## PAPER

# Synthetic studies toward the brasilinolides: controlled assembly of a protected C1−C38 polyol based on fragment union by complex aldol reactions†

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The brasilinolides are an architecturally complex family of 32-membered macrolides, characterised by potent immunosuppressant and antifungal properties, which represent challenging synthetic targets. By adopting a highly convergent strategy, a range of asymmetric aldol/reduction sequences and catalytic protocols were employed to assemble a series of increasingly elaborate fragments. The controlled preparation of suitable C1−C19 and C20−C38 acyclic fragments **5** and **6**, containing seven and 12 stereocentres respectively, was first achieved. An adventurous C19−C20 fragment union was then explored to construct the entire carbon chain of the brasilinolides. This pivotal coupling step could be performed in a complex boron-mediated aldol reaction to install the required C19 hydroxyl stereocentre when alternative Mukaiyama-type aldol protocols proved unrewarding. A protected C1−C38 polyol **93** was subsequently prepared, setting the stage for future late-stage diversification toward the various brasilinolide congeners. Throughout this work, asymmetric boron-mediated aldol reactions of chiral ketones with aldehydes proved effective both for controlled fragment assembly and coupling with predictable stereoinduction from the enolate component.

## Introduction

The polyketides represent a diverse array of structurally elaborate natural products having a wide range of biological activity, with many members having important therapeutic utility in human and veterinary medicine.[1] The brasilinolides (Fig. 1), isolated by Mikami and Kobayashi and co-workers in 1996 from the pathogenic actinomycetes *Nocardia brasiliensis*, constitute a unique family of immunosuppressive and antifungal polyketides based on a highly hydroxylated macrolide scaffold, which presumably arises in the biosynthesis from a PKS-mediated cyclisation of a linear 38-carbon chain.[2] As X-ray quality crystals of the brasilinolides proved elusive, and analysis of the ^{1}H and ^{13}C NMR data did not allow a full structural assignment, detailed stereochemical information was gleaned by controlled chemical degradation and spectroscopic studies of the resulting fragments. This work enabled the elucidation of the relative and absolute configuration of brasilinolide A (**1**), along with the congeneric brasilinolides B (**2**) and C (**3**).[3] Notably, brasilinolide A (**1**) was reported to exhibit pronounced immunosuppressive activity *in vivo* (IC$_{50}$ value of 0.625 μg mL$^{-1}$, mouse mixed lymphocyte assay) with no significant toxicity. In addition, brasilinolide A showed antifungal activity and brasilinolide B was found to be active against a range of fungi and bacteria. Altogether, their notable biological activities, along with the low toxicity profile and favourable physicochemical properties, make further evaluation of the brasilinolides as promising lead structures of interest, with potential therapeutic applications to autoimmune diseases and fungal infections, and in the prophylaxis of organ transplant rejection.[4]

Each member of the brasilinolide family contains several distinctive structural features, including some 26 stereocentres, of which 16 are embedded in the macrocyclic lactone, and an elaborate propionate-derived side chain with a glycosyl appendage at C37. The signature 32-membered macrolide core itself contains a six-membered hemiacetal ring, an epoxide and a characteristic 1,3-polyol array, with an acidic 23-*O*-malonyl residue present in brasilinolide A (**1**). Herein, we report in full on progress to date toward the total synthesis of the brasilinolides, documenting the multiple selectivity and logistical issues addressed in this eventful journey.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ob00498e. All data accompanying this publication are directly available within the publication and the ESI.
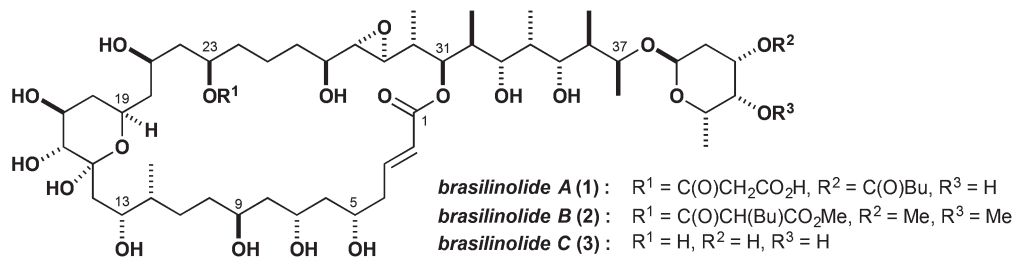
5716 | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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**Fig. 1** Structures of brasilinolides A–C.

# Results and discussion

## Overview of synthesis plan

Our initially devised synthesis plan for brasilinolide A (**1**) is outlined in Scheme 1. Such rich stereochemical features, particularly with the preponderance of secondary hydroxyl groups within the aglycon, inspired the pursuit of a strategy using asymmetric aldol chemistry[5] for realising the critical fragment assembly steps to configure many of these stereocentres. Additionally, a carefully planned protecting group regime was devised for the purposes of achieving predictable stereoinduction, along with enabling the late-stage introduction of the defining brasilinolide substituents, and to ensure the necessary control in progressing the synthetic route. Building on our earlier preliminary studies,[6] the highly convergent assembly of a suitably protected C1–C38 linear precursor **4** was initially targeted. Further simplification was proposed by the late-stage attachment of the polar C23-O-malonyl substituent and C37-O-glycosylation, following macrolactonisation of the C1–C38 intermediate **4** after liberation of the C31 hydroxyl group. The pivotal linear precursor **4** was therefore designed to allow for precise site-controlled functionalisation. Furthermore, it was envisaged that a high level of stereoinduction might be leveraged in its controlled aldol-based assembly from suitable ketone building blocks.

Following this overall plan, **4** was disconnected at the C19–C20 bond to afford the C1–C19 fragment **5**, as the corresponding southern hemisphere region, and the methyl ketone **6**, corresponding to the brasilinolide northern hemisphere. It was envisaged that these two major fragments would be connected by a strategic aldol coupling between **6** and a suitable C19 aldehyde derived from **5**. Further analysis of **5** suggested that favourable carbon–carbon bond scissions might be made at C8–C9 and C13–C14 to reveal three chiral building blocks **7–9** of roughly equal complexity. Examination of the C20–C38 fragment **6** suggested that a Horner–Wadsworth–Emmons (HWE) disconnection would serve to isolate the C23 stereocentre, leading back to the β-ketophosphonate **10** and the aldehyde **11**. Following this synthesis plan, **4** is conveniently broken down to give five building blocks: with **7–10** having only one or two stereocentres along with the more complex polypropionate array embedded in **11**.

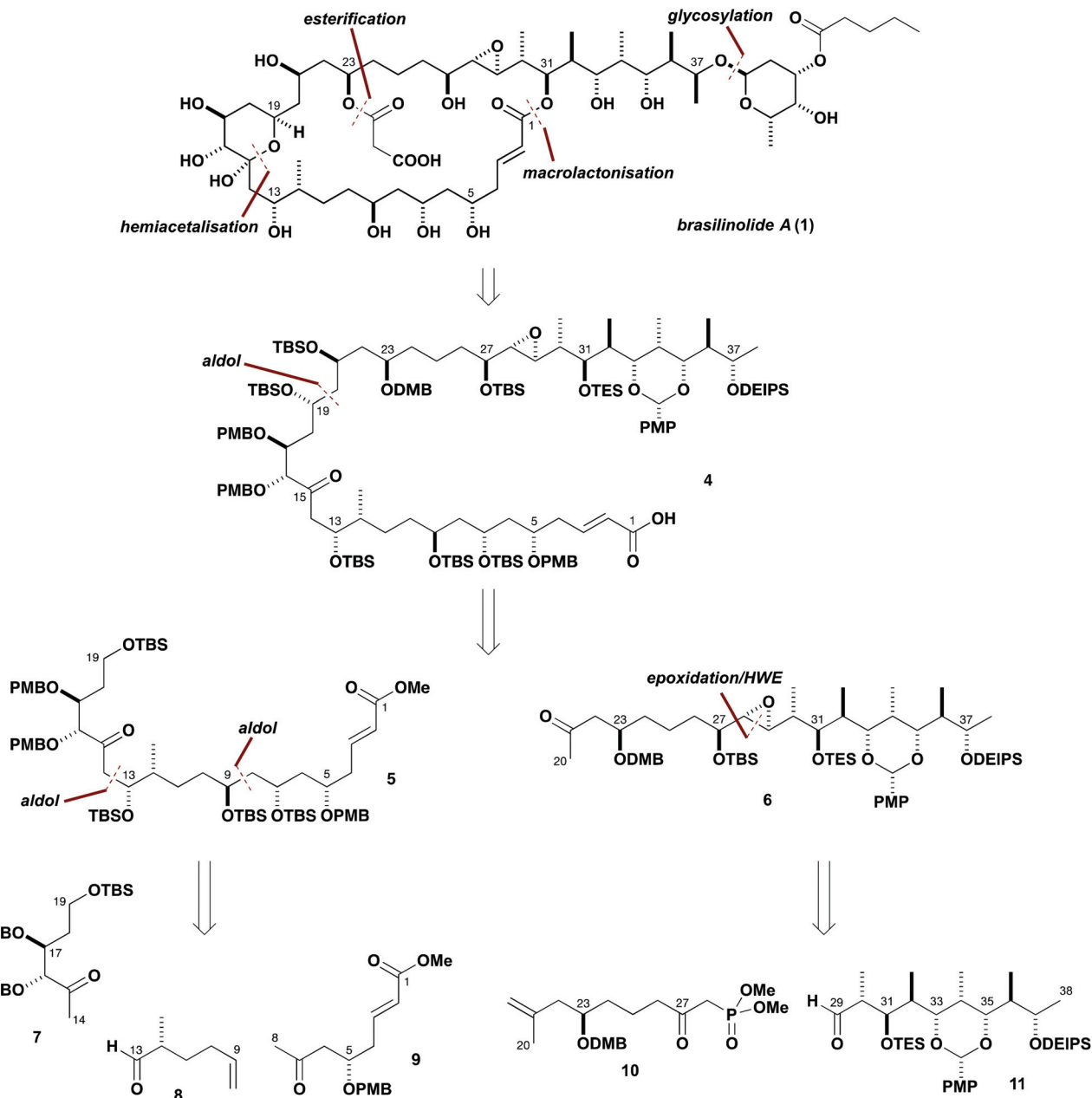With regard to the critical issue of controlling stereochemistry, it was envisaged that asymmetric aldol methodology developed in our group could be exploited in several situations to construct **5** and **11**. As discussed in more detail later, a suitably flexible strategy to assemble and couple the five building blocks shown in Scheme 1 was devised to allow modification based on experimental findings. In two preliminary communications,[6] we had previously reported synthetic routes to two major brasilinolide fragments, which now needed to be refined and optimised. This entailed some modification to the protecting groups, and scale up to enable access to larger quantities of advanced intermediates.

### The C1–C19 southern fragment 5

Our initial focus was on efficiently assembling the southern hemisphere fragment **5** in Scheme 1. This contains seven oxygen-bearing stereocentres, a ketone at C15, and terminates in an enoate and TBS ether as a latent form of C19 aldehyde. Configurational analysis of **5** revealed a pivotal 1,5-*anti* relationship between the protected hydroxyl groups at C5 and C9, and also between C13 and C17, that would represent interesting cases for studying long-range asymmetric induction using aldol reactions of methyl ketones.[7] Disconnection across the C8–C9 and C13–C14 bonds to afford β-alkoxy methyl ketones **7** and **9** was then anticipated to facilitate a useful degree of remote asymmetric induction during fragment assembly. In order to advance to exploring the projected aldol-based construction of the C1–C19 fragment **5**, an efficient gram-scale preparation of the three chiral building blocks **7**, **8** and **9** in high enantiomeric purity was first deemed necessary. The preparation of these building blocks is now considered in turn.

As shown in Scheme 2, our initial approach towards accessing the C1–C8 methyl ketone **9** started out with the commercially available (*S*)-(+)-epichlorohydrin (**12**) as a convenient means of installing the C5 stereocentre in high configurational purity. In following this route A, epoxide opening of **12** with vinylmagnesium bromide proceeded in the presence of CuBr (10 mol%) in Et₂O at −40 °C to afford an intermediate chlorohydrin; where KOH-mediated cyclisation then gave the known epoxide **13** (55%, two steps).[8] Reopening of this epoxide with lithium acetylide ethylene diamine complex proceeded in DMSO to give the corresponding allylic alcohol, which was converted into its PMB ether **14** (NaH, PMBBr) in 69% overall yield. Next, the two unsaturated moieties attached to the C5 stereocentre were sequentially elaborated. Firstly, controlled
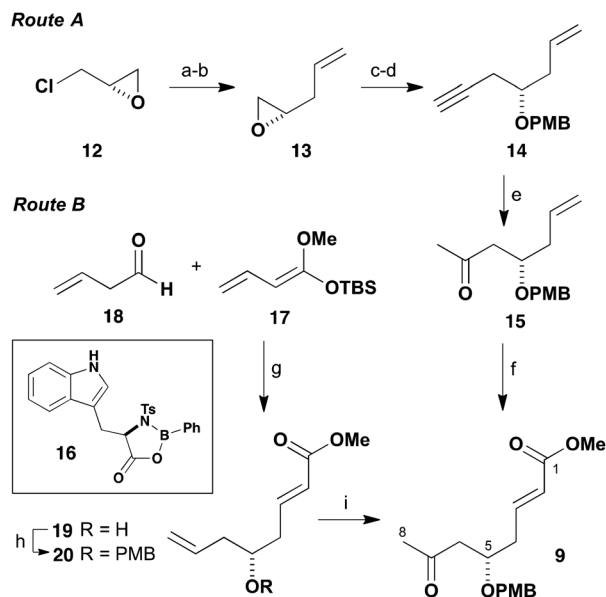
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**Scheme 1** Overview of synthesis plan for brasilinolide A (**1**) leading back to the five chiral building blocks **7–11**.

oxymercuration (Hg(OAc)$_2$ (30 mol%), PPTS) of the alkyne in wet acetone afforded the methyl ketone **15**, which was followed by cross-metathesis of the olefin with methyl acrylate using Grubbs II catalyst (1 mol%) to generate enoate **9** (75%, two steps).[9] This sequence afforded the enantiopure C1–C8 ketone **9** in 29% yield over six steps from (S)-(+)-epichlorohydrin (**12**).

Although methyl ketone **9** was available in high enantiomeric purity *via* the foregoing route A, preliminary attempts to perform this sequence on a suitably large scale encountered a number of issues. The first three steps generate volatile compounds and the associated handling difficulties depleted yields on a larger scale. Disconnection of the δ-alkoxyenoate

functionality of **9** based on a vinylogous Mukaiyama aldol reaction[10] leads to an opportunity for exploring an alternative construction of this fragment using asymmetric catalysis. Following the work of Kalesse and co-workers, a complementary route B to prepare **9** was therefore developed using the D-tryptophan-derived oxazaborolidinone **16**.[11] In practice, a Mukaiyama aldol addition of silyl dienolate **17** to but-3-enal[12] (**18**) in the presence of **16** afforded the required γ-adduct **19** (57%) in >95% ee. Following PMB ether formation to give **20** (PMBTCA, Ph$_3$CBF$_4$, 64%),[13] a Wacker oxidation[14] of the terminal olefin (PdCl$_2$ (10 mol%), CuCl$_2$, O$_2$) then provided the methyl ketone **9** (63%). Both the above routes to **9** were then

**5718** | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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**Scheme 2** Synthesis of methyl ketone **9** using either a chiral starting material or by an asymmetric vinylogous Mukaiyama aldol reaction. *Reagents and conditions*: (a) $H_2C$=CHMgBr, CuBr (10 mol%) $Et_2O$, −40 °C, 73%; (b) KOH, 75%; (c) HCCLi·$(CH_2NH_2)_2$, DMSO; (d) NaH, PMBBr, THF, 69% (two steps); (e) $Hg(OAc)_2$ (30 mol%), PPTS, $H_2O$, acetone, 82%; (f) methyl acrylate, Grubbs II catalyst (1 mol%), $CH_2Cl_2$, 92%; (g) **16**, i-PrOH, i-PrCN, 57%, >95% ee; (h) PMB-2,2,2-trichloroacetimidate, $Ph_3CBF_4$, THF, 64%; (i) $PdCl_2$ (10 mol%), $CuCl_2$, $O_2$, DMF–$H_2O$ (7:1), 63%.

used to generate useful stocks of the planned C1–C19 southern fragment **5**.

As shown in Scheme 3, control over the C12 methyl-bearing stereocentre in aldehyde **8** was conveniently achieved through the use of the chiral auxiliary methodology developed by Myers.[15] Alkylation of the lithium enolate derived from propionamide **21** with 4-iodobut-1-ene gave the desired amide **22**, which was isolated in high yield (94%) and >95:5 dr on multigram scale. The auxiliary was then reductively cleaved with LDA/$NH_3$·$BH_3$ (88%) and Swern oxidation[16] of the resulting alcohol **23** gave the desired C9–C13 aldehyde **8** (97%). This
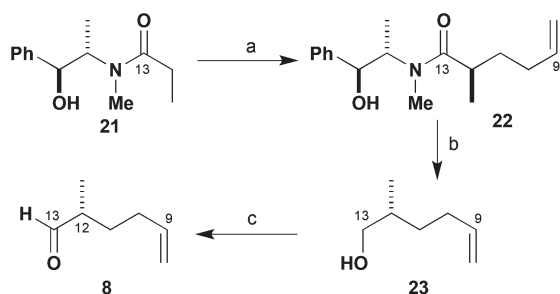


**Scheme 3** Synthesis of aldehyde **8**. *Reagents and conditions*: (a) LDA, LiCl, THF, −78 °C; 4-iodobut-1-ene, 94%, >95:5 dr; (b) LDA, $NH_3$·$BH_3$, THF, 0 °C, 88%; (c) $(COCl)_2$, DMSO, $CH_2Cl_2$; $Et_3N$, −78 to 0 °C, 97%.

scalable synthesis of **8** bearing a masked aldehyde at C9 was thus completed in three steps from **21** in 87% yield and in high enantiomeric purity (97% ee).

As shown in Scheme 4, the synthesis of the remaining chiral building block **7** required for constructing the brasilinolide southern fragment **5** relied on asymmetric catalysis. It commenced with the TBS ether **24** prepared from but-3-en-1-ol. Ozonolysis and *in situ* Wittig reaction of the resulting aldehyde with $Ph_3P$=CHCOMe gave the corresponding enone **25** (69%), solely as the *E*-isomer.[17] This was then subjected to a Sharpless asymmetric dihydroxylation,[18] where a ligand screen indicated that $(DHQ)_2AQN$ (1 mol%) reliably gave chiral diol **26** with excellent enantioselectivity (91%, 97% ee). By exposure to PMBTCA in the presence of catalytic $Ph_3CBF_4$ (0.5 mol%),[13] this diol was then converted into its bis-PMB ether **7** (77%). This scalable route gave methyl ketone **7** in three steps from **24** in high yield (48%) and enantiomeric purity (97% ee).
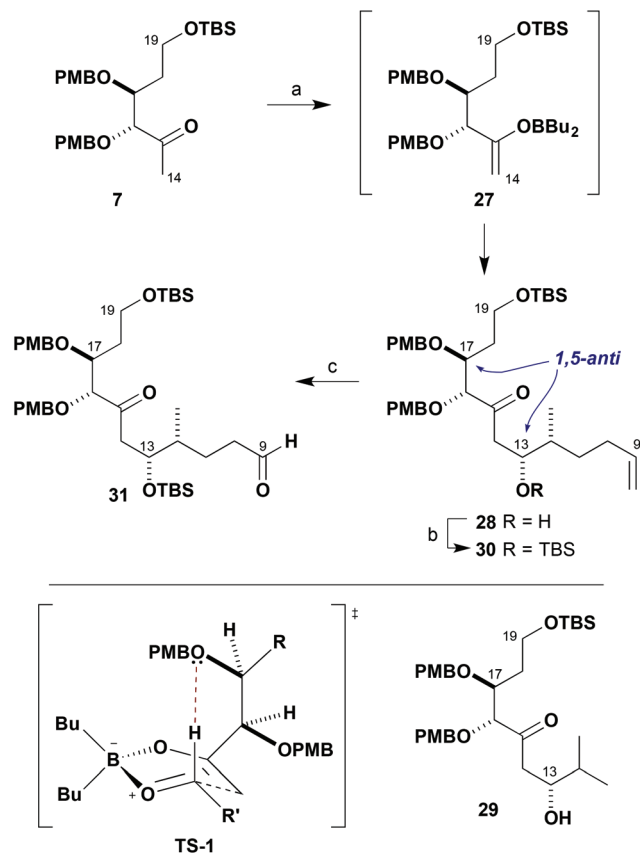
In assembling the C1–C19 southern fragment **5**, we planned to use two strategic boron-mediated aldol reactions to couple together the three fragments **7**, **8** and **9**. With boron enolates derived from β-alkoxy methyl ketones such as **9**, remote 1,5-*anti* stereoinduction is known to be enhanced in addition to aldehydes by employing a PMB ether.[7] This facilitates aldol transition state organisation by formyl hydrogen bonding involving this ether oxygen atom. We first needed to explore the scope of this reaction to include β-alkoxy methyl ketones such as **7** that have an additional α-alkoxy stereocentre. In support of this approach, DFT calculations predicted that these aldol reactions are also likely to proceed preferentially through a bicyclic boat **TS-1**, where π-facial discrimination is controlled by a stabilising formyl hydrogen bond involving only the PMB ether oxygen at the β-centre and minimisation of steric interactions.[19]

After some optimisation, it was found that methyl ketone **7** was best treated with $Bu_2BOTf$/i-$Pr_2NEt$ in $Et_2O$ and the resulting enolate **27** reacted with aldehyde **8** at −78 °C, leading on work-up to the isolation of adduct **28** with excellent diastereo-
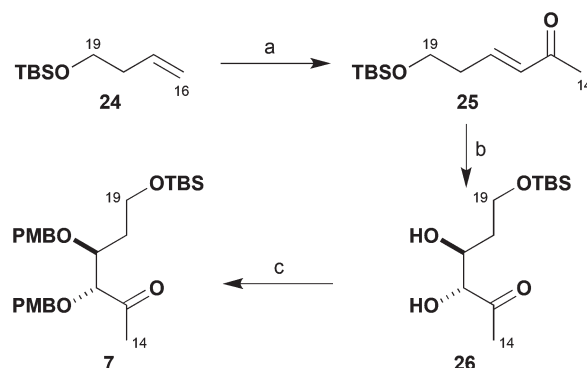


**Scheme 4** Synthesis of methyl ketone **7**. *Reagents and conditions*: (a) $O_3$, $CH_2Cl_2$, −78 °C; $Ph_3P$=CHCOMe, 0 °C, 69%, >95:5 *E*:*Z*; (b) $K_2OsO_2(OH)_4$ (1 mol%), $(DHQ)_2AQN$ (1 mol%), $K_3[Fe(CN)_6]$, $K_2CO_3$, $NaHCO_3$, $MeSO_2NH_2$, t-BuOH–$H_2O$ (1:1), 91%, 97% ee; (c) PMB-2,2,2-trichloroacetimidate, $Ph_3CBF_4$ (0.5 mol%), THF, 77%.

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*Org. Biomol. Chem.*, 2015, **13**, 5716–5733 | **5719**

**Scheme 5** Synthesis of aldehyde **31**. *Reagents and conditions*: (a) Ketone **7**, Bu$_2$BOTf, i-Pr$_2$NEt, Et$_2$O, −78 °C; aldehyde **8**, Et$_2$O, −78 °C, 98%, >95 : 5 dr; (b) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 98%; (c) O$_3$, NaHCO$_3$, Sudan Red 7B, CH$_2$Cl$_2$−MeOH (1 : 1), −78 °C, 95%.

selectivity and in high yield (>95 : 5 dr, 98%, Scheme 5). The newly formed stereocentre in **28** was installed with the required (13$R$)-configuration[20] in the anticipated 1,5-*anti* sense relative to C17.[21] As predicted in **TS-1**, this indicated that the β-alkoxy stereocentre was presumably responsible for controlling the π-facial selectivity of the boron enolate in this complex aldol fragment coupling. A similar aldol reaction of **7** with iso-butyraldehyde also gave the corresponding 1,5-*anti* adduct **29** in high diastereoselectivity, suggesting that Felkin–Anh-type 1,2-stereoinduction from the α-chiral aldehyde component **8** was not significantly contributing to the outcome.[22]

Moving forward, the resulting aldol adduct **28** was next transformed into the TBS ether **30** (TBSOTf, 2,6-lutidine) and the olefin oxidatively cleaved *via* ozonolysis to afford **31** (97%, two steps). This served to generate the aldehyde functionality at C9 in readiness for performing the next aldol fragment coupling with methyl ketone **9** (Scheme 6). In this case, **9** was treated with $c$-Hex$_2$BCl/Et$_3$N in Et$_2$O and the resulting boron enolate **32** added smoothly to aldehyde **31** at −78 °C to give the β-hydroxyketone **33** (>95 : 5 dr, 95%). This complex aldol coupling reaction delivers equally high 1,5-*anti* diastereo-selectivity and is considered to preferentially proceed through the related boat **TS-2**, again invoking a formyl hydrogen bond
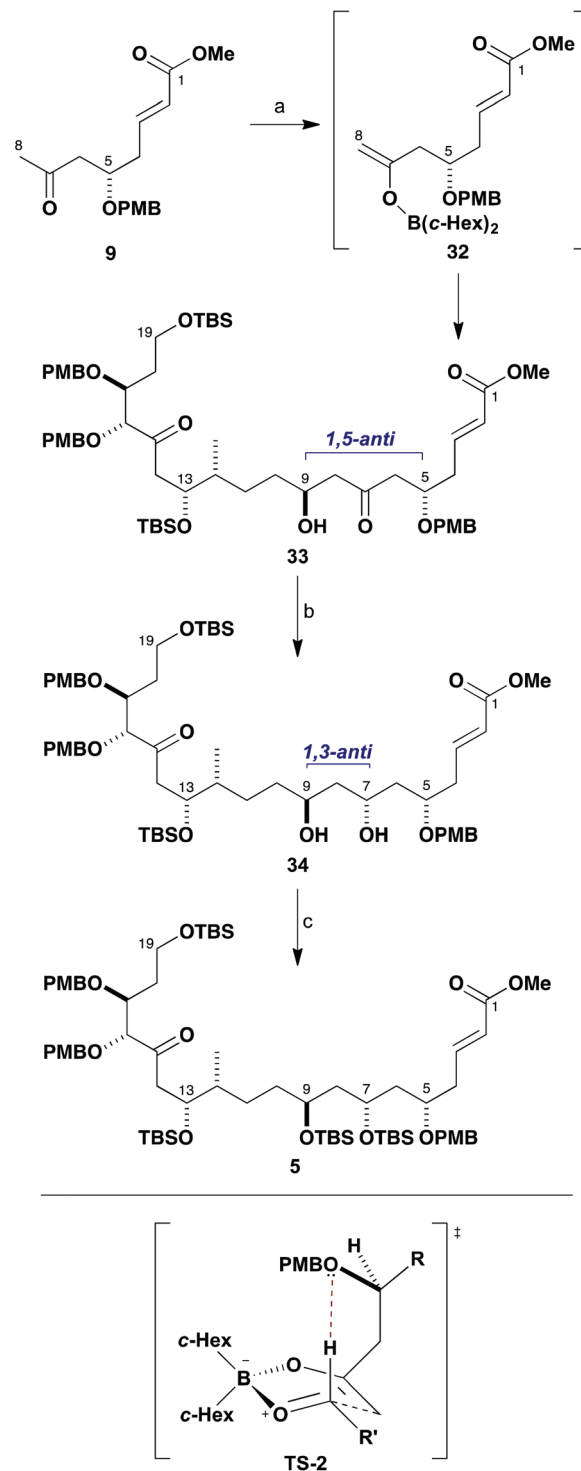


**Scheme 6** Assembly of the southern hemisphere fragment **5**. *Reagents and conditions*: (a) Ketone **9**, $c$-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; aldehyde **31**, −78 to −23 °C, 95%, >95 : 5 dr; (b) Me$_4$NBH(OAc)$_3$, MeCN, AcOH (4 : 1), −30 °C, 95%, >95 : 5 dr; (c) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 97%.

from a β-positioned PMB ether oxygen in the boron enolate. An Evans–Saksena[23] 1,3-*anti* reduction of **33** with Me$_4$NBH (OAc)$_3$ at −30 °C then served to efficiently configure the

remaining stereocentre at C7, again proceeding with high diastereoselectivity (>95 : 5 dr, 95%). While the resulting diol **34** was protected as its cyclic di-*tert*-butylsilylene (Si(*t*-Bu)$_2$) derivative in our previous studies,[6a] to facilitate progression of material on a larger scale it was decided instead to now derivatise the C7 and C9 hydroxyl groups as the bis-TBS ether **5** (TBSOTf, 2,6-lutidine, 97%). This revised approach was preferred both in terms of a substantially improved yield and to ensure that the carbon skeleton was not unduly conformationally restricted for the later macrocyclisation step. In earlier work,[6a] we had also explored the effect of reversing the order of the fragment couplings whereby the C8–C9 bond was forged ahead of the C13–C14 bond – however, this longer route gave a lower overall yield so was not pursued further.

The fully protected C1–C19 southern fragment **5** was obtained by this improved route in a satisfying 43% overall yield in 10 steps over the longest linear sequence (16 total steps) from the alcohol precursor to **24**. Implementation of this reaction sequence on multi-gram scale served to generate useful quantities of the pivotal major fragment **5** with all of the seven stereocentres installed in high configurational purity, as required for advancing synthetic efforts toward the brasilinolides.
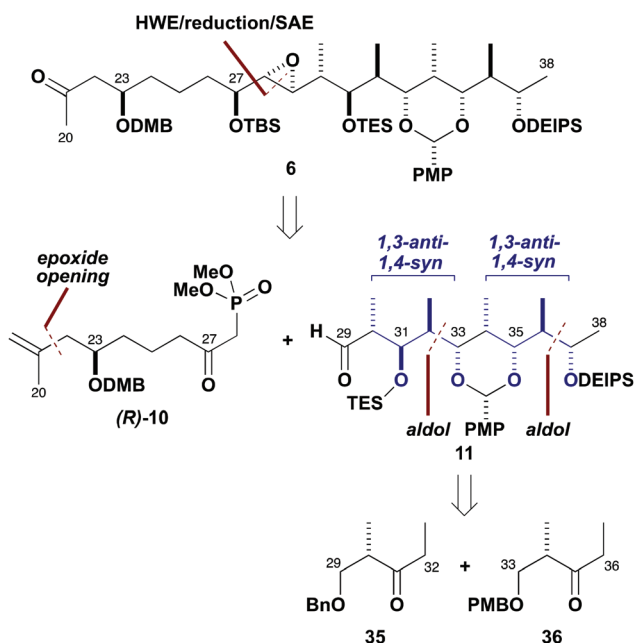
### The C20–C38 northern fragment 6

With an efficient synthesis of the C1–C19 fragment **5** in place, the construction of the C20–C38 fragment **6** was addressed next, as shown in Scheme 7. The methyl ketone **6**, corresponding to the northern hemisphere of the brasilinolides, is characterised by having 11 contiguous stereocentres together with a remote oxygenated stereocentre at C23. Suitable differentiation of six hydroxyl groups is required, as well as the

controlled installation of a potentially sensitive *trans*-epoxide moiety.

Strategically, an HWE-type disconnection across C28–C29 was proposed, leading back to the β-ketophosphonate (*R*)-**10** (having a C21 methylene as a latent ketone) and the aldehyde **11**, which contains the extended polypropionate region. Detailed configurational analysis of the aldehyde **11** reveals two similar stereotetrads with an epimeric relationship between C31 and C35. Two iterative aldol chain extensions of acetaldehyde employing the (*S*)-Roche ester-derived ethyl ketones **35** and **36** were chosen to install the required stereocentres associated with the C32–C33 and C36–C37 bonds *via* substrate-controlled induction based on aldol methodology developed in our group. The appropriate oxygenated stereocentres at C31 and C35 in **11** would then be set by controlled reductions of the corresponding ketones.

Following this plan (Scheme 8), the enantioselective preparation of the β-ketophosphonate (*R*)-**10** was first targeted. This route relied on asymmetric catalysis through use of Jacobsen's hydrolytic kinetic resolution of terminal epoxides to configure the C23 stereocentre.[24] In the event, 5-hexen-1-ol (**37**) was first derivatised as the TBS ether and converted into the racemic epoxide with *m*-CPBA. The hydrolytic resolution of this epoxide then proceeded with operational ease with (*R*,*R*)-Co(salen) precatalyst (0.5 mol%) to give multi-gram quantities of (*R*)-**38** (41%) in >98% ee. Opening the epoxide (*R*)-**38** with iso-propenylmagnesium bromide in the presence of catalytic CuI (15 mol%) then gave alcohol (*R*)-**39** (99%). The C23 hydroxyl group was subsequently protected (NaH, DMBCl) as its DMB ether (*R*)-**40** (82%). TBS ether cleavage of (*R*)-**40** (PPTS, MeOH) afforded alcohol (*R*)-**41**, which was then oxidised to the aldehyde (*R*)-**42** with Dess–Martin periodinane (84%, two steps).[25] Reaction of (*R*)-**42** with lithiated methyl dimethylphosphonate, followed by a further Dess–Martin oxidation then provided the



**Scheme 7** Retrosynthetic analysis of northern fragment 6.
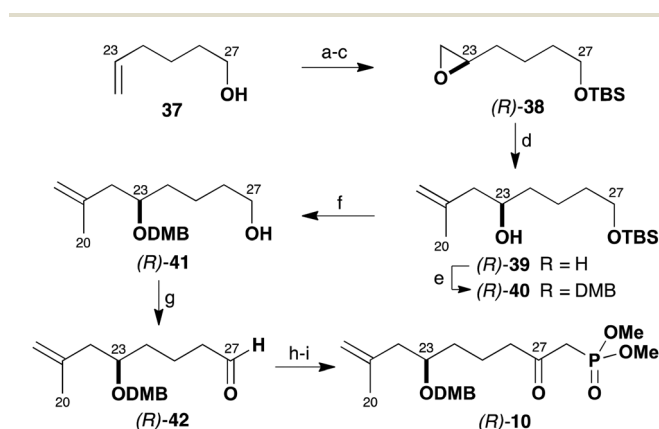


**Scheme 8** Synthesis of β-ketophosphonate (*R*)-**10**. *Reagents and conditions*: (a) TBSCl, imidazole, CH$_2$Cl$_2$, 96%; (b) *m*-CPBA, CH$_2$Cl$_2$, 96%; (c) (*R*,*R*)-Co(salen) (0.5 mol%), AcOH (1 mol%), H$_2$O (55 mol%), THF, 41%, >98% ee; (d) iso-propenylmagnesium bromide, CuI (15 mol%), THF, −78 to −50 °C, 99%; (e) NaH, DMBCl, DMF, 82%; (f) PPTS, MeOH, 99%; (g) DMP, CH$_2$Cl$_2$, 85%; (h) MeP(O)(OMe)$_2$, BuLi, THF, −78 °C; (i) DMP, CH$_2$Cl$_2$, 73% (two steps).

required β-ketophosphonate (*R*)-**10** (73%, two steps) in high enantiomeric purity.

With the β-ketophosphonate (*R*)-**10** in hand, attention turned to the preparation of the C29–C38 aldehyde **11** for the planned assembly of the northern fragment **6**. This started out with the known ethyl ketone **36** (Scheme 9), readily derived from (*S*)-Roche ester.[26] We have extensively used such chiral ketones for the aldol-based construction of elaborate polypropionate sequences in a variety of complex polyketides,[27] where inherently high levels of control can be attained over both their enolate geometry and π-facial selectivity in addition to

the aldehyde component. Following our standard conditions, **36** was treated with *c*-Hex$_2$BCl/Et$_3$N at 0 °C in Et$_2$O to selectively form the *E*-dicyclohexylboron enolate **43** and addition to acetaldehyde at −78 °C gave the expected 1,4-*syn* aldol adduct with high diastereoselectivity. This reaction is considered to proceed through the preferred formyl hydrogen bonded **TS-3**, where allylic strain is minimised. Interception of the cyclic boron intermediate **44** by preferred axial attack of an external hydride *via* **TS-4** also allowed the C35 stereocentre in **45** to be configured *in situ*. Thus, a Narasaka-type reduction of intermediate **44** with LiBH$_4$ at −78 °C efficiently set the 1,3-*syn* relationship between C35 and C37 in diol **45** (88%, >95 : 5 dr).[28] This convenient one-pot procedure efficiently installed three new stereogenic centres in excellent diastereoselectivity in **45** and proved easily scalable.

A key requirement for constructing the northern fragment **6** was that the hydroxyl stereocentres are appropriately differentiated to facilitate macrocyclisation and the sequential attachment of appendages. With this in mind, oxidation of the PMB ether **45** with DDQ under anhydrous conditions induced cyclisation to give the corresponding PMP acetal **46** (92%).[29] The remaining free hydroxyl group at C37 (the future site for glycosylation) was efficiently converted into the DEIPS (Et$_2$i-PrSi) ether **47** under standard silylation conditions (DEIPSCl, imidazole, 97%). Reductive opening of the PMP acetal, mediated by DIBAL at −78 °C, then regioselectively generated the secondary PMB ether **48** and the remaining primary alcohol was subsequently oxidised with Dess–Martin periodinane under buffered conditions to give aldehyde **49** (86%, two steps).
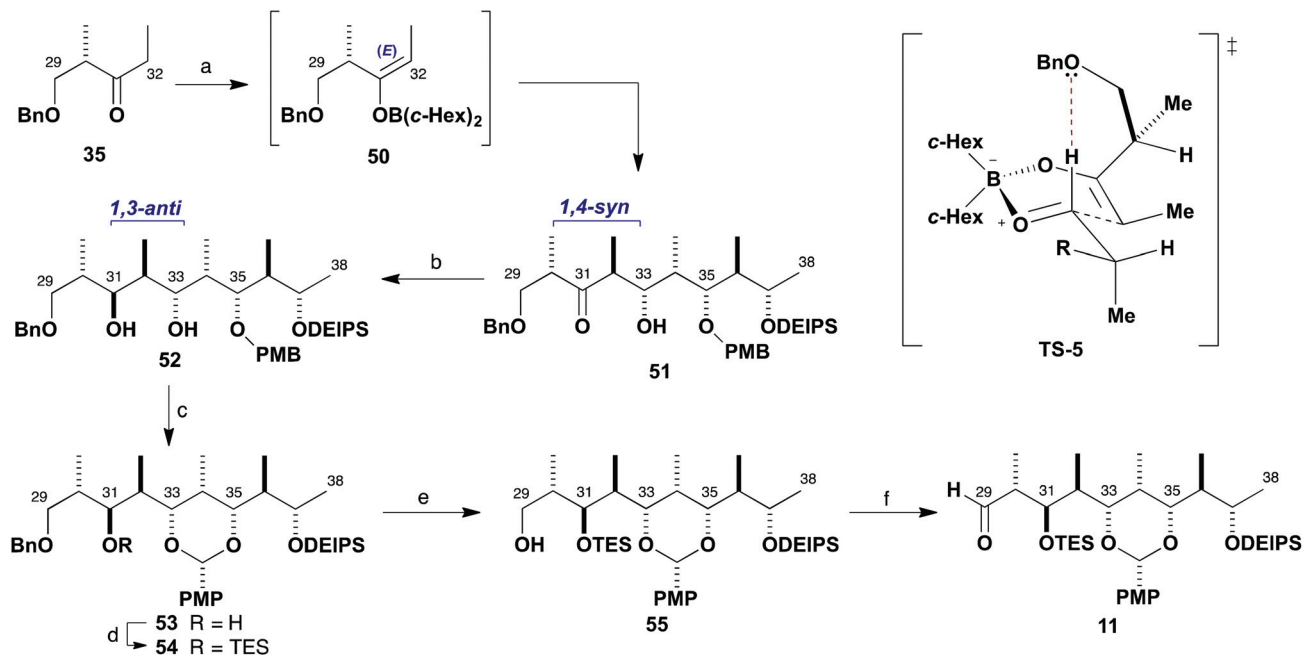
At this point, another boron aldol reaction was employed for chain extension to complete the full C29–C38 backbone of fragment **11** (Scheme 10). Selective *E*-enolisation (*c*-Hex$_2$BCl, Et$_3$N) of ethyl ketone **35**[30] to give enolate **50** and subsequent reaction with aldehyde **49** proceeded smoothly to provide adduct **51** (>95 : 5 dr, 96%). Pleasingly, this reaction was found to be higher yielding when performed on multi-gram scale than previously observed during route investigation.[6b] This highly selective 1,4-*syn* aldol reaction is considered to proceed *via* **TS-5**, with a stabilising formyl hydrogen bond and avoidance of allylic strain in the enolate matched with Felkin–Anh induction from the aldehyde component. It results in the controlled installation of the stereocentres at C32 and C33 with the requisite 1,2-*anti* configuration and C30 and C33 in a 1,4-*syn* relationship.

Directed reduction of the resulting β-hydroxyketone **51** under Evans–Saksena conditions[23] using Me$_4$NBH(OAc)$_3$ then provided the desired 1,3-*anti* diol **52** with high diastereoselectivity (>95 : 5 dr, 91%). This reduction set the final stereogenic centre of the characteristic stereooctet spanning the C24–C38 region of the brasilinolides. Further protecting group manipulation was required at this stage to differentiate the newly formed C31 hydroxyl group, which corresponds to the site for eventual macrolactonisation. Oxidative cyclisation of the PMB ether **52** with DDQ in CH$_2$Cl$_2$ under anhydrous conditions proceeded cleanly and afforded the PMP acetal **53** (85%). Conversion into the TES ether **54** (TESOTf, 2,6-lutidine)
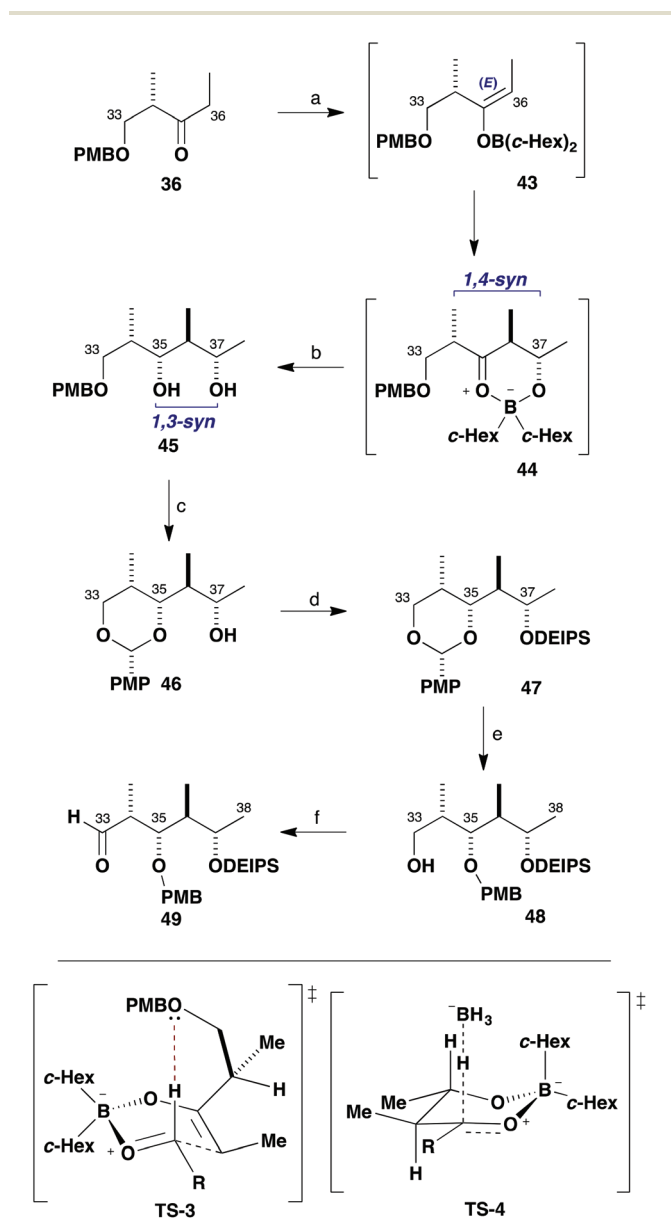


**Scheme 9** Synthesis of aldehyde **49**. *Reagents and conditions*: (a) *c*-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; MeCHO, −78 to −20 °C; (b) LiBH$_4$, THF, −78 °C; NaOH, MeOH, H$_2$O$_2$, 88%, >95 : 5 dr; (c) DDQ, 4 Å mol. sieves, CH$_2$Cl$_2$, −10 °C, 92%; (d) DEIPSCl, imidazole, CH$_2$Cl$_2$, 97%; (e) DIBAL, CH$_2$Cl$_2$, −78 °C, 93%; (f) DMP, NaHCO$_3$, CH$_2$Cl$_2$, 93%.

**5722** | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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**Scheme 10** Synthesis of aldehyde **11**. *Reagents and conditions*: (a) Ketone **35**, c-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C; aldehyde **49**, Et$_2$O, −78 to −20 °C, 96%, >95 : 5 dr; (b) Me$_4$NBH(OAc)$_3$, MeCN–AcOH (4 : 1), −30 °C, 91%, >95 : 5 dr; (c) DDQ, 4 Å mol. sieves, CH$_2$Cl$_2$, −10 °C, 85%; (d) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 99%; (e) H$_2$, RANEY-Nickel®, EtOH, 92%; (f) DMP, NaHCO$_3$, CH$_2$Cl$_2$, 92%.

was followed by selective hydrogenolysis of the benzyl ether in the presence of the PMP acetal using RANEY®-Nickel in EtOH to reveal the primary alcohol **55**,[31] which was oxidised using buffered Dess–Martin periodinane to give aldehyde **11** (85%, two steps).
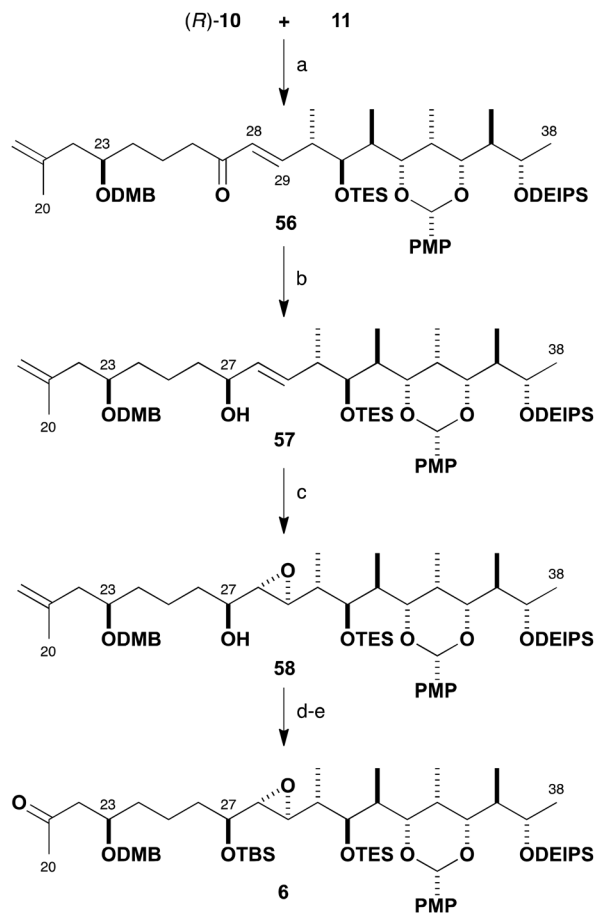
With the β-ketophosphonate (*R*)-**10** and the aldehyde **11** in hand, fragment union *via* HWE olefination was examined (Scheme 11). Following our standard conditions,[32] this transformation was mediated by Ba(OH)$_2$ in wet THF to efficiently afford enone **56** (96%) in excellent selectivity (>95 : 5 *E* : *Z*). Reagent-controlled CBS reduction[33] of **56** to generate the required allylic alcohol **57** was found to be highly diastereoselective (88%, >95 : 5 dr) with the use of (*R*)-Me-CBS catalyst and BH$_3$·SMe$_2$ at −50 °C. Having installed the requisite (27*S*)-hydroxyl-bearing centre, the Sharpless asymmetric epoxidation of this elaborate allylic alcohol was investigated.[34] In this case, the desired epoxide configuration indicated the deployment of the Ti(O*i*-Pr)$_4$–(+)-DIPT reagent system. On small scale, the Sharpless epoxidation of **57** was found to proceed to afford **58** in 59% yield, attaining an acceptable 7 : 1 dr, but this proved to be capricious and difficult to reproduce on a larger scale. Nevertheless, with some of the desired epoxide in hand, the synthesis of the planned northern fragment **6** (86%, two steps) was completed by TBS ether formation (TBSOTf, 2,6-lutidine) followed by a dihydroxylation–oxidative diol cleavage step (OsO$_4$; NaIO$_4$–SiO$_2$) to reveal the methyl ketone functionality.[35] Following this route, the preparation of the C20–C38 northern fragment **6** was achieved in 13% overall yield over 16 linear steps from ethyl ketone **36**.

### Preliminary studies on the aldol coupling of the northern and southern fragments

With routes to the major fragments **5** and **6** developed, attention now turned to exploring the pivotal C19–C20 aldol bond construction to enable completion of the full carbon skeleton of the brasilinolides. As outlined in Scheme 12, it was initially planned that the C19 configuration could be controlled in a 1,3-*anti* sense relative to C17 *via* a Mukaiyama-type aldol bond construction.[5a,36] This envisaged addition of the silyl enol ether **59** (derived from **6**) to a suitable aldehyde such as **60** to be prepared from the available southern fragment **5**. The anticipated β-hydroxyketone **61** resulting from this coupling would then be expected to undergo *in situ* hemiacetalisation at C15 to give **62**. The advanced nature of both components dictated that this complex system should first be modelled by investigating the aldol coupling reactions of suitable truncated fragments, which could be readily prepared by interception of intermediates already in hand.

As shown in Scheme 13, the truncated methyl ketone (*R*)-**63** was easily accessed from the previously described intermediate (*R*)-**40**. Thus dihydroxylation of olefin (*R*)-**40** (OsO$_4$, NMO) and oxidative glycol cleavage with NaIO$_4$–SiO$_2$ provided (*R*)-**63** (86%). The model aldehyde **64** was prepared from the β-hydroxyketone **29** obtained in exploratory studies (Scheme 5) for the southern fragment synthesis. In this case, the secondary alcohol was first protected as the TBS ether (TBSOTf, 2,6-lutidine) and the ketone reduced (NaBH$_4$). Then, the primary TBS ether was cleaved (PPTS, MeOH) and both hydroxyl groups oxidised under Swern conditions to give the δ-ketoaldehyde **64**

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*Org. Biomol. Chem.*, 2015, **13**, 5716–5733 | **5723**

**Scheme 11** Synthesis of methyl ketone **6**. *Reagents and conditions*: (a) Ba(OH)$_2$, THF–H$_2$O (40 : 1), 96%, >95 : 5 *E* : *Z*; (b) (*R*)-Me-CBS catalyst, BH$_3$·SMe$_2$, THF, −50 °C, 88%, >95 : 5 dr; (c) Ti(Oi-Pr)$_4$, (+)-DIPT, *t*-BuOOH, 4 Å mol. sieves, CH$_2$Cl$_2$, −20 °C, 59%, 7 : 1 dr; (d) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C; (e) OsO$_4$, NMO, THF–H$_2$O; NaIO$_4$–SiO$_2$, CH$_2$Cl$_2$, 86% (two steps).

(74%, four steps). This sequence served to circumvent deleterious cyclisation–elimination pathways, which can occur in the oxidative manipulation of 1,5-hydroxyketones.[37]

Given the β-oxygenation at C17 in the aldehyde component **64**, it was anticipated that addition of the silyl enol ether (*R*)-**65** derived from (*R*)-**63** would install the C19 hydroxyl stereocentre in a 1,3-*anti* sense (Scheme 14). The predicted 1,3-stereoinduction in such Mukaiyama aldol reactions of β-alkoxyaldehydes to **66** invokes an acyclic transition state based on the Evans polar model.[38] In support of this plan, a similar Mukaiyama aldol coupling (Scheme 15) of silyl enol ether **67** with the δ-ketoaldehyde **68** mediated by BF$_3$·OEt$_2$ at −98 °C gave the hemiacetal adduct **70** (cyclised version of **69**) as a single diastereomer, which served as a key step in our total synthesis of auriside A (**71**).[39]

However, although the aldol reaction of silyl enol ether (*R*)-**65** using BF$_3$·OEt$_2$ at −78 °C was found to proceed smoothly with simple aldehydes, many attempts to form the requisite C19–C20 bond in the more elaborate aldehyde **64** failed. As
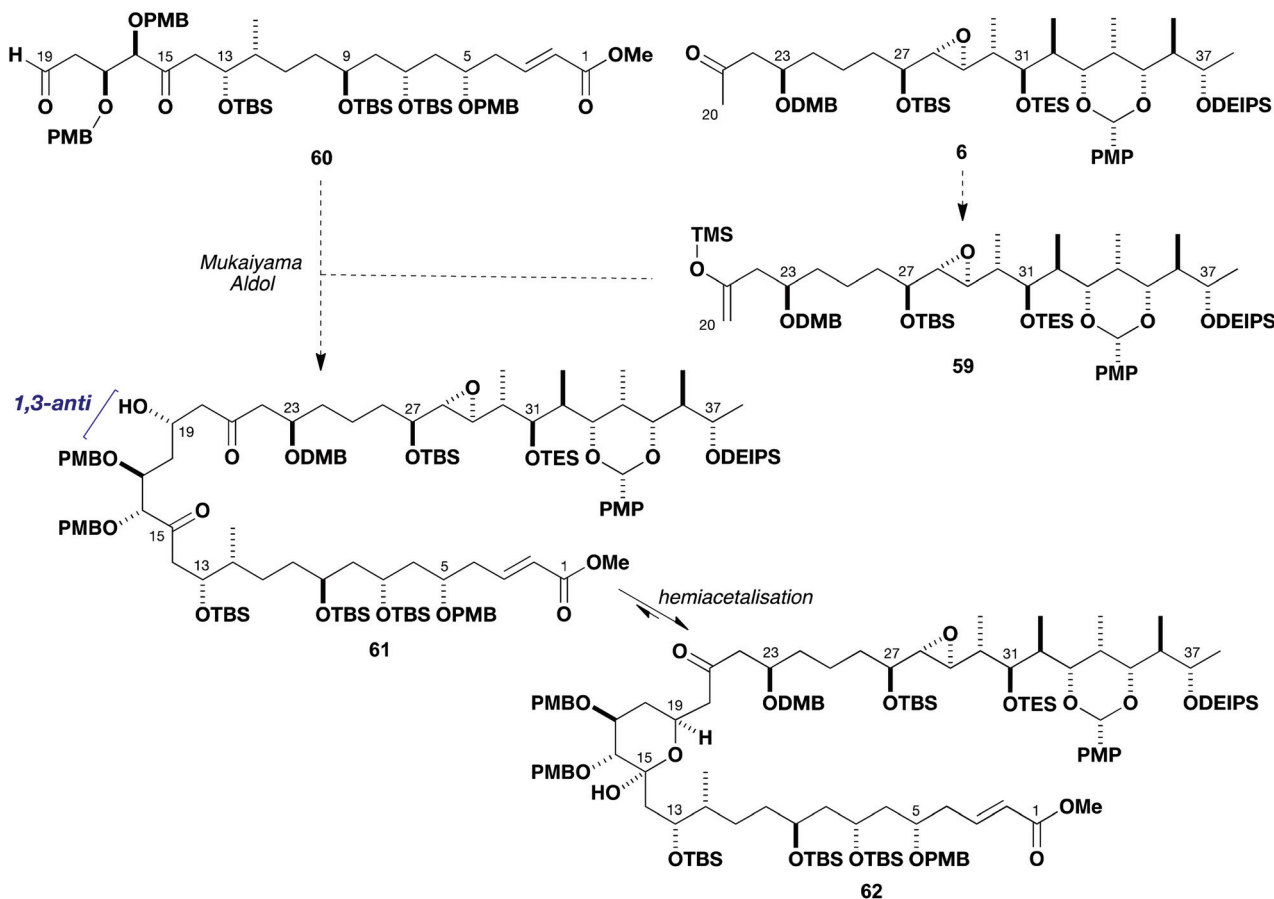
indicated in Scheme 14, the use of BF$_3$·OEt$_2$, B(C$_6$F$_5$)$_3$, Me$_2$AlCl, TiCl$_2$(Oi-Pr)$_2$, Sc(OTf)$_3$ or Yb(OTf)$_3$ all led to decomposition of the δ-ketoaldehyde component **64**. Disappointingly, screening further Lewis acids such as MgBr$_2$, ZnCl$_2$ or Zn(OTf)$_2$ also did not affect the desired aldol addition but served to only cleave the silyl enol ether to afford the corresponding methyl ketone (*R*)-**63**. In all of these cases, no product-derived material was observed in the crude $^1$H NMR spectra.

As the Mukaiyama aldol approach failed in this situation due to the unanticipated sensitivity of **64** to Lewis acids, it was proposed that the desired construction of the C19–C20 bond might be realised through the much milder conditions associated with a boron-mediated aldol reaction (Scheme 16). By comparison with the known reactivity of such β-alkoxy methyl ketones, the newly formed C19 hydroxyl centre likely would preferentially form with the undesired configuration due to the inherent 1,5-*anti* induction from the (23*R*)-stereocentre.

As the stereocentre at C23 was anticipated to control the installation of the C19 hydroxyl group in a 1,5-*anti* sense,[7,21] it was decided to consider inverting the configuration of the enolate component to achieve the requisite diastereoselectivity in the coupling step and this might help simplify the NMR analysis. This revised strategy was adopted having noted that a late-stage installation of an ester appendage at C23 might be performed with inversion of configuration under Mitsunobu conditions instead of the previously anticipated direct esterification suggested earlier in Scheme 1. Therefore, model studies using the enantiomeric methyl ketone (*S*)-**63** were pursued next, where this was easily prepared by changing the enantiomer of the Jacobsen catalyst used in the established route (Scheme 8). In the event, enolisation of methyl ketone (*S*)-**63** under standard conditions (*c*-Hex$_2$BCl, Et$_3$N) and addition to **64** resulted in, for the first time, evidence of adduct formation in the crude $^1$H NMR spectrum. The NMR analysis, however, was complicated due to the presumed equilibrium formed between the β-hydroxyketone **72** and the cyclic hemiacetal form **73** and diastereomers thereof. These observations were taken as a promising indication that further investigations of these types of model systems would yield the desired outcome to be deployed in the real fragment coupling.

It was also apparent from several attempted manipulations of the mixture of **72** and **73** that in the full system (*cf.* Scheme 12) clean formation of the C15 hemiacetal product would be difficult to realise. Faced with these problems, it was proposed that masking the C15 ketone as an alkene might help attain more control in this critical fragment coupling step. Previously prepared ketone **30** allowed for such exploratory investigations to be performed (Scheme 17). It was found to be possible to methylenate ketone **30** under both Takai–Lombardo[40] and Nysted reagent[41] protocols to give **74** (94% and 74% yields, respectively). Selective cleavage of the primary TBS ether (HF·pyr) then gave alcohol **75** (96%), which was oxidised to give the revised model aldehyde **76** (95%) with Dess–Martin periodinane in readiness for further fragment coupling studies (Tables 1 and 2).

5724 | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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**Scheme 12** Proposed Mukaiyama-type aldol coupling between **59** and **60** to assemble the advanced C1–C38 intermediate **62**.
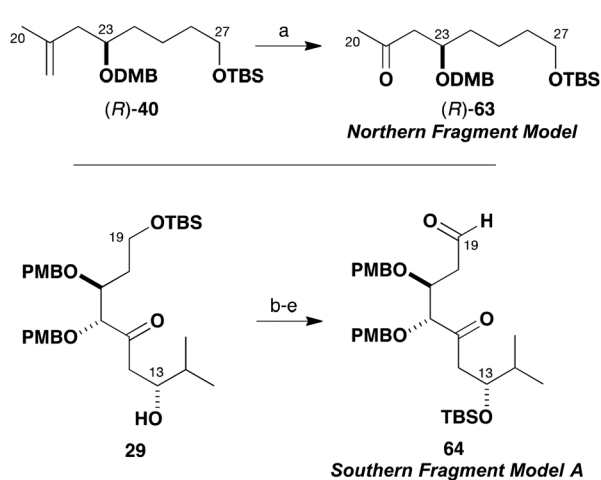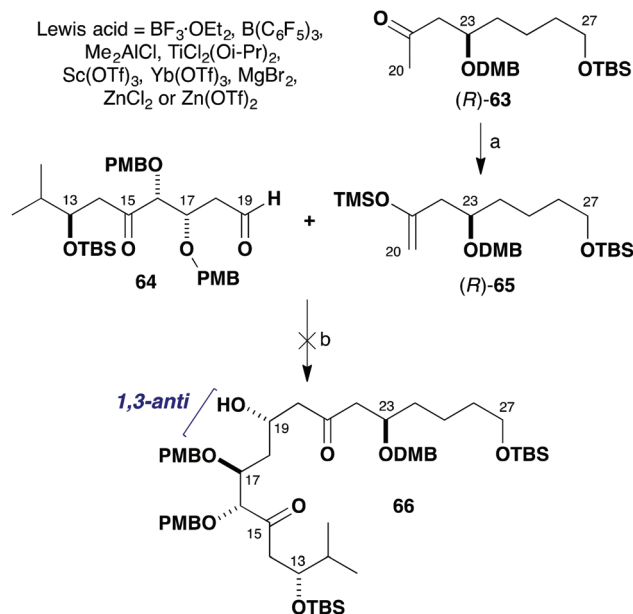


**Scheme 13** Preparation of model fragments (*R*)-**63** and **64**. *Reagents and conditions*: (a) OsO₄, *N*-morpholine-*N*-oxide, THF–H₂O; NaIO₄–SiO₂, 86%; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C, 95%; (c) NaBH₄, MeOH, 99%; (d) PPTS, MeOH, 85%; (e) (COCl)₂, DMSO, CH₂Cl₂, −78 °C; Et₃N, 93%.

Enolisation of methyl ketone (*S*)-**63** (*epi*-C23 series) and subsequent aldol addition to aldehyde **76** was first performed in Et₂O at low temperature with a variety of achiral boron

reagents (Scheme 18, Table 1, entries 1–5). As anticipated, there was some selectivity for the desired 1,5-*anti* product **77**, although not as high as previously observed in these types of reaction. There was a modest increase in diastereoselectivity to a more promising 4.8 : 1 dr (entry 5), when using 9-BBNCl/i-Pr₂NEt. In this complex aldol coupling, it was conjectured that the aldehyde component **76** has a π-facial bias in the opposing sense to that desired and 1,3-*syn* to the C17 stereogenic centre. This would appear to violate the bias for 1,3-*anti* stereoinduction observed in simple systems according to the Evans polar model.[38] There is, however, some evidence to suggest that additional stereochemical features and steric bulk in the γ-position of β-alkoxyaldehydes can disrupt this model by way of a gearing effect, such as that described by Sulikowski and co-workers.[42]

Having achieved a promising level of selectivity for setting the desired C19 configuration in **77**, switching to a chiral boron reagent ((−)-Ipc₂BCl) was expected to help reinforce the enolate π-facial preference (entries 6–8).[43] Unfortunately, the product **77** was only observed to form with moderate diastereoselectivity (2.5 : 1 dr, **77** : **78**) and changing the reaction solvent to pentane or CH₂Cl₂ was also found to give no improvement. This reduced diastereoselectivity was further observed by reaction with the enantiomeric (+)-Ipc₂BCl (entry 9), whereby the

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*Org. Biomol. Chem.*, 2015, **13**, 5716–5733 | **5725**

**Scheme 14** Attempted Mukaiyama aldol addition between (R)-**65** and **64**. *Reagents and conditions*: (a) LiHMDS, THF, −78 °C; TMSCl·Et$_3$N, 90%; (b) Lewis acid, CH$_2$Cl$_2$, −98 to −78 °C.

chiral reagent reversed the sense of stereoinduction to the undesired C19 configuration.

The unexpected sense of π-facial bias of aldehyde **76** towards boron-mediated aldol additions prompted further investigation of this reaction. Further studies were performed with the methyl ketone (R)-**63** (natural C23 configuration as in the brasilinolides). This was anticipated to expand the data set
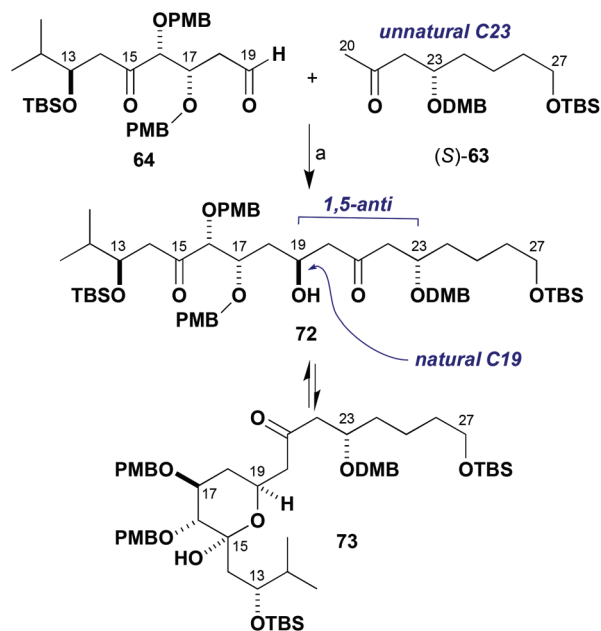
for the effects of stereochemical bias from the enolate, aldehyde and boron reagent (Scheme 19, Table 2). Reaction of aldehyde **76** with the dicyclohexylboron enolate of (R)-**63** proceeded in 5 : 1 dr for the 1,5-*anti* product **79** corresponding to the unnatural configuration at C19 (entry 1). Comparison to the corresponding result with (S)-**63** (Table 1, entry 1) shows an increase in 1,5-*anti* selectivity, indicating a small matched effect between the enolate and aldehyde. Indeed, reinforcement of this substrate-based stereoinduction with the appropriate (+)-Ipc$_2$BCl reagent (Table 2, entry 2) now achieved excellent levels of diastereoselectivity (17 : 1 dr, **79** : **80**) in favour of the 1,5-*anti* product. Unsurprisingly, when the enantiomeric (−)-Ipc$_2$BCl was employed to help favour the 1,5-*syn* product **80** with the desired C19 configuration (entry 3), the diastereoselectivity was poor (1 : 1.5 dr, **79** : **80**, 1,5-*anti* : *syn*) as the chiral reagent is tasked with overriding the inherent substrate reactivity.

This preliminary investigation of the unexpectedly complex C19–C20 aldol coupling step gave a helpful steer as to how to best evolve our strategy to advance the synthesis of the brasilinolides. It was concluded that it would be highly challenging to achieve excellent diastereoselectivity for the correct C19 configuration using boron-mediated aldol reactions. The completely matched reactivity between all components was identified as the scenario where (R)-**63** (natural C23 configuration), aldehyde **76** (facial preference 1,3-*syn* to C17) and (+)-Ipc$_2$BCl were used to give product **79** with the incorrect C19 configuration (Table 2, entry 2). Although as discussed previously, the C23 stereocentre could potentially be inverted at a later stage on esterification, selective inversion of C19 would be considerably more problematic. Having established a set of workable, albeit unoptimised, conditions for the formation of the C19–C20
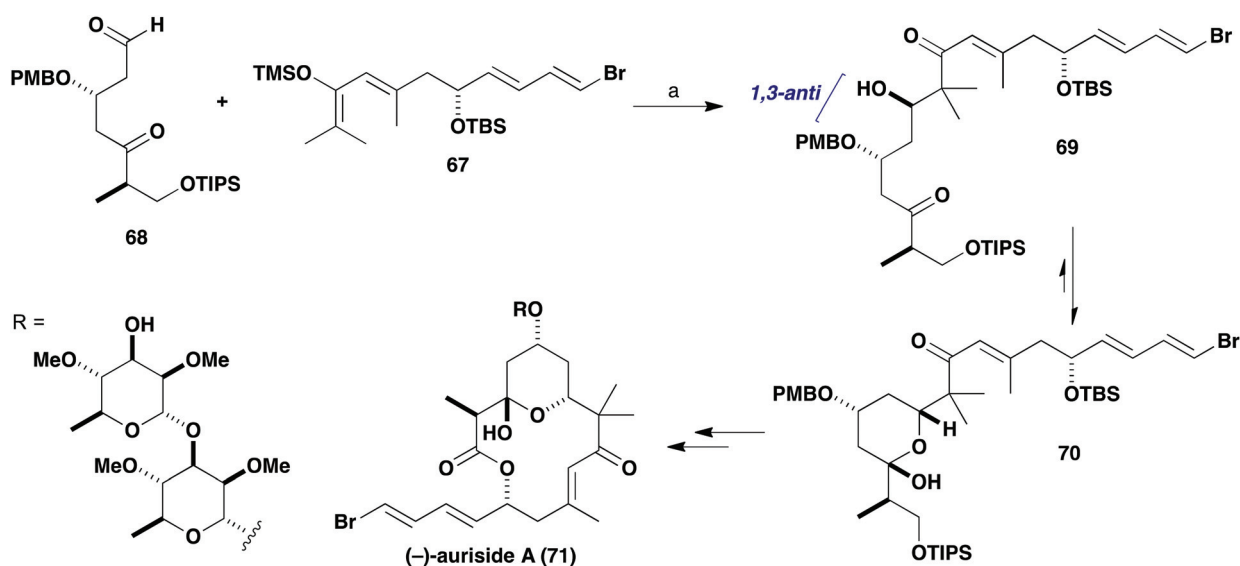


**Scheme 15** Fragment coupling using a Mukaiyama aldol reaction in the synthesis of (−)-auriside A (**71**). *Reagents and conditions*: (a) BF$_3$·OEt$_2$, CaH$_2$, CH$_2$Cl$_2$, −98 °C, 10 min, 66%, single diastereomer.

5726 | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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**Scheme 16** Model boron-mediated aldol reaction between (*S*)-**63** and **64**. *Reagents and conditions*: (a) Ketone (*S*)-**63**, *c*-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1 h; aldehyde **64**, −78 to −20 °C.



**Scheme 17** Preparation of aldehyde **76**. *Reagents and conditions*: (a) Nysted reagent (*cyclo*-dibromodi-μ-methylene[μ-(tetrahydrofuran)]-trizinc), TiCl$_4$, THF, 94% or PbI$_2$, CH$_2$I$_2$, Zn, THF, 74%; (b) HF·pyr, pyr, THF, 96%; (c) DMP, NaHCO$_3$, CH$_2$Cl$_2$, 95%.

bond with the C15-methylene model substrate **76**, it was important in going forward to able to transfer this chemistry to the real system. Disappointingly, the C15-methylene functionality proved to be unreactive towards standard oxidation conditions to regenerate the required ketone presumably due to steric congestion. This shortcoming necessitated a change in strategy for masking the C15 ketone in the southern fragment as discussed below.

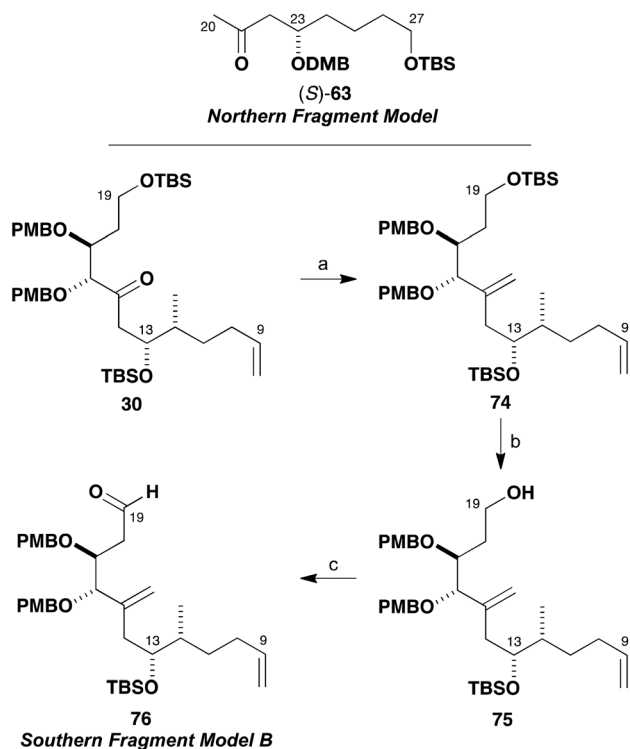**Elaboration of 5 to the advanced southern fragment 81**

Based on the foregoing findings, a C15-acetoxy aldehyde **81** (Scheme 20) was proposed as the revised southern fragment to be used in the pivotal C19–C20 aldol coupling step. It was envisaged that the C15 ketone could subsequently be reinstalled by oxidation after selective cleavage of the acetate. Given the already high level of molecular complexity of the northern and southern fragments, it was advantageous that any reduction of the C15 ketone moiety was performed in a highly stereo-controlled fashion. In practice, reduction of **5** with Zn(BH$_4$)$_2$ at low temperature proceeded cleanly to afford alcohol **82** with high diastereoselectivity (99%, >95 : 5 dr).[44] As expected from the reaction proceeding by a chelation pathway, this was assigned as the C15,C16-*anti* stereoisomer with the (15*S*)-configuration. Acetylation then gave ester **83** in 97% yield.

Selective desilylation of **83** (TBAF, AcOH) at C19 to give **84** was followed by oxidation with Dess–Martin periodinane to afford aldehyde **81** (89%, two steps). This high yielding sequence gave the required stereodefined C15-acetoxy aldehyde **81** in 37% overall yield over 14 steps from **24**.

**Revisiting the northern fragment**

One of the concerns in our planned synthesis of the brasilinolides was the potential reactivity of the C28–C29 epoxide moiety in the northern hemisphere. In the context of the structure determination studies performed on brasilinolide C (**3**), it was demonstrated that the epoxide was prone to intramolecular nucleophilic opening by pendant hydroxyl groups.[3b] Fortunately, this had not been a problem to date, where presumably the adjacent protecting groups shielded the epoxide even towards exposure to Lewis acids such as dibutylboron triflate. An unexpected hurdle, however, was the reliable installation of the epoxide itself in acceptable yield, diastereoselectivity, and on a reasonable scale. At the time, Sharpless asymmetric epoxidation of the allylic alcohol **57** (Scheme 11) did not appear to satisfy all these requirements and a screen of reaction conditions and other hydroxyl-directed electrophilic epoxidation protocols was performed to no avail.

With the exploration of alternative electrophilic epoxidation methods on **57** proving unrewarding, it was proposed that the enone **85** (Scheme 21) could be employed as a substrate for nucleophilic epoxidation. This enone was prepared by an analogous route to that shown in Scheme 11 for the corresponding C23-*epi* compound **56** but now using the (23*S*)-β-ketophosphonate (*S*)-**10** for the HWE step.[20] Serendipitously, epoxidation of
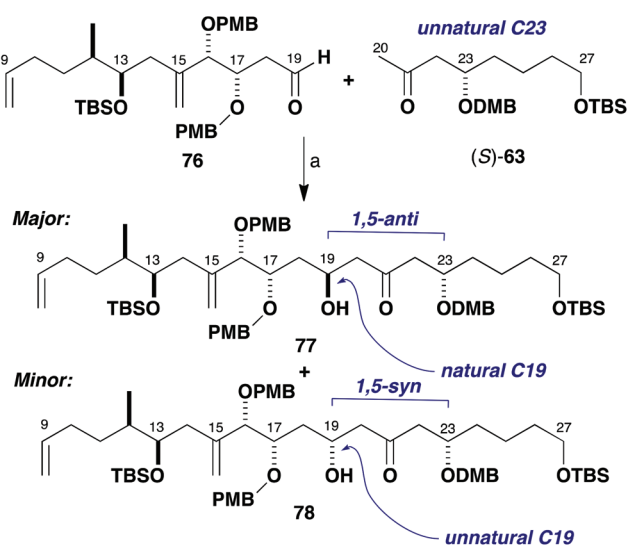
**Table 1**  Model aldol coupling between (S)-**63** and **76**

| Entry | Lewis acid | Base | Enolisation temp. (Time) | Reaction temp. (Time) | Solvent | Crude dr 77 : 78 |
|---|---|---|---|---|---|---|
| 1 | c-Hex$_2$BCl | Et$_3$N | −78 °C (1 h) | −78 °C (3 h) → −23 °C (16 h) | Et$_2$O | 3 : 1 |
| 2 | Bu$_2$BOTf | i-Pr$_2$NEt | −78 °C (1 h) | −78 °C (3 h) | Et$_2$O | 3.5 : 1 |
| 3 | 9-BBNOTf | i-Pr$_2$NEt | −78 °C (1 h) | −78 °C (1 h) | Et$_2$O | 4 : 1 |
| 4 | 9-BBNCl | i-Pr$_2$NEt | −78 °C (1 h) | −78 °C (3 h) | Et$_2$O | 4 : 1 |
| 5 | 9-BBNCl | i-Pr$_2$NEt | −78 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 4.8 : 1 |
| 6 | (−)-Ipc$_2$BCl | Et$_3$N | 0 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 2.5 : 1 |
| 7 | (−)-Ipc$_2$BCl | Et$_3$N | 0 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Pentane | 2 : 1 |
| 8 | (−)-Ipc$_2$BCl | Et$_3$N | 0 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | CH$_2$Cl$_2$ | 1 : 1 |
| 9 | (+)-Ipc$_2$BCl | Et$_3$N | 0 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 1 : 2 |

**Table 2**  Model aldol coupling between (R)-**63** and **76**

| Entry | Lewis acid | Base | Enolisation temp. (Time) | Reaction temp. (Time) | Solvent | Crude dr 79 : 80 |
|---|---|---|---|---|---|---|
| 1 | c-Hex$_2$BCl | Et$_3$N | −78 °C (1 h) | −78 °C (3 h) → −23 °C (16 h) | Et$_2$O | 5 : 1 |
| 2 | (+)-Ipc$_2$BCl | Et$_3$N | −78 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 17 : 1 |
| 3 | (−)-Ipc$_2$BCl | Et$_3$N | −78 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 1 : 1.5 |



**Scheme 18**  Model aldol coupling between (S)-**63** and **76**. *Reagents and conditions*: (a) Ketone (S)-**63**, L$_2$BX, R$_3$N; aldehyde **76**, conditions in Table 1.
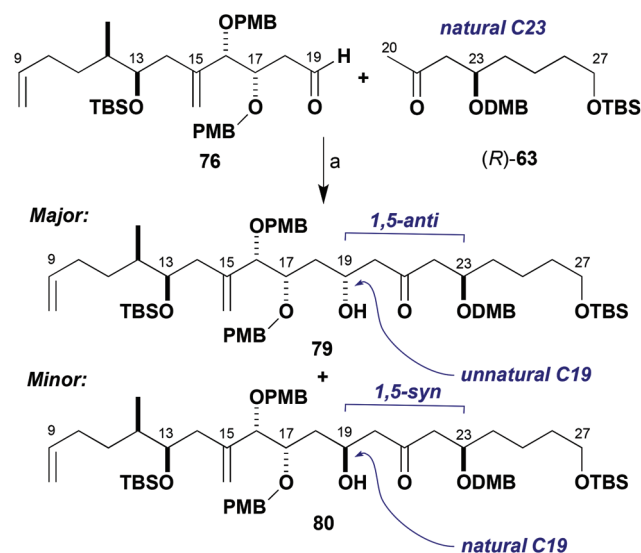


**Scheme 19**  Model aldol coupling between (R)-**63** and **76**. *Reagents and conditions*: (a) Ketone (R)-**63**, L$_2$BX, R$_3$N; aldehyde **76**, conditions in Table 2.

**85** with t-BuOOLi was found to be effective at −78 °C to afford **86** in both high diastereoselectivity (30 : 1 dr) and yield (91%). The configuration at C28 and C29, however, was subsequently determined to be epimeric to that required for the brasilinolides.[20] Given this unexpectedly high selectivity and the enhanced scalability of the transformation, it was decided at this stage to go forward to advance the chemistry required for constructing the brasilinolides, chiefly examination of the major fragment coupling and further manipulation. The greater availability of the advanced intermediate **86** with the opposite epoxide configuration was considered to be a good

opportunity for embarking on this intelligence gathering exercise.

As shown in Scheme 21, stereocontrolled reduction of ketone **86** was affected by treatment with DIBAL in t-BuOMe at −98 °C to give the alcohol **87** (83%) with 10 : 1 dr for the natural C27 configuration (Mosher ester analysis[20]). Alcohol **87** was protected as the TBS ether **88** (TBSOTf, 2,6-lutidine) and oxidative cleavage of the alkene (OsO$_4$, NaIO$_4$–SiO$_2$) afforded the methyl ketone **89** (80%, two steps). With this modified route established, sufficient quantities of a full northern fragment mimic **89** were now generated to develop suitable con-
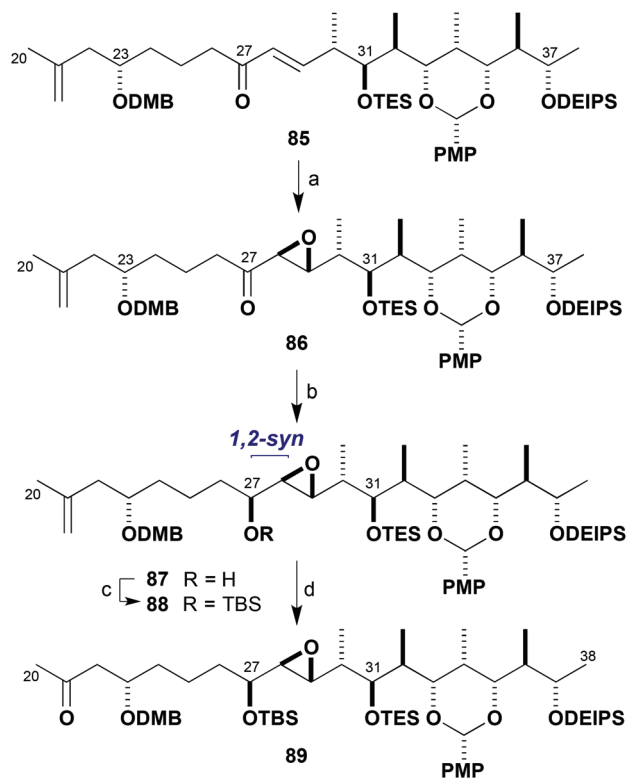
5728 | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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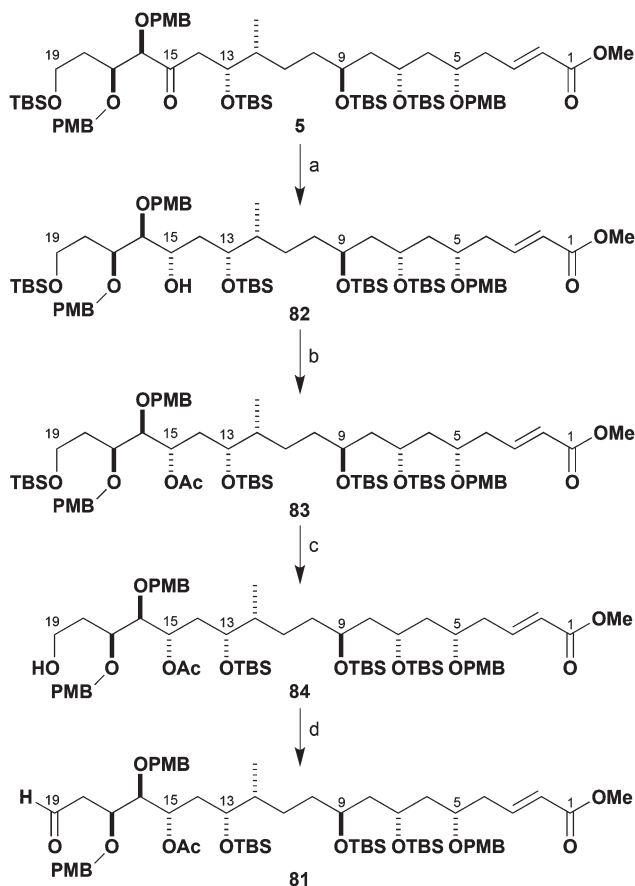
**Scheme 20** Preparation of C1–C19 aldehyde **81**. *Reagents and conditions*: (a) Zn(BH₄)₂, Et₂O, −78 to 0 °C, 99%, >95 : 5 dr; (b) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 97%; (c) TBAF, AcOH, THF, 90% (brsm); (d) DMP, NaHCO₃, CH₂Cl₂, 98%.



**Scheme 21** Synthesis of ketone **89**. *Reagents and conditions*: (a) *t*-BuOOH, BuLi, THF, −78 to −20 °C, 91%, 30 : 1 dr; (b) DIBAL, *t*-BuOMe, −98 °C, 83%, 10 : 1 dr; (c) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C, 91%; (d) OsO₄, *N*-methylmorpholine-*N*-oxide, THF–H₂O; NaIO₄–SiO₂, CH₂Cl₂, 88%.

ditions for achieving the complex aldol coupling with the full southern aldehyde **81**.

### Realising the aldol coupling of the northern and southern fragments

With useful stocks of the major fragments now in hand, their planned aldol union to assemble an advanced C1–C38 intermediate for the brasilinolides could be studied and any pitfalls identified. From experience gained earlier of boron-mediated aldol reactions using truncated systems, the desired 1,5-*anti* selective addition reaction between **81** and **89** was much anticipated (Scheme 22). At the outset, preliminary screenings of standard conditions using *c*-Hex₂BCl/Et₃N were found to give a modest 2 : 1 dr in favour of the 1,5-*anti* product **90** (Table 3, entry 1). Use of (−)-Ipc₂BCl as the matched chiral boron reagent proceeded with an improved 3 : 1 dr in favour of the desired C19 diastereomer (entry 2) but in low conversion. By contrast, use of (+)-Ipc₂BCl resulted in negligible diastereoselectivity for this transformation (entry 3). While all of these exploratory reactions gave a disappointingly low conversion, both starting materials were recoverable (Table 3).
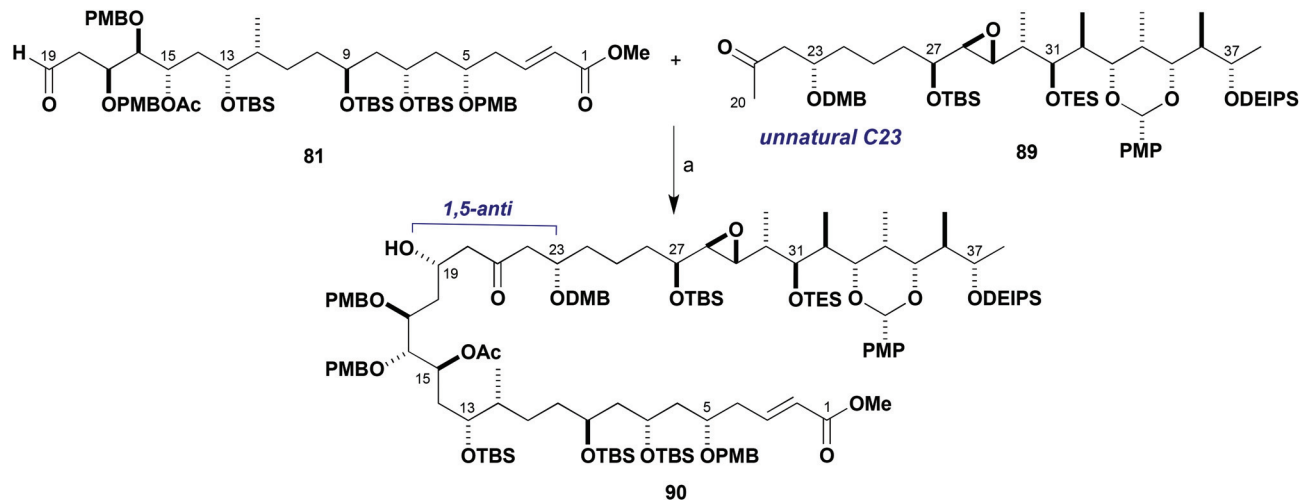
With a view to enhancing the reactivity of the boron enolate, the Lewis acid was changed to Bu₂BOTf (entries 4–8). Conducting the aldol reaction at −78 °C led to a 32% isolated yield of a separable 2.5 : 1 mixture of adducts in favour of the desired C19 configuration in **90** with good recovery of unreacted ketone **89** and aldehyde **81** (entry 4). Use of the more reactive dibutylboron enolate was compatible with performing the reaction at a lower temperature (−98 °C), resulting in both higher diastereoselectivity and isolated yield (entry 5), with both starting materials also recoverable. This provided the aldol adducts in 95% yield brsm with a workable 3.5 : 1 dr in favour of **90**. This would prove to be the preferred set of conditions for carrying out this challenging aldol fragment union, despite varying different reaction parameters (entries 6–8).

### Further elaboration to a C1–C38 advanced intermediate

With access to the configurationally pure aldol product **90** representing the full C1–C38 carbon skeleton, studies into its manipulation to afford an advanced brasilinolide intermediate were commenced (Scheme 23). Hydroxyl-directed reduction of the ketone **90** under Evans–Saksena conditions[23] proceeded smoothly to give the 1,3-*anti* diol **91** (>95 : 5 dr, 85%). This transformation represented the controlled installation of the remaining C21 stereocentre. The hydroxyl groups were then

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*Org. Biomol. Chem.*, 2015, **13**, 5716–5733 | **5729**

**Scheme 22** Aldol coupling of fragments **81** and **89**. *Reagents and conditions*: (a) Ketone **89**, $L_2BX$, $R_3N$; aldehyde **81**, conditions in Table 3.

both derivatised as TBS ethers (TBSOTf, 2,6-lutidine) to give the fully protected intermediate **92** (98%).

We now required to saponify the acetate group at C15 in **92** with concomitant generation of the free carboxylic acid at C1 (Scheme 23). However, a screen of standard reagents (*e.g.* LiOH) led to hydrolysis of the methyl ester but without achieving the acetate cleavage. Gratifyingly, reduction of **92** with DIBAL at −78 °C successfully cleaved the acetate and also reduced the ester to an inconsequential mixture of allylic alcohol and enal. The crude mixture of these products was subjected to Dess–Martin oxidation to afford solely enal **93** (90%, two steps), also reintroducing the required ketone oxidation level at C15.[45] While this has the wrong configuration for the epoxide, it is anticipated that this sequence should be directly applicable to the desired epoxide series.

As a prelude to these future efforts, we returned to earlier intermediates to address the incorrectly configured epoxide (Scheme 24). Reagent-controlled CBS reduction of enone **85** to generate allylic alcohol **94** proceeded smoothly at −50 °C (88%, >95 : 5 dr) as had been observed with the *epi*-C23 compound **56**. After some experimentation, it was found that Sharpless asymmetric epoxidation directed by the (27*S*)-hydroxy-bearing stereocentre could be affected using a Ti(Oi-Pr)$_4$–(+)-DET reagent system to give **95** in high yield (86%) but

only moderate diastereoselectivity (2 : 1 dr **95** : **87**). Nonetheless, this reproducible transformation now gave ready access to useful amounts of **95** possessing the requisite epoxide configuration. Thus epoxide **95** was converted into TBS ether **96** (TBSOTf, 2,6-lutidine, 86%) and finally to the revised northern fragment **97** by a dihydroxylation–oxidative diol cleavage step (OsO$_4$; NaIO$_4$–SiO$_2$, 85%), in readiness for repeating the aldol coupling with aldehyde **81** (*cf.* Scheme 22).
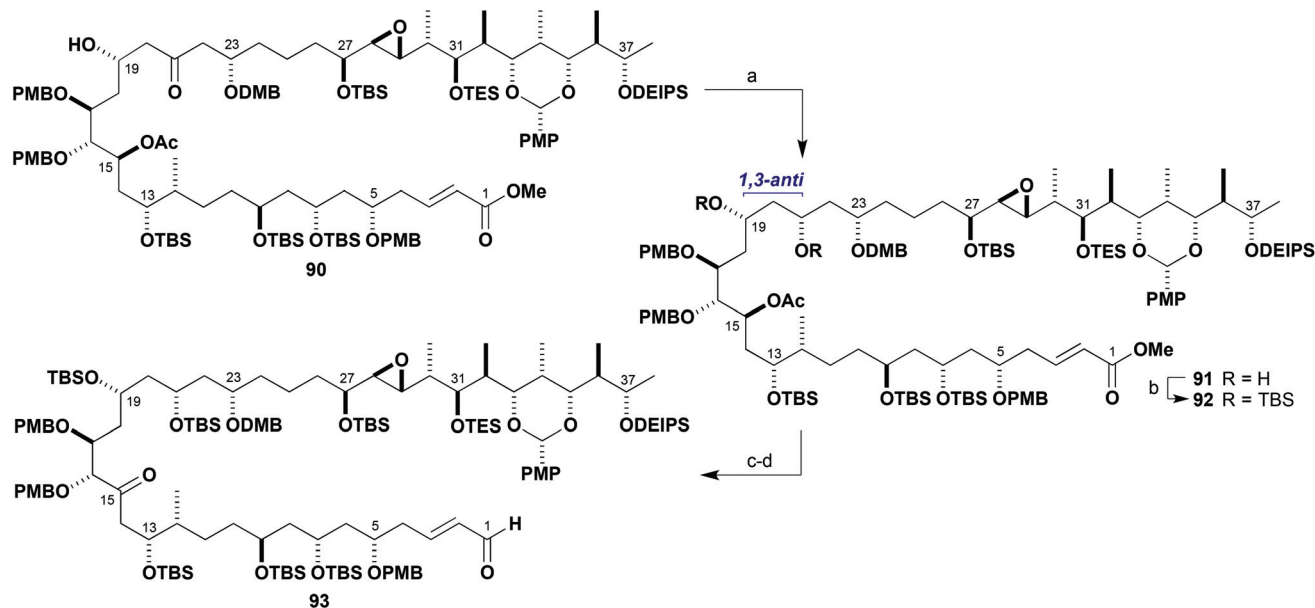
## Conclusions and outlook

The brasilinolides are an architecturally complex family of polyhydroxylated 32-membered macrolides, characterised by their potent immunosuppressant and antifungal properties. In work directed toward their total synthesis, a range of asymmetric aldol/reduction sequences and catalytic protocols were employed to assemble a series of increasingly elaborate fragments. By adopting the highly convergent strategy outlined in Scheme 1, the preparation of the required C1–C19 and C20–C38 acyclic fragments **5** (10 steps, 43%) and **6** (16 steps, 13% from **36**), containing seven and 12 stereocentres respectively, was first achieved. An adventurous fragment union by controlled C19–C20 bond formation was then extensively explored

**Table 3** Aldol coupling of fragments **81** and **89**

| Entry | Lewis acid | Base | Enolisation temp. (Time) | Reaction temp. (Time) | Solvent | Isolated yield (%) | dr 1,5-*anti* : *syn* |
|---|---|---|---|---|---|---|---|
| 1 | *c*-Hex$_2$BCl | Et$_3$N | −78 °C (1 h) | −78 °C (3 h) → −23 °C (16 h) | Et$_2$O | 8 | 2 : 1 |
| 2 | (−)-Ipc$_2$BCl | Et$_3$N | 0 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 5 | 3 : 1 |
| 3 | (+)-Ipc$_2$BCl | Et$_3$N | 0 °C (1 h) | −78 °C (3 h) → −20 °C (1 h) | Et$_2$O | 4 | 1 : 1.2 |
| 4 | Bu$_2$BOTf | i-Pr$_2$NEt | −78 °C (1 h) | −78 °C (4 h) | Et$_2$O | 32 | 2.5 : 1 |
| 5 | Bu$_2$BOTf | i-Pr$_2$NEt | −78 °C (1 h) | −98 °C (1 h) → −78 °C (4 h) | Et$_2$O | 48 (95% brsm) | 3.5 : 1 |
| 6 | Bu$_2$BOTf | i-Pr$_2$NEt | −78 °C (0.5 h) | −98 °C (1 h) → −78 °C (4 h) | Et$_2$O | 44 | 3 : 1 |
| 7 | Bu$_2$BOTf | i-Pr$_2$NEt | −50 °C (0.5 h) | −98 °C (1 h) → −78 °C (4 h) | Et$_2$O | <5 | — |
| 8 | Bu$_2$BOTf | i-Pr$_2$NEt | −78 °C (1 h) | −98 °C (1 h) → −78 °C (4 h) | Pentane | 23 | 2.5 : 1 |

5730 | *Org. Biomol. Chem.*, 2015, **13**, 5716–5733

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**Scheme 23** Preparation of the advanced C1–C38 coupled product **93**. *Reagents and conditions*: (a) Me$_4$NBH(OAc)$_3$, MeCN–AcOH (4 : 1), −30 °C, 85%, >95 : 5 dr; (b) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 98%; (c) DIBAL, CH$_2$Cl$_2$, −78 °C; (d) DMP, NaHCO$_3$, CH$_2$Cl$_2$, 90% (2 steps).
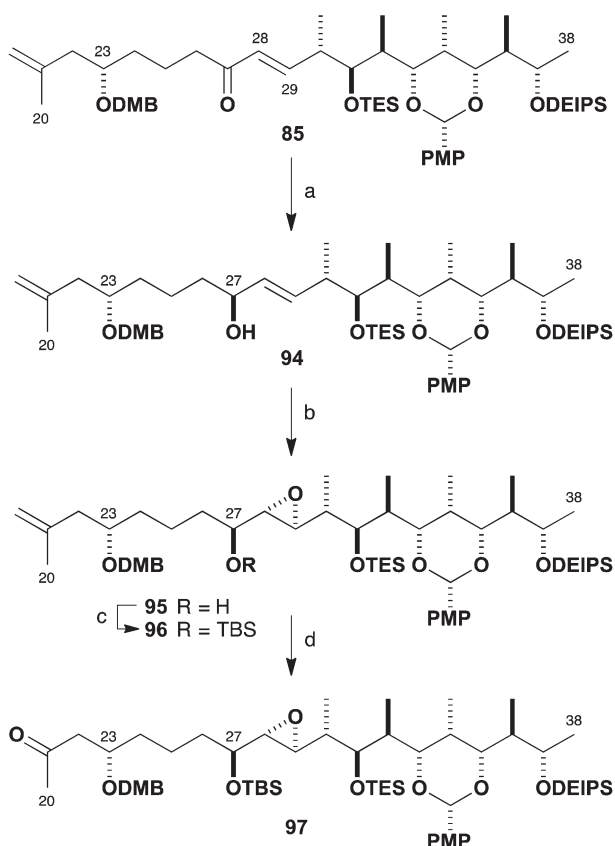


**Scheme 24** Preparation of C20–C38 methyl ketone **97**. *Reagents and conditions*: (a) (*R*)-Me-CBS catalyst, BH$_3$·SMe$_2$, THF, −50 °C, 88%, >95 : 5 dr; (b) Ti(O*i*-Pr)$_4$ (10 mol%), (+)-DIPT (15 mol%), *t*-BuOOH, 4 Å mol. sieves, CH$_2$Cl$_2$, −25 °C, 86%, 2 : 1 dr; (c) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 86%; (d) OsO$_4$, NMO, THF–H$_2$O; NaIO$_4$–SiO$_2$, CH$_2$Cl$_2$, 85%.

to construct the entire carbon chain of the brasilinolides. Notably, the use of boron-mediated aldol reactions of chiral ketones proved efficient on multiple occasions to assemble and then couple key fragments, with predictable installation of the required configuration *via* either 1,4- or 1,5-stereoinduction from the enolate component. In particular, this chemistry proved crucial for achieving the complex aldol coupling between methyl ketone **89** and aldehyde **81** to give adduct **90**, where Mukaiyama-type aldol protocols had earlier proved unrewarding in model studies. Following the controlled manipulation of various intermediates derived from **90**, the preparation of the protected C1–C38 polyol **93** (21 steps from **36** in the longest linear sequence) was then achieved, thus setting the stage for future efforts directed at late-stage diversification to access the various brasilinolide congeners.

From our perspective, the controlled assembly of the highly oxygenated and stereochemically elaborate molecular architecture of the brasilinolides serves to test the limits of chemical synthesis. Moreover, this adventurous endeavour underscores the multiple logistical and selectivity issues that are regularly faced in tackling the synthesis of such promising polyketide natural products of biological and medicinal importance.[1b,d,46] In future work, it is anticipated that we can build on the supportive findings reported here to further progress a unified approach to the construction of the brasilinolides.

## Experimental

Full experimental and characterisation details are provided in the ESI.†

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