester **270** (from **Scheme 4.19**) would involve silyl deprotection, conversion of the ester **243** to the Weinreb amide **194**, and reprotection of the alcohol **194** as its TBS ether. Thankfully, TBS protection of the  $\beta$ -hydroxy-Weinreb amide **194** under standard conditions gave the product TBS-ether **217** in 96% yield; submission of **217** to the conditions detailed above gives the C(10)–C(19) fragment of disorazole C<sub>1</sub> **86** (**Scheme 4.23**).

#### 4.5 Conclusions and Future Work

The synthesis of the C(10)–C(19) fragment **86** of disorazole C<sub>1</sub> was achieved in 13 steps, 28% yield and 88 to 89 %*ee* from aldehyde **244** (**Scheme 4.24**), or 16 steps and 19% yield from commercially available PMBOH; and the preparation of this fragment represented a key triumph in our goal of successfully completing the total synthesis of disorazole C<sub>1</sub> and its analogues according to our ET–AM methodology. Despite this success, carrying out the route highlighted inherent problems associated with reproducibility at key steps and the apparently unavoidable requirement for the use of extra protecting groups.

The purpose of this section is to highlight one further study towards the synthesis of fragment **86** (which for reasons of relevance was not outlined above); and to offer alternative, improved syntheses of the required fragment for future investigation.

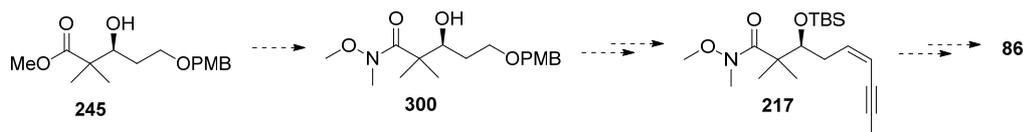


**Scheme 4.24** Overall synthesis of the C(10)–C(19) fragment **86** of disorazole C<sub>1</sub>.

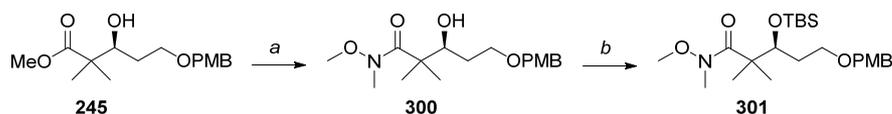
#### 4.5.1 Early Installation of the Weinreb Amide

The main problem encountered in carrying out the synthesis of the C(10)–C(19) fragment **86** was the difficulty in installing the C(16) Weinreb amide. It was suggested in **Section 4.4.2.2** that either a base hydrolysis or a silyl deprotection, followed by amidation of the ester moiety, could give a reliable route to the Weinreb amide **217**. The deprotection route was the one that was ultimately successful, albeit requiring an additional two steps relative to the planned route to successfully complete the fragment; but it is worth noting that a third option was briefly explored.

This alternative route required early-stage conversion of the ester moiety in the aldol product **245** to its corresponding Weinreb amide **300** followed by installation of the (*Z*)-enyne; with a Grignard addition and silyl deprotection used to complete the C(10)–C(19) fragment **86** (**Scheme 4.25**). To investigate this route (**Scheme 4.26**), aldol product **245** was subjected to amidation conditions, which involved treatment of ester **245** with 3 equivalents of Weinreb's lithium amide to give the product **300** in



**Scheme 4.25** Proposed forward synthesis with early Weinreb amide installation.



**Reagents and conditions:** (a) (i) HNMe(OMe)·HCl (3.0 eq), <sup>t</sup>BuLi (6.0 eq), -78 °C to rt, 35 min; (ii) **245**, THF/Hexane (2:1), -78 to 0 °C, 1.5 h, 78%; (b) TBSOTf (1.3 eq), 2,6-lutidine (2.0 eq), DCM, -78 °C, 2.5 h, 94%.

**Scheme 4.26** Successful steps in the early-stage installation of the Weinreb amide.

78% yield. TBS protection of **300** under standard conditions provided a precursor **301** for generation of the (*Z*)-enyne.

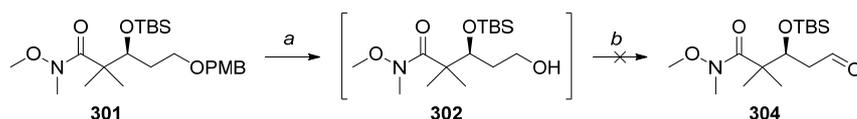
Unfortunately, attempted oxidative cleavage of the PMB-ether **301** with DDQ to reveal the primary alcohol **302** did not lead to the expected product, and instead **301** was converted to a 6-membered-ring lactone **303** in excellent yield (86%; **Table 4.4**, Entry 1). A change of reagent to CAN also led to quantitative conversion to this product **303**, as determined by <sup>1</sup>H NMR of the crude material (**Table 4.4**, Entry 2). As such, one final standard deprotection protocol was attempted, and this involved catalytic hydrogenation of the PMB-ether **301** in the presence of 10% Pd/C. Although this procedure seemed promising because the desired alcohol **302** was the major product observed by <sup>1</sup>H NMR (**Table 4.4**, Entry 3), the highly unstable synthetic intermediate decomposed on attempted flash chromatography to give the lactone **303** in quantitative yield (99%).

Attempts to counteract this instability by immediate conversion of the crude product **302** to the aldehyde **304** using a Swern oxidation failed, and gave only unreacted starting material (**Scheme 4.27**). Consequently, as a result of the instability of the intermediate alcohol **302**, which we believed could prove problematic in large-scale preparation, this approach to the fragment's synthesis was discontinued.

**Table 4.4** Deprotection of PMB-ether **301**.

Entry	Deprotection Reagent	Solvent	Time (h)	Yield 302	Yield 303
1	DDQ	DCM/H <sub>2</sub> O (18:1)	1	0	86
2	CAN	MeCN/H <sub>2</sub> O (9:1)	1	0	~100 <sup>a</sup>
3	H <sub>2</sub> , Pd/C (25 mol%)	MeOH	24	~100 <sup>a</sup> (0) <sup>b</sup>	0 <sup>a</sup> (99) <sup>b</sup>

<sup>a</sup>As determined by <sup>1</sup>H NMR of the crude material; <sup>b</sup>Isolated yield after flash chromatography.

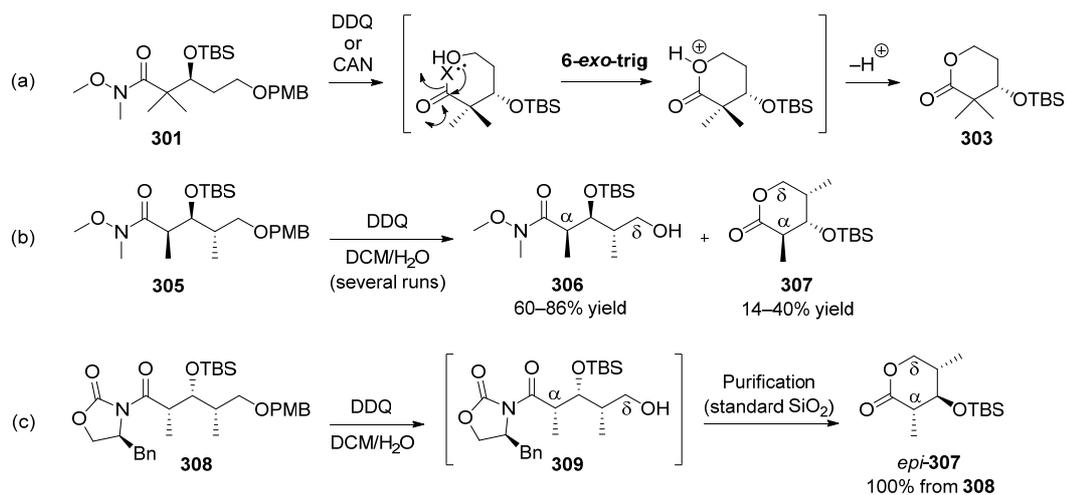


**Reagents and conditions:** (a) H<sub>2</sub>, Pd/C (25 mol%), MeOH, 24 h, assumed quant; (b) (i) (COCl)<sub>2</sub> (2.0 eq), DMSO (6.0 eq), DCM, -78 °C, 20 min; (ii) Crude **302**, 1 h; (iii) Et<sub>3</sub>N (8.0 eq), -78 °C to rt, 0%.

**Scheme 4.27** Attempted synthesis of aldehyde **304** by Swern oxidation of crude **302**.

In hindsight it is perhaps unsurprising that the cyclisation was observed. On revealing the alcohol after deprotection, the ring-formation – likely to occur *via* a 6-*exo*-trig cyclisation (**Scheme 4.28a**) – becomes highly favourable owing to the presence of a tethered nucleophile (hydroxyl group), the sterically hindered TBS-ether, the *gem*-dimethyl substituents and the formation of a 6-membered ring; all of which make the structure a prime candidate for cyclisation as a result of the Thorpe–Ingold effect.

Previous studies have observed the same phenomenon with structurally similar substrates, for example, Weinreb amide **305**<sup>167a</sup> (**Scheme 4.28b**) and oxazolidinone **308**<sup>167b</sup> (**Scheme 4.28c**) were both prone to a similar cyclisation, even in the absence of the *gem*-dimethyl substituents, which implies that formation of a lactone is particularly favourable in the open chain  $\delta$ -hydroxyamide structural motif. In the case of Weinreb amide **305**, problems of cyclisation were overcome by recycling of any recovered lactone **307**, through use of an alternative PMB-deprotection protocol (catalytic hydrogenation), and by the immediate use of the (crude) unstable alcohol



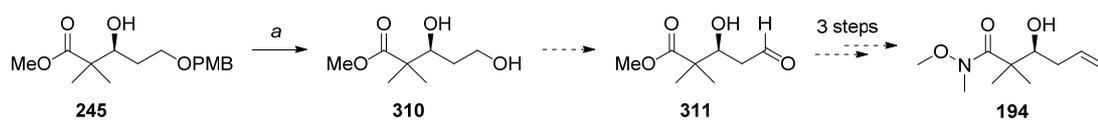
**Scheme 4.28** (a) Mechanism of the cyclisation observed on deprotection of PMB-ether **301**. Cyclisation of structurally similar (b) Weinreb amide,<sup>167a</sup> and (c) oxazolidinone substrates.<sup>167b</sup>

**306.** In the case of oxazolidinone **308**, neutralisation of the commercially obtained silica gel used in purification allowed isolation of the alcohol product **309**.

#### 4.5.2 Improvements to the Synthetic Route

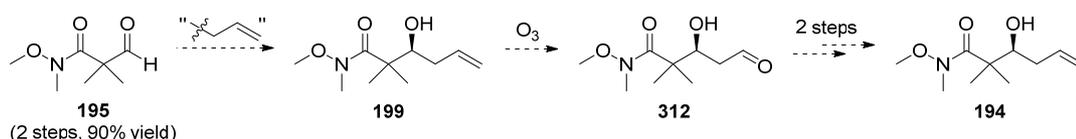
It became clear from our results that the size of the protecting group was a particular issue associated with our lack of success in obtaining a Weinreb amide from  $\beta$ -hydroxyester **270**. Large steric bulk made the substrate vulnerable to cyclisation; and given that large excesses of the lithium amide were required for quantitative conversions (*cf.* free alcohol **243**), the TBS group also acted to hamper the extent of the reaction, probably as a result of shielding the reaction site from the incoming nucleophile. One obvious way to remedy this problem would be to alter the identity of the protecting group from the start of the synthesis because a change to a smaller group may yield improved results at the problematic Weinreb amide synthesis stage of the reaction. On the basis of size, the conditions that must be withstood throughout our synthetic route, and the conditions allowable for deprotection of the final protected C(10)–C(19) fragment (which cannot be reductive), potential options include the TES, SEM, MOM, MEM and MTM groups.<sup>144</sup>

Of course, the ideal scenario would involve the generation of key fragments with minimal reliance on protecting groups, and this remains a possibility in the synthesis of the fragment **86**. Hydrogenation of the PMB-ether **245** gives the diol **310**, from which the aldehyde **311** could be obtained *via* a selective TEMPO oxidation;<sup>168</sup> giving a product that may be suitable for conversion to an enyne should a Wittig reaction in the presence of the free alcohol be successful<sup>169</sup> (**Scheme 4.29**). This would give access to the Weinreb amide **194** (**Scheme 4.29**) from which the fragment can be synthesised, but would negate the requirement for the first protection/deprotection cycle. Instead of protection at the Weinreb amide **194** stage,



**Reagents and conditions:** (a) H<sub>2</sub>, Pd/C (25 mol%), MeOH, rt, 18 h, 80%.

**Scheme 4.29** Potential protecting group free route to the Weinreb amide **194**.



**Scheme 4.30** Enantioselective allylation/ozonolysis route to key Weinreb amide **194**.

optimisation of the reaction conditions from **Chapter 3, Section 3.5** – which used 1-propenylmagnesium bromide to introduce the propene moiety and was, regrettably, not considered in our large-scale, linear approach – could give the product in a single step and as few as 8 steps overall from aldehyde **244**, which would represent a sizable improvement to our synthetic route.

One further route, which would not rely on an initial aldol reaction, involves the use of asymmetric allylation. Successful asymmetric allylation of aldehyde **195** (easily synthesised in two steps; see: **Chapter 3, Section 3.2.2**) would give homoallylic alcohol **199**, which could be converted in a single step to a useful aldehyde **312** using ozonolysis (**Scheme 4.30**). This could then be transformed stepwise to the enyne **194** from which the required fragment can be derived (**Scheme 4.30**).

#### 4.6 Summary

The synthesis of the C(10)–C(19) fragment of disorazole C<sub>1</sub> **86** was successfully achieved in 16 steps, 19% overall yield and 88 to 89 %*ee* from commercially available starting materials. Key steps in the sequence included: an enantioselective Mukaiyama aldol reaction to generate the required (*S*)-stereochemistry at C(14) inspired by the work of Hoffmann *et al.*; and a (*Z*)-selective Stork–Zhao iodo-olefination reaction followed by a palladium-catalysed Negishi coupling to generate the C(10)–C(12) (*Z*)-enyne. Problems were encountered during the installation of the C(17)–C(19) (*E*)-propene group owing to the difficulty in synthesising the Weinreb amide required to introduce the olefin. The best route was found to involve a deprotection, amidation and reprotection strategy, followed by Grignard addition and a final silyl deprotection. Although this is laborious, the approach reliably gave high yields at each reaction step and avoided the need to cope with capricious yields and the formation of side products at advanced stages of the

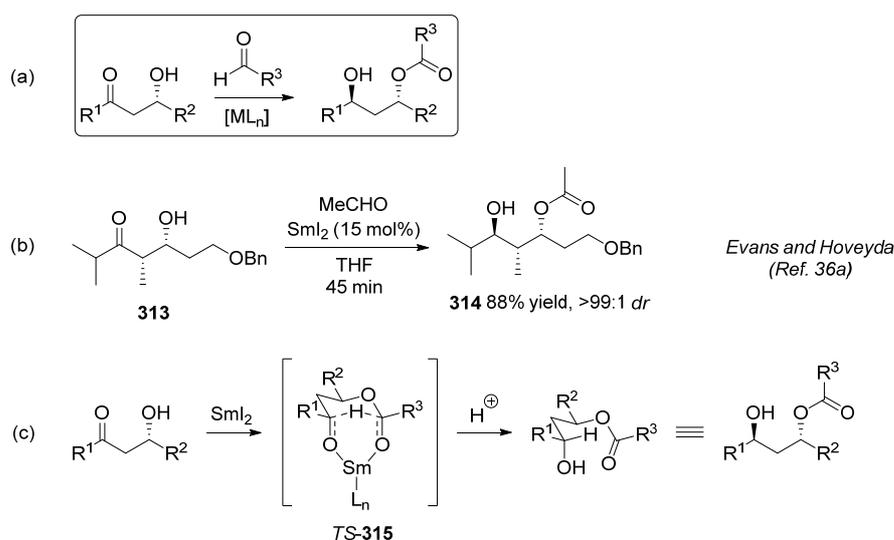
fragment synthesis. The main improvements required to be addressed in the future have also been highlighted, which would involve reduction in the number of steps and use of alternative protecting groups to prevent side reactions; alternative fragment preparations have also been proposed. With gram quantities of the key fragment now able to be synthesised in high enantiopurity, attention could now be focussed on the Evans–Tishchenko reaction which we hoped would lead to the highly convergent and diastereoselective synthesis of C(1)–C(9)/C(10')–C(19') bis-alkyne analogues.

## Evans–Tishchenko Coupling of Model Heterocycles

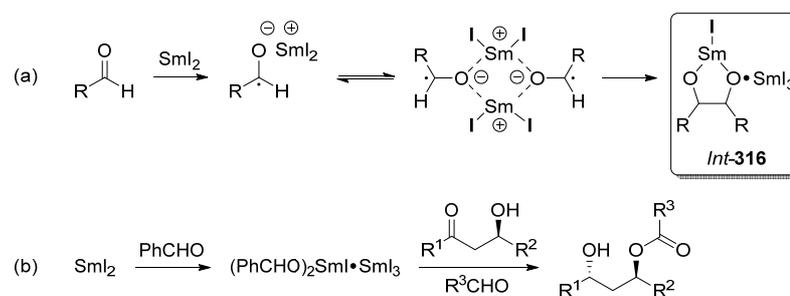
## 5.1 Introduction

The synthesis of the C(10)–C(19)  $\beta$ -hydroxyketone fragment **86** of disorazole C<sub>1</sub> proved to be a turning point in our approach towards the synthesis of the natural product since, with this fragment now in hand, attention could be focussed on the key Evans–Tishchenko (ET) coupling step of our proposed ET–AM strategy. ET coupling<sup>36</sup> is the Lewis acid catalysed reaction between a  $\beta$ -hydroxyketone and an aldehyde to generate a 1,3-*anti* diol monoester (**Scheme 5.1a**), and was first demonstrated by Evans and Hoveyda. For example, in their studies,  $\beta$ -hydroxyketone **313** was found to react with MeCHO in the presence of SmI<sub>2</sub> to give 1,3-*anti* diol monoester **314** in excellent yield and diastereoselectivity (**Scheme 5.1b**).<sup>36a</sup> The mechanism of the reaction (**Scheme 5.1c**) is believed to involve a Lewis acid catalysed hemiacetal formation, followed by intramolecular hydride transfer from the aldehyde to the newly formed carbinol centre *via* a 6,6-chair type transition state (*TS-315*), and it is the intramolecular delivery of the hydride in the aforementioned conformation that accounts for the observed *anti*-diastereoselectivity in the product.<sup>36</sup>

The most common reagent used as the Lewis acid in the ET reaction is SmI<sub>2</sub>,<sup>36b,170</sup> although active species in the reaction is not the Sm(II) species. Instead, reaction of



**Scheme 5.1** (a) General Lewis acid catalysed ET reaction; (b) example ET reaction from Evans and Hoveyda's initial publication; (c) mechanism of the SmI<sub>2</sub>-mediated ET reaction.<sup>36a</sup>



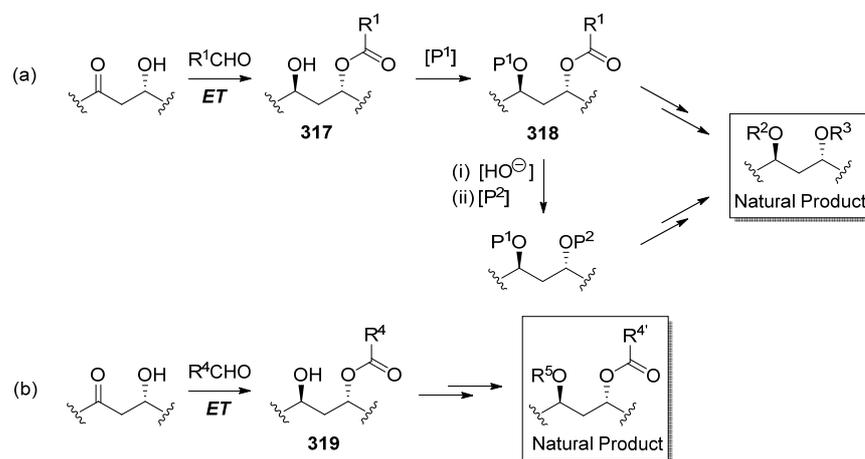
**Scheme 5.2** (a) Formation of the active samarium pinacol adduct catalytic species;<sup>36b,170a</sup> (b) use of a sacrificial aldehyde in ET coupling.<sup>36b</sup>

$\text{SmI}_2$  with an aldehyde generates a pinacol intermediate *Int-316*, (**Scheme 5.2a**) and it is this species that is the active catalyst in ET coupling.<sup>36b,170a</sup> Since an equivalent of an aldehyde is required to generate the active samarium pinacolate catalyst, it would be wasteful to use an aldehyde which was a valuable synthetic intermediate for this purpose. Fortunately, an inexpensive sacrificial aldehyde (*e.g.* PhCHO) can be used to generate the active catalyst before addition of the reactant aldehyde for reaction with a  $\beta$ -hydroxyketone (**Scheme 5.2b**).<sup>36b</sup>

### 5.1.1 Applications of Evans–Tishchenko Coupling

The ET reaction has found extensive use in natural product synthesis, and its various applications can be broadly categorised to include protection/asymmetric induction, and fragment coupling. Because these applications have been recently reviewed,<sup>36b</sup> a thorough background that deals with the use of the ET reaction in natural product synthesis is not presented herein. However, a brief description of these processes is worthy of note in the context of the current study.

In the protection/asymmetric induction strategy (**Scheme 5.3a**), an ET reaction is used to set, from a  $\beta$ -hydroxyketone, 1,3-*anti* stereochemistry in a diol unit in the target molecule. In the process this generates what is effectively a mono-protected 1,3-*anti* diol **317**; the free hydroxyl group may then be protected as, for example, a silyl or PMB-ether, giving a differentially protected 1,3-*anti* diol **318**. This bis-protected diol **318** may be carried forward through other steps in the synthesis of the target natural product, or the ester may be hydrolysed and an alternative protecting group installed before pursuing further steps; in either case, the diol may

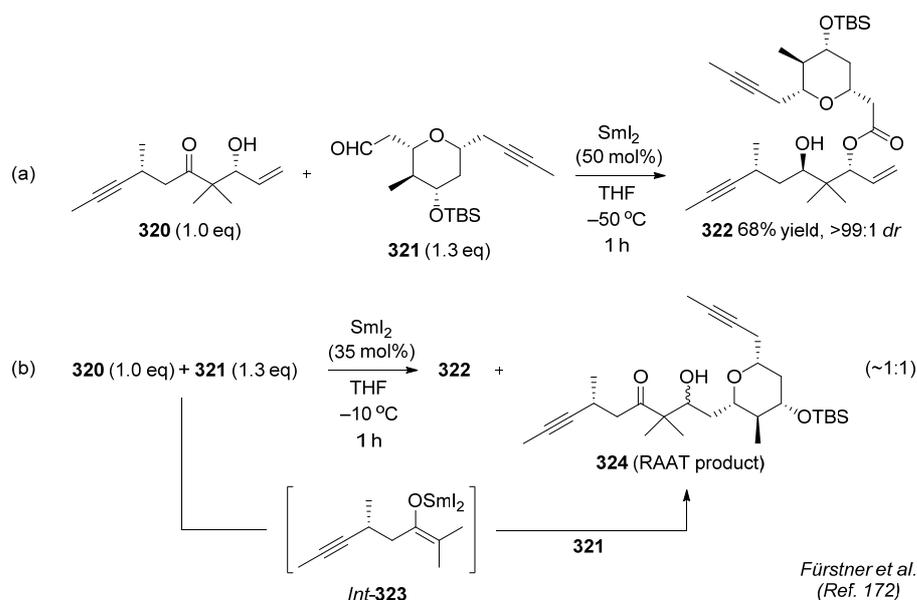


**Scheme 5.3** Simplified schematic diagram showing two key applications of ET coupling: (a) protection/asymmetric induction; and (b) fragment coupling.

be differentially functionalised at a later stage of the synthesis by selective cleavage of the protecting groups.<sup>36b</sup> An alternative strategy involves immediate ester hydrolysis following ET coupling, and subsequent installation of a diol protecting group (*e.g.* an acetonide), with the diol revealed at a later stage of the synthesis.<sup>171</sup>

ET fragment coupling, as the term suggests, involves the combination of two advanced synthetic intermediates which are to be incorporated into the framework of the target molecule (**Scheme 5.3b**). The use of ET coupling for this purpose is comparably rare (*cf.* protection/asymmetric induction),<sup>36b</sup> owing to the (typical) requirement for the use of an excess of the aldehyde component for successful ET coupling,<sup>172</sup> although a small number of examples do exist of such a process being performed with only a modest excess (up to ~2 eq) of the aldehyde substrate.<sup>172,173</sup>

One particularly noteworthy example, which was not previously reviewed, was reported by Fürstner in his synthesis of (–)-polycavernoside A.<sup>172</sup> The  $\beta$ -hydroxyketone **320** (synthesised in 13 steps) was coupled to the aldehyde **321** (synthesised in 12 steps) to give the 1,3-*anti* diol monoester **322**, impressively, in 68% yield with only a 30% excess of the aldehyde **321** (**Scheme 5.4a**). A high catalyst loading and a reduced temperature (50 mol% SmI<sub>2</sub>, –50 °C) was required to achieve the transformation, because under more typical, higher-temperature conditions (35 mol% SmI<sub>2</sub>, –10 °C) the reaction led to formation of the retro-aldol aldol–Tishchenko<sup>36b,90,172,174</sup> product **324** (*via* reaction of enolate *Int-323* with aldehyde **321**) in approximately equal quantity to the desired product **322**



**Scheme 5.4** (a) Successful low-stoichiometry fragment coupling in Fürstner's formal total synthesis of (–)-polycavernoside A; (b) formation of the RAAT product **324** observed at an alternative temperature and  $\text{SmI}_2$  stoichiometry.<sup>172</sup>

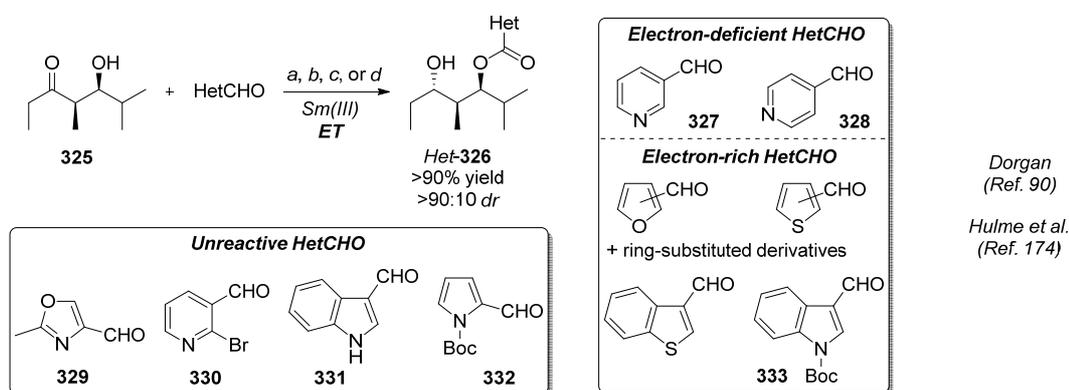
(**Scheme 5.4b**; combined yield not reported). Nevertheless, the success obtained in this reaction represents a large advancement in the use of the ET methodology; and the results were particularly promising in light of the fragment coupling we intended to carry out in the current study, especially given the structural similarity of the reactant  $\beta$ -hydroxyketone to our own substrate.

### 5.1.2 The Heteroaryl Evans–Tishchenko Reaction

Critical to our efforts towards the synthesis of disorazole  $\text{C}_1$ , ET coupling was recently shown to be successful with heteroaryl aldehydes.<sup>90,174</sup> When  $\beta$ -hydroxyketone **325** was allowed to react with a range of heteroaryl aldehydes in the presence of  $\text{Sm(III)}$ , the product 1,3-*anti* diol monoesters *Het-326* were obtained in excellent yields and *dr* (**Scheme 5.5**). A feature of this reaction was the difference in reactivity between electron-rich and electron-deficient heteroaryl aldehydes.\* The electron-deficient 3- and 4-formylpyridines **327/328**, were found to react in the presence of only a catalytic quantity (10 mol%) of  $\text{SmI}_2$ ; but, by contrast, electron-rich heteroaryl aldehydes [such as furans, (benzo)thiophenes, and the Boc-protected indole **333**] required a stoichiometric loading of the  $\text{Sm(III)}$  pinacolate

catalyst (2 eq SmI<sub>2</sub>) for quantitative levels of conversion (**Scheme 5.5**).<sup>90,174</sup> In both cases, the required Sm(III) pre-catalyst could (generally)<sup>90</sup> be prepared by reaction of SmI<sub>2</sub> with an equimolar quantity of the heterocyclic aldehyde, or by reaction with sacrificial PhCHO.

Despite the successful coupling of a range of heteroaryl aldehydes, a number of substrates failed to undergo ET coupling. These included: aldehydes containing a nitrogen atom (*e.g.* oxazole **329**), an amino group or a halogen (*e.g.* pyridine **330**) at the 2-position relative to the formyl group; very electron-rich and *N*-unsubstituted 1*H*-heterocycles (*e.g.* indole **331**); and sterically hindered aldehyde substrates (*e.g.* *N*-Boc-pyrrole **332**). Nevertheless, the heteroaryl ET reaction was highly successful with a number of substrates, and the results provide an excellent basis for investigation of our ET approach towards the C(1)–C(19) fragment of disorazole C<sub>1</sub>.



**Reagents and conditions:** *ET coupling with electron-deficient heteroaryl aldehydes:* (a) (i) SmI<sub>2</sub> (10 mol%), HetCHO (4.0 eq), THF, rt, 30 min; (ii) **325**, 1 h; (b) (i) SmI<sub>2</sub> (10 mol%), PhCHO (10 mol%), THF, rt, 30 min; (ii) **325**, HetCHO (4.0 eq), 1 h; *ET coupling with electron-rich heteroaryl aldehydes:* (c) (i) SmI<sub>2</sub> (2.0 eq), HetCHO (4.0 eq), THF, rt, 30 min; (ii) **325**, –15 °C, 1 h; (d) (i) SmI<sub>2</sub> (2.0 eq), PhCHO (2.0 eq), THF, rt, 30 min; (ii) **325**, HetCHO (4.0 eq), –15 °C, 1 h.

**Scheme 5.5** The heteroaryl Evans–Tishchenko reaction.<sup>90,174</sup>

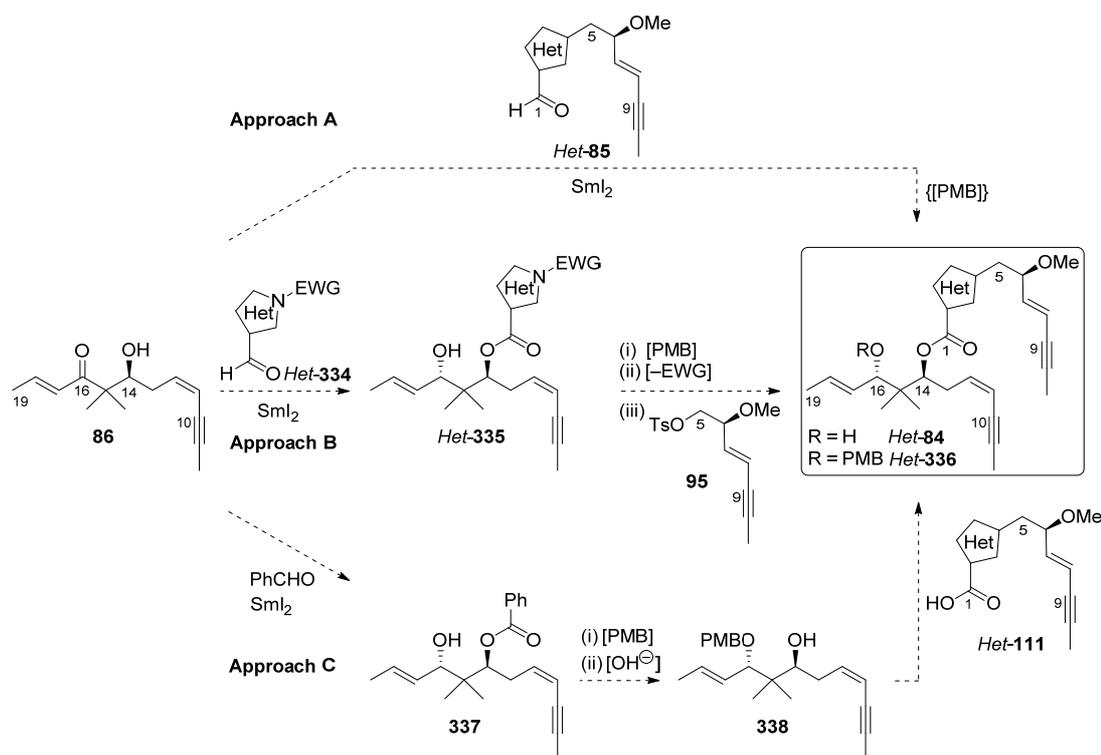
\*For the purpose of both the present discussion and the work described throughout the remainder of this thesis, electron-rich heterocycles are defined as those whereby the number of  $\pi$ -electrons in the ring exceeds the number of atoms, and therefore includes most 5-membered-ring heterocycles and their benzo-fused derivatives. By contrast, electron-deficient heterocycles are 6-membered rings that contain an electron-withdrawing atom within the aryl framework (*e.g.* pyridine). The relative level of electron deficiency on comparing any two heterocycles (and indeed, in some cases, the appropriate definition for any one heterocycle) is dependent upon the identity of the substituents attached to the ring, in addition to the number of electron-withdrawing heteroatoms within the aryl framework, and their identities.

### 5.1.3 Retrosynthesis: C(1)–C(9)/C(10')–C(19') Fragment Analogues

The heteroaryl ET study highlights heterocycles which would be promising candidates for development as C(1)–C(9) analogues, and identifies potential pitfalls in the ET approach towards the synthesis of the C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkynes required for subsequent AM. The C(5)–C(9) alkyl substitution on the C(1)–C(9) heterocyclic aldehydes *Het-85* provides negligible electron-withdrawing capacity, which would not increase the likelihood of smooth coupling with the C(10)–C(19)  $\beta$ -hydroxyketone **86**. Furthermore, unprotected 1*H-N*-heterocycles; and those containing a nitrogen atom, amino group or halogen at the  $\alpha$ -position relative to the carbon atom bearing the formyl group are likely to fail. With these considerations in mind, three approaches towards the synthesis of C(1)–C(9)/C(10')–C(19') analogue fragments can be envisaged (**Scheme 5.6**).

**Approach A** is the preferred route towards the synthesis of the required 1,3-*anti* diol monoesters *Het-85/Het-336*. In this route, the C(1)–C(9) heterocyclic aldehyde *Het-85* couples directly with the C(10)–C(19)  $\beta$ -hydroxyketone **86** to give *Het-84* in a single step; although depending on the functional group tolerance of the chosen AM catalyst, the free alcohol may be required to be protected (to give *Het-336*) prior to attempted ACM–RCAM dimerisation. **Approach B** represents a contingency strategy for use with *N*-heterocycles that only display reactivity in the ET reaction with  $\beta$ -hydroxyketone **86** when functionalised with an electron-withdrawing group. Following ET coupling of *Het-334* with  $\beta$ -hydroxyketone **86**, the alcohol is protected, the electron-withdrawing group is cleaved, and the heterocycle is *N*-alkylated by reaction with the C(5)–C(9) tosylate **95** to generate the desired product *Het-336* (**Scheme 5.6**).

**Approach C** follows the ET protection/asymmetric induction strategy and is a last resort for use only with heterocycles which fail to couple with either alkyl or electron-withdrawing *N*-substitution.  $\beta$ -Hydroxyketone **86** would be reacted with a sacrificial aldehyde (*e.g.* PhCHO) to give 1,3-*anti* diol monoester **337**. The free alcohol would then be protected and the ester hydrolysed to give mono-protected diol **338**. Esterification of **338** with C(1)–C(9) heterocyclic carboxylic acids *Het-111* completes the synthesis of the protected bis-alkynes *Het-336* (**Scheme 5.6**).



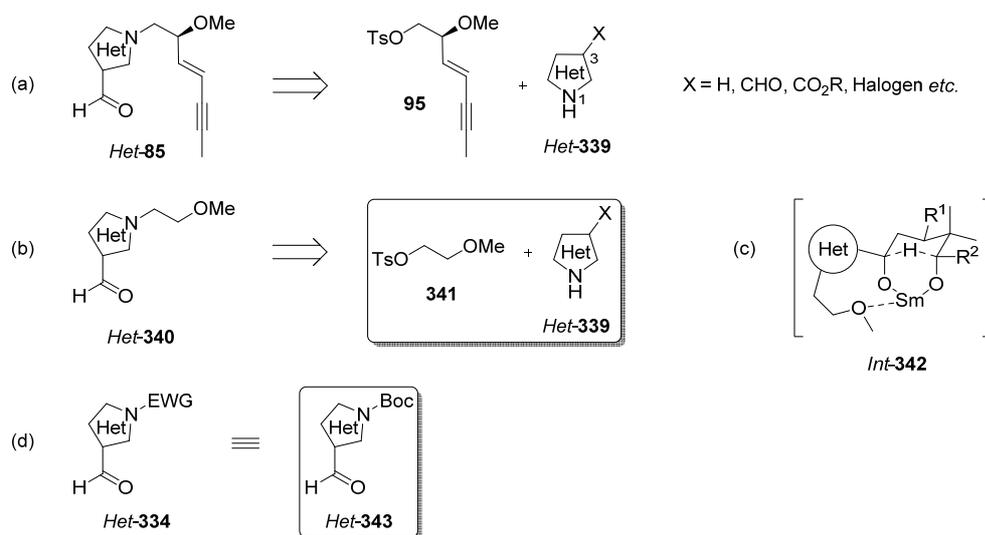
**Scheme 5.6** The ET approach towards the synthesis of C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne fragments and analogues *Het-84/Het-336*.

## 5.2 Synthesis of Model *N*-Heterocycles

### 5.2.1 Introduction

It is necessary that a range of model heterocycles are reacted with  $\beta$ -hydroxyketone **86** under ET coupling conditions with in order to determine the likely reactivity of their corresponding C(1)–C(9) fragment analogues *Het-85*. This also means that useful conditions for ET coupling can be found and the required route (**Approach A** to **C**) towards the synthesis of the bis-alkynes *Het-84/Het-336* can be determined.

Alkylation of *N*-heterocycles offers the most straightforward route towards the synthesis of heterocyclic analogues of disorazole  $\text{C}_1$ .<sup>16</sup> The C(1)–C(4) oxazole of disorazole  $\text{C}_1$  is a 1,3-disubstituted (or more specifically, based on the heteroatoms present, a 2,4-disubstituted) heterocycle, and therefore any *N*-heterocycles *Het-339* that bear the aldehyde (or a derivative) functionality at the 3-position relative to the nitrogen atom and can be readily *N*-alkylated (using tosylate **95**) are suitable candidates for development as C(1)–C(9) analogues *Het-85* (**Scheme 5.7a**).



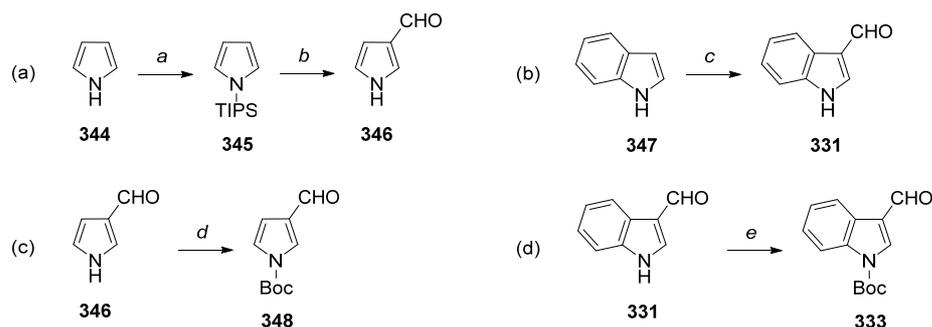
**Scheme 5.7** Retrosynthesis of (a) *N*-heterocyclic C(1)–C(9) analogues *Het-85*; (b) model *N*-heterocyclic analogues *Het-340*. (c) Potential O→Sm chelation *Int-342*; and (d) the Boc group as a suitable electron-withdrawing group for *N*-heterocycles.

Although a methyl group would perhaps be the most straightforward model *N*-substitution, the 2-methoxyethanol derived tosylate **341** represents a superior model for the C(5)–C(9) *N*-alkyl substitution (**Scheme 5.7b**). Firstly, the presence of the methoxy group better replicates the subtle differences in electronics that may be present and would identify potential deleterious O→Sm chelation during the ET reaction (*Int-342*, **Scheme 5.7c**). Furthermore, use of this model would allow conditions for *N*-alkylation to be identified with a tosylate as opposed to, for example, an iodide or bromide, which potentially could offer different reactivity.

To circumvent problems associated with poor reactivity of electron-rich heterocycles, protection of the nitrogen atom with an electron-withdrawing group was also necessary. For this purpose, the Boc group was chosen on the basis of both ease of synthesis, and its precedent in the heteroaryl ET reaction<sup>90,174</sup> (**Scheme 5.7d**).

A range of *N*-heterocyclic aldehydes were chosen for the ET model study, some of which were not studied previously. These included pyrrole, pyrazole, indole and triazole substrates, which could all be developed as analogues of the C(1)–C(9) fragment by either *N*-alkylation or (in the case of triazole) through use of the CuAAC reaction. A brief discussion of the syntheses of the relevant heterocycles along with *N*-Boc protection and *N*-alkylation will be presented in the following section.

## 5.2.2 Pyrrole and Indole Heterocycles



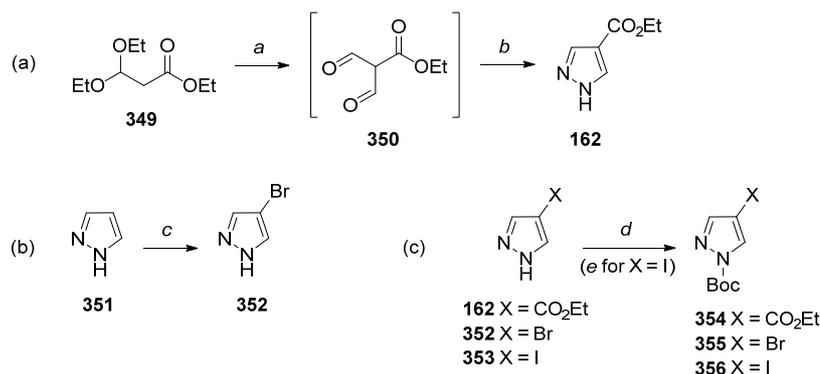
**Reagents and conditions:** (a) (i)  $n$ BuLi (1.1 eq), THF/hexane (~1:1),  $-78$  °C, 30 min; (ii) TIPSCl (1.0 eq), THF/hexane (~1:1),  $-78$  °C to rt, 30 min, absence of light, 98%; (b) (i)  $(\text{COCl})_2$  (1.3 eq), DMF (1.3 eq), 0 °C, DCM, 40 min; (ii) **345**, DCM, reflux, 30 min, absence of light; (iii) NaOH (8.3 eq),  $\text{H}_2\text{O}$ , rt, 18 h, 58%; (c) (i)  $(\text{COCl})_2$  (1.2 eq), DMF (10 eq), 1.25 h; (ii) **347**, DMF, 0 to 40 °C, 2 h; (iii) NaOH (10 eq), DMF/ $\text{H}_2\text{O}$  (~4:1), 100 °C, 20 min then DMF/ $\text{H}_2\text{O}$  (~6:1), 4 °C, 18 h, 63%; (d)  $\text{Boc}_2\text{O}$  (1.2 eq), DIPEA (2.2 eq), DMAP (5 mol%), DCM, 3 h, 73%; (e)  $\text{Boc}_2\text{O}$  (1.2 eq),  $\text{Et}_3\text{N}$  (2.2 eq), DMAP (5 mol%), THF, 24 h, 71%.

**Scheme 5.8** Synthesis of 3-formyl (a) -pyrrole **346**; and (b) -indole **331** and their respective *N*-Boc derivatives (c) **348**; and (d) **333**.

The required 3-formylpyrrole and -indole substrates were synthesised using variants of the Vilsmeier protocol<sup>175</sup> according to literature procedures. Gram-scale (~1.5 g) synthesis of 3-formylpyrrole **346** (**Scheme 5.8a**) was achieved by initial protection of freshly distilled pyrrole **344** as its *N*-TIPS-derivative **345** and subsequent Vilsmeier formylation with the iminium salt generated by reaction of  $(\text{COCl})_2$  and DMF; basic workup (NaOH) gave the product aldehyde **346** in 58% yield.<sup>176</sup> Preparation of 3-formylindole **331** was accomplished in 63% yield directly from indole **347** using the Vilsmeier reaction followed by purification by recrystallisation<sup>177</sup> (**Scheme 5.8b**). It is worth noting that Vilsmeier formylation of pyrroles normally occurs at the 2-position.<sup>176a</sup> Regioselectivity was controlled by the steric hindrance provided by the bulky TIPS group, which forces reaction at the 3-position and gives the 3-formyl derivative **346** selectively.<sup>176a</sup> By contrast, indole preferentially reacts with electrophiles at the 3-position, and therefore *N*-protection was unnecessary.<sup>178</sup>

Boc derivatisation was achieved in both cases using standard Boc coupling conditions. *N*-Boc-pyrrole **348** was synthesised in 73% yield by reaction of pyrrole **346** with  $\text{Boc}_2\text{O}$  in the presence of DIPEA and catalytic DMAP (5 mol%) in DCM<sup>179</sup> (**Scheme 5.8c**). *N*-Boc-indole **333** was synthesised analogously in 71% yield using  $\text{Et}_3\text{N}$  as the auxiliary base and THF as the solvent (**Scheme 5.8d**).

## 5.2.3 Pyrazole Heterocycles

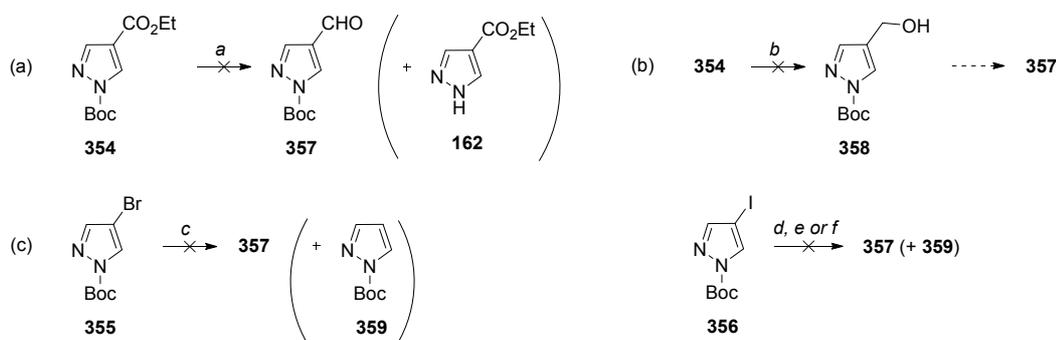


**Reagents and conditions:** (a) (i) NaH (2.0 eq), ethyl formate (10 eq), Et<sub>2</sub>O, 0 °C to rt, 24 h; (b) Crude **350**, H<sub>2</sub>NNH<sub>2</sub>·2HCl (1.2 eq), EtOH, 0 °C to rt, 50 h, 87% (2 steps); (c) NBS (1.0 eq), H<sub>2</sub>O, rt, 18 h, 90%; (d) Boc<sub>2</sub>O (1.2 eq), Et<sub>3</sub>N (2.2 eq), DMAP (5 mol%), THF, rt, 4 h, **354** 91%, **355** 91%; (e) Boc<sub>2</sub>O (1.0 eq), Et<sub>3</sub>N (2.2 eq), DMAP (5 mol%), THF, rt, 18 h, 92%.

**Scheme 5.9** Synthesis of (a) pyrazole ester **162**; (b) pyrazole bromide **352**; and (c) the Boc-protected derivatives **354**, **355**<sup>184</sup> and **356** of 4-substituted pyrazoles **162**, **352** and **353**.

Gram-scale (~6 g) preparation of pyrazole-4-ethyl ester **162** was achieved by condensation of ethyl formate and ethyl 3,3-diethoxypropionate **349** with NaH followed by acidic workup to give the crude bis-aldehyde **350**. Reaction of **350** with hydrazine dihydrochloride gave the pyrazole **162** in 87% yield (2 steps; **Scheme 5.9a**).<sup>180</sup> Because the reduction of *N*-alkyl-pyrazole-4-esters to aldehydes is poorly precedented,<sup>181</sup> and two-stage semi-reduction of *N*-Boc-pyrazole-4-ethyl ester **354** was expected to be poor yielding,<sup>182</sup> the synthesis of 4-halogenated pyrazoles was also performed to provide an alternate means of generating the aldehyde (after alkylation/Boc protection) should standard one- or two-step reduction protocols fail. Synthesis of 4-bromopyrazole **352** was accomplished by bromination of pyrazole **351** with NBS (**Scheme 5.9b**).<sup>183</sup> Boc protection of the pyrazole ester **162**, bromide **352**,<sup>184</sup> and commercially available iodide **353** was achieved in excellent yield (>91%) under standard Boc-protection conditions (**Scheme 5.9c**).

The synthesis of *N*-Boc-4-formylpyrazole **357** proved to be particularly problematic and ultimately unsuccessful. Attempted semi-reduction of the ester **354** to the aldehyde **357** with lithium diisobutyl-*tert*-butoxyaluminium hydride (LDBBA)<sup>185</sup> (**Scheme 5.10a**) led only to quantitative Boc deprotection, although this was probably inadvertently effected during (acidic; HCl) quenching and aqueous workup.

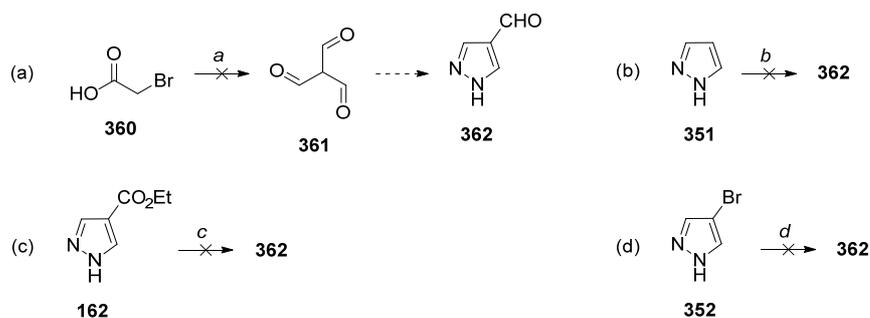


**Reagents and conditions:** (a) LDBBA (1.5 eq), THF, 0 °C, 3.5 h, **357** 0%, **162** quant; (b) DIBAL (10 eq), THF, 0 °C, 4 h, 6%; (c) (i) <sup>i</sup>PrMgBr (1.3 eq), THF, 0 °C, 1 h; (ii) DMF (5.0 eq), rt, 1 h, **357** trace, **359** 17% conv.; (d) (i) <sup>i</sup>PrMgBr (1.3 eq), THF, 0 °C, 30 min; (ii) DMF (5.0 eq), rt, 1 h, **357** 0%, **359** quant conv.; (e) (i) <sup>i</sup>PrMgCl·LiCl (1.3 eq), THF, -15 °C, 30 min; (ii) DMF (5.0 eq), -15 to 0 °C, 2 h, **357** 0%, **359** quant conv.; (f) (i) <sup>n</sup>BuLi (1.3 eq), -78 °C, THF, 30 min; (ii) DMF (5.0 eq), -78 °C, 3 h, complex mixture.

**Scheme 5.10** Attempted synthesis of *N*-Boc-4-formylpyrazole **357**.

Two-stage reduction of the ester **354** via the intermediate alcohol **358** using DIBAL was also attempted with the intention of later MnO<sub>2</sub> oxidation to the aldehyde **357**.<sup>182</sup> However, reaction of the ester **354** with 3 equivalents of DIBAL led to no reaction (as determined by <sup>1</sup>H NMR of the crude material), while an increase in the DIBAL stoichiometry to 10 equivalents gave quantitative conversion but a very poor isolated yield (6%) of the crude product and therefore oxidation was never attempted (**Scheme 3.10b**). The reasons for this poor result are unknown, but it is likely that the product **358** was either water soluble or remained chelated to residual aluminium salts during aqueous workup and was unknowingly discarded.

Finally, generation of the aldehyde **357** was also attempted by *in situ* metallation and formylation of *N*-Boc-4-halopyrazoles **355/356** (**Scheme 5.10c** and **d**) but this too was unsuccessful. Magnesiation (<sup>i</sup>PrMgBr or <sup>i</sup>PrMgCl·LiCl)<sup>186</sup> of the substrates **355/356** and reaction with DMF led only to hydrodehalogenation: the peaks at 8.11 (1H, dd, *J* = 2.8, 0.6 Hz), 7.72 (1H, dd, *J* = 1.6, 0.6 Hz), 6.39 (1H, dd, *J* = 2.8, 1.6 Hz) and 1.66 (9H, s) apparent in the crude <sup>1</sup>H NMR spectra are consistent with the literature data<sup>187</sup> for *N*-Boc-pyrazole **359**, which would have formed by acidic quenching of the metallated pyrazole intermediate, which had apparently failed to undergo reaction with DMF under our conditions. Metallation/formylation (of **356**) with <sup>n</sup>BuLi gave only a complex mixture of products implying that this method, too, would be unsatisfactory. In light of these disappointing results, efforts were then focussed on generating 4-formylpyrazole **362** from which the *N*-Boc (and *N*-alkyl)



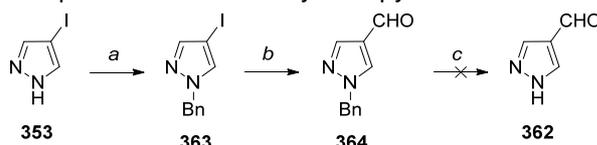
**Reagents and conditions:** (a) (i)  $\text{POCl}_3$  (3.0 eq), DMF (10 eq), 0 °C to rt, 1.5 h; (ii) **360**, 70 °C, 24 h, 0%; (b) (i)  $(\text{COCl}_2)$ , (1.2 eq), DMF (10 eq), 0 °C, 30 min; (ii) **351**, 40 °C, 1 h; (iii) NaOH (10 eq), DMF/ $\text{H}_2\text{O}$ , 105 °C, 20 min, then 4 °C, 18 h, 0% conv.; (c) LDBBA (1.3 eq), THF, 0 °C to rt, 18 h, trace conv.; (d) (i)  ${}^t\text{BuLi}$  (3.0 eq), THF, -78 °C to rt, 2.5 h; (ii) DMF (1.5 eq), -78 °C to rt, 18 h, 0%.

**Scheme 5.11** Attempted synthesis of 4-formylpyrazole **362**.

derivatives could be accessed directly.

Surprisingly, synthesis of the aldehyde **362** according to literature procedure was also unsuccessful, and these efforts are summarised in **Scheme 5.11**. Synthesis of **362** *via* the reported preparation from hydrazine and triformylmethane<sup>188a</sup> was made impossible because the reaction used to generate the key tris-aldehyde precursor **361**<sup>188b</sup> from bromoacetic acid **360** was unsuccessful, showing none of the desired product in the crude  ${}^1\text{H}$  NMR spectrum after aqueous workup (**Scheme 5.11a**). Vilsmeier formylation of 1*H*-pyrazole **351** using  $(\text{COCl})_2/\text{DMF}$  as the active reagent precursor (*cf.* preparation of indole **331**; **Scheme 5.11b**) also proved futile, giving only unreacted starting material. Reduction of the ester **162** with LDBBA<sup>189</sup> (**Scheme 5.11c**), and a lithiation/formylation reaction<sup>188a</sup> with 4-bromopyrazole (**Scheme 5.11d**) were also ineffective means of synthesising **362**, although these cases of failure are perhaps less surprising: the reported protocol for the reduction of **162**<sup>189</sup> was conducted in a flow reactor, meaning that the conditions are not necessarily transferable to a batch reaction such as that described herein. Similarly, the lithiation/formylation (of **352**) failure is probably as easily explained by deviation from the reported protocol<sup>188a</sup> by substitution (on the basis of in-house availability) of the more hazardous  ${}^t\text{BuLi}$  with the less hazardous, but also less reactive  ${}^n\text{BuLi}$ .<sup>190</sup>

In a final effort to generate 4-formylpyrazole, it was thought that *N*-protection of 4-iodopyrazole **353** followed by metallation/formylation and subsequent deprotection would yield the desired product in a straightforward albeit convoluted manner.

**Table 5.1** Attempted deprotection of *N*-benzylated pyrazole **364**.

**Reagents and conditions:** (a) BnBr (1.2 eq), K<sub>2</sub>CO<sub>3</sub> (2.0 eq), acetone, reflux, 3 h, 94%; (b) (i) <sup>i</sup>PrMgBr (1.3 eq), THF, 0 °C, 1 h; (ii) DMF (5.0 eq), 0 °C to rt, 1.75 h, 85%; (c) See table entries.

Entry	Reagents and conditions for (c)	Conv. (%) <sup>a</sup>	Ref.
1	HCO <sub>2</sub> H (175 eq), 10% Pd/C (65 mol%), EtOH, rt, 5 h.	0	191
2	HCO <sub>2</sub> H (175 eq), 5% Pd/C (100 mol%), EtOH, reflux, 5 h.	0	191
3	<sup>t</sup> BuOK (7.0 eq), DMSO (10 eq), THF, 0 °C to rt, 18 h.	Decomp.	192
4	<sup>t</sup> BuOK (10 eq), DMSO (10 eq), THF, rt, 72 h.	Decomp.	192
5	H <sub>2</sub> , 5% Pd/C (25 mol%), MeOH, rt, 18 h.	0	193

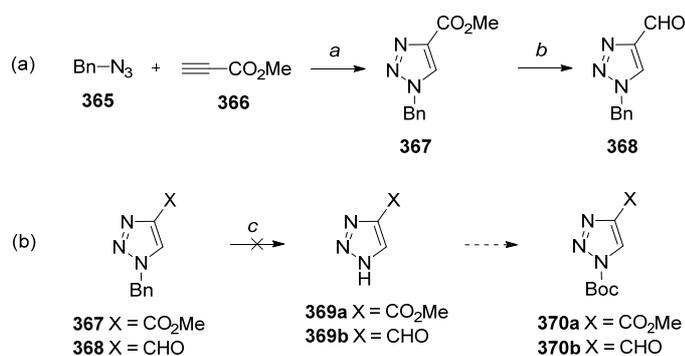
<sup>a</sup>As determined by <sup>1</sup>H NMR of the crude material.

Towards this end (see scheme from **Table 5.1**), iodopyrazole **353** was *N*-benzylated by reaction with BnBr in acetone in the presence of K<sub>2</sub>CO<sub>3</sub>.<sup>194</sup> Subsequent magnesiation and formylation with <sup>i</sup>PrMgBr/DMF<sup>186a</sup> gave the product **364** in 80% yield (over 2 steps). Unfortunately, a range of debenzoylation conditions (**Table 5.1**) which included transfer hydrogenation protocols (**Table 5.1**, Entry 1 and 2), basic cleavage (**Table 5.1**, Entry 3 and 4) and standard catalytic hydrogenation (**Table 5.1**, Entry 5) were unsuccessful in generating the pyrazole **362** and efforts towards its synthesis were therefore drawn to a close.<sup>195</sup>

#### 5.2.4 Triazole Heterocycles

For reasons of convenience, the synthesis of the *N*-benzylated triazole **368** was carried out, as opposed to the preparation of a methoxyethanol derivative. Benzyl azide **365** was reacted with methyl propiolate **366** in the presence of Cu(I) (formed by the reduction of CuSO<sub>4</sub>•5H<sub>2</sub>O with sodium ascorbate) and TBTA<sup>196</sup> to give the triazole ester **367** in 93% yield<sup>197</sup> (**Scheme 5.12a**). Exclusion of atmospheric O<sub>2</sub> and the use of the stabilising ligand TBTA was found to be essential for this transformation, because isolated yields for the CuAAC reaction greatly decreased (to ~30%) without implementation of these measures, probably as a result of undesired oxidation of the active Cu(I) species to the inactive Cu(II) by atmospheric O<sub>2</sub>.

DIBAL-mediated reduction of ester **367** gave the aldehyde **368** in 73% yield<sup>198</sup> (68%



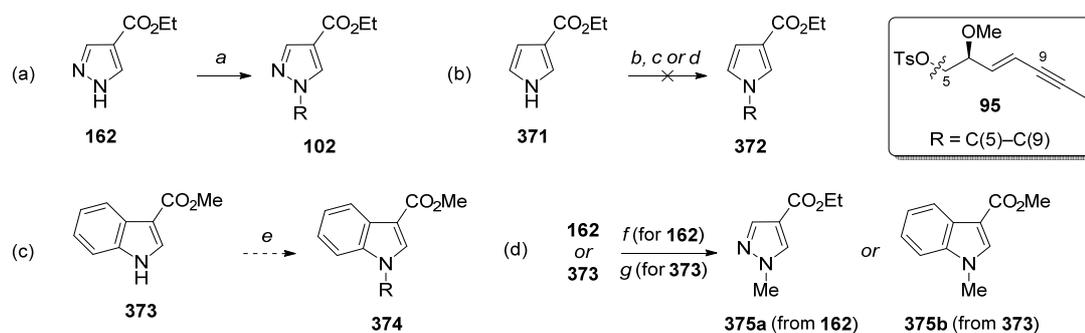
**Reagents and conditions:** (a) (i) Sodium ascorbate (20 mol%), CuSO<sub>4</sub>·5H<sub>2</sub>O (10 mol%), <sup>t</sup>BuOH/H<sub>2</sub>O (3:1), 5 min; (ii) TBTA (13 mol%), 15 min; (iii) **365**, **366** (1.2 eq), 18 h, 93%; (b) DIBAL (3.3 eq), hexane/DCM (~2:1), -78 °C, 2.5 h, 73%; (c) H<sub>2</sub>, Pd/C (5 mol%), 1,1,2-TCE (1.1 eq), MeOH, 24 h, **370** 0%.

**Scheme 5.12** (a) Synthesis of 4-formyl-*N*-benzyl triazole **368**; (b) attempted reductive cleavage of the *N*-benzyl triazoles **367** and **368** to give their corresponding 1*H*-triazoles **369**.

yield over 2 steps; **Scheme 5.12a**). Although we were satisfied that the benzylated derivative **368** was an adequate *N*-alkylated triazole model for ET coupling it is worth noting that with a view to synthesising a Boc derivative (and in the process provide a triazole substrate for potential *N*-alkylation), synthesis of the free 1*H*-triazoles **369** was attempted by benzyl cleavage using catalytic hydrogenation of both ester and formyl triazoles **367/368** in the presence of 1,1,2-TCE (**Scheme 5.12b**).<sup>199</sup> However, neither substrate was debenzylated under these conditions, and as a consequence, the Boc derivatives **370** were not synthesised, and we were restricted to the use of the benzyl derivative **368** as a model triazole for ET coupling.

### 5.2.5 *N*-Alkylation of 1*H*-*N*-Heterocycles

Niblock<sup>16</sup> showed that the C(1)–C(9) pyrazole analogue **102** could be synthesised by the reaction of pyrazole **162** with the C(5)–C(9) fragment tosylate **95** in the presence of K<sub>2</sub>CO<sub>3</sub> (**Scheme 5.13a**). Although these conditions gave a moderate yield of the product **102** (58%), an extended reaction time was required (48 h) and the conditions were not transferable for use with other heterocycles; for example, no reaction was observed with pyrrole **371** under the same conditions (**Scheme 5.13b**).<sup>16</sup> Pyrrole **371** also failed to react usefully with tosylate **95** using stronger, alternative bases (KOH or NaH), while indole **373** gave only trace conversion to the product **374** on reaction with **95** upon heating to 80 °C following reaction with NaH (**Scheme 5.13c**).



(a) to (c): Niblock (Ref. 16); (d) **375a**: Dewolf Jr. et al. (Ref. 200a); **375b**: Dunten et al. (Ref. 200b)

**Reagents and conditions:** (a) **95**,  $\text{K}_2\text{CO}_3$ , DMF, rt, 48 h, 58%; (b) **95**,  $\text{K}_2\text{CO}_3$ , DMF, rt, 72 h, 0%; (c) **95**, NaH, DMF, rt, 48 h, 0%; (d) **95**, KOH, DMSO, rt, 18 h, trace; (e) **95**, NaH, DMF, 80 °C, 72 h, trace; (f) MeI, NaH, THF, 0 °C to rt, 18 h, **375a** 90%; (g) MeI, NaH, DMF, 0 °C to rt, 18 h, **375b** quant.

**Scheme 5.13** Early studies on *N*-alkylation of (a) pyrazole **162**; (b) pyrrole **371**; (c) indole **373** with tosylate **95**.<sup>16</sup> (d) *N*-Methylation of pyrazole **162** and indole **373** with MeI.<sup>200</sup>

Aside from the substrate dependence of the bases used in promoting *N*-alkylation of 1*H*-*N*-heterocycles, a brief examination of the literature highlights the importance of using the correct electrophile. Only trace conversion was observed upon attempted NaH-mediated *N*-alkylation of indole **373** with the C(5)–C(9) tosylate **95**, even at elevated temperature (80 °C; **Scheme 5.13c**);<sup>16</sup> but the NaH-mediated reaction of indole **373** (and indeed pyrazole **162**) with MeI has been shown<sup>200</sup> to give high yields of the corresponding *N*-methylated products **375** at only room temperature (**Scheme 5.13d**), thus supporting the notion that a *tosylate* model system would be a likely requirement for reliable transfer of model conditions to the synthesis of C(1)–C(9) fragment analogues. With these points in mind, a straightforward and high-yielding *N*-alkylation protocol was required which would have a wide (*N*-heterocycle) substrate scope and be permissive of the use of an alkyl tosylate electrophile.

Given that the use of  $\text{K}_2\text{CO}_3$  at room temperature gave promising results for the reaction of pyrazole **162** with the C(5)–C(9) tosylate **95**,<sup>16</sup> the use of a carbonate base represented the best starting point for exploring the required conditions for *N*-alkylation of heterocycles in the current study. However, it was reasoned that changing to the stronger base  $\text{Cs}_2\text{CO}_3$  and heating the reaction mixture would perhaps push the moderate yield obtained previously towards quantitative levels. To investigate these modifications to Niblock's conditions,<sup>16</sup> *N*-alkylation of a range of 3- (or 4- in the case of pyrazole) substituted heterocycles with 1 equivalent of the (easily synthesised)<sup>201</sup> model tosylate **341** was attempted (**Table 5.2**).

**Table 5.2** Synthesis of model *N*-alkylated heterocycles

Entry	Series	Het	X	Eq Cs <sub>2</sub> CO <sub>3</sub>	Solv.	Temp (°C)	Time (h)	Prod.	Yield (%) <sup>a,b</sup>
1	A	<b>346</b>	CHO	2	THF	72	18	<b>376</b>	(50)
2 <sup>c</sup>	A	<b>346</b>	CHO	2	THF	72	48	<b>376</b>	95 <sup>d</sup>
3	A	<b>346</b>	CHO	2	DMF	120	18	<b>376</b>	25 (100)
4	B	<b>162</b>	CO <sub>2</sub> Et	2	THF	72	18	<b>377a</b>	94
5	B	<b>351</b>	H	2	THF	72	18	<b>377b</b>	(Trace)
6	B	<b>351</b>	H	2	DMF	158	18	<b>377b</b>	(79)
7	B	<b>351</b>	H	5	DMF	158	18	<b>377b</b>	27 (100)
8	B	<b>352</b>	Br	2	THF	72	18	<b>377c</b>	68
9	B	<b>353</b>	I	2	DMF	120	18	<b>377d</b>	80
10	C	<b>331</b>	CHO	2	THF	72	18	<b>378a</b>	63 (100)
11	C	<b>373</b>	CO <sub>2</sub> Me	5	THF	72	18	<b>378b</b>	97

<sup>a</sup>Isolated yield; <sup>b</sup>Values in parentheses refer to the extent of the conversion to the product as determined by <sup>1</sup>H NMR of the crude material; <sup>c</sup>10 mol% TBAI was also added to the reaction; <sup>d</sup>Based on isolated yield of the crude material (>95% purity by <sup>1</sup>H NMR).

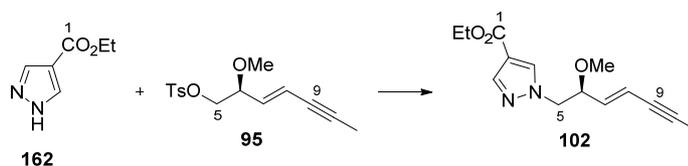
Gratifyingly, high conversion was generally observed in all cases, with any poor or moderate yields obtained by heating in the relatively low-boiling-point solvent THF easily increased by addition of 10 mol% TBAI (**Table 5.2**, Entry 2), by reaction at higher temperatures in DMF (**Table 5.2**, Entries 3, 6, and 7) or by use of increased base stoichiometry (**Table 5.2**, Entry 7). As a side note, use of a larger quantity of base with indole-3-methyl ester **373** (**Table 5.2**, Entry 11) was not a consequence of poor yield during early screening, but rather was performed strategically to ensure maximum conversion to *N*-alkylated product **378b** owing to the identical TLC R<sub>f</sub> values of the starting material and product.

The only poor to moderate isolated yields of the alkylated pyrrole **376** (**Table 5.2**, Entry 3) and indole **378a** (**Table 5.2**, Entry 10) are somewhat surprising when compared to the extent of (NMR) conversion, but this anomaly stems from the apparent instability of these products to silica gel chromatography<sup>202</sup> and therefore these compounds should be used without further purification (*cf.* **Table 5.2**, Entry 2).

Although inconsequential for a model study, this potential for diminished yield should be taken into consideration during synthesis of the C(1)–C(9) fragment analogues that incorporate these heterocycles. A similar anomaly with respect to NMR conversion and isolated yield was observed for the *N*-alkylation of 1*H*-pyrazole **351** (Table 5.2, Entry 7), but in this case the product **377b** was found to be volatile, and thus a poor isolated yield owing to issues of handling is less likely to be a problem on alkylation with the higher molecular weight C(5)–C(9) fragment.

It is worthwhile to comment on the differences in reactivity observed in the *N*-alkylation of the series of heterocycles. Variations in reactivity stem from the influence that each group has over the basicity of the nitrogen atom and thus the lability of the proton attached to the reactive nitrogen atom. As a consequence of resonance and inductive effects, an electron-withdrawing substituent (at the 3-position; or in the case of pyrazole, the 4-position), an additional ring heteroatom or an additional resonance contribution by a fused aromatic group would be expected to simultaneously increase the acidity of the *NH* proton and stabilise the conjugate amide base leading to more facile reaction. The substituent effect was observed directly in the *N*-alkylation of pyrazoles, whereby the pyrazole ester **162** (Table 5.2, Entry 4) reacted more efficiently than the bromopyrazole **352** (Table 5.2, Entry 8) or iodopyrazole **353** (Table 5.2, Entry 9), which in turn reacted more efficiently than 4-unsubstituted 1*H*-pyrazole **351** (Table 5.2, Entries 5 to 7). On comparing the systems of heterocycles, the benzofused heteroaromatic indoles (Table 5.2, Entries 10 and 11) reacted equally efficiently to the most reactive pyrazole **162**, while 3-formylpyrrole **346** (Table 5.2, Entries 1 to 3) was the least reactive of the (substituted) heterocycles because it lacks both an additional ring heteroatom (*cf.* pyrazole) or fusion with an aromatic ring system (*cf.* indole).

To confirm the applicability of these conditions to potential C(1)–C(9) fragment syntheses, alkylation of pyrazole **162** with the C(5)–C(9) tosylate **95**,<sup>203a</sup> was attempted using the optimised conditions (Table 5.2, Entry 4). A 67% yield of the product **102** was obtained, which although represented a small improvement over the yield obtained in previous study, still fell short of the almost quantitative yield obtained in the model study. It is therefore likely that a harsher set of conditions from



**Reagents and conditions:** Cs<sub>2</sub>CO<sub>3</sub> (2.0 eq), THF, reflux, 18 h, 67%.

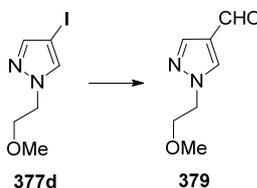
**Scheme 5.14** Alkylation of pyrazole **162** with the C(5)–C(9) fragment alkyl tosylate **95**.

**Table 5.2** would need to be applied when using the more sterically demanding C(5)–C(9) fragment alkyl tosylate **95**. Fortunately, the *N*-alkylation study indicates that a multitude of options are available including increased base stoichiometry, addition of catalytic TBAI, or heating in DMF at higher temperatures.

### 5.2.6 Completion of the Series of Model Heterocycles

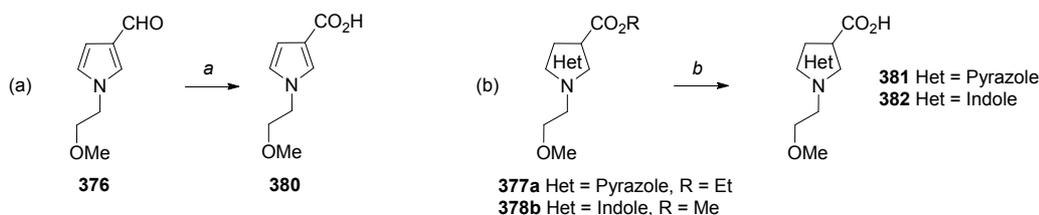
Having established effective alkylation conditions, attempts could be made synthesise the remaining *N*-alkylated pyrazolyl aldehyde for ET coupling (**Approach A**, **Scheme 5.6**); and in case a contingency strategy was required (**Approach C**, **Scheme 5.6**), convert the *N*-alkylated heterocycles to their carboxylic acids.

*N*-Alkylated 4-formylpyrazole **379** was synthesised according to the conditions used for *N*-benzylated 4-formylpyrazole **364** (see: **Table 5.1**). Thus, metallation of iodopyrazole **377d** with <sup>*i*</sup>PrMgBr followed by reaction with DMF gave the product aldehyde **379** in 71% yield (**Scheme 5.15**). Unfortunately, **379** is unstable, and rapidly decomposed under standard storage conditions and therefore was not practical for use in ET coupling. Fortunately, the prior synthesis of the stable *N*-benzylated analogue **364** meant that a suitable substitute was readily available.



**Reagents and conditions:** (i) <sup>*i*</sup>PrMgBr (1.3 eq), THF, 0 °C, 1 h; (ii) DMF (5.0 eq), 0 °C to rt, 2 h, 71%.

**Scheme 5.15** Synthesis of the *N*-alkylated pyrazole aldehyde **379**.

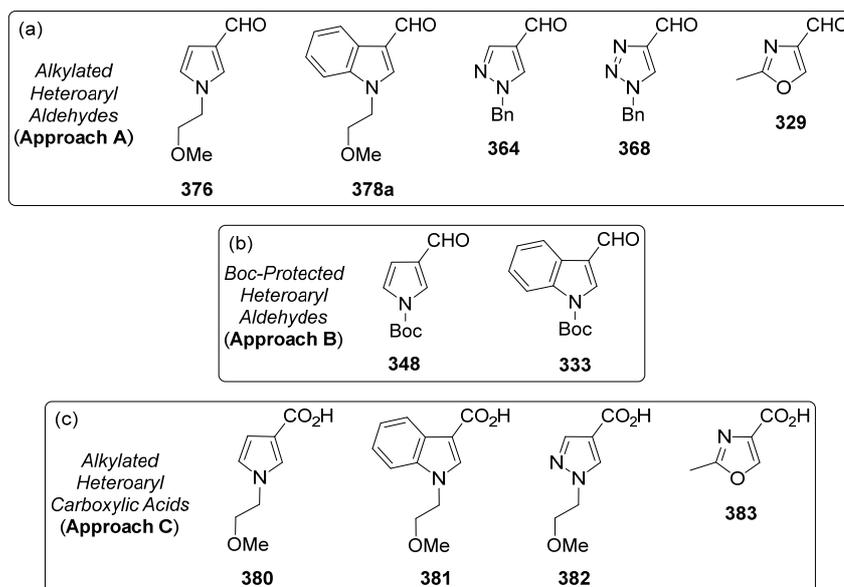


**Reagents and conditions:** (a) AgNO<sub>3</sub> (2.0 eq), NaOH (6.5 eq), MeOH/H<sub>2</sub>O (5:4), 70 °C, 18 h, 30%; (b) KOH (5.0 eq), EtOH/H<sub>2</sub>O (9:1), reflux, 18 h, **381** 97%, **382** quant.

**Scheme 5.16** Synthesis of model heterocyclic carboxylic acids: (a) pyrrole **380**; and (b) pyrazole **381** and indole **382**.

Synthesis of the pyrrole-3-carboxylic acid **380** was carried out by reaction of aldehyde **376** with AgNO<sub>3</sub> and NaOH<sup>204</sup> in MeOH to give the product **380** (**Scheme 5.16a**) in poor yield (30%), and contaminated with what is believed to be polymeric or decomposition material. Unfortunately, no attempts were made to purify the product (~86% purity by <sup>1</sup>H NMR) beyond aqueous workup; and owing to lack of starting material **376** at the time of reaction, no optimisation or use of other conditions was investigated. Fortunately, the syntheses of the pyrazole **381** and indole **382** carboxylic acid derivatives<sup>205</sup> were achieved more cleanly by hydrolysis of the corresponding esters **377a/378b** with KOH in aqueous EtOH (**Scheme 5.16b**). It is worth noting that the workup procedure for obtaining pyrazole **381** was problematic owing to its low solubility in DCM, whereby a very poor isolated yield (27%) was initially obtained. Fortunately, this was easily overcome by the re-extraction of the aqueous layers with EtOAc (to give a further 70% isolated yield), but because this problem occurred in the model studies, care should be taken to select a sufficiently polar solvent for workup when synthesising C(1)–C(9) heterocyclic fragment carboxylic acids from valuable C(1)–C(9) ester precursors.

Further model systems for ET coupling or esterification could be derived from commercially available substrates, for example the key 2-methyl-substituted oxazoles **329/383**. The substrate library thus developed (summarised in **Figure 5.1**) allowed ET coupling of model heterocyclic aldehydes with the C(10)–C(19) β-hydroxyketone fragment **86** to commence, and thus the approach required (**Approach A, B or C, Scheme 5.6**) for the synthesis of the C(1)–C(9)/C(10')–C(19') bis-alkynes to be determined.

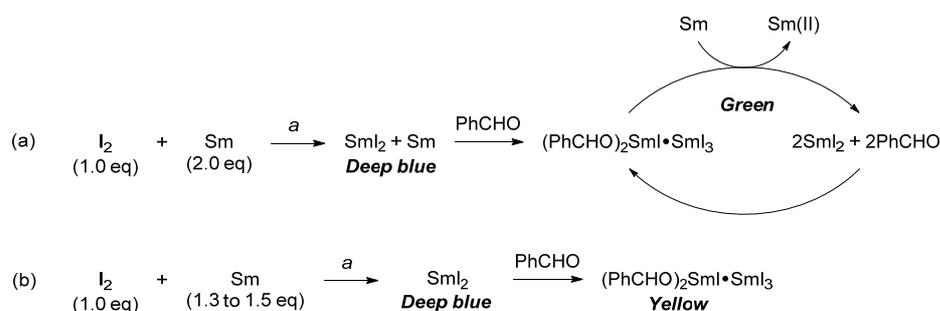


**Figure 5.1** Model (a) *N*-alkylated and (b) *N*-Boc heterocyclic aldehydes for ET coupling; (c) *N*-alkylated heterocyclic carboxylic acids for esterification.

### 5.3 Evans–Tischenko Coupling: the C(10)–C(19) $\beta$ -Hydroxyketone (86)

Initially it was deemed necessary to investigate ET coupling with a commercially available aldehyde for which precedent exists for successful reaction. Benzaldehyde was chosen because its use is frequently described,<sup>36b,90,174</sup> the formyl group contains aryl substitution (and so the electronics are similar to heteroaryl systems), and it is cheap and easily purified by reduced-pressure distillation over  $K_2CO_3$ . Furthermore, it was used as a sacrificial aldehyde for the generation of the active pre-catalyst in the heteroaryl ET reaction<sup>90,174</sup> and for the purposes of coupling valuable aldehydes, it would be necessary to use a similar methodology in the current study.

Before a discussion of ET reaction screening, it is important to comment on the synthesis of  $SmI_2$ .  $SmI_2$  (0.1 M in THF) was initially prepared by the ultrasound-promoted reaction between  $I_2$  (1 eq) and powdered metallic samarium (2 eq) in THF under an atmosphere of argon in an amalgamation of the procedures described by Proctor<sup>206</sup> and Hulme.<sup>174</sup> Although this led to the desired deep-blue solution, addition of the reagent when prepared in this fashion to PhCHO did not lead to the desired yellow reaction mixture [indicative of oxidation of Sm(II) to Sm(III)]<sup>170a,c</sup> and instead led to the formation of a green solution (**Scheme 5.17a**).<sup>207</sup>



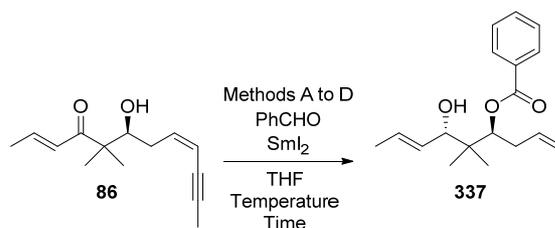
**Reagents and conditions:** (a) THF (0.1 M wrt  $I_2$ ), ultrasonic vibration, absence of light, Ar atmosphere, 1 h.

**Scheme 5.17** Generation of the (a) Sm(III) pinacol adduct from  $SmI_2$  prepared with 2 equivalents of samarium; (b) Sm(III) pinacol adduct upon minimisation of the quantity of residual metallic samarium.

Speculating that this was due to residual metallic samarium causing reduction of the newly formed Sm(III) pinacol species back to Sm(II),<sup>208</sup> the samarium stoichiometry was reduced (to 1.3 eq), and this proved successful in generating the required yellow solution upon addition of  $SmI_2$  to PhCHO (**Scheme 5.17b**).

With a reliable procedure for the generation of  $SmI_2$  accomplished, ET coupling between  $\beta$ -hydroxyketone **86** and PhCHO was attempted towards the synthesis of 1,3-*anti* diol monoester **337** (**Table 5.3**). Unfortunately, results were generally poor across the range of conditions screened, which included four different orders of reagent addition (**Methods A to D**); use of catalytic (**Table 5.3**, Entries 1, 2, 5 and 10) and stoichiometric (**Table 5.3**, remaining entries) loadings of the  $SmI_2$  pre-catalyst; and different temperatures ( $-20$ ,  $-10$  and  $25$  °C). On runs where product was isolated by column chromatography (**Table 5.3**, Entries 7 to 10), yields were typically poor and the product was contaminated with the starting material and/or unidentified side products. It was therefore immediately apparent that: (i)  $\beta$ -hydroxyketone **86** was likely to be poorly reactive under ET coupling conditions; and (ii) PhCHO was not a suitable substrate, and that a more electron-deficient aryl system would require to be investigated to establish suitable reaction conditions. Attention was therefore focussed on an alternative aryl system for ET coupling.

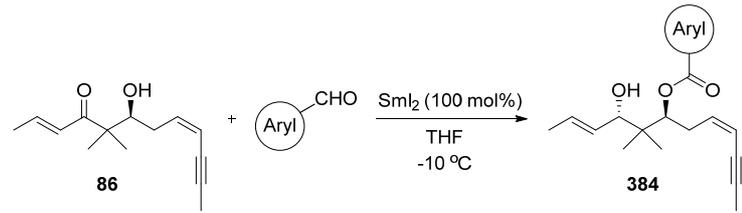
Given that 3- and 4-formylpyridines showed the most facile reactivity in the heteroaryl ET study with what is effectively a model system, the use of formylpyridines was investigated. To our delight, following addition of 100 mol%

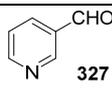
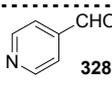
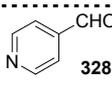
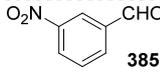
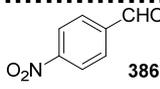
**Table 5.3** ET reaction between  $\beta$ -hydroxyketone **86** and benzaldehyde.

Entry	Method <sup>a</sup>	Eq PhCHO (Reactant) <sup>b</sup>	Eq PhCHO (Pre-catalyst) <sup>c</sup>	mol% SmI <sub>2</sub>	Temp (°C)	Time (h)	Yield (%) <sup>d,e</sup>
1	A	5.0	—	15	-10	1	(0)
2	A	5.0	—	50	-10	6	(0)
3	A	6.0	—	100	-10	1.5	(0)
4	A	6.0	—	200	-10	1	(nd) <sup>f</sup>
5	B	—	4.0	40	25	4	0
6	B	—	8.0	300	-10	1	0
7	C	4.0	2.0	200	-20	3	~41 <sup>g</sup>
8	C	4.0	2.0	200	25	5	5
9	C	4.0	4.0	300	-10	1	14
10	D	2.0	1.0	50	25	18	(20)

<sup>a</sup>Method A (one-pot protocol): **86**, PhCHO, SmI<sub>2</sub>, THF, absence of light; Method B (pre-catalyst protocol with early addition of the reactant aldehyde): (i) PhCHO, SmI<sub>2</sub>, rt, 30 min, absence of light; (ii) **86**; Method C (pre-catalyst protocol with addition of reactant aldehyde with the  $\beta$ -hydroxyketone): (i) PhCHO, SmI<sub>2</sub>, THF, 30 min, absence of light; (ii) **86**, PhCHO; Method D (pre-catalyst method with delayed addition of the  $\beta$ -hydroxyketone): (i) PhCHO, SmI<sub>2</sub>, THF, 0 °C, absence of light; (ii) PhCHO, 30 min; (iii) **86**; <sup>b</sup>Number of equivalents of PhCHO for reaction with substrate **86**; <sup>c</sup>Number of equivalents of PhCHO used during the Sm(III) pre-catalyst generation stage in Methods B to D; <sup>d</sup>Isolated yield; <sup>e</sup>Values in parentheses refer to the extent of conversion to the product as determined by <sup>1</sup>H NMR of the crude material. <sup>f</sup>The crude NMR spectrum was unclear but appeared to lack any characteristic signals and purification was not attempted; <sup>g</sup>The isolated product contained a marked proportion of impurities.

SmI<sub>2</sub> to THF solutions of the  $\beta$ -hydroxyketone **86** and 3- or 4-formylpyridine at -10 °C (*cf.* Method A, Table 5.4), good yields of the desired products were obtained as single diastereomers (Table 5.4, Entries 1 and 2). In each case, successful reaction was clear owing to additional peaks corresponding to aryl and allylic *CHOH* protons, and a pronounced ( $\geq 1$  ppm) upfield shift in the resonances of the C(17) ( $\delta = 6.56 \rightarrow 5.58$  ppm) and C(18) ( $\delta = 7.01 \rightarrow 5.70$  ppm) protons and the large downfield shift of the C(14) proton ( $\delta = 3.84 \rightarrow 5.39$  ppm; exemplified for the 3-formylpyridine derivative **384a**, Figure 5.2). In the case of the C(17) and C(18) protons, the reduction of the ketone to the allylic alcohol results in a loss of conjugation and therefore shielding on these protons is increased, while in the case of C(14), shielding is decreased as a consequence of being in the vicinity of an ester as opposed to the hydroxyl group. It is also worth noting that the C(11) and C(12)

**Table 5.4** Successful ET reactions between  $\beta$ -hydroxyketone **86** and aryl aldehydes.


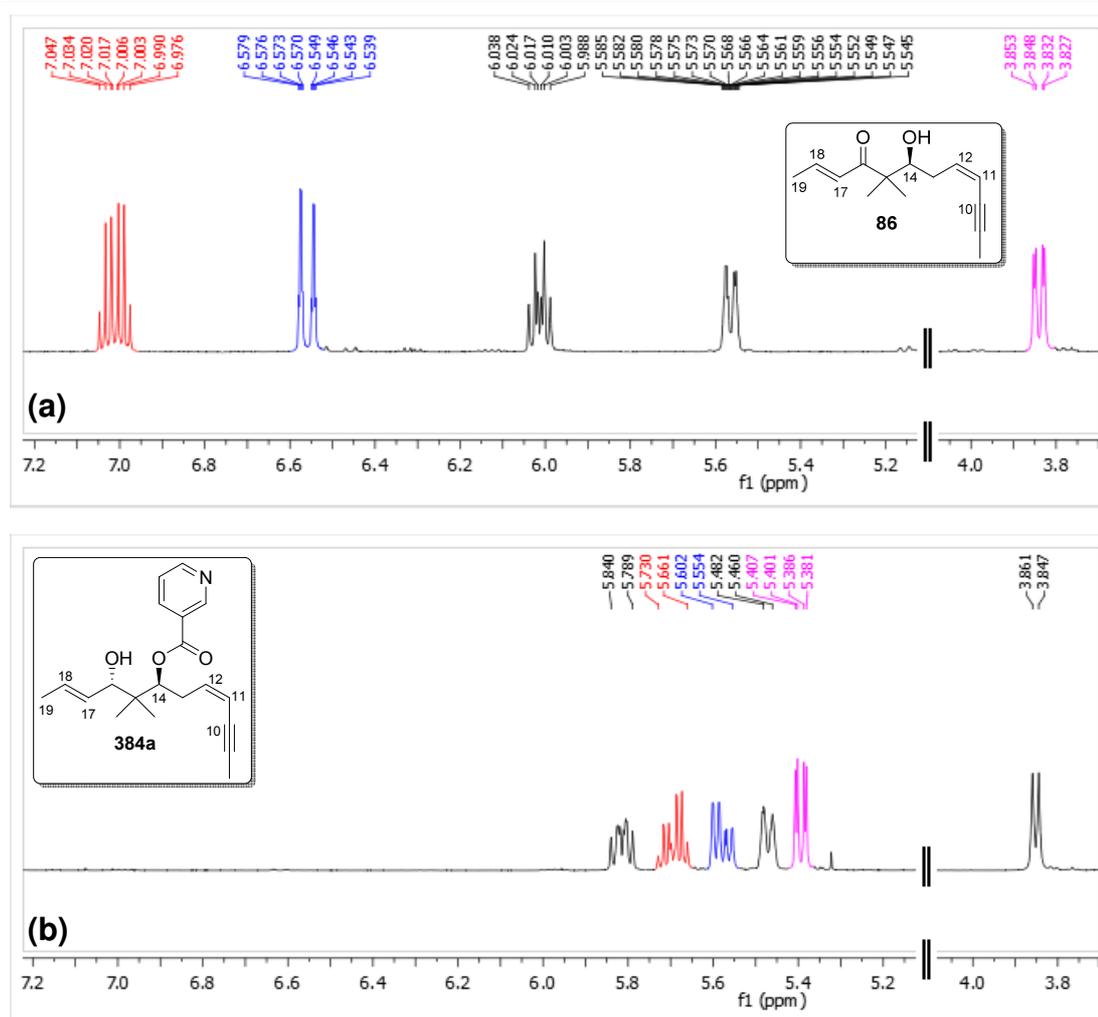
Entry	Aldehyde	Eq Aldehyde	Time (h)	Product	Yield (%) <sup>a</sup>	<i>dr</i> <sup>b</sup>
1	 <b>327</b>	6	4	<b>384a</b>	59	>95:5
2	 <b>328</b>	6	1.5	<b>384b</b>	65	>95:5
3 <sup>c</sup>	 <b>328</b>	1 then 5	2		53	>95:5
4	 <b>385</b>	6	4	<b>384c</b>	99	>95:5
5	 <b>386</b>	6	4	<b>384d</b>	64 <sup>d</sup>	>95:5

<sup>a</sup>Isolated yield; <sup>b</sup>As determined by <sup>1</sup>H NMR spectroscopy; <sup>c</sup>Sm(III) pre-catalyst was prepared by addition of SmI<sub>2</sub> to 1 eq of the aldehyde in THF at the stated temperature followed, after 30 mins, by addition of further aldehyde and  $\beta$ -hydroxyketone **86** cf. **Method C**, **Table 5.3**; <sup>d</sup>Ketone byproduct **387** was also isolated in 12% yield.

olefinic protons were slightly shielded (0.1–0.2 ppm) relative to the same protons in the  $\beta$ -hydroxyketone **86** precursor, probably as a result of  $\pi$ – $\pi$  interactions with the newly introduced aryl system leading to subtle electronic changes as a result of the induced magnetic field created by the aromatic ring-current.<sup>209</sup>

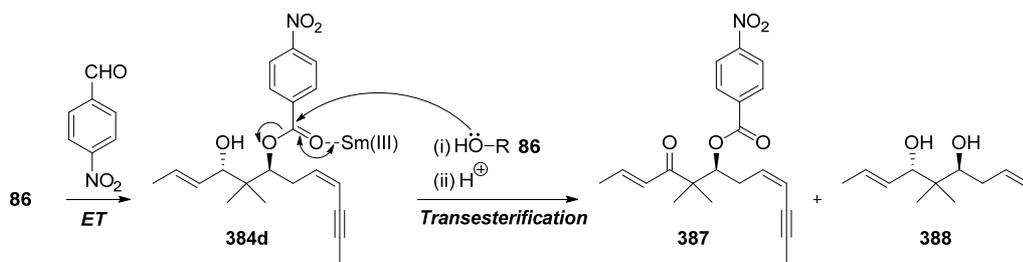
Because studies using valuable aldehydes would require the generation of the active Sm(III) catalyst from a sacrificial aldehyde, the protocol for 4-formylpyridine was repeated; but in this instance, with pre-stirring of 1 equivalent of the aldehyde with the SmI<sub>2</sub> followed by addition of the remaining reactant aldehyde and finally, after 10 minutes, the  $\beta$ -hydroxyketone (**Table 5.4**, Entry 3). This led to a slightly diminished but nonetheless acceptable 53% yield of the product, and indicated that the pre-catalyst method of Sm(III) generation would be a viable alternative to using the one-pot procedure employed in the first two reactions.

Because PhCHO was found not to react usefully in ET coupling, we were interested in discovering whether or not a derivative would give a successful reaction. Obvious substitutes were the (more electron-deficient) nitrobenzaldehydes and so the use of



**Figure 5.2** Change in chemical shift of the C(14) (magenta), C(17) (blue), and C(18) (red) protons on conversion of the (a) β-hydroxyketone starting material **86** to the (b) 3-formylpyridine derived 1,3-*anti* diol monoester **384a** [for clarity, only the left- and right-most peak values have been shown for the olefinic proton resonances in Figure (b)].

these substrates was investigated. Perhaps unsurprisingly, reaction of 3- and 4-nitrobenzaldehydes (**Table 5.4**, Entries 4 and 5 respectively) gave the desired products **384** in good to excellent yield. Somewhat curiously (on the basis of close intramolecular hydroxyl group proximity in **384d**), some 12% of the β-ketoester **387** was also isolated on reaction of 4-nitrobenzaldehyde with the β-hydroxyketone **86**. The most likely explanation for its formation would involve an intermolecular transesterification<sup>210</sup> whereby the nitrobenzoate ester moiety of the ET product **384d** is transferred to the unreacted starting material **86** following Lewis acid activation of the ester by Sm(III) (**Scheme 5.18**). This would give rise to the β-ketoester **387** and the diol **388**; although the latter was not isolated following chromatography,



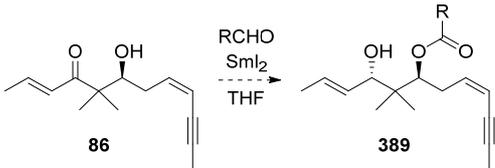
**Scheme 5.18** Mechanism of transesterification in the reaction of 4-nitrobenzaldehyde with  $\beta$ -hydroxyketone **86** under Sm(III) catalysis.

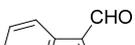
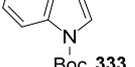
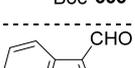
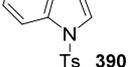
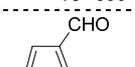
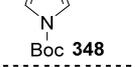
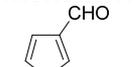
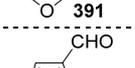
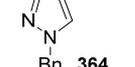
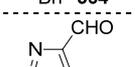
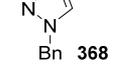
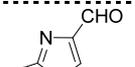
probably as a simple consequence of high polarity and thus a reduced propensity for elution on silica gel.

Despite the isolation of this minor side product **387** from the reaction of  $\beta$ -hydroxyketone **86** with 4-nitrobenzaldehyde, the quantitative isolation of the 3-nitrobenzoate-derived 1,3-*anti* diol monoester **384c** (Table 5.4, Entry 4) was particularly reassuring. This is because the high yield obtained for the reaction lends itself to the use of 3-nitrobenzaldehyde as a sacrificial aldehyde in the event that any model *N*-alkylated or *N*-Boc-protected *N*-heterocycles failed to react in the ET reaction, which in this instance would necessitate an esterification route towards the preparation of the heteroaryl 1,3-*anti* diol monoester derivative of **86**. Unfortunately, the use of this esterification contingency strategy was to become a requirement, because all of the model heteroaryl aldehydes, in addition to a small sample of other aldehyde substrates, failed to react usefully under our previously established ET coupling conditions (Table 5.5).

Reaction of the *N*-Boc-indole **333** (Table 5.5, Entries 1 to 3) and *N*-Ts-indole **390** [which was synthesised under standard tosylation conditions (TsCl/Et<sub>3</sub>N in DCM)<sup>211</sup> and screened owing to the larger electron-withdrawing capacity of the tosyl group when compared to the Boc group; Table 5.5, Entry 4] did not lead to the formation or isolation of the desired products **389** in so much as trace quantities after chromatography, even with large loadings of SmI<sub>2</sub> and extended reaction times. *N*-Boc-pyrrole **348** also failed to react, either under the conditions established herein (Table 5.5, Entry 5), or Hulme's heteroaryl coupling conditions (Table 5.5, Entry 6).

Reaction of 3-furancarboxaldehyde **391** under ET coupling conditions provided some

**Table 5.5** Unsuccessful ET reactions between  $\beta$ -hydroxyketone **86** and aldehydes.


Entry	Aldehyde	Eq Aldehyde	Pre-catalyst	mol% Sml <sub>2</sub>	Temp (°C)	Time (h)	Product	Yield (%) <sup>a</sup>
1		3.0	3-PyCHO	100	-10	3		0
2		4.0	None	10	25	18	<b>389a</b>	0
3		4.0	4-NO <sub>2</sub> ArCHO	800	25	18		0
4		6.0	None	100	-20	3	<b>389b</b>	0
5		3.0	4-PyCHO	100	-10 to 25	21	<b>389c</b>	0
6		4.0	None	200	-10	3		0
7		6.0	None	100	-20	4	<b>389d</b>	~65
8		6.0	None	100	-10	4	<b>389e</b>	7 <sup>b</sup>
9		6.0	None	100	-20	4	<b>389f</b>	0
10		6.0	None	100	-10	4	<b>389g</b>	0
11		6.0	None	100	-10	3	<b>389h</b>	0
12		6.0	None	100	-20	4	<b>389i</b>	0

<sup>a</sup>Yields as determined by <sup>1</sup>H NMR of the crude material unless otherwise stated; <sup>b</sup>Isolated yield;

promise, giving (tentatively) an ~65% conversion to the 1,3-*anti* diol monoester **389d** by <sup>1</sup>H NMR (Table 5.5, Entry 7). Unfortunately, the product **389d** could not be separated from residual (unidentified) contaminants; and attempts to repeat the reaction under the same conditions were unsuccessful. As a result, an accurate yield could not be determined, and the product could not be isolated in sufficient purity for full characterisation. *N*-Benzyl-pyrazole **364** (Table 5.5, Entry 8) also coupled successfully under ET conditions, albeit giving only a meagre 7% isolated yield following purification. Given the difficulties in performing an esterification with *N*-alkylated pyrazole-4-carboxylic acid **382** (reported *vide infra*), ET coupling under

alternative conditions, which could lead to useful yields of the desired product **389e**; and/or coupling of its *N*-Boc analogue, which is predicted to react more smoothly, would certainly be worthy of future investigation.

Further heterocycles investigated in our ET studies include the *N*-benzyltriazole **368** (Table 5.5, Entry 9) and the 2-methyloxazole **329** (Table 5.5, Entry 10). Reaction of these substrates under Sm(III) catalysis gave only unreacted starting material, which is perhaps unsurprising given that both heterocyclic aldehydes contain a nitrogen atom in the  $\alpha$ -position relative to the reactant formyl group, and such substrates have been shown to be inert to ET coupling.<sup>90,174</sup> Finally, alkyl aldehydes **392/393** (Table 5.5, Entries 11 and 12) failed to react to give the desired 1,3-*anti* diol monoesters **389** under the conditions screened. In particular, the outcome of these final two reactions perhaps serve to highlight the comparably inert nature of the C(10)–C(19) fragment under ET redox esterification conditions versus the model system **325** (see: Scheme 5.5) as used by Hulme,<sup>174</sup> and indeed other similar, *gem*-dimethyl-functionalised  $\beta$ -hydroxyketones.<sup>172,212</sup>

In the context of the synthesis of C(1)–C(9)/C(10')–C(19') fragments of disorazole C<sub>1</sub> these results were very disappointing, because none of the heterocycles (even in their more electron-deficient, *N*-Boc form) which had been targeted as good C(1)–C(9) analogues, or other aldehydes with desirable cyclic structural motifs led to reactivity under SmI<sub>2</sub> ET coupling conditions, implying that fully functionalised C(1)–C(9) analogues of these (hetero)cyclic systems would also be unsuccessful. The reasons for such poor reactivity are difficult to speculate upon considering the comparative success in the published heteroaryl ET study<sup>174</sup> of at least two of the substrates investigated (*N*-Boc-indole **333** and 3-formylfuran **391**). However, it is likely that the steric demands imparted by the enyne and *gem*-dimethyl groups in the  $\beta$ -hydroxyketone **86** probably had a role in the observed lack of reactivity, and the electronic stability provided by the enone over a standard ketone may also have made the reaction less energetically favourable. To confirm which of these groups had the largest detrimental influence, reactions with analogous substrates that do not contain one of the enyne, *gem*-dimethyl or enone groups would require to be studied.

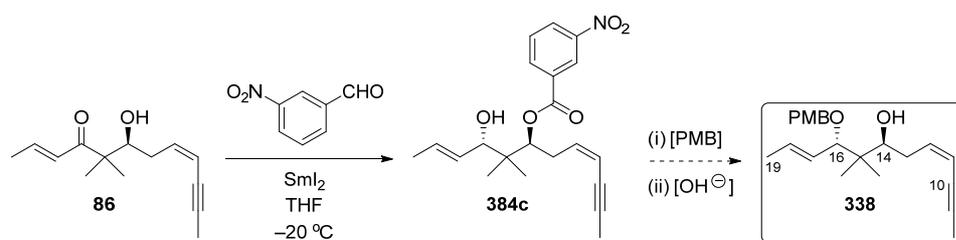
Also worthy of note is that the conditions found to be successful for the pyridyl and

nitrophenyl series of heterocyclic aldehydes were also slightly different (reduced  $\text{SmI}_2$  loading) from those found to be successful in the publication; although even those conditions were found not to give the desired product in the case of *N*-Boc-pyrrole or benzaldehyde, further implicating the  $\beta$ -hydroxyketone **86** as the cause of poor ET reactivity. Fortunately, a number of substrates were successful, and this meant that our contingency approach could be examined as a potential means of generating C(1)–C(9)/C(10')–C(19') fragments.

## 5.4 Esterification Approach

Having established that a strategy involving direct ET coupling of C(1)–C(9) heterocyclic aldehyde fragments or Boc-protected heterocycles (with subsequent deprotection and *N*-alkylation) would most likely prove to be unsuccessful, attention was directed towards a stepwise approach. This would involve the use of a sacrificial aldehyde to introduce the 1,3-*anti* stereochemistry at C(14)–C(16), subsequent hydroxyl protection, ester hydrolysis and esterification of C(1)–C(9) carboxylic acids *Het-111* to generate the required (*O*-protected) C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis alkynes *Het-336* (**Approach C, Scheme 5.6, Section 5.1.4**).

Substrate screening results from the ET model study with  $\beta$ -hydroxyketone **86** indicated that 3-nitrobenzaldehyde would be the best choice as a sacrificial aldehyde for the ET reaction owing to the superior yield obtained when compared to other counterparts; Wipf's total synthesis of disorazole  $\text{C}_1$ <sup>26</sup> indicates that PMB protection would provide the safest means of maintaining the somewhat sensitive diene-yne moiety for the subsequent deprotection step (*cf.* silyl protection; see **Chapter 1, Section 1.2**) and thus, a PMB group was chosen as the alcohol protecting group. Subsequent ester hydrolysis following protection would generate the requisite mono-*O*-protected 1,3-*anti* diol **338** for esterification (**Scheme 5.19**).



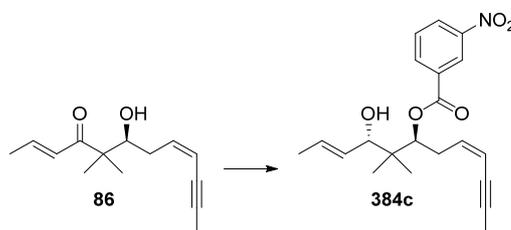
**Scheme 5.19** Proposed forward synthesis of mono-protected diol **338**.

### 5.4.1 Synthesis of the C(10)–C(19) Mono-Protected Diol (**384c**)

Before a discussion of PMB protection, it is important to comment on the synthesis of the ET product **384c**, because this would be required on a large scale. No problems of scalability were encountered, and large-scale (~350 mg) coupling of the  $\beta$ -hydroxyketone **86** was achieved using the same conditions as those in screening (Scheme 5.20), with yields typically between 60 and 94% and no apparent reduction in diastereoselectivity as determined by  $^1\text{H}$  NMR spectroscopy (>95:5 *dr*). On larger scales, stirring of the crude mixture with  $\text{NaHSO}_3$  (in aqueous EtOH) is advised for removal of excess 3-nitrobenzaldehyde (as its bisulfite adduct), as failure to do so tended to lead to co-elution of the aldehyde on silica with the desired product **384c**.

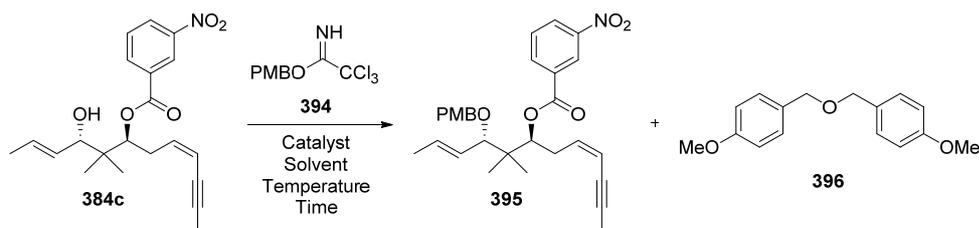
PMB protection of the alcohol **384c** was then to be carried out, and it was required that this be performed under acidic conditions to minimise the potential for problems associated with concomitant cleavage of the base-labile C(14) ester. The reagent typically used for this process is PMB-TCA **394**, and this was synthesised quantitatively by the reaction of PMBOH with trichloroacetonitrile under base catalysis (10 mol% NaH) according to literature procedure.<sup>213</sup> The product trichloroacetimidate was unstable to flash chromatography, but was obtained in high purity (>95% by  $^1\text{H}$  NMR) and was therefore deemed suitable for PMB protection of the required substrate.

PMB protection was not as straightforward as anticipated because a number of organic acid catalysts such as CSA (Table 5.6, Entry 1), TfOH (Table 5.6, Entry 2) and TFA (Table 5.6, Entry 3) failed to give satisfactory results and resulted in poor conversion to the desired product **395** and required long reaction times; thus, attention was focussed on the use of Lewis acid catalysis.



**Reagents and conditions:** (i) 3-Nitrobenzaldehyde (5.6 eq),  $\text{SmI}_2$  (94 mol%), THF,  $-20^\circ\text{C}$ , 4 h; (ii)  $\text{NaHSO}_3$  (11.3 eq), EtOH/ $\text{H}_2\text{O}$  (5:1), 3 h, 94%, >95:5 *dr*.

**Scheme 5.20** Large-scale preparation of 1,3-*anti* diol monoester **384c**.

**Table 5.6** PMB protection of 1,3-*anti* diol monoester **384c**.

Entry	Eq 394	Catalyst	mol% Catalyst	Solv.	Temp (°C)	Time (h)	Yield (%) <sup>a,b</sup>	Ratio 395:396
1	1.5	CSA	20 + 130 <sup>c</sup>	DCM	25	144	(~50)	—
2	1.5	TfOH	20	DCM	25	1	0	—
3	1.5	TFA	20	DCM	0 to 25	18	43	3.8:1
4	2.0	Sc(OTf) <sub>3</sub>	5	PhMe	25	1	65 (88)	3.6:1
5	3.0	Sc(OTf) <sub>3</sub>	10	PhMe	0 to 25	1	79 (100)	1.8:1
6	1.2	Sc(OTf) <sub>3</sub>	10	PhMe	25	18	(60)	—
7	3.0	Sc(OTf) <sub>3</sub>	10	PhMe	25	1	74 <sup>d</sup>	2:1

<sup>a</sup>Isolated Yield; <sup>b</sup>Values in parentheses refer to the extent of conversion to the product as determined by <sup>1</sup>H NMR of the crude material. <sup>c</sup>The reaction commenced with 20 mol% CSA but after 24 h, an additional 130 mol% was added due to lack of apparent reactivity as determined by TLC; <sup>d</sup>Isolated yield, calculated on the basis of purified product mass and subsequent comparison of the **395:396** ratio as determined by <sup>1</sup>H NMR spectroscopy; <sup>e</sup>Reaction was quenched with 20 eq 1,3-propanediol before aqueous workup;

Rai and Basu<sup>214</sup> found that excellent yields were obtained when PMB-TCA was used to protect alcohols in the presence of lanthanide-based Lewis acids, in particular Sc(OTf)<sub>3</sub>. Thus, our initial Sc(OTf)<sub>3</sub>-mediated conditions (**Table 5.6**, Entry 4) involved the use of 2 equivalents of PMB-TCA and 5 mol% of the catalyst in toluene according to the reported conditions. After 1 h, excellent conversion (88%) was observed, and this was increased to quantitative conversion on doubling the catalyst loading and increasing the PMB-TCA stoichiometry, with good isolated yields obtained in each case. Unfortunately, it was found that in both cases the product **395** was contaminated with significant quantities of PMB<sub>2</sub>O **396** after purification by silica-gel chromatography, as measured by comparison of the integrals of the CH<sub>2</sub>Ar protons for the product **395** [ $\delta$  = 4.38 and 4.07 (2 × 1H, d)] and side product **396** [ $\delta$  = 4.49 (4H, s)].<sup>215</sup> The formation of the dimer was thought to be a consequence of both the large excess of the PMB-TCA, and the use of an aqueous quench during workup.

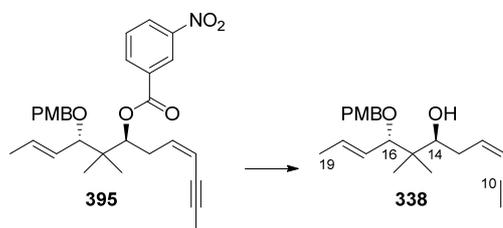
Attempts were then made to minimise the formation of the dimer by reducing the loading of PMB-TCA and by quenching with an alcohol substrate to consume residual PMB-TCA. Unfortunately, both measures proved ineffective: a reduction in the quantity of PMB-TCA used for reaction with the substrate lead to incomplete

reaction (**Table 5.6**, Entry 6), while quenching of the reaction with a large excess of 1,3-propanediol [which in a test reaction was found to react quantitatively with PMB-TCA in only 10 minutes under 10 mol% Sc(OTf)<sub>3</sub> catalysis] also did not lead to a diminished quantity of PMB<sub>2</sub>O **396** in the purified product (**Table 5.6**, Entry 7).

It is worth noting that product **395**:PMB<sub>2</sub>O ratios varied following purification on repeated runs using conditions as in **Table 5.6**, Entry 5, typically between 2 to 7:1. This may have been a consequence of solubility (in DCM, used in column loading), and it is possible that crystallisation and filtration of the side product could be performed on larger scales. It is also plausible that direct chromatography without aqueous workup could reduce the quantity of PMB<sub>2</sub>O, although this was never attempted because attempted chromatography of PMB-TCA led to marked column streaking and it was believed that this may also lead to contamination of the product.

Despite the problems of purity, the use of Sc(OTf)<sub>3</sub> consistently gave high levels of conversion and good isolated yields (~80%) on moderate reaction scales (up to ~1 g) using conditions from **Table 5.6** Entry 5, and so the product/PMB<sub>2</sub>O mixture was taken forward to the hydrolysis step required for the generation of the key mono-protected diol **338**. It was expected that ester **395** would still react smoothly given the likely inertness of PMB<sub>2</sub>O, and it was hoped that the hydrolysis product **338** would be separable on revealing the polar hydroxyl group. Ester hydrolysis was achieved by treatment of the protected 1,3-*anti* diol monoester **395** with LiOH in aqueous MeOH, which gave the product in excellent yield (91% by <sup>1</sup>H NMR), **Scheme 5.21**).

Unfortunately, separation of PMB<sub>2</sub>O **396** at this stage was not possible, because the starting material **395**, side product **396** and product **338** have identical R<sub>f</sub> values on



**Reagents and conditions:** LiOH (12 eq), MeOH/H<sub>2</sub>O (10:1), reflux, 18 h, 91%.

**Scheme 5.21** Completion of the C(10)–C(19) mono-protected diol **338** by hydrolysis of protected 1,3-*anti* diol monoester **395**.

TLC. Although likely to be inert to most reaction conditions, the presence of the side product complicates the operation of experiments, and it is therefore clear that the PMB protection step will require a more rigorous optimisation in future studies to eliminate this contaminant. Other than changing existing conditions, other potential options would involve use of an alternative ET product (for example, the more polar pyridines **384a/b**), or an acylation–purification–hydrolysis sequence; but since the latter option would add further steps it must be considered a last resort in the event that the esterification product was inseparable from the PMB<sub>2</sub>O side product.

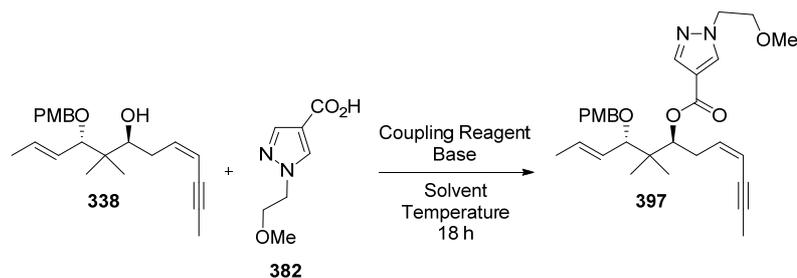
## 5.4.2 Esterification Reactions

### 5.4.2.1 Pyrazole Esterification

With the key C(10)–C(19) mono-protected diol **338** successfully synthesised, model esterification reactions were carried out in order to establish suitable conditions for coupling with the C(1)–C(9) heterocyclic carboxylic acid fragments *Het-111*. The pyrazole heterocycle was initially selected because a reliable route to the synthesis of its C(1)–C(9) analogue had already been devised within the group,<sup>16,44,216</sup> and because the 2-heteroatom system closely mirrors that of the oxazole (which at the time was not readily available). Critically, we were also hopeful that the discovery of appropriate conditions would allow the successful generation of at least one heterocyclic 1,3-*anti* diol monoester bis-alkyne C(1)–C(9)/C(10')–C(19') analogue for future alkyne metathesis.

In their total synthesis of disorazole C<sub>1</sub>, Wipf and Graham<sup>26</sup> reported the successful esterification of an oxazole carboxylic acid to an alcohol fragment, which was not dissimilar to the one used in the current study (See: **Chapter 1, Section 1.2.4**). It was therefore thought that use of their conditions – which involved use of a standard Steglich esterification<sup>27</sup> – would allow the coupling of heterocyclic carboxylic acids with our alcohol substrate **338** and therefore their conditions were used as a starting point for the esterification reaction with pyrazole **382**, albeit with a slight reduction in the stoichiometry of the carboxylic acid (1.5 as opposed to 1.9 eq).

Wipf's conditions<sup>26</sup> (**Table 5.7**, Entry 1) proved, surprisingly, to be unsuccessful;

**Table 5.7** Attempted esterification of alcohol **338** with the pyrazole carboxylic acid **382**.

Entry	Eq <b>382</b>	C. R. <sup>a</sup>	Eq C. R.	Base	Eq Base	Solvent <sup>b</sup>	Temp (°C)	Yield (%) <sup>c</sup>
1	1.5	DCC	5.0	DMAP	1.0	DCM	25	0
2	1.0	DCC	1.3	DMAP	1.3	PhMe	25	11
3 <sup>d</sup>	1.0	DCC	10	DMAP	3.0	PhMe	0 to 25	12
4	1.0	DCC	10	DMAP <sup>d</sup>	3.0	PhMe	0 to 25	12
5	1.0	Boc <sub>2</sub> O	1.3	DMAP	0.05	MeNO <sub>2</sub>	50	0
6	1.0	(COCl) <sub>2</sub> /DMF <sup>e</sup>	3.0/0.25	Et <sub>3</sub> N	3.0	DCM	25	0 <sup>f</sup>

<sup>a</sup>Coupling reagent; <sup>b</sup>In all cases, alcohol **338** was used as a solution in DCM and this typically accounted for 20% of the solvent mixture in non-DCM systems; <sup>c</sup>As determined by <sup>1</sup>H NMR of the crude material unless otherwise stated; <sup>d</sup>Reaction was conducted for 72 h; <sup>e</sup>20 mol% 4-PPy was also added to the reaction; <sup>e</sup>Carboxylic acid **382** was reacted for 3 h with (COCl)<sub>2</sub>/DMF to generate the corresponding acid chloride, followed by reaction of the crude product with alcohol **338** and Et<sub>3</sub>N; <sup>f</sup>Isolated yield.

and in any case required the use of an excess of the carboxylic acid component, which was undesirable given the synthetic value of the highly functionalised heterocyclic C(1)–C(9) fragments, and therefore the remaining the runs were conducted using an equimolar alcohol-to-carboxylic acid ratio. Unfortunately, the lack of success using the precedented conditions was mirrored in other attempted preparations of the ester **397** using DCC. Reaction using an approximately stoichiometric quantity of DCC and DMAP led to only 11% conversion as determined by <sup>1</sup>H NMR (**Table 5.7**, Entry 2), while a larger excess of the reagents (**Table 5.7**, Entry 3) and use of a more efficient DMAP analogue<sup>217</sup> in catalytic quantity (20 mol% 4-PPy; **Table 5.7**, Entry 4) gave similarly disappointing results

As an alternative to the Steglich protocol, use of Goossen's Boc<sub>2</sub>O-mediated esterification<sup>218</sup> was also investigated but this too proved unsuccessful, giving only unreacted starting material (**Table 5.7**, Entry 5). Finally, attempts were made to synthesise the ester **397** by acylation of the alcohol using the acid chloride derivative of pyrazole **382**, which was prepared under standard chlorination conditions with (COCl)<sub>2</sub>/catalytic DMF in DCM.<sup>219</sup> Unfortunately, this approach also proved futile, because immediate reaction of the crude acid chloride with alcohol **338** in the

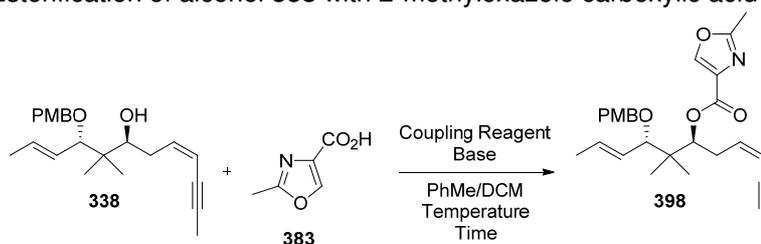
presence of Et<sub>3</sub>N led only to the recovery of alcohol **338** after aqueous workup and flash chromatography (**Table 5.7**, Entry 6).

The results with pyrazole **382** were disappointing, but perhaps unsurprising because few examples exist of either direct esterification of secondary alcohols with *N*-alkylated pyrazole-4-carboxylic acids, or acylation of alcohols with pyrazoloyl chlorides.<sup>220</sup> Those which do exist tend to be low yielding<sup>215a</sup> or involve reactions with simple alcohol substrates such as *i*PrOH,<sup>215b</sup> which can be used in vast excess and for the purposes of an advanced fragment coupling this is not a viable means of esterification. The reasons for such poor reactivity are probably related to a combination of slow formation and/or instability of the pyrazole activated ester<sup>166</sup> and the large steric hindrance imparted by the PMB-ether in the alcohol **338**. Although there clearly remains scope for optimisation of the pyrazole esterification reaction – for example through use of alternative coupling reagents – attention was instead focussed on coupling C(10)–C(19) mono-protected diol **338** with oxazoles.

#### 5.4.2.2 Oxazole Esterification

Successful esterification of an oxazole carboxylic acid was particularly important because – assuming successful AM dimerisation – it would allow access to natural disorazole C<sub>1</sub>. A number of esterification conditions were screened using both the (model) 2-methyloxazole **383** (**Table 5.8**) and the C(1)–C(9) oxazole fragment **111**<sup>203b</sup> (**Table 5.9**). Again, screening commenced with use of the Steglich protocol; and conditions invoked the use of a number of different of DCC stoichiometries, or different loadings of DMAP or the (theoretically) more active analogue 4-PPy. In addition, given that the esterification products were found to be readily separable from both of the starting materials on silica gel, an excess of the alcohol **338** [as opposed to the C(1)–C(9) oxazole **111** on the basis of availability and ease of recovery] was also used on some runs in an attempt to force the reaction.

In general, the Steglich esterification conditions were low yielding, albeit improved over those obtained upon attempted esterification of the pyrazole **382**. Runs included the use of stoichiometric DCC and catalytic DMAP (**Table 5.8**, Entry 1), or a large

**Table 5.8** Esterification of alcohol **338** with 2-methylazole carboxylic acid **383**.

Entry <sup>a</sup>	Eq 338	Coupling Reagent	Eq Coupling Reagent	Base	Eq Base	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>
1	1.3	DCC	1.1	DMAP	0.2	0 to 25	18	0
2	2.0	DCC	5.0	DMAP	10	0 to 25	18	0
3	2.0	DCC	10	DMAP	5.0	0 to 25	18	34
4	1.0	DCC	20	DMAP	10	0 to 25	18	29
5	2.0	DCC	5.0	4-PPy	0.5	0 to 25	86	23
6	2.0	DCC	5.0	4-PPy	1.0	0 to 25	18	43
7	2.0	DCC	5.0	4-PPy	1.0	0 to 25	86	15
8	2.0	DCC	10	4-PPy	1.0	0 to 25	86	14
9	1.0	DCC	25 <sup>c</sup>	4-PPy	5.0 <sup>c</sup>	0	5	0
10	1.0	YR/Et <sub>3</sub> N <sup>d</sup>	4.0/5.7	DMAP	3.0	40	4	93 <sup>e</sup>

<sup>a</sup>All reactions were conducted in PhMe with the alcohol **338** added as a solution in DCM to make up approximately 30 to 50% of the solvent mixture with the following exceptions (solvent in brackets): Entry 1 (DCM reaction solvent), Entry 10 (PhMe alcohol carrier solvent); <sup>b</sup>As determined by <sup>1</sup>H NMR of the crude material; <sup>c</sup>These reagents were added in 5 equal portions at hourly intervals (from t = 0) up to the values stated; <sup>d</sup>YR = Yamaguchi reagent. This reagent was combined with Et<sub>3</sub>N and made up as in a stock solution in PhMe and reacted portionwise (5 portions) with the acid **383** at room temperature for 15 min. The mixture was then added (5 additions in total) to a heated solution of the alcohol and base in PhMe at 15 min intervals over 1 h, and heating was continued until the time specified was reached; <sup>e</sup>Isolated yield.

excess of DMAP and moderate excess of DCC (**Table 5.8**, Entry 2); but both conditions gave rise to only unreacted starting material. Swapping the relative stoichiometry of the DMAP and DCC (**Table 5.8**, Entry 3) gave more promising results, but doubling these stoichiometries in the hope that this would allow a reduction in the loading of the alcohol **338** did not improve the conversion to the desired product **398** (**Table 5.8**, Entry 4).

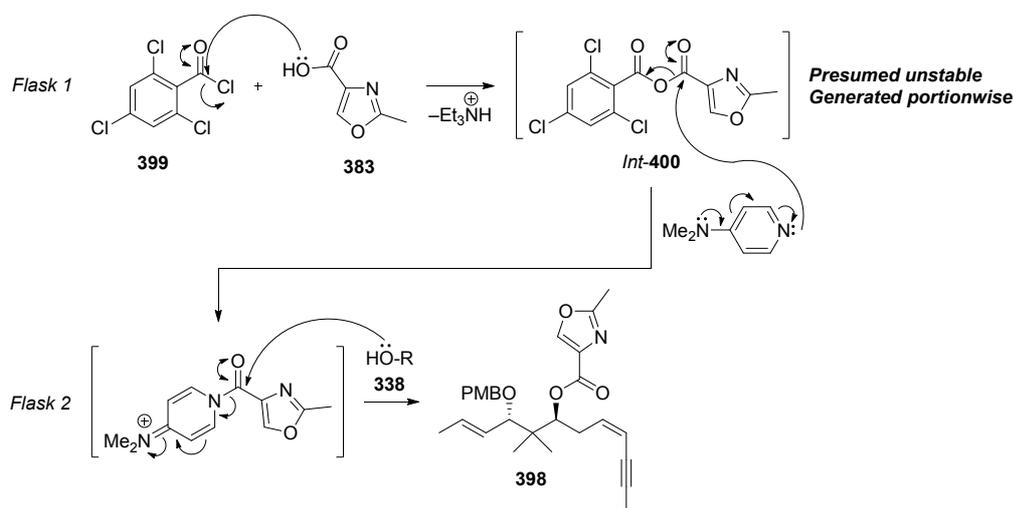
A change of base to 4-PPy gave a poor yield with 50 mol% of the base (**Table 5.8**, Entry 5), which was improved to a more workable 43% on addition of stoichiometric base (**Table 5.8**, Entry 6). Increased reaction times (**Table 5.8**, Entries 7 and 8) (surprisingly) reduced conversion below useful levels, perhaps indicative of a capricious reaction efficiency or large degree of reversibility. Finally, use of a more forcing reagent stoichiometry with a reduced reaction time and staggered reagent addition was found to be completely ineffectual, indicating the presence of only

unreacted starting material on examination of the crude  $^1\text{H}$  NMR spectrum (**Table 5.8**, Entry 9).

On the basis of these results – which did not appear to show any clear correlation between yield and reagent loading, and where the reaction could not be forced to completion by use of large reagent excesses or long reaction times – it was clear that the use of the Steglich protocol would not be the most useful method for esterification of the alcohol **338** with oxazolyl carboxylic acids. Hoffmann *et al.*<sup>25</sup> reported the use of the Yamaguchi reagent<sup>22</sup> in their efforts to synthesise disorazole C<sub>1</sub>, and the method was particularly attractive owing to the equivalent acid-to-alcohol stoichiometric ratio used in conducting the transformation. Furthermore, the slow nature of their reagent addition implies that activated oxazole ester intermediates exist only transiently. This would support the need to deviate from DCC-mediated conditions because an instability of the *in situ* generated activated ester would explain why the DCC-mediated reactions – which in general are often performed in a one-pot operation with bulk addition of reagents – were largely unsuccessful.

The Yamaguchi protocol was therefore attempted using alcohol **338** and oxazole **383**. For simplicity, the procedure was modified from that reported,<sup>25</sup> which required the use of a syringe pump in order to add the activated ester in a very slow and controlled manner. The protocol investigated in the current study involved portionwise generation and addition of an activated ester to a heated solution of the alcohol. This was achieved by addition of a portion of a pre-prepared stock solution containing the Yamaguchi reagent **399** and Et<sub>3</sub>N to a portion of the carboxylic acid **383**, followed by transfer of the activated ester *Int-400* solution thus obtained to a heated (40 °C) mixture of the alcohol and DMAP (**Scheme 5.22**). To our delight, the application of these conditions (**Table 5.8**, Entry 10) gave a 93% isolated yield of the desired ester **398** after 5 activated ester additions over a period of 1 h, and a further 3 h of reaction. Furthermore, this was achieved using an equal alcohol-to-carboxylic acid stoichiometry, making the process highly efficient.

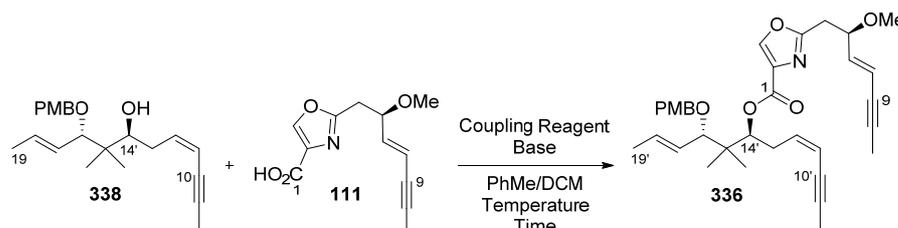
Having achieved successful esterification with a model oxazolyl carboxylic acid, conditions were investigated using the C(1)–C(9) carboxylic acid fragment **111**. A



**Scheme 5.22** Mechanism and implementation of the Yamaguchi protocol in the synthesis of the ester **398** from alcohol **338** and carboxylic acid **383**.<sup>22</sup>

small number of conditions were investigated in early stage screening using DCC and are worthy of note, including the use of Wipf and Graham's esterification conditions<sup>26</sup> between the carboxylic acid **111** and an equimolar ratio (**Table 5.9**, Entry 1) and twofold excess (**Table 5.9**, Entry 2) of the alcohol **338**; and these conditions led to moderate yields of the desired 1,3-*anti* diol monoester bis-alkyne **336**. Conditions were also investigated using 4-PPy either as a direct DMAP substitute (**Table 5.9**, Entry 3 with respect to conditions described in Entry 2) or as part of an attempt to achieve forcing conditions (**Table 5.9**, Entry 4), but these offered no improvement over the initial DMAP-mediated conditions, and indeed in the latter case led to no reaction. It is interesting to note however, that in general, yields were higher with the more sterically demanding C(5)–C(9)-fragment 2-substituted oxazole, when compared to those obtained with the 2-methyl substituted oxazole.

Finally the Yamaguchi protocol – as elucidated for the model system – was applied to the reaction between alcohol **338** and carboxylic acid **111** (**Table 5.9**, Entries 6 and 7). As expected, this led to the highest yield of the desired product, albeit requiring a slight increase in reagent stoichiometry, and an increased activated ester generation reaction time (**Table 5.9**, Entry 7) because use of identical conditions gave only a moderate yield of the desired product (**Table 5.9**, Entry 6).

**Table 5.9** Esterification of alcohol **338** with C(1)–C(9) oxazole carboxylic acid **111**.

Entry <sup>a</sup>	Eq <b>338</b>	Coupling Reagent	Eq Coupling Reagent	Base	Eq Base	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>
1	1.0	DCC	5.0	DMAP	1.0	0 to 25	18	57
2	2.0	DCC	5.0	DMAP	1.0	0 to 25	18	39
3	2.0	DCC	5.0	4-PPy	1.0	0 to 25	18	56
4	1.0	DCC	10	4-PPy	10	50	18	0
5	1.0	YR/Et <sub>3</sub> N <sup>c</sup>	3.6/4.8	DMAP	3.0	40	4	56
6	1.0	YR/Et <sub>3</sub> N <sup>c</sup>	4.0/5.7	DMAP	3.1	40	20	71

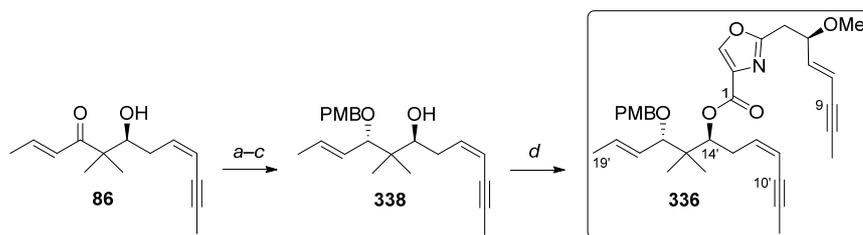
<sup>a</sup>All reactions were conducted in PhMe with the alcohol **338** added as a solution in DCM to make up approximately 30 to 50% of the solvent mixture with the following exception (solvent in brackets): Entry 6 (PhMe alcohol carrier solvent); <sup>b</sup>Isolated yield; <sup>c</sup>YR = Yamaguchi reagent. This reagent was combined with Et<sub>3</sub>N and made up as in a stock solution in PhMe and reacted portionwise (5 portions) with the acid **111** at room temperature for 15 min. The mixture was then added (5 additions in total) to a heated solution of the alcohol and base in PhMe at 15 min (Entry 5) or 30 min (Entry 6) intervals over 1 (Entry 5) or 2 (Entry 6) h, and heating was continued until the time specified was reached.

The optimal set of conditions translated reasonably well to a larger-scale preparation of the ester **336** (~150 mg), giving the product in a respectable albeit slightly diminished 63% yield. It is worth noting that, unlike with the alcohol precursor **338**, the fragment material was now fully separable from the PMB<sub>2</sub>O byproduct (carried over from the PMB protection step) by silica-gel chromatography. The product also appeared as a single diastereomer, and no apparent racemisation had occurred during any of the transformations as judged by <sup>1</sup>H NMR spectroscopy; although these potential problems will perhaps require further confirmation using analytical techniques such as HPLC. The successful implementation of the Yamaguchi esterification between the C(1)–C(9) oxazole carboxylic acid **111** and the C(10)–C(19) alcohol **338** concluded the synthesis of the C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne, and therefore efforts can now be focussed on dimerisation of this fragment *via* AM to generate the macrocyclic scaffold of disorazole C<sub>1</sub>.

## 5.5 Conclusions and Future Work

The reaction of the C(10)–C(19)  $\beta$ -hydroxyketone **86** with a number of model heteroaryl aldehydes under ET coupling was investigated. Unfortunately, **86** was found to react poorly with the majority of the substrates screened, although the electron-deficient formylpyridines and nitrobenzaldehydes were successful, giving the products in good to excellent yield (~60 to 99%). A contingency strategy was then explored whereby the ET reaction was used to introduce the 1,3-*anti* stereochemistry in the product, and subsequent protection, hydrolysis and esterification steps allowed the synthesis of the C(16)-*O*-PMB-protected C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne **336** in 43% yield (4 steps from  $\beta$ -hydroxyketone **86**; **Scheme 5.23**). However, the synthesis of a pyrazole derivative was unsuccessful, and so the conditions required for the preparation of this C(1)–C(9)/C(10')–C(19') analogue will require further investigation.

Future work with respect to ET coupling requires that conditions be found for which: (i) electron-rich heteroaryl aldehydes react to give 1,3-*anti* diol monoesters; and (ii) the reaction proceeds smoothly with sterically crowded or electronically modified  $\beta$ -hydroxyketones. However, formylpyridines and nitrobenzaldehydes reacted successfully and so little further work is required with these systems; thus synthesis of their C(1)–C(9) derivatives would be worthy of investigation in view of a direct ET approach to their corresponding 1,3-*anti* diol monoester bis-alkynes. With these two points in mind, modifications to the ET reaction which may improve substrate scope, and the synthesis of further C(1)–C(9) analogues will be briefly discussed.



**Reagents and conditions:** (a) (i) 3-Nitrobenzaldehyde (5.6 eq),  $\text{SmI}_2$  (94 mol%), THF,  $-20^\circ\text{C}$ , 4 h; (ii)  $\text{NaHSO}_3$  (11.3 eq), EtOH/ $\text{H}_2\text{O}$  (5:1), 3 h, 94%, >95:5 *dr*; (b) PMB-TCA (3.0 eq),  $\text{Sc}(\text{OTf})_3$  (10 mol%), PhMe,  $0^\circ\text{C}$  to rt, 1 h, 79%; (c) LiOH (12 eq), MeOH/ $\text{H}_2\text{O}$  (10:1), reflux, 18 h, 91%. (d) (i) C(1)–C(9) oxazole **111** (0.2 eq), 2,4,6-TCBC (0.8 eq),  $\text{Et}_3\text{N}$  (1.1 eq), PhMe, rt, 30 min; (ii) Addition of mixture from (i) to **338**, DMAP (3.0 eq), PhMe,  $40^\circ\text{C}$ , 30 min; (iii) 4 further iterations of steps (i) and (ii); (iv)  $40^\circ\text{C}$ , 18 h, 63%.

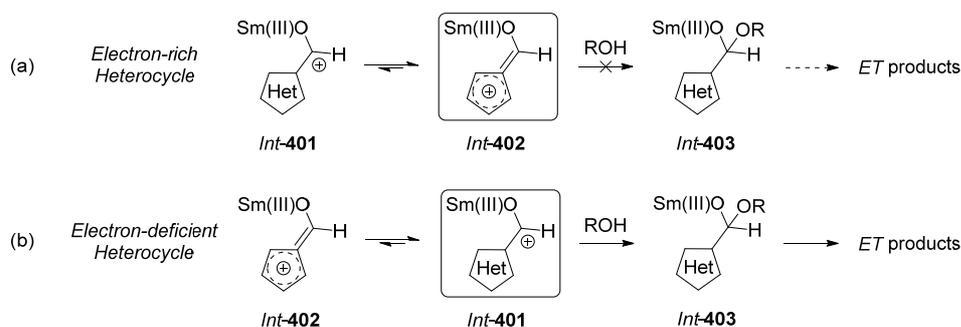
**Scheme 5.23** Preparation of the C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne **336** from  $\beta$ -hydroxyketone **86**.

### 5.5.1 The Evans–Tishchenko Reaction

The ET reaction with the  $\beta$ -hydroxyketone **86** was found to have a limited substrate scope, with only the most electron-deficient systems reacting successfully to give useful product yields. Because some substrates investigated were found to react successfully with a simpler  $\beta$ -hydroxyketone (see: **Section 5.1.3**), this poor reactivity can probably be ascribed to the structure of the  $\beta$ -hydroxyketone **86**; which is not only very sterically hindered, but contains an enone, which would modify the energetics of the reaction in terms of the reduction potential at the site of hydride transfer. In addition, some heterocycles (such as pyrrole) may have been too electron-rich to undergo successful reaction. In such situations, it would be highly desirable to have a contingency set of reaction conditions – applicable to demanding substrates – for performing the ET reaction.

Fürstner<sup>172</sup> found that reduced temperature ( $-50\text{ }^{\circ}\text{C}$ ) was successful in promoting an ET fragment coupling, and therefore a straightforward modification such as this may prove to be successful using the C(10)–C(19)  $\beta$ -hydroxyketone **86** (and indeed provides an excellent starting point for further optimisation). If such measures were unsuccessful however, modifications to the reagent would be a requirement. The addition of (coordinating) additives was briefly investigated by Dorgan<sup>90</sup> in the context of forcing  $\alpha$ -formyl *N*-heterocycles to react under ET coupling conditions. However, in the context of forcing heterocycles that were found to be ‘too electron-rich’ to react under standard conditions applicable to other heterocycles, the use of additives was never investigated.

The ET reaction with heterocycles may fail if an enolate intermediate *Int-402* forms in preference to the cationic species *Int-401*,<sup>16,90</sup> which is required for formation of the hemiacetal *Int-403* (which reacts to give the ET product). In electron-rich systems, it is likely that the positive charge is stabilised by delocalisation within the ring-system (**Scheme 5.24a**), whereas in electron-deficient systems, an excess of positive charge in the ring would be comparably disfavoured and the cationic form *Int-401* would predominate (**Scheme 5.24b**); any conditions which favour *Int-401* should lead to successful ET coupling. The use of the Boc group (and tosyl group) to reduce electron density in the heterocycle proved unsuccessful on reaction of those



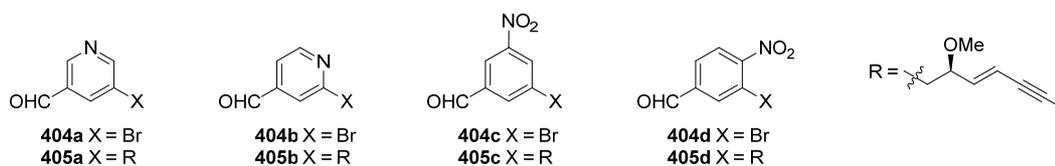
**Scheme 5.24** Selectivity between the cationic and enolate forms of the Sm(III) species. Preference in (a) electron-rich; and (b) electron-deficient heterocyclic systems. The favoured species are shown in boxes.

substrates with the C(10)–C(19) fragment, although it is possible that more powerful electron-withdrawing groups such as the nosyl group could lead to positive results.

Any additives that would increase the stability of the cationic intermediate *Int-401* may also aid in promoting the ET pathway. Such an additive could be a polar aprotic solvent compatible with  $\text{SmI}_2$  such as HMPA,<sup>221</sup> which has been shown to promote reductive processes with  $\text{SmI}_2$ ,<sup>170,221</sup> and increases solvent conductivity,<sup>221</sup> and therefore may shift the course of the reaction in favour the desired, more ionic intermediate *Int-401*. The nature of the active Sm(III) catalyst is also worthy of investigation because the effects of the substitution on the aldehyde used for forming the active pinacol intermediate could have a minor influence over the *Int-401/Int-402* selectivity, in the sense that electron-withdrawing substituents on the aryl ring could have an effect on the electrophilicity of the cationic intermediate *Int-401*. Finally, the use of an alternative catalyst could be investigated. The ET reaction and the related aldol–Tishchenko reaction<sup>222</sup> have been performed with a number of Lewis acids,<sup>36b</sup> for example  $\text{Sc}(\text{OTf})_3$ <sup>223a</sup> and  $\text{Cp}_2\text{ZrH}_2$ ,<sup>223b</sup> and so catalyst screening may unearth a superior system to the samarium pincolate for ET coupling of (hetero)aryl aldehydes.

### 5.5.2 Synthesis of Further C(1)–C(9) Analogues

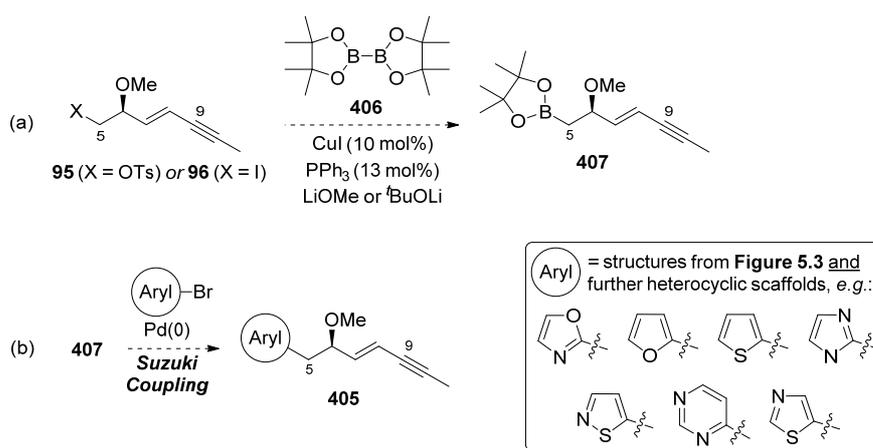
Given that pyridine- and nitrobenzene-derived aldehydes reacted successfully in ET coupling, the synthesis of C(1)–C(9) analogues that incorporate these frameworks would be worthy of investigation. Not only would they provide additional analogues for further SAR studies, but given that they are 6-membered-ring heterocycles



**Figure 5.3** Pyridine and nitrobenzene analogues of the C(1)–C(9) fragment of disorazole C<sub>1</sub>.

pyridine and nitrobenzaldehyde analogues would provide a slight structural change relative to the 5-membered-ring oxazole. On considering the reactivity of the pyridines (whereby 2-formylpyridine is known to react poorly)<sup>90,174</sup> and the angle required for similarity to the 5-membered-ring heterocycles (a 1,3-substitution) the formyl group would be required to be at the 3- or 4-position, with the C(5)–C(9) ('R') group in a 1,3-relationship to this functionality (**405a** and **b**, **Figure 5.3**). Similarly, 1-formyl-3-nitro-5-R **405c** and 1-formyl-4-nitro-5-R **405d** derivatives are viable analogues in terms of complementarity to the 5-membered-ring heterocycles for the nitrobenzaldehyde series of analogues (**Figure 5.3**).

Cross-coupling of an organoboronate derivative of the C(5)–C(9) fragment would represent a highly convergent means of generating the required pyridyl or nitrophenyl C(1)–C(9) analogues. The known C(5)–C(9) tosylate **95** or iodide **96**<sup>16</sup> would be converted to its boronate ester derivative **407** according to, for example, Liu's copper-catalysed borylation protocol<sup>224</sup> (**Scheme 5.25a**). Suzuki–Miyaura coupling<sup>225</sup> between **407** and the bromopyridines<sup>226</sup> or bromonitrobenzenes<sup>227</sup> **404** (**Figure 5.3**) would then provide access to the desired C(1)–C(9) fragment analogues **405** (**Scheme 5.25b**).



**Scheme 5.25** (a) Synthesis of a C(5)–C(9) boronic ester **407** from tosylate **95** or iodide **96**; (b) Potential Suzuki–Miyaura coupling route towards the syntheses of **405** and further C(1)–C(9) fragment analogues.

Extension of this methodology towards the synthesis of other (hetero)aryl systems<sup>228</sup> would permit the preparation of further C(1)–C(9) analogues (**Scheme 5.25b**). The approach, importantly, may also provide a direct route towards the C2 alkylation of the oxazole,<sup>228c</sup> which has proven problematic in previous efforts to synthesise the natural C(1)–C(9) fragment.<sup>16</sup> For novel (hetero)aryl analogues, model ET and esterification reactions would be required to identify the appropriate route for the synthesis of the corresponding C(1)–C(9)/C(10')–C(19') bis-alkynes. However, the successful synthesis of novel bis-alkynes will allow investigation into the generation of their tetrahydro-disorazole C<sub>1</sub> analogue derivatives, and thus their disorazole C<sub>1</sub> (hetero)aryl analogues, according to our proposed alkyne metathesis strategy.

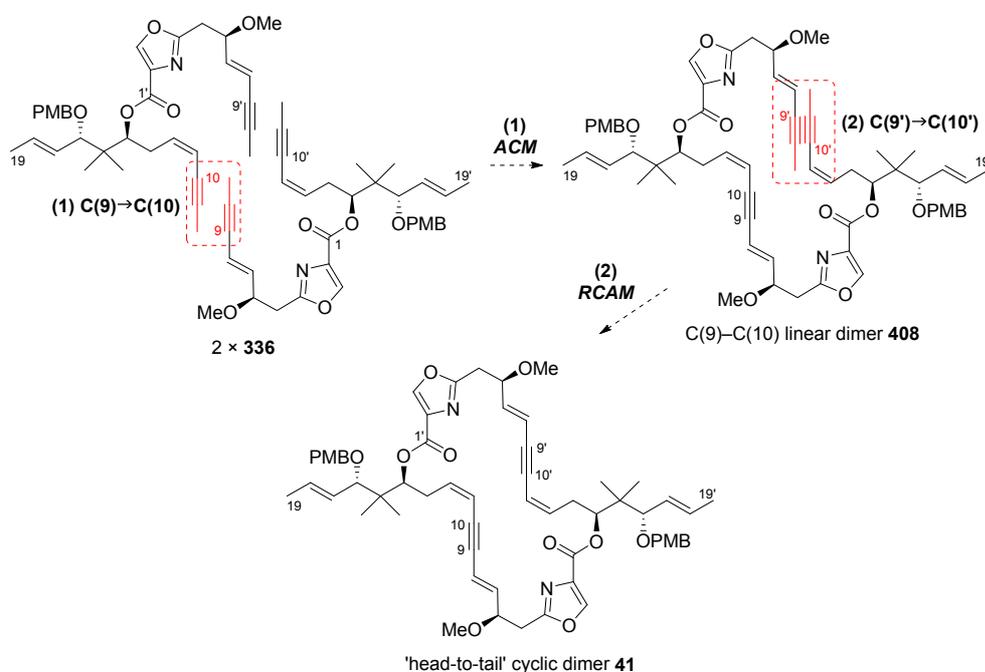
## 5.6 Summary

The Evans–Tishchenko coupling between the C(10)–C(19)  $\beta$ -hydroxyketone **86** and range of aryl and heteroaryl aldehydes was investigated. Highly electron-deficient aryl aldehydes reacted successfully to give good yields of their corresponding 1,3-*anti* diol monoester products. However, moderately electron-deficient aldehydes failed to react usefully under our conditions, and these included a range of potential *N*-heterocycles which would be synthesised by straightforward *N*-alkylation with the C(5)–C(9) tosylate **95**; potential conditions for which were developed in the herein. To circumvent the problems associated with ET coupling, a contingency strategy for the introduction of heterocycles to a C(10)–C(19) mono-protected diol **338** *via* esterification was investigated and although unsuccessful for a model pyrazole, it was successful in generating the ester derivatives of both a model and C(1)–C(9) fragment oxazole. The latter step of the reaction sequence concluded the synthesis of a C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne **336** and thus further progress can be made towards the construction of the disorazole C<sub>1</sub> macrocyclic framework using an alkyne metathesis strategy. Future work should aim to develop the ET reaction methodology in order to allow the synthesis of 1,3-*anti* diol monoesters from sterically hindered  $\beta$ -hydroxyketones and electron-rich (hetero)aryl aldehydes; and to investigate the synthesis of further heterocyclic C(1)–C(9) analogues with a focus in the first instance on the pyridine series of heterocycles.

## 6.1 Overview: Alkyne Metathesis Dimerisation

Having successfully achieved the synthesis of the requisite C(16)-*O*-PMB-protected C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne **336**, the next step involves subjecting the substrate to alkyne metathesis dimerisation conditions in order to examine the viability of this approach as a means of constructing the 30-membered-ring, protected tetrahydro-disorazole C<sub>1</sub> **41**. Of course, **41** was an advanced synthetic intermediate in Wipf's disorazole C<sub>1</sub> total synthesis,<sup>26</sup> and so successful dimerisation will represent a formal total synthesis, therefore providing access to the natural product **1** for use in biological testing after elaboration according to literature procedure.

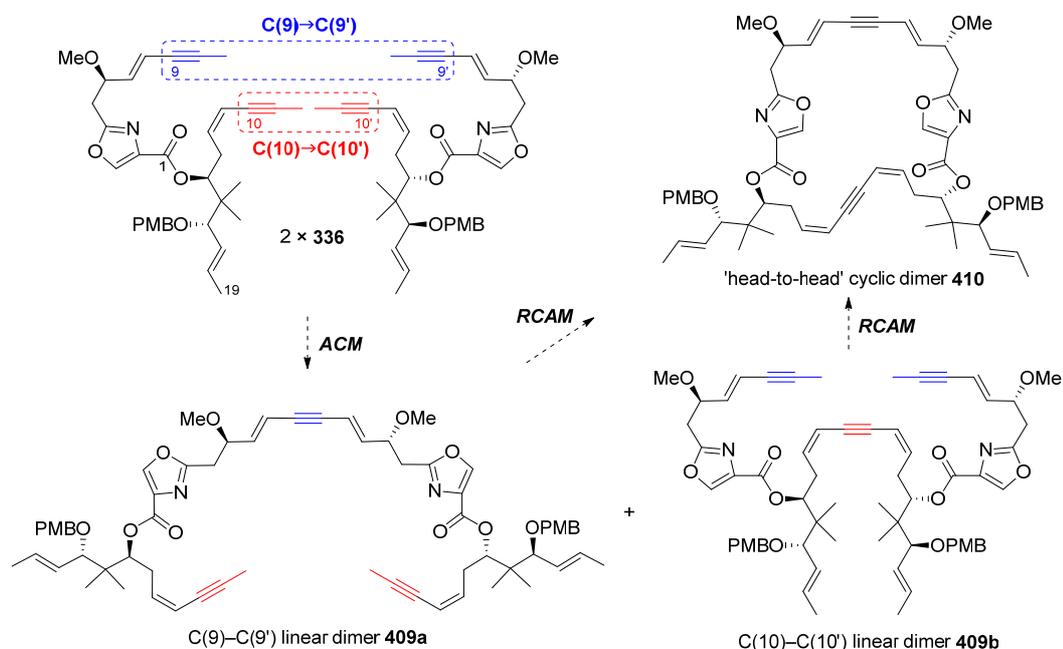
In order to achieve the synthesis of **41** using AM, two processes are required to take place during the course of the reaction: (1) an alkyne cross-metathesis (ACM) reaction must occur between one alkyne moiety (each) of two reactant molecules of the bis-alkyne **336**; and (2) after the ACM event, an intramolecular ring-closing alkyne metathesis (RCAM) reaction must take place within the newly-formed linear dimer **408** between the two remaining methyl-capped alkynes (**Scheme 6.1**). Unfortunately, neither of these outcomes can be considered to be a formality.



**Scheme 6.1** Dimerisation of the C(1)–C(9)/C(10')–C(19') bis-alkyne fragment **336** to give the tetrahydro-disorazole C<sub>1</sub> ('head-to-tail') scaffold **41** using an ACM–RCAM approach.

Firstly, formation of the desired  $C_2$ -symmetric scaffold **41** requires that the molecules approach in the correct ‘head-to-tail’ [C(9)→C(10)] orientation (*cf.* **Scheme 6.1**). However, it is possible that ACM could occur in an undesired ‘head-to-head’ fashion (to form either or both of the dimers **409** and thus cyclic dimer **410**; **Scheme 6.2**) or undergo intramolecular RCAM to form a cyclic monomer (not shown). Although computational studies performed within the Hulme group<sup>229</sup> indicate a thermodynamic preference for head-to-tail dimerisation, these results will require experimental verification. Secondly, following ACM, the intramolecular RCAM event must take place, as opposed to oligomerisation *via* further ACM. This problem is perhaps easier to overcome, because such a process would be disfavoured (over intramolecular RCAM), especially at moderate-to-high dilution.<sup>38a,c</sup>

Alkyne metathesis has been widely applied as a means of ring-closing and is growing in stature as an alternative to olefin metathesis or metal-mediated cross-coupling for carbon–carbon bond formation.<sup>37</sup> However, perhaps unsurprisingly given the inherent difficulties present, use of alkyne metathesis for cross-metathesis dimerisation has rarely been reported.<sup>38</sup> Indeed, the reaction presents a challenging proposition, but is one that must be overcome in our quest to synthesise the disorazoles and their analogues according to our retrosynthesis. Pleasingly, early work has been promising, and this is detailed in the following section.



**Scheme 6.2** ‘Head-to-head’ ACM of the C(1)–C(9)/C(10')–C(19') bis-alkyne and subsequent RCAM of the linear dimers **409** thus formed to give the cyclic dimer **410**.

## 6.2 Preliminary Alkyne Metathesis Dimerisation Results\*

Time constraints applicable to the current project prevented investigation into AM dimerisation using the C(1)–C(9)/C(10')–C(19') bis-alkyne **336**, but it has been investigated by co-workers within the Hulme group and some promising preliminary results have been obtained that are certainly worthy of discussion in the context of future research. In terms of a catalyst system, model studies indicated that Fürstner's molybdenum alkylidyne catalyst **411** was the most active in promoting alkyne metathesis and so this was selected for reaction with the bis-alkyne **336**.<sup>224–226</sup>

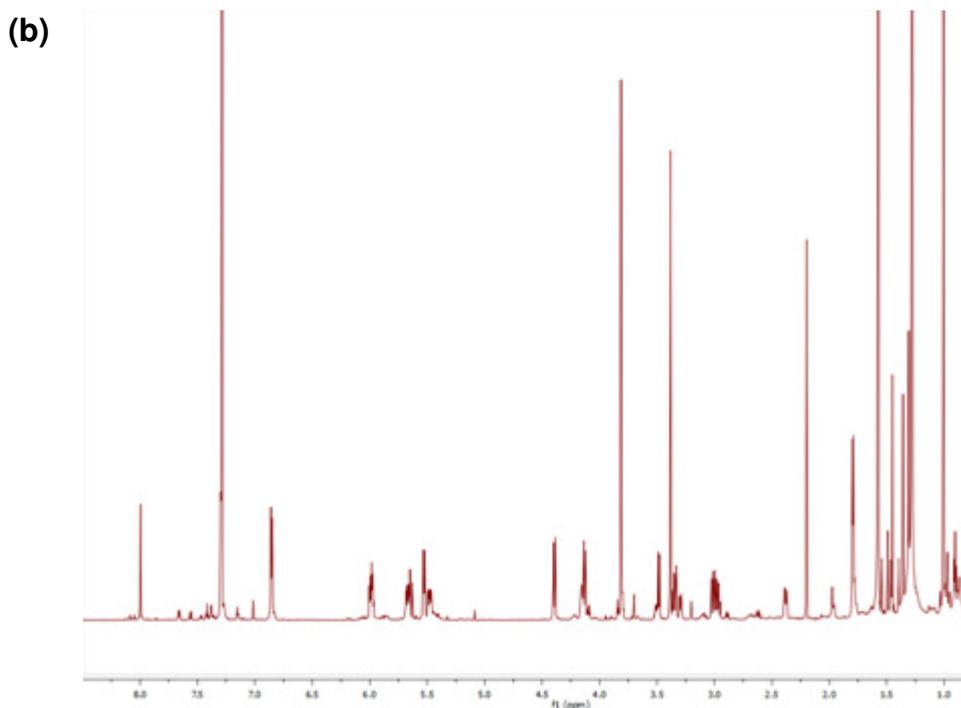
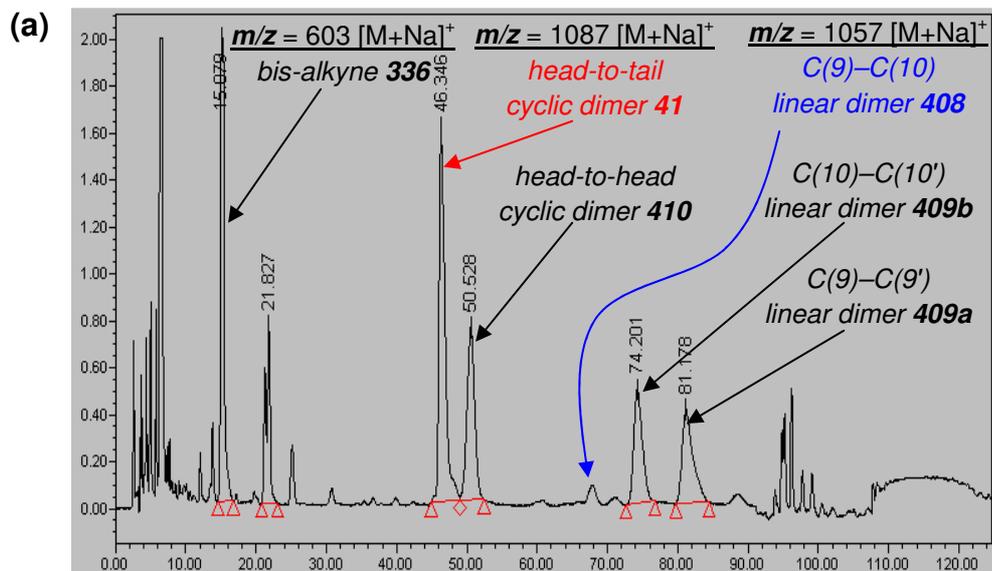
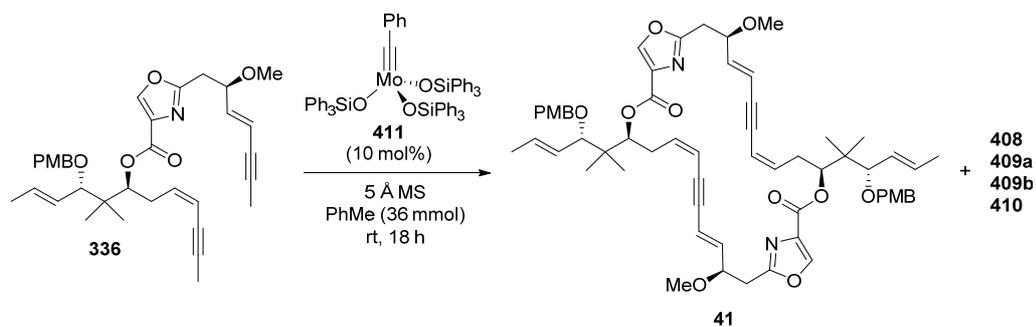
In a glovebox, a solution/suspension of the C(1)–C(9)/C(10')–C(19') bis-alkyne **336** (36 mM) and 5 Å MS in toluene was treated with the catalyst **411** (10 mol%) in a sealed tube (**Scheme 6.3**). After reaction overnight (~18 h), the crude product was submitted to RP-HPLC, and each fraction was then isolated (preparative HPLC, shown in **Figure 6.1**)<sup>†</sup> and analysed by mass spectrometry. Mass-spectral analysis of the isolates indicated that the crude mixture contained the bis-alkyne starting material **336** ( $R_t = 15$  min), two ring-closed dimers (46 and 51 min), and three linear dimers (~68, 71 and 78 min).

Following mass-spectral analysis, NMR analysis has allowed identification of the unknown products of the reaction. The two large linear-dimer peaks ( $R_t = 71$  and 78 min) were identified as the two head-to-head dimers **409**, while the remaining linear-dimer peak (~68 min) was confirmed as the head-to-tail dimer **408**. Of particular note is that the peak intensity for the desired, intermediate, head-to-tail linear dimer is greatly diminished compared to the head-to-head dimers, implying that either its initial formation is unfavourable; or – and far more likely on the basis of relative cyclised dimer peak intensity – ring-closure of this dimer *via* RCAM is rapid and more energetically favourable than with the head-to-head dimers. This is important, not only with respect to the success of our synthesis, but also in terms of optimisation of the reaction, because the knowledge that formation of the head-to-tail

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\*All experimental work described in this section was carried out by Richard Brewster, Hulme group, The University of Edinburgh. The description of the experimental protocol and the figures presented herein have been reproduced with his kind permission, and the permission of Dr. Alison Hulme.

<sup>†</sup>Unfortunately integration data for each peak was unavailable.



**Scheme 6.3** ACM-RCAM reaction; and **Figure 6.1** (a) Preparative HPLC output from the ACM-RCAM reaction; and (b) the  $^1\text{H}$  NMR spectrum (800 MHz,  $\text{CDCl}_3$ ) of the desired head-to-tail cyclic dimer **41**.

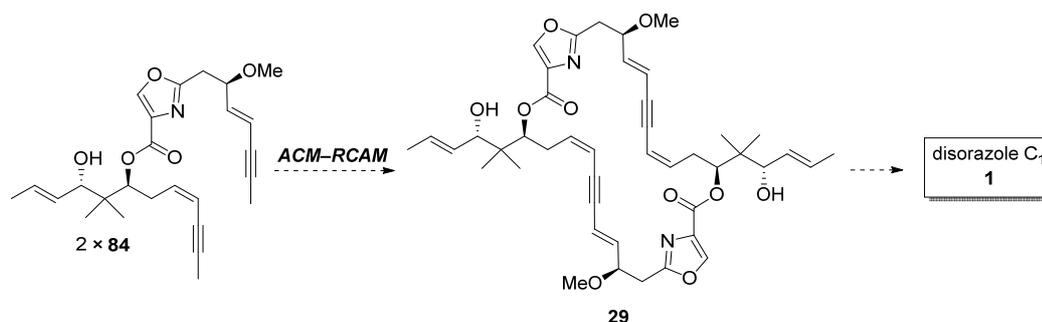
dimer is more favourable energetically means that is tuning of the reaction conditions towards formation of this product may be more straightforward.

Finally, formation and successful isolation of the desired cyclic head-to-tail dimer was confirmed. The  $^1\text{H}$  NMR spectrum for the product obtained at  $R_t = 51$  min did not visually match that for known disorazole intermediate **41**, and was therefore tentatively ascribed to being the head-to-head cyclic dimer **410**; although the small quantity of material prevented a full characterisation. However, the  $^1\text{H}$  NMR spectrum (**Figure 6.1b**) of the material isolated at  $R_t = 46$  min was in good agreement with that reported by Wipf and Graham,<sup>26</sup> which confirmed the successful application of AM dimerisation to the construction of the protected tetrahydro-disorazole  $C_1$  **41** scaffold, and completed the formal total synthesis of disorazole  $C_1$ .

### 6.3 Implications for Future Work

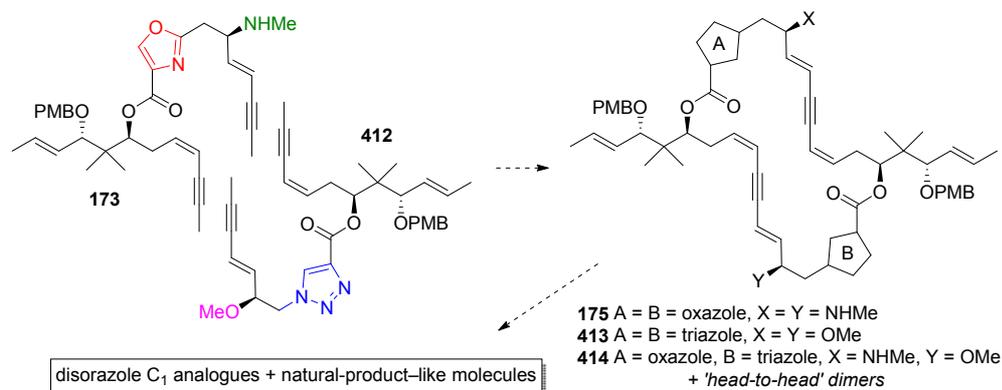
As evidenced by the successful synthesis of protected tetrahydro-disorazole  $C_1$  **41**, early results validate the use of an AM dimerisation strategy as a means of constructing the large-ring macrocyclic core of disorazole  $C_1$ . Future work should seek to discover conditions that both maximise the yield of the reaction (which currently leads to large proportions of starting material and intermediate ACM products) and to control reaction selectivity such that the cyclic C(9)–C(10) dimer is formed preferentially. Potential methods include concentration studies; and metal templating strategies,<sup>233</sup> which could aid the desired ACM process by co-ordination to oxygen and nitrogen moieties and orientating the monomers for the desired head-to-tail reaction. Additionally, our initial retrosynthesis envisaged the use of an AM dimerisation of a bis-alkyne **84** bearing a free alcohol at C(16) (which was hoped would be obtained immediately after ET coupling; **Scheme 6.4**), and work with this substrate is currently under investigation.<sup>234</sup> If results prove to be more successful with this substrate **84**, a PMB deprotection prior to ACM–RCAM may streamline the optimisation process.

Once an optimised procedure with the C(1)–C(9)/C(10')–C(19') oxazole is fully



**Scheme 6.4** ACM–RCAM using the C(1)–C(9)/C(10′)–C(19′) 1,3-*anti* diol bis-alkyne **84**.

developed, work can commence towards the use of AM dimerisation for the synthesis of disorazole C<sub>1</sub> analogues. Potential analogues include those derived from dimerisation of C(6)-methoxy C(1)–C(9)/C(10′)–C(19′) heterocyclic fragment analogues and from C(6)-amino analogues of the C(1)–C(9)/C(10′)–C(19′) fragment. Mixed heterocyclic and/or C(6)-amino analogues would also provide interesting entries in the library of disorazole analogues; and the likelihood of obtaining a mixture of alkyne metathesis products in the reaction between two (or more) distinct bis-alkynes may allow the tetrahydro-disorazole C<sub>1</sub> scaffold of several different disorazoles to be assembled in a small-scale combinatorial<sup>235</sup> fashion (**Scheme 6.5**), rapidly providing analogues for biological testing. The head-to-head disorazole C<sub>1</sub> alkyne metathesis products are also natural-product-like structures, and therefore the biological testing of these products (and that of their tetrahydro-disorazole-C<sub>1</sub>-like derivatives) would also be worthy of investigation. Biological testing of disorazole analogues and related compounds on the basis of their cytotoxicity and anti-tubulin activity will allow SARs in the disorazole family to be further elucidated.



**Scheme 6.5** Synthesis of mixed disorazole C<sub>1</sub> analogues using an ACM–RCAM methodology in a combinatorial fashion.

## 6.4 Concluding Remarks

A number of studies towards the total synthesis of disorazole C<sub>1</sub> and its analogues, centred around a novel Evans–Tishchenko/alkyne metathesis methodology, have been investigated and were detailed herein.

The synthesis of a novel C(6)-amino C(5)–C(9) fragment analogue was achieved, and further route optimisation and elaboration of the molecule to C(1)–C(9) fragment analogues according to established procedures will allow the development of novel C(6)-amino analogues of disorazole C<sub>1</sub>.

Convergent and linear strategies towards the synthesis of the key C(10)–C(19)  $\beta$ -hydroxyketone were investigated. This synthesis was eventually achieved using a linear strategy, and large-scale preparation of the fragment has allowed investigation into the scope of the Evans–Tishchenko reaction with model heteroaryl aldehydes.

Although it was deemed unsatisfactory as a potential fragment coupling strategy, the Evans–Tishchenko reaction has allowed esterification to be investigated as a means of synthesising the C(1)–C(9)/C(10')–C(19') oxazole fragment of disorazole C<sub>1</sub>. Optimisation of the esterification route to the C(1)–C(9)/C(10')–C(19') oxazole fragment, and application of the methodology to the synthesis of heterocyclic analogues will maximise the potential of our synthetic strategy toward the synthesis of the disorazole core. Further Evans–Tishchenko investigations may yet allow the pursuit of this route as a means of fragment coupling.

Synthesis of the C(1)–C(9)/C(10')–C(19') fragment has allowed investigation into its dimerisation using AM. This allowed others within the research group to complete the formal total synthesis of disorazole C<sub>1</sub>, and efforts towards its total synthesis and the synthesis of analogues are ongoing.

Research into the construction of the tetrahydro-disorazole C<sub>1</sub> macrocycle *via* an AM methodology is still very much in its infancy, and so future work in this area should focus on the optimisation of the ACM–RCAM procedure. Early results have been promising, and the development of a general procedure for the critical ACM–RCAM step will allow the synthesis of a library of disorazole analogues for biological testing, and will elucidate further SARs in the disorazole family.

### 7.1 General Experimental

Nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature (298 K) on a Bruker AV400, AV500 or AV600 spectrometer running at 400, 500 or 600 MHz ( $^1\text{H}$  spectra) or 100, 125 or 150 MHz ( $^{13}\text{C}$  spectra), respectively;  $^{31}\text{P}$  NMR spectra were recorded on a Bruker AV400 spectrometer running at 162 MHz. Chemical shifts ( $\delta$  values) are reported in parts-per-million (ppm) relative to tetramethylsilane ( $^1\text{H}$  and  $^{13}\text{C}$  spectra;  $\delta_{\text{TMS}} = 0$ ) or 85% aqueous phosphoric acid ( $^{31}\text{P}$  spectra;  $\delta_{\text{H}_3\text{PO}_4} = 0$ ) and are calibrated to the residual solvent peak.  $^1\text{H}$  NMR data are reported as chemical shift, relative intensity, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, m = multiplet; br = broad), coupling constant ( $J$  value, Hz), and interpretation.  $^{13}\text{C}$  spectra are reported as chemical shift, coupling constant (where relevant), relative intensity, and assignment ( $\text{CH}_3$  = methyl,  $\text{CH}_2$  = methylene,  $\text{CH}$  = methine, C = quaternary);  $^{31}\text{P}$  spectra are reported analogously. All  $^{13}\text{C}$  assignments were confirmed by DEPT90 and/or DEPT135 (distortionless enhancement by polarisation transfer) spectra

Infra red (IR) spectra were recorded using a Shimadzu IRAffinity-1 solid state IR instrument. Values of peaks corresponding to absorbance maxima ( $\nu_{\text{max}}$ ) are expressed in wavenumbers ( $\text{cm}^{-1}$ ).

Electron ionisation (EI) and chemical ionisation (CI) mass spectra were obtained using a MAT 900 XP mass spectrometer. Electrospray ionisation (ESI) was performed using a Bruker micrOTOF II or a Finnigan LCQ mass spectrometer. Fast-atom bombardment (FAB) mass spectra were obtained using a Finnigan LCQ mass spectrometer. All mass-spectral analyses were performed at The University of Edinburgh. Mass-to-charge ratios ( $m/z$ ) of all parent (molecular) ions ( $[\text{M}]^+$ ) and their intensities are reported, followed by (major) fragment ions and their intensities.

HPLC was carried out using an Agilent Systems T100 Series HPLC instrument. Retention times ( $R_t$ , minutes) are reported according to the elution parameters as specified in **Table 7.1** (Method A or B). Samples were dissolved in propan-2-ol and filtered through iso-disc filters (4 mm  $\times$  0.45  $\mu\text{m}$ , Supelco) prior to measurement.

**Table 7.1** HPLC methods used for determining enantiomeric excess.

	Method A	Method B
Stationary Phase	AS-H (ChiralPAK)	IC (ChiralCEL)
Column Particle Size ( $\mu\text{m}$ )	5	20
Column Length (mm)	250	250
Column Internal Diameter (mm)	4.6	4.6
Solvent (isocratic mixtures)	Hexane:PrOH, 95:5	Hexane:PrOH, 95:5
Runtime (min)	45	60

Optical rotations were obtained at ambient temperature with a cell of 1 dm length using an AA Series PolAAR 20 polarimeter running at a wavelength of 589 nm (sodium D-line). Concentrations ( $c$ ) for the derived specific rotations ( $[\alpha]_D$  values) are expressed in  $\text{g}/100 \text{ cm}^3$ .<sup>\*</sup> Melting points (**mp**) were measured using a Gallenkamp melting point apparatus; the temperature range and whether the substance undergoes decomposition (dec.) over this range is reported.

Flash chromatography was carried out on powdered silica (Kieselgel 60, Sigma–Aldich, procedures pertaining to **Chapter 3**; or Geduran 60, Merck, all other procedures) of pore size 60 Å and particle size 40 to 63  $\mu\text{m}$ . Thin-layer chromatography (TLC) was performed using aluminium/silica plates (0.25 mm, F<sub>254</sub> silica gel 60, Merck) and visualised by ultraviolet irradiation or  $\text{KMnO}_4$  stain.<sup>†</sup>

All non-aqueous reactions were performed using oven-dried glassware (140 °C) with magnetic stirring under a positive pressure of argon gas using anhydrous solvents [obtained from a Grubbs solvent purification system (GlassContour)] unless otherwise stated. Reactions at reflux were carried out at a bath temperature 5 °C above accepted literature solvent boiling points. Reactions involving ultrasonic vibration were carried out using a Grant XB2 ultrasonic bath.

<sup>\*</sup>For compounds **338** and **395**, where an achiral contaminant was present in the sample, the calculated concentration was corrected-for according to the analyte:contaminant ratio (as determined by <sup>1</sup>H NMR spectroscopy) to account for the mass discrepancy that the contaminant presented. For example, 30.0 mg of optically active and achiral material of equal molecular mass dissolved in 2  $\text{cm}^3$  of solvent in a 2:1 molar ratio would have a concentration,  $c$ , equal to 1.00  $\text{g}/100 \text{ cm}^3$ .

<sup>†</sup>Prepared by stirring  $\text{KMnO}_4$  (1.00 % w/v),  $\text{K}_2\text{CO}_3$  (0.40 % w/v) and NaOH (4 pellets/ $\text{dm}^3$ ) in  $\text{H}_2\text{O}$  in the absence of light until full reactant dissolution had occurred.

Aqueous (aq) solutions of acids, bases or inorganic salts are reported as: solution (volume; molarity or level of saturation). Concentrated aqueous (conc aq) HCl refers to the commercially obtained (Fisher) ~37% w/v solution. Solutions described as “25% sat aq” or “50% sat aq” refer, respectively, to the saturated aqueous (sat aq) solution diluted 1:3 or 1:1 with H<sub>2</sub>O. Reduced pressure removal of solvents was carried out at a bath temperature of 40 °C unless otherwise stated. All distillations, unless otherwise stated, were carried out under an atmosphere of nitrogen.

The following solvents and reagents were purified and dried by distillation over the drying agent (in its powdered, anhydrous form) that is indicated in parentheses: acetone (K<sub>2</sub>CO<sub>3</sub>); DIPEA, Et<sub>3</sub>N, morpholine, <sup>i</sup>Pr<sub>2</sub>NH, TMSCl (CaH<sub>2</sub>); glacial acetic acid (CuSO<sub>4</sub>); oxalyl chloride (CaCl<sub>2</sub>). Pyrrole was purified by short-path distillation in the absence of light. BnBr was purified by washing its Et<sub>2</sub>O solution (0.3 M) with 20 % v/v of H<sub>2</sub>SO<sub>4</sub> (1.0 M aq), NaHCO<sub>3</sub> (sat aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (0.1 M aq), H<sub>2</sub>O and brine; before drying (MgSO<sub>4</sub>), removing the solvent under reduced pressure and subjecting the liquid thus obtained to short-path distillation. Benzaldehyde was purified by washing its Et<sub>2</sub>O solution (0.1 M) with 20% v/v of NaOH (1.0 M aq), Na<sub>2</sub>SO<sub>3</sub> (sat aq), H<sub>2</sub>O and brine; before drying (MgSO<sub>4</sub>), removing the solvent under reduced pressure and subjecting the liquid thus obtained to reduced-pressure distillation over anhydrous K<sub>2</sub>CO<sub>3</sub>. Unless otherwise stated, distilled reagents were stored under nitrogen gas over their respective drying agents (where relevant) and used within 2 d.

Anhydrous DMF was obtained commercially (VWR BakerDRY) and used as purchased. Solvents and glassware used in CuAAC reactions and Pd/C mediated catalytic hydrogenations were purged with a stream of nitrogen gas for ~15 min prior to experiment. Magnesium turnings used in Grignard reagent preparations were activated by washing with HCl (0.1 M aq), H<sub>2</sub>O, acetone, Et<sub>2</sub>O and anhydrous Et<sub>2</sub>O immediately prior to experiment. HNMe(OMe)•HCl was recrystallised from EtOH. TsOH•H<sub>2</sub>O was recrystallised from its concentrated aqueous solution, washing with toluene following filtration. ZnCl<sub>2</sub> and anhydrous CrCl<sub>2</sub> were dried by heating with a hot-air blower (200–300 °C) under vacuum for 10 to 15 min prior to use. The molarity of NaOCl in commercially obtained bleach (10–15%, Sigma Aldrich) was

determined by iodometric titration with KI, HCl and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>.<sup>236</sup> Molecular sieves (4 Å) were pulverised and activated by oven-heating for at least 24 h before use.

The following metal catalysts and metals were obtained from the supplier that is indicated in brackets and used as purchased unless otherwise stated: CrCl<sub>2</sub> [Alfa Aesar]; Grubbs' II, 10% Pd/C, Pd(PPh<sub>3</sub>)<sub>4</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, indium (100 mesh), magnesium (turnings), tin (325 mesh), zinc (170 mesh) [Sigma–Aldrich]; samarium (40 mesh) [Strem]. The following reagents were obtained in the purity or formulation that is indicated in parentheses from the supplier that is indicated brackets and used as purchased unless otherwise stated: BnN<sub>3</sub> (94%) [Alfa Aesar]; <sup>n</sup>BuLi (2.4 M, hexanes), LiAlH<sub>4</sub> (2.4 M, hexanes), NaHMDS (2.4 M, THF), <sup>i</sup>PrMgBr (3.0 M, 2-MeTHF) [Fisher]; <sup>n</sup>BuLi (1.6 M, hexanes), DIBAL (1.0 M, hexanes), ethyl 3,3-diethoxypropionate (90%), NaH (60%, dispersion in mineral oil), 1-propenyl- and 1-propynylmagnesium bromide (both 0.5 M, THF) [Sigma-Aldrich]. All other reagents (specified >98% purity) were obtained from one of the aforementioned suppliers and were used as purchased unless otherwise stated.

### 7.1.1 Index for General Procedures

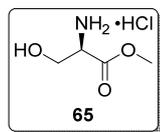
General Procedures for the preparation of compounds according to standard protocols can be found on the following pages:

<b>General Procedure A: Weinreb Amide Synthesis with <sup>n</sup>BuLi</b>	196
<b>General Procedure B: Swern Oxidation</b>	196
<b>General Procedure C: TBS Protection of Alcohols with TBSOTf</b>	196
<b>General Procedure D: <i>N</i>-Boc Protection of <i>N</i>-Heterocycles</b>	232
<b>General Procedure E: <i>N</i>-Alkylation of <i>N</i>-Heterocycles</b>	232
<b>General Procedure F: The Evans–Tishchenko Reaction</b>	250

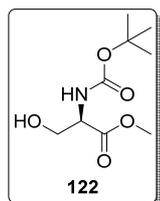
Noteworthy protocol deviations are underlined in the experimental description.

In addition to General Procedures, it should be noted that three syntheses of compounds from **Chapter 3** are presented alongside those from **Chapter 4** in order to keep the relevant spectroscopic data collated. The index for these reactions can be found at the end of the experimental section for **Chapter 3** (page 210).

## 7.2 Experimental from Chapter 2

**(R)-2-Amino-3-hydroxy-propionic acid methyl ester hydrochloride (65)**

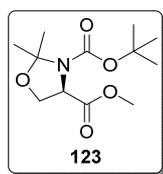
*D*-serine methyl ester hydrochloride **65** was prepared according to a modification of the procedure described by Joullié *et al.*<sup>50b</sup> SOCl<sub>2</sub> (18.9 cm<sup>3</sup>, 260 mmol) was added dropwise (~15 min) to a suspension of *D*-serine (21.0 g, 200 mmol) in MeOH (200 cm<sup>3</sup>) at 0 °C and the solution was stirred for 1 h, warmed to rt, and stirred overnight (~18 h). The solvent was removed under reduced pressure and the beige solid thus obtained was recrystallised (MeOH/Et<sub>2</sub>O) to give *D*-serine methyl ester hydrochloride **65** as a colourless solid (29.3 g, 94%). **R<sub>f</sub>** (DCM:MeOH:Et<sub>3</sub>N, 200:20:1) = 0.27; **mp** 162–163 °C, lit<sup>237</sup> 163–164 °C; **[α]<sub>D</sub>** = –5.00 (*c* 1.00, MeOH), lit<sup>237</sup> **[α]<sub>D</sub>** = –4.30 (*c* 1.80, EtOH); **IR** (neat, cm<sup>-1</sup>) 3345 (OH), 3070 (NH), 3028 (NH), 2990 (NH), 2922 (NH), 1745 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, D<sub>2</sub>O) 4.23 (1H, dd, *J* = 4.4, 3.5 Hz, NCH), 4.05 (1H, dd, *J* = 12.6, 4.4 Hz, NCHCH<sub>A</sub>H<sub>B</sub>OH), 3.95 (1H, dd, *J* = 12.6, 3.5 Hz, NCHCH<sub>A</sub>H<sub>B</sub>OH), 3.80 (3H, s, OCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, D<sub>2</sub>O) 168.9 (C), 59.2 (CH<sub>2</sub>), 54.7 (CH), 53.7 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 142 ([M+Na]<sup>+</sup>, 16%), 120 ([M]<sup>+</sup>, 37), 60 ([M+H]<sup>2+</sup>, 100). The spectroscopic data are in good agreement with the literature.<sup>237</sup>

**(R)-2-tert-Butoxycarbonylamino-3-hydroxy-propionic acid methyl ester (122)**

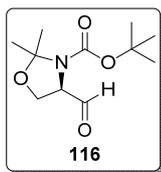
*N*-Boc-*D*-serine methyl ester **122** was prepared according to a modification of the procedure described by Chang *et al.*<sup>50a</sup> Freshly distilled Et<sub>3</sub>N (65.6 cm<sup>3</sup>, 471 mmol) was added to a suspension of *D*-serine methyl ester hydrochloride **65** (29.3 g, 188 mmol) in DCM (300 cm<sup>3</sup>) at 0 °C and the mixture was stirred for 15 min before slow addition (~20 min) of Boc<sub>2</sub>O (49.3 g, 226 mmol) in DCM (100 cm<sup>3</sup>). The reaction mixture was warmed to rt, stirred overnight (~16 h) and diluted with DCM (600 cm<sup>3</sup>). The organic layer was washed with HCl (3 × 400 cm<sup>3</sup>; 0.5 M aq), NaHCO<sub>3</sub> (400 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (400 cm<sup>3</sup>), brine (400 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave *N*-Boc-*D*-serine methyl ester **122** as a yellow syrup (35.3 g, ~76% by <sup>1</sup>H NMR; ~8–9% Boc<sub>2</sub>O present), which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.40; **[α]<sub>D</sub>** = –7.80 (*c* 1.15, CHCl<sub>3</sub>), lit<sup>50b</sup> **[α]<sub>D</sub>**

= -9.37 (*c* 3.18, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3397 (OH), 1748 (C=O), 1715 (C=O), 1697 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 5.49 (1H, br s, NH), 4.42 (1H, br s, NCH), 3.99 (1H, dd, *J* = 11.2, 3.8 Hz, NCHCH<sub>A</sub>H<sub>B</sub>OH), 3.93 (1H, dd, *J* = 11.2, 3.5 Hz, NCHCH<sub>A</sub>H<sub>B</sub>OH), 3.81 (3H, s, OCH<sub>3</sub>), 1.48 (9H, s, 3C(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 171.3 (C), 155.8 (C), 80.4 (C), 63.6 (CH<sub>2</sub>), 55.7 (CH), 52.7 (CH<sub>3</sub>), 28.3 (3CH<sub>3</sub>); *m/z* (EI) 219 ([M]<sup>+</sup>, 15%), 191 (15), 60 (21), 59 (21), 57 (100). The spectroscopic data are in good agreement with the literature.<sup>50a,b</sup>

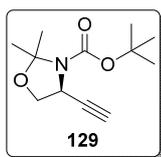
**(*R*)-2,2-Dimethyl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**123**)**



Garner's ester **123** was prepared according to a modification of the procedure described by Chang *et al.*<sup>50a</sup> To a cooled (0 °C) solution of *N*-Boc-*D*-serine methyl ester **122** (35.1 g, 160 mmol) and 2,2-dimethoxypropane (294 cm<sup>3</sup>, 2.40 mol) in DCM (300 cm<sup>3</sup>) was added TsOH•H<sub>2</sub>O (3.04 g, 16.0 mmol, 10 mol%) and the solution was stirred for 30 min, warmed to rt and stirred overnight (~16 h). NaHCO<sub>3</sub> (500 cm<sup>3</sup>; sat aq) was added to quench the reaction, and the aqueous layer was extracted with DCM (3 × 100 cm<sup>3</sup>). The combined organic layers were washed with NaHCO<sub>3</sub> (3 × 200 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (200 cm<sup>3</sup>), brine (400 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave Garner's ester **123** as a light-yellow syrup (39.3 g, 95%), which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.35; **[α]<sub>D</sub>** = +53.3 (*c* 1.05, CHCl<sub>3</sub>), lit<sup>50b</sup> **[α]<sub>D</sub>** = +49.8 (*c* 1.04, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 1757 (C=O), 1705 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, DMSO-*d*<sub>6</sub>, 353 K) 4.42 (1H, dd, *J* = 7.2, 3.0 Hz, NCH), 4.18 (1H, dd, *J* = 9.2, 7.2 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.95 (1H, dd, *J* = 9.2, 3.0 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.71 (3H, s, OCH<sub>3</sub>), 1.58 (3H, s, NCCH<sub>3</sub>), 1.48 (3H, s, NCCH<sub>3</sub>), 1.42 (9H, br s, 3C(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, DMSO-*d*<sub>6</sub>, 353 K) 171.6 (C), 151.3 (C), 94.5 (C), 80.1 (C), 66.1 (CH<sub>2</sub>), 59.3 (CH), 52.3 (CH<sub>3</sub>), 28.4 (3CH<sub>3</sub>), 25.5–24.9 (2CH<sub>3</sub>); *m/z* (ESI+, MeOH) 541 ([2M+Na]<sup>+</sup>, 29), 342 ([M+2MeCN+H]<sup>+</sup>, 100), 282 ([M+Na]<sup>+</sup>, 84). The spectroscopic data are in good agreement with the literature.<sup>50a,b</sup>

**(R)-4-Formyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (116)**

Garner's aldehyde **116** was prepared according to the procedure described by Chang *et al.*<sup>50a</sup> A cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of DIBAL ( $17.0\text{ cm}^3$ ,  $8.50\text{ mmol}$ ;  $0.50\text{ M}$  in Hexane/PhMe, 1:1) was added *via* cannula to a solution of Garner's ester **123** ( $1.30\text{ g}$ ,  $5.00\text{ mmol}$ ) in PhMe ( $10\text{ cm}^3$ ) at  $-78\text{ }^{\circ}\text{C}$  at a rate such that the internal temperature of the solution did not exceed  $-70\text{ }^{\circ}\text{C}$  ( $\sim 45\text{ min}$ ). The mixture was stirred for 3 h before cold ( $-78\text{ }^{\circ}\text{C}$ ) MeOH ( $2.27\text{ cm}^3$ ,  $89.4\text{ mmol}$ ) was added *via* cannula, keeping the temperature below  $-70\text{ }^{\circ}\text{C}$  [CAUTION:  $\text{H}_2$  gas evolution]. Stirring was continued at  $-78\text{ }^{\circ}\text{C}$  until a constant internal temperature (below  $-70\text{ }^{\circ}\text{C}$ ) was maintained ( $\sim 10\text{ min}$ ); and the emulsion was then poured into a slurry of ice ( $\sim 20\text{ g}$ ) and HCl ( $15\text{ cm}^3$ ;  $1.0\text{ M}$  aq) and warmed to rt. Sodium potassium tartrate ( $20\text{ cm}^3$ ; sat aq) was added, and the mixture was stirred for a further 30 min and subsequently poured into sodium potassium tartrate ( $20\text{ cm}^3$ ; sat aq) and DCM ( $50\text{ cm}^3$ ). The aqueous layer was extracted with DCM ( $5 \times 20\text{ cm}^3$ ), and the combined organic layers were washed with brine ( $50\text{ cm}^3$ ) and dried ( $\text{MgSO}_4$ ). Removal of the solvent under reduced pressure gave Garner's aldehyde **116** as a colourless oil ( $1.09\text{ g}$ ,  $94\%$ ), which was used without further purification.  $R_f$  (Hexane:EtOAc, 6:1) = 0.19;  $[\alpha]_D = +67.5$  ( $c$  1.20,  $\text{CHCl}_3$ ), lit<sup>50b</sup>  $[\alpha]_D = +83.8$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\text{IR}$  (neat,  $\text{cm}^{-1}$ ) 1738 (C=O), 1693 (C=O);  $^1\text{H NMR}$   $\delta$  (400 MHz,  $\text{DMSO-}d_6$ , 353 K) 9.55 (1H, d,  $J = 1.9\text{ Hz}$ , CHO), 4.37 (1H, ddd,  $J = 7.1, 3.5, 1.9\text{ Hz}$ , NCH), 4.10 (1H, dd,  $J = 9.5, 7.1\text{ Hz}$ , NCHCH<sub>A</sub>H<sub>B</sub>O), 4.05 (1H, dd,  $J = 9.5, 3.5\text{ Hz}$ , NCHCH<sub>A</sub>H<sub>B</sub>O), 1.56 (3H, s, NCCH<sub>3</sub>), 1.50 (3H, s, NCCH<sub>3</sub>), 1.44 (9H, m, 3C(CH<sub>3</sub>)<sub>3</sub>);  $^{13}\text{C NMR}$   $\delta$  (100 MHz,  $\text{DMSO-}d_6$ , 353 K) 199.6 (CH), 151.6 (C), 94.4 and 94.0 (C), 80.0 and 79.7 (C), 65.0 (CH), 63.5 (CH<sub>2</sub>), 28.4 (3CH<sub>3</sub>), 26.2 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>);  $m/z$  (EI) 229 ( $[\text{M}]^+$ , 3%), 200 (23), 144 (16), 100 (38), 57 (100). The spectroscopic data are in good agreement with the literature.<sup>50a,b</sup>

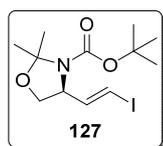
**(R)-4-Ethynyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (129)**

**Method A** (from Garner's aldehyde **116**): According a modification of the procedure described by Meffre *et al.*,<sup>55</sup>  $\text{K}_2\text{CO}_3$  (7.09 g, 51.3 mmol) was added to a solution of Garner's aldehyde (1.16 g, 5.13 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate<sup>63</sup> (5.98 g, 21.1 mmol; 67% purity) in MeOH (40 cm<sup>3</sup>) at 0 °C, and the reaction mixture was left to warm to rt overnight (~18 h). The solvent was removed under reduced pressure, and  $\text{H}_2\text{O}$  (50 cm<sup>3</sup>) was added to the residue, followed by extraction of the aqueous layer with DCM (4 × 20 cm<sup>3</sup>). The combined organic layers were washed with brine (20 cm<sup>3</sup>), dried ( $\text{MgSO}_4$ ), and the solvent was removed under reduced pressure. Flash chromatography (Hexane:EtOAc, 6:1) of the resulting yellow residue gave alkyne **129** as a colourless oil (575 mg, 50%).

**Method B** (from Garner's ester **123**): According to a modification of the procedure described by Hinkle *et al.*,<sup>56</sup> a cooled (−78 °C) solution of DIBAL (3.40 cm<sup>3</sup>, 1.70 mmol; 0.50 M in hexane/PhMe, 1:1) was added *via* cannula to a solution of Garner's ester **123** (259 mg, 1.00 mmol) in PhMe (3 cm<sup>3</sup>) at a rate such that the internal temperature of the solution did not exceed −65 °C (~20 min). The mixture was stirred for 3 h at −78 °C and cold (−78 °C) MeOH (5 cm<sup>3</sup>, 124 mmol) was added *via* cannula at a rate such that the internal temperature of the solution did not exceed −70 °C [~20 min; CAUTION:  $\text{H}_2$  gas evolution]. The reaction mixture was warmed to 0 °C, then MeOH (5 cm<sup>3</sup>),  $\text{K}_2\text{CO}_3$  (829 mg, 6.00 mmol) and a solution of dimethyl-1-diazo-2-oxopropylphosphonate<sup>63</sup> (773 mg, 2.73 mmol; 67% purity) in MeOH (5 cm<sup>3</sup>) were added and stirring was continued overnight (~18 h) at rt. Sodium potassium tartrate (20 cm<sup>3</sup>; sat aq) was added, and the mixture was stirred for 1 h and poured into  $\text{H}_2\text{O}$  (20 cm<sup>3</sup>). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (5 × 10 cm<sup>3</sup>), and the combined organic layers were washed with brine (20 cm<sup>3</sup>) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the crude yellow oil thus obtained was purified by flash chromatography (Hexane:EtOAc, 6:1) to give alkyne **129** as a colourless oil (71.7 mg, 32% over 2 steps).  $R_f$  (Hexane:EtOAc, 6:1) = 0.47;  $[\alpha]_D = +125$  ( $c$  1.30,  $\text{CHCl}_3$ ), lit<sup>238</sup>  $[\alpha]_D = +96.6$  ( $c$  1.00,  $\text{CHCl}_3$ ); **IR** (neat, cm<sup>−1</sup>) 3294 (CC–H), 3257 (CC–H), 2116 (C≡C), 1697 (C=O); **<sup>1</sup>H NMR**  $\delta$  (500 MHz,  $\text{DMSO}-d_6$ , 323 K) 4.56–4.54 (1H, m, NCH), 4.03 (1H, dd,  $J = 8.7, 5.9$  Hz,  $\text{CH}_A\text{H}_B\text{O}$ ), 3.89 (1H, dd,

$J = 8.7, 2.0$  Hz,  $\text{CH}_A\text{H}_B\text{O}$ ), 3.15 (1H, br s,  $\text{C}\equiv\text{CH}$ ), 1.53 (3H, s,  $\text{NCCH}_3$ ), 1.45 (9H, s,  $3\text{C}(\text{CH}_3)_3$ ), 1.43 (3H, s,  $\text{NCCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{DMSO}-d_6$ , 323 K) 151.3 (C), 93.9 (C), 83.8 (C), 80.1 (C), 72.9 (CH), 68.8 ( $\text{CH}_2$ ), 48.4 (CH), 28.5 ( $3\text{CH}_3$ ), 27.3–26.0 ( $\text{CH}_3$ ), 25.6–24.3 ( $\text{CH}_3$ );  $m/z$  (EI) 228 ( $[\text{M}+3\text{H}]^+$ , 37%), 227 ( $[\text{M}+2\text{H}]^+$ , 3), 226 ( $[\text{M}+\text{H}]^+$ , 14), 225 ( $[\text{M}]^+$ , 2), 224 ( $[\text{M}-\text{H}]^+$ , 8), 223 ( $[\text{M}-2\text{H}]^+$ , 17), 210 (100), 170 (49). The spectroscopic data are in reasonable agreement with the literature.<sup>55,238</sup>

**(1'E,4S)-4-(2'-Iodoethenyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (127)**



**Method A** (*Takai olefination using anhydrous  $\text{CrCl}_2$  as the chromium source*): According to a modification of the conditions described by Marquez<sup>60</sup> for the Takai olefination<sup>40</sup> of an (alternative) aldehyde, a solution containing Garner's aldehyde **116** (1.63 g, 7.20 mmol) and  $\text{CHI}_3$  (17.0 g, 43.2 mmol) in THF (50  $\text{cm}^3$ ) was added to a suspension of anhydrous  $\text{CrCl}_2$  (16.0 g, 130 mmol) in THF (150  $\text{cm}^3$ ), and the mixture was stirred for 1 d in the absence of light.  $\text{H}_2\text{O}$  (100  $\text{cm}^3$ ) was added to quench the reaction, the slurry was stirred for 30 min, and the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (100  $\text{cm}^3$ ). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $4 \times 50 \text{ cm}^3$ ), and the combined organic layers were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  ( $2 \times 50 \text{ cm}^3$ ; sat aq),  $\text{H}_2\text{O}$  ( $2 \times 50 \text{ cm}^3$ ), brine (50  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the brown residual oil thus obtained was purified twice by flash chromatography (Hexane: $\text{EtOAc}$ , 6:1) to give vinyl iodide **127** as a yellow solid (1.14 g, 45%, >99:1 *E:Z*).

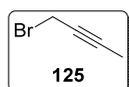
**Method B** (*Takai olefination using  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  as the chromium source*): In this protocol,  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  was dehydrated according to the protocol described by Augé *et al.*,<sup>53a</sup> and the anhydrous  $\text{CrCl}_3$  thus obtained was reduced with  $\text{LiAlH}_4$  according to Hiyama's conditions<sup>61</sup> to give the active Cr(II) reagent that was then used for the iodo-olefination of Garner's aldehyde **116**. A 1  $\text{dm}^3$  round-bottomed flask fitted with a cold-trap ( $-10 \text{ }^\circ\text{C}$ ) was charged with  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  (124 g, 465 mmol), and the system was placed under high-vacuum ( $\sim 10$  mmHg), heated to  $120 \text{ }^\circ\text{C}$ , and stirred gently for 30 min. The pale-green solid thus obtained was heated to  $250 \text{ }^\circ\text{C}$ , and maintained at this temperature until effervescence of the solid had ceased and a violet colour persisted ( $\sim 20$  min), indicative of the formation of anhydrous  $\text{CrCl}_3$ . Residual

H<sub>2</sub>O apparent in the flask was removed through the use of a hot-air blower, the solid was cooled to rt, the vacuum was released and the system was placed under an atmosphere of argon. THF (300 cm<sup>3</sup>) was added, the purple suspension was cooled to 0 °C and LiAlH<sub>4</sub> (75.0 cm<sup>3</sup>, 180 mmol; 2.4 M in THF) was added dropwise (~1 h) [CAUTION: H<sub>2</sub> gas evolved, exothermic]. The black slurry was warmed to rt, stirred for 1 h and re-cooled to 0 °C. In the absence of light, a solution containing Garner's aldehyde **116** (5.26 g, 23.3 mmol) and CHI<sub>3</sub> (54.9 g, 140 mmol) in THF (100 cm<sup>3</sup>) was then added, and the mixture was stirred for 1 h, warmed to rt and stirred overnight (~18 h). Pyridine (10.8 cm<sup>3</sup>, 151 mmol) was added, the slurry was stirred for 30 min, cooled to 0 °C and brine (500 cm<sup>3</sup>) was added to quench the reaction. The aqueous layer was extracted with EtOAc (5 × 300 cm<sup>3</sup>) and the combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (500 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (500 cm<sup>3</sup>), brine (500 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the brown residue thus obtained was purified by flash chromatography (Hexane:EtOAc, 10:1; dry loaded) to give vinyl iodide **127** as a yellow oil that solidifies to a yellow solid on cooling (2.71 g, 33%, >99:1 *E:Z*).

**Method C (hydrostannylation/iododestannylation of alkyne 129):** According to a modification of the procedure described by Ramstadius<sup>44</sup> for the hydroiodination of an analogous alkyne, <sup>n</sup>BuSnH (0.11 cm<sup>3</sup>, 0.40 mmol) was added to a solution of alkyne **129** (46.0 mg, 0.20 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1.60 mg, 2.00 μmol, 1 mol%) in THF (2 cm<sup>3</sup>) at -30 °C and the solution was stirred for 1 h. A solution of I<sub>2</sub> (105 mg, 0.25 mmol) in THF (2 cm<sup>3</sup>) was added dropwise (~10 min), and the violet solution was warmed to rt and stirred for 1 h. The reaction was quenched with a combined solution of KF (5 cm<sup>3</sup>; sat aq) and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 cm<sup>3</sup>; sat aq) and after 20 min, the aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 cm<sup>3</sup>; sat aq), KF (10 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (10 cm<sup>3</sup>), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the resulting brown oil was purified by flash chromatography (Hexane:EtOAc, 10:1; SiO<sub>2</sub> doped with 10% *w/w* powdered KF) to give vinyl iodide **127** as a yellow oil (27.5 mg, 39%, >99:1 *E:Z*). **R<sub>f</sub>** (Hexane:EtOAc, 10:1) = 0.28; **mp** 35–39 °C; [**α**]<sub>D</sub> = +101 (*c* 0.73, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 1694 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, DMSO-*d*<sub>6</sub>, 328 K) 6.50 (1H, dd, *J* = 14.1, 7.5 Hz, CH=CHI), 6.39 (1H, d, *J* = 14.5

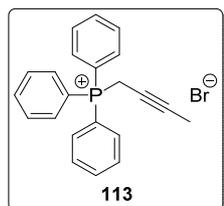
Hz, CH=CHI), 4.32 (1H, m, NCH), 3.99 (1H, dd,  $J =$  Hz, 9.1, 6.1 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.76 (1H, dd,  $J =$  9.1, 2.5 Hz, NCHCH<sub>A</sub>CH<sub>B</sub>O), 1.51 (3H, s, NCCH<sub>3</sub>), 1.44 (3H, s, NCCH<sub>3</sub>), 1.41 (9H, s, 3C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  (125 MHz, DMSO-*d*<sub>6</sub>, 328 K) 151.6 (C), 145.0 (CH), 93.7 (C), 79.8 (C), 79.6 (CH), 67.1 (CH<sub>2</sub>), 61.1 (CH), 28.5 (3CH<sub>3</sub>), 27.4–26.5 (CH<sub>3</sub>), 24.7–23.8 (CH<sub>3</sub>);  $m/z$  (EI) 353 ([M]<sup>+</sup>, 1%), 297 (16), 282 (83), 238 (43), 170 (96), 84 (23), 57 (100). The spectroscopic data are in good agreement with the literature.<sup>53a,54</sup>

### 1-Bromo-but-2-yne (125)



Propargylic bromide **125** was prepared according to the procedure described by Lu *et al.*<sup>51</sup> PBr<sub>3</sub> (7.52 cm<sup>3</sup>, 80.0 mmol) was added to a solution of 2-butyne-1-ol (14.0 g, 200 mmol) and pyridine (1.61 cm<sup>3</sup>, 20.0 mmol) in Et<sub>2</sub>O (150 cm<sup>3</sup>) at –30 °C and the mixture, which immediately turned cloudy, was stirred for 10 min, warmed to rt, stirred for 1.5 h and subsequently heated to reflux for 1 h. The yellow mixture was cooled to rt, poured into a slurry of ice (200 g) and brine (200 cm<sup>3</sup>), and stirred until the biphasic mixture reached rt. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 50 cm<sup>3</sup>) and the combined organic layers were washed with brine (200 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed at atmospheric pressure (bath temperature = 60 °C) and the resulting orange oil was subjected to reduced-pressure distillation to afford propargylic bromide **125** as a volatile, colourless to pale-yellow liquid (19.4 g, 73%). **R<sub>f</sub>** (Hexane) = 0.63; **bp** 60 °C (113 mmHg), lit<sup>51</sup> 89–90 °C (150 mmHg); **IR** (neat, cm<sup>-1</sup>) 2239 (C≡C); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 3.93 (2H, q,  $J =$  2.5 Hz, CH<sub>2</sub>), 1.91 (3H, t,  $J =$  2.5 Hz, CH<sub>3</sub>); **<sup>13</sup>C NMR**  $\delta$  (125 MHz, CDCl<sub>3</sub>) 83.7 (C), 74.4 (C), 16.7 (CH<sub>2</sub>), 3.9 (CH<sub>3</sub>);  $m/z$  (EI) 135 ([<sup>81</sup>BrM+H]<sup>+</sup>, 13%), 134 ([<sup>81</sup>BrM]<sup>+</sup>, 23), 133 ([<sup>79</sup>BrM+H]<sup>+</sup>, 13), 132 (<sup>79</sup>BrM<sup>+</sup>, 23), 53 (100). The spectroscopic data are in good agreement with the literature.<sup>51</sup>

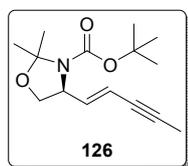
### 2-Butynyltriphenylphosphonium bromide (113)



2-Butynyltriphenylphosphonium bromide **113** was prepared according to a modification of the procedure described by Niblock.<sup>16</sup> A solution of propargylic bromide **125** (18.2 g, 137 mmol) and PPh<sub>3</sub> (37.6 g, 143 mmol) in PhMe (250 cm<sup>3</sup>) was

heated to 70 °C for 1 d (~24 h), after which time an orange-yellow suspension had formed. The precipitate was filtered, washed with hexane (5 × 100 cm<sup>3</sup>) and dried *in vacuo* to give 2-butynyltriphenylphosphonium bromide **113** as a beige solid (48.5 g, 90%). **R<sub>f</sub>** (DCM:MeOH, 10:1) = 0.50; **mp** 196–199 °C (dec.), lit<sup>16</sup> 195–197 °C; **IR** (neat, cm<sup>-1</sup>) 2236 (C≡C), 1684 (C=C), 1585 (C=C), 1568 (C=C), 1545 (C=C), 1485 (C=C), 1435 (P–Ar); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 7.94–7.80 (6H, m, 6ArH), 7.84–7.82 (3H, m, 3ArH), 7.74–7.70 (6H, m, 6ArH), 5.10 (2H, dq, *J* = 14.8, 2.3 Hz, CH<sub>2</sub>), 1.70 (3H, dt, *J* = 6.5, 2.3 Hz, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 135.2 (d, *J* = 3.0 Hz, 3CH), 134.0 (d, *J* = 10.0 Hz, 6CH), 130.3 (d, *J* = 12.7 Hz, 6CH), 117.9 (d, *J* = 87.3 Hz, 3C), 84.8 (d, *J* = 9.5 Hz, C), 66.4 (d, *J* = 13.6 Hz, C), 18.3 (d, *J* = 55.7 Hz, CH<sub>2</sub>), 3.72 (d, *J* = 3.3 Hz, CH<sub>3</sub>); **<sup>31</sup>P NMR** δ (162 MHz, CDCl<sub>3</sub>) 21.9 (P); ***m/z*** (ESI+, DCM) 397 ([<sup>81</sup>BrM+H]<sup>+</sup>, 4%), 395 ([<sup>79</sup>BrM+H]<sup>+</sup>, 4), 347 ([{M–Br}+MeOH+H]<sup>+</sup>, 50)], 315 ([M–Br]<sup>+</sup>, 100). The spectroscopic data are in good agreement with the literature.<sup>16</sup>

**(1'*E*,4*S*)-2,2-Dimethyl-4-(pent-1'-en-3'-ynyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester (126)**



**Method A** (from Garner's aldehyde **116**): According to a modification of the procedure described by Ersack and Krause<sup>49</sup> for the preparation of analogous 1,3-enynyl Garner aldehyde derivatives, NaHMDS (16.3 cm<sup>3</sup>, 32.5 mmol; 2.0 M in THF) was added to a suspension of 2-butynyltriphenylphosphonium bromide **113** (12.9 g, 32.5 mmol) in THF (110 cm<sup>3</sup>) at rt and the deep-red solution was stirred for 5 min before cooling to –78 °C. Aldehyde **116** (2.94 g, 13.0 mmol) in THF (20 cm<sup>3</sup>) was added, the solution was stirred for 6 h, and the reaction was quenched with H<sub>2</sub>O (50 cm<sup>3</sup>). The slurry was poured into H<sub>2</sub>O (100 cm<sup>3</sup>) and the aqueous layer was extracted with DCM (5 × 50 cm<sup>3</sup>). The combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 cm<sup>3</sup>; 50% sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give a red residue that was suspended in cold (–20 °C) Et<sub>2</sub>O and filtered, rinsing with cold Et<sub>2</sub>O (3 × 100 cm<sup>3</sup>). Removal of the solvent under reduced pressure gave an oil that was purified by flash

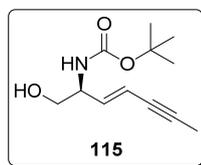
chromatography (Hexane:EtOAc, 10:1; dry loaded) to give enyne **126** as a yellow oil that solidifies to a light-yellow solid on cooling (1.69 g, 49%, ~5:1 *E:Z*).

**Method B** (from vinyl iodide **127**): According to a modification of the standard Negishi coupling protocol,<sup>44</sup> 1-propynylmagnesium bromide (60.0 cm<sup>3</sup>, 30.0 mmol; 0.5 M in THF) was added to a suspension of ZnCl<sub>2</sub> (4.50 g, 33.0 mmol) in THF (5 cm<sup>3</sup>) and the slurry was stirred for 30 min at 0 °C. Vinyl iodide **127** (2.56 g, 7.22 mmol) in THF (10 cm<sup>3</sup>) was added, followed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (263 mg, 0.38 mmol, 5 mol%) and the pale-yellow mixture was warmed to rt and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and to the brown paste thus obtained was added NH<sub>4</sub>Cl (50 cm<sup>3</sup>; 50% sat aq). The reaction mixture was poured into H<sub>2</sub>O (50 cm<sup>3</sup>), the aqueous layer was extracted with DCM (3 × 50 cm<sup>3</sup>), and the combined organic layers were washed with brine (50 cm<sup>3</sup>), dried (MgSO<sub>4</sub>), and the solvent was removed under reduced pressure. Flash chromatography (Hexane:EtOAc, 10:1; dry loaded) of the black residue thus obtained gave enyne **126** as an orange oil that solidifies to a yellow solid on cooling (1.70 g, 89%, >99:1 *E:Z*). N.B. All subsequent steps were carried out using material derived from enyne **126** that was prepared in this fashion (*i.e.* >99:1 *E:Z*). **R<sub>f</sub>** (Hexane:EtOAc, 10:1) = 0.34; **mp** 47–51 °C; **[α]<sub>D</sub>** = +70.0 (*c* 0.10, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2220 (C≡C), 1694 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, DMSO-*d*<sub>6</sub>, 328 K) 5.93 (1H, ddd, *J* = 15.8, 7.3, 0.6 Hz, NCHCH=CH), 5.57 (1H, dqd, *J* = 15.8, 2.2, 1.1 Hz, NCHCH=CH), 4.33–4.31 (1H, m, NCH), 4.02 (1H, dd, *J* = 9.0, 6.3 Hz, CH<sub>A</sub>H<sub>B</sub>O), 3.70 (1H, dd, *J* = 9.0, 2.5 Hz, CH<sub>A</sub>H<sub>B</sub>O), 1.93 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.51 (3H, s, NCCH<sub>3</sub>), 1.44 (3H, s, NCCH<sub>3</sub>), 1.41 (9H, s, 3OC(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, DMSO-*d*<sub>6</sub>, 328 K) 151.6 (C), 141.2 (CH), 111.6 (CH), 93.6 (C), 87.6 (C), 79.6 (C), 78.1 (C), 67.8 (CH<sub>2</sub>), 58.7 (CH), 28.5 (3CH<sub>3</sub>), 27.4–26.6 (CH<sub>3</sub>), 24.8–23.8 (CH<sub>3</sub>), 4.2 (CH<sub>3</sub>); ***m/z*** (EI) 265 ([M]<sup>+</sup>, 1%), 209 (21), 194 (60), 150 (27), 134 (18), 108 (48), 107 (100); **HRMS** (EI) [M]<sup>+</sup> found 265.1670, C<sub>15</sub>H<sub>23</sub>NO<sub>3</sub> requires 265.1673.

**(Z)-isomer:** **<sup>1</sup>H NMR** δ (500 MHz, DMSO-*d*<sub>6</sub>, 328 K) 5.82 (1H, dd, *J* = 10.6, 8.8 Hz, NCHCH=CH), 5.57 (1H, dq, *J* = 10.6, 2.2 Hz, NCHCH=CH), 4.75–4.71 (1H, m, NCH), 4.11 (1H, dd, *J* = 8.8, 6.5 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.64 (1H, dd, *J* = 8.8, 3.0 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 1.97 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.52 (3H, s, NCCH<sub>3</sub>), 1.45 (3H,

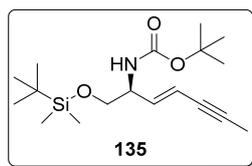
s,  $\text{NCCCH}_3$ ), 1.41 (9H, s,  $3\text{OC}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{DMSO}-d_6$ , 325 K) 151.7 (C), 141.2 (CH), 110.5 (CH), 93.7 (C), 87.6 (C), 79.6 (C), 76.3 (C), 68.2 (CH<sub>2</sub>), 56.9 (CH), 28.6 (3CH<sub>3</sub>), 27.4–26.6 (CH<sub>3</sub>), 24.8–23.8 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>).

**(2*S*,3*E*)-2-(*tert*-Butoxycarbonyl)amino-hept-3-en-5-yn-1-ol (115)**



Amino alcohol **115** was prepared according to the acetonide deprotection protocol described by Iwata.<sup>68</sup>  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (1.68 g, 9.86 mmol) was added to a solution of oxazolidine **126** (1.70 g, 6.40 mmol) in MeCN (70 cm<sup>3</sup>) and the orange-brown solution was stirred for 1 h.  $\text{NH}_4\text{Cl}$  (150 cm<sup>3</sup>; sat aq) was added to quench the reaction, and the mixture was poured into DCM (100 cm<sup>3</sup>). The aqueous layer was extracted with DCM (4 × 50 cm<sup>3</sup>), and the combined organic layers were washed with  $\text{NH}_4\text{Cl}$  (50 cm<sup>3</sup>; sat aq),  $\text{H}_2\text{O}$  (50 cm<sup>3</sup>), brine (50 cm<sup>3</sup>) and dried ( $\text{MgSO}_4$ ). Removal of the solvent under reduced pressure and flash chromatography (DCM:MeOH, 20:1) of the yellow-brown solid thus obtained gave amino alcohol **115** as a yellow solid (1.26 g, 87%).  $R_f$  (DCM:MeOH, 20:1) = 0.39; mp 90–93 °C;  $[\alpha]_D^{25} = +50.0$  ( $c$  0.24,  $\text{CHCl}_3$ ); IR (neat, cm<sup>-1</sup>) 3348 (NH), 3307 (OH), 2220 (C≡C), 1678 (C=O), 1518 (C=C);  $^1\text{H}$  NMR  $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 6.00 (1H, dd,  $J = 15.9, 6.0$  Hz, NCHCH=CH), 5.70 (1H, ddq,  $J = 15.9, 2.2, 2.0$  Hz, NCHCH=CH), 4.85 (1H, br s, NH), 4.29 (1H, br s, NCH), 3.72 (1H, dd,  $J = 11.2, 4.1$  Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.66 (1H, dd,  $J = 11.2, 5.4$  Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 1.96 (3H, d,  $J = 2.2$  Hz, C≡CCH<sub>3</sub>), 1.47 (9H, s,  $3\text{OC}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 155.7 (C), 138.5 (CH), 112.7 (CH), 87.3 (C), 80.0 (C), 65.2 (CH<sub>2</sub>), 54.1 (CH), 28.4 (3CH<sub>3</sub>), 4.3 (CH<sub>3</sub>);  $m/z$  (ESI+, MeOH) 473 ([2M+Na]<sup>+</sup>, 46%), 248 ([M+Na]<sup>+</sup>, 100), 226 ([M+H]<sup>+</sup>, 2); HRMS (ESI+, MeOH) [M+H]<sup>+</sup> found 225.1354,  $\text{C}_{12}\text{H}_{19}\text{NO}_3$  requires 225.1359.

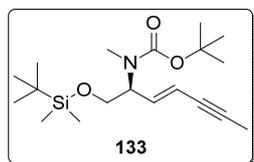
**(2*S*, 3*E*)-1-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butoxycarbonyl)amino-hept-3-en-5-yne (135)**



To a suspension of alcohol **115** (1.24 g, 5.50 mmol) and imidazole (1.12 g, 16.5 mmol) in DMF (55 cm<sup>3</sup>) was added TBSCl (1.24 g, 8.25 mmol) and the reaction mixture was stirred overnight (~18 h) at rt.  $\text{NH}_4\text{Cl}$  (500 cm<sup>3</sup>; sat aq) was

added to quench the reaction, and the aqueous layer was extracted with Et<sub>2</sub>O (5 × 100 cm<sup>3</sup>). The combined organic layers were washed with NH<sub>4</sub>Cl (100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (3 × 100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography (Hexane:EtOAc, 10:1) to give TBS-protected amino alcohol **135** as a light-yellow oil (1.79 g, 96%). **R<sub>f</sub>** (Hexane:EtOAc, 10:1) = 0.39; [**α**]<sub>D</sub> = +71.4 (*c* 0.14, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3451 (NH), 2224 (C≡C), 1705 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 6.02 (1H, dd, *J* = 15.9, 6.1 Hz, NCHCH=CH), 5.66 (1H, m, NCHCH=CH), 4.82 (1H, br s, NH), 4.21 (1H, br s, NCH), 3.69 (1H, dd, *J* = 10.1, 4.4 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.62 (1H, dd, *J* = 10.1, 3.9 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 1.96 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.47 (9H, s, 3OC(CH<sub>3</sub>)<sub>3</sub>), 0.92 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.08 (6H, s, 2SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 155.2 (C), 139.8 (CH), 111.6 (CH), 86.4 (C), 79.5 (C), 77.7 (C), 65.1 (CH<sub>2</sub>), 53.6 (CH), 28.4 (3CH<sub>3</sub>), 25.9 (3CH<sub>3</sub>), 18.3 (C), 4.3 (CH<sub>3</sub>), -5.4 (CH<sub>3</sub>), -5.5 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 379 ([M+K]<sup>+</sup>, 16), 340 ([M+H]<sup>+</sup>, 39), 284 [M-C(CH<sub>3</sub>)<sub>3</sub>+H]<sup>+</sup>, 100); **HRMS** (EI) [M+H]<sup>+</sup> found 339.2220, C<sub>18</sub>H<sub>33</sub>NO<sub>3</sub>Si requires 339.2224.

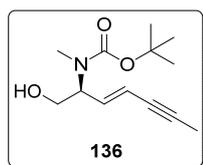
**(2*S*,3*E*)-1-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butoxycarbonyl)methylamino-hept-3-en-5-yne (**133**)**



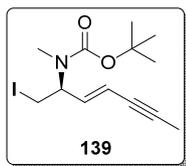
*N*-Methylated carbamate **133** was prepared according to a modification of the procedures described by Boger<sup>72a</sup> and Benoiton<sup>72b</sup> for the *N*-methylation of amino acids. To a suspension of NaH (1.25 g, 31.2 mmol; 60% dispersion in mineral oil) in THF (30 cm<sup>3</sup>) was added a solution of carbamate **135** (1.77 g, 5.20 mmol) in THF (20 cm<sup>3</sup>) at 0 °C, and the solution was warmed to rt and stirred for 1 h. MeI (6.47 cm<sup>3</sup>, 104 mmol) in DMF (5 cm<sup>3</sup>) was added, and the solution was heated to 35 °C and stirred overnight (~18 h) in the absence of light before cooling to rt. NH<sub>4</sub>Cl (100 cm<sup>3</sup>; sat aq) was added to quench the reaction and the aqueous layer was extracted with Et<sub>2</sub>O (5 × 50 cm<sup>3</sup>). The combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (3 × 50 cm<sup>3</sup>), brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (Hexane:EtOAc, 12:1) to give *N*-methylated carbamate **133** as

a light-yellow oil (1.84 g, quant)  $R_f$  (Hexane:EtOAc, 12:1) = 0.35;  $[\alpha]_D = +32.4$  ( $c$  0.74,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 2224 ( $\text{C}\equiv\text{C}$ ), 1694 ( $\text{C}=\text{O}$ );  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{DMSO-}d_6$ , 323 K) 5.96 (1H, ddd,  $J = 16.1, 6.1, 0.5$  Hz,  $\text{NCHCH}=\text{CH}$ ), 5.59 (1H, ddq,  $J = 16.1, 2.2, 1.8$  Hz,  $\text{NCHCH}=\text{CH}$ ), 4.53 (1H, br s,  $\text{NCH}$ ), 3.68 (1H, d,  $J = 2.2$  Hz,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 3.67 (1H, d,  $J = 0.9$  Hz,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 2.69 (3H, s,  $\text{NCH}_3$ ), 1.93 (3H, d,  $J = 2.2$  Hz,  $\text{C}\equiv\text{CCH}_3$ ), 1.40 (9H, s,  $3\text{OC}(\text{CH}_3)_3$ ), 0.87 (9H, s,  $3\text{SiC}(\text{CH}_3)_3$ ), 0.05 (6H, s,  $2\text{SiCH}_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{DMSO-}d_6$ , 323 K) 155.4 (C), 138.1 (CH), 112.8 (CH), 87.6 (C), 79.2 (C), 78.3 (C), 62.6 ( $\text{CH}_2$ ), 59.9–58.4 (CH), 30.3 ( $\text{CH}_3$ ), 28.6 ( $3\text{CH}_3$ ), 26.1 ( $3\text{CH}_3$ ), 18.2 (C), 4.2 ( $\text{CH}_3$ ),  $-5.0$  ( $\text{CH}_3$ ),  $-5.1$  ( $\text{CH}_3$ );  **$m/z$**  (ESI+, MeOH) 729 ( $[2\text{M}+\text{Na}]^+$ , 15%), 376 ( $[\text{M}+\text{Na}]^+$ , 100), 354 ( $[\text{M}+\text{H}]^+$ , 31), 353 ( $[\text{M}]^+$ , 2); **HRMS** (EI)  $[\text{M}]^+$  found 353.2381,  $\text{C}_{19}\text{H}_{35}\text{NO}_3\text{Si}$  requires 353.2381.

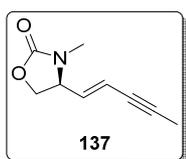
**(2*S*,3*E*)-2-(*tert*-butoxycarbonyl)methylamino-hept-3-en-5-yn-1-ol (136)**



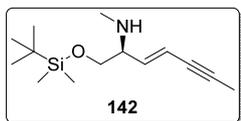
TBAF (2.08  $\text{cm}^3$ , 2.08 mmol, 1.0 M in THF) was added to a solution of TBS-ether **133** (491 mg, 1.39 mmol) in THF (14  $\text{cm}^3$ ) and the yellow solution was stirred for 30 min. The solvent was removed under reduced pressure and the brown oil thus obtained was purified by flash chromatography (Hexane:EtOAc, 1:1) to give alcohol **136** as a light-yellow oil (253 mg, 93%).  $R_f$  (Hexane:EtOAc, 1:1) = 0.47;  $[\alpha]_D = +68.1$  ( $c$  1.10,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 3435 (OH), 2224 ( $\text{C}\equiv\text{C}$ ), 1690 ( $\text{C}=\text{C}$ ), 1667 ( $\text{C}=\text{O}$ );  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{DMSO-}d_6$ , 323 K) 5.96 (1H, ddd,  $J = 16.1, 6.0, 0.6$  Hz,  $\text{NCHCH}=\text{CH}$ ), 5.53 (1H, ddq,  $J = 16.1, 2.3, 1.9$  Hz,  $\text{NCHCH}=\text{CH}$ ), 4.72 (1H, t,  $J = 5.9$  Hz, OH), 4.48 (1H, br s,  $\text{NCH}$ ), 3.50 (2H, dd,  $J = 6.9, 5.9$  Hz,  $\text{CH}_2\text{OH}$ ), 2.68 (3H, s,  $\text{NCH}_3$ ), 1.92 (3H, d,  $J = 2.3$  Hz,  $\text{C}\equiv\text{CCH}_3$ ), 1.41 (9H, s,  $3\text{OC}(\text{CH}_3)_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{DMSO-}d_6$ , 323 K) 155.6 (C), 138.8 (CH), 112.2 (CH), 87.3 (C), 79.1 (C), 78.4 (C), 61.3 ( $\text{CH}_2$ ), 59.1 (CH), 30.0 ( $\text{CH}_3$ ), 28.6 ( $3\text{CH}_3$ ), 4.2 ( $\text{CH}_3$ );  **$m/z$**  (ESI+, MeOH/DCM) 501 ( $[2\text{M}+\text{Na}]^+$ , 44%), 262 ( $[\text{M}+\text{Na}]^+$ , 100), 240 ( $[\text{M}+\text{H}]^+$ , 1); **HRMS** (EI)  $[\text{M}]^+$  found 239.1516,  $\text{C}_{13}\text{H}_{21}\text{NO}_3$  requires 239.1516.

**(2*S*,3*E*)-1-iodo-2-(*tert*-butoxycarbonyl)methylamino-hept-3-en-5-yne (139)**

**Attempted synthesis of 139:** I<sub>2</sub> (1.53 g, 6.01 mmol) was added to a solution of PPh<sub>3</sub> (1.70 g, 6.00 mmol), imidazole (817 mg, 12.0 mmol) and alcohol **136** (239 mg, 1.00 mmol) in MeCN (10 cm<sup>3</sup>) at 0 °C and the solution was warmed to rt, stirred for 30 min and subsequently heated to reflux overnight (~18 h) in the absence of light. The red solution thus obtained was cooled to rt, quenched with NaHCO<sub>3</sub> (20 cm<sup>3</sup>; sat aq) and diluted with Et<sub>2</sub>O (50 cm<sup>3</sup>). The biphasic mixture was filtered, and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (20 cm<sup>3</sup>), brine (20 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (Hexane:EtOAc, 1:1) to give oxazolidinone **137** as a yellow liquid (116 mg, 70%); iodide **139** was not observed.

**(1*E*',4*S*)-3-Methyl-4-(pent-1'-en-3'-ynyl)-oxazolidin-2-one (137)**

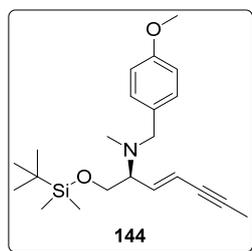
**R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.37; [**α**]<sub>D</sub> = +3.60 (*c* 1.10, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2222 (C≡C), 1746 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 5.86 (1H, dd, *J* = 15.7, 8.7 Hz, NCHCH=CH), 5.76 (1H, dq, *J* = 15.7, 2.2 Hz, NCHCH=CH), 4.44 (1H, t, *J* = 8.7 Hz, CH<sub>A</sub>H<sub>B</sub>O), 4.14 (1H, dt, *J* = 8.7, 7.3 Hz, NCH), 3.95 (1H, dd, *J* = 8.7, 7.3 Hz, CH<sub>A</sub>H<sub>B</sub>O), 2.80 (3H, s, NCH<sub>3</sub>), 1.99 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 158.1 (C), 136.8 (CH), 116.5 (CH), 89.1 (C), 76.5 (C), 66.6 (CH<sub>2</sub>), 60.2 (CH), 29.2 (CH<sub>3</sub>), 4.1 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 353 ([2M+Na]<sup>+</sup>, 17%), 188 ([M+Na]<sup>+</sup>, 100), 166 ([M+H]<sup>+</sup>, 13); **HRMS** (ESI+, MeOH) [M+Na]<sup>+</sup> found 188.0680, C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>Na requires 188.0682.

**(2*S*,3*E*)-1-(*tert*-Butyldimethylsilanyloxy)-2-methylamino-hept-3-en-5-yne (142)**

Amine **142** was prepared according to a modification of the *N*-Boc deprotection protocol described by Burgess.<sup>79</sup> TMSOTf (3.58 cm<sup>3</sup>, 19.8 mmol) was added dropwise to a solution of carbamate **133** (2.34 g, 6.60 mmol) and 2,6-lutidine (2.68 cm<sup>3</sup>, 23.1 mmol) in DCM (20 cm<sup>3</sup>) at 0 °C and the solution was stirred for 45 min before quenching of the reaction with NaHCO<sub>3</sub> (25 cm<sup>3</sup>; sat aq) and stirring for a further 10 min. The aqueous

layer was extracted with DCM ( $3 \times 20 \text{ cm}^3$ ), and the combined organic layers were washed with  $\text{NaHCO}_3$  ( $20 \text{ cm}^3$ ; sat aq),  $\text{H}_2\text{O}$  ( $20 \text{ cm}^3$ ), brine ( $20 \text{ cm}^3$ ) and dried ( $\text{MgSO}_4$ ). Removal of the solvent and residual 2,6-lutidine under reduced pressure ( $70 \text{ }^\circ\text{C}$ ) and flash chromatography (DCM:MeOH, 20:1) gave amine **142** as a brown oil (1.54 g, 92%).  $R_f$  (DCM:MeOH, 20:1) = 0.17;  $[\alpha]_D = +52.3$  ( $c$  0.65,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 2224 ( $\text{C}\equiv\text{C}$ );  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 5.84 (1H, ddd,  $J = 15.9, 8.0, 0.4 \text{ Hz}$ ,  $\text{NCHCH}=\text{CH}$ ), 5.68 (1H, dqd,  $J = 15.9, 2.2, 0.8 \text{ Hz}$ ,  $\text{NCHCH}=\text{CH}$ ), 3.63 (1H, dd,  $J = 9.9, 4.1 \text{ Hz}$ ,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 3.50 (1H, dd,  $J = 9.9, 7.9 \text{ Hz}$ ,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 3.10 (1H, tdd,  $J = 7.9, 4.1, 0.8 \text{ Hz}$ ,  $\text{NCH}$ ), 2.39 (3H, s,  $\text{NCH}_3$ ), 1.97 (3H, dd,  $J = 2.2, 0.4 \text{ Hz}$ ,  $\text{C}\equiv\text{CCH}_3$ ), 0.91 (9H, s,  $3\text{SiC}(\text{CH}_3)_3$ ), 0.08 (6H, s,  $2\text{SiCH}_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 140.9 (CH), 113.2 (CH), 86.2 (C), 77.7 (C), 65.8 ( $\text{CH}_2$ ), 64.5 (CH), 34.1 ( $\text{CH}_3$ ), 25.9 ( $3\text{CH}_3$ ), 18.3 (C), 4.3 ( $\text{CH}_3$ ),  $-5.4$  ( $2\text{CH}_3$ );  **$m/z$**  (ESI+, MeOH) 254 ( $[\text{M}+\text{H}]^+$ , 98%), 223 ( $[\text{M}-\text{CH}_3\text{NH}]^+$ , 100); **HRMS** (ESI+, MeOH)  $[\text{M}+\text{H}]^+$  found 254.1943,  $\text{C}_{14}\text{H}_{28}\text{NOSi}$  requires 254.1935.

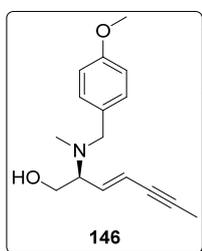
**(2*S*,3*E*)-1-(*tert*-Butyldimethylsilanyloxy)-2-(4-methoxybenzyl)methylaminohept-3-en-5-yne (**144**)**



A suspension of amine **142** (50.6 mg, 0.20 mmol), freshly prepared PMBCl (47.6 mg, 0.28 mmol; for preparation, see **Section 7.4**),  $\text{K}_2\text{CO}_3$  (68.0 mg, 0.49 mmol) and TBAI (17.0 mg, 0.05 mmol, 23 mol%) in THF ( $2 \text{ cm}^3$ ) was heated to reflux for 2 d. The orange solution thus obtained was cooled to rt, the reaction was quenched with  $\text{NH}_4\text{Cl}$  ( $10 \text{ cm}^3$ ; sat aq) and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10 \text{ cm}^3$ ). The combined organic layers were washed with  $\text{H}_2\text{O}$  ( $10 \text{ cm}^3$ ), brine ( $10 \text{ cm}^3$ ) and dried ( $\text{MgSO}_4$ ); and the solvent was removed under reduced pressure. The brown residual oil thus obtained was purified by flash chromatography (Hexane:EtOAc, 10:1) to give PMB-protected amine **144** as an orange-yellow syrup (68.2 mg, 91%).  $R_f$  (Hexane:EtOAc, 10:1) = 0.37;  $[\alpha]_D = +47.9$  ( $c$  0.73,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 2210 ( $\text{C}\equiv\text{C}$ ), 1610 ( $\text{C}=\text{C}$ ), 1585 ( $\text{C}=\text{C}$ ), 1510 ( $\text{C}=\text{C}$ );  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{DMSO}-d_6$ , 323 K) 7.22–7.19 (2H, m,  $2\text{ArH}$ ), 6.88–6.85 (2H, m,  $2\text{ArH}$ ), 6.02 (1H, ddd,  $J = 16.0, 7.8, 0.6 \text{ Hz}$ ,  $\text{NCHCH}=\text{CH}$ ), 5.64 (1H, dqd,  $J = 16.0, 2.2, 1.2 \text{ Hz}$ ,  $\text{NCHCH}=\text{CH}$ ), 3.77 (1H, dd,  $J = 10.3, 5.8 \text{ Hz}$ ,  $\text{NCHCH}_A\text{H}_B\text{O}$ ),

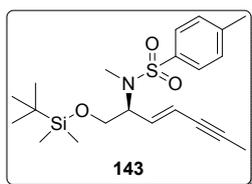
3.75 (3H, s,  $\text{OCH}_3$ ), 3.68 (1H, dd,  $J = 10.3, 6.6$  Hz,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 3.57 (1H, d,  $J = 13.4$  Hz,  $\text{CH}_A\text{H}_B\text{Ar}$ ), 3.45 (1H, d,  $J = 13.4$  Hz,  $\text{CH}_A\text{H}_B\text{Ar}$ ), 3.16–3.12 (1H, m, NCH), 2.14 (3H, s,  $\text{NCH}_3$ ), 1.94 (3H, d,  $J = 2.2$  Hz,  $\text{C}\equiv\text{CCH}_3$ ), 0.88 (9H, s,  $3\text{SiC}(\text{CH}_3)_3$ ), 0.05 (3H, s,  $\text{SiCH}_3$ ), 0.04 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{DMSO}-d_6$ , 323 K) 158.7 (C), 140.0 (CH), 132.0 (C), 129.9 (2CH), 114.1 (2CH), 113.4 (CH), 86.5 (C), 78.8 (C), 65.9 (CH), 64.1 ( $\text{CH}_2$ ), 58.1 ( $\text{CH}_2$ ), 55.5 ( $\text{CH}_3$ ), 38.2 ( $\text{CH}_3$ ), 26.2 (3 $\text{CH}_3$ ), 18.3 (C), 4.2 ( $\text{CH}_3$ ),  $-4.9$  ( $\text{CH}_3$ ),  $-5.0$  ( $\text{CH}_3$ );  $m/z$  (ESI+, MeOH) 396 ( $[\text{M}+\text{Na}]^+$ , 5%), 374 ( $[\text{M}+\text{H}]^+$ , 100); HRMS  $[\text{M}+\text{H}]^+$  found 374.2509,  $\text{C}_{14}\text{H}_{36}\text{NO}_2\text{Si}$  requires 374.2510.

**(2*S*,3*E*)-2-(4-Methoxybenzyl)methylamino-hept-3-en-5-yn-1-ol (146)**

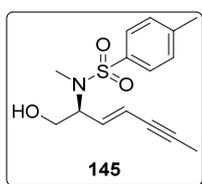


TBAF ( $13.5\text{ cm}^3$ , 13.5 mmol; 1.0 M in THF) was added to a solution of silyl ether **144** (843 mg, 2.26 mmol) in THF ( $5\text{ cm}^3$ ) at  $0\text{ }^\circ\text{C}$  and the solution was stirred for 30 min, warmed to rt and stirred for a further 30 min.  $\text{NH}_4\text{Cl}$  ( $10\text{ cm}^3$ ; sat aq) was added, and the mixture was stirred for 1 h before dilution with  $\text{H}_2\text{O}$  ( $20\text{ cm}^3$ ).

The aqueous layer was extracted with DCM ( $5 \times 10\text{ cm}^3$ ), and the combined organic layers were washed with brine ( $10\text{ cm}^3$ ) and dried ( $\text{MgSO}_4$ ); and the solvent was removed under reduced pressure. Flash chromatography (Hexane:EtOAc, 1:1) of the brown residual oil gave alcohol **146** as an orange-yellow oil (583 mg, quant).  $R_f$  (Hexane:EtOAc, 1:1) = 0.42;  $[\alpha]_D = +109$  ( $c$  0.33,  $\text{CHCl}_3$ ); IR (neat,  $\text{cm}^{-1}$ ) 3431 (OH), 2220 ( $\text{C}\equiv\text{C}$ ), 1610 ( $\text{C}=\text{C}$ ), 1585 ( $\text{C}=\text{C}$ ), 1510 ( $\text{C}=\text{C}$ );  $^1\text{H}$  NMR  $\delta$  (500 MHz,  $\text{DMSO}-d_6$ , 323 K) 7.23–7.20 (2H, m, 2ArH), 6.89–6.86 (2H, m, 2ArH), 6.04 (1H, ddd,  $J = 16.0, 7.9, 0.5$  Hz,  $\text{NCHCH}=\text{CH}$ ), 5.64 (1H, dqd,  $J = 16.0, 2.2, 1.1$  Hz,  $\text{NCHCH}=\text{CH}$ ), 4.30 (1H, br s, OH), 3.75 (3H, s,  $\text{OCH}_3$ ), 3.60 (1H, br dd,  $J = 10.8, 6.2$  Hz,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 3.55 (1H, d,  $J = 13.3$  Hz,  $\text{CH}_X\text{H}_Y\text{Ar}$ ), 3.49–3.46 (1H, m,  $\text{NCHCH}_A\text{H}_B\text{O}$ ), 3.41 (1H, d,  $J = 13.3$  Hz,  $\text{CH}_X\text{H}_Y\text{Ar}$ ), 3.13–3.09 (1H, m, NCH), 2.11 (3H, s,  $\text{NCH}_3$ ), 1.94 (3H, d,  $J = 2.2$  Hz,  $\text{C}\equiv\text{CCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{DMSO}-d_6$ , 323 K) 158.7 (C), 140.3 (CH), 132.0 (C), 130.0 (2CH), 114.1 (2CH), 113.4 (CH), 86.5 (C), 78.9 (C), 66.2 (CH), 62.2 ( $\text{CH}_2$ ), 57.9 ( $\text{CH}_2$ ), 55.5 ( $\text{CH}_3$ ), 37.9 ( $\text{CH}_3$ ), 4.2 ( $\text{CH}_3$ );  $m/z$  (EI) 259 ( $[\text{M}]^+$ , 5%), 229 (74), 228 (100), 122 (59), 121 (96); HRMS (EI)  $[\text{M}]^+$  found 259.1568,  $\text{C}_{16}\text{H}_{21}\text{NO}_2$  requires 259.1567.

**(2*S*,3*E*)-1-(*tert*-Butyldimethylsilanyloxy)-2-(4-toluenesulfonyl)methylamino-hept-3-en-5-yne (143)**

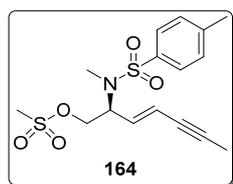
To a solution of amine **142** (278 mg, 1.09 mmol), Et<sub>3</sub>N (0.46 cm<sup>3</sup>, 3.28 mmol) and DMAP (15.0 mg, 0.11 mmol, 11 mol%) in DCM (10 cm<sup>3</sup>) was added TsCl (313 mg, 1.64 mmol), and the brown solution was stirred overnight (~18 h) at rt. The reaction mixture was poured into cold (~0 °C) HCl (30 cm<sup>3</sup>; 0.5 M aq) and the aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with HCl (2 × 10 cm<sup>3</sup>; 0.5 M aq), NaHCO<sub>3</sub> (2 × 10 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (10 cm<sup>3</sup>), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give sulfonamide **143** (378 mg, 85%) as a brown oil, which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 10:1) = 0.39; **[α]<sub>D</sub>** = +45.4 (*c* 0.22, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2216 (C≡C), 1597 (C=C), 1341 (S=O); **<sup>1</sup>H NMR** δ (500 MHz, DMSO-*d*<sub>6</sub>, 323 K) 7.68–7.66 (2H, m, 2ArH), 7.40 (2H, d, *J* = 8.0 Hz, 2ArH), 5.80 (1H, dd, *J* = Hz, 16.0, 6.8 Hz, NCHCH=CH), 5.57 (1H, dqd, *J* = 16.0, 2.2, 1.5 Hz, NCHCH=CH), 4.41 (1H, m, NCH), 3.63 (1H, dd, *J* = 10.6, 6.0 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 3.60 (1H, dd, *J* = 10.6, 6.8 Hz, NCHCH<sub>A</sub>H<sub>B</sub>O), 2.69 (3H, s, NCH<sub>3</sub>), 2.40 (3H, s, ArCH<sub>3</sub>), 1.90 (3H, d, *J* = 2.0 Hz, C≡CCH<sub>3</sub>), 0.84 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.01 (6H, s, 2SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, DMSO-*d*<sub>6</sub>, 323 K) 143.5 (C), 137.1 (C), 136.5 (CH), 130.1 (2CH), 127.4 (2CH), 114.3 (CH), 88.2 (C), 78.0 (C), 63.4 (CH<sub>2</sub>), 60.0 (CH), 30.3 (CH<sub>3</sub>), 26.1 (3CH<sub>3</sub>), 21.4 (CH<sub>3</sub>), 18.3 (C), 4.2 (CH<sub>3</sub>), -5.0 (CH<sub>3</sub>), -5.1 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 1245 ([3M+Na]<sup>+</sup>, 1%), 837 ([2M+Na]<sup>+</sup>, 100), 430 ([M+Na]<sup>+</sup>, 26), 408 ([M+H]<sup>+</sup>, 1); **HRMS** (ESI+, MeOH) [M+Na]<sup>+</sup> found 430.1851, C<sub>21</sub>H<sub>33</sub>NO<sub>3</sub>SSiNa requires 430.1843.

**(2*S*,3*E*)-2-(4-toluenesulfonyl)methylamino-hept-3-en-5-yn-1-ol (145)**

TBAF (4.80 cm<sup>3</sup>, 4.80 mmol; 1.0 M in THF) was added to a solution of silyl ether **143** (326 mg, 0.80 mmol) in THF (2 cm<sup>3</sup>), and the solution was stirred for 1 h at 0 °C. NH<sub>4</sub>Cl (10 cm<sup>3</sup>; sat aq) was added, the mixture was stirred for 1 h, and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with brine (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced

pressure. Flash chromatography (Hexane:EtOAc, 2:1) of the residual brown oil gave alcohol **145** as an orange oil (221 mg, 94%).  $R_f$  (Hexane:EtOAc, 2:1) = 0.24;  $[\alpha]_D = +41.6$  ( $c$  0.24,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 3512 (OH), 2224 ( $\text{C}\equiv\text{C}$ ), 1734 ( $\text{C}=\text{C}$ ), 1630 ( $\text{C}=\text{C}$ ), 1597 ( $\text{C}=\text{C}$ ), 1329 ( $\text{S}=\text{O}$ );  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{DMSO-}d_6$ , 323 K) 7.69 (2H, m, 2ArH), 7.39 (2H, d,  $J = 8.0$  Hz, 2ArH), 5.80 (1H, ddd,  $J = 16.1, 6.6, 0.6$  Hz, NCHCH=CH), 5.53 (1H, dqd,  $J = 16.1, 2.2, 1.3$  Hz, NCHCH=CH), 4.76 (1H, t,  $J = 5.7$  Hz, OH), 4.41–4.37 (1H, m, NCH), 3.45–3.42 (2H, m,  $\text{CH}_2\text{O}$ ), 2.66 (3H, s, Ar $\text{CH}_3$ ), 2.40 (3H, s, NCH $_3$ ), 1.90 (3H, d,  $J = 2.3$  Hz,  $\text{C}\equiv\text{CCH}_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{DMSO-}d_6$ , 323 K) 143.4 (C), 137.1 (C), 137.0 (2CH), 130.0 (2CH), 127.5 (2CH), 113.8 (CH), 88.0 (C), 78.2 (C), 61.7 ( $\text{CH}_2$ ), 60.3 (CH), 30.0 ( $\text{CH}_3$ ), 21.4 ( $\text{CH}_3$ ), 4.2 ( $\text{CH}_3$ );  **$m/z$**  (ESI+, MeOH) 609 ( $[\text{2M}+\text{Na}]^+$ , 42), 332 ( $[\text{M}+\text{K}]^+$ , 5), 316 ( $[\text{M}+\text{Na}]^+$ , 100), 294 ( $[\text{M}+\text{H}]^+$ , 3); **HRMS** (ESI+, MeOH)  $[\text{M}+\text{Na}]^+$  found 316.0929,  $\text{C}_{15}\text{H}_{19}\text{NO}_3\text{SNa}$  requires 316.0978.

**(2*S*,3*E*)-1-(Methanesulfonyloxy)-2-(4-toluenesulfonyl)methylamino-hept-3-en-5-yne (164)**



MsCl (0.40  $\text{cm}^3$ , 0.40 mmol; 1.0 M in DCM) was added dropwise to a solution of alcohol **145** (29.0 mg, 0.10 mmol),  $\text{Et}_3\text{N}$  (0.50  $\text{cm}^3$ , 3.58 mmol), and DMAP (2.40 mg, 0.02 mmol, 20 mol%) in DCM (0.5  $\text{cm}^3$ ) at 0 °C and the cloudy suspension was stirred for 1 h, warmed to rt and stirred for 2.5 h. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (30  $\text{cm}^3$ ), and the organic layer was washed with HCl (2  $\times$  10  $\text{cm}^3$ ; 1.0 M aq),  $\text{NaHCO}_3$  (2  $\times$  10  $\text{cm}^3$ ; sat aq),  $\text{H}_2\text{O}$  (10  $\text{cm}^3$ ), brine (10  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure to give mesylate **164** as an orange-yellow oil (35.0 mg, 95%), which was used without further purification.  $R_f$  (Hexane:EtOAc, 2:1) = 0.37;  $[\alpha]_D = +37.2$  ( $c$  0.51,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 2222 ( $\text{C}\equiv\text{C}$ ), 1736 ( $\text{C}=\text{C}$ ), 1630 ( $\text{C}=\text{C}$ ), 1597 ( $\text{C}=\text{C}$ ), 1354 ( $\text{S}=\text{O}$ ), 1335 ( $\text{S}=\text{O}$ );  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{DMSO-}d_6$ , 323 K) 7.71–7.68 (2H, m, 2ArH), 7.42–7.40 (2H, m, 2ArH), 5.77 (1H, ddd,  $J = 16.0, 6.9, 0.6$  Hz, NCHCH=CH), 5.65 (1H, dqd,  $J = 16.0, 2.3, 1.2$  Hz, NCHCH=CH), 4.79–4.74 (1H, m, NCH), 4.27 (1H, dd,  $J = 10.7, 8.0$  Hz, NCHCH $_A$ H $_B$ O), 4.22 (1H, dd,  $J = 10.7, 5.7$  Hz, NCHCH $_A$ H $_B$ O), 3.14 (3H, s,  $\text{SO}_2\text{CH}_3$ ), 2.69 (3H, s, Ar $\text{CH}_3$ ), 2.41 (3H, s, NCH $_3$ ), 1.91 (3H, d,  $J = 2.3$  Hz,

$\text{C}\equiv\text{CCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz, DMSO- $d_6$ , 323 K) 143.8 (C), 136.5 (C), 134.0 (CH), 130.2 (2CH), 127.6 (2CH), 115.9 (CH), 89.3 (C), 77.7 (C), 68.2 (CH<sub>2</sub>), 57.5 (CH), 37.4 (CH<sub>3</sub>), 29.9 (CH<sub>3</sub>), 21.4 (CH<sub>3</sub>), 4.2 (CH<sub>3</sub>); *m/z* (ESI+, MeOH) 765 ([2M+Na]<sup>+</sup>, 9%), 394 ([M+Na]<sup>+</sup>, 15), 372 ([M+H]<sup>+</sup>, 3), 225 ([M+2K]<sup>2+</sup>, 100); HRMS (ESI+, MeOH) [M+H]<sup>+</sup> found 372.0956, C<sub>16</sub>H<sub>22</sub>NO<sub>5</sub>S<sub>2</sub> requires 372.0934.

### 7.3 Experimental from Chapter 3

#### General Procedure A: Weinreb Amide Synthesis with <sup>t</sup>BuLi

To a suspension of HNMe(OMe)•HCl (1.5 to 9.0 eq) in THF was added <sup>t</sup>BuLi (3.0 to 18 eq) at  $-78\text{ }^{\circ}\text{C}$ , and the mixture was stirred for 15 min, warmed to rt [CAUTION: butane gas evolution], stirred for 20 min and re-cooled to  $-78\text{ }^{\circ}\text{C}$  to give a light-yellow solution of the lithium amide of Weinreb's amine. A solution of the reactant ester (1.0 eq) in THF was added, and the reaction mixture was stirred at the temperature(s) and time(s) indicated before quenching of the reaction with  $\text{NH}_4\text{Cl}$  (aq). The solution was stirred vigorously until a clean phase separation was visible (~30 min) and the biphasic mixture was separated. The aqueous layer was extracted with DCM or  $\text{Et}_2\text{O}$ , and the combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure. Flash chromatography gave the product Weinreb amide.

#### General Procedure B: Swern Oxidation<sup>101</sup>

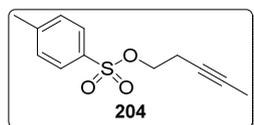
DMSO (3.0 to 6.0 eq) in DCM, was added dropwise over the stated time to a solution of  $(\text{COCl})_2$  (1.3 to 2.0 eq) in DCM at  $-78\text{ }^{\circ}\text{C}$ , and the solution was stirred for the stated time [CAUTION: gases evolved]. The reactant alcohol (1.0 eq), in DCM, was added dropwise [CAUTION: gases evolved] over the stated time, and the mixture was stirred for 1 h before cautious addition of freshly distilled  $\text{Et}_3\text{N}$  (5.0 to 8.0 eq) over the stated time. The slurry thus obtained was warmed to rt (typically ~1 h) and the reaction was quenched with  $\text{H}_2\text{O}$ . The aqueous layer was extracted with DCM, and the combined organic layers were washed with  $\text{H}_2\text{O}$  and brine. Drying ( $\text{MgSO}_4$ ), removal of the solvent and  $\text{Me}_2\text{S}$  byproduct under reduced pressure [CAUTION: toxic, malodorous] and purification of the crude material by flash chromatography gave the product aldehyde.

#### General Procedure C: TBS Protection of Alcohols with TBSOTf

Cautiously, TBSOTf (1.3 to 1.5 eq) was added to a solution of the reactant alcohol (1.0 eq) and 2,6-lutidine (2.0 eq) in DCM and the reaction mixture was stirred for the stated time and temperature, before quenching of the reaction with  $\text{NaHCO}_3$  (sat aq) [CAUTION: gases evolved]. The aqueous layer was extracted with DCM, and the

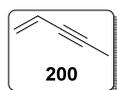
combined organic layers were washed with the indicated aqueous solutions. Drying ( $\text{MgSO}_4$ ), removal of the solvent and residual 2,6-lutidine under reduced pressure (bath temperature =  $70\text{ }^\circ\text{C}$ ), and purification of the crude material by flash chromatography gave the product TBS-ether.

#### Toluene-4-sulfonic acid pent-3-ynyl ester (**204**)



Tosylate ester **204** was prepared according to the procedure described by Niblock.<sup>16</sup>  $\text{TsCl}$  (12.7 g, 66.4 mmol) was added to boiling pyridine ( $6.00\text{ cm}^3$ , 75.9 mmol) and the yellow solution was cooled rapidly to  $0\text{ }^\circ\text{C}$  (immediate ice-bath immersion) to give a suspension of pale-yellow crystals to which 3-pentyn-1-ol (5.00 g, 59.4 mmol) was added dropwise (~30 min) [CAUTION: exothermic reaction]. The mixture was stirred vigorously for 30 min, warmed to rt, stirred overnight (~19 h) and the resulting colourless slurry was diluted with  $\text{H}_2\text{O}$  ( $10\text{ cm}^3$ ) and  $\text{Et}_2\text{O}$  ( $50\text{ cm}^3$ ). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20\text{ cm}^3$ ), and the combined organic layers were washed with  $\text{HCl}$  ( $3 \times 20\text{ cm}^3$ ; 1.0 M aq),  $\text{NaHCO}_3$  ( $50\text{ cm}^3$ ; sat aq), brine ( $50\text{ cm}^3$ ) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure to give tosylate ester **204** as a colourless syrup that solidifies to a colourless wax on standing (13.3 g, 94%), which was used without further purification.  $R_f$  (Hexane) = 0.17; **mp**  $35\text{--}40\text{ }^\circ\text{C}$ , lit<sup>97b</sup>  $39\text{ }^\circ\text{C}$ ; **bp**  $170\text{ }^\circ\text{C}$  (3.2 mmHg); **IR** (neat,  $\text{cm}^{-1}$ ) 2237 ( $\text{C}\equiv\text{C}$ ), 1595 ( $\text{C}=\text{C}$ ), 1358 ( $\text{S}=\text{O}$ );  **$^1\text{H NMR}$**   $\delta$  (400 MHz,  $\text{CDCl}_3$ ) 7.85–7.82 (2H, m, 2ArH), 7.39–7.36 (2H, m, 2ArH), 4.08 (2H, t,  $J = 7.2\text{ Hz}$ ,  $\text{OCH}_2$ ), 2.51 (2H, tq,  $J = 7.2, 2.6\text{ Hz}$ ,  $\text{C}\equiv\text{CCH}_2$ ), 2.48 (3H, s,  $\text{ArCH}_3$ ), 1.74 (3H, t,  $J = 2.6\text{ Hz}$ ,  $\text{C}\equiv\text{CCH}_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 144.9 (C), 133.0 (C), 129.9 (2CH), 128.0 (2CH), 78.2 (C), 73.1 (C), 68.3 ( $\text{CH}_2$ ), 21.7 ( $\text{CH}_3$ ), 19.7 ( $\text{CH}_2$ ), 3.4 ( $\text{CH}_3$ );  **$m/z$**  (EI) 238 ( $[\text{M}]^+$ , 1%), 155 (100), 91 (93); **HRMS** (EI)  $[\text{M}]^+$  found 238.0656,  $\text{C}_{12}\text{H}_{14}\text{O}_3\text{S}$  requires 238.0658. The spectroscopic data are in good agreement with the literature.<sup>16,97b</sup>

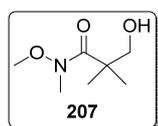
#### Pent-1-en-3-yne (**200**)



Enyne **200** was prepared according to a modification of the procedure described by Niblock.<sup>16</sup>  $\text{KOH}$  (19.7 g, 351 mmol) and tosylate ester **204** (14.5 g, 50.8 mmol) were added to 1-octanol ( $100\text{ cm}^3$ ) and general-purpose

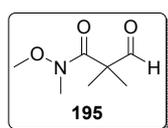
detergent (0.1 cm<sup>3</sup>) at rt. A Liebig condenser was attached to the flask, and the reaction mixture was heated with stirring to 135 °C, keeping the still-head temperature below 70 °C and the collecting flask at 0 °C. Distillation for 4 h gave enyne **200** as a volatile colourless liquid (2.51 g, 65%). **R<sub>f</sub>** (Hexane) = 0.21; **bp** 60 °C (760 mmHg), lit<sup>16</sup> 60 °C (760 mmHg); **IR** (neat, cm<sup>-1</sup>) 2236 (C≡C), 1714 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 5.78 (1H, ddq, *J* = 17.5, 11.0, 2.3 Hz, H<sub>2</sub>C=CH), 5.41–5.59 (1H, ddq, *J* = 17.5, 2.3, 0.6 Hz, HC=CH<sub>trans</sub>H<sub>cis</sub>), 5.40 (1H, ddq, *J* = 11.0, 2.3, 0.6 Hz, HC=CH<sub>trans</sub>H<sub>cis</sub>), 1.97 (3H, dt, *J* = 2.3, 0.6 Hz, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 125.5 (CH<sub>2</sub>), 117.6 (CH), 86.6 (C), 78.5 (C), 4.2 (CH<sub>3</sub>). The spectroscopic data are in good agreement with the literature.<sup>16,97,172</sup>

### 3-Hydroxy-*N*-methoxy-2,2-*N*-trimethyl-propionamide (**207**)



**General Procedure A** was followed with HNMe(OMe)•HCl (11.7 g, 120 mmol) in THF (130 cm<sup>3</sup>); <sup>*n*</sup>BuLi (150 cm<sup>3</sup>, 240 mmol; 1.6 M in hexanes); and 3-hydroxy-2,2-dimethyl-propionic acid methyl ester (5.29 g, 40.0 mmol) in THF (20 cm<sup>3</sup>) with reaction at -78 °C (30 min), -78 °C to rt (~1 h) and rt (30 min). Quenching with NH<sub>4</sub>Cl (400 cm<sup>3</sup>; 50% sat aq); workup with DCM (1 × 300 cm<sup>3</sup>, 3 × 100 cm<sup>3</sup>) and brine (200 cm<sup>3</sup>); and flash chromatography (EtOAc:Hexane, 2:1) gave Weinreb amide **207** as a light-yellow oil (6.19 g, 95%). **R<sub>f</sub>** (EtOAc:Hexane, 2:1) = 0.25; **IR** (neat, cm<sup>-1</sup>) 3456 (OH), 1620 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 3.73 (3H, s, OCH<sub>3</sub>), 3.54 (2H, s, CH<sub>2</sub>), 3.25 (1H, br s, OH), 3.22 (3H, s, NCH<sub>3</sub>), 1.28 (6H, s, 2CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 178.6 (C), 71.9 (CH<sub>2</sub>), 60.8 (CH<sub>3</sub>), 44.3 (C), 33.3 (CH<sub>3</sub>), 21.1 (2CH<sub>3</sub>); ***m/z*** (CI) 162 ([M+H]<sup>+</sup>, 100%); **HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 162.1124, C<sub>7</sub>H<sub>16</sub>NO<sub>3</sub> requires 162.1125.

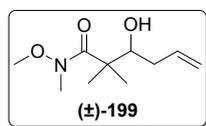
### *N*-Methoxy-2,2-*N*-trimethyl-3-oxo-propionamide (**195**)



**General Procedure B** was followed with DMSO (3.20 cm<sup>3</sup>, 45.0 mmol) in DCM (10 cm<sup>3</sup>), added over 10 min; (COCl)<sub>2</sub> (1.27 cm<sup>3</sup>, 15.0 mmol) in DCM (10 cm<sup>3</sup>), with stirring for 15 min; alcohol **207** (1.61 g, 10.0 mmol) in DCM (5 cm<sup>3</sup>), added over 5 min; and Et<sub>3</sub>N (8.34 cm<sup>3</sup>, 60.0 mmol), added over 5 min. Quenching with H<sub>2</sub>O (20 cm<sup>3</sup>); workup with DCM (3 ×

20 cm<sup>3</sup>), H<sub>2</sub>O (3 × 20 cm<sup>3</sup>) and brine (30 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 1:1) of the yellow residue thus obtained gave the aldehyde **195** as a yellow oil (1.51 g, 95%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.23; **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.45; **bp** 136 °C (760 mmHg, slight dec.); **IR** (neat, cm<sup>-1</sup>) 2714 (CHO), 1721 (C=O), 1657 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 9.53 (1H, s, CHO), 3.58 (3H, s, OCH<sub>3</sub>), 3.22 (3H, s, NCH<sub>3</sub>), 1.34 (6H, s, 2CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 197.7 (CH), 173.9 (C), 60.7 (CH<sub>3</sub>), 52.69 (C), 33.0 (CH<sub>3</sub>), 20.2 (2CH<sub>3</sub>); **m/z** (CI) 160 ([M+H]<sup>+</sup>, 100%), 131 (24). The spectroscopic data are in good agreement with the literature.<sup>90</sup>

**(±)-3-Hydroxy-2,2-dimethyl-hex-5-enoic acid methoxy-methyl-amide [(±)-199]**

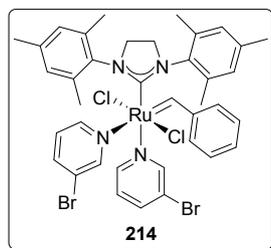


**Method A** (*indium-mediated Barbier allylation*): Allyl bromide (0.23 cm<sup>3</sup>, 2.66 mmol) was slowly added to a stirred solution of aldehyde **195** (70.4 mg, 0.44 mmol) and indium (101 mg, 0.88 mmol) in THF (14 cm<sup>3</sup>) at rt. The reaction mixture was stirred vigorously for 24 h after which time a grey solution had developed. The reaction was quenched with NH<sub>4</sub>Cl (10 cm<sup>3</sup>; sat aq) and the mixture was poured into H<sub>2</sub>O (20 cm<sup>3</sup>) and Et<sub>2</sub>O (20 cm<sup>3</sup>). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 cm<sup>3</sup>) and the combined organic layers were washed with NH<sub>4</sub>Cl (10 cm<sup>3</sup>; sat aq), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the resulting pale-yellow residue was purified by flash chromatography (Hexane:EtOAc, 2:1) to give homoallylic alcohol (±)-**199** as a yellow oil (85.2 mg, 97%).

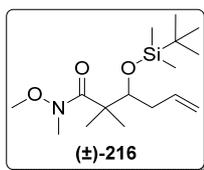
**Method B** (*tin-mediated Barbier allylation*): According to a modification of the procedure described by Malvestiti *et al.*,<sup>103</sup> HCl (100 cm<sup>3</sup>, 100 mmol; 1.0 M aq) was added to tin (1.87 g, 15.8 mmol) and the mixture was stirred vigorously until complete dissolution of the solid had occurred (~45 min). Allyl bromide (2.02 cm<sup>3</sup>, 23.3 mmol) was added, followed by aldehyde **195** (1.00 g, 6.28 mmol) and the reaction mixture was stirred vigorously for a further 2.5 h. The aqueous layer was extracted with DCM (5 × 20 cm<sup>3</sup>), and the combined organic layers were washed with NaHCO<sub>3</sub> (20 cm<sup>3</sup>; sat aq), brine (20 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave a yellow residue that was purified by flash chromatography (Hexane:EtOAc, 2:1) to give homoallylic alcohol (±)-**199** as a

yellow oil (1.07 g, 85%).  $R_f$  (Hexane:EtOAc, 2:1) = 0.25;  $R_t$  (Method A) = 21.0, 27.5; **IR** (neat,  $\text{cm}^{-1}$ ) 3451 (OH), 1639 (C=O), 1622 (C=C);  $^1\text{H NMR}$   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 5.98 (1H, ddt,  $J = 17.2, 10.1, 6.6$  Hz,  $\text{HC}=\text{CH}_2$ ), 5.17–5.10 (2H, m,  $\text{HC}=\text{CH}_2$ ), 3.80 (1H, ddd,  $J = 10.1, 6.1, 2.5$  Hz,  $\text{CHOH}$ ), 3.73 (3H, s,  $\text{OCH}_3$ ), 3.21 (3H, s,  $\text{NCH}_3$ ), 3.12 (1H, d,  $J = 6.1$  Hz,  $\text{OH}$ ), 2.33–2.28 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.23–2.17 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.30 (3H, s,  $\text{CCH}_3$ ), 1.29 (3H, s,  $\text{CCH}_3$ );  $^{13}\text{C NMR}$   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 178.4 (C), 136.6 (CH), 116.7 ( $\text{CH}_2$ ), 76.9 (CH), 60.7 ( $\text{CH}_3$ ), 47.2 (C), 36.3 ( $\text{CH}_2$ ), 33.7 ( $\text{CH}_3$ ), 21.4 ( $\text{CH}_3$ ), 20.1 ( $\text{CH}_3$ );  $m/z$  (EI) 202 ( $[\text{M}]^+$ , 3%), 160 (30), 71 (58), 61 (88), 43 (100). The spectroscopic data are in good agreement with the literature.<sup>90</sup>

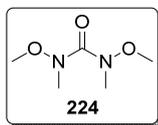
**Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene][(benzylidene)bis(3-bromopyridine)ruthenium(II) (214)**



Grubbs' catalyst **214** was prepared according to the procedure described by Grubbs *et al.*<sup>104</sup> Grubbs' II (500 mg, 0.59 mmol) was added to 3-bromopyridine (0.57  $\text{cm}^3$ , 5.92 mmol) and the red mixture was stirred for 5 min, after which time a lime-green slurry had formed to which pentane (20  $\text{cm}^3$ ) was added. The mixture was then cooled and maintained at 4 °C (fridge) overnight (~18 h); and the precipitate was filtered, washed with pentane (5  $\times$  10  $\text{cm}^3$ ) and dried thoroughly *in vacuo* to give Grubbs' catalyst **214** as a green solid (459 mg, 88%). **mp** 142–146 °C (dec.), lit<sup>239</sup> 140 °C (dec.); **IR** (neat,  $\text{cm}^{-1}$ ) 2369, 2324, 1961, 1732, 1629, 1609, 1585, 1555, 1481, 1466, 1406;  $m/z$  (FAB, 3-NOBA) 892 ( $[\text{Br}_2^{37}\text{Cl}_2\text{M}+\text{H}]^+$ , 1%), 890 ( $[\text{Br}_2^{37}\text{Cl}^{35}\text{ClM}+\text{H}]^+$ , 1), 888 ( $[\text{Br}_2^{35}\text{Cl}_2\text{M}+\text{H}]^+$ , 2), 886 ( $[\text{Br}^{81}\text{Br}^{79}\text{Br}^{35}\text{Cl}_2\text{M}+\text{H}]^+$ , 2), 884 ( $[\text{Br}_2^{35}\text{Cl}_2\text{M}+\text{H}]^+$ , 2), 405 (19), 307 (97), 154 (100), 136 (62).

**(±)-3-(*tert*-Butyl-dimethyl-silyloxy)-2,2-dimethyl-hex-5-enoic acid methoxy-methyl-amide [(±)-216]**

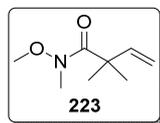
**General Procedure C** was followed with TBSOTf (0.43 cm<sup>3</sup>, 1.86 mmol), alcohol (±)-**199** (251 mg, 1.24 mmol) and 2,6-lutidine (0.29 cm<sup>3</sup>, 2.28 mmol) in DCM (10 cm<sup>3</sup>) with reaction for 2 h at 0 °C. Quenching with NaHCO<sub>3</sub> (10 cm<sup>3</sup>; sat aq); workup with DCM (3 × 10 cm<sup>3</sup>) and brine (10 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 1:1) gave silyl ether (±)-**216** as a yellow oil (380 mg, 97%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.71; **IR** (neat, cm<sup>-1</sup>) 1651 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 5.81 (1H, ddt, *J* = 17.0, 10.1, 7.2 Hz, H<sub>2</sub>C=CH), 5.04–5.00 (2H, m, HC=CH<sub>2</sub>), 4.31 (1H, t, *J* = 5.2 Hz, SiOCH), 3.69 (3H, s, OCH<sub>3</sub>), 3.16 (3H, s, NCH<sub>3</sub>), 2.26–2.14 (2H, m, CH<sub>2</sub>), 1.26 (3H, s, CCH<sub>3</sub>), 1.20 (3H, s, CCH<sub>3</sub>), 0.92 (9H, s, 3SiC(CH<sub>3</sub>)), 0.09 (3H, s, SiCH<sub>3</sub>), 0.07 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 177.8 (C), 136.5 (CH), 116.4 (CH<sub>2</sub>), 74.6 (CH), 60.5 (CH<sub>3</sub>), 49.1 (C), 39.4 (CH<sub>2</sub>), 33.9 (CH<sub>3</sub>), 26.1 (3CH<sub>3</sub>), 23.3 (CH<sub>3</sub>), 19.1 (CH<sub>3</sub>), 18.3 (C), -3.3 (CH<sub>3</sub>), -4.1 (CH<sub>3</sub>); ***m/z*** (EI) 316 ([M+H]<sup>+</sup>, 12%), 274 (31), 258 (100), 185 (20), 115 (30); **HRMS** (EI) [M+H]<sup>+</sup> found 316.2299, C<sub>16</sub>H<sub>34</sub>NO<sub>3</sub>Si requires 316.2303.

***N,N'*-Dimethoxy-*N,N'*-dimethylurea (224)**

Weinreb urea **224** was prepared according to a modification of the procedure described by Marshall and Yanik.<sup>116</sup> To a suspension of HNMe(OMe)•HCl (2.50 g, 25.0 mmol) and pyridine (1.71 cm<sup>3</sup>, 30.0 mmol) in DCM (120 cm<sup>3</sup>) was added CDI (1.68 g, 10.0 mmol), and the white suspension was heated to reflux overnight (~19 h). The resulting yellow solution was cooled to rt and quenched with HCl (40 cm<sup>3</sup>; 1.0 M aq). The aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>), the combined organic layers were washed with HCl (5 × 10 cm<sup>3</sup>; 1.0 M aq), and the combined aqueous layers were backwashed with DCM (10 cm<sup>3</sup>). The combined organic layers were washed with brine (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure to give a yellow oil that was purified by flash chromatography (Hexane:EtOAc, 3:1) to afford Weinreb urea **224** as a pale-yellow oil (1.35 g, 91%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.33; **IR** (neat, cm<sup>-1</sup>) 1661 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 3.70 (6H, s, 2OCH<sub>3</sub>), 3.11

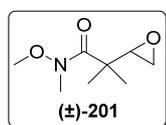
(6H, s, 2NCH<sub>3</sub>); <sup>13</sup>C NMR δ (100 MHz, CDCl<sub>3</sub>) 163.4 (C), 60.6 (2CH<sub>3</sub>), 36.2 (2CH<sub>3</sub>); *m/z* (EI) 148 ([M]<sup>+</sup>, 63%), 88 (100), 61 (38), 60 (100). The spectroscopic data are in good agreement with the literature.<sup>115b,c;116</sup>

### 2,2-Dimethyl-but-3-enoic acid methoxymethyl-amide (**223**)



NaHMDS (8.50 cm<sup>3</sup>, 8.50 mmol; 1.0 M in THF) was added dropwise (~10 min) to a suspension of [Ph<sub>3</sub>PMe]<sup>+</sup>T<sup>-</sup> (3.54 g, 8.78 mmol) in THF (20 cm<sup>3</sup>) at 0 °C and the yellow solution was stirred for 30 min after which time a deepening of the colour had ensued. Aldehyde **195** (451 mg, 2.83 mmol) in THF (5 cm<sup>3</sup>) was added, and the red solution was stirred for 140 min before quenching of the reaction with H<sub>2</sub>O (20 cm<sup>3</sup>). The mixture was warmed to rt, diluted with Et<sub>2</sub>O (50 cm<sup>3</sup>) and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 20 cm<sup>3</sup>). The combined organic layers were washed with brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>); and the solvent was removed under reduced pressure. The yellow oil thus obtained was purified by flash chromatography (Hexane:EtOAc, 3:1) to give alkene **223** as a light-yellow oil (165 mg, 37%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.50; **IR** (neat, cm<sup>-1</sup>) 1654 (C=O), 1637 (C=C); <sup>1</sup>H NMR δ (600 MHz, CDCl<sub>3</sub>) 6.06 (1H, dd, *J* = 17.8, 10.4 Hz, H<sub>2</sub>C=CH), 5.08 (1H, d, *J* = 10.4 Hz, HC=CH<sub>cis</sub>H<sub>trans</sub>), 5.07 (1H, d, *J* = 17.8 Hz, HC=CH<sub>cis</sub>H<sub>trans</sub>), 3.60 (3H, s, OCH<sub>3</sub>), 3.18 (3H, s, NCH<sub>3</sub>), 1.33 (6H, s, 2CCH<sub>3</sub>); <sup>13</sup>C NMR δ (100 MHz, CDCl<sub>3</sub>) 177.0 (C), 143.4 (CH), 111.9 (CH<sub>2</sub>), 60.5 (CH<sub>3</sub>), 45.0 (C), 33.8 (CH<sub>3</sub>), 25.2 (2CH<sub>3</sub>); *m/z* (EI) 157 ([M]<sup>+</sup>, 8%), 69 (100); **HRMS** (EI) [M]<sup>+</sup> found 157.1095, C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub> requires 157.1097.

### (±)-*N*-Methoxy-*N*-methyl-2-oxiranyl-isobutyramide [(±)-**201**]

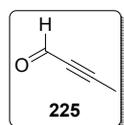


**Method A** (epoxidation of alkene **223**): According to a modification of the procedure described by Liu *et al.*<sup>121</sup> for the epoxidation of an analogous alkene, oxone (696 mg, 1.13 mmol) and NaHCO<sub>3</sub> (218 mg, 2.59 mmol) were added simultaneously to a solution of alkene **223** (58.8 mg, 0.37 mmol) and EDTA (~1.00 mg, 0.34 μmol, 0.92 mol%; disodium salt) in acetone/H<sub>2</sub>O (10 cm<sup>3</sup>, 1:1) at 0 °C and the mixture warmed to rt and stirred vigorously for 3 h before a second addition of oxone (696 mg, 1.13 mmol) and NaHCO<sub>3</sub> (218 mg, 2.59 mmol). The mixture was stirred for a further 3 h at rt, extracted with Et<sub>2</sub>O (5 × 5

cm<sup>3</sup>), and the combined organic layers were washed with brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give a yellow residue that was purified by flash chromatography (Hexane:EtOAc, 3:1) to give epoxide (±)-**201** as a colourless oil (39.0 mg, 61%).

**Method B** (*Corey–Chaykovski epoxidation of aldehyde 195*): <sup>n</sup>BuLi (0.56 cm<sup>3</sup>, 1.40 mmol; 2.5 M in hexanes) was added to suspension of trimethylsulfonium iodide (306 mg, 1.50 mmol) in THF (3 cm<sup>3</sup>) and the solution was stirred for 15 min at 0 °C. Aldehyde **195** (159 mg, 1.00 mmol) in THF (12 cm<sup>3</sup>) was then added, and the pale-yellow suspension was stirred for 1 h, warmed to rt and stirred for 2 h. H<sub>2</sub>O (10 cm<sup>3</sup>) was added to quench the reaction, and the aqueous layer was extracted with Et<sub>2</sub>O (5 × 10 cm<sup>3</sup>). The combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (10 cm<sup>3</sup>), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent and Me<sub>2</sub>S byproduct under reduced pressure [CAUTION: toxic, malodorous] gave epoxide (±)-**201** as a light-yellow residue (quantitative conversion by <sup>1</sup>H NMR), which was used without further purification. N.B. This procedure was not reproducible. **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.50; **IR** (neat, cm<sup>-1</sup>) 1643 (C=O), 1277 (COC), 995 (COC); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 3.72 (3H, s, OCH<sub>3</sub>), 3.25 (1H, dd, *J* = 4.0, 2.8 Hz, CHCH<sub>2</sub>), 3.22 (3H, s, NCH<sub>3</sub>), 2.78 (1H, dd, *J* = 4.6, 4.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.69 (1H, dd, *J* = 4.6, 2.8 Hz, CH<sub>A</sub>H<sub>B</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 196.7 (C), 60.9 (CH<sub>3</sub>), 56.3 (CH), 46.5 (C), 44.8 (CH<sub>2</sub>), 33.6 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>); ***m/z*** (EI) 173 ([M]<sup>+</sup>, 44%), 113 (68), 85 (100); **HRMS** (EI) [M]<sup>+</sup> found 173.1043, C<sub>8</sub>H<sub>15</sub>NO<sub>3</sub> requires 173.1046.

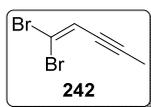
### But-2-yn-al (**225**)



Aldehyde **225** was prepared according to a modification of the procedure described by Tietze *et al.*<sup>127</sup> A suspension of MnO<sub>2</sub> (86.9 g, 1.00 mol) in Et<sub>2</sub>O (120 cm<sup>3</sup>) was treated with ultrasonic vibration for 30 min and cooled to 0 °C before dropwise addition (~10 min) of 2-butyn-1-ol (7.01 g, 100 mmol) in Et<sub>2</sub>O (10 cm<sup>3</sup>) [CAUTION: exothermic reaction]. The reaction mixture was stirred vigorously for 30 min at 0 °C, warmed to rt and stirred overnight (~18 h). The black slurry was filtered through a pad of celite, the filter cake was rinsed with Et<sub>2</sub>O (10 × 25 cm<sup>3</sup>) and the solvent was removed by distillation. Further distillation of the

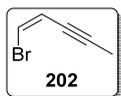
crude orange oil thus obtained afforded aldehyde **225** as a pale-yellow liquid (4.14 g, 61%).  $R_f$  (Pentane) = 0.33;  $bp$  107 °C (760 mmHg), lit<sup>127</sup> 105–108 °C (760 mmHg); **IR** (neat,  $cm^{-1}$ ) 2860 (CHO), 2207 (C≡C), 1664 (C=O); **<sup>1</sup>H NMR**  $\delta$  (400 MHz,  $CDCl_3$ ) 9.18 (1H, q,  $J$  = 1.0 Hz, CHO), 2.11 (3H, d,  $J$  = 1.0 Hz,  $CH_3$ ); **<sup>13</sup>C NMR**  $\delta$  (100 MHz,  $CDCl_3$ ) 177.2 (CH), 95.0 (C), 81.0 (C), 4.30 ( $CH_3$ );  $m/z$  (EI) 69 ( $[M+H]^+$ , 100%), 67 (50), 53 (43), 39 (39). The spectroscopic data are in good agreement with the literature.<sup>127</sup>

### 1,1-Dibromo-pent-1-en-3-yne (**242**)



Dibromoene **242** was prepared according to the procedure described by Buchwald for the preparation of analogous vicinal 1,1-dibromo-1,3-enynes.<sup>125b</sup> A solution of  $PPh_3$  (15.4 g, 58.8 mmol) in DCM (35  $cm^3$ ) was added dropwise (30 min) to a suspension of zinc (3.85 g, 58.8 mmol) and  $CBr_4$  (19.5 g, 58.8 mmol) in DCM (20  $cm^3$ ) at 0 °C [CAUTION: exothermic reaction]. The green-brown mixture was stirred for 5 min, warmed to rt, and stirred for 30 min before cooling of the reaction mixture back to 0 °C. Aldehyde **225** (2.00 g, 29.3 mmol) in DCM (5  $cm^3$ ) was then added slowly (~5 min) and the mixture was warmed to rt and stirred overnight (~24 h). The resulting dark-brown slurry was filtered through a plug of silica, eluting with DCM (50  $cm^3$ ), and the solvent was removed under reduced pressure. Flash chromatography (PE 40–60) of the red residue thus obtained gave dibromoene **242** as a yellow liquid (5.56 g, 85%).  $R_f$  (PE 40–60) = 0.73; **IR** (neat) 2222 (C≡C) 1572 (C=C); **<sup>1</sup>H NMR**  $\delta$  (400 MHz,  $CDCl_3$ ) 6.54 (1H, q,  $J$  = 2.4 Hz, CH), 2.00 (3H, d,  $J$  = 2.4 Hz,  $CH_3$ ); **<sup>13</sup>C NMR**  $\delta$  (100 MHz,  $CDCl_3$ ) 120.1 (CH), 100.1 (C), 94.9 (C), 76.9 (C), 4.8 ( $CH_3$ );  $m/z$  (EI) 226 ( $[^{81}Br_2M]^+$ , 45%), 224 ( $[^{79}Br^{81}BrM]^+$ , 100), 222 ( $[^{79}Br_2M]^+$ , 46), 145 (71), 143 (76); **HRMS** (EI)  $[M]^+$  found 221.8672,  $C_5H_4^{79}Br_2$  requires 221.8674.

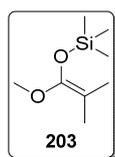
### (Z)-1-Bromo-pent-1-en-3-yne (**202**)



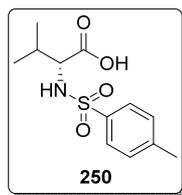
The preparation of (*Z*)-bromoene **202** was attempted according to the procedures described by Uenishi<sup>125a</sup> and Buchwald.<sup>125b</sup>  $Pd(PPh_3)_4$  (0.58 g, 0.50 mmol, 5 mol%) was added to a solution of dibromoene **242** (2.23 g, 10.0 mmol) in DCM (30  $cm^3$ ) and the mixture was stirred for 10 min at rt.  $^nBu_3SnH$  (2.82

cm<sup>3</sup>, 10.5 mmol) in DCM (10 cm<sup>3</sup>) was then added, and the mixture was stirred for 2 h after which time the reaction was quenched with H<sub>2</sub>O (10 cm<sup>3</sup>) and the organic layer was separated. The aqueous layer was extracted with DCM (5 × 5 cm<sup>3</sup>) and the combined organic layers were washed with brine (20 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed carefully under reduced pressure at rt and purification of the resulting brown oily residue (*ca.* quantitative conversion by <sup>1</sup>H NMR) by flash chromatography (PE 40–60) was attempted. Volatility and co-elution of byproducts prevented the isolation of (*Z*)-bromoenyne **202**. **R<sub>f</sub>** (PE 40–60) = 0.50; <sup>1</sup>H NMR δ (400 MHz, CDCl<sub>3</sub>) 6.50 (1H, dq, *J* = 7.4, 0.6 Hz, HC=CHBr), 6.30 (1H, dq, *J* = 7.4, 2.4 Hz, HC=CHBr), 2.05 (3H, dd, *J* = 2.4, 0.6 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR δ (100 MHz, CDCl<sub>3</sub>) 116.1 (CH), 116.0 (CH), 94.6 (C), 75.7 (C), 4.7 (CH<sub>3</sub>) [residual stannane impurities present].

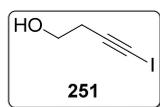
#### (1-Methoxy-2-methyl-propenyloxy)-trimethylsilane (**203**)



Silyl ketene acetal **203** was prepared according to the procedure described by Paquette *et al.*<sup>131</sup> To a solution of freshly distilled <sup>i</sup>Pr<sub>2</sub>NH (5.65 cm<sup>3</sup>, 40.0 mmol) in THF (40 cm<sup>3</sup>) was added <sup>n</sup>BuLi (22.9 cm<sup>3</sup>, 36.6 mmol; 1.6 M in hexanes) over 10 min and the reaction mixture was stirred for 30 min at 0 °C. Methyl isobutyrate (3.07 g, 30.0 mmol) in THF (10 cm<sup>3</sup>) was then added and the mixture was stirred for 1 h before addition of freshly distilled TMSCl (7.61 cm<sup>3</sup>, 60.0 mmol) over 5 min and stirring for a further 1 h. The resulting cloudy mixture was twice filtered, each time washing the residue with Et<sub>2</sub>O (3 × 10 cm<sup>3</sup>) and the filtrate was concentrated under reduced pressure. The resulting yellow residue was purified by reduced-pressure distillation to afford silyl ketene acetal **203** as a colourless liquid (3.79 g, 72%), which was filtered through cotton wool or an iso-disc HPLC filter prior to use. **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.14; **bp** 89 °C (128 mmHg), lit<sup>131</sup> 68–70 °C (30 mmHg); **IR** (neat, cm<sup>-1</sup>) 1705 (C=C); <sup>1</sup>H NMR δ (400 MHz, CDCl<sub>3</sub>) 3.53 (3H, s, OCH<sub>3</sub>), 1.60 (3H, s, CCH<sub>3</sub>), 1.54 (3H, s, CCH<sub>3</sub>), 0.23 (9H, s, 3SiCH<sub>3</sub>); <sup>13</sup>C NMR δ (100 MHz, CDCl<sub>3</sub>) 149.3 (C), 90.9 (C), 56.5 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>), 0.0 (3CH<sub>3</sub>); **m/z** (CI) 175 ([M+H]<sup>+</sup>, 21%), 159 (15), 143 (21), 89 (27), 85 (19), 73 (69), 71 (100). The spectroscopic data are in good agreement with the literature.<sup>131</sup>

**(R)-3-Methyl-2-(toluene-4-sulfonylamino)-butyric acid (250)**

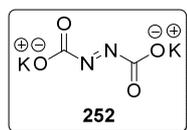
*N*-Ts-*D*-Valine **250** was prepared according to a modification of the procedure described by Schröder *et al.* for the preparation of analogous *N*-sulfonylated amino acids.<sup>132</sup> To a vigorously stirred solution of *D*-(-)-valine (17.6 g, 150 mmol) and K<sub>2</sub>CO<sub>3</sub> (30.4 g, 221 mmol) in H<sub>2</sub>O (300 cm<sup>3</sup>) was added TsCl (28.6 g, 150 mmol) and the suspension was heated to 70 °C until complete dissolution of the reactants had occurred (~30 min). The reaction mixture was maintained at 70 °C for a further 1 h and cooled slowly (~1 h) to 0 °C before acidification of the reaction mixture to pH 1 by dropwise addition of HCl (50 cm<sup>3</sup>; conc aq) [CAUTION: gases evolved]. The resulting precipitate was filtered, washed with cold (~0 °C) H<sub>2</sub>O (3 × 150 cm<sup>3</sup>) and dried thoroughly *in vacuo* to give *N*-Ts-*D*-valine **250** as a colourless solid (30.7 g, 75%). **R<sub>f</sub>** (DCM:MeOH, 10:1) = 0.28; **mp** 144–147 °C, lit<sup>240a</sup> 150–151 °C; [α]<sub>D</sub> = –24.7 (*c* 1.01, EtOH), lit<sup>240a</sup> [α]<sub>D</sub> = –27.7 (*c* 1.00, EtOH); **IR** (neat, cm<sup>-1</sup>) 3291 (NH), 2967 (OH), 1705 (C=O), 1331 (S=O), 1161 (S=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 7.76–7.74 (2H, m, ArH), 7.32–7.30 (2H, m, ArH), 5.05 (1H, d, *J* = 9.8 Hz, NH), 3.84 (1H, dd, *J* = 9.8, 4.7 Hz, CHNH) 2.44 (3H, s, ArCH<sub>3</sub>), 2.18–2.09 (1H, m, NCHCH), 1.00 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>), 0.90 (3H, d, *J* = 6.9 Hz, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 175.3 (C), 143.9 (C), 136.6 (C), 129.7 (2CH), 127.3 (2CH), 60.6 (CH), 31.4 (CH), 21.6 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>), 17.2 (CH<sub>3</sub>); ***m/z*** (EI) 271 ([M]<sup>+</sup>, 1%), 226 (100), 155 (50), 91 (30), 78 (26), 63 (18). The spectroscopic data are in good agreement with the reported literature data for racemic *N*-Ts-Valine.<sup>240b</sup>

**4-iodo-but-3-yn-1-ol (251)**

Iodoacetylene **251** was prepared according to a modification of the procedure described by Yenjai and Isobe.<sup>134</sup> Freshly distilled morpholine (18.5 cm<sup>3</sup>, 214 mmol) in PhMe (25 cm<sup>3</sup>) was added over 10 min to a solution of I<sub>2</sub> (18.3 g, 72.0 mmol) [CAUTION: gases evolved] in PhMe (250 cm<sup>3</sup>) at 45 °C and the mixture was stirred vigorously for 30 min, after which time a deep-red mixture had developed. A solution of 3-butyn-1-ol (5.00 g, 71.3 mmol) in PhMe (10 cm<sup>3</sup>) was added, and the reaction mixture stirred at 45 °C for 24 h before cooling to rt. The brown suspension was filtered, and the residue was

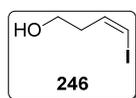
rinsed with Et<sub>2</sub>O (5 × 50 cm<sup>3</sup>). The solution was washed with Na<sub>2</sub>HPO<sub>4</sub> (100 cm<sup>3</sup>; 0.1 M aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 cm<sup>3</sup>; 0.1 M aq) and NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq); and the combined aqueous layers were backwashed with Et<sub>2</sub>O (2 × 50 cm<sup>3</sup>). The combined organic layers were washed with brine (100 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure to give iodoacetylene **251** as a red oil (13.5 g, 97%), which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.22; **IR** (neat, cm<sup>-1</sup>) 3335 (OH), 2183 (C≡C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 3.78–3.74 (2H, m, CH<sub>2</sub>OH), 2.67 (2H, t, *J* = 6.2 Hz, CH<sub>2</sub>CH<sub>2</sub>OH), 1.86 (1H, t, *J* = 5.5 Hz, OH); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 91.2 (C), 61.0 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), -4.4 (C); ***m/z*** (EI) 196 ([M]<sup>+</sup>, 100%), 166 (45). The spectroscopic data are in good agreement with the literature.<sup>90</sup>

### Dipotassium Azodicarboxylate (**252**)



PADA **252** was prepared according to a modification of the procedure described by Dorgan.<sup>90</sup> Azodicarbonamide (29.0 g, 250 mmol) was added in 5 portions over 30 min to a solution of KOH (70.1 g, 1.25 mol) in H<sub>2</sub>O (175 cm<sup>3</sup>) at 0 °C. The orange solution was stirred for 5 h at rt before cooling of the yellow suspension overnight (~18 h) at -15 °C (freezer). The precipitate was filtered, washed with cold (~0 °C) MeOH (2 × 250 cm<sup>3</sup>) and dried thoroughly under reduced pressure at rt to afford PADA **252** as a bright-yellow solid (43.9 g, 90%). **IR** (neat, cm<sup>-1</sup>) 1682 (C=O); **<sup>13</sup>C NMR** δ (100 MHz, D<sub>2</sub>O) 164.8 (C); ***m/z*** (EI) 194 ([M]<sup>+</sup>, 1%), 91 (35), 83 (32), 78 (16), 63 (15), 44 (100). The spectroscopic data are in good agreement with the literature.<sup>90</sup>

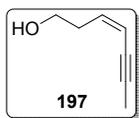
### (*Z*)-4-Iodo-but-3-en-1-ol (**246**)



Vinyl iodide **246** was prepared according to an amalgamation of the procedures described by Yenjai and Isobe,<sup>134</sup> and Dorgan.<sup>90</sup> Freshly distilled glacial AcOH (24.0 cm<sup>3</sup>, 418 mmol) in MeOH (25 cm<sup>3</sup>) was added dropwise (~2 h) [CAUTION: gases evolved] to a suspension of PADA **252** (38.6 g, 199 mmol) and iodoacetylene **251** (13.0 g, 66.3 mmol) in MeOH (225 cm<sup>3</sup>) and pyridine (32.1 cm<sup>3</sup>, 398 mmol) and the suspension was stirred vigorously overnight (~23 h), after which time a pale–orange–yellow mixture had developed. HCl (400 cm<sup>3</sup>; 1.0 M aq)

was added to quench the reaction, and the reaction mixture was diluted with Et<sub>2</sub>O (500 cm<sup>3</sup>). The aqueous layer was extracted with Et<sub>2</sub>O (5 × 100 cm<sup>3</sup>), and the combined organic layers were washed with NaHCO<sub>3</sub> (200 cm<sup>3</sup>; sat aq), brine (200 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the yellow oil thus obtained was added to <sup>n</sup>BuNH<sub>2</sub> (66.0 cm<sup>3</sup>, 668 mmol), and the solution was stirred for 7 h at rt before pouring of the mixture into Et<sub>2</sub>O (200 cm<sup>3</sup>) and HCl (100 cm<sup>3</sup>; 1.0 M aq). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 100 cm<sup>3</sup>), the combined organic layers were washed with HCl (3 × 100 cm<sup>3</sup>; 1.0 M aq) and the combined aqueous layers were backwashed with Et<sub>2</sub>O (100 cm<sup>3</sup>). The combined organic layers were washed with NaHCO<sub>3</sub> (200 cm<sup>3</sup>; sat aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (200 cm<sup>3</sup>; 0.1 M aq), brine (200 cm<sup>3</sup>), and dried (MgSO<sub>4</sub>). The solvent and residual <sup>n</sup>BuNH<sub>2</sub> were removed under reduced pressure and the crude brown oil thus obtained was subjected to flash chromatography (Hexane:EtOAc, 1:1) to give vinyl iodide **246** as a light-sensitive orange-yellow oil (9.10 g, 69%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.46; **IR** (neat, cm<sup>-1</sup>) 3321 (OH), 1611 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 6.41–6.39 (1H, m, CH<sub>2</sub>CH=CHI), 6.31 (1H, dt, *J* = 7.3, 6.8 Hz, CH<sub>2</sub>CH=CHI), 3.78 (2H, t, *J* = 6.4 Hz, CH<sub>2</sub>OH), 2.67 (1H, t, *J* = 6.2 Hz, OH), 2.47 (1H, q, *J* = 6.4 Hz, CH<sub>2</sub>CH=CHI); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 137.7 (CH), 84.8 (CH), 61.0 (CH<sub>2</sub>), 38.1 (CH<sub>2</sub>); ***m/z*** (EI) 198 ([M]<sup>+</sup>, 75%), 196 (49), 168 (55), 167 (23), 166 (26), 127 (16), 71 (71), 41 (100). The spectroscopic data are in good agreement with the literature.<sup>90,134</sup>

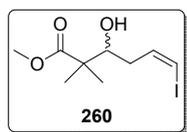
#### (*Z*)-Hept-3-en-5-yn-1-ol (**197**)



Enyne **197** was prepared according to the modification of the Negishi protocol<sup>41</sup> described by Dorgan.<sup>90</sup> To ZnCl<sub>2</sub> (24.1 g, 177 mmol) was added, over a period of 30 min, 1-propynylmagnesium bromide (303 cm<sup>3</sup>, 152 mmol; 0.5 M in THF) at 0 °C and the mixture was stirred vigorously for 45 min. Vinyl iodide **246** (10.0 g, 50.5 mmol) in THF (50 cm<sup>3</sup>) was added to the slurry, followed by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (3.55 g, 5.05 mmol, 10 mol%) in THF (50 cm<sup>3</sup>) and the beige mixture was warmed to rt and stirred overnight (~18 h) before quenching of the dark-brown mixture thus obtained by addition of NH<sub>4</sub>Cl (100 cm<sup>3</sup>; sat aq). The aqueous layer was extracted with Et<sub>2</sub>O (5 × 200 cm<sup>3</sup>) and the combined organic

layers were washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue was purified twice by flash chromatography (Hexane:EtOAc, 3:1) to give enyne **197** as a light-brown oil (4.23 g, 77%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.19; **bp** 132 °C (98 mmHg); **IR** (neat, cm<sup>-1</sup>) 3337 (OH), 2222 (C≡C), 1618 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 5.88 (1H, dt, *J* = 10.7, 7.4 Hz, CH<sub>2</sub>CH=CH), 5.60 (1H, dqt, *J* = 10.7, 2.3, 1.3 Hz, CH<sub>2</sub>CH=CH), 3.74 (3H, t, *J* = 6.4 Hz, CH<sub>2</sub>OH), 2.60 (2H, dtd, *J* = 7.4, 6.4, 1.3 Hz, CH<sub>2</sub>CH=CH), 2.01 (3H, d, *J* = 2.3 Hz, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 137.8 (CH), 112.2 (CH), 90.6 (C), 76.2 (C), 61.9 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (EI) 110.1 ([M]<sup>+</sup>, 61%), 95 (44), 91 (32), 80 (81), 79 (99), 77 (100). The spectroscopic data are in good agreement with the literature.<sup>90</sup>

### (*Z*)-3-Hydroxy-6-iodo-2,2-dimethylhex-5-enoic acid methyl ester (**260**)



$\beta$ -Hydroxyester **260** was prepared by Dess–Martin oxidation<sup>28</sup> of alcohol **246** (according to Hinkle's conditions),<sup>135</sup> followed by reaction of the crude aldehyde **254** with silyl ketene acetal **203** under Kiyooka's aldolisation conditions.<sup>130</sup> Dess–Martin periodinane (509 mg, 1.20 mmol) and NaHCO<sub>3</sub> (336 mg, 2.00 mmol) were added in succession to a solution of alcohol **246** (198 mg, 1.00 mmol) in DCM (10 cm<sup>3</sup>), and the mixture was stirred for 75 min at rt. The suspension was diluted with DCM (10 cm<sup>3</sup>) and poured into a mixture of NaHCO<sub>3</sub> (10 cm<sup>3</sup>; sat aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 cm<sup>3</sup>; sat aq), and H<sub>2</sub>O (20 cm<sup>3</sup>). The aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>), and the combined organic layers were washed with brine (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated to a volume of ~15 cm<sup>3</sup> under reduced pressure. The solution, which contained crude aldehyde **254**, was added to a solution of (*R*)-4-isopropyl-3-(toluene-4-sulfonyl)-[1,3,2]oxazaborolidin-5-one in DCM at -78 °C [which had been pre-prepared by dropwise addition of BH<sub>3</sub>•THF (1.00 cm<sup>3</sup>, 1.00 mmol; 1.0 M in THF) to *N*-Ts-*D*-Valine **250** (272 mg, 1.00 mmol) in DCM (10 cm<sup>3</sup>) and stirring for 30 min at rt before cooling] and stirred for 5 min before addition of silyl ketene acetal **203** (262.4 mg, 1.50 mmol) in DCM (2 cm<sup>3</sup>). The mixture was stirred for 4 h before quenching of the reaction with phosphate buffer solution (10 cm<sup>3</sup>; pH 7). The slurry was poured into DCM (30 cm<sup>3</sup>) and H<sub>2</sub>O (30 cm<sup>3</sup>) and the aqueous layer was

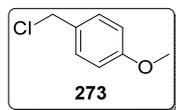
extracted with DCM ( $3 \times 10 \text{ cm}^3$ ). The combined organic layers were washed with brine ( $50 \text{ cm}^3$ ), dried ( $\text{MgSO}_4$ ), and the solvent was removed under reduced pressure to give a yellow oil that was subjected to flash chromatography (Hexane:EtOAc, 3:1) to afford  $\beta$ -hydroxyester **260** as an orange-yellow oil (110 mg, 37% over 2 steps, %*ee* not determined).  $R_f$  (Hexane:EtOAc, 3:1) = 0.34; **IR** (neat,  $\text{cm}^{-1}$ ) 3505 (OH), 1721 (C=O), 1611 (C=C);  **$^1\text{H}$  NMR**  $\delta$  (400 MHz,  $\text{CDCl}_3$ ) 6.45–6.35 (2H, m,  $\text{HC}=\text{CH}$ ), 3.81–3.77 (1H, m,  $\text{CHOH}$ ), 3.76 (3H, s,  $\text{OCH}_3$ ), 2.69 (1H, br d,  $J = 6.8 \text{ Hz}$ , OH), 2.43–2.36 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.27–2.19 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.29 (3H, s,  $\text{CCH}_3$ ), 1.27 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR**  $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 177.9 (C), 138.5 (CH), 84.3 (CH), 75.7 (CH), 52.1 ( $\text{CH}_3$ ), 47.0 (C), 37.4 ( $\text{CH}_2$ ), 22.6 ( $\text{CH}_3$ ), 20.3 ( $\text{CH}_3$ );  **$m/z$**  (EI) 299 ( $[\text{M}+\text{H}]^+$ , 1%), 221 (17), 153 (56), 131 (100), 102 (92), 99 (84); **HRMS** (EI)  $[\text{M}]^+$  found 298.0067,  $\text{C}_9\text{H}_{15}\text{O}_3\text{I}$  requires 298.0071.

N.B. The remaining syntheses from **Chapter 3** are presented alongside procedures from **Chapter 4**. Procedures pertaining to **Chapter 3** are clearly indicated, and can be found on the following pages:

Mukaiyama aldol reaction to synthesise Ester <b>243</b> from Alcohol <b>197</b>	221
Conversion of Ester <b>243</b> to Weinreb Amide <b>194</b>	223
Synthesis of $\beta$ -hydroxyketone <b>86</b> from Weinreb Amide <b>194</b>	225

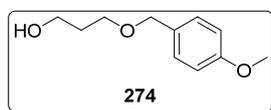
## 7.4 Experimental from Chapter 4

### 4-Methoxybenzyl chloride (273)



PMBCl **273** was prepared according to a modification of the procedure described by Luzzio and Chen.<sup>141</sup> A molten suspension of PMBOH (34.5 g, 250 mmol) in HCl (250 cm<sup>3</sup>; conc aq) was treated with ultrasonic vibration. On completion of the reaction (TLC monitoring, typically 1–2 h) the pale-yellow mixture thus obtained was poured into H<sub>2</sub>O (200 cm<sup>3</sup>) and the aqueous layer was extracted with DCM (3 × 100 cm<sup>3</sup>). The combined organic layers were washed with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave PMBCl **273** as a malodorous yellow oil (39.1 g, quant), which was used immediately without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 12:1) = 0.50; **IR** (neat, cm<sup>-1</sup>) 1611 (C=C), 1585 (C=C), 1514 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 7.37–7.34 (2H, m, 2ArH), 6.94–6.91 (2H, m, 2ArH), 4.61 (2H, s, CH<sub>2</sub>), 3.85 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 159.7 (C), 130.1 (2CH), 129.7 (C), 114.2 (2CH), 55.3 (CH<sub>3</sub>), 45.3 (CH<sub>2</sub>). The spectroscopic data are in good agreement with the literature.<sup>241</sup>

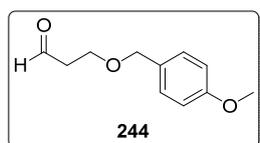
### 3-(4-Methoxybenzyloxy)-propan-1-ol (274)



Alcohol **274** was prepared according to a modification of the procedure described by Hatakeyama *et al.*<sup>142</sup> To a suspension of powdered KOH (56.1 g, 1.00 mol) in DMSO (230 cm<sup>3</sup>) at 0 °C was added 1,3-propanediol (72.3 cm<sup>3</sup>, 1.00 mol) and mixture was warmed to rt, stirred for 30 min and cooled back down to 0 °C. A solution of PMBCl **273** (39.2 g, 250 mmol) in DMSO (20 cm<sup>3</sup>) was added dropwise, and the solution was warmed to rt and stirred for 3 h. After cooling of the reaction mixture to 0 °C, HCl (200 cm<sup>3</sup>; 5.0 M aq) was slowly added (~30 min) to quench the reaction, and the yellow mixture was poured into H<sub>2</sub>O (500 cm<sup>3</sup>). The aqueous layer was extracted with DCM (5 × 100 cm<sup>3</sup>) and the combined organic layers were washed with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (3 × 100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave an orange-yellow oil that was purified by flash chromatography (Hexane:EtOAc, 1:1) to give alcohol **274** as a yellow oil (38.5 g, 78%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.35; **bp** 212 °C (41 mmHg; dec.); **IR** (neat, cm<sup>-1</sup>)

3407 (OH), 1612 (C=C), 1587 (C=C), 1513 (C=C);  $^1\text{H NMR}$   $\delta$  (400 MHz,  $\text{CDCl}_3$ ) 7.30–7.27 (2H, m, 2ArH), 6.93–6.89 (2H, m, 2ArH), 4.49 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.84 (3H, s,  $\text{CH}_3$ ), 3.81 (2H, t,  $J = 5.7$  Hz,  $\text{CH}_2\text{OCH}_2\text{CH}_2$ ), 3.67 (2H, t,  $J = 5.7$  Hz,  $\text{CH}_2\text{OH}$ ), 2.28 (1H, br s, OH). 1.89 (2H, qn,  $J = 5.7$  Hz,  $\text{CH}_2\text{CH}_2\text{OH}$ );  $^{13}\text{C NMR}$   $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 159.3 (C), 130.2 (C), 129.3 (2CH), 113.9 (2CH), 73.0 ( $\text{CH}_2$ ), 69.3 ( $\text{CH}_2$ ), 55.3 ( $\text{CH}_3$ ), 32.1 ( $\text{CH}_2$ );  $m/z$  (ESI+, MeOH) 415 ( $[\text{2M}+\text{Na}]^+$ , 24%), 219 ( $[\text{M}+\text{Na}]^+$ , 100%). The spectroscopic data are in good agreement with the literature.<sup>142</sup>

### 3-(4-Methoxybenzyloxy)-propionaldehyde (**244**)



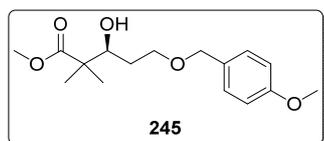
**Method A** (*Swern oxidation of alcohol 274*): **General**

**Procedure B** was followed with DMSO (63.9  $\text{cm}^3$ , 900 mmol), added over 20 min;  $(\text{COCl})_2$  (25.8  $\text{cm}^3$ , 300 mmol) in DCM (500  $\text{cm}^3$ ), with stirring for 10 min; alcohol **274** (39.3 g, 300 mmol) in DCM (100  $\text{cm}^3$ ) added over 10 min; and  $\text{Et}_3\text{N}$  (167  $\text{cm}^3$ , 1.20 mol), added over 10 min. Quenching with  $\text{H}_2\text{O}$  (800  $\text{cm}^3$ ); workup with DCM ( $3 \times 100$   $\text{cm}^3$ ),  $\text{H}_2\text{O}$  ( $3 \times 200$   $\text{cm}^3$ ) and brine (300  $\text{cm}^3$ ); and flash chromatography (Hexane:EtOAc, 3:1) of the orange residual oil thus obtained gave aldehyde **244** as a yellow oil (33.1 g, 85%).

**Method B** (*TEMPO-mediated oxidation of alcohol 274*): A cooled (0 °C) solution of bleach (6.85  $\text{cm}^3$ , 9.60 mmol; 1.40 M) buffered with  $\text{NaHCO}_3$  (6.85  $\text{cm}^3$ ; sat aq) was added to alcohol **274** (1.96 g, 10.0 mmol), TEMPO (78.1 mg, 0.50 mmol, 5 mol%) and KBr (119 mg, 0.10 mmol, 10 mol%) in a biphasic mixture of DCM (10  $\text{cm}^3$ ) and  $\text{NaHCO}_3$  (10  $\text{cm}^3$ ; sat aq) at 0 °C over a period of ~10 min by which time the deep-red mixture had become pallid. Stirring was continued for 15 min, further cooled bleach (1.80  $\text{cm}^3$ , 2.52 mmol; 1.40 M) buffered with  $\text{NaHCO}_3$  (1.80  $\text{cm}^3$ ; sat aq) was added and the mixture was stirred for 20 min before MeOH (2  $\text{cm}^3$ ) was added to quench the reaction. After warming to rt, the reaction mixture was diluted with  $\text{H}_2\text{O}$  (30  $\text{cm}^3$ ) and the aqueous layer was extracted with DCM ( $3 \times 20$   $\text{cm}^3$ ). The combined organic layers were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  (10  $\text{cm}^3$ ; 50% sat aq) [CAUTION:  $\text{Cl}_2$  gas evolution],  $\text{H}_2\text{O}$  (20  $\text{cm}^3$ ), brine (20  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the resulting orange oil was purified by flash chromatography (Hexane:EtOAc, 3:1) to give aldehyde **244** as a light-yellow oil (1.94 g, quant).  $R_f$  (Hexane:EtOAc, 3:1) = 0.22; IR (neat,  $\text{cm}^{-1}$ ) 2731

(CHO), 1722 (C=O), 1612 (C=C), 1585 (C=C), 1512 (C=C);  $^1\text{H NMR}$   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 9.81 (1H, t,  $J = 1.9$  Hz,  $\text{CH}_2\text{CHO}$ ), 7.29–7.26 (2H, m, 2ArH), 6.92–6.89 (2H, m, 2ArH), 4.49 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.83 (3H, s,  $\text{CH}_3$ ), 3.81 (2H, t,  $J = 6.1$  Hz,  $\text{OCH}_2\text{CH}_2$ ), 2.71 (2H, td,  $J = 6.1, 1.9$  Hz,  $\text{CH}_2\text{CHO}$ );  $^{13}\text{C NMR}$   $\delta$  (126 MHz,  $\text{CDCl}_3$ ) 201.3 (CH), 159.3 (C), 129.9 (C), 129.4 (2CH), 113.9 (2CH), 72.9 ( $\text{CH}_2$ ), 63.5 ( $\text{CH}_2$ ), 55.3 ( $\text{CH}_3$ ), 43.9 ( $\text{CH}_2$ );  $m/z$  (EI) 194 ( $[\text{M}]^+$ , 87%), 137 (94), 122 (72), 121 (100), 109 (59). The spectroscopic data are in good agreement with the literature.<sup>142</sup>

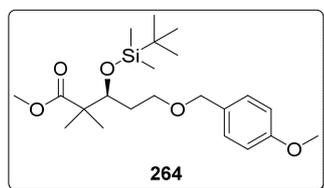
**(S)-3-Hydroxy-5-(4-methoxybenzyloxy)-2,2-dimethylpentanoic acid methyl ester (245)**



Alcohol **245** was prepared according to a modification of the procedure described by Hartung.<sup>14b</sup>  $\text{BH}_3 \cdot \text{THF}$  (106  $\text{cm}^3$ , 106 mmol; 1.0 M in THF) was added dropwise over 15 min to a suspension of *N*-Ts-*D*-valine **250** (28.8 g, 106 mmol) [CAUTION: gases evolved] in DCM (500  $\text{cm}^3$ ) at rt and the solution was stirred until gas evolution ceased (~1.5 h) before cooling of the reaction mixture to  $-78$  °C. Aldehyde **244** (19.4 g, 100 mmol) in DCM (300  $\text{cm}^3$ ) was added at such a rate as to maintain the internal temperature below  $-70$  °C (~15 min) before dropwise addition (30 min) of silyl ketene acetal **203** (30.5 g, 175 mmol) in DCM (100  $\text{cm}^3$ ). The solution was stirred for 5.5 h, quenched by addition of phosphate buffer solution (500  $\text{cm}^3$ ; pH 7) and the reaction mixture was warmed to rt. The aqueous layer was extracted with DCM ( $3 \times 100$   $\text{cm}^3$ ), and the combined organic layers were washed with brine (400  $\text{cm}^3$ ), dried ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure. The yellow oil thus obtained was dissolved in THF (100  $\text{cm}^3$ ) and HCl (100  $\text{cm}^3$ ; 5.0 M aq), the solution was stirred for 3 h at rt, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $4 \times 100$   $\text{cm}^3$ ). The combined organic layers were washed with NaOH ( $2 \times 100$   $\text{cm}^3$ ; 1.0 M aq),  $\text{NaHCO}_3$  (100  $\text{cm}^3$ ; sat aq), brine (100  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ), and the solvent was removed under reduced pressure. The combined aqueous layers from both aqueous workups were acidified to pH 1 by addition of HCl (200  $\text{cm}^3$ ; conc aq), extracted with EtOAc ( $3 \times 400$   $\text{cm}^3$ ), washed with brine (400  $\text{cm}^3$ ), dried ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure. Two recrystallisations ( $\text{EtOH}/\text{H}_2\text{O}$ ) of the resulting solid gave *N*-Ts-*D*-valine **250** as colourless needles

(17.2 g, 60% recovery). Purification of the resulting pale-yellow oil (obtained from the Et<sub>2</sub>O layers) by flash chromatography (Hexane:EtOAc, 3:1) gave  $\beta$ -hydroxyester **245** as a light-yellow oil (24.0 g, 85%, 89 %*ee*). N.B. Repeated runs typically gave comparable yield (75–85%) and enantioselectivity (88–89 %*ee*). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.36; **R<sub>f</sub>** (Method B) = 30.5 [(*S*)-isomer], 33.5 [(*R*)-isomer]; [ $\alpha$ ]<sub>D</sub> = -1.50 (*c* 2.52, CHCl<sub>3</sub>), lit<sup>14</sup> [ $\alpha$ ]<sub>D</sub> = -1.04 (*c* 1.15, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3516 (OH), 1726 (C=O), 1612 (C=C), 1585 (C=C), 1512 (C=C); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 7.28–7.27 (2H, m, 2ArH), 6.91–6.88 (2H, m, 2ArH), 4.49 (1H, d, *J* = 11.4 Hz, OCH<sub>A</sub>H<sub>B</sub>Ar), 4.46 (1H, d, *J* = 11.4 Hz, OCH<sub>A</sub>H<sub>B</sub>Ar), 3.93 (1H, dt, *J* = 8.7, 3.8 Hz, CHOH), 3.83 (3H, s, ArOCH<sub>3</sub>), 3.75–3.72 (1H, m, CH<sub>X</sub>H<sub>Y</sub>OCH<sub>2</sub>Ar), 3.72 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.69–3.65 (1H, m, CH<sub>X</sub>H<sub>Y</sub>OCH<sub>2</sub>Ar), 3.23 (1H, d, *J* = 3.8 Hz, OH), 1.74–1.68 (2H, m, CH<sub>2</sub>CHOH), 1.21 (3H, s, CCH<sub>3</sub>), 1.20 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR**  $\delta$  (125 MHz, CDCl<sub>3</sub>) 177.8 (C), 159.3 (C), 130.1 (C), 129.4 (2CH), 113.8 (2CH), 75.7 (CH), 73.0 (CH<sub>2</sub>), 69.1 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 47.0 (C), 31.4 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 20.4 (CH<sub>3</sub>); ***m/z*** (EI) 296 ([M]<sup>+</sup>, 1%), 142 (15), 137 (47), 135 (19), 121 (100). The spectroscopic data are in good agreement with the literature.<sup>14</sup>

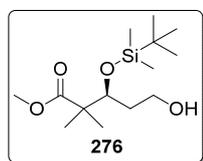
**(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,2-dimethylpentanoic acid methyl ester (**264**)**



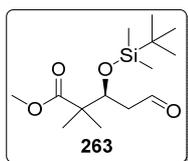
**General Procedure C** was followed with TBSOTf (13.9 cm<sup>3</sup>, 56.5 mmol),  $\beta$ -hydroxyester **245** (10.9 g, 38.3 mmol) and 2,6-lutidine (8.92 cm<sup>3</sup>, 76.6 mmol) in DCM (120 cm<sup>3</sup>) with reaction for 2.5 h at -78 °C. Quenching with NaHCO<sub>3</sub> (200 cm<sup>3</sup>; sat aq); workup with DCM (3 × 50 cm<sup>3</sup>), NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>) and brine (100 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 3:1) gave TBS-ether **264** as a colourless oil (14.8 g, 94%). N.B. Provided residual 2,6-lutidine is completely removed, the crude product may be taken forward to the subsequent PMB-deprotection step without chromatography. **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.72; [ $\alpha$ ]<sub>D</sub> = -4.20 (*c* 1.17, CHCl<sub>3</sub>), lit<sup>14</sup> [ $\alpha$ ]<sub>D</sub> = -4.20 (*c* 1.02, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 1732 (C=O), 1612 (C=C), 1585 (C=C), 1512 (C=C); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 7.30–7.27 (2H, m, 2ArH), 7.92–7.90 (2H, m, 2ArH), 4.46 (1H, d, *J* = 11.5 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 4.43 (1H, d, *J* = 11.5 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 4.07 (1H,

dd,  $J = 7.7, 3.1$  Hz,  $\text{CHOSi}$ ), 3.83 (3H, s,  $\text{ArOCH}_3$ ), 3.66 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.54–3.46 (2H, m,  $\text{CH}_2\text{OCH}_2\text{Ar}$ ), 1.84–1.78 (1H, m,  $\text{CH}_X\text{H}_Y\text{CHOSi}$ ), 1.70–1.63 (1H, m,  $\text{CH}_X\text{H}_Y\text{OSi}$ ), 1.18 (3H, s,  $\text{CCH}_3$ ), 1.11 (3H, s,  $\text{CCH}_3$ ), 0.88 (9H, s,  $3\text{SiC}(\text{CH}_3)_3$ ), 0.06 (3H, s,  $\text{SiCH}_3$ ), 0.03 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 177.5 (C), 159.2 (C), 130.6 (C), 129.2 (2CH), 113.8 (2CH), 73.9 (CH), 72.5 ( $\text{CH}_2$ ), 67.4 ( $\text{CH}_2$ ), 55.3 ( $\text{CH}_3$ ), 51.7 ( $\text{CH}_3$ ), 48.4 (C), 33.9 ( $\text{CH}_2$ ), 26.0 (3 $\text{CH}_3$ ), 21.5 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ), 18.3 (C),  $-4.0$  ( $\text{CH}_3$ ),  $-4.3$  ( $\text{CH}_3$ );  $m/z$  (ESI+, MeOH) 433 ( $[\text{M}+\text{Na}]^+$ , 100%). The spectroscopic data are in good agreement with the literature.<sup>14</sup>

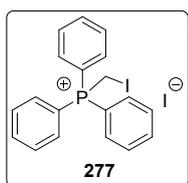
**(S)-3-(tert-Butyldimethylsilanyloxy)-5-hydroxy-2,2-dimethyl-pentanoic acid methyl ester (276)**



DDQ (25.7 g, 113 mmol) was added in 5 portions ( $5 \times 5.14$  g) over 10 min to a solution of PMB-ether **264** (31.0 g, 75.5 mmol; telescoped) in DCM ( $302 \text{ cm}^3$ ) and  $\text{H}_2\text{O}$  ( $17 \text{ cm}^3$ ) at  $0^\circ\text{C}$  and the red-brown mixture was stirred for 1.5 h. The reaction was quenched by cautious addition of  $\text{NaHCO}_3$  ( $400 \text{ cm}^3$ ; sat aq) [CAUTION: potential for HCN gas evolution; careful, controlled extrusion is required] and stirred until gas evolution ceased ( $\sim 1$  h). The black emulsion was poured into  $\text{H}_2\text{O}$  ( $3 \text{ dm}^3$ ), and the aqueous layer was extracted with DCM ( $5 \times 500 \text{ cm}^3$ ). The combined organic layers were washed with  $\text{NaHCO}_3$  ( $1 \text{ dm}^3$ ; sat aq),  $\text{H}_2\text{O}$  ( $1 \text{ dm}^3$ ), brine ( $1 \text{ dm}^3$ ) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the brown oil thus obtained was purified by flash chromatography (DCM:MeOH, 50:1) to give alcohol **276** as a brown oil (21.9 g, quant).  $R_f$  (DCM:MeOH, 50:1) = 0.32;  $[\alpha]_D = -1.80$  ( $c$  1.10,  $\text{CHCl}_3$ ); IR (neat,  $\text{cm}^{-1}$ ) 3468 (OH), 1720 (C=O);  $^1\text{H}$  NMR  $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 4.11 (1H, dd,  $J = 6.9, 4.3$  Hz,  $\text{CHOSi}$ ), 3.75–3.66 (2H, m,  $\text{CH}_2\text{OH}$ ), 3.70 (3H, s,  $\text{OCH}_3$ ), 1.75–1.66 (2H, m,  $\text{CH}_2\text{CHOSi}$ ), 1.52 (1H, br s, OH), 1.21 (3H, s,  $\text{CCH}_3$ ), 1.14 (3H, s,  $\text{CCH}_3$ ), 0.91 (9H, s,  $3\text{SiC}(\text{CH}_3)_3$ ), 0.13 (3H, s,  $\text{SiCH}_3$ ), 0.08 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 177.8 (C), 73.6 (CH), 60.1 ( $\text{CH}_2$ ), 51.8 ( $\text{CH}_3$ ), 48.1 (C), 36.9 ( $\text{CH}_2$ ), 26.0 (3 $\text{CH}_3$ ), 22.4 ( $\text{CH}_3$ ), 19.8 ( $\text{CH}_3$ ), 18.3 (C),  $-4.0$  ( $\text{CH}_3$ ),  $-4.3$  ( $\text{CH}_3$ );  $m/z$  (ESI+, MeOH/DCM) 314 ( $[\text{M}+\text{Na}]^+$ , 100%), 292 ( $[\text{M}+\text{H}]^+$ , 4%); HRMS (ESI+, MeOH/DCM)  $[\text{M}+\text{H}]^+$  found 291.1985,  $\text{C}_{14}\text{H}_{31}\text{O}_4\text{Si}$  requires 291.1986.

**(S)-3-(tert-Butyldimethylsilanyloxy)-2,2-dimethyl-5-oxo-pentanoic acid methyl ester (263)**

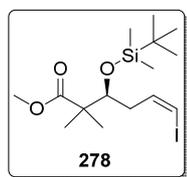
**General Procedure B** was followed with DMSO (63.9 cm<sup>3</sup>, 900 mmol) in DCM (50 cm<sup>3</sup>), added over 15 min; (COCl)<sub>2</sub> (11.4 cm<sup>3</sup>, 134 mmol) in DCM (100 cm<sup>3</sup>), with stirring for 15 min; alcohol **276** (19.5 g, 67.1 mmol) in DCM (100 cm<sup>3</sup>), added over 25 min; and Et<sub>3</sub>N (74.8 cm<sup>3</sup>, 537 mmol), added over 15 min. Quenching with H<sub>2</sub>O (250 cm<sup>3</sup>); workup with DCM (3 × 50 cm<sup>3</sup>), H<sub>2</sub>O (3 × 250 cm<sup>3</sup>) and brine (250 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 6:1) of the orange residual oil thus obtained gave aldehyde **263** as a yellow oil (18.4 g, 95%). **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.47; [**α**]<sub>D</sub> = +11.2 (*c* 0.80, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2723 (CHO), 1725 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 9.83 (1H, dd, *J* = 2.4, 1.6 Hz, CHO), 4.57 (1H, dd, *J* = 5.8, 4.7 Hz, CHOSi), 3.69 (3H, s, OCH<sub>3</sub>), 2.62 (1H, ddd, *J* = 17.2, 4.7, 1.6 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.57 (1H, ddd, *J* = 17.2, 5.8, 2.4 Hz, CH<sub>A</sub>H<sub>B</sub>), 1.22 (3H, s, CCH<sub>3</sub>), 1.14 (3H, s, CCH<sub>3</sub>), 0.88 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.10 (3H, s, SiCH<sub>3</sub>), 0.05 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 201.1 (CH), 176.8 (C), 71.5 (CH), 51.9 (CH<sub>3</sub>), 48.4 (CH<sub>2</sub>), 48.1 (C), 25.8 (3CH<sub>3</sub>), 21.3 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 18.1 (C), -4.1 (CH<sub>3</sub>), -4.9 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH/DCM) 343 ([M+MeOH+Na]<sup>+</sup>, 100%), 311 ([M+Na]<sup>+</sup>, 62%); **HRMS** (ESI+, MeOH/DCM) [M+Na]<sup>+</sup> found 311.1643, C<sub>14</sub>H<sub>28</sub>O<sub>4</sub>NaSi requires 311.1649.

**(Iodomethyl)triphenylphosphonium iodide (277)**

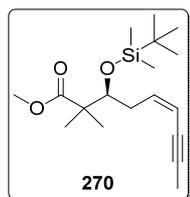
Wittig reagent **277** was prepared according to the procedure described by Quayle *et al.*<sup>153</sup> In the absence of light, a suspension of PPh<sub>3</sub> (26.2 g, 100 mmol) and CH<sub>2</sub>I<sub>2</sub> (11.5 cm<sup>3</sup>, 142 mmol) in PhMe (25 cm<sup>3</sup>) was heated to 70 °C with vigorous stirring for 1 d (~24 h). The resulting suspension was cooled to rt, the precipitate was filtered, washed with hexane (5 × 100 cm<sup>3</sup>), and dried *in vacuo* to give [Ph<sub>3</sub>PCH<sub>2</sub>I]<sup>+</sup>I<sup>-</sup> **277** as a colourless solid (48.5 g, 91%). **R<sub>f</sub>** (DCM:MeOH, 10:1) = 0.46; **mp** 225–226 °C (dec.), lit<sup>153</sup> 230 °C (dec.); **IR** (neat, cm<sup>-1</sup>) 1726 (C=C), 1660 (C=C), 1585 (C=C), 1533 (C=C), 1483 (C=C), 1467 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, DMSO-*d*<sub>6</sub>) 7.95–7.91 (3H, m, 3ArH), 7.88–7.84 (6H, m, 6ArH), 7.82–7.78 (6H, m, 6ArH), 5.09 (2H, d, *J* = 8.7 Hz, CH<sub>2</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 135.7 (d, *J* = 3.0 Hz, 3CH), 134.4 (d, *J* = 10.0

Hz, 6CH), 130.7 (d,  $J = 12.0$  Hz, 6CH), 118.7 (d,  $J = 88.8$  Hz, 3C),  $-16.1$  (d,  $J = 52.4$  Hz,  $\text{CH}_2$ );  $^{31}\text{P}$  NMR  $\delta$  (162 MHz,  $\text{DMSO-}d_6$ ) 23.8 (P). The spectroscopic data are in good agreement with the literature.<sup>153</sup>

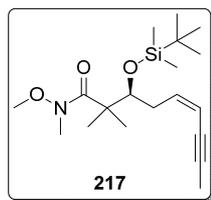
**(3*S*,5*Z*)-3-(*tert*-Butyldimethylsilanyloxy)-6-iodo-2,2-dimethylhex-5-enoic acid methyl ester (278)**



Vinyl iodide **278** was prepared according to a modification of Stork and Zhao's iodo-olefination procedure.<sup>145</sup> NaHMDS (58.4 cm<sup>3</sup>, 126 mmol; 2.0 M in THF) was added to a suspension of freshly prepared  $[\text{Ph}_3\text{PCH}_2\text{I}]^+\text{I}^-$  (67.0 g, 126 mmol) in THF (365 cm<sup>3</sup>) and the red solution was stirred for 5 min before cooling to  $-78$  °C. HMPA (43.9 cm<sup>3</sup>, 243 mmol) was added, and the solution was stirred for a further 5 min before aldehyde **263** (18.2 g, 63.2 mmol) in THF (60 cm<sup>3</sup>) was added dropwise (15 min). The reaction mixture was stirred for 2 h and quenched with  $\text{H}_2\text{O}$  (200 cm<sup>3</sup>); and the suspension thus obtained was warmed to rt and filtered through celite, rinsing the filter cake with  $\text{Et}_2\text{O}$  ( $5 \times 100$  cm<sup>3</sup>). The filtrate was further diluted with  $\text{Et}_2\text{O}$  (500 cm<sup>3</sup>), and the combined organic layers were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  (200 cm<sup>3</sup>; sat aq),  $\text{H}_2\text{O}$  ( $3 \times 200$  cm<sup>3</sup>), brine ( $3 \times 200$  cm<sup>3</sup>) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (Hexane:EtOAc, 15:1) to give vinyl iodide **278** as an orange oil (19.5 g, 75%, >99:1 *Z:E*).  $R_f$  (Hexane:EtOAc, 15:1) = 0.50;  $[\alpha]_D^{25} = +12.0$  ( $c$  1.25,  $\text{CHCl}_3$ ); IR (neat,  $\text{cm}^{-1}$ ) 1730 (C=O);  $^1\text{H}$  NMR  $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 6.33–6.27 (2H, m,  $\text{HC}=\text{CH}$ ), 4.15 (1H, t,  $J = 5.7$  Hz, SiOCH), 3.69 (3H, s, OCH<sub>3</sub>), 2.35–2.33 (2H, m,  $\text{CH}_2$ ), 1.22 (3H, s, CCH<sub>3</sub>), 1.17 (3H, s, CCH<sub>3</sub>), 0.91 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.10 (3H, s, SiCH<sub>3</sub>), 0.07 (3H, s, SiCH<sub>3</sub>);  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 177.3 (C), 138.7 (CH), 83.6 (CH), 75.3 (CH), 51.8 (CH<sub>3</sub>), 48.4 (C), 39.4 (CH<sub>2</sub>), 25.9 (3CH<sub>3</sub>), 22.0 (CH<sub>3</sub>), 20.3 (CH<sub>3</sub>), 18.2 (C),  $-3.6$  (CH<sub>3</sub>),  $-4.6$  (CH<sub>3</sub>);  $m/z$  (ESI+, MeOH/DCM) 639 ( $[\text{3M}+\text{H}+\text{K}]^{2+}$ , 100%), 413 ( $[\text{M}+\text{H}]^+$ , 49), 400 (34), 372 (29); HRMS (ESI+, MeOH/DCM)  $[\text{M}+\text{H}]^+$  found 413.1010,  $\text{C}_{15}\text{H}_{30}\text{IO}_3\text{Si}$  requires 413.1003.

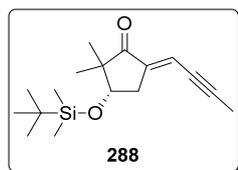
**(3*S*,5*Z*)-3-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethyl-5-nonen-7-ynoic acid methyl ester (270)**

Enyne **270** was prepared according to a modification of the standard Negishi coupling protocol.<sup>44</sup> To a suspension of ZnCl<sub>2</sub> (23.3 g, 171 mmol) in THF (180 cm<sup>3</sup>) was added 1-propynylmagnesium bromide (244 cm<sup>3</sup>, 142 mmol; 0.5 M in THF) over 15 min and the pale-yellow slurry was stirred for 15 min at 0 °C. Vinyl iodide **278** (19.5 g, 47.4 mmol) in THF (30 cm<sup>3</sup>) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1.66 g, 2.37 mmol, 5 mol%) rinsed into the flask with THF (10 cm<sup>3</sup>) were added in quick succession, and the pale-yellow mixture was warmed to rt and stirred overnight (~16 h). The solvent was removed under reduced pressure and NH<sub>4</sub>Cl (300 cm<sup>3</sup>; sat aq) was added to the resulting brown paste to quench the reaction. The aqueous layer was extracted with DCM (4 × 100 cm<sup>3</sup>), and the combined organic layers were washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give a brown residue that was purified by flash chromatography (Hexane:DCM, 3:1; dry loaded) to afford enyne **270** as an orange oil (14.2 g, 92%). **R<sub>f</sub>** (Hexane:DCM, 3:1) = 0.24; **[α]<sub>D</sub>** = +2.90 (*c* 1.01, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2218 (C≡C), 1732 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 5.88 (1H, dt, *J* = 10.7, 7.4 Hz, CH<sub>2</sub>CH=CH), 5.47 (1H, dqt, *J* = 10.7, 2.4, 1.4 Hz, CHC≡CCH<sub>3</sub>), 4.09 (1H, t, *J* = 5.7 Hz, CHOSi), 3.67 (3H, s, OCH<sub>3</sub>), 2.55–2.43 (2H, m, CH<sub>2</sub>), 2.01 (3H, d, *J* = 2.4 Hz, C≡CCH<sub>3</sub>), 1.21 (3H, s, CCH<sub>3</sub>), 1.16 (3H, s, CCH<sub>3</sub>), 0.90 (9H, s, 3SiC(CH<sub>3</sub>)), 0.10 (3H, s, SiCH<sub>3</sub>), 0.06 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 177.5 (C), 139.1 (CH), 110.7 (CH), 90.7 (C), 76.5 (C), 76.2 (CH), 51.6 (CH<sub>3</sub>), 48.4 (C), 34.8 (CH<sub>2</sub>), 25.9 (3CH<sub>3</sub>), 21.9 (CH<sub>3</sub>), 20.2 (CH<sub>3</sub>), 18.1 (C), 4.4 (CH<sub>3</sub>), -3.7 (CH<sub>3</sub>), -4.7 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH/DCM) 347 ([M+Na]<sup>+</sup>, 70%), 325 ([M+H]<sup>+</sup>, 34), 165 ([M+2H]<sup>2+</sup>, 100); **HRMS** (ESI+, MeOH/DCM) [M+H]<sup>+</sup> found 325.2195, C<sub>18</sub>H<sub>33</sub>O<sub>3</sub>Si requires 325.2194.

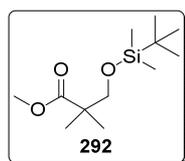
**(3*S*,5*Z*)-3-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethyl-5-nonen-7-ynoic acid methoxy-methyl-amide (217)**

**Method A** (*amidation of ester 270*): **General Procedure A** was followed with HNMe(OMe)•HCl (1.05 g, 10.8 mmol) in THF (10 cm<sup>3</sup>); <sup>*n*</sup>BuLi (8.64 cm<sup>3</sup>, 21.6 mmol; 2.5 M in hexanes); and ester **270** (1.17 g, 3.60 mmol) in THF (5 cm<sup>3</sup>); with reaction at –78 °C (30 min), –78 °C to rt (~30 min) and rt (1.5 h). Quenching with NH<sub>4</sub>Cl (10 cm<sup>3</sup>; sat aq); workup with Et<sub>2</sub>O (5 × 10 cm<sup>3</sup>) and brine (20 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 9:1) gave Weinreb amide **217** as a yellow oil (738 mg, 58%). N.B. Repeated runs under identical or very similar conditions did not give reproducible yields of product **217**. On repetition of the experiment, the cyclised product **288** occasionally co-eluted on silica with any recovered starting material **270**.

**Method B** (*TBS protection of β-hydroxy-Weinreb amide 194, below*): **General Procedure C** was followed with TBSOTf (8.50 cm<sup>3</sup>, 37.0 mmol), alcohol **194** (6.81 g, 28.5 mmol) and 2,6-lutidine (6.62 cm<sup>3</sup>, 56.9 mmol) in DCM (30 cm<sup>3</sup>); with reaction for 1.5 h at –78 °C, then –78 to rt (~30 min). Quenching with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq); workup with DCM (3 × 50 cm<sup>3</sup>) and brine (100 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 6:1) gave TBS-ether **217** as an orange oil (9.67 g, 96%). **R<sub>f</sub>** (Hexane:EtOAc, 9:1) = 0.15; [**α**]<sub>D</sub> = +3.30 (*c* 0.54, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2218 (C≡C), 1651 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 5.88 (1H, dt, *J* = 10.6, 7.6 Hz, CH<sub>2</sub>CH=CH), 5.46 (1H, br d, *J* = 10.6 Hz, CHC≡CCH<sub>3</sub>), 4.37 (1H, t, *J* = 5.8 Hz, CHOSi), 3.70 (3H, s, OCH<sub>3</sub>), 3.17 (3H, s, NCH<sub>3</sub>), 2.51–2.41 (2H, m, CH<sub>2</sub>), 1.99 (3H, br s, C≡CCH<sub>3</sub>), 1.27 (3H, s, CCH<sub>3</sub>), 1.23 (3H, s, CCH<sub>3</sub>), 0.93 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.11 (3H, s, SiCH<sub>3</sub>), 0.08 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 177.6 (C), 139.7 (CH), 110.6 (CH), 90.3 (C), 76.7 (C), 74.3 (CH), 60.4 (CH<sub>3</sub>), 49.1 (C), 35.4 (CH<sub>2</sub>), 33.9 (CH<sub>3</sub>), 26.0 (3CH<sub>3</sub>), 23.0 (CH<sub>3</sub>), 19.4 (CH<sub>3</sub>), 18.2 (C), 4.5 (CH<sub>3</sub>), –3.6 (CH<sub>3</sub>), –4.3 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH/DCM) 729 ([2M+Na]<sup>+</sup>, 47%), 376 ([M+Na]<sup>+</sup>, 100), 354 ([M+H]<sup>+</sup>, 32); **HRMS** (ESI+, MeOH/DCM) [M+H]<sup>+</sup> found 354.2459, C<sub>19</sub>H<sub>36</sub>NO<sub>3</sub>Si requires 354.2459.

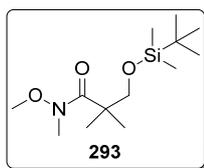
**(1'E, 3S)-(tert-Butyldimethylsilyloxy)-5-(but-1'-ynylidene)-2,2-dimethyl-cyclopentanone (288)**

**Cyclisation product diagnostic peaks:**  $^1\text{H NMR}$   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 6.49–6.46 (1H, m,  $\text{H}_3\text{CC}\equiv\text{CCH}$ ), 3.96 (1H, t,  $J = 6.5$  Hz,  $\text{CHOSi}$ ), 2.97 (1H, dddq,  $J = 17.6, 6.5, 2.5, 0.6$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.97 (1H, dddq,  $J = 17.6, 6.5, 3.2, 1.0$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.11 (3H, dt,  $J = 2.4, 0.8$  Hz,  $\text{H}_3\text{CC}\equiv\text{CCH}$ ), 1.07 (3H, s,  $\text{CCH}_3$ ), 1.03 (3H, s,  $\text{CCH}_3$ ), 0.92 (9H, s,  $3\text{SiC}(\text{CH}_3)$ ), 0.12 (3H, s,  $\text{SiCH}_3$ ), 0.10 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C NMR}$   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 207.6 (C), 144.0 (C), 115.0 (CH), 99.3 (C), 77.6 (C), 75.9 (CH), 51.0 (C), 35.6 ( $\text{CH}_2$ ), 25.7 ( $3\text{CH}_3$ ), 21.9 ( $\text{CH}_3$ ), 18.1 (C), 17.7 ( $\text{CH}_3$ ), 5.1 ( $\text{CH}_3$ ),  $-4.5$  ( $\text{CH}_3$ ),  $-4.9$  ( $\text{CH}_3$ ).

**3-(tert-Butyl-dimethyl-silyloxy)-2,2-dimethyl-propionic acid methyl ester (292)**

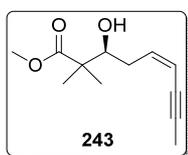
**General Procedure C** was followed with TBSOTf (8.17  $\text{cm}^3$ , 40.0 mmol), 3-hydroxy-2,2-dimethyl-propionic acid methyl ester (3.96 g, 30.0 mmol) and 2,6-lutidine (6.95  $\text{cm}^3$ , 60.0 mmol) in DCM (30  $\text{cm}^3$ ); with reaction for 1.5 h at  $-78$   $^\circ\text{C}$ , then  $-78$  to rt ( $\sim 30$  min). Quenching with  $\text{NaHCO}_3$  (50  $\text{cm}^3$ ; sat aq); workup with DCM ( $3 \times 20$   $\text{cm}^3$ ),  $\text{NaHCO}_3$  (20  $\text{cm}^3$ ; sat aq),  $\text{H}_2\text{O}$  ( $3 \times 20$   $\text{cm}^3$ ) and brine (20  $\text{cm}^3$ ); and flash chromatography (Hexane:EtOAc, 10:1) gave TBS-ether **292** as a colourless liquid (7.31 g, 99%).  $R_f$  (Hexane:EtOAc, 10:1) = 0.54; **IR** (neat,  $\text{cm}^{-1}$ ) 1738 (C=O);  $^1\text{H NMR}$   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 3.68 (3H, s,  $\text{OCH}_3$ ), 3.59 (2H, s,  $\text{CH}_2$ ), 1.18 (6H, s,  $2\text{CCH}_3$ ), 0.89 (9H, s,  $3\text{SiC}(\text{CH}_3)_3$ ), 0.05 (6H, s,  $2\text{SiCH}_3$ );  $^{13}\text{C NMR}$   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 177.2 (C), 70.0 ( $\text{CH}_2$ ), 51.6 ( $\text{CH}_3$ ), 44.9 (C), 25.8 ( $3\text{CH}_3$ ), 21.9 ( $2\text{CH}_3$ ), 18.8 (C),  $-5.6$  ( $2\text{CH}_3$ );  $m/z$  (ESI+, MeOH/DCM) 333 (100%), 269 ( $[\text{M}+\text{Na}]^+$ , 93), 247 ( $[\text{M}+\text{H}]^+$ , 73). The spectroscopic data are in good agreement with the literature.<sup>162</sup>

### 3-(*tert*-Butyl-dimethyl-silanyloxy)-*N*-methoxy-2,2,*N*-trimethyl-propionamide (293)



**General Procedure A** was followed with HNMe(OMe)•HCl (3.66 g, 37.5 mmol) in THF (20 cm<sup>3</sup>); <sup>n</sup>BuLi (30.0 cm<sup>3</sup>, 75.0 mmol; 2.5 M in hexanes); and ester **292** (6.16 g, 25.0 mmol) in THF (10 cm<sup>3</sup>); with reaction at –78 °C (30 min), –78 °C to rt (~30 min) and rt (1 h). Quenching with NH<sub>4</sub>Cl (50 cm<sup>3</sup>; sat aq); workup with Et<sub>2</sub>O (5 × 25 cm<sup>3</sup>) and brine (50 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 9:1) gave Weinreb amide **293** as a colourless oil (5.03 g, 73%). **R<sub>f</sub>** (Hexane:EtOAc, 9:1) = 0.20; **IR** (neat, cm<sup>-1</sup>) 1651 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 3.71 (5H, s, OCH<sub>3</sub> and CH<sub>2</sub>), 3.20 (3H, s, NCH<sub>3</sub>), 1.24 (6H, s, 2CCH<sub>3</sub>), 0.91 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.06 (6H, s, 2SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 177.2 (C), 69.2 (CH<sub>2</sub>), 60.6 (CH<sub>3</sub>), 45.3 (C), 33.7 (CH<sub>3</sub>), 25.9 (3CH<sub>3</sub>), 22.2 (2CH<sub>3</sub>), 28.3 (C), –5.5 (2CH<sub>3</sub>); **m/z** (ESI+, MeOH/DCM) 276 ([M+H]<sup>+</sup>, 100), 298 ([M+Na]<sup>+</sup>, 65), 573 ([2M+Na]<sup>+</sup>, 24). The spectroscopic data are in good agreement with the literature.<sup>162</sup>

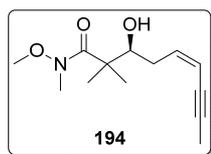
### (3*S*,5*Z*)-3-Hydroxy-2,2-dimethyl-non-5-en-7-ynoic acid methyl ester (243)



**Method A** [oxidation/Mukaiyama aldol approach from alcohol **197** (from *Chapter 3*): β-Hydroxyester **243** was prepared by Dess–Martin oxidation<sup>28</sup> of alcohol **197** (according to Hinkle's conditions),<sup>135</sup> followed by reaction of the crude aldehyde **193**<sup>90</sup> with silyl ketene acetal **203** under Kiyooka's aldolisation conditions.<sup>130</sup> Dess–Martin periodinane (2.55 g, 6.00 mmol) and NaHCO<sub>3</sub> (0.84 g, 10.0 mmol) were added in succession to a solution of alcohol **197** (0.54 g, 4.90 mmol) in DCM (10 cm<sup>3</sup>) and the mixture was stirred for 1.5 h at rt. The yellow suspension was poured into NaHCO<sub>3</sub> (10 cm<sup>3</sup>; sat aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 cm<sup>3</sup>; sat aq) and H<sub>2</sub>O (20 cm<sup>3</sup>). The aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>), and the combined organic layers were washed with brine (20 cm<sup>3</sup>) and twice dried (MgSO<sub>4</sub>), with DCM (30 cm<sup>3</sup>) rinsing of the desiccant. The solvent was reduced to a volume of ~30 cm<sup>3</sup> under reduced pressure and the yellow solution of the crude aldehyde **193** was immediately added to (*R*)-4-isopropyl-3-(toluene-4-sulfonyl)-[1,3,2]oxazaborolidin-5-one in DCM at –78 °C [which had been pre-prepared by dropwise addition of BH<sub>3</sub>•THF (6.00 cm<sup>3</sup>, 6.00 mmol; 1.0 M in

THF) to *N*-Ts-*D*-Valine **250** (1.63 g, 6.00 mmol) [CAUTION: gases evolved] in DCM (70 cm<sup>3</sup>), and stirring for 30 min at rt before addition of 4 Å molecular sieves (2.00 g) and subsequent cooling] and stirred for 10 min before addition of silyl ketene acetal **203** (1.32 g, 7.50 mmol) in DCM (5 cm<sup>3</sup>). The mixture was stirred for 6 h before quenching of the reaction with H<sub>2</sub>O (30 cm<sup>3</sup>). The slurry was warmed to rt, filtered through celite, and the filter cake was rinsed with DCM (3 × 20 cm<sup>3</sup>). The organic layer was washed with H<sub>2</sub>O (30 cm<sup>3</sup>), and the aqueous layer was backwashed with DCM (10 cm<sup>3</sup>). The combined organic layers were washed with brine (50 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. Flash chromatography (Hexane:EtOAc, 3:1) of the orange-yellow residual oil thus obtained gave ester **243** as an orange-yellow oil (0.50 g, 49% over 2 steps, %*ee* not determined). N.B. This procedure was not reproducible.

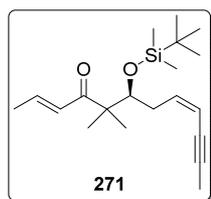
**Method B** (*silyl deprotection of TBS-ether 270*): HF (37.7 cm<sup>3</sup>, 1.05 mol; 48% aq) was added to a solution of TBS-ether **270** (11.3 g, 34.9 mmol) in MeCN (70 cm<sup>3</sup>) at 0 °C and the solution was stirred for 15 min, warmed to rt, stirred for 1 h and cooled back down to 0 °C. A suspension of NaHCO<sub>3</sub> (84.0 g, 1.00 mol) in NaHCO<sub>3</sub> (600 cm<sup>3</sup>; sat aq) was added in small portions over ~15 min [CAUTION: vigorous gas evolution] and the mixture was warmed to rt and stirred for 30 min. The aqueous layer was extracted with DCM (4 × 200 cm<sup>3</sup>) and the combined organic layers were washed with NaHCO<sub>3</sub> (200 cm<sup>3</sup>; sat aq), brine (200 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the resulting oil was purified by flash chromatography (Hexane:EtOAc, 3:1) to give β-hydroxyester **243** as a yellow oil (7.28 g, 99%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.44; [**α**]<sub>D</sub> = -29.7 (*c* 1.01, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3503 (OH), 2220 (C≡C), 1726 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 6.00 (1H, dt, *J* = 10.6, 7.3 Hz, CH<sub>2</sub>CH=CH), 5.59 (1H, dqt, *J* = 10.6, 2.3, 1.0 Hz, CHC≡CH<sub>3</sub>), 3.80–3.76 (1H, m, CHOH), 3.74 (3H, s, OCH<sub>3</sub>), 2.56–2.50 (2H, m, OH and CH<sub>A</sub>H<sub>B</sub>), 2.40–2.31 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.00 (3H, d, *J* = 2.3 Hz, C≡CCH<sub>3</sub>), 1.28 (3H, s, CCH<sub>3</sub>), 1.27 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 177.9, (C), 138.8 (CH), 111.7 (CH), 90.7 (C), 76.4 (CH), 76.3 (C), 52.0 (CH<sub>3</sub>), 47.1 (C), 32.7 (CH<sub>2</sub>), 22.3 (CH<sub>3</sub>), 20.3 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (EI) 210 ([M]<sup>+</sup>, 1%), 192 (34), 177 (26), 131 (95), 102 (100); **HRMS** (EI) [M]<sup>+</sup> found 210.1259, C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> requires 210.1261.

**(3*S*,5*Z*)-3-Hydroxy-2,2-dimethyl-non-5-en-7-ynoic acid methoxymethyl amide (194)**

**Method A** [*low-temperature preparation (from Chapter 3)*]:

**General Procedure A** was followed with HNMe(OMe)•HCl (1.03 g, 10.6 mmol) in THF (18 cm<sup>3</sup>); <sup>n</sup>BuLi (13.2 cm<sup>3</sup>, 21.1 mmol; 1.6 M in hexanes); and ester **243** (247 mg, 1.17 mmol) in THF (2 cm<sup>3</sup>); with reaction at –78 °C (2.5 h). Quenching with NH<sub>4</sub>Cl (20 cm<sup>3</sup>; sat aq); workup with EtOAc (3 × 20 cm<sup>3</sup>) and brine (20 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 1:1) gave Weinreb amide **194** as a yellow oil (247 mg, 88%).

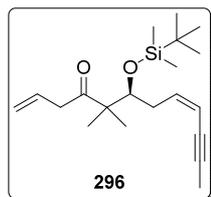
**Method B** [*large-scale preparation*]: **General Procedure A** was followed with HNMe(OMe)•HCl (13.5 g, 138 mmol) in THF (130 cm<sup>3</sup>); <sup>n</sup>BuLi (173 cm<sup>3</sup>, 277 mmol; 1.6 M in hexanes); and ester **243** (7.28 g, 34.6 mmol) in THF (50 cm<sup>3</sup>); with reaction at –78 °C (30 min), –78 °C to rt (~1 h) and rt (5 min). Quenching with NH<sub>4</sub>Cl (400 cm<sup>3</sup>; 50% sat aq); workup with Et<sub>2</sub>O (5 × 100 cm<sup>3</sup>), H<sub>2</sub>O (100 cm<sup>3</sup>) and brine (100 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 1:1) gave Weinreb amide **194** as an orange-red oil (6.81 g, 82%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.33; [**α**]<sub>D</sub> = –45.2; **IR** (neat, cm<sup>–1</sup>) 3453 (OH), 2220 (C≡C), 1624 (C=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 6.08 (1H, dt, *J* = 10.6, 7.2 Hz, CH<sub>2</sub>CH=CH), 5.56 (1H, dtq, *J* = 10.6, 2.1, 1.0 Hz, CHC≡CH<sub>3</sub>), 3.79 (1H, ddd, *J* = 10.2, 6.7, 2.6 Hz, CHOH), 3.73 (3H, s, OCH<sub>3</sub>), 3.29 (1H, d, *J* = 6.7 Hz, OH), 3.22 (3H, s, NCH<sub>3</sub>), 2.61–2.55 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.45–2.37 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.00 (3H, d, *J* = 2.1 Hz, C≡CCH<sub>3</sub>), 1.33 (3H, s, CCH<sub>3</sub>), 1.32 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 178.5 (C), 140.1 (CH), 110.8 (CH), 90.3 (C), 77.6 (CH), 76.5 (C), 60.7 (CH<sub>3</sub>), 47.2 (C), 33.7 (CH<sub>3</sub>), 32.5 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH/DCM) 501 ([2M+Na]<sup>+</sup>, 41%), 262 ([M+Na]<sup>+</sup>, 100), 240 ([M+H]<sup>+</sup>, 34); **HRMS** (ESI+, MeOH/DCM) [M+Na]<sup>+</sup> found 262.1407, C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>Na requires 262.1414.

**(2E,6S,8Z)-6-(tert-Butyl-dimethyl-silyloxy)-5,5-dimethyl-dodeca-2,8-dien-10-yn-4-one (271)**

TBS-protected  $\beta$ -hydroxyketone **271** was prepared according to a modification of the procedure described by Scheidt<sup>165</sup> for the preparation of an analogous enone from a Weinreb amide. A solution of allyl bromide (6.30 cm<sup>3</sup>, 72.8 mmol) in Et<sub>2</sub>O (100 cm<sup>3</sup>) was added dropwise to a suspension of magnesium turnings (1.98 g, 81.3 mmol) in Et<sub>2</sub>O (46 cm<sup>3</sup>) and the solution was stirred until spontaneous boiling ceased (~30 min), heated to reflux for a further 15 min, cooled to rt and stirred for 1 h to give allylmagnesium bromide (146 cm<sup>3</sup>, 73.0 mmol; 0.50 M in Et<sub>2</sub>O) as a grey solution. The Grignard reagent thus obtained was transferred *via* cannula over ~20 min to a solution of Weinreb amide **217** (3.22 g, 9.10 mmol) in Et<sub>2</sub>O (20 cm<sup>3</sup>) and the reaction mixture was stirred for 2 h, cooled to -78 °C and quenched by cautious addition (~10 min) of NH<sub>4</sub>Cl (100 cm<sup>3</sup>; sat aq). After warming to rt, the aqueous layer was extracted with Et<sub>2</sub>O (3 × 100 cm<sup>3</sup>) and the combined organic layers were washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give the crude allylic ketone **296** as an orange oil to which Et<sub>3</sub>N (25.4 cm<sup>3</sup>, 182 mmol) and DBU (5.44 cm<sup>3</sup>, 36.4 mmol) were added, and the solution was heated to 50 °C overnight (~18 h). The reaction mixture was cooled to rt, diluted with Et<sub>2</sub>O (100 cm<sup>3</sup>) and washed with HCl (3 × 50 cm<sup>3</sup>; 1.0 M aq) [CAUTION: exothermic], NaHCO<sub>3</sub> (50 cm<sup>3</sup>; sat aq) and brine (50 cm<sup>3</sup>). Drying (MgSO<sub>4</sub>), removal of the solvent under reduced pressure and purification of the orange oil thus obtained by flash chromatography (Hexane:EtOAc, 10:1) gave the product TBS-protected  $\beta$ -hydroxyketone **271** as a yellow oil (2.45 g, 81%, 98:2 *E:Z*). N.B. Repeated runs typically gave comparable stereoselectivity in the product enone (greater than 96:4 *E:Z*). **R<sub>f</sub>** (Hexane:EtOAc, 10:1) = 0.53; [ $\alpha$ ]<sub>D</sub> = -5.90 (*c* 1.01, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2220 (C≡C), 1687 (C=O), 1626 (C=C); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 6.91 (1H, dq, *J* = 15.1, 6.9 Hz, CH<sub>3</sub>CH=CH), 6.58 (1H, dq, *J* = 15.1, 2.2, 1.6 Hz, CH<sub>3</sub>CH=CH), 5.88 (1H, dt, *J* = 10.7, 7.4 Hz, CH<sub>2</sub>CH=CH), 5.44 (1H, br d, *J* = 10.7 Hz, CHC≡CCH<sub>3</sub>), 4.05 (1H, dd, *J* = 5.8, 5.6 Hz, SiOCH), 2.52–2.41 (2H, m, CH<sub>2</sub>), 1.99 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.90 (3H, dd, *J* = 6.9, 1.6 Hz, C=CHCH<sub>3</sub>), 1.16 (3H, s, CCH<sub>3</sub>), 1.14 (3H, s, CCH<sub>3</sub>), 0.91 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.10 (3H, s, SiCH<sub>3</sub>), 0.06 (3H,

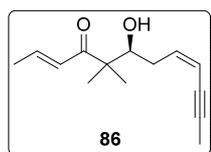
s, SiCH<sub>3</sub>); <sup>13</sup>C NMR δ (125 MHz, CDCl<sub>3</sub>) 203.1 (C), 142.2 (CH), 139.4 (CH), 127.4 (CH), 110.9 (CH), 90.7 (C), 76.5 (CH), 76.4 (C), 52.1 (C), 35.0 (CH<sub>2</sub>), 26.0 (3CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 20.3 (CH<sub>3</sub>), 18.2 (CH<sub>3</sub>), 18.1 (C), 4.4 (CH<sub>3</sub>), -3.7 (CH<sub>3</sub>), -4.5 (CH<sub>3</sub>); *m/z* (ESI+, MeOH/DCM) 357 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI+, MeOH/DCM) [M+H]<sup>+</sup> found 335.2395, C<sub>20</sub>H<sub>35</sub>O<sub>2</sub>Si requires 335.2400.

**(6*S*,8*Z*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-5,5-dimethyl-dodeca-1,8-dien-10-yn-4-one (296)**



**R<sub>f</sub>** (Hexane:EtOAc, 10:1) = 0.50; **<sup>1</sup>H NMR** δ (600 MHz, CDCl<sub>3</sub>) 5.96 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, CH<sub>2</sub>=CH), 5.84 (1H, dt, *J* = 10.6, 7.4 Hz, CH<sub>2</sub>CH=CH), 5.45 (1H, br d, *J* = 10.6 Hz, CHC≡CCH<sub>3</sub>), 5.17 (1H, br d, *J* = 10.3, 2.9 Hz, CH<sub>cis</sub>H<sub>trans</sub>=CH), 5.10 (1H, br d, *J* = 17.1, 2.9 Hz, CH<sub>cis</sub>H<sub>trans</sub>=CH), 4.06 (1H, t, *J* = 5.7 Hz, CHOSi), 3.40 (1H, br dd, *J* = 18.1, 6.8 Hz H<sub>2</sub>C=CHCH<sub>A</sub>H<sub>B</sub>), 3.29 (1H, br dd, *J* = 18.1, 6.8 Hz, H<sub>2</sub>C=CHCH<sub>A</sub>H<sub>B</sub>), 2.53–2.39 (2H, m, CH<sub>2</sub>CH=CH), 2.00 (3H, d, *J* = 2.3 Hz, C≡CCH<sub>3</sub>), 1.17 (3H, s, CCH<sub>3</sub>), 1.15 (3H, s, CCH<sub>3</sub>), 0.92 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.11 (3H, s, SiCH<sub>3</sub>), 0.07 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (150 MHz, CDCl<sub>3</sub>) 213.0 (C), 139.0 (CH), 131.7 (CH), 117.8 (CH<sub>2</sub>), 111.0 (CH), 91.0 (C), 76.5 (CH), 76.4 (C), 53.3 (C), 43.5 (CH<sub>2</sub>), 35.1 (CH<sub>2</sub>), 26.0 (3CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 20.2 (C), 18.2 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>), -3.8 (CH<sub>3</sub>), -4.5 (CH<sub>3</sub>).

**(2*E*,6*S*,8*Z*)-6-Hydroxy-5,5-dimethyl-dodeca-2,8-dien-10-yn-4-one (86)**



**Method A** [Grignard addition with Weinreb amide **194** using 1-propenylmagnesium bromide (from **Chapter 3**): To a solution of Weinreb amide **194** (366 mg, 1.53 mmol) in THF (3 cm<sup>3</sup>) was added 1-propenylmagnesium bromide (15.3 cm<sup>3</sup>, 15.3 mmol; 0.5 M in THF) at 0 °C and the reaction mixture was warmed to rt and treated with ultrasonic vibration for 1.5 h. Vibration was ceased, and the reaction mixture was cooled to 0 °C and quenched with cold (~0 °C) NH<sub>4</sub>Cl (20 cm<sup>3</sup>; sat aq). The aqueous layer was extracted with Et<sub>2</sub>O (5 × 10 cm<sup>3</sup>) and the combined organic layers were washed with brine (20 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. Flash

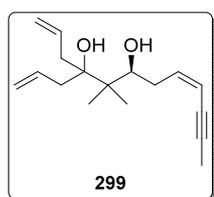
chromatography (Hexane:EtOAc, 3:1) of the residual brown oil thus obtained gave  $\beta$ -hydroxyketone **86** as a light-brown oil (222 mg, 66%).

**Method B** (*Grignard addition with Weinreb amide 194 using allylmagnesium bromide*): In duplicate, a solution of allyl bromide (19.4 cm<sup>3</sup>, 224 mmol) in Et<sub>2</sub>O (112 cm<sup>3</sup>) was added dropwise (~1 h) to a suspension of magnesium turnings (8.14 g, 336 mmol) spiked with I<sub>2</sub> (1 large crystal, ~15.0 mg, 0.06 mmol) in Et<sub>2</sub>O (112 cm<sup>3</sup>) and the suspension, which boiled spontaneously, was heated to reflux for 30 min, cooled to rt and stirred for 1 h to give a solution of allylmagnesium bromide (224 cm<sup>3</sup>, 224 mmol; 1.0 M in Et<sub>2</sub>O). Stirring was discontinued for ~10 min to allow excess magnesium to settle, then both solutions of allylmagnesium bromide (448 cm<sup>3</sup>, 448 mmol; 1.0 M in Et<sub>2</sub>O) were transferred *via* cannula (~20 min) to a solution of Weinreb amide **194** (6.70 g, 28.0 mmol) in Et<sub>2</sub>O (100 cm<sup>3</sup>) at -20 °C and the reaction mixture was stirred for 40 min, cooled to -78 °C and quenched by addition of NH<sub>4</sub>Cl (300 cm<sup>3</sup>; sat aq). The reaction mixture was warmed to rt, and the organic layer was separated and concentrated to a volume of ~100 cm<sup>3</sup> by rotary evaporation. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 100 cm<sup>3</sup>) and the combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>), brine (2 × 100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give an orange-yellow oil to which Et<sub>3</sub>N (78.1 cm<sup>3</sup>, 560 mmol) and DBU (21.8 cm<sup>3</sup>, 140 mmol) were added. The mixture was heated to 50 °C overnight (~18 h), cooled to rt and diluted with Et<sub>2</sub>O (300 cm<sup>3</sup>). The organic layer was washed with cold (~0 °C) HCl (3 × 50 cm<sup>3</sup>; 5.0 M aq) [CAUTION: exothermic], NaHCO<sub>3</sub> (50 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (50 cm<sup>3</sup>), brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the brown residue was purified by flash chromatography (Hexane:EtOAc, 6:1) to give a mixture of  $\beta$ -hydroxyketone **86** and diol **299** as a brown oil. A further two chromatographic purifications (Hexane:EtOAc, 4:1; then DCM:Et<sub>2</sub>O, 25:1) of material containing  $\beta$ -hydroxyketone **86** gave  $\beta$ -hydroxyketone **86** (1.34 g, 22%, >99:1 *E:Z*) and diol **299** (2.28 g, 31%) as yellow oils.

**Method C** (*silyl deprotection of TBS-ether 271*): HF (18.3 cm<sup>3</sup>, 510 mmol; 48% aq) was added to a solution of TBS-ether **271** (5.71 g, 17.0 mmol) in MeCN (40 cm<sup>3</sup>) at 0 °C and the solution was stirred for 15 min, warmed to rt, stirred for 30 min and

cooled back down to 0 °C. A suspension of NaHCO<sub>3</sub> (50.4 g, 600 mmol) in NaHCO<sub>3</sub> (300 cm<sup>3</sup>; sat aq) was added in small portions [CAUTION: vigorous gas evolution] and the mixture was warmed to rt and stirred for 30 min. The aqueous layer was extracted with DCM (4 × 100 cm<sup>3</sup>) and the combined organic layers were washed with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the resulting orange oil was purified by flash chromatography (Hexane:EtOAc, 6:1) to give β-hydroxyketone **86** as a light-yellow oil (3.18 g, 85%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.44; **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.25; **R<sub>f</sub>** (DCM:Et<sub>2</sub>O, 25:1) = 0.63; [**α**]<sub>D</sub> = -56.1 (*c* 1.05, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3487 (OH), 2218 (C≡C), 1682 (C=O), 1620 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 7.01 (1H, dq, *J* = 15.1, 6.9 Hz, CH<sub>3</sub>CH=CH), 6.56 (1H, dq, *J* = 15.1, 1.7 Hz, CH=CHCO), 6.01 (1H, dt, *J* = 10.6, 7.3 Hz, CH<sub>2</sub>CH=CH), 5.57 (1H, br dq, *J* = 10.6, 2.2 Hz, CHC≡CCH<sub>3</sub>), 3.84 (1H, dd, *J* = 10.2, 2.5 Hz, CHOH), 2.68 (1H, br s, OH), 2.53–2.48 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.39–2.33 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 1.99 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.93 (3H, dd, *J* = 6.9, 1.7 Hz, C=CHCH<sub>3</sub>), 1.23 (3H, s, CCH<sub>3</sub>), 1.20 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 204.5 (C), 143.9 (CH), 139.3 (CH), 126.4 (CH), 111.5 (CH), 90.6 (C), 76.3 (C), 76.1 (CH), 50.3 (C), 32.5 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>), 18.4 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH/DCM) 463 ([2M+Na]<sup>+</sup>, 7%), 243 ([M+Na]<sup>+</sup>, 100), 221 ([M+H]<sup>+</sup>, 7); **HRMS** (ESI+, MeOH/DCM) [M+Na]<sup>+</sup> found 243.1356, C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>Na requires 243.1356.

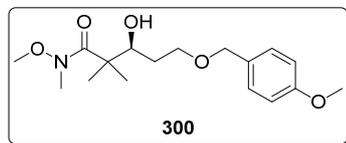
**(6*S*,8*Z*)-4-Allyl-5,5-dimethyl-dodeca-1,8-dien-10-yne-4,6-diol (299)**



**R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.30; **R<sub>f</sub>** (DCM:Et<sub>2</sub>O, 25:1) = 0.50; [**α**]<sub>D</sub> = -43.8 (*c* 1.05, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3352 (OH), 3074 (OH), 2222 (C≡C), 1638 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 6.04–5.93 (3H, m, 2CH<sub>2</sub>=CH and CH<sub>2</sub>CH=CHC≡C), 5.61 (1H, br dq, *J* = 10.6, 2.3 Hz, CHC≡CCH<sub>3</sub>), 5.18–5.11 (4H, m, 2CH<sub>2</sub>=CH), 4.06 (1H, dd, *J* = 9.9, 2.8 Hz, CHOH), 3.04 (2H, br s, 2OH), 2.59–2.41 (6H, m, 3CH<sub>2</sub>CH=CH<sub>n</sub>), 2.00 (3H, d, *J* = 2.3 Hz, C≡CCH<sub>3</sub>), 1.10 (3H, s, CCH<sub>3</sub>), 0.90 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 139.6 (CH), 135.3 (CH), 135.0 (CH), 118.3 (CH<sub>2</sub>), 118.1 (CH<sub>2</sub>), 111.9 (CH), 90.8 (C), 79.0 (C), 76.4 (C), 76.1 (CH), 44.2 (C), 40.7 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 32.9 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 16.2 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 547

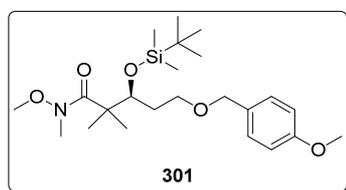
([2M+Na]<sup>+</sup>, 34%), 525 ([2M+H]<sup>+</sup>, 59), 285 ([M+Na]<sup>+</sup>, 17), 263 ([M+H]<sup>+</sup>, 100);  
**HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 263.2021, C<sub>17</sub>H<sub>27</sub>O<sub>2</sub> requires 263.2006.

**(S)-3-Hydroxy-5-(4-methoxy-benzyloxy)-2,2-dimethyl-pentanoic acid methoxy-methyl-amide (300)**



**General Procedure A** was followed with HNMe(OMe)•HCl (14.6 g, 150 mmol) in THF (188 cm<sup>3</sup>); <sup>n</sup>BuLi (188 cm<sup>3</sup>, 300 mmol; 1.6 M in hexanes); addition of THF (163 cm<sup>3</sup>) then ester **245** (7.11 g, 25.0 mmol) in THF (25 cm<sup>3</sup>); with reaction at -78 °C (1.5 h) then -78 °C to 0 °C (~1 h). Quenching with NH<sub>4</sub>Cl (500 cm<sup>3</sup>; 50% sat aq); workup with Et<sub>2</sub>O (5 × 100 cm<sup>3</sup>), H<sub>2</sub>O (100 cm<sup>3</sup>) and brine (100 cm<sup>3</sup>); and flash chromatography (EtOAc:Hexane, 3:2) gave Weinreb amide **300** as a light-yellow oil (6.11 g, 78%). **R<sub>f</sub>** (EtOAc:Hexane, 3:2) = 0.41; [**α**]<sub>D</sub> = +36.3 (*c* 0.11, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3472 (OH), 1612 (C=O), 1585 (C=O); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 7.30–7.27 (2H, m, 2ArH), 6.91–6.88 (2H, m, 2ArH), 4.48 (2H, s, OCH<sub>2</sub>Ar), 3.97 (1H, dd, *J* = 8.8, 3.6 Hz, CHOH), 3.83 (3H, s, ArOCH<sub>3</sub>), 3.73–3.68 (2H, m, CH<sub>2</sub>OCH<sub>2</sub>Ar), 3.71 (3H, s, NOCH<sub>3</sub>), 3.20 (3H, s, NCH<sub>3</sub>), 1.79–1.73 (2H, m, CH<sub>2</sub>CHOH), 1.29 (3H, s, CCH<sub>3</sub>), 1.27 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 178.5 (C), 159.2 (C), 130.5 (C), 129.3 (2CH), 113.8 (2CH), 75.4 (CH), 72.9 (CH<sub>2</sub>), 68.9 (CH<sub>2</sub>), 60.7 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 47.2 (C), 33.7 (CH<sub>3</sub>), 31.6 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>), 20.2 (CH<sub>3</sub>); ***m/z*** (EI) 325 ([M]<sup>+</sup>, 1%), 171 (16), 122 (19), 121 (100); **HRMS** (EI) [M]<sup>+</sup> found 325.1888, C<sub>17</sub>H<sub>27</sub>NO<sub>5</sub> requires 325.1888.

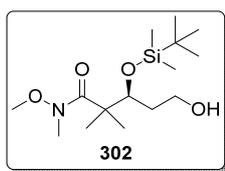
**(S)-3-(tert-Butyl-dimethyl-silyloxy)-5-(4-methoxy-benzyloxy)-2,2-dimethyl-pentanoic acid methoxy-methyl-amide (301)**



**General Procedure C** was followed with TBSOTf (5.67 cm<sup>3</sup>, 24.7 mmol), β-hydroxy-Weinreb amide **300** (5.95 g, 19.0 mmol) and 2,6-lutidine (4.41 cm<sup>3</sup>, 38.0 mmol) in DCM (40 cm<sup>3</sup>); with reaction for 2.5 h at -78 °C. Quenching with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq); workup with DCM (3 × 50 cm<sup>3</sup>), NaHCO<sub>3</sub> (50 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (50 cm<sup>3</sup>) and brine (50 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 2:1) gave TBS-ether **301** as a colourless oil that solidifies to a colourless wax on cooling (7.89 g, 94%). **R<sub>f</sub>** (Hexane:EtOAc, 2:1) =

0.63; **mp** 44–47 °C;  $[\alpha]_D = +12.6$  (*c* 0.63, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 1636 (C=O), 1612 (C=C); **<sup>1</sup>H NMR**  $\delta$  (400 MHz, CDCl<sub>3</sub>) 7.28–7.25 (2H, m, 2ArH), 6.91–6.87 (2H, m, 2ArH), 4.42 (2H, br d, *J* = 1.3 Hz, OCH<sub>2</sub>Ar), 4.37 (1H, dd, *J* = 7.9, 3.0 Hz, CHOSi), 3.83 (3H, s, ArOCH<sub>3</sub>), 3.65 (3H, s, NOCH<sub>3</sub>), 3.54–3.50 (2H, m, CH<sub>2</sub>OCH<sub>2</sub>Ar), 3.15 (3H, s, NCH<sub>3</sub>), 1.80–1.64 (2H, m, CH<sub>2</sub>CHOSi), 1.26 (3H, s, CHCCH<sub>3</sub>), 1.18 (3H, s, CHCCH<sub>3</sub>), 0.91 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.09 (3H, s, SiCH<sub>3</sub>), 0.07 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR**  $\delta$  (125 MHz, CDCl<sub>3</sub>) 177.7 (C), 159.1 (C), 130.8 (C), 129.2 (2CH), 113.7 (2CH), 72.4 (CH<sub>2</sub>), 71.7 (CH), 67.4 (CH<sub>2</sub>), 60.4 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 49.1 (C), 34.5 (CH<sub>2</sub>), 33.8 (CH<sub>3</sub>), 26.1 (3CH<sub>3</sub>), 22.8 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>), 18.4 (C), -3.8 (CH<sub>3</sub>), -3.9 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 901 ([2M+Na]<sup>+</sup>, 100%), 462 ([M+Na]<sup>+</sup>, 52), 440 ([M+H]<sup>+</sup>, 83); **HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 439.2752, C<sub>17</sub>H<sub>27</sub>NO<sub>5</sub> requires 439.2748.

**(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-hydroxy-2,2-dimethyl-pentanoic acid methoxy-methyl-amide (302)**



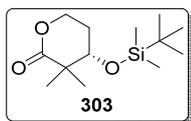
**Attempted Synthesis of 302**

**Method A:** DDQ (5.79 g, 25.5 mmol) was added to a solution of PMB-ether **301** (7.47 g, 17.0 mmol) in DCM (72 cm<sup>3</sup>) and H<sub>2</sub>O (4 cm<sup>3</sup>) and the mixture, which turned immediately green-black was stirred for 1 h, by which time an orange-brown mixture had developed. The reaction was quenched with NaHCO<sub>3</sub> (200 cm<sup>3</sup>; sat aq) [CAUTION: potential for HCN gas evolution, careful, controlled extrusion is required]. The orange mixture was diluted with H<sub>2</sub>O (200 cm<sup>3</sup>) and the aqueous layer was extracted with DCM (5 × 100 cm<sup>3</sup>). The combined organic layers were washed with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give a brown oil which was dissolved in EtOH (40 cm<sup>3</sup>). NaHSO<sub>3</sub> (4 cm<sup>3</sup>; 5.1 M aq) was added, and the mixture was stirred for 1 h, filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et<sub>2</sub>O (100 cm<sup>3</sup>) and washed with Na<sub>2</sub>HSO<sub>3</sub> (20 cm<sup>3</sup>, 0.25 M aq), H<sub>2</sub>O (20 cm<sup>3</sup>), brine (20 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (Hexane:Et<sub>2</sub>O, 3:2).

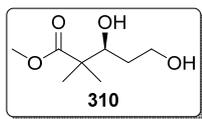
However, alcohol **302** was not observed; instead lactone **303** was obtained as a yellow crystalline solid (3.76 g, 86%).

**Method B:** CAN (275 mg, 0.50 mmol) was added to a solution of PMB-ether **301** (109 mg, 0.25 mmol) in MeCN (4.5 cm<sup>3</sup>) and H<sub>2</sub>O (0.5 cm<sup>3</sup>). The orange solution was stirred for 1 h, by which time the initially bright-orange colour had faded to pale-yellow. NaHCO<sub>3</sub> (20 cm<sup>3</sup>; sat aq) was added to quench the reaction, and the aqueous layer was extracted with DCM (3 × 20 cm<sup>3</sup>). The combined organic layers were washed with brine (10 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (10 cm<sup>3</sup>), NaHSO<sub>3</sub> (1.00 cm<sup>3</sup>; 0.4 M aq) was added and the solution was stirred overnight (~18 h) at rt and filtered, rinsing with EtOH (3 × 10 cm<sup>3</sup>). The solvent was removed under reduced pressure, the residue was dissolved in EtOAc (20 cm<sup>3</sup>) and the organic layer was washed with NaHSO<sub>3</sub> (10 cm<sup>3</sup>; 0.4 M aq), H<sub>2</sub>O (10 cm<sup>3</sup>), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave a yellow oil. <sup>1</sup>H NMR of the crude material indicated *ca.* quantitative conversion to lactone **303**.

**Method C:** H<sub>2</sub> was bubbled through a suspension of PMB-ether **301** (87.9 mg, 0.20 mmol) and 10% Pd/C (53.9 mg, 0.05 mmol, 25 mol% Pd) in MeOH (10 cm<sup>3</sup>) over a period of 30 min, and the reaction mixture was stirred for 24 h under an atmosphere of H<sub>2</sub>. The mixture was filtered through celite, the filter cake was rinsed with MeOH (5 × 10 cm<sup>3</sup>) and the solvent was removed under reduced pressure. <sup>1</sup>H NMR of the crude material indicated *ca.* quantitative conversion to alcohol **302**. <sup>1</sup>H NMR δ (500 MHz, CDCl<sub>3</sub>) 4.36 (1H, t, *J* = 5.4 Hz, CHOSi), 3.81–3.80 (1H, m, OH), 3.72 (3H, s, OCH<sub>3</sub>), 3.71–3.63 (2H, m, CH<sub>2</sub>OH), 3.19 (3H, s, NCH<sub>3</sub>), 1.70 (2H, dt, *J* = 6.1, 5.4 Hz, CHCH<sub>2</sub>), 1.26 (3H, s, CCH<sub>3</sub>), 1.23 (3H, s, CCH<sub>3</sub>), 0.93 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.14 (3H, s, SiCH<sub>3</sub>), 0.10 (3H, s, SiCH<sub>3</sub>). However, purification by flash chromatography (DCM:MeOH, 50:1) gave lactone **303** (50.9 mg, 99%) as a green oil.

**(R)-4-(tert-Butyl-dimethyl-silyloxy)-3,3-dimethyl-tetrahydro-pyran-2-one (303)**

$R_f$  (Hexane:Et<sub>2</sub>O, 3:2) = 0.30;  $R_f$  (DCM:MeOH, 50:1) = 0.19; **mp** 59–61 °C;  $[\alpha]_D = +39.1$  (*c* 1.20, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 1724 (C=O), 1697 (C=O); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 4.59 (1H, ddd, *J* = 10.1, 9.9, 4.4 Hz, CH<sub>A</sub>H<sub>B</sub>O), 4.31 (1H, ddd, *J* = 10.4, 10.1, 5.5 Hz, CH<sub>A</sub>H<sub>B</sub>O), 3.81 (1H, dd, *J* = 6.1, 2.5 Hz, CHOSi), 2.22 (1H, dddd, *J* = 14.2, 9.9, 5.5, 2.5 Hz, CH<sub>X</sub>H<sub>Y</sub>CH<sub>2</sub>O), 1.84 (1H, ddt, *J* = 14.2, 6.1, 4.4 Hz, CH<sub>X</sub>H<sub>Y</sub>CH<sub>2</sub>O), 1.31 (3H, s, CCH<sub>3</sub>), 1.29 (3H, s, CCH<sub>3</sub>), 0.93 (9H, s, 3SiC(CH<sub>3</sub>)<sub>3</sub>), 0.12 (3H, s, SiCH<sub>3</sub>), 0.10 (3H, s, SiCH<sub>3</sub>); **<sup>13</sup>C NMR**  $\delta$  (125 MHz, CDCl<sub>3</sub>) 176.9 (C), 73.0 (CH), 65.4 (CH<sub>2</sub>), 45.0 (C), 28.0 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 25.7 (3CH<sub>3</sub>), 22.5 (CH<sub>3</sub>), 18.0 (C), -4.5 (CH<sub>3</sub>), -5.0 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 517 ([2M+H]<sup>+</sup>, 9%), 347 ([4M+3H]<sup>+</sup>, 43), 315 ([6M+5H]<sup>+</sup>, 100), 259 ([M+H]<sup>+</sup>, 94); **HRMS** (CI) [M+H]<sup>+</sup> found 259.1725, C<sub>13</sub>H<sub>27</sub>O<sub>3</sub>Si requires 259.1724.

**(S)-3,5-Dihydroxy-2,2-dimethyl-pentanoic acid methyl ester (310)**

H<sub>2</sub> was bubbled through a suspension of PMB-ether **245** (812 mg, 2.85 mmol) and 10% Pd/C (759 mg, 0.71 mmol, 25 mol% Pd) in MeOH (20 cm<sup>3</sup>) over a period of 30 min and the reaction mixture was subsequently stirred for 24 h under an atmosphere of H<sub>2</sub>. The mixture was filtered, the residue was rinsed with EtOAc (5 × 10 cm<sup>3</sup>), and the solvent was removed under reduced pressure to give a colourless oil. Flash chromatography (EtOAc:Hexane, 3:1) afforded diol **310** as a turbid oil that solidifies to a colourless wax on cooling (400 mg, 80%).  $R_f$  (EtOAc:Hexane, 3:1) = 0.19; **mp** 39–42 °C;  $[\alpha]_D = -1.30$  (*c* 1.50, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3428 (OH), 3300 (OH), 1728 (C=O), 1661 (C=O); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 3.94 (1H, ddd, *J* = 9.8, 5.2, 3.3 Hz, CHOH), 3.90–3.88 (2H, m, CH<sub>2</sub>OH), 3.74 (3H, s, OCH<sub>3</sub>), 3.27 (1H, br d, *J* = 5.2 Hz, CHOH), 2.58 (1H, br s, CH<sub>2</sub>OH), 1.72–1.61 (2H, m, CHCH<sub>2</sub>), 1.23 (3H, s, CCH<sub>3</sub>), 1.22 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR**  $\delta$  (125 MHz, CDCl<sub>3</sub>) 178.2 (C), 76.7 (CH), 62.1 (CH<sub>2</sub>), 52.1 (CH<sub>3</sub>), 46.9 (C), 32.9 (CH<sub>2</sub>), 22.3 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>); ***m/z*** (EI) 177 ([M+H]<sup>+</sup>, 2%), 131 (22), 102 (100); **HRMS** (EI) [M+H]<sup>+</sup> found 177.1120, C<sub>8</sub>H<sub>17</sub>O<sub>4</sub> requires 177.1121.

## 7.5 Experimental from Chapter 5

### General Procedure D: *N*-Boc Protection of *N*-Heterocycles

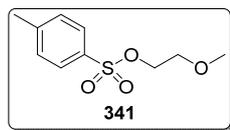
To a solution of the *N*-heterocycle (1.0 eq), Et<sub>3</sub>N or DIPEA (2.2 eq) and DMAP (5 mol%) in DCM or THF was added a solution of Boc<sub>2</sub>O (1.0 to 1.2 eq) in the appropriate solvent (DCM or THF) and the solution was stirred for the specified time at rt. The solvent was removed under reduced pressure, and the residue thus obtained was either (i) partitioned between an organic solvent and H<sub>2</sub>O (with extraction of the aqueous layer and combination of the organic layers); or (ii) dissolved in EtOAc. In both cases, the (combined) organic layers were washed with the stated aqueous solutions, dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. Purification of the crude material by flash chromatography or recrystallisation gave the product *N*-Boc-heterocycle.

### General Procedure E: *N*-Alkylation of *N*-Heterocycles

The *N*-heterocycle (1.0 eq) and Cs<sub>2</sub>CO<sub>3</sub> (2.0 to 5.0 eq) in THF were heated to reflux for 1 h before the addition of tosylate ester **341** (1.0 eq) in THF. Heating was continued overnight (~18 h), the resulting suspension was cooled to rt, and the reaction was quenched with excess HCl (aq) [CAUTION: gases evolved]. The mixture was stirred at rt until a clear solution was obtained (~10 min) and in some cases, further diluted with an aqueous solvent. The aqueous layer was extracted with DCM, Et<sub>2</sub>O or EtOAc (volumes/iterations as indicated), and the combined organic layers were washed with appropriate volumes (25 to 50% v/v of the combined organic layers) of NaHCO<sub>3</sub> (sat aq), H<sub>2</sub>O and brine. Drying (MgSO<sub>4</sub>), removal of the solvent under reduced pressure and purification of the crude material by flash chromatography gave the product *N*-alkylated heterocycle.

### 7.5.1 Preparation of Model Heterocycles

#### Toluene-4-sulfonic acid 2-methoxy-ethyl ester (**341**)

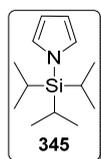


Tosylate ester **341** was prepared according to the procedure described by Howell *et al.*<sup>201</sup> To a solution of 2-methoxyethanol (7.61 g, 100 mmol) in pyridine (17.0 cm<sup>3</sup>, 211 mmol) was added

TsCl (19.1 g, 100 mmol) at 0 °C in small portions over 10 min [CAUTION: exothermic reaction]. The suspension was stirred vigorously for 4 h, warmed to rt, diluted with DCM (100 cm<sup>3</sup>) and poured into HCl (100 cm<sup>3</sup>; 5.0 M aq). The aqueous layer was extracted with DCM (2 × 50 cm<sup>3</sup>) and the combined organic layers were washed with HCl (2 × 50 cm<sup>3</sup>; 5.0 M aq), NaHCO<sub>3</sub> (2 × 100 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give tosylate ester **341** as a colourless oil (21.8 g, 92%), which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.27; **IR** (neat, cm<sup>-1</sup>) 1597 (C=C), 1495 (C=C), 1450 (C=C), 1402 (C=C), 1354 (S=O); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 7.85–7.82 (2H, m, 2ArH), 7.38–7.36 (2H, m, 2ArH), 4.20–4.18 (2H, m, SOCH<sub>2</sub>), 3.62–3.60 (2H, m, COCH<sub>2</sub>), 3.34 (3H, s, OCH<sub>3</sub>), 2.48 (3H, s, ArCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 144.8 (C), 133.0 (C), 129.8 (2CH), 128.0 (2CH), 69.9 (CH<sub>2</sub>), 69.1 (CH<sub>2</sub>), 59.0 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>); **m/z** (ESI+, MeOH) 483 ([2M+Na]<sup>+</sup>, 30%), 253 ([M+Na]<sup>+</sup>, 100). The spectroscopic data are in good agreement with the literature.<sup>201</sup>

### 7.5.1.1 Pyrroles

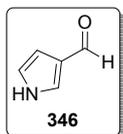
#### 1-Triisopropylsilyl-1H-pyrrole (345)



*N*-TIPS-pyrrole **345** was prepared according to the procedure described by Muchowski *et al.*<sup>176b</sup> To a solution of freshly distilled 1*H*-pyrrole (10.1 g, 150 mmol) in THF (100 cm<sup>3</sup>) at –78 °C was added <sup>n</sup>BuLi (103 cm<sup>3</sup>, 165 mmol; 1.6 M in hexanes) over 15 min and the pale-yellow mixture was stirred for 15 min in the absence of light. A solution of TIPSCl (28.9 g, 150 mmol) in THF (25 cm<sup>3</sup>) was then added and the mixture was stirred for 15 min, warmed to rt and stirred for a further 15 min before H<sub>2</sub>O (100 cm<sup>3</sup>) was added to quench the reaction. The mixture was poured into H<sub>2</sub>O (150 cm<sup>3</sup>) and Et<sub>2</sub>O (150 cm<sup>3</sup>), and the aqueous layer was extracted with Et<sub>2</sub>O (5 × 100 cm<sup>3</sup>). The combined organic layers were washed with H<sub>2</sub>O (250 cm<sup>3</sup>), brine (250 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave *N*-TIPS-pyrrole **345** as a brown oil (32.9 g, 98%), which was used without further purification. **R<sub>f</sub>** (Hexane) = 0.34; **IR** (neat, cm<sup>-1</sup>) 1460 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 6.83 (2H, t, *J* = 1.9 Hz, 2*NCH*),

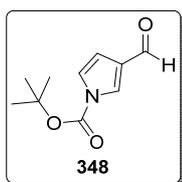
6.35 (2H, t,  $J = 1.9$  Hz, 2NCCH), 1.48 (3H, sept,  $J = 7.6$  Hz, 3SiCH), 1.13 (18H, d,  $J = 7.6$  Hz, 6CH<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  (125 MHz, CDCl<sub>3</sub>) 124.1 (2CH), 110.0 (2CH), 17.9 (6CH<sub>3</sub>), 11.7 (3CH);  $m/z$  (EI) 223 ([M]<sup>+</sup>, 63%), 181 (36), 180 (100), 152 (34), 124 (18), 110 (17). The spectroscopic data are in good agreement with the literature.<sup>176</sup>

### 1H-Pyrrole-3-carboxylic acid ethyl ester (346)



3-Formylpyrrole **346** was prepared according to the procedure described by Griengl *et al.*<sup>176a</sup> DMF (2.97 cm<sup>3</sup>, 38.4 mmol) in DCM (10 cm<sup>3</sup>) was added in portions over 10 min to a solution of (COCl)<sub>2</sub> (3.30 cm<sup>3</sup>, 39.0 mmol) in DCM (200 cm<sup>3</sup>) and the white suspension was stirred for 30 min at 0 °C. A solution of *N*-TIPS-pyrrole **345** (7.42 cm<sup>3</sup>, 30.0 mmol) in DCM (10 cm<sup>3</sup>) was added, and the mixture was heated to reflux for 30 min in the absence of light. The pale-yellow suspension was cooled to rt, the solvent was removed under reduced pressure and the residue was treated with NaOH (200 cm<sup>3</sup>, 250 mmol; 1.25 M aq). The solution was stirred overnight (~18 h), and the aqueous layer was extracted with DCM (5 × 50 cm<sup>3</sup>). The combined organic layers were washed with brine (100 cm<sup>3</sup>), dried (MgSO<sub>4</sub>), and the solvent was removed under reduced pressure. Flash chromatography (Hexane:EtOAc, 1:1) of the resulting orange-brown oil gave 3-formylpyrrole **346** as a brown solid (1.64 g, 58%).  $R_f$  (Hexane:EtOAc, 1:1) = 0.27; **mp** 60–62 °C, lit<sup>176b</sup> 68 °C; **IR** (neat, cm<sup>-1</sup>) 3252 (NH), 2853 (CHO), 1643 (C=O), 1632 (C=N), 1504 (C=C), 1433 (C=C), 1413 (C=C); <sup>1</sup>H NMR  $\delta$  (400 MHz, CDCl<sub>3</sub>) 9.87 (1H, s, CHO), 8.92–8.66 (1H, br m, NH), 7.49–7.47 (1H, m, NCHCCHO), 6.88–6.87 (1H, m, NCHCH), 6.75–6.73 (1H, m, NCHCH); <sup>13</sup>C NMR  $\delta$  (100 MHz, CDCl<sub>3</sub>) 185.8 (CH), 127.0 (C), 126.8 (CH), 120.4 (CH), 107.8 (CH);  $m/z$  (EI) 95 ([M]<sup>+</sup>, 100%), 94 (79), 92 (18), 66 (68). The spectroscopic data are in good agreement with the literature.<sup>176</sup>

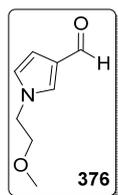
### Pyrrole-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-ethyl ester (348)



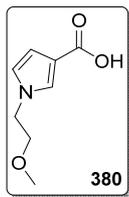
**General Procedure D** was employed with 3-formylpyrrole **346** (406 mg, 5.00 mmol), DIPEA (1.88 cm<sup>3</sup>, 11.0 mmol) and DMAP (30.9 mg, 0.25 mmol, 5 mol%) in DCM (5 cm<sup>3</sup>); and Boc<sub>2</sub>O (10.5 g, 40.1 mmol) in DCM (5 cm<sup>3</sup>). Reaction for 3 h; partitioning between

DCM (10 cm<sup>3</sup>) and H<sub>2</sub>O (20 cm<sup>3</sup>) with DCM (2 × 10 cm<sup>3</sup>) extraction; washing with HCl (3 × 10 cm<sup>3</sup>; 1.0 M aq), NaHCO<sub>3</sub> (10 cm<sup>3</sup>; sat aq) and brine (10 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 6:1) gave *N*-Boc-3-formylpyrrole **348** as a light-yellow oil that solidifies to a pale-yellow solid on cooling (717 mg, 73%). **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.34; **mp** 35–38 °C, lit<sup>179</sup> 35–36 °C; **IR** (neat, cm<sup>-1</sup>) 2980 (CHO), 1748 (C=O), 1717 (C=N), 1678 (C=O), 1549 (C=C), 1497 (C=C), 1416 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 9.87 (1H, s, CHO), 7.87 (1H, t, *J* = 1.7 Hz, NCHCCHO), 7.30–7.29 (1H, m, NCHCH), 6.68 (1H, dd, *J* = 3.3, 1.7 Hz, NCHCH), 1.66 (9H, s, 3CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 185.7 (CH), 147.9 (C), 128.9 (C), 128.3 (CH), 122.1 (CH), 109.3 (CH), 85.6 (C), 27.9 (3CH<sub>3</sub>); ***m/z*** (EI) 195 ([M]<sup>+</sup>, 34%), 140 (17), 136 (18), 122 (57), 95 (63), 94 (41), 66 (22), 57 (100). The spectroscopic data are in good agreement with the literature.<sup>179</sup>

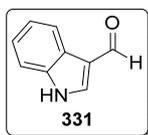
### 1-(2-Methoxy-ethyl)-1*H*-pyrrole-3-carbaldehyde (**376**)



In a modification of **General Procedure E**, 3-formylpyrrole **346** (190 mg, 2.00 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.30 g, 4.00 mmol), tosylate ester **341** (461 mg, 2.00 mmol), and **TBAI** (73.9 mg, 0.20 mmol, 10 mol%) in THF (10 cm<sup>3</sup>) were reacted for 2 d with no 1 h aging period prior to electrophile addition. HCl (10 cm<sup>3</sup>; 1.0 M aq) quenching and an Et<sub>2</sub>O (5 × 10 cm<sup>3</sup>) workup afforded *N*-alkylated 3-formylpyrrole **376** as a brown oil (290 mg, 95%), which was unstable to silica gel chromatography and was therefore used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.20; **IR** (neat, cm<sup>-1</sup>) 2984 (CHO), 1661 (C=O), 1531 (C=C), 1514 (C=C), 1440 (C=C), 1398 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 9.77 (1H, s, CHO), 7.38 (1H, t, *J* = 1.9 Hz, NCHCCHO), 6.75–6.73 (1H, m, NCHCH), 6.65 (1H, dd, *J* = 2.9, 1.6 Hz, NCHCH), 4.10 (2H, t, *J* = 5.3 Hz, OCH<sub>2</sub>), 3.69 (2H, t, *J* = 5.3 Hz, NCH<sub>2</sub>), 3.38 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 185.4 (CH), 129.5 (CH), 126.7 (C), 123.7 (CH), 108.3 (CH), 71.9 (CH<sub>2</sub>), 59.1 (CH<sub>3</sub>), 50.2 (CH<sub>2</sub>); ***m/z*** (EI) 153 ([M]<sup>+</sup>, 100%), 108 (33). **HRMS** (EI) [M]<sup>+</sup> found 153.0783, C<sub>8</sub>H<sub>11</sub>NO<sub>2</sub> requires 153.0784.

**1-(2-Methoxy-ethyl)-1H-pyrrole-3-carboxylic acid (380)**

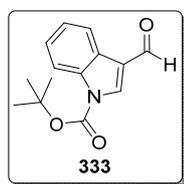
*N*-Alkylated pyrrole-3-carboxylic acid **380** was prepared according to the procedure described by Mai *et al.*<sup>204</sup> for the preparation of an analogous pyrrole-3-carboxylic acid. NaOH (4.13 cm<sup>3</sup>, 12.4 mmol; 3.0 M aq) and AgNO<sub>3</sub> (646 mg, 3.80 mmol) were added to a solution of *N*-alkylated 3-formylpyrrole **376** (290 mg, 1.90 mmol) in MeOH (5 cm<sup>3</sup>) and the black mixture was heated to reflux for 1 d. The reaction mixture was cooled to rt and filtered; and the residue was rinsed with MeOH (3 × 10 cm<sup>3</sup>) and H<sub>2</sub>O (3 × 10 cm<sup>3</sup>). The filtrate was concentrated under reduced pressure, washed with DCM (3 × 30 cm<sup>3</sup>) and acidified to pH 1 by addition of HCl (15.0 cm<sup>3</sup>; conc aq). The aqueous layer was extracted with Et<sub>2</sub>O (5 × 20 cm<sup>3</sup>), and the combined organic layers were washed with brine (50 cm<sup>3</sup>), dried (MgSO<sub>4</sub>), and the solvent was removed under reduced pressure to give *N*-alkylated pyrrole-3-carboxylic acid **380** (97.8 mg, 30%) as a gummy brown solid, which was used without further purification (~86% purity by <sup>1</sup>H NMR). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.20; **mp** 75–78 °C; **IR** (neat, cm<sup>-1</sup>) 2920 (OH), 1759 (C=N), 1705 (C=N), 1651 (C=O), 1614 (C=C), 1593 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 7.44 (1H, t, *J* = 1.9 Hz, NCHCO<sub>2</sub>H), 6.69 (1H, dd, *J* = 2.9, 2.6 Hz, NCHCH), 6.65 (1H, dd, *J* = 2.9, 1.7 Hz, NCHCH), 4.07 (2H, t, *J* = 5.3 Hz, OCH<sub>2</sub>), 3.68 (2H, t, *J* = 5.3 Hz, NCH<sub>2</sub>), 3.37 (3H, s, OCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 169.4 (C), 127.8 (CH), 122.4 (CH), 115.2 (C), 110.6 (CH), 71.8 (CH<sub>2</sub>), 59.2 (CH<sub>3</sub>), 49.9 (CH<sub>2</sub>); ***m/z*** (EI) 170 ([M+H]<sup>+</sup>, 10%), 169 ([M]<sup>+</sup>, 100), 139 (15), 124 (37); **HRMS** (EI) [M]<sup>+</sup> found 169.0727, C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub> requires 169.0733.

**7.5.1.2 Indoles****1H-Indole-3-carbaldehyde (331)**

3-Formylindole **331** was prepared according to a modification of the procedure described by James and Snyder.<sup>177</sup> Freshly distilled (COCl)<sub>2</sub> (5.08 cm<sup>3</sup>, 60.0 mmol) was added dropwise over 1 h to DMF (40 cm<sup>3</sup>, 515 mmol) [CAUTION: vigorous reaction, gases evolved] at 0 °C and the mixture was stirred for 15 min to form an orange-pink slurry. Indole (5.86 g, 50.0 mmol) in DMF (40 cm<sup>3</sup>) was added and the slurry, which turned pale-yellow immediately, was

stirred for 1 h at 0 °C, warmed to 40 °C and stirred for 1 h. The reaction mixture was removed from the heating source, and crushed ice (~100 g) was added, giving an opaque-yellow slurry. NaOH (200 cm<sup>3</sup>, 500 mmol; 2.5 M aq) was added cautiously, and the solution was heated to reflux for 20 min. The orange-red solution thus obtained was diluted with H<sub>2</sub>O (200 cm<sup>3</sup>) and cooled to 4 °C overnight (~18 h) after which time a suspension had formed. The precipitate was filtered, washed with H<sub>2</sub>O (5 × 50 cm<sup>3</sup>), and recrystallised (EtOH) to give 3-formylindole **331** as an orange solid (4.56 g, 63%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.33; **mp** 199–203 °C, lit<sup>177</sup> 196–197 °C; **IR** (neat, cm<sup>-1</sup>) 3144 (NH), 2818 (CHO), 1628 (C=O), 1612 (C=N), 1574 (C=C), 1520 (C=C), 1497 (C=C), 1437 (C=C), 1393 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, DMSO-*d*<sub>6</sub>) 12.13 (1H, br s, NH), 9.95 (1H, s, CHO), 8.29 (1H, s, NCH), 8.11–8.10 (1H, m, ArH), 7.53–7.51 (1H, m, ArH), 7.29–7.21 (2H, m, 2ArH); **<sup>13</sup>C NMR** δ (125 MHz, DMSO-*d*<sub>6</sub>) 185.4 (CH), 138.9 (CH), 137.5 (C), 124.6 (C), 123.9 (CH), 122.6 (CH), 121.3 (CH), 118.6 (C), 112.9 (CH); **m/z** (EI) 146 ([M+H]<sup>+</sup>, 10%), 145 ([M]<sup>+</sup>, 100), 144 (45). The spectroscopic data are in good agreement with the literature.<sup>242</sup>

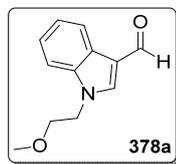
### 3-Formyl-indole-1-carboxylic acid *tert*-butyl ester (**333**)



**General Procedure D** was employed with 3-formylindole **331** (2.90 g, 20.0 mmol), Et<sub>3</sub>N (6.14 cm<sup>3</sup>, 44.0 mmol) and DMAP (122 mg, 1.00 mmol, 5 mol%) in THF (20 cm<sup>3</sup>); and Boc<sub>2</sub>O (5.24 g, 24.0 mmol) in THF (20 cm<sup>3</sup>). Reaction for 24 h; dissolution in EtOAc (200 cm<sup>3</sup>); washing with H<sub>2</sub>O (50 cm<sup>3</sup>), HCl (2 × 50 cm<sup>3</sup>; 0.5 M aq), NaHCO<sub>3</sub> (50 cm<sup>3</sup>; sat aq) and brine (50 cm<sup>3</sup>); and recrystallisation (EtOH) afforded *N*-Boc-3-formylindole **333** in the form of colourless needles (3.50 g, 71%). **R<sub>f</sub>** (Hexane:EtOAc, 5:1) = 0.47; **mp** 125–126 °C, lit<sup>243</sup> 124–126 °C; **IR** (neat, cm<sup>-1</sup>) 2814 (CHO), 1740 (C=O), 1676 (C=O), 1557 (C=C), 1450 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 10.13 (1H, s, CHO), 8.33–8.31 (1H, m, ArH), 8.18 (1H, br d, *J* = 8.2 Hz, ArH), 7.46–7.39 (2H, m, ArH), 1.74 (9H, s, 3CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 185.8 (CH), 148.8 (C), 136.5 (CH), 136.0 (C), 126.2 (C), 126.1 (CH), 124.6 (CH), 122.2 (CH), 121.6 (C), 115.2 (CH), 85.7 (C), 28.1 (3CH<sub>3</sub>); **m/z** (EI) 245 ([M]<sup>+</sup>,

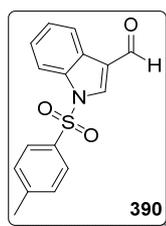
40%), 189 (55), 145 (58), 144 (31), 116 (16), 57 (100). The spectroscopic data are in good agreement with the literature.<sup>243</sup>

### 1-(2-Methoxy-ethyl)-1*H*-indole-3-carbaldehyde (**378a**)



**General Procedure E** was employed using 3-formylindole **331** (1.43 g, 9.86 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (6.52 g, 20.0 mmol) in THF (80 cm<sup>3</sup>); and tosylate ester **341** (2.30 g, 10.0 mmol) in THF (20 cm<sup>3</sup>). HCl (100 cm<sup>3</sup>; 1.0 M aq) quenching; EtOAc (1 × 100 cm<sup>3</sup>, 3 × 50 cm<sup>3</sup>) workup; and flash chromatography (Hexane:EtOAc, 1:1) gave *N*-alkylated 3-formylindole **378a** as a red oil (1.26 g, 63%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.27; **IR** (neat, cm<sup>-1</sup>) 2826 (CHO), 1654 (C=O), 1612 (C=N), 1578 (C=C), 1531 (C=C), 1485 (C=C), 1465 (C=C), 1447 (C=C), 1400 (C=C), 1386 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 10.04 (1H, s, CHO), 8.37–8.33 (1H, m, ArH), 7.84 (1H, s, CH<sub>2</sub>NCH), 7.42–7.33 (3H, m, 3ArH), 4.37 (2H, t, *J* = 5.2 Hz, OCH<sub>2</sub>), 3.78 (2H, t, *J* = 5.2 Hz, NCH<sub>2</sub>), 3.36 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 184.7 (CH), 139.4 (CH), 137.2 (C), 125.3 (C), 123.9 (CH), 122.9 (CH), 122.3 (CH), 118.3 (C), 109.8 (CH), 70.7 (CH<sub>2</sub>), 59.1 (CH<sub>3</sub>), 47.0 (CH<sub>2</sub>); ***m/z*** (EI) 204 ([M+H]<sup>+</sup>, 19%), 203 ([M]<sup>+</sup>, 100%), 158 (99), 130 (16); **HRMS** (EI) [M]<sup>+</sup> found 203.0941, C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub> requires 203.0941.

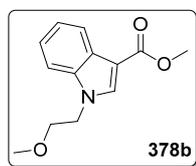
### 1-(Toluene-4-sulfonyl)-1*H*-indole-3-carbaldehyde (**390**)



*N*-Tosyl-3-formylindole **390** was prepared according to a modification of the procedure described by Plietker *et al.*<sup>211</sup> To a solution of 3-formylindole **331** (1.45 g, 10.0 mmol) and Et<sub>3</sub>N (4.18 cm<sup>3</sup>, 30.0 mmol) in DCM (40 cm<sup>3</sup>) was added TsCl (2.86 g, 15.0 mmol), and the orange mixture was stirred overnight (~18 h) at rt. The reaction mixture was poured into HCl (50 cm<sup>3</sup>; 1.0 M aq), which resulted in violet colouration of the organic layer. The aqueous layer was extracted with DCM (3 × 20 cm<sup>3</sup>), and the combined organic layers were washed with HCl (30 cm<sup>3</sup>; 1.0 M aq), NaHCO<sub>3</sub> (30 cm<sup>3</sup>; sat aq), H<sub>2</sub>O (30 cm<sup>3</sup>), brine (30 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure and recrystallisation (EtOAc/Hexane) of the orange residue thus obtained afforded *N*-tosyl-3-formylindole **390** as a pale-red solid (2.52 g, 84%). **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.20; **mp** 144–148 °C, lit<sup>211</sup>

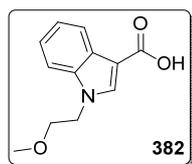
142 °C; **IR** (neat,  $\text{cm}^{-1}$ ) 1676 (C=O), 1593 (C=C), 1541 (C=C), 1479 (C=C), 1443 (C=C), 1377 (S=O);  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 10.12 (1H, s, CHO), 8.29–8.27 (1H, m, ArH), 8.25 (1H, s, ArH), 7.98–7.97 (1H, m, ArH), 7.89–7.87 (2H, m, 2ArH), 7.46–7.36 (2H, m, 2ArH), 7.33–7.32 (2H, m, 2ArH), 2.41 (3H, s,  $\text{CH}_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 185.3 (CH), 146.2 (C), 136.2 (CH), 135.3 (C), 134.4 (C), 130.3 (2CH), 127.3 (2CH), 126.3 (CH), 126.2 (C), 125.1 (CH), 122.6 (CH), 122.4 (C), 113.3 (CH), 21.7 ( $\text{CH}_3$ );  **$m/z$**  (EI) 299 ( $[\text{M}]^+$ , 80%), 155 (75), 116 (16), 91 (100). The spectroscopic data are in good agreement with the literature.<sup>211</sup>

### 1-(2-Methoxy-ethyl)-1*H*-indole-3-carboxylic acid methyl ester (**378b**)



**General Procedure E** was employed using indole-3-methyl ester (8.76 g, 50.0 mmol) and  $\text{Cs}_2\text{CO}_3$  (81.5 g, 250 mmol) in THF (250  $\text{cm}^3$ ); and tosylate ester **341** (11.5 g, 50.0 mmol) in THF (50  $\text{cm}^3$ ). HCl (250  $\text{cm}^3$ ; 5.0 M aq) quenching;  $\text{H}_2\text{O}$  (250  $\text{cm}^3$ ) dilution; workup with  $\text{Et}_2\text{O}$  ( $5 \times 100 \text{ cm}^3$ ); and flash chromatography (Hexane:EtOAc, 3:1) gave *N*-alkylated indole-3-methyl ester **378b** as an orange-pink syrup that solidifies to a light-pink wax on cooling (11.3 g, 97%).  **$R_f$**  (Hexane:EtOAc, 3:1) = 0.20; **mp** 38–40 °C; **IR** (neat,  $\text{cm}^{-1}$ ) 1684 (C=O), 1530 (C=N), 1487 (C=C), 1466 (C=C), 1437 (C=C), 1404 (C=C);  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 8.24–8.19 (1H, m, ArH), 7.92 (1H, s,  $\text{CH}_2\text{NCH}$ ), 7.42–7.38 (1H, m, ArH), 7.33–7.30 (2H, m, 2ArH), 4.34 (2H, t,  $J = 5.4 \text{ Hz}$ ,  $\text{OCH}_2$ ), 3.94 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.76 (2H, t,  $J = 5.4 \text{ Hz}$ ,  $\text{NCH}_2$ ), 3.34 (3H, s,  $\text{CH}_2\text{OCH}_3$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 165.5 (C), 136.6 (C), 135.0 (CH), 126.7 (C), 122.7 (CH), 121.9 (CH), 121.8 (CH), 109.8 (CH), 107.2 (C), 70.9 ( $\text{CH}_2$ ), 59.1 ( $\text{CH}_3$ ), 51.0 ( $\text{CH}_3$ ), 46.8 ( $\text{CH}_2$ );  **$m/z$**  (EI) 233 ( $[\text{M}]^+$ , 57%), 188 (100), 153 (21), 126 (22), 107 (21); **HRMS** (EI)  $[\text{M}]^+$  found 233.1046,  $\text{C}_{13}\text{H}_{15}\text{NO}_3$  requires 233.1046. The spectroscopic data are in good agreement with the literature.<sup>244</sup>

### 1-(2-Methoxy-ethyl)-1*H*-indole-3-carboxylic acid (**382**)

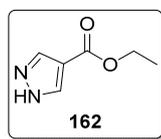


A solution of *N*-alkylated indole-3-methyl ester **378b** (4.67 g, 20.0 mmol) and KOH (5.61 g, 100 mmol) in EtOH (90  $\text{cm}^3$ ) and  $\text{H}_2\text{O}$  (10  $\text{cm}^3$ ) was heated to reflux overnight (~18 h). The light-yellow reaction mixture was cooled to rt, concentrated under reduced

pressure and the residue was dissolved in H<sub>2</sub>O (100 cm<sup>3</sup>). The aqueous layer was washed with DCM (3 × 20 cm<sup>3</sup>) and acidified to pH 1 by addition of HCl (10 cm<sup>3</sup>; conc aq). The aqueous layer was extracted with DCM (5 × 50 cm<sup>3</sup>), and the combined organic layers were washed with H<sub>2</sub>O (50 cm<sup>3</sup>), brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give *N*-alkylated indole-3-carboxylic acid **382** as a beige solid (4.39 g, quant), which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.27; **mp** 122–124 °C; **IR** (neat, cm<sup>-1</sup>) 2879 (OH), 1658 (C=O), 1614 (C=N), 1576 (C=C), 1526 (C=C), 1491 (C=C), 1468 (C=C), 1443 (C=C), 1402 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 8.28–8.25 (1H, m, *ArH*), 8.02 (1H, s, CH<sub>2</sub>NCH), 7.44–7.41 (1H, m, *ArH*), 7.35–7.32 (2H, m, 2*ArH*), 4.37 (2H, t, *J* = 5.4 Hz, OCH<sub>2</sub>), 3.78 (2H, t, *J* = 5.4 Hz, NCH<sub>2</sub>), 3.36 (3H, s, OCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 169.2 (C), 136.8 (C), 136.2 (CH), 126.9 (C), 122.9 (CH), 122.2 (CH), 121.9 (CH), 109.9 (CH), 106.4 (C), 70.8 (CH<sub>2</sub>), 59.1 (CH<sub>3</sub>), 46.9 (CH<sub>2</sub>); ***m/z*** (EI) 220 ([M+H]<sup>+</sup>, 6%), 219 ([M]<sup>+</sup>, 53), 174 (100). The spectroscopic data are in good agreement with the literature.<sup>245</sup>

### 7.5.1.3 Pyrazoles

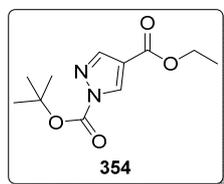
#### 1*H*-Pyrazole-4-carboxylic acid ethyl ester (**162**)



Pyrazole-4-ethyl ester **162** was prepared according to a modification of the procedure described by Allin *et al.*<sup>180</sup> To NaH (4.00 g, 100 mmol; 60% dispersion in mineral oil) in Et<sub>2</sub>O (80 cm<sup>3</sup>) at 0 °C was added ethyl formate (40.4 cm<sup>3</sup>, 500 mmol), followed by a solution of ethyl 3,3-diethoxypropionate (10.6 g, 50.0 mmol) in Et<sub>2</sub>O (20 cm<sup>3</sup>). The suspension was stirred for 1.5 h at 0 °C, warmed to rt and stirred for 24 h [CAUTION: H<sub>2</sub> gas evolved, safe gas extrusion required], after which time the reaction was quenched with H<sub>2</sub>O (200 cm<sup>3</sup>). The aqueous layer was washed with Et<sub>2</sub>O (3 × 50 cm<sup>3</sup>) and acidified to pH 1 by addition of HCl (10 cm<sup>3</sup>; conc aq). The aqueous layer was extracted with DCM (3 × 50 cm<sup>3</sup>), and the combined DCM layers were washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave crude bis-aldehyde **350** as an orange liquid (~7.20 g, assumed quant) which was dissolved in EtOH (20 cm<sup>3</sup>) and added to a suspension of hydrazine dihydrochloride

(6.30 g, 60.0 mmol) in EtOH (280 cm<sup>3</sup>) at 0 °C. The orange solution was stirred for 2 h, warmed to rt, stirred for 48 h and the solvent was removed under reduced pressure to give an orange residue. To this residue was added EtOAc (200 cm<sup>3</sup>) and NaHCO<sub>3</sub> (200 cm<sup>3</sup>; sat aq), and the biphasic mixture was stirred vigorously for 5 min [CAUTION: gases evolved]. The aqueous layer was extracted with EtOAc (3 × 50 cm<sup>3</sup>), and the combined organic layers were washed with NaHCO<sub>3</sub> (50 cm<sup>3</sup>; sat aq), brine (100 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. Purification of the red residue thus obtained by flash chromatography (Hexane:EtOAc, 3:1) gave pyrazole-4-ethyl ester **162** as a red oil that solidifies to an orange solid on cooling (6.09 g, 87% over 2 steps). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.10; **mp** 72–76 °C, lit<sup>246</sup> 69 °C; **IR** (neat, cm<sup>-1</sup>) 1721 (C=O), 1703 (C=N), 1525 (C=C), 1402 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 8.10 (2H, s, 2NCH), 4.34 (2H, q, *J* = 7.2 Hz, CH<sub>2</sub>), 1.37 (3H, t, *J* = 7.2 Hz, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 163.4 (C), 136.5 (2CH), 115.0 (C), 60.4 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>); ***m/z*** (EI) 140 ([M]<sup>+</sup>, 100%), 126 (10), 112 (58), 96 (25), 95 (78). The spectroscopic data are in good agreement with the literature.<sup>180,246</sup>

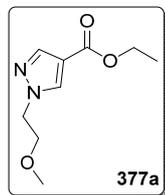
#### Pyrazole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (**354**)



**General Procedure D** was employed with pyrazole-4-ethyl ester **162** (1.40 g, 10.0 mmol), Et<sub>3</sub>N (3.07 cm<sup>3</sup>, 22.0 mmol) and DMAP (64.3 mg, 0.53 mmol, 5 mol%) in THF (10 cm<sup>3</sup>); and Boc<sub>2</sub>O (2.63 g, 12.0 mmol) in THF (10 cm<sup>3</sup>). Reaction for 4 h; partitioning between EtOAc (20 cm<sup>3</sup>) and H<sub>2</sub>O (20 cm<sup>3</sup>) with EtOAc (4 × 10 cm<sup>3</sup>) extraction; washing with HCl (3 × 10 cm<sup>3</sup>; 1.0 M aq), NaHCO<sub>3</sub> (20 cm<sup>3</sup>; sat aq) and brine (20 cm<sup>3</sup>); and flash chromatography (Hexane:EtOAc, 3:1) afforded *N*-Boc-pyrazole-4-ethyl ester **354** as a yellow oil (2.20 g, 91%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.47; **IR** (neat, cm<sup>-1</sup>) 1782 (C=O), 1757 (C=O), 1721 (C=O), 1568 (C=N), 1396 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 8.58 (1H, s, CONCH), 8.08 (1H, s, CONNCH), 4.36 (2H, q, *J* = 7.2 Hz, CH<sub>2</sub>), 1.69 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.39 (3H, t, *J* = 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 162.1 (C), 146.8 (C), 143.9 (CH), 133.9 (CH), 117.7 (C), 86.8 (C), 60.8 (CH<sub>2</sub>), 27.9 (3CH<sub>3</sub>), 14.3 (CH<sub>3</sub>); ***m/z*** (EI) 240

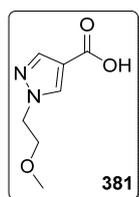
( $[M]^+$ , 5%), 181 (41), 95 (100). The spectroscopic data are in good agreement with the literature.<sup>182</sup>

### 1-(2-Methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**377a**)



**General Procedure E** was employed using pyrazole-4-ethyl ester **162** (2.80 g, 20.0 mmol) and  $\text{Cs}_2\text{CO}_3$  (13.0 g, 40.0 mmol) in THF (80  $\text{cm}^3$ ); and tosylate ester **341** (4.61 g, 20.0 mmol) in THF (40  $\text{cm}^3$ ). HCl (200  $\text{cm}^3$ ; 1.0 M aq) quenching; EtOAc (5  $\times$  50  $\text{cm}^3$ ) workup; and flash chromatography (Hexane:EtOAc, 1:1) gave *N*-alkylated pyrazole-4-ethyl ester **377a** as a colourless oil (3.81 g, 96%).  $R_f$  (Hexane:EtOAc, 1:1) = 0.40; **IR** (neat,  $\text{cm}^{-1}$ ) 1710 (C=O), 1554 (C=N), 1449 (C=C), 1462 (C=C), 1408 (C=C);  **$^1\text{H}$  NMR**  $\delta$  (400 MHz,  $\text{CDCl}_3$ ) 7.99 (1H, s,  $\text{CH}_2\text{NNCH}$ ), 7.94 (1H, s,  $\text{CH}_2\text{NCH}$ ), 4.32 (2H, q,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.32 (2H, dd,  $J = 5.2, 5.0$  Hz,  $\text{OCH}_2\text{CH}_2$ ), 3.77 (2H, dd, 5.2, 5.0 Hz,  $\text{NCH}_2\text{CH}_2$ ), 3.36 (3H, s,  $\text{OCH}_3$ ), 1.37 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR**  $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 163.1 (C), 141.1 (CH), 133.5 (CH), 115.2 (C), 70.7 ( $\text{CH}_2$ ), 60.1 ( $\text{CH}_3$ ), 59.0 ( $\text{CH}_2$ ), 52.6 ( $\text{CH}_2$ ), 14.4 ( $\text{CH}_3$ );  $m/z$  (EI) 198 ( $[M]^+$ , 9%), 168 (98), 153 (100), 140 (17), 125 (18), 112 (31); **HRMS** (EI)  $[M]^+$  found 198.0997,  $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_3$  requires 198.0999.

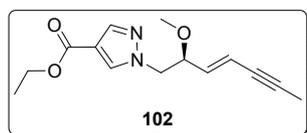
### 1-(2-Methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid (**381**)



A solution of *N*-alkylated pyrazole-4-ethyl ester **377a** (1.98 g, 10.0 mmol) and KOH (2.81 g, 50.0 mmol) in EtOH (45  $\text{cm}^3$ ) and  $\text{H}_2\text{O}$  (5  $\text{cm}^3$ ) was heated to reflux overnight (~18 h). The reaction mixture was cooled to rt, concentrated under reduced pressure and the residue was dissolved in  $\text{H}_2\text{O}$  (50  $\text{cm}^3$ ). The aqueous layer was washed with DCM (3  $\times$  10  $\text{cm}^3$ ) and acidified to pH 1 by the addition of HCl (6  $\text{cm}^3$ ; conc aq). The aqueous layer was extracted with DCM (5  $\times$  10  $\text{cm}^3$ ), and the combined organic layers were washed with  $\text{H}_2\text{O}$  (20  $\text{cm}^3$ ), brine (20  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ). Removal of the solvent under reduced pressure gave *N*-alkylated pyrazole-3-carboxylic acid **381** as a beige solid (457 mg, 27%). The combined aqueous layers were made basic (pH 14) by the addition of KOH (~7.5 g; pellets), washed with DCM (20  $\text{cm}^3$ ), and acidified to pH 1 by the addition of HCl (10  $\text{cm}^3$ ; conc aq). Extraction with EtOAc (5  $\times$  20

cm<sup>3</sup>), washing of the combined organic layers with brine (50 cm<sup>3</sup>), drying (MgSO<sub>4</sub>) and removal of the solvent under reduced pressure gave further *N*-alkylated pyrazole-4-carboxylic acid **381** as a beige solid (1.19 g, 70%; thus 1.65 g, 97% total yield). **R<sub>f</sub>** (EtOAc:Hexane, 2:1) = 0.19; **mp** 82–85 °C; **IR** (neat, cm<sup>-1</sup>) 2737 (OH), 1699 (C=O), 1557 (C=N); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 8.07 (1H, s, CH<sub>2</sub>NCH), 8.01 (1H, s, CH<sub>2</sub>NNCH), 4.36 (2H, dd, *J* = 5.0, 4.9 Hz, OCH<sub>2</sub>), 3.78 (2H, dd, *J* = 5.0, 4.9 Hz, NCH<sub>2</sub>), 3.36 (3H, s, OCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 168.0 (C), 141.7 (CH), 134.5 (CH), 114.2 (C), 70.5 (CH<sub>2</sub>), 59.0 (CH<sub>3</sub>), 52.7 (CH<sub>2</sub>); ***m/z*** (EI) 171 ([M+H]<sup>+</sup>, 3%), 170 ([M]<sup>+</sup>, 6), 140 (100), 125 (23), 112 (29). The spectroscopic data are in good agreement with the literature.<sup>247</sup>

**(2*S*,3*E*)-1-(2-Methoxy-hept-3-en-5-ynyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**102**)**

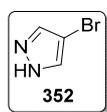


In a modification of **General Procedure E** which replaced tosylate ester **341** with C(5)–C(9) tosylate ester **95**,<sup>203a</sup> pyrazole-4-ethyl ester **162** (46.4 mg, 0.33 mmol), tosylate ester **95**, (97.4 mg, 0.33 mmol; 14:1 *E:Z*) and Cs<sub>2</sub>CO<sub>3</sub> (216 mg, 0.66 mmol) in THF (5 cm<sup>3</sup>) were reacted with no 1 h aging period prior to electrophile addition. HCl (10 cm<sup>3</sup>; 1.0 M aq) quenching; DCM (3 × 10 cm<sup>3</sup>) workup; and flash chromatography (Hexane:EtOAc, 3:1; dry loaded) gave the C(1)–C(9) fragment pyrazole-4-ethyl ester analogue **102** as a light-yellow syrup (58.3 mg, 67%, 14:1 *E:Z*). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.34; **[α]<sub>D</sub>** = +26.0 (*c* 0.50, CHCl<sub>3</sub>), lit<sup>16</sup> = +28.2 (*c* 0.43, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2224 (C≡C), 1713 (C=O), 1633 (C=N), 1553 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 7.93 (1H, s, ArCH), 7.90 (1H, s, ArCH), 5.82 (1H, dd, *J* = 15.9, 7.2 Hz, HC=CHC≡CCH<sub>3</sub>), 5.72 (1H, dqd, *J* = 15.9, 2.2, 0.8 Hz, HC=CHC≡CCH<sub>3</sub>), 4.29 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.19 (1H, dd, *J* = 13.9, 3.9 Hz, CH<sub>A</sub>H<sub>B</sub>CHOCH<sub>3</sub>), 4.09 (1H, dd, *J* = 13.9, 8.0 Hz, CH<sub>A</sub>H<sub>B</sub>CHOCH<sub>3</sub>), 4.02 (1H, ddd, *J* = 8.0, 7.2, 3.8 Hz, CHOCH<sub>3</sub>), 3.22 (3H, s, OCH<sub>3</sub>), 1.95 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.34 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 163.0 (C), 141.1 (CH), 137.2 (CH), 133.9 (CH), 115.1 (C), 115.0 (CH), 88.1 (C), 80.1 (CH), 76.9 (C), 60.1 (CH<sub>2</sub>), 56.9 (CH<sub>3</sub>), 56.5 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 4.2 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 547 ([2M+Na]<sup>+</sup>,

65%), 285 ( $[M+Na]^+$ , 100); **HRMS** (ESI+, MeOH)  $[M+Na]^+$  found 285.1211,  $C_{14}H_{18}N_2O_3Na$  requires 285.1210.

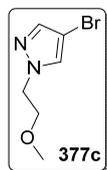
**(Z)-isomer diagnostic peaks:**  $^1H$  NMR  $\delta$  (500 MHz,  $CDCl_3$ ) 7.96 (1H, s, ArCH), 3.27 (3H, s,  $OCH_3$ ), 1.98 (3H, d,  $J = 2.4$  Hz,  $C\equiv CCH_3$ );  $^{13}C$  NMR  $\delta$  (125 MHz,  $CDCl_3$ ) 163.1 (C), 140.8 (CH), 137.3 (CH), 133.8 (CH), 115.3 (CH), 114.9 (C), 93.1 (CH), 75.0 (C), 60.0 ( $CH_2$ ), 56.7 ( $CH_3$ ), 55.9 ( $CH_2$ ), 4.4 ( $CH_3$ ). The spectroscopic data for both the (*E*)- and (*Z*)-stereoisomers of **102** are in good agreement with the literature.<sup>16</sup>

#### 4-Bromopyrazole (352)



4-Bromopyrazole **352** was prepared according to the procedure described by Moslin *et al.*<sup>183</sup> A suspension of 1*H*-pyrazole (6.81 g, 100 mmol) and NBS (17.9 g, 101 mmol) in  $H_2O$  ( $125\text{ cm}^3$ ) was stirred overnight (~18 h) at rt. The reaction mixture was extracted with EtOAc ( $3 \times 100\text{ cm}^3$ ), and the combined organic layers were washed  $Na_2S_2O_3$  ( $100\text{ cm}^3$ ; 50% sat aq),  $NaHCO_3$  ( $2 \times 100\text{ cm}^3$ ; sat aq),  $H_2O$  ( $100\text{ cm}^3$ ), brine ( $100\text{ cm}^3$ ) and dried ( $MgSO_4$ ). The solvent was removed under reduced pressure to give 4-bromopyrazole **352** as a colourless solid (13.3 g, 90%), which was used without further purification.  $R_f$  (Hexane:EtOAc, 1:1) = 0.40; **mp** 94–95 °C, lit<sup>248</sup> 89–91 °C; **IR** (neat,  $cm^{-1}$ ) 3136 (NH), 1714 (C=N), 1557 (C=C), 1533 (C=C), 1516 (C=C), 1496 (C=C);  $^1H$  NMR  $\delta$  (500 MHz,  $CDCl_3$ ) 7.63 (2H, s, 2CH);  $^{13}C$  NMR  $\delta$  (100 MHz,  $CDCl_3$ ) 134.5 (2CH), 93.9 (C); *m/z* (EI) 148 ( $[^{81}BrM]^+$ , 99%), 146 ( $[^{79}BrM]^+$ , 100), 121 (46), 119 (52). The spectroscopic data are in good agreement with the literature.<sup>248</sup>

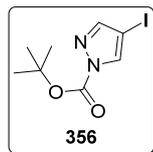
#### 4-Bromo-1-(2-methoxy-ethyl)-1*H*-pyrazole (377c)



**General Procedure E** was employed using 4-bromopyrazole **377c** (266 mg, 2.00 mmol) and  $Cs_2CO_3$  (1.30 g, 4.00 mmol) in THF ( $8\text{ cm}^3$ ); and tosylate ester **341** (461 mg, 2.00 mmol) in THF ( $1\text{ cm}^3$ ). HCl ( $20\text{ cm}^3$ ; 1.0 M aq) quenching; HCl ( $10\text{ cm}^3$ ; 1.0 M aq) dilution;  $Et_2O$  ( $1 \times 20\text{ cm}^3$ ,  $5 \times 10\text{ cm}^3$ ) workup; and flash chromatography (DCM:MeOH, 100:1) gave *N*-alkylated 4-bromopyrazole **377c** as a light-yellow oil (261 mg, 68%).  $R_f$  (DCM:MeOH, 100:1) = 0.42; **IR** (neat,  $cm^{-1}$ ) 1670 (C=N), 1442 (C=C), 1381 (C=C);  $^1H$  NMR  $\delta$  (500

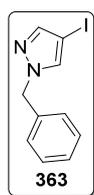
MHz, CDCl<sub>3</sub>) 7.53 (1H, s, CH<sub>2</sub>NNCH), 7.49 (1H, s, CH<sub>2</sub>NCH), 4.28 (2H, dd,  $J = 5.2, 5.0$  Hz, OCH<sub>2</sub>), 3.74 (2H, dd,  $J = 5.2, 5.0$  Hz, NCH<sub>2</sub>), 3.36 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR δ (125 MHz, CDCl<sub>3</sub>) 139.9 (CH), 130.2 (CH), 92.9 (C), 71.0 (CH<sub>2</sub>), 59.0 (CH<sub>3</sub>), 52.8 (CH<sub>2</sub>);  $m/z$  (EI) 206 ([<sup>81</sup>BrM]<sup>+</sup>, 54%), 204 ([<sup>79</sup>BrM]<sup>+</sup>, 55%), 176 (88), 174 (92), 161 (88), 159 (89), 148 (96), 146 (100); HRMS (EI) [M]<sup>+</sup> found 203.9893, C<sub>6</sub>H<sub>9</sub><sup>79</sup>BrN<sub>2</sub>O requires 203.9892.

#### 4-Iodo-pyrazole-1-carboxylic acid *tert*-butyl ester (356)



**General Procedure D** was employed with 4-iodopyrazole (7.76 g, 40.0 mmol), Et<sub>3</sub>N (12.3 cm<sup>3</sup>, 88.0 mmol) and DMAP (244 mg, 2.00 mmol, 5 mol%) in THF (40 cm<sup>3</sup>); and Boc<sub>2</sub>O (10.5 g, 40.1 mmol) in THF (40 cm<sup>3</sup>). Reaction for 18 h; dissolution in EtOAc (300 cm<sup>3</sup>); washing with HCl (3 × 100 cm<sup>3</sup>; 0.5 M aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (80 cm<sup>3</sup>; 50% sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>) and brine (100 cm<sup>3</sup>); and recrystallisation (EtOH/H<sub>2</sub>O) gave *N*-Boc-4-iodopyrazole **356** as a colourless to pale-yellow solid (10.8 g, 92%). **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.49; **mp** 62–64 °C; **IR** (neat, cm<sup>-1</sup>) 1758 (C=O); <sup>1</sup>H NMR δ (500 MHz, CDCl<sub>3</sub>) 8.17 (1H, s, CONCH), 7.72 (1H, s, CONNCH), 1.67 (9H, s, 3CH<sub>3</sub>); <sup>13</sup>C NMR δ (125 MHz, CDCl<sub>3</sub>) 148.5 (CH), 146.4 (C), 135.0 (CH), 86.3 (C), 61.3 (C), 27.9 (3CH);  $m/z$  (EI) 295 ([M]<sup>+</sup>, 27%), 194 (100). The spectroscopic data are in good agreement with the literature.<sup>249</sup>

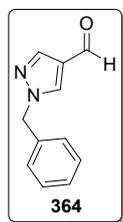
#### 1-Benzyl-4-iodo-1*H*-pyrazole (363)



*N*-Benzyl-4-iodopyrazole **363** was prepared according to the procedure described by Chaplin *et al.*<sup>194</sup> A suspension of 4-iodopyrazole (9.70 g, 50.0 mmol), freshly distilled BnBr (7.14 cm<sup>3</sup>, 60.0 mmol) and K<sub>2</sub>CO<sub>3</sub> (13.8 g, 100 mmol) in acetone (100 cm<sup>3</sup>) was heated to reflux for 3 h after which time the slurry was cooled to room temperature and concentrated under reduced pressure. H<sub>2</sub>O (300 cm<sup>3</sup>) was added to dissolve the residue and the aqueous layer was extracted with EtOAc (3 × 100 cm<sup>3</sup>). The combined organic layers were washed with NaHCO<sub>3</sub> (100 cm<sup>3</sup>; sat aq), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 cm<sup>3</sup>; 50% sat aq), H<sub>2</sub>O (100 cm<sup>3</sup>), brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give a yellow syrup that was purified by flash chromatography (Hexane:EtOAc, 6:1)

to afford *N*-benzyl-4-iodopyrazole **363** as a colourless solid (13.3 g, 94%).  $R_f$  (Hexane:EtOAc, 6:1) = 0.31; **mp** 64–65 °C, lit<sup>250</sup> 58–59 °C; **IR** (neat,  $\text{cm}^{-1}$ ) 1653 (C=N), 1506 (C=C), 1494 (C=C), 1452 (C=C), 1433 (C=C);  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 7.57 (1H, d,  $J = 0.3$  Hz,  $\text{CH}_2\text{NNCH}$ ), 7.42 (1H, d,  $J = 0.3$  Hz,  $\text{CH}_2\text{NCH}$ ), 7.41–7.34 (3H, m, 3ArH), 7.26–7.24 (2H, m, 2ArH), 5.33 (2H, s,  $\text{CH}_2$ );  **$^{13}\text{C NMR}$**   $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 144.6 (CH), 135.8 (C), 133.6 (CH), 129.0 (2CH), 128.4 (CH), 127.9 (2CH), 56.5 ( $\text{CH}_2$ ), 56.4 (C);  **$m/z$**  (EI) 285 ( $[\text{M}+\text{H}]^+$ , 45%), 284 ( $[\text{M}]^+$ , 100), 283 ( $[\text{M}-\text{H}]^+$ , 85), 91 (87). The spectroscopic data are in good agreement with the literature.<sup>250</sup>

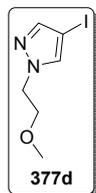
### 1-Benzyl-1*H*-pyrazole-4-carbaldehyde (**364**)



*N*-Benzyl-4-formylpyrazole **364** was prepared according to a modification of the procedure described by Vedsø *et al.*<sup>186a</sup> for the functionalisation of an analogous *N*-substituted 4-iodopyrazole.  $i\text{PrMgBr}$  (13.0  $\text{cm}^3$ , 39.0 mmol; 3.0 M in 2-MeTHF) was added dropwise (10 min) to a solution of *N*-benzyl-4-iodopyrazole **363** (8.52 g, 30.0 mmol) in THF (120  $\text{cm}^3$ ) at 0 °C, and the light-yellow solution was stirred for 1 h. A solution of DMF (11.6  $\text{cm}^3$ , 150 mmol) in THF (60  $\text{cm}^3$ ) was added over 5 min, and the bright-yellow mixture was warmed to rt and stirred for 1.75 h.  $\text{NH}_4\text{Cl}$  (100  $\text{cm}^3$ ; sat aq) was added to quench the reaction, and the mixture was diluted with  $\text{H}_2\text{O}$  (100  $\text{cm}^3$ ) to dissolve residual precipitates. The aqueous layer was extracted with DCM (4  $\times$  50  $\text{cm}^3$ ), and the combined organic layers were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  (100  $\text{cm}^3$ ; 50% sat aq),  $\text{H}_2\text{O}$  (2  $\times$  100  $\text{cm}^3$ ), brine (100  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure to give a yellow oil that was purified by flash chromatography (Hexane:EtOAc, 3:2) to afford *N*-benzyl-4-formylpyrazole **364** as a light-yellow oil that solidifies to form a pale-yellow to colourless solid on cooling (4.76 g, 85%).  $R_f$  (Hexane:EtOAc, 3:2) = 0.39; **mp** 45–47 °C; **IR** (neat,  $\text{cm}^{-1}$ ) 1667 (C=O), 1631 (C=N), 1541 (C=N), 1497 (C=C);  **$^1\text{H NMR}$**   $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 9.86 (1H, s, CHO), 8.03 (1H, s,  $\text{CH}_2\text{NCH}$ ), 7.90 (1H, s,  $\text{CH}_2\text{NNCH}$ ), 7.44–7.37 (3H, m, 3ArH), 7.31–7.29 (2H, m, 2ArH), 5.36 (2H, s,  $\text{CH}_2$ );  **$^{13}\text{C NMR}$**   $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 194.0 (CH), 141.0 (CH), 134.7 (C), 132.5 (CH), 129.2 (2CH), 128.9 (CH), 128.2 (2CH), 124.7 (C), 56.7 ( $\text{CH}_2$ );  **$m/z$**  (EI) 187 ( $[\text{M}+\text{H}]^+$ , 9%), 186 ( $[\text{M}]^+$ , 84), 185

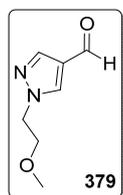
( $[M-H]^+$ , 100), 158 (35), 157 (52), 99 (99); **HRMS** (EI)  $[M]^+$  found 186.0782,  $C_{11}H_{10}N_2O$  requires 186.0788.

#### 4-Iodo-1-(2-methoxy-ethyl)-1H-pyrazole (377d)



In a modification of **General Procedure E**, 4-iodopyrazole (3.88 g, 20.0 mmol),  $Cs_2CO_3$  (13.0 g, 40.0 mmol) and tosylate ester **341** (4.61 g, 20.0 mmol) in DMF (100  $cm^3$ ) was reacted at 120 °C with no 1 h aging period prior to electrophile addition. Concentration of the solution under reduced pressure; HCl (200  $cm^3$ ; 1.0 M aq) quenching; DCM (4 × 50  $cm^3$ ) workup; and flash chromatography (Hexane:EtOAc, 2:1) gave *N*-alkylated 4-iodopyrazole **377d** as a malodorous colourless oil (4.05 g, 80%). **R<sub>f</sub>** (Hexane:EtOAc, 2:1) = 0.29; **IR** (neat,  $cm^{-1}$ ) 1732 (C=N); **<sup>1</sup>H NMR**  $\delta$  (500 MHz,  $CDCl_3$ ) 7.55 (1H, s,  $CH_2NNCH$ ), 7.53 (1H, s,  $CH_2NCH$ ), 4.31 (2H, dd,  $J = 5.2, 5.0$  Hz,  $OCH_2$ ), 3.73 (2H, dd,  $J = 5.2, 5.0$  Hz,  $NCH_2$ ), 3.36 (3H, s,  $CH_3$ ); **<sup>13</sup>C NMR**  $\delta$  (125 MHz,  $CDCl_3$ ) 144.4 (CH), 134.5 (CH), 71.0 ( $CH_2$ ), 59.0 ( $CH_3$ ), 55.9 (C), 52.6 ( $CH_2$ ); ***m/z*** (EI) 252 ( $[M]^+$ , 54%), 222 (66), 207 (40), 194 (100); **HRMS** (EI)  $[M]^+$  found 251.9758,  $C_6H_9IN_2O$  requires 251.9754.

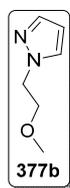
#### 1-(2-Methoxy-ethyl)-1H-pyrazole-4-carbaldehyde (379)



*N*-Alkylated 4-formylpyrazole **379** was prepared according to a modification of the procedure described by Vedsø *et al.*<sup>186a</sup> for the functionalisation of an analogous *N*-substituted 4-iodopyrazole. To a solution of *N*-alkylated 4-iodopyrazole **377d** (756 mg, 3.00 mmol) in THF (18  $cm^3$ ) was added  $i$ PrMgBr (1.30  $cm^3$ , 3.90 mmol; 3.0 M in 2-MeTHF) at 0 °C and the grey slurry was stirred for 1 h. DMF (1.16  $cm^3$ , 15.0 mmol) in THF (2  $cm^3$ ) was added, and the solution was warmed to rt and stirred for 2 h. The reaction was quenched by the addition of  $NH_4Cl$  (20  $cm^3$ ; sat aq), diluted with  $H_2O$  (10  $cm^3$ ), and the aqueous layer was extracted with DCM (4 × 20  $cm^3$ ). The combined organic layers were washed with  $Na_2S_2O_3$  (40  $cm^3$ ; 50% sat aq), brine (40  $cm^3$ ) and dried ( $MgSO_4$ ); and the solvent was removed under reduced pressure. Flash chromatography (EtOAc:Hexane, 3:1) of the crude yellow oil gave *N*-alkylated 4-formylpyrazole **379** as a colourless to light-yellow oil (330 mg, 71%). N.B.

Aldehyde **379** decomposes spontaneously in the presence of light and under standard laboratory storage conditions ( $-18\text{ }^{\circ}\text{C}$ , freezer) and should be used immediately.  $R_f$  (EtOAc:Hexane, 3:1) = 0.38; IR (neat,  $\text{cm}^{-1}$ ) 1710 (C=N), 1676 (C=O), 1543 (C=C);  $^1\text{H NMR } \delta$  (500 MHz,  $\text{CDCl}_3$ ) 9.89 (1H, s, CHO), 8.05 (1H, s,  $\text{CH}_2\text{NCH}$ ), 8.00 (1H, s,  $\text{CH}_2\text{NNCH}$ ), 4.36 (2H, dd,  $J = 5.1, 5.0$  Hz,  $\text{OCH}_2$ ), 3.78 (2H, dd,  $J = 5.1, 5.0$  Hz,  $\text{NCH}_2$ ), 3.37 (3H, s,  $\text{OCH}_3$ );  $^{13}\text{C NMR } \delta$  (125 MHz,  $\text{CDCl}_3$ ) 184.1 (CH), 140.7 (CH), 133.9 (CH), 124.4 (C), 70.4 ( $\text{CH}_2$ ), 59.0 ( $\text{CH}_3$ ), 52.8 ( $\text{CH}_2$ );  $m/z$  (EI) 154 ( $[\text{M}]^+$ , 6%), 124 (89), 95 (18), 58 (54), 49 (20), 45 (100). The spectroscopic data are in good agreement with the literature.<sup>251</sup>

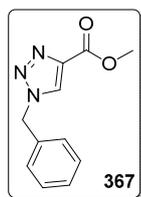
### 1-(2-Methoxy-ethyl)-1H-pyrazole (377b)



In a modification of **General Procedure E**, 1H-pyrazole (1.37 g, 20.0 mmol),  $\text{Cs}_2\text{CO}_3$  (32.5 g, 100 mmol) and tosylate ester **341** (4.61 g, 20.0 mmol) in DMF ( $100\text{ cm}^3$ ) was reacted at reflux with no 1 h aging period prior to electrophile addition. Concentration of the solution under reduced pressure; HCl ( $300\text{ cm}^3$ ; 1.0 M aq) quenching; DCM ( $5 \times 100\text{ cm}^3$ ) workup; and flash chromatography (Hexane:EtOAc, 1:1  $\rightarrow$  1:3) gave *N*-alkylated 1H-pyrazole **377b** as a volatile colourless oil (670 mg, 27%).  $R_f$  (Hexane:EtOAc, 1:1) = 0.37;  $^1\text{H NMR } \delta$  (500 MHz,  $\text{CDCl}_3$ ) 7.54 (1H, d,  $J = 1.5$  Hz,  $\text{CH}_2\text{NNCH}$ ), 7.49 (1H, d,  $J = 2.1$  Hz,  $\text{CH}_2\text{NCH}$ ), 6.27 (1H, t,  $J = 2.1$  Hz,  $\text{CH}_2\text{NCHCH}$ ), 4.33 (2H, t,  $J = 5.3$  Hz,  $\text{OCH}_2$ ), 3.77 (2H, t,  $J = 5.3$  Hz,  $\text{NCH}_2$ ), 3.35 (3H, s,  $\text{OCH}_3$ );  $^{13}\text{C NMR } \delta$  (125 MHz,  $\text{CDCl}_3$ ) 139.4 (CH), 130.0 (CH), 105.5 (CH), 71.3 ( $\text{CH}_2$ ), 59.0 ( $\text{CH}_3$ ), 52.0 ( $\text{CH}_2$ ). The spectroscopic data are in good agreement with the literature.<sup>251</sup>

## 7.5.1.4 Triazoles

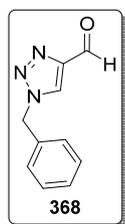
### 1-Benzyl-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (367)



Triazole-4-methyl ester **367** was prepared according to a modification of the procedure described by Schwink *et al.*<sup>197</sup> Sodium ascorbate (0.80 g, 4.00 mmol, 20 mol%) was added to a solution of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (0.50 g, 2.00 mmol, 10 mol%) in  $t\text{BuOH}/\text{H}_2\text{O}$  ( $100\text{ cm}^3$ , 3:1) and the solution was stirred for 5 min before addition of TBTA (1.32 g, 2.51 mmol, 13 mol%).

Stirring was continued for 15 min, and to the resulting orange-brown mixture was subsequently added, in succession, <sup>t</sup>BuOH/H<sub>2</sub>O (10 cm<sup>3</sup>, 3:1) solutions of BnN<sub>3</sub> (2.83 g, 20.0 mmol) and methyl propiolate (2.19 g, 26.0 mmol) and the mixture was stirred overnight (~18 h) [CAUTION: blast shield required] after which time a yellow solution had developed. The reaction mixture was diluted with DCM (100 cm<sup>3</sup>) and H<sub>2</sub>O (100 cm<sup>3</sup>) and the aqueous layer was extracted with DCM (3 × 50 cm<sup>3</sup>). The combined organic layers were washed with NH<sub>4</sub>Cl (50 cm<sup>3</sup>; sat aq), brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure, and purification of the yellow residue thus obtained by flash chromatography (Hexane:EtOAc, 1:1) afforded triazole-4-methyl ester **367** as a colourless solid (4.03 g, 93%). **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.40; **mp** 106–107 °C, lit<sup>252</sup> 115–117 °C; **IR** (neat, cm<sup>-1</sup>) 1722 (C=O), 1541 (C=C), 1454 (C=C), 1433 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 8.00 (1H, s, NCH), 7.46–7.41 (3H, m, 3ArH), 7.33–7.31 (2H, m, 2ArH), 5.61 (2H, s, CH<sub>2</sub>), 3.96 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 161.1 (C), 140.4 (C), 133.6 (C), 129.4 (2CH), 129.2 (CH), 128.4 (2CH), 127.4 (CH), 54.5 (CH<sub>2</sub>), 52.2 (CH<sub>3</sub>); **m/z** (EI) 217 ([M]<sup>+</sup>, 4%), 174 (26), 130 (24), 91 (100). The spectroscopic data are in good agreement with the literature.<sup>197,252</sup>

### 1-Benzyl-1H-[1,2,3]triazole-4-carbaldehyde (**368**)



4-Formyltriazole **368** was prepared according to the procedure described by Fray *et al.* for the semi-reduction of an analogous triazole-4-methyl ester.<sup>198</sup> DIBAL (33.0 cm<sup>3</sup>, 33.0 mmol; 1.0 M in hexanes) was added dropwise (20 min) to a solution of triazole-4-methyl ester **367** (2.17 g, 10.0 mmol) in DCM (15 cm<sup>3</sup>) at –78 °C. The mixture was stirred for 2.5 h before quenching of the reaction with MeOH (10 cm<sup>3</sup>) followed, after 5 min, by the addition of sodium potassium tartrate (40 cm<sup>3</sup>; sat aq). The reaction mixture was warmed to rt, diluted with DCM (20 cm<sup>3</sup>) and sodium potassium tartrate (20 cm<sup>3</sup>; sat aq), and stirred vigorously until the aqueous layer had become homogenous and a clean phase separation was visible (~1 h). The aqueous layer was extracted with DCM (4 × 20 cm<sup>3</sup>), and the combined organic layers were washed with brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (Hexane:EtOAc, 1:1) to give

4-formyltriazole **368** as a colourless solid (1.38 g, 73%).  $R_f$  (Hexane:EtOAc, 1:1) = 0.45; **mp** 90–92 °C, lit<sup>253a</sup> 89–90 °C; **IR** (neat,  $\text{cm}^{-1}$ ) 2855 (CHO), 1724 (C=N), 1692 (C=O), 1612 (C=C), 1585 (C=C), 1533 (C=C), 1514 (C=C); **<sup>1</sup>H NMR**  $\delta$  (400 MHz,  $\text{CDCl}_3$ ) 10.16 (1H, s, CHO), 8.01 (1H, s, NCH), 7.46–7.42 (3H, m, 3ArH), 7.35–7.32 (2H, m, 2ArH), 5.62 (2H, s,  $\text{CH}_2$ ); **<sup>13</sup>C NMR**  $\delta$  (100 MHz,  $\text{CDCl}_3$ ) 185.1 (CH), 148.1 (C), 133.3 (C), 129.5 (2CH), 129.4 (CH), 128.4 (2CH), 125.1 (CH), 54.6 ( $\text{CH}_2$ ); ***m/z*** (EI) 187 ( $[\text{M}]^+$ , 10%), 158 (37), 130 (22), 91 (100). The spectroscopic data are in good agreement with the literature.<sup>253b</sup>

## 7.5.2 Evans-Tishchenko Reactions

### Preparation of $\text{SmI}_2$

An oven- or flame-dried round bottomed flask was cooled under argon and charged with samarium (196 mg, 1.30 mmol),  $\text{I}_2$  (255 mg, 1.00 mmol) and THF (10  $\text{cm}^3$ ). The suspension was purged with argon (balloon; ~3–5 min) and treated with ultrasonic vibration in the absence of light, where the colour of the solution progressed from brown, to orange, to yellow, to green, to green-blue. After an induction time of, typically, 10 min to 1 h, the deep-blue solution of  $\text{SmI}_2$  (~0.1 M in THF) was obtained, which was allowed to stand for ~10 min and was used immediately thereafter.

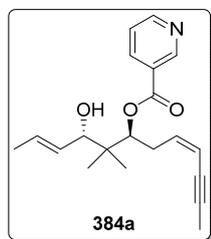
N.B. Solutions were reacted for 1 h to ensure complete  $\text{I}_2$  consumption. Smaller-scale reactions (5.00  $\text{cm}^3$ , 0.50 mmol) failed, while larger-scale preparation (up to 65.0  $\text{cm}^3$ , 6.50 mmol) was successful but may require a longer induction time.

### General Procedure F: The Evans–Tishchenko Reaction

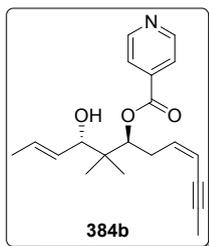
$\text{SmI}_2$  (2.50  $\text{cm}^3$ , 0.25 mmol; 0.1 M in THF) was added to a solution of  $\beta$ -hydroxyketone **86** (55.1 mg, 0.25 mmol) and the reactant aldehyde (6.0 eq) in THF (1  $\text{cm}^3$ ) at –20 °C, and the solution was stirred for the stated time, keeping the bath temperature below –10 °C. The reaction was quenched by the addition of sodium potassium tartrate (10  $\text{cm}^3$ ; sat aq), diluted with  $\text{H}_2\text{O}$  (10  $\text{cm}^3$ ), and the aqueous layer was extracted with DCM (3  $\times$  10  $\text{cm}^3$ ). The combined organic layers were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  (10  $\text{cm}^3$ ; sat aq),  $\text{NaHSO}_3$  (10  $\text{cm}^3$ ; 0.1 M aq), brine (10  $\text{cm}^3$ ) and dried

(MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the products of the reaction were isolated by flash chromatography.

**(2*E*,4*S*,6*S*,8*Z*)-5,5-dimethyl-6-[(3-pyridoyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (384a)**



Following **General Procedure F** with 3-pyridinecarboxaldehyde (0.14 cm<sup>3</sup>, 1.50 mmol), reaction for 4 h gave an orange-yellow residue after performing aqueous workup. Flash chromatography (Hexane:EtOAc, 3:2) gave 1,3-*anti* diol monoester **384a** (48.0 mg, 59%) as an orange-yellow syrup. **R<sub>f</sub>** (Hexane:EtOAc, 3:2) = 0.26; **[α]<sub>D</sub>** = +72.5 (*c* 0.51, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3374 (OH), 2220 (C≡C), 1720 (C=O), 1670 (C=C), 1591 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 9.27 (1H, br s, COCCHN), 8.82 (1H, br s, CHCHN), 8.33 (1H, dt, *J* = 7.9, 1.8 Hz, COCCHCH), 7.43 (1H, br dd, *J* = 7.9, 4.9 Hz, COCCHCH), 5.81 (1H, ddd, *J* = 10.6, 8.0, 6.8 Hz, C=CHCH<sub>2</sub>), 5.70 (1H, dqd, *J* = Hz, 15.2, 6.5, 0.6 Hz, CH<sub>3</sub>CH), 5.58 (1H, ddq, *J* = 15.2, 7.3, 1.4 Hz, CH<sub>3</sub>C=CH), 5.47 (1H, dqt, *J* = 10.6, 2.3, 1.1 Hz, CHC≡CCH<sub>3</sub>), 5.39 (1H, dd, *J* = 10.2, 2.8 Hz, CH<sub>2</sub>CHOCAr), 3.85 (1H, d, *J* = 7.3 Hz, CHOH), 2.87–2.80 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.68–2.63 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.47 (1H, br s, OH), 2.01 (3H, d, *J* = 2.3 Hz, C≡CCH<sub>3</sub>), 1.73 (3H, dd, *J* = 6.5, 1.4 Hz, C=CHCH<sub>3</sub>), 1.04 (3H, s, CCH<sub>3</sub>), 1.00 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 165.7 (C), 153.5 (CH), 151.1 (CH), 137.4 (2CH), 129.4 (CH), 129.3 (CH), 126.0 (C), 123.4 (CH), 112.5 (CH), 91.0 (C), 78.3 (CH), 76.2 (CH), 76.1 (C), 41.9 (C), 30.6 (CH<sub>2</sub>), 18.8 (CH<sub>3</sub>), 18.4 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 677 ([2M+Na]<sup>+</sup>, 17%), 350 ([M+Na]<sup>+</sup>, 100), 328 ([M+H]<sup>+</sup>, 9); **HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 328.1904, C<sub>20</sub>H<sub>26</sub>NO<sub>3</sub> requires 328.1907.

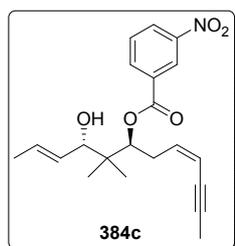
**(2E,4S,6S,8Z)-5,5-dimethyl-6-[(4-pyridoyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (384b)**

**Method A:** Following **General Procedure F** with 4-pyridinecarboxaldehyde (161 mg, 1.50 mmol), reaction for 1.5 h gave a brown residue after performing aqueous workup.\* Flash chromatography (PE 40–60:EtOAc, 1:1; dry loaded) gave 1,3-*anti* diol monoester **384b** (52.8 mg, 65%) as a colourless oil.\* Washing with NaHSO<sub>3</sub> was not performed on this run.

**Method B** (*Evans–Tishchenko reaction with an in situ-generated pre-catalyst*): SmI<sub>2</sub> (2.50 cm<sup>3</sup>, 0.25 mmol; 0.1 M in THF) was added to a solution of 4-pyridinecarboxaldehyde (26.8 mg, 0.25 mmol) in THF (1 cm<sup>3</sup>) and the resulting green-brown solution was stirred for 30 min at –10 °C. A second portion of 4-pyridinecarboxaldehyde (134 mg, 1.25 mmol) in THF (1 cm<sup>3</sup>) was added and the solution was stirred for 10 min before the addition of β-hydroxyketone **86** (55.1 mg, 0.25 mmol) in THF (1 cm<sup>3</sup>). After stirring for 1.5 h, the reaction was quenched with sodium potassium tartrate (10 cm<sup>3</sup>; sat aq) and the mixture was warmed to rt. The reaction mixture was diluted with H<sub>2</sub>O (10 cm<sup>3</sup>) and the aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with NaHSO<sub>3</sub> (10 cm<sup>3</sup>; sat aq), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (Hexane:EtOAc, 1:1) to give 1,3-*anti* diol monoester **384b** as an orange-yellow syrup (43.0 mg, 53%). **R<sub>f</sub>** (PE 40–60:EtOAc, 1:1) = 0.41; **R<sub>f</sub>** (Hexane:EtOAc, 1:1) = 0.51; [**α**]<sub>D</sub> = +60.0 (*c* 0.45, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3366 (OH), 2220 (C≡C), 1724 (C=O), 1560 (C=C), 1512 (C=C); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 8.81 (2H, br d, *J* = 5.8 Hz, 2CHN), 7.89 (2H, d, *J* = 5.8 Hz, 2NCHCH), 5.81 (1H, ddd, *J* = 10.6, 8.0, 6.9 Hz, C=CHCH<sub>2</sub>), 5.70 (1H, dqd, *J* = Hz, 15.3, 6.5, 0.6 Hz, CH<sub>3</sub>CH), 5.58 (1H, ddq, *J* = 15.3, 7.4, 1.4 Hz, CH<sub>3</sub>C=CH), 5.48 (1H, dqt, *J* = 10.6, 2.2, 1.1 Hz, CHC≡CCH<sub>3</sub>), 5.39 (1H, dd, *J* = 10.2, 2.8 Hz, CH<sub>2</sub>CHOCAr), 3.85 (1H, d, *J* = 7.4 Hz, CHOH), 2.86–2.79 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.69–2.64 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.34 (1H, br s, OH), 2.01 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.73 (3H, dd, *J* = 6.5, 1.4 Hz, C=CHCH<sub>3</sub>), 1.04 (3H, s, CCH<sub>3</sub>), 1.00 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 165.4 (C), 150.5 (2CH), 137.4 (C), 137.3 (CH), 129.5 (CH), 129.4 (CH), 123.1 (2CH), 112.6 (CH), 91.0 (C),

78.8 (CH), 76.3 (CH), 76.2 (C), 41.9 (C), 30.6 (CH<sub>2</sub>), 18.9 (CH<sub>3</sub>), 18.5 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); *m/z* (ESI+, MeOH) 677 ([2M+Na]<sup>+</sup>, 15%), 350 ([M+Na]<sup>+</sup>, 100), 328 ([M+H]<sup>+</sup>, 9); **HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 328.1924, C<sub>20</sub>H<sub>26</sub>NO<sub>3</sub> requires 328.1907.

**(2E,4S,6S,8Z)-5,5-dimethyl-6-[(3-nitrobenzoyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (384c)**

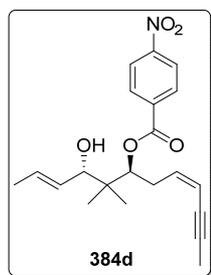


Following **General Procedure F** with 3-nitrobenzaldehyde (227 mg, 1.50 mmol), reaction for 4 h gave an orange-red oil after aqueous workup. Flash chromatography (DCM:Hexane, 20:1 → DCM) gave 1,3-*anti* diol monoester **384c** as a brown oil (92.0 mg, 99%).

**Large-scale preparation:** To a solution of  $\beta$ -hydroxyketone **86** (353 mg, 1.60 mmol) and 3-nitrobenzaldehyde (1.36 g, 9.00 mmol) in THF (2 cm<sup>3</sup>) at -20 °C was added freshly prepared SmI<sub>2</sub> (15.0 cm<sup>3</sup>, 1.50 mmol; 0.1 M in THF) and the solution was stirred for 4 h before quenching of the reaction with sodium potassium tartrate (20 cm<sup>3</sup>; sat aq). The aqueous layer was extracted with DCM (3 × 20 cm<sup>3</sup>) and the combined organic layers were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 cm<sup>3</sup>; 50% sat aq), brine (20 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the brown residue thus obtained was dissolved in EtOH (20 cm<sup>3</sup>), NaHSO<sub>3</sub> (4.00 cm<sup>3</sup>; 4.5 M aq) was added, and the mixture was stirred for 3 h. The precipitate was filtered, washed with Et<sub>2</sub>O (5 × 10 cm<sup>3</sup>) and the solvent was removed under reduced pressure from the filtrate. The resulting oil was dissolved in Et<sub>2</sub>O (50 cm<sup>3</sup>), and the organic layer was washed with H<sub>2</sub>O (10 cm<sup>3</sup>), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the yellow residual oil thus obtained was purified by flash chromatography (Hexane:EtOAc, 6:1) to give 1,3-*anti* diol monoester **384c** as a yellow syrup (558 mg, 94%). **R<sub>f</sub>** (Hexane:DCM, 20:1) = 0.27; **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.17; [ $\alpha$ ]<sub>D</sub> = +44.0 (*c* 0.50, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3528 (OH), 2218 (C≡C), 1721 (C=O), 1690 (C=O), 1616 (C=C), 1585 (C=C), 1531 (NO); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 8.90 (1H, t, *J* = 1.8 Hz, ArH), 8.46 (1H, ddd, *J* = 8.2, 2.2, 1.1 Hz, ArH), 8.41 (1H, ddd, *J* = 8.2, 1.3, 1.1 Hz, ArH), 7.69 (1H, t, *J* = 8.0 Hz, ArH), 5.81 (1H, ddd, *J* = 10.6, 8.9, 6.3 Hz, C=CHCH<sub>2</sub>), 5.70 (1H, dq,

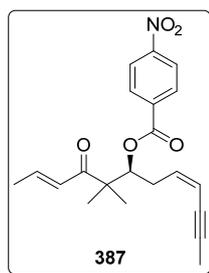
$J = 15.3, 6.3$  Hz,  $\text{CH}_3\text{CH}$ ), 5.60 (1H, ddq,  $J = 15.3, 7.3, 1.3$  Hz,  $\text{CH}_3\text{C}=\text{CH}$ ), 5.46 (1H, dqt,  $J = 10.6, 2.3, 1.2$  Hz,  $\text{CHC}\equiv\text{CCH}_3$ ), 5.42 (1H, dd,  $J = 10.6, 2.7$  Hz,  $\text{CH}_2\text{CHOCAr}$ ), 3.86 (1H, d,  $J = 7.3$  Hz,  $\text{CHOH}$ ), 2.93–2.87 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.66–2.61 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.34 (1H, br s,  $\text{OH}$ ), 2.04 (3H, d,  $J = 2.3$  Hz,  $\text{C}\equiv\text{CCH}_3$ ), 1.73 (3H, dd,  $J = 6.3, 1.3$  Hz,  $\text{C}=\text{CHCH}_3$ ), 1.05 (3H, s,  $\text{CCH}_3$ ), 1.02 (3H, s,  $\text{CCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 164.9 (C), 148.3 (C), 137.2 (CH), 135.6 (CH), 131.9 (C) 129.6 (CH), 129.5 (CH), 129.4 (CH), 127.5 (CH), 124.8 (CH), 112.8 (CH), 91.2 (C), 78.8 (CH), 76.3 (CH), 76.1 (C), 41.9 (C), 30.6 ( $\text{CH}_2$ ), 18.9 ( $\text{CH}_3$ ), 18.5 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 4.3 ( $\text{CH}_3$ );  $m/z$  (EI) 371 ( $[\text{M}]^+$ , 1%), 177 (14), 150 (100), 134 (26), 119 (86); HRMS (EI)  $[\text{M}]^+$  found 371.1738,  $\text{C}_{21}\text{H}_{25}\text{NO}_5$  requires 371.1727.

**(2E,4S,6S,8Z)-5,5-dimethyl-6-[(4-nitrobenzoyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (384d)**

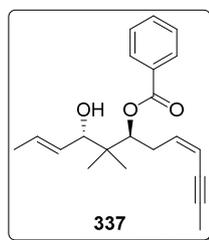


Following **General Procedure F** with 4-nitrobenzaldehyde (227 mg, 1.50 mmol), reaction for 4 h gave an orange residue after aqueous workup. Flash chromatography (DCM:Hexane, 2:1  $\rightarrow$  DCM:Hexane, 5:1) gave 1,3-*anti* diol monoester **384d** (59 mg, 64%) as an orange-yellow syrup and  $\beta$ -ketoester **387** as a light-yellow oil (10.9 mg, 12%).  $R_f$  (DCM:Hexane, 5:1) = 0.21;

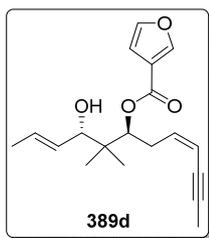
$[\alpha]_D = +96.0$  ( $c$  0.50,  $\text{CHCl}_3$ ); IR (neat,  $\text{cm}^{-1}$ ) 3537 (OH), 2216 ( $\text{C}\equiv\text{C}$ ), 1721 ( $\text{C}=\text{O}$ ), 1607 ( $\text{C}=\text{C}$ ), 1526 (NO);  $^1\text{H}$  NMR  $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 8.33–8.31 (2H, m, 2ArH), 8.26–8.23 (2H, m, 2ArH), 5.81 (1H, ddd,  $J = 10.6, 8.5, 6.5$  Hz,  $\text{C}=\text{CHCH}_2$ ), 5.70 (1H, dq,  $J = 15.3, 6.5$  Hz,  $\text{CH}_3\text{CH}$ ), 5.58 (1H, ddq,  $J = 15.3, 7.4, 1.4$  Hz,  $\text{CH}_3\text{C}=\text{CH}$ ), 5.47 (1H, br d,  $J = 10.6$  Hz,  $\text{CHC}\equiv\text{CCH}_3$ ), 5.40 (1H, dd,  $J = 10.6, 2.8$  Hz,  $\text{CH}_2\text{CHOCAr}$ ), 3.85 (1H, d,  $J = 7.4$  Hz,  $\text{CHOH}$ ), 2.89–2.82 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.68–2.64 (1H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.32 (1H, br s,  $\text{OH}$ ), 2.03 (3H, d,  $J = 2.2$  Hz,  $\text{C}\equiv\text{CCH}_3$ ), 1.73 (3H, dd,  $J = 6.5, 1.4$  Hz,  $\text{C}=\text{CHCH}_3$ ), 1.05 (3H, s,  $\text{CCH}_3$ ), 1.01 (3H, s,  $\text{CCH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 165.0 (C), 150.6 (C), 137.3 (CH), 135.5 (C), 131.0 (2CH), 129.5 (CH), 129.4 (CH), 123.5 (2CH), 112.6 (CH), 91.0 (C), 78.9 (CH), 76.3 (CH), 76.2 (C), 41.9 (C), 30.6 ( $\text{CH}_2$ ), 18.9 ( $\text{CH}_3$ ), 18.5 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 4.4 ( $\text{CH}_3$ );  $m/z$  (EI) 371 ( $[\text{M}]^+$ , 1%), 151 (18), 150 (99), 134 (76), 133 (36) 119 (100), 106 (27), 105 (26), 104 (37). HRMS (EI)  $[\text{M}]^+$  found 371.1738,  $\text{C}_{21}\text{H}_{25}\text{NO}_5$  requires 371.1727.

**(2E,6S,8Z)-5,5-dimethyl-6-[(4-nitrobenzoyl)oxy]-dodeca-2,8-dien-10-yn-4-one (387)**

**R<sub>f</sub>** (DCM:Hexane, 5:1) = 0.50; **[α]<sub>D</sub>** = -36.3 (*c* 0.11, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2230 (C≡C), 1726 (C=O), 1695 (C=O), 1626 (C=C), 1608 (C=C), 1530 (NO); **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 8.32–8.29 (2H, m, 2ArH), 8.21–8.18 (2H, m, 2ArH), 6.99 (1H, dq, *J* = 15.1, 6.9 Hz, CH<sub>3</sub>CH), 6.61 (1H, dq, *J* = 15.1, 1.7 Hz, CH<sub>3</sub>C=CH), (1H, td, *J* = 10.6, 10.4 Hz, C=CHCH<sub>2</sub>), 5.64 (1H, dd, *J* = 9.9, 3.2 Hz, CH<sub>2</sub>CHOCAr), 5.48–5.45 (1H, m, CHC≡CCH<sub>3</sub>), 2.80–2.73 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.59–2.54 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 1.99 (3H, d, *J* = 2.4 Hz, C≡CCH<sub>3</sub>), 1.92 (3H, dd, *J* = 6.9, 1.7 Hz, C=CHCH<sub>3</sub>), 1.32 (3H, s, CCH<sub>3</sub>), 1.30 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (125 MHz, CDCl<sub>3</sub>) 200.6 (C), 164.2 (C), 150.6 (C), 144.3 (CH), 136.5 (CH), 135.6 (C), 130.8 (2CH), 126.0 (CH), 123.5 (2CH), 112.8 (CH), 91.1 (C), 77.8 (CH), 76.0 (C), 50.3 (C), 31.4 (CH<sub>2</sub>), 21.0 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>), 18.4 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 392 ([M+Na]<sup>+</sup>, 15%), 370 ([M+H]<sup>+</sup>, 2), 288 (100); **HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 370.1643, C<sub>21</sub>H<sub>24</sub>NO<sub>5</sub> requires 370.1649.

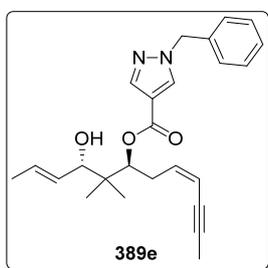
**Diagnostic data for other Evans–Tishchenko products:****(2E,4S,6S,8Z)-5,5-dimethyl-6-[(benzoyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (337)**

**Aldehyde substrate:** benzaldehyde. **<sup>1</sup>H NMR** δ (500 MHz, CDCl<sub>3</sub>) 8.09–8.07 (2H, m, 2ArH), 7.61–7.59 (1H, m, ArH), 7.51–7.45 (2H, m, 2ArH), 5.83 (1H, dt, *J* = 10.5, 7.2 Hz, C=CHCH<sub>2</sub>), 5.69 (1H, dq, *J* = 15.2, 6.4 Hz, CH<sub>3</sub>CH), 5.57 (1H, ddq, *J* = 15.2, 7.2, 1.4 Hz, CH<sub>3</sub>C=CH), 5.49–5.45 (1H, m, CHC≡CCH<sub>3</sub>), 5.35 (1H, dd, *J* = 10.0, 2.5 Hz, CH<sub>2</sub>CHOCAr), 3.85 (1H, d, *J* = 7.2 Hz, CHOH), 2.82–2.75 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.72–2.68 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.02 (3H, d, *J* = 2.3 Hz, C≡CCH<sub>3</sub>), 1.72 (3H, dd, *J* = 6.4, 1.4 Hz, C=CHCH<sub>3</sub>), 1.04 (3H, s, CCH<sub>3</sub>), 0.98 (3H, s, CCH<sub>3</sub>).

**(2E,4S,6S,8Z)-5,5-dimethyl-6-[(3-furoyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (389d)**

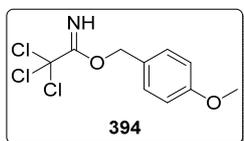
**Aldehyde substrate:** 3-furancarboxaldehyde. **Diagnostic peaks:**

**<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 8.06 (1H, ddd,  $J = 4.5, 1.4, 0.7$  Hz, ArH), 7.46 (1H, dt,  $J = 3.3, 1.7$  Hz, ArH), 6.78–6.77 (1H, m, ArH), 5.81 (1H, dt,  $J = 10.7, 7.3$  Hz, C=CHCH<sub>2</sub>), 5.52–5.47 (1H, m, CHC $\equiv$ CCH<sub>3</sub>), 3.40 (1H, dt,  $J = 7.1, 1.5$  Hz, CHOH), 2.79–2.70 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.66–2.59 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.03–2.01 (3H, m, C $\equiv$ CCH<sub>3</sub>), 1.74 (3H, dt,  $J = 7.3, 1.5$  Hz, C=CHCH<sub>3</sub>), 1.00 and 0.97 (3H, 2  $\times$  s, CCH<sub>3</sub>), 0.94 and 0.91 (3H, 2  $\times$  s, CCH<sub>3</sub>). [Product appears as a rotameric mixture].

**(2E,4S,6S,8Z)-5,5-dimethyl-6-[(1-benzyl-1H-pyrazol-3-oyl)oxy]-dodeca-2,8-dien-10-yn-4-ol (389e)**

**Aldehyde substrate:** *N*-benzyl-4-formylpyrazole **364**.

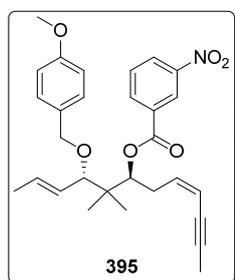
**Diagnostic peaks:** **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 7.96 (1H, s, CH<sub>2</sub>NCH), 7.90 (1H, s, CH<sub>2</sub>NNCH), 5.79 (1H, dt,  $J = 10.5, 7.3$  Hz, C=CHCH<sub>2</sub>), 5.68 (1H, dq,  $J = 15.3, 6.4$  Hz, CH<sub>3</sub>CH), 5.55 (1H, ddq,  $J = 15.3, 7.2, 1.5$  Hz, CH<sub>3</sub>C=CH), 5.49–5.45 (1H, m, CHC $\equiv$ CCH<sub>3</sub>), 5.33 (2H, s, CH<sub>2</sub>Ar), 5.22 (1H, dd,  $J = 10.3, 2.8$  Hz, CH<sub>2</sub>CHOCAr), 3.82 (1H, d,  $J = 7.2$  Hz, CHOH), 2.75–2.69 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 2.65–2.59 (1H, m, CH<sub>A</sub>H<sub>B</sub>), 1.99 (3H, d,  $J = 2.3$  Hz, C $\equiv$ CCH<sub>3</sub>), 1.73 (3H, dd,  $J = 6.4, 1.5$  Hz, C=CHCH<sub>3</sub>), 0.99 (3H, s, CCH<sub>3</sub>), 0.92 (3H, s, CCH<sub>3</sub>).

**7.5.3 Completion of the C(1)–C(9)/C(10')–C(19') Fragment (336)****2,2,2-Trichloro-acetimidic acid 4-methoxybenzyl ester (394)**

PMB-TCA **394** was prepared according to the procedure described by Joly and Jacobsen.<sup>213</sup> A solution of PMBOH (11.1 g, 80.0 mmol) in Et<sub>2</sub>O (50 cm<sup>3</sup>) was added over 20 min to a suspension of NaH (0.32 g, 8.00 mmol, 10 mol%; 60% dispersion in mineral oil which was pre-rinsed with hexane, 3  $\times$  2 cm<sup>3</sup>) in Et<sub>2</sub>O (10 cm<sup>3</sup>) and the solution was stirred at rt for 30 min before cooling to 0 °C. Trichloroacetonitrile (8.85 cm<sup>3</sup>, 88.0 mmol) was added over 10 min, and the deep-orange solution was stirred for 1 h at

0 °C, warmed to rt and stirred for a further 1 h. The solvent was removed under reduced pressure and a solution of MeOH (0.40 cm<sup>3</sup>, 10.0 mmol) in pentane (84 cm<sup>3</sup>) and was added to the dark-orange oil. After stirring for 30 min, the mixture was filtered through celite and the filter cake was rinsed with pentane (5 × 20 cm<sup>3</sup>). Dilution of the filtrate with Et<sub>2</sub>O (100 cm<sup>3</sup>), drying (MgSO<sub>4</sub>), and removal of the solvent under reduced pressure gave PMB-TCA **394** as a yellow oil (22.6 g, quant), which was used without further purification. **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.53; **IR** (neat, cm<sup>-1</sup>) 3337 (NH), 1663 (C=N), 1612 (C=C), 1585 (C=C), 1514 (C=C), 1464 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 8.40 (1H, br s, NH), 7.43–7.39 (2H, m, ArH), 6.96–6.93 (2H, m, ArH), 5.31 (2H, s, CH<sub>2</sub>), 3.85 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>) 162.6 (C), 159.7 (C), 129.8 (2CH), 127.5 (C), 113.9 (2CH), 91.5 (C), 70.7 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>); **m/z** (EI) 283 ([<sup>35</sup>Cl<sup>37</sup>Cl<sub>2</sub>M]<sup>+</sup>, 3%), 281 ([<sup>35</sup>Cl<sub>2</sub><sup>37</sup>ClM]<sup>+</sup>, 3%), 155 (19), 147 (26), 145 (26), 137 (60), 121 (100). The spectroscopic data are in good agreement with the literature.<sup>213</sup>

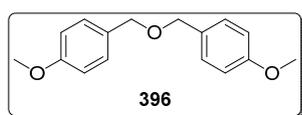
**(2E,4S,6S,8Z)-4-(4-Methoxy-benzyloxy)-5,5-dimethyl-6-[(3-nitrobenzoyl)oxy]-dodeca-2,8-dien-10-yne (395)**



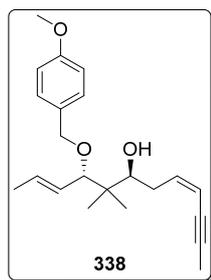
PMB-protected 1,3-*anti* diol monoester **395** was prepared according to a modification of the *O*-PMB-protection procedure described by Rai and Basu.<sup>214</sup> To a solution of 1,3-*anti* diol monoester **384c** (186 mg, 0.50 mmol) and PMB-TCA (424 mg, 1.50 mmol) in PhMe (25 cm<sup>3</sup>) was added Sc(OTf)<sub>3</sub> (24.6 mg, 0.05 mmol, 10 mol%) at 0 °C and the reaction mixture was warmed to rt and stirred for 1 h, after which time a yellowing of the solution had occurred. H<sub>2</sub>O (50 cm<sup>3</sup>) was added to quench the reaction, the aqueous layer was extracted with DCM (3 × 20 cm<sup>3</sup>), and the combined organic layers were washed with brine (20 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). Removal of the solvent under reduced pressure gave a yellow residue which was purified by flash chromatography (Hexane:EtOAc, 6:1) to give an inseparable mixture (~1.8:1) of PMB-protected 1,3-*anti* diol monoester **395** and PMB<sub>2</sub>O **396** (242 mg, 0.39 mmol **395**, 79% by <sup>1</sup>H NMR) as a yellow syrup, which was used as a 0.05 M solution in MeOH for subsequent reactions. N.B. Ratios of **395:396** after purification were variable

(minimum 1.8:1, maximum 6.7:1).  $R_f$  (Hexane:EtOAc, 6:1) = 0.40;  $[\alpha]_D = +82.0$  ( $c$  1.00,  $\text{CHCl}_3$ ); **IR** (neat,  $\text{cm}^{-1}$ ) 2216 ( $\text{C}\equiv\text{C}$ ), 1722 ( $\text{C}=\text{O}$ ), 1612 ( $\text{C}=\text{C}$ ), 1585 ( $\text{C}=\text{C}$ ), 1533 ( $\text{C}=\text{C}$ ), 1512 ( $\text{C}=\text{C}$ );  **$^1\text{H}$  NMR**  $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 8.79 (1H, ddd,  $J = 2.4, 1.5, 0.3$  Hz,  $\text{NO}_2\text{ArH}$ ), 8.39 (1H, ddd,  $J = 8.2, 2.4, 1.2$  Hz,  $\text{NO}_2\text{ArH}$ ), 8.29 (1H, ddd,  $J = 7.7, 1.5, 1.2$  Hz,  $\text{NO}_2\text{ArH}$ ), 7.56 (1H, ddd,  $J = 8.2, 7.7, 0.3$  Hz,  $\text{NO}_2\text{ArH}$ ), 7.22–7.19 (2H, m,  $2\text{CH}_3\text{OArH}$ ), 6.78–6.75 (2H, m,  $2\text{CH}_3\text{OArH}$ ), 5.84 (1H, ddd,  $J = 10.6, 8.4, 6.8$  Hz,  $\text{C}=\text{CHCH}_2$ ), 5.69 (1H, dq,  $J = 15.4, 6.5$  Hz,  $\text{CH}_3\text{CH}$ ), 5.51 (1H, ddq,  $J = 15.4, 8.7, 1.7$  Hz,  $\text{CH}_3\text{C}=\text{CH}$ ), 5.47 (1H, dd,  $J = 9.9, 3.2$  Hz,  $\text{CH}_2\text{CHOCO}$ ), 5.42 (1H, dqt,  $J = 10.6, 2.2, 1.2$  Hz,  $\text{CHC}\equiv\text{CCH}_3$ ), 4.38 (1H, d,  $J = 11.0$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$ ), 4.07 (1H, d,  $J = 11.0$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$ ), 3.78 (3H, s,  $\text{OCH}_3$ ), 3.52 (1H, d,  $J = 8.7$  Hz,  $\text{CHOCH}_2\text{Ar}$ ), 2.84–2.77 (1H, m,  $\text{NO}_2\text{ArCOCHCH}_\text{C}\text{H}_\text{D}$ ), 2.66–2.61 (1H, m,  $\text{NO}_2\text{ArCOCHCH}_\text{C}\text{H}_\text{D}$ ), 1.98 (3H, d,  $J = 2.2$  Hz,  $\text{C}\equiv\text{CCH}_3$ ), 1.80 (3H, dd,  $J = 6.5, 1.7$  Hz,  $\text{C}=\text{CHCH}_3$ ), 1.07 (3H, s,  $\text{CCH}_3$ ), 1.04 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR**  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 163.9 (C), 158.8 (C), 148.1 (C), 137.9 (CH), 135.4 (CH), 132.6 (C), 131.4 (CH), 130.7 (C), 129.6 (2CH), 129.3 (CH), 128.0 (CH), 127.0 (CH), 124.6 (CH), 113.4 (2CH), 112.0 (CH), 90.7 (C), 84.4 (CH), 77.8 (CH), 76.2 (C), 69.7 ( $\text{CH}_2$ ), 55.1 ( $\text{CH}_3$ ), 41.8 (C), 31.0 ( $\text{CH}_2$ ), 19.8 ( $\text{CH}_3$ ), 19.7 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 4.3 ( $\text{CH}_3$ );  **$m/z$**  (EI) 492 ( $[\text{M}+\text{H}]^+$ , 3%), 491 ( $[\text{M}]^+$ , 10%), 349 (16), 348 (75), 332 (47), 228 (55), 227 (63), 211 (39), 197 (50), 151 (100); **HRMS** (EI)  $[\text{M}]^+$  found 491.2306,  $\text{C}_{29}\text{H}_{33}\text{NO}_6$  requires 491.2302.

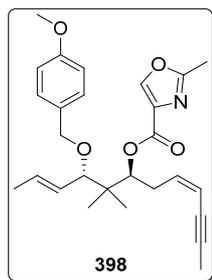
#### 4-Methoxy{[(4-methoxyphenyl)methoxy]methyl}benzene (396)



**PMB<sub>2</sub>O diagnostic data:**  $R_f$  (Hexane:EtOAc, 6:1) = 0.40;  **$^1\text{H}$  NMR**  $\delta$  (500 MHz,  $\text{CDCl}_3$ ) 7.32–7.30 (4H, m,  $4\text{ArH}$ ), 6.93–6.90 (4H, m,  $4\text{ArH}$ ), 4.49 (4H, s,  $2\text{CH}_2$ ), 3.84 (6H, s,  $2\text{OCH}_3$ );  **$^{13}\text{C}$  NMR**  $\delta$  (125 MHz,  $\text{CDCl}_3$ ) 159.2 (2C), 130.5 (2C), 129.4 (4CH), 113.8 (4CH), 71.5 ( $2\text{CH}_2$ ), 55.3 ( $2\text{CH}_3$ ).

**(2E,4S,6S,8Z)-4-(4-Methoxy-benzyloxy)-5,5-dimethyl-dodeca-2,8-dien-10-yn-6-ol (338)**

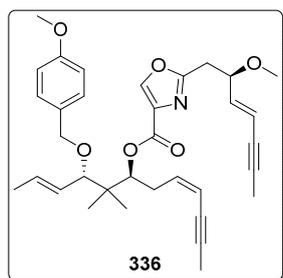
A solution of PMB-protected 1,3-*anti* diol monoester **395** (6.80 cm<sup>3</sup>, 0.39 mmol; 0.05 M in MeOH), LiOH (196 mg, 4.68 mmol) and H<sub>2</sub>O (0.68 cm<sup>3</sup>) was heated to reflux overnight (~18 h) and cooled to rt. The reaction mixture was concentrated under reduced pressure and partitioned between Et<sub>2</sub>O (20 cm<sup>3</sup>) and NaOH (20 cm<sup>3</sup>; 2.0 M aq), and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with NaOH (3 × 10 cm<sup>3</sup>; 3.0 M aq), H<sub>2</sub>O (10 cm<sup>3</sup>), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure to give yellow oil that was purified by flash chromatography (Hexane:EtOAc, 6:1) to give an inseparable mixture (~2:1) of alcohol **338** contaminated with PMB<sub>2</sub>O **396** as a light-yellow oil (167.8 mg, 0.35 mmol **338**, 91% by <sup>1</sup>H NMR), which was used as a 0.05 to 0.1 M solution in PhMe in subsequent reactions without further purification. N.B. Ratios of **338:396** obtained after purification were variable (minimum 2:1, maximum 7.4:1). **R<sub>f</sub>** (Hexane:EtOAc, 6:1) = 0.40; [ $\alpha$ ]<sub>D</sub> = -6.00 (*c* 0.50, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 3487 (OH), 2216 (C≡C), 1610 (C=C), 1665 (C=C), 1585 (C=C), 1510 (C=C), 1463 (C=C), 1441 (C=C); **<sup>1</sup>H NMR**  $\delta$  (500 MHz, CDCl<sub>3</sub>) 7.26–7.23 (2H, m 2ArH), 6.90–6.87 (2H, m, 2ArH), 6.07 (1H, dt, *J* = 10.7, 7.2 Hz, C=CHCH<sub>2</sub>), 5.71 (1H, dq, *J* = 15.4, 6.4 Hz, CH<sub>3</sub>CH), 5.54–4.49 (2H, m, CH<sub>3</sub>C=CH and CHC≡CCH<sub>3</sub>), 4.54 (1H, d, *J* = 11.2 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 4.22 (1H, d, *J* = 11.2 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 3.82 (3H, s, OCH<sub>3</sub>), 3.74 (1H, br s, OH), 3.68 (1H, d, *J* = 8.6 Hz, CHOCH<sub>2</sub>Ar), 3.61 (1H, dd, *J* = 10.1, 2.1 Hz, CHOH), 2.57–2.52 (1H, m, CH<sub>C</sub>H<sub>D</sub>CHOH), 2.31–2.25 (1H, m, CH<sub>C</sub>H<sub>D</sub>CHOH), 1.98 (3H, d, *J* = 2.3 Hz, C≡CCH<sub>3</sub>), 1.82 (3H, dd, *J* = 6.4, 1.6 Hz, C=CHCH<sub>3</sub>), 0.94 (3H, s, CCH<sub>3</sub>), 0.92 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR**  $\delta$  (125 MHz, CDCl<sub>3</sub>) 159.2 (C), 140.8 (CH), 131.5 (CH), 130.1 (C), 129.5 (2CH), 127.6 (CH), 113.8 (2CH), 110.2 (CH), 90.0 (C), 87.8 (CH), 77.3 (CH), 76.7 (C), 69.9 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>), 40.9 (C), 32.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 21.0 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 707 ([2M+Na]<sup>+</sup>, 100%), 685 ([2M+H]<sup>+</sup>, 7), 381 ([M+K]<sup>+</sup>, 14); **HRMS** (ESI+) [M+H]<sup>+</sup> found 343.2272, C<sub>22</sub>H<sub>31</sub>O<sub>3</sub> requires 343.2268.

**(2E,4S,6S,8Z)-4-(4-methoxy-benzyloxy)-5,5-dimethyl-6-[(2-methyloxazol-4-oyl)oxy]-dodeca-2,8-dien-10-yne (398)**

Oxazole ester **398** (and **336**, below) was prepared according to a modification of the procedure described by Hoffmann<sup>25</sup> for the Yamaguchi esterification<sup>22</sup> of an alcohol and an oxazolyl carboxylic acid. Two stock solutions, the first (Solution 1) containing 2-methyloxazole-4-carboxylic acid (6.50 mg, 0.05 mmol) in PhMe (1 cm<sup>3</sup>); and the second (Solution 2) containing 2,4,6-TCBC (48.6 mg, 0.20 mmol) and Et<sub>3</sub>N (0.03 cm<sup>3</sup>, 0.29 mmol) in PhMe (1.5 cm<sup>3</sup>), were prepared for the purpose of generating, portionwise, an activated ester. Solution 2 (0.3 cm<sup>3</sup>) was added to Solution 1 (0.2 cm<sup>3</sup>), and the mixture was stirred for 15 min at rt, before addition of the resulting activated ester solution (Solution 3) to a heated (40 °C) solution of alcohol **338** (1.00 cm<sup>3</sup>, 0.05 mmol; 0.05 M in PhMe) and DMAP (19.0 mg, 0.16 mmol); and stirring of the reaction mixture, which turned pale-yellow on addition, for 15 min. This procedure was repeated until all activated ester solutions were added to alcohol **338** (5 additions over 75 min) and stirring was continued for 2 h. The reaction mixture was cooled to rt, diluted with DCM (20 cm<sup>3</sup>), poured into NH<sub>4</sub>Cl (10 cm<sup>3</sup>; sat aq) and the aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with HCl (10 cm<sup>3</sup>; 1.0 M aq), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>); and the solvent was removed under reduced pressure. Flash chromatography (Hexane:EtOAc, 3:1) of the resulting yellow residue gave oxazole ester **398** as a turbid, colourless syrup (22.0 mg, 93%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.33; [**α**]<sub>D</sub> = +30.0 (c 0.50, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2218 (C≡C), 1737 (C=O), 1717 (C=N), 1668 (C=C), 1612 (C=C), 1589 (C=C), 1514 (C=C); **<sup>1</sup>H NMR** δ (400 MHz, CDCl<sub>3</sub>) 7.96 (1H, s, NC=CH), 7.28–7.25 (2H, m, 2ArH), 6.86–6.83 (2H, m, 2ArH), 5.85 (1H, dt, *J* = 10.8, 7.2 Hz, C=CHCH<sub>2</sub>), 5.67 (1H, dq, *J* = 15.1, 6.3 Hz, CH<sub>3</sub>CH), 5.48 (1H, ddq, *J* = 15.1, 8.6, 1.6 Hz, CH<sub>3</sub>C=CH), 5.45–5.41 (1H, m, CHC≡CCH<sub>3</sub>), 5.41 (1H, dd, *J* = 9.3, 3.9 Hz, CH<sub>2</sub>CHOCO), 4.39 (1H, d, *J* = 10.8 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 4.12 (1H, d, *J* = 10.8 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 3.81 (3H, s, OCH<sub>3</sub>), 3.51 (1H, d, *J* = 8.6 Hz, CHOCH<sub>2</sub>Ar), 2.73–2.59 (2H, m, OCHCH<sub>2</sub>), 2.52 (3H, s, ArCH<sub>3</sub>), 1.98 (3H, d, *J* = 2.2 Hz, C≡CCH<sub>3</sub>), 1.79 (3H, dd, *J* = 6.3, 1.6 Hz, C=CHCH<sub>3</sub>), 1.00 (3H, s, CCH<sub>3</sub>), 0.97 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (100 MHz, CDCl<sub>3</sub>)

162.2 (C), 160.7 (C), 158.9 (C), 143.3 (CH), 138.4 (CH), 133.5 (C), 131.0 (CH), 129.6 (2CH), 127.9 (CH), 113.5 (2CH), 111.5 (CH), 90.3 (C), 84.0 (CH), 77.2 (C), 76.9 (CH), 76.5 (C), 69.8 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 41.8 (C), 30.9 (CH<sub>2</sub>), 19.5 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>), 4.4 (CH<sub>3</sub>); *m/z* (ESI+, MeOH/DCM) 925 ([2M+Na], 48%), 474 ([M+Na]<sup>+</sup>, 100); **HRMS** (ESI+, MeOH/DCM) [M+Na]<sup>+</sup> found 474.2247, C<sub>27</sub>H<sub>33</sub>NO<sub>5</sub>Na requires 474.2251.

**(2*E*,2'*R*,3'*E*,4*S*,6*S*,8*Z*)-4-(4-methoxy-benzyloxy)-5,5-dimethyl-6-{2-[(2'-methoxy-hept-3'-en-5'-yne)oxazol-4-oyl]oxy}-dodeca-2,8-dien-10-yne (336)**



Two stock solutions, the first (Solution 1) containing C(1)–C(9) oxazole carboxylic acid **111**<sup>203b</sup> (11.8 mg, 0.05 mmol) in PhMe (2 cm<sup>3</sup>; ultrasound assisted dissolution); and the second (Solution 2) containing 2,4,6-TCBC (48.6 mg, 0.20 mmol) and Et<sub>3</sub>N (0.03 cm<sup>3</sup>, 0.29 mmol) in PhMe (3 cm<sup>3</sup>), were prepared for the purpose of generating, portionwise, an activated ester. Solution 2 (0.6 cm<sup>3</sup>) was added to Solution 1 (0.4 cm<sup>3</sup>), and the mixture was stirred for 30 min at rt, before addition of the resulting activated ester solution (Solution 3) to a heated (40 °C) solution of alcohol **338** (1.00 cm<sup>3</sup>, 0.05 mmol; 0.05 M in PhMe) and DMAP (19.0 mg, 0.16 mmol); and stirring of the pale-yellow reaction mixture for 30 min. This procedure was repeated until all activated ester solutions were added to alcohol **338** (5 additions over 2.5 h) and stirring was continued overnight (~18 h). The reaction mixture was cooled to rt, diluted with DCM (30 cm<sup>3</sup>), poured into NH<sub>4</sub>Cl (10 cm<sup>3</sup>; sat aq) and the aqueous layer was extracted with DCM (3 × 10 cm<sup>3</sup>). The combined organic layers were washed with HCl (10 cm<sup>3</sup>; 1.0 M aq), NaHCO<sub>3</sub> (10 cm<sup>3</sup>; sat aq), brine (10 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>); and the solvent was removed under reduced pressure. Flash chromatography with gradient elution (Hexane:EtOAc, 6:1 → 3:1; dry loaded) of the resulting brown residue gave C(1)–C(9)/C(10')–C(19') oxazole ester **336** as a yellow syrup (20.0 mg, 71%).

**Large-scale preparation:** The above procedure was repeated commencing from C(1)–C(9) oxazole carboxylic acid **111**<sup>203b</sup> (106 mg, 0.45 mmol) in PhMe (10 cm<sup>3</sup>) [Solution 1]; 2,4,6-TCBC (444 mg, 1.80 mmol) and Et<sub>3</sub>N (0.36 cm<sup>3</sup>, 2.57 mmol) in

PhMe (10 cm<sup>3</sup>) [Solution 2]; and alcohol **338** (4.50 cm<sup>3</sup>, 0.45 mmol; 0.1 M in PhMe) and DMAP (171 mg, 3.11 mmol) in PhMe (0.5 cm<sup>3</sup>); with Solution 3 generated portionwise from proportionate volumes of Solution 1 and Solution 2 [2 cm<sup>3</sup> of each *per* Solution 3 preparation] and added to the alcohol **338** solution with a PhMe rinse (0.2 cm<sup>3</sup>) on each of the 5 additions. Quenching with NH<sub>4</sub>Cl (10 cm<sup>3</sup>, sat aq) and subsequent concentration of the reaction mixture under reduced pressure; workup with DCM (3 × 20 cm<sup>3</sup>), HCl (25 cm<sup>3</sup>, 0.2 M aq), NaHCO<sub>3</sub> (10 cm<sup>3</sup>, sat aq), H<sub>2</sub>O (10 cm<sup>3</sup>) and brine (10 cm<sup>3</sup>); and drying (MgSO<sub>4</sub>) followed by removal of the solvent under reduced pressure and submission of the residue thus obtained to the same conditions of flash chromatography gave C(1)–C(9)/C(10')–C(19') oxazole ester **336** as a yellow syrup (158 mg, 63%). **R<sub>f</sub>** (Hexane:EtOAc, 3:1) = 0.51; [**α**]<sub>D</sub> = +30.2 (*c* 1.09, CHCl<sub>3</sub>); **IR** (neat, cm<sup>-1</sup>) 2224 (C≡C), 1738 (C=O), 1717 (C=N), 1667 (C=C), 1612 (C=C), 1584 (C=C), 1514 (C=C); **<sup>1</sup>H NMR** δ (600 MHz, CDCl<sub>3</sub>) 8.00 (1H, s, NC=CH), 7.28 (2H, d, *J* = 8.6 Hz, 2ArCH), 6.85 (2H, d, *J* = 8.6 Hz, 2ArCH), 5.94 (1H, dd, *J* = 15.9, 7.7 Hz, CH<sub>3</sub>OCHCH=CH), 5.85 (1H, dt, *J* = 10.3, 7.3 Hz, HC=CHCH<sub>2</sub>), 5.71 (1H, br dq, *J* = 15.9, 2.1 Hz, CH<sub>3</sub>OCHCH=CH), 5.67 (1H, dq, *J* = 15.3, 6.4 Hz, CH<sub>3</sub>CH), 5.46 (1H, ddq, *J* = 15.3, 8.6, 1.3 Hz, CH<sub>3</sub>C=CH), 5.44 (1H, br dq, *J* = 10.3, 2.1 Hz, HC=CHCH<sub>2</sub>), 5.40 (1H, dd, *J* = 9.5, 3.5 Hz, CH<sub>2</sub>CHOCO), 4.39 (1H, d, *J* = 10.8 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 4.17 (1H, ddd, *J* = 7.7, 7.3, 5.6 Hz, CH<sub>3</sub>OCH), 4.12 (1H, d, *J* = 10.8 Hz, CH<sub>A</sub>H<sub>B</sub>Ar), 3.81 (3H, s, ArOCH<sub>3</sub>), 3.51 (1H, d, *J* = 8.6 Hz, CHOCH<sub>2</sub>Ar), 3.29 (3H, s, CH<sub>3</sub>OCH), 3.10 (1H, dd, *J* = 15.1, 7.7 Hz, CH<sub>C</sub>H<sub>D</sub>CHOCH<sub>3</sub>), 2.99 (1H, dd, *J* = 15.1, 5.6 Hz, CH<sub>C</sub>H<sub>D</sub>CHOCH<sub>3</sub>), 2.71–2.62 (2H, m, HC=CHCH<sub>2</sub>), 1.98 (3H, d, *J* = 2.1 Hz, CH<sub>2</sub>CH=CHC≡CCH<sub>3</sub>), 1.96 (3H, d, *J* = 2.1 Hz, CH<sub>3</sub>OCHCH=CHC≡CCH<sub>3</sub>), 1.78 (3H, dd, *J* = 6.4, 1.3 Hz, CH<sub>3</sub>CH), 1.00 (3H, s, CCH<sub>3</sub>), 0.97 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ (150 MHz, CDCl<sub>3</sub>) 162.3 (C), 160.7 (C), 158.9 (C), 143.5 (CH), 139.8 (CH), 138.3 (CH), 133.6 (C), 131.1 (C), 131.0 (CH), 129.5 (2CH), 127.9 (CH), 114.0 (CH), 113.5 (2CH), 111.5 (CH), 90.4 (C), 87.7 (C), 84.1 (CH), 79.2 (CH), 77.1 (CH), 76.5 (C), 69.8 (CH<sub>2</sub>), 56.7 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 41.8 (C), 34.6 (CH<sub>2</sub>), 30.9 (CH<sub>2</sub>), 30.3 (C), 19.5 (CH<sub>3</sub>), 19.4 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>), 4.3 (CH<sub>3</sub>), 4.2 (CH<sub>3</sub>); ***m/z*** (ESI+, MeOH) 1142 ([2M+Na]<sup>+</sup>, 62%), 598 ([M+K]<sup>+</sup>, 7), 582 ([M+Na]<sup>+</sup>, 100), 560 ([M+H]<sup>+</sup>, 17); **HRMS** (ESI+, MeOH) [M+H]<sup>+</sup> found 582.2802, C<sub>34</sub>H<sub>41</sub>NO<sub>6</sub>Na requires 582.2826.

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## Abbreviations

[*]	unspecified transformation, where * is replaced by a functional group or synthetic process, <i>e.g.</i> [O] = oxidation
Å	Ångstrom ( $10^{-10}$ metres)
Ac	acetyl
ACM	alkyne cross-metathesis
Addt.	additive
AM	alkyne metathesis
Ar	unspecified aryl group
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BORSM	based on recovered starting material
bp	boiling point
<sup>n</sup> Bu / <sup>t</sup> Bu	<i>n</i> -butyl / <i>tert</i> -butyl
CAN	ceric ammonium nitrate
CDI	1,1'-carbonyldiimidazole
cm	complex mixture
CM	(olefin) cross-metathesis
conv.	conversion
Cp	cyclopentadienyl
CP	cyclopropenyl
C. R.	coupling reagent
CSA	camphorsulfonic acid
CuAAC	copper-catalysed azide–alkyne cycloaddition
Cy	cyclohexyl
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine, Hünig's base
Dis. C <sub>1</sub>	disorazole C <sub>1</sub>
DMF	<i>N,N</i> -dimethylformamide
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMSO	dimethylsulfoxide
DOWEX-H <sup>+</sup>	cationic Dow ion-exchange resin
DPTC	dipyridylthionocarbonate
<i>dr</i>	diastereomeric ratio
EC <sub>50</sub>	half-maximal effective concentration
EDTA	ethylenediaminetetraacetic acid
<i>ee</i>	enantiomeric excess
<i>ent</i>	enantiomer
<i>epi</i>	epimer

Eq / eq	equivalent(s)
Et	ethyl
ET	Evans–Tishchenko
EWG	electron withdrawing group
h	hour(s)
HBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
Het	unspecified heterocycle
<sup>n</sup> Hex	<i>n</i> -hexyl
HMDS	hexamethyldisilazide, bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
IC <sub>50</sub>	half-maximal inhibitory concentration
Im	imidazole
<i>Int</i>	intermediate
μL	microlitre(s)
L	unspecified ligand
LDA	lithium diisopropylamide
LDBBA	lithium diisobutyl- <i>tert</i> -butoxyaluminium hydride
lit	literature value
M	moles <i>per</i> cubic decimetre, mol dm <sup>-3</sup>
Me	methyl
MEM	(2-methoxyethoxy)methyl
Mes	mesityl, 2,4,6-trimethylphenyl
2-MeTHF	2-methyltetrahydrofuran
min	minute(s)
mmHg	millimetres of mercury
MNBA	2-methyl-6-nitrobenzoic anhydride
mol%	mole percent
MOM	(methoxy)methyl
Ms	methanesulfonyl, mesyl
MS	molecular sieves
MTM	(methylthio)methyl
<i>N</i>	sample size
<i>nd</i>	not determined
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance *
3-NOBA	3-nitrobenzyl alcohol
NR	no reaction
Ns	2-nitrobenzenesulfonyl, nosyl
ox.	2,5-oxazole
P	unspecified protecting group
PADA	dipotassium azodicarboxylate
PE	petroleum ether
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl, 4-methoxybenzyl

PMB-TCA	<i>para</i> -methoxybenzyl-2,2,2-trichloroacetimidate
PMP	<i>para</i> -methoxyphenyl, 4-methoxyphenyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
4-PPy	4-pyrrolidinopyridine
<sup><i>i</i></sup> Pr	<i>iso</i> -propyl
Prod.	product
Py	pyridine
quant	quantitative
R <sup>n</sup>	unspecified group <sup>†</sup> (n = 1, 2, 3 <i>etc.</i> )
RAAT	retro-aldol aldol–Tishchenko
RCAM	ring-closing alkyne metathesis
Ref.	reference
R <sub>f</sub>	retention factor
RP-HPLC	reverse-phase high-performance liquid chromatography
Rslt.	result
R <sub>t</sub>	retention time
rt	room temperature
salen	<i>N,N'</i> -ethylenebis(salicylimine)
SAR(s)	structure–activity relationship(s)
SEM	[2-(trimethylsilyl)ethoxy]methyl
<i>Si</i>	unspecified silicon protecting group
Solv.	solvent
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBTA	tris[(1-benzyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amine
2,4,6-TCBC	2,4,6-trichlorobenzoyl chloride, Yamaguchi reagent
1,1,2-TCE	1,1,2-trichloroethane
Temp	temperature
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl radical
TES	triethylsilyl
Tf	trifluoromethanesulfonate, triflate
TFA	trifluoroacetic acid, 2,2,2-trifluoroethanoic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tol	<i>para</i> -tolyl, 4-methylphenyl
Ts	<i>para</i> -toluenesulfonyl, 4-toluenesulfonyl, tosyl
<i>TS</i>	transition state
X	unspecified leaving group
XtalFluor	(diethylamino)difluorosulfonium tetrafluoroborate

\*Abbreviations related to NMR spectroscopy and (most) abbreviations that are not used in discussion prior to **Chapter 7: Experimental** may be found in **Section 7.1: General Experimental** (page 174).

<sup>†</sup>Further abbreviations for “unspecified group” include A, B, X and Y.

<sup>‡</sup>All further abbreviations are base units or unit multiples that follow SI conventions.<sup>254</sup>

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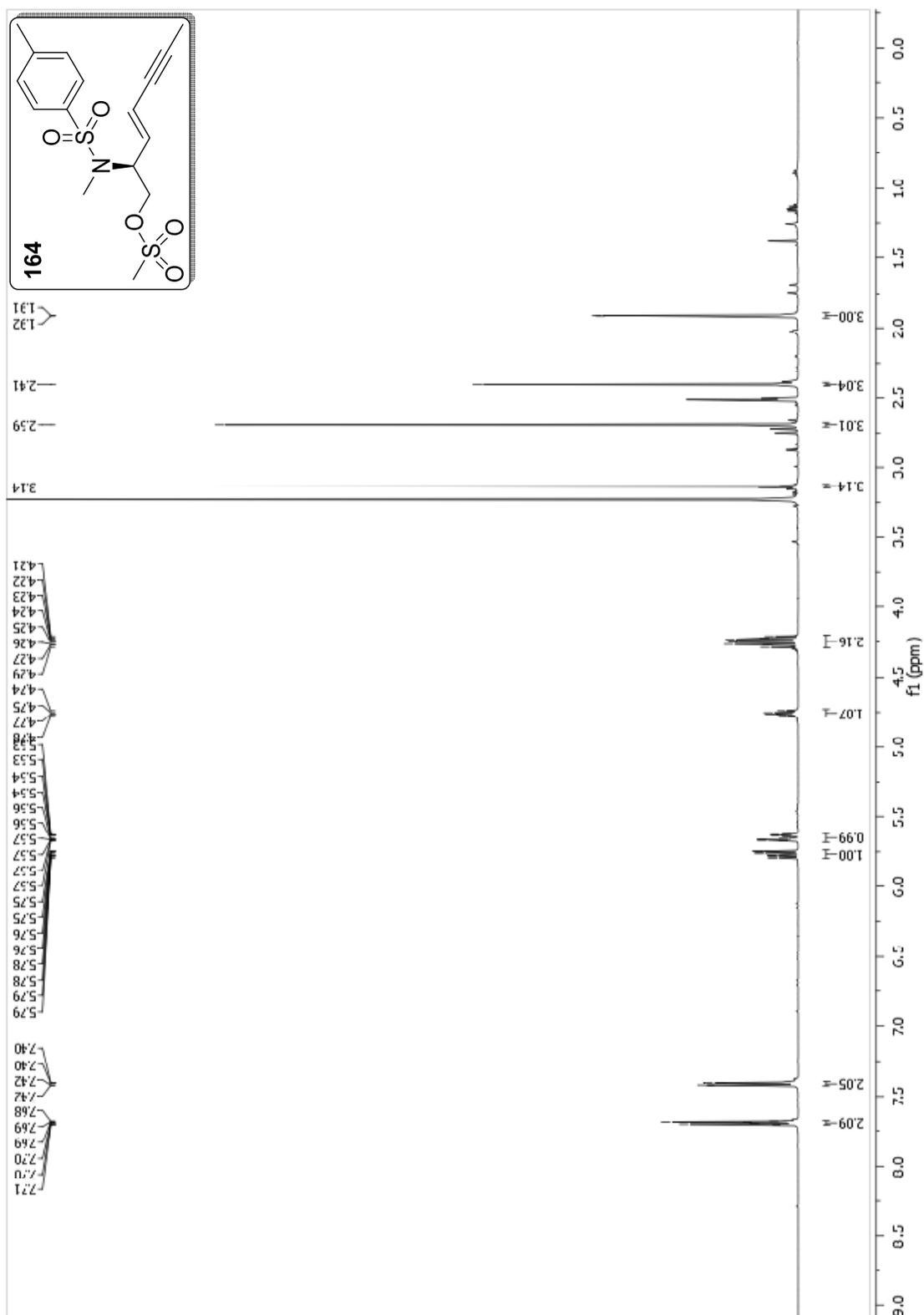
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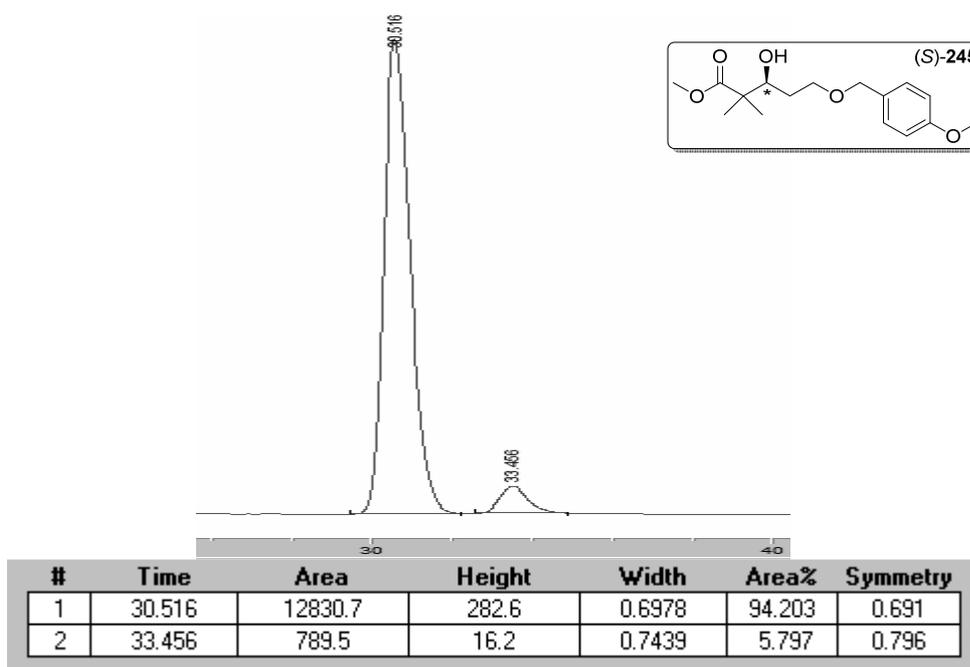
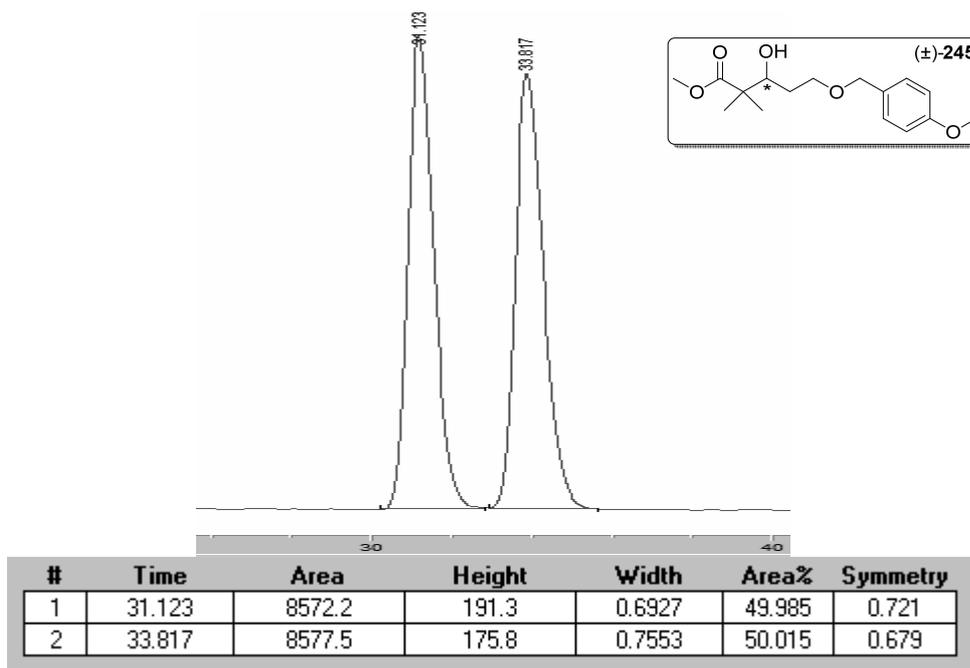
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## Appendix

- Appendix 1  $^1\text{H}$  NMR spectrum of the C(5)–C(9) C(6)-amino analogue mesylate **164** recorded at 500 MHz in  $\text{DMSO-}d_6$  at 323 K.
- Appendix 2 HPLC chromatograms and data for  $\beta$ -hydroxyester **245**.
- Appendix 3  $^1\text{H}$  NMR spectrum of the C(10)–C(19)  $\beta$ -hydroxyketone fragment **86** recorded at 500 MHz in  $\text{CDCl}_3$  at 298 K.
- Appendix 4  $^1\text{H}$  NMR spectrum of the C(10)–C(19) mono-protected diol fragment **338** recorded at 500 MHz in  $\text{CDCl}_3$  at 298 K.
- Appendix 5  $^1\text{H}$  NMR spectrum of the C(1)–C(9)/C(10')–C(19') 1,3-*anti* diol monoester bis-alkyne fragment **336** recorded at 600 MHz in  $\text{CDCl}_3$  at 298 K.
- Appendix 6 Permission letter obtained for the use of **Figure 1.3**.
- Appendix 7 List of publications.

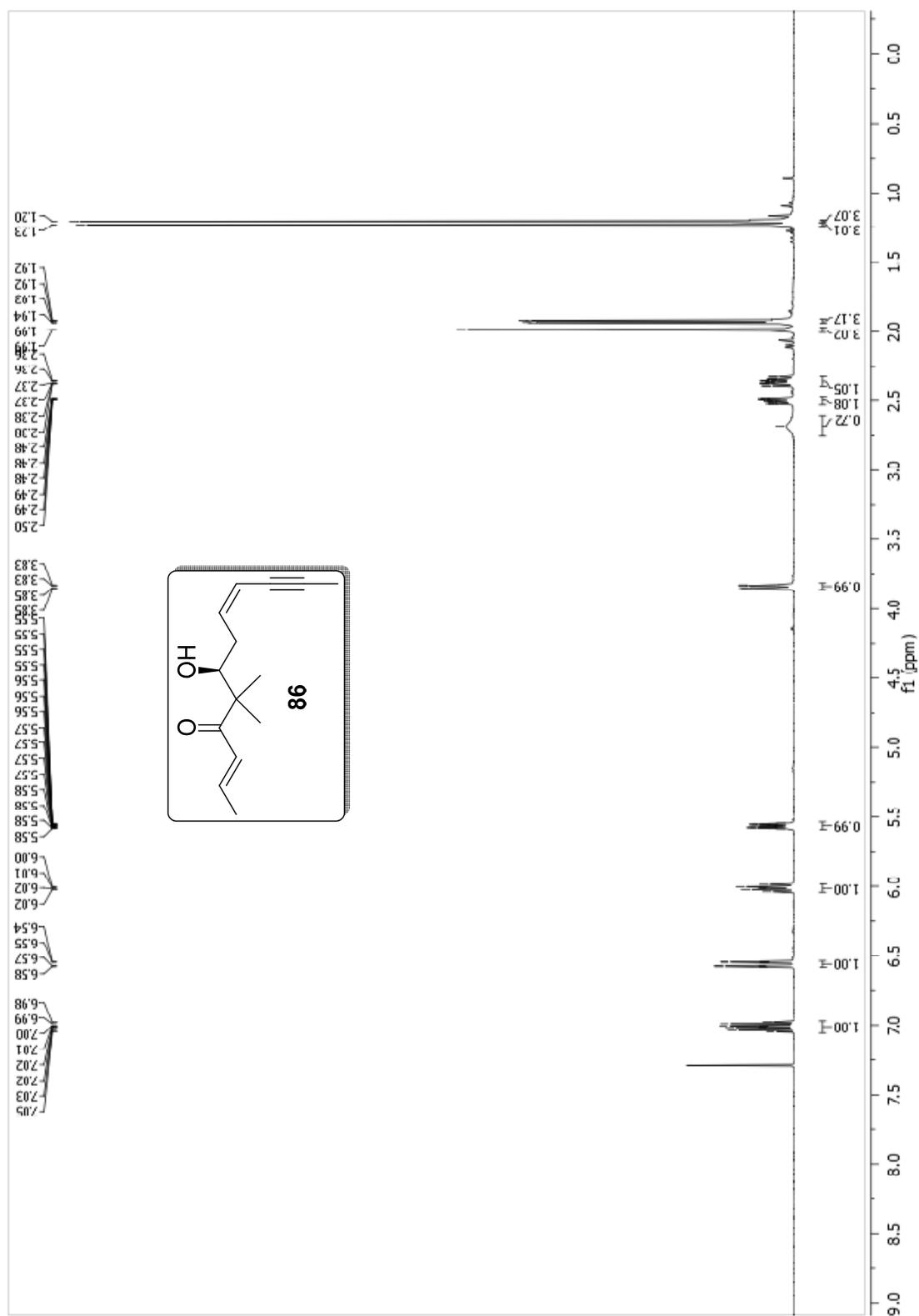


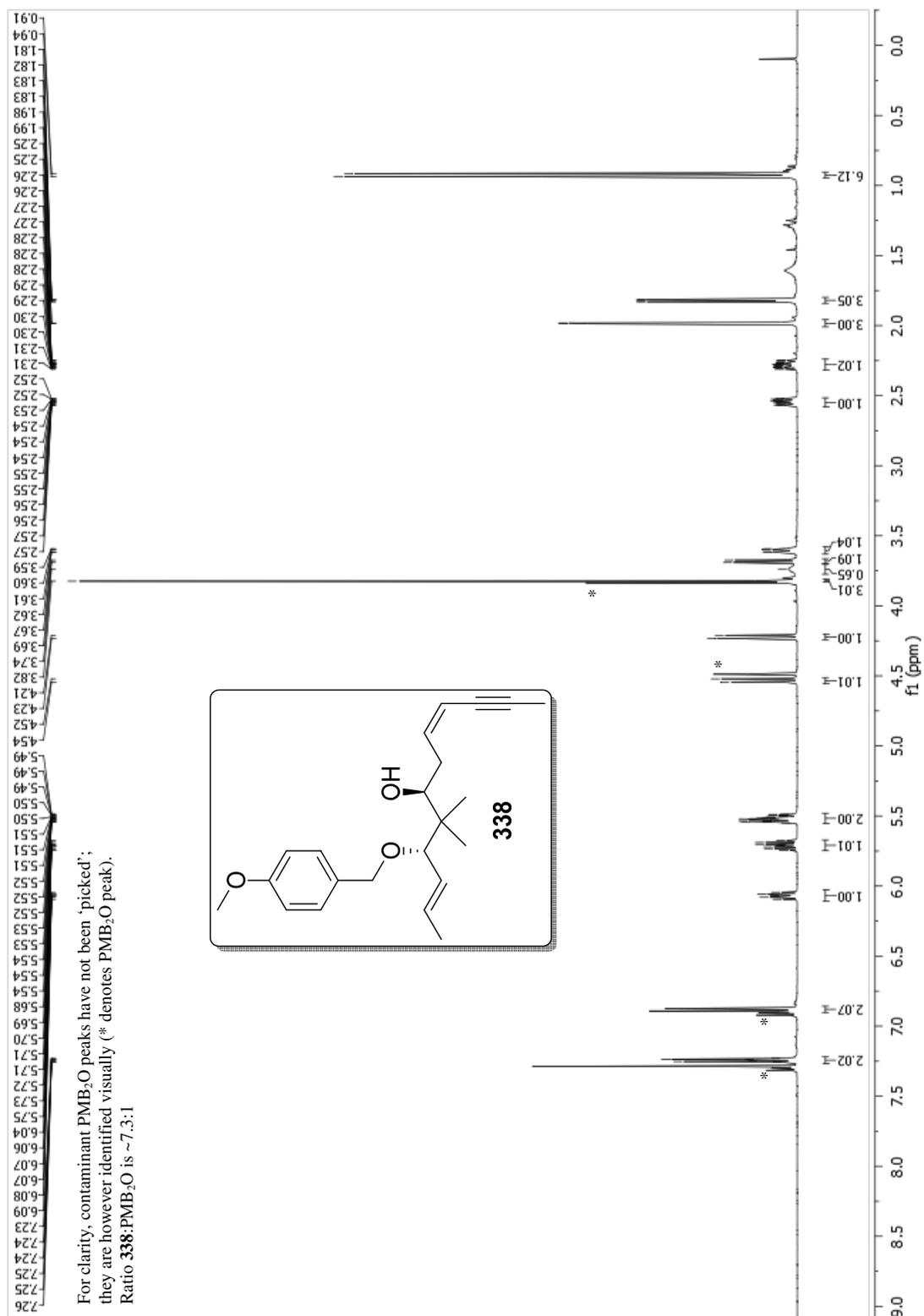
HPLC chromatograms and data for  $\beta$ -hydroxyester (245)**Racemic Sample [(±)-245]**

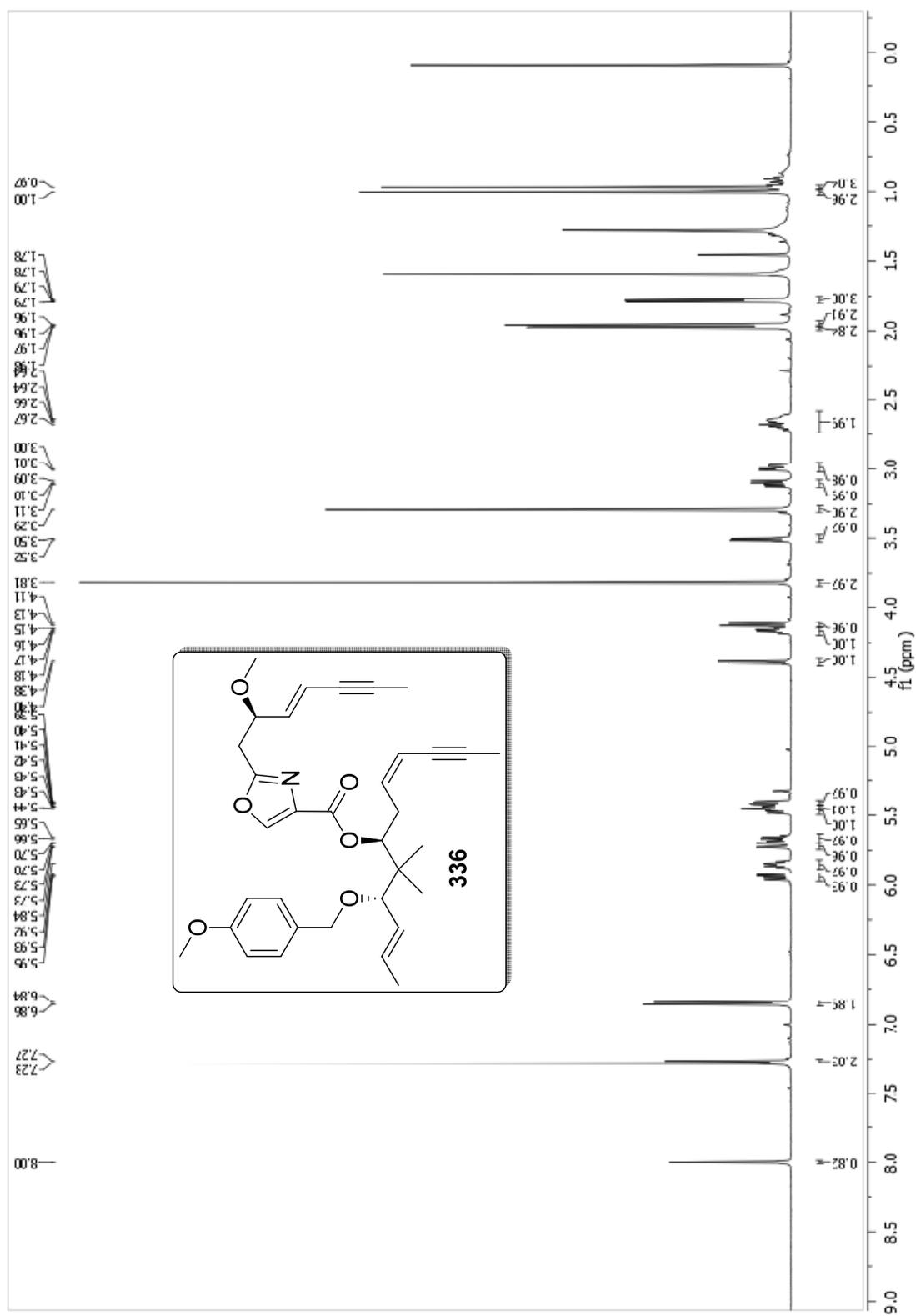
Area% ( $R_t = 33.8$ )  
 - Area% ( $R_t = 31.1$ )  
 %ee 0.0 %

**Enantioenriched Sample [(S)-245]**

Area% ( $R_t = 30.5$ )  
 - Area% ( $R_t = 33.4$ )  
 %ee 88.4 %







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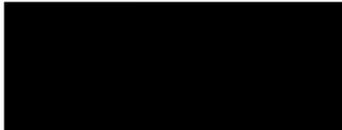
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## List of Publications

“The Evans–Tishchenko Reaction: Scope and Applications”

Ralston, K. J.; Hulme, A. N. *Synthesis* **2012**, *44*, 2310–2324.

DOI: 10.1055/s-0032-1316544

<http://dx.doi.org/10.1055/s-0032-1316544>