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Studies towards the synthesis of Salvinorin A

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Abstract. Salvinorin A **1**, a psychoactive neoclerodane diterpenoid from the Mexican sage *S. divinorum*, has gained interest as a selective κ-opioid receptor agonist. Non-racemic 3-furylamines **9a** and **9b** have been prepared from (+)-pseudoephedrine and (-)-ephedrine for application in the stereoselective synthesis of the ketone ring of **1**. Diels-Alder reaction of **9b** with methyl acrylate in aqueous media, followed by selective ether bridge cleavage has allowed access to the cyclohexenone **17** with preservation of stereochemistry at C-2. A model route to the lactone ring has also been achieved *via* a one pot deconjugation/esterification procedure of 2-bromocrotonyl chloride **20** to the furyl alcohol **19** followed by Reformatski mediated ring closure.

Key words. Salvinorin A, Clerodane, Diels-Alder reaction, non-racemic 3-furylamines, 7-oxabicyclo[2.2.1]heptanones, ether cleavage, aldol reaction, β,γ-unsaturated esters, Reformatski reaction, 3-furyl lactones.

Introduction.

Infusions prepared from the leaves of the lamiaceae *Salvia divinorum* (Epling and Jativa-M.), are traditionally used in divinatory rites by the Mazatec Indians of Oaxaca, Mexico. The *trans*-neoclerodane diterpene salvinorin A **1** has been isolated[1, 2] from bioactive fractions of the plant extract and identified to be the principal pharmacologically active component[3]. The absolute stereochemistry of salvinorin A has been determined by a number of methods[2, 4].

Extensive receptor assays have indicated that salvinorin A acts selectively as a potent κ-opioid receptor (KOR) agonist[5, 6] exhibiting similar efficacy to known KOR agonists U69,593 and TRK-820[7]. The biological properties of salvinorin A are unique considering it is a non-nitrogenous opioid agonist and displays hallucinogenic effects similar to LSD **3**, mescaline **4** and DMT **5** (Figure 1), whilst lacking structural similarity to these classical alkaloids.

It has been reported that the diterpene **1** is localized within glandular trichomes[8] as a secondary metabolite in concentrations up to 0.37% (dry leaf). Salvinorins B[2] **2**, C[9], D-F[10] and G[11] have also been isolated from leaf extracts, along with salvinicins A-B[12] and divinatorins A-C[13] and D-E[11] in low concentrations. So far there have been no reports of isolated metabolites possessing KOR activity higher than that of **1**. Recent efforts to elucidate structure-activity relationships of **1** have involved the modification of the C-2 acetoxy and C-4 ester substituents. The semisynthetic methoxymethyl C-2 analogue has shown increased potency as a KOR agonist[14] and affinity for the μ-opioid receptor has been reported in analogues containing aromatic C-2 ester substituents[15]. C-4 modified analogues have been reported to possess reduced binding affinity[16] and byproducts from ester hydrolysis under basic conditions have been shown to involve the oxidation of ring A [17].

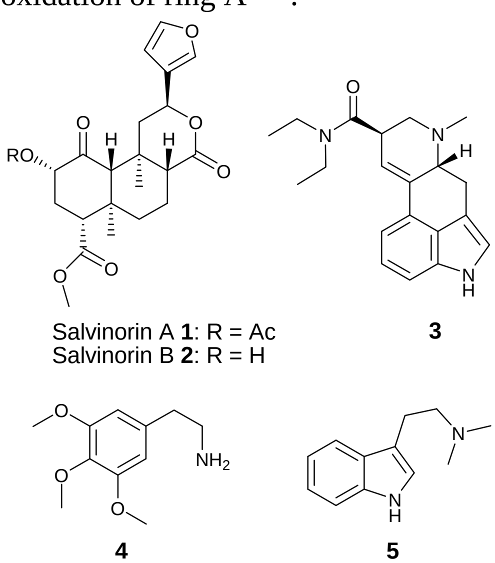


Figure 1.

Growing concern in regards to its potential as a drug of abuse has led to prohibition of both plant material and active component in some countries (Australia, Denmark, Italy)[18]. However, interest by the medicinal and pharmacological community has grown since novel psychotomimetic structures offer opportunities to explore the role of the receptor systems in humans. The use of KOR agonists has gained interest as a novel approach to relief from CNS-acting drug dependence[19]. However such medication may be problematic as **1** produces dysphoric effects, which are considered undesirable in medicinal use.

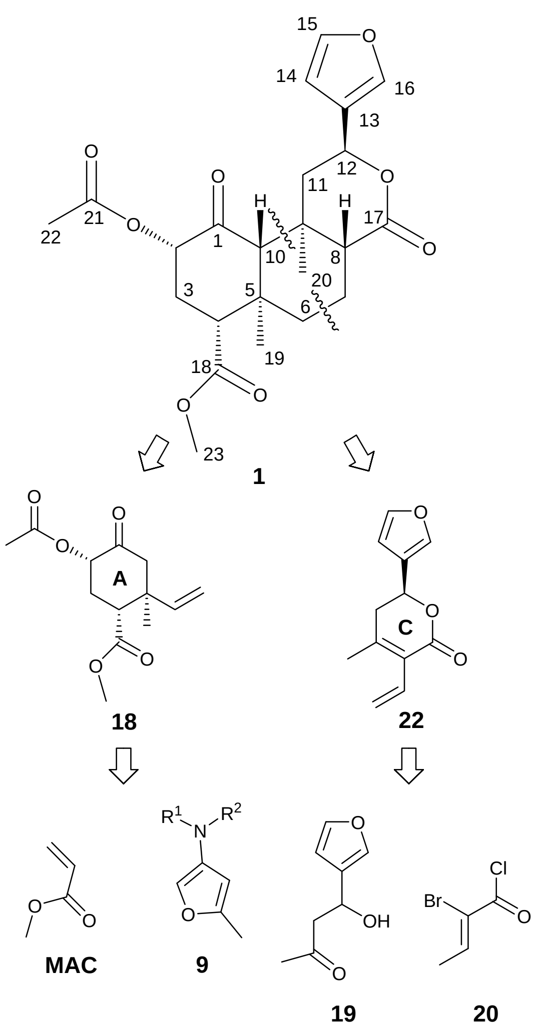
Many labdane and clerodane diterpenes possess similar structures to salvinorin A but differ vastly in bioactivity. The furyl lactone moiety in salvinorin A is identical to that observed in the molluscicide ricciocarpin A[20] and has been found necessary for the insect antifeedant properties of bacchotricuneatin A[21]. Syntheses of neoclerodane diterpenes are not common in the literature and novel synthetic pathways are necessary to prepare these biologically important diterpenes. In this paper we wish to report on our progress towards an enantioselective route to ketone ring **A** of **1**, along with preliminary studies towards a model route to the lactone ring **C**.

Retrosynthetic analysis.

Dissection of the tricyclic ring structure at C-9/C-10 and C-6/C-7 presents a functionalised cyclohexanone **A (18)** and an α,β-unsaturated lactone **C** (**22**) as precursors in a convergent synthesis (Scheme 1). Stereocentres adjacent to ketone and ester functionalities contain acidic protons and were identified as potential sites for racemization during preparation and purification.

Cyclohexanone ring **A** was retrosynthetically derived from the Diels-Alder adduct between a 3-furylamine **9** and methyl acrylate (MAC). Hydrolysis of the amine substituent provides a direct route to the 7-oxabicyclo[2.2.1]heptane (or 7-oxanorbornane) species **12** (Scheme 3). The chemistry of 7-oxabicyclo[2.2.1]heptane compounds has been extensively explored and reviewed by Vogel and Le Drain[22]. Ring opening of **12** to the cyclohexenone **16** provides the core of the ketone ring present in both **1** and **2** (Scheme 5). Acetylation followed by 1,4-addition allows access to the convergent precursor **A**.

Ring **C** was derived from rudimentary precursors, as α-halovinyl esters may be achieved through a deconjugation/esterification procedure using α-bromocrotonyl chloride. Reformatski mediated ring closure of the α-bromoester followed by dehydration leads to the lactone ring **C** (**22**). Coupling of rings **A** and **C** should be possible *via* a Michael type addition using methodology developed by Stork[23], followed by olefin metathesis and hydrogenation.



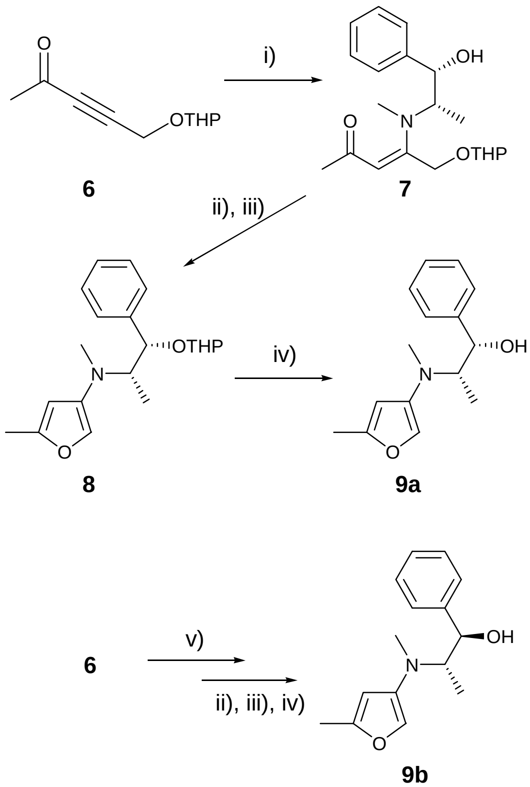
Scheme 1. Retrosynthesis of Salvinorin A.

Results and Discussion

7-Oxa[2.2.1]bicycloheptane structures serve as useful intermediates in the preparation of specifically functionalised molecules for natural product synthesis. Heterosubstituted furans have found use as reactive dienes in the preparation of 7-oxa[2.2.1]bicycloheptane structures using Diels-Alder methodology. A general method for the preparation of 3-furylamines has been developed by our group[24] and products have shown high reactivity in cycloaddition reactions with methyl acrylate[25]. This has allowed the preparation of racemic 7-oxabicyclo[2.2.1]heptanone structures and investigation into their chemical transformations has been part of ongoing studies.

Face selectivity in the cycloaddition reactions of chiral 3-furylamines has been reported by Schlessinger[26] and is mediated by steric interactions of a proline derived auxiliary. This methodology has been applied successfully to the total synthesis of (+)-cyclophellitol[27]. Our current investigation has led us to examine the utility of the naturally occurring ephedrine isomers as asymmetric amine substituents on the furan moiety.

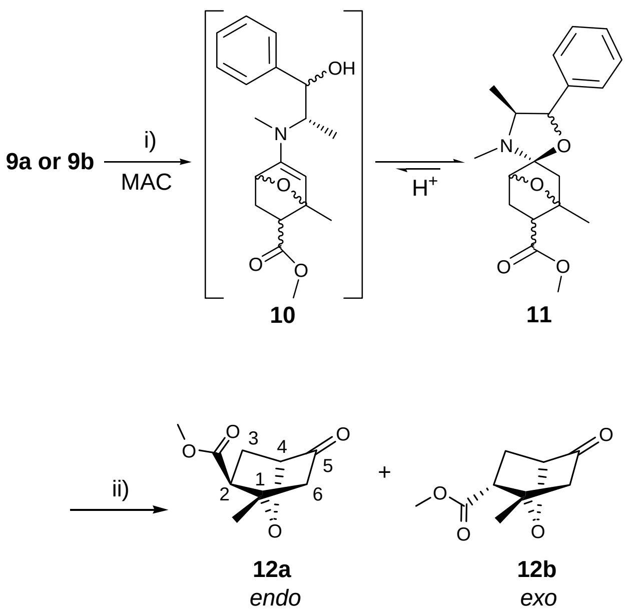
Furans prepared from (1S, 2S)-(+)-pseudoephedrine **9a** and (1R, 2S)-(-)-ephedrine **9b** were obtained in high yields from the starting amines by optimised procedures. Under conditions required for cyclization, tetrahydropyran-2-yloxy (THP)-group migration to the benzylic oxygen was observed in NMR and GCMS analysis, indicating the formation of furan **8** (Scheme 2). THP deprotection was subsequently performed by gentle heating with p-toluenesulphonic acid in ethanol. Furan products were stable for long periods upon storage at -18°C.



Scheme 2. (i) (+)-Pseudoephedrine, THF; ii) TFA, DCE; (iii) Aq. NaOH; (iv) p-TsOH, EtOH, 60^{o}C, (v) (-)-Ephedrine.

Studies of Diels-Alder reactions involving achiral 5-methyl-3-furylamines with MAC demonstrated both dichloromethane (DCM) and water to be suitable reaction media[25]. Cycloadditions of **9a** and **9b** carried out in DCM were quantitative as were heterogeneous reactions in water with the aid of ultrasonic irradiation. Furylamines containing aromatic substituents have been shown to react to completion without sonication[25], suggesting that the sonication in this case is simply a means of suspending the furan in solution, rather than a rate enhancing phenomenon.

NMR studies on the cycloadduct of **9a** prepared in DCM showed the product to exist preferentially as the oxazolidine **11**. The disappearance of both the spiro- and methylene carbon signals at 108.5 and 41.5 ppm in acidic D_2O suggests facile reversion to the enamine **10,** although full characterisation of **10** could not be obtained. Upon heating in strong acidic solutions (pH = 1), **10** underwent a retro Diels-Alder reaction rather than hydrolysis. This led to a loss in enantio- and diastereomeric excesses along with slow decomposition. After many attempts, effective hydrolysis was achieved by gentle heating in a buffer solution of sodium acetate/acetic acid (pH = 5.5) to give the ketones **12a** and **12b** in good combined yields (81 - 90%) (Scheme 3). Diastereomeric ratio (*endo*:*exo*) and enantiomeric excesses (*ee*) of **12a** and **12b** were measured by chiral gas chromatography on a diethyl-*tert*-butyl-β-cyclodextrin column (MeGA, Italy) (Table 1). Chiral GC analysis revealed both ephedrine isomers to direct face selectivity in the same manner, whereas the diastereomeric outcome was quite different.



Scheme 3. (i) DCM or Water; (ii) AcOH, NaOAc, H_2O

Table 1. Enantioselective Diels-Alder reactions using ephedrine auxiliaries.

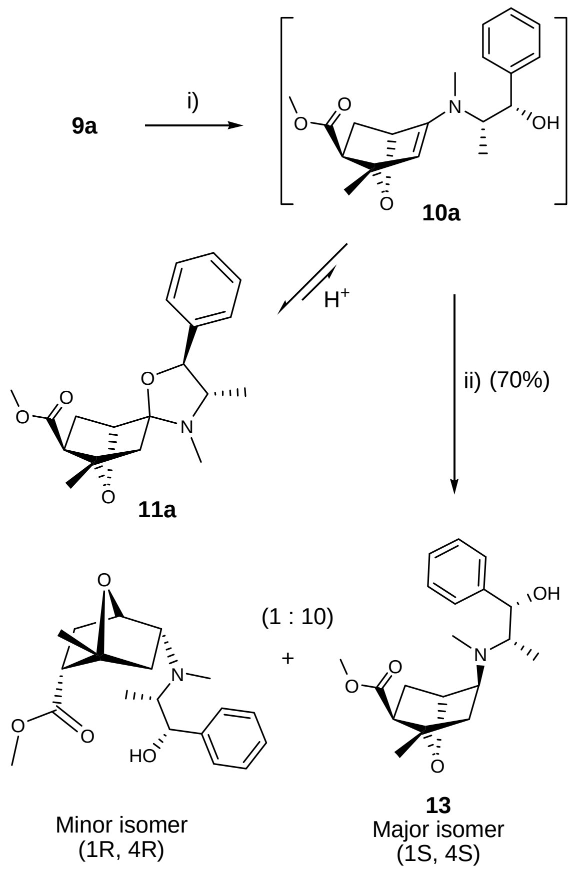
Run	**9**	MAC (eq.)	Solvent	Temp (^{o}C)	Time (hr.)	*endo:exo*^{A}	ee (**12a**)	ee (**12b**)	% yield^{B}
1	a	3.0	DCM	-50 to r.t.	8.0	99:1	85	n.d.	90
2	a	1.5	Water	10 - 20	1.5	9:1	75	75	83
3	b	3.0	DCM	-50 to r.t.	8.0	3:1	56	46	87
4	b	1.5	Water	10 - 20	1.5	1:1	18	60	81

^{A}Ratio of diastereoisomers (**12a**:**12b**)
^{B}Combined yield of *endo* and *exo* products.
Results produced on $\leq$ 1.0 mmol scales.

Small scale reactions carried out using **9a** in aqueous media achieved good enantioselectivity for both diastereomers of **12**. Reasonable enantiomeric excess was observed for the *exo*- cycloadduct using **9b**, achieving 60% ee and providing a 1:1 ratio of diastereoisomers when bath temperature was maintained between 10 and 20^{o}C (Table

1, entry 4). Aqueous reactions on multigram scales required 3 equivalents of acrylate to ensure the consumption of all starting materials, but did not perform as well and a loss of 12 to 15% ee was commonly encountered. The addition of miscible co-solvents (DMF, dioxane, alcohols) or surfactants (TBAI) to aid in the aqueous solubility of reagents, led to a noticeable decrease in enantioselectivity.

High selectivity was observed for the *endo*- adduct prepared from **9a** in DCM and the multigram reaction performed comparably well (80% ee). Clean reduction of the enamine **10a** was achieved using sodium triacetoxyborohydride[28], preformed from $NaBH_4$ in acetic acid (Scheme 4). The distilled amine **13** underwent crystallization as the perchlorate salt to provide a diastereomerically pure product as shown by ^{1}H and ^{13}C NMR data. X-ray crystal structure data on the major isomer revealed facial selectivity in the [4π + 2π] cycloaddition for the (1S, 4S) isomer (Figure 2). The enamine reduction was observed to be selective for the less hindered *exo*- face.



Scheme 4. (i) DCM, -50^{o}C to r.t.; (ii) $NaBH_4$, AcOH

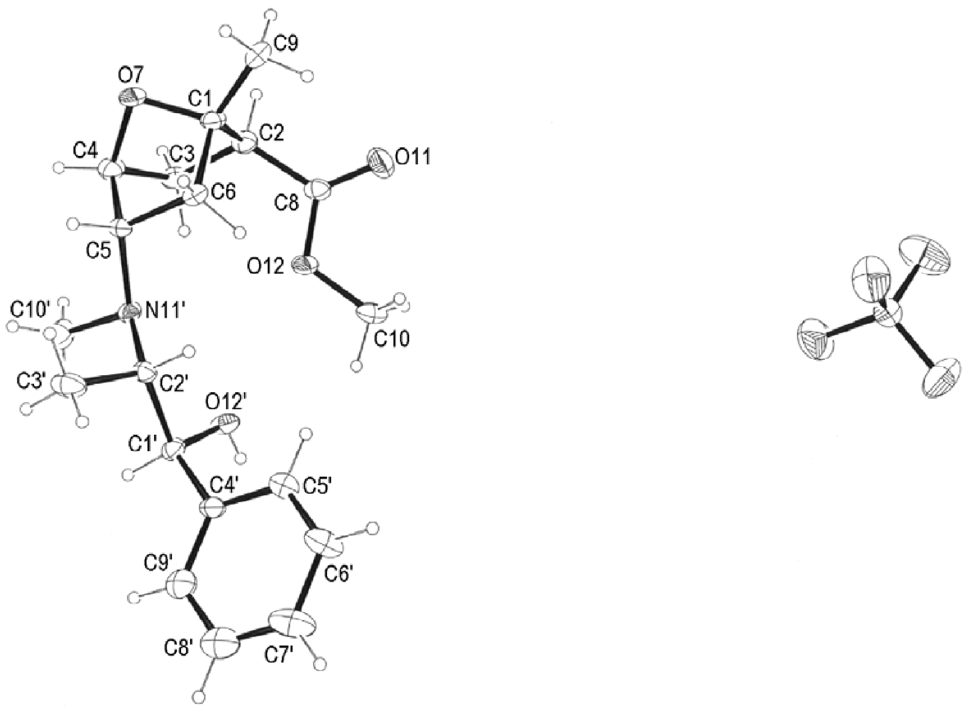


Figure 2. ORTEP drawing of (1S,2S,4S,5S)-methyl 5-(N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylamino)-1-methyl-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **13** perchlorate salt.

Recrystallization of an enantioenriched mixture of **12b** in ether at –18^{o}C gave a single enantiomer as indicated by chiral GC analysis. **(+)-12b** enriched in the supernatant as the racemic precipitate was removed and was found to be a colourless resin at room temperature.

Ether cleavage of **12a** and **12b** using TBDMSOTf in the presence of base as reported by Vogel[29] gave unexpected results. The appearance of furan signals in ^{13}C NMR and a propionate ester in ^{1}H NMR analysis indicated C-C bond cleavage had occurred between the ester and the tertiary bridgehead (C-1, C-2) to give **14**. Ring opening reactions using LHMDS[30] in the absence of silylating agent gave the furanone **15** as confirmed by COSY and HMBC 2D NMR data (Figure 3). Desilylation of **14** with TBAF revealed the formation of **15** by GC-MS analysis.

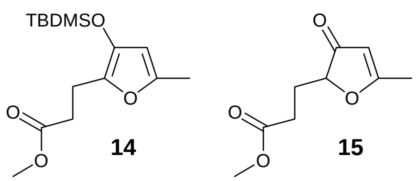
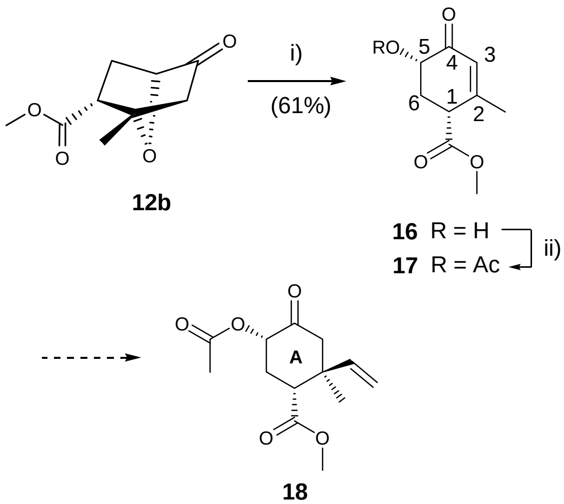


Figure 3.

BBr$_3$ ring cleavage followed by quenching in collidine gave clean conversion to the desired cyclohexenone **16** (61%) with no detectable epimerisation at C-5. COSY analysis showed correlations between H-1-H-6, H-6-H-5 indicating that the six-membered ring was intact. The appearance of the olefinic proton at 6.00 ppm gave evidence of the α,β-unsaturated system and connectivity was confirmed by HMBC analysis. Subsequent acetylation of the alcohol was performed in the quenching solution without isolation to give **17** in 40% yield from **12b** (Scheme 5). NOESY analysis of **17** showed correlation between H-1, H-5 which was absent in the C-5 epimer confirming the retention of relative stereochemistry. Interestingly, BBr$_3$ cleavage on the *endo* product **12a** gave the corresponding cyclohexenone in 60% yield but stereochemistry at C-5 was not retained.

Ether cleavage was unsuccessful using BBr$_3$-Me$_2$S, TiCl$_4$, FeSO$_4$, and ZrCl$_4$ and returned only starting material.



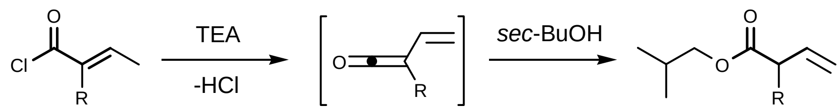
Scheme 5. (i) a) BBr_3, DCM b) Collidine, DCM; (ii) AcCl.

Attempted isolation of **16** and **17** by flash column chromatography on silica, neutral alumina and fluorosil led to almost complete isomerization at C-5. Semi-preparative HPLC was trialled and we were pleasantly surprised to achieve complete separation on a Phenomenex C-18 column using ACN/H_2O as eluent. The C-5 stereoisomer was not observed in GC and NMR studies on products **16** and **17** after purification by HPLC. 1,4-Addition with vinyl Gilman reagent is expected to produce the convergent precursor **A** and is the subject of future work.

Studies towards the synthesis of Ring C.

Intramolecular cyclization of an ester side chain by an aldol or Reformatski reaction provides a practical formation of lactone fragments in a number of syntheses[31]. Likewise, the preparation of lactone **22** was thought possible by ring closure of a vinylacetic ester. 4-(Furan-3-yl)-4-hydroxybutan-2-one **19** was prepared by an aldol reaction between acetone and 3-furaldehyde based on an optimised literature procedure. Dehydration of **19** was facile in the presence of acidic and basic reagents at ambient temperature. Literature searches revealed a mild preparation of vinyl acetic esters from crotonyl chlorides[32]. Iwakura and co-workers have reported the action of triethylamine

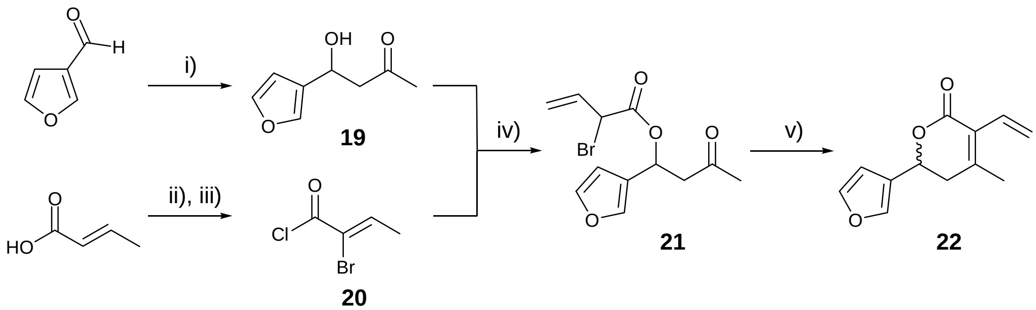
(TEA) on crotonyl chloride to give a ketene intermediate which provides the β,γ-unsaturated esters in good yields upon reactions with *sec*-BuOH (Scheme 6). To date this methodology appears not to have been utilized in the preparation of larger organic molecules.



Scheme 6. Where R = H, Br.

Initial reactions were performed using crotonyl chloride. Upon reaction with **19**, esterification was successful providing the deconjugated ester in high yield. Subsequent ring closure using LDA failed and attempts at vinylic bromination using Br_2/dibenzoylperoxide in CCl_4 led to a mixture of brominated products. 2-Bromocrotonyl chloride **20** (R = Br) was then prepared in 3 steps from crotonic acid by literature methods[33, 34]. Under conditions described by Cardillo *et al.*[35], the reaction of **19** in the presence of **20** gave the deconjugated α-bromoester **21** as shown by the appearance of terminal olefinic signals in ^{1}H NMR. The formation of the ketene was accompanied by the appearance of a deep blue colour which gradually progressed to dark red as esterification took place. Ratios of β,γ- to α,β- esters obtained were 10:1 and results were surprisingly reproducible given that the reaction mixture had a tendency to cake and required mechanical stirring to ensure proper mixing.

Ring closure of **21** to the lactone **22** was achieved by a Reformatski reaction using Rieke Zinc in THF. Conveniently, dehydration of the intermediate alcohol was achieved by prolonged stirring in the aqueous acidic quenching solution, producing **22** in high purity and yield (92%) (Scheme 7). Further studies are focused on an efficient stereoselective aldol addition procedure of acetone to 3-furaldehyde to complete ring **C** in the convergent synthetic pathway.



Scheme 7. (i) Acetone, dil. NaOH; (ii) a) Br_2, DCM, b) Pyridine; (iii) $SOCl_2$; (iv) TEA, Et_2O; (v) a) Rieke Zinc in THF b) H_3O^+.

Conclusion

The Diels-Alder reaction of 5-methyl-3-aminofurans possessing (+)-pseudoephedrine and (-)-ephedrine amine substituents have demonstrated face selectivity in reactions conducted in both organic and aqueous reaction media. The diastereomeric outcome has been observed to be dependant on both the amine substituent and the polarity of the solvent. As a result, both *exo*- and *endo*- products **12a** and **12b** have been prepared in enantioenriched form using the methodology described.

Lewis acid assisted ether cleavage using boron tribromide has provided conversion of **12b** to the corresponding cyclohexenone (**16**) in moderate yields, and subsequent acetylation has been carried out in a two step, one pot procedure providing clean reaction mixtures of **17** with total retention of stereochemistry at C-5.

Since both acetoxy and ester substituents occupy a single face on the cyclohexanone ring, further work towards 1,4-conjugate addition is expected to occur at the opposite face due to steric considerations.

A model route to the lactone ring of **1** has also been accomplished under mild reaction conditions and in high yields.

Experimental

Unless noted, materials were obtained from Aldrich Chemical Co. and used without further purification. Diethyl ether and THF were dried first with CaH_2, then distilled from sodium/benzophenone before use. Dry acetone (BDH) was obtained by refluxing over $KMnO_4$ followed by distillation and storage over molecular sieves (4Å). Triethylamine was dried over KOH pellets before use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (300MHz) NMR spectrometer and are indirectly referenced to TMS *via* $CHCl_3$. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 2000 Fourier transform IR spectrometer. GC-MS data was recorded using a Hewlett Packard 6890 GC with BPX-5 column, and Hewlett Packard 5973 Mass Selective Detector. Chiral GC separation was achieved using a diEt-TBS-β-CD column (MeGA, Italy), 20 m, 0.25 mm x 0.25 μm (film thickness). Semipreparative HPLC was performed using a Varian Prostar (Model 210), with Phenomenex C18 column (250 x 10 mm, 5u ODS (3), 50 x 10 mm, 5u ODS (3) guard column). Separation was achieved using ACN:H_2O (55:45) at 3.5 mL/min flow rate, with UV-Vis detection. Reactions performed under ultrasonic irradiation were performed using a Elma Transsonic Digital S, 40kHz variable power ultrasonic bath. Optical rotations were determined on a Perkin-Elmer 241 MC Polarimeter at 690nm wavelength, 20°C and at the concentration *c* (g/100 mL). 5-(Tetrahydropyran-2-yloxy)-pent-3-yn-2-one **6** was prepared by previously reported procedures[24]. (E)-2-Bromo-but-2-enoic acid was prepared by method of Pfeiffer in a two step procedure[33]. (E)-2-Bromobut-2-enoyl chloride **20** was prepared from (E)-2-Bromo-but-2-enoic acid by method of Klein and Zitrin[34] and was freshly distilled before use.

^{1}H and ^{13}C NMR spectra reported for isolated compounds of purity >97% unless quoted as a mixture. Where ^{13}C data is included assignments are based on 2D experiments (DEPT, HMQC, HMBC, COSY) in each case.

Preparation of Furans 9a and 9b

Preparation of ***7***.

(1S, 2S)-(+)-Pseudoephedrine (1.62 g, 9.8 mmol) in warm dry THF (15 mL) was added quickly with stirring to neat 5-(tetrahydropyran-2-yloxy)pent-3-yn-2-one (1.95 g, 10.7 mmol) and allowed to stir at room temperature for 4 h or until the Michael addition was complete as monitored by GC-MS. The THF was removed under vacuum to leave a 1:1 mixture of *E/Z-4-(N-((1S, 2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylamino)-5-(tetrahydro-2H-pyran-2-yloxy)pent-3-en-2-one* **7** as a viscous yellow resin (>97%, GCMS). ^{1}H (300MHz, $CDCl_3$): δ 7.50-7.25 (5H, m), 7.50-7.25 (5H, m), 4.67 (1H, s), 4.67 (1H, s), 4.44 (1H, d, J = 8.7 Hz), 4.44 (1H, d, J = 8.7 Hz), 4.02 (1H, d, J = 10.6 Hz), 3.97 (1H, d, J = 10.6 Hz), 3.87 (1H, m), 3.87 (1H, m), 3.56 (1H, m), 3.56 (1H, m), 3.57 (1H, d, J1 = 10.6 Hz), 3.49 (1H, d, J = 10.6 Hz), 2.95-2.75 (2H, m), 2.95-2.75 (2H, m), 2.46 (3H, s), 2.44 (3H, s), 2.29 (3H, s), 2.27 (3H, s), 1.90-1.47 (6H, m), 1.90-1.47 (6H, m), 1.06 (3H, d, J = 6.0 Hz), 1.06 (3H, d, J = 6.0 Hz).
^{13}C (75MHz, $CDCl_3$): δ 207.4, 207.3, 139.6, 139.6, 128.4, 128.4, 128.2, 128.2, 127.0, 127.0, 99.5, 99.5, 96.4, 96.4, 85.9, 85.8, 72.6, 72.1, 70.4, 69.9, 65.2, 65.2, 62.3, 62.1, 46.5, 46.0, 49.8, 49.7, 32.3, 32.3, 32.2, 32.1, 30.7, 30.7, 25.6, 25.6, 19.4, 19.3, 15.1, 14.9. Mass spectrum *m/z* 347 ($M^{+\cdot}$, 0.1%), 233 (16.7), 232 (93.7), 205 (13.5), 149 (10.3), 148 (100), 118 (34.9), 117 (19.0), 115 (7.1), 91 (11.9), 85 (19.8), 57 (7.9), 56 (17.5).

Preparation of ***9a***.

Freshly prepared **7** from the previous step was dissolved in 1,2-dichloroethane (135 mL). Anhydrous trifluoroacetic acid (5 mL) was added in one portion and the solution stirred at ambient temperature for 40 min after which time the solution had become dark red in colour. The solution was poured into a mixture of 4M NaOH (100 mL) and ice (300 g) then immediately shaken vigorously in a separating funnel. The organic layer was separated and the aqueous layer extracted with DCM (3 x 100 mL).

Removal of the THP- group: The combined organic layers were evaporated and the orange resin **8** was re-dissolved in ethanol (200 mL) and used without purification. p-Toluenesulphonic acid (4.0 g, 23.3 mmol) was added in one portion and the solution stirred for 4 h at 60°C. The ethanol was then evaporated under vacuum and the residue dissolved in HCl (250 mL, 1M aq.). The aqueous acidic solution was extracted with DCM (3 x 150 mL) and the organic layers re-extracted with HCl (3 x 100 mL, 1M aq.). The combined aqueous phases were extracted once more with DCM (50 mL) and ice (200g) was added to chill the solution to 5°C. The solution was then basified with ice cold 4M NaOH to pH 14, followed by extraction with DCM (4 x 100 mL). The organic phases were combined, dried with Na_2SO_4 and evaporated to leave *(1S, 2S)-2-(N-methyl-N-(5-methylfuran-3-yl)amino)-1-phenylpropan-1-ol* **9a** as a viscous dark yellow oil (2.26g, 94% overall yield calculated from (+)-pseudoephedrine, >97% pure GCMS). If necessary, discolouration and impurities of pseudoephedrine can be removed by dissolving the material in Et_2O and rapidly eluting the solution through a short silica column, deactivated with triethylamine.

^{1}H (300MHz; $CDCl_3$) δ 7.45-7.25 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.88 (1H, s, H-2''), 5.95 (1H, s, H-4''), 4.47 (1H, d, *J* = 9.6 Hz, H-1), 3.49 (1H, s, OH), 3.26 (1H, dq, *J*1 = 6.6 Hz, *J*2 = 9.6 Hz, H-2), 2.62 (3H, s, NC$\underline{H}_3$), 2.25 (3H, s, H-6''), 0.81 (3H, d, *J* = 6.6 Hz, H-3). ^{13}C (75MHz; $CDCl_3$) δ 152.5 (C-5''), 141.5 (C-1'), 140.9 (C-3''), 128.6 (C-3', C-5'), 128.2 (C-4'), 127.5 (C-2', C-6'), 125.5 (C-2''), 101.3 (C-4''), 75.1 (C-1), 64.8 (C-2), 33.0 (N$\underline{C}H_3$), 14.1 (C-6''), 10.0 (C-3). Mass Spectrum *m/z* 245 ($M^{+\cdot}$, 1.0%), 139 (11.1), 138 (100), 96 (8.7), 94 (6.3), 77 (8.7), 43 (7.9), 42 (11.9). Compound **9b** was prepared following an identical procedure.

Diels-Alder reactions of 9a and 9b

Chiral Gas Chromatography analyses were conducted using a Hewlett Packard 5890 GC. A DiEtTBS-β-CD coated column of dimensions 20m, 0.25mm x 0.25 μm (film thickness) (MeGA, Italy) was used. Flame ionisation detection was used to monitor analytes, and was operated at 230°C. Injections were performed at 200°C using split (50:1) conditions, with a hydrogen carrier gas, flow rate of 1.33 mL/min and linear velocity of 40.07 cm/sec. Temperature programming conditions were optimised for the separation of stereoisomers of **11**. The GC oven was heated to 60^{o}C and ramped to 180^{o}C at 2^{o}C/min (held for 20 min).

*Preparation of **11a**.*

The phenylpropanol **9a** (150 mg, 0.61 mmol) was dissolved in DCM (20 mL) and cooled to –50°C. Methyl acrylate (158 mg, 1.84 mmol) was then added and the solution allowed to warm to -10°C where it was kept for 2 h, then gradually warmed to room temperature and stirred overnight. Evaporation of the solvent and excess acrylate under vacuum gave a mixture of *(1S,4S,5S)/(1R,4R,5R)-methyl 3',4,4'S-trimethyl-5'S-phenylspiro[7-oxa-bicyclo[2.2.1]heptane-2,2'-[1,3]oxazolidine]-5-carboxylate* **11a** as a viscous red semisolid. (199 mg, 97% yield via GCMS, d.r. >99:1).^{1}H (300MHz, $CDCl_3$): δ 7.40-7.22 (5H, m, arom., H-2'', H-3'', H-4'', H-5'', H-6''), δ4.60 (1H, d, *J* = 15.1, H-5'), 4.54 (1H, s, H-1), 3.73 (3H, s, H-10), 3.05 (1H, dq, *J*1 = 6.7 Hz, *J*2 = 9.1 Hz, H-4'), 2.70 (1H, m, H-6_A), 2.46 (3H, s, $NC\underline{H}_3$), 2.43 (1H, m, H-3_A), 2.04 (1H, m, H-6_B), 1.85 (1H, m, H-3_B), 1.64 (3H, s, H-9), 1.26 (3H, d, *J* = 6.7 Hz, H-6').

^{13}C (300MHz, $CDCl_3$): δ 173.2 (C-8), 140.9 (C-13), 128.6 (C-5'', C-3''), 127.5 (C-6'', C-2''), 126.0 (C-4''), 108.8 (C-2/2'), 85.3 (C-4), 83.1 (C-1), 81.8 (C-5'), 67.1 (C-4'), 52.1 (C-10), 51.8 (C-5), 41.7 (C-3), 33.9 ($N\underline{C}H_3$), 29.8 (C-6), 21.0 (C-9), 13.9 (C-6').

Mass Spectrum *m/z* 331 ($M^{+\cdot}$, 3.5%), 300 (9.2), 289 (20.8), 288 (100), 272 (12.3), 204 (7.8), 149 (7.4), 148 (68.7), 141 (11.8), 118 (34.0), 117 (27.2), 115 (8.9), 109 (10.7), 91 (14.3), 77 (6.8), 69 (7.4), 56 (14.7), 55 (10.3), 43 (11.4), 42 (11.0), 41 (13.3).HRESI Found $[M]^{+\cdot}$, 332.1855. $[C_{19}H_{26}NO_4]^+$ $[M]^{+\cdot}$ requires 332.1862.An identical procedure was used for the reaction of **9b** in DCM.

*Preparation of **12a**.*

To a solution of acetic acid (0.5 mL), sodium acetate (3 g), distilled H_2O (15 mL) was added **11a** (196 mg, 0.61 mmol) and the solution heated with stirring in an oil bath at 70^{o}C. After 2 h the solution was cooled and extracted with DCM (3 x 40 mL). The combined organic phases were evaporated and the oil purified by column chromatography on silica gel (pentane:EtOAc, 5:1) to give (1S,2S,4S)-methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **12a** as a pale yellow oil (101 mg, 90% yield, 85% ee, >98% pure GCMS). NMR spectroscopic data was consistent with the reported values for **12a**[25].

*Preparation of **12b**.*

To **9b** (100 mg, 0.41 mmol) was added distilled H_2O (10 mL) followed by methyl acrylate (53 mg, 0.62 mmol) and the solution irradiated in an ultrasonic bath (80% power) for 95 min. The bath temperature was maintained between 10 and 20°C. After removing the excess methyl acrylate under high vacuum at room temperature the solution was extracted with DCM (3 x 15 mL). The combined organic layers were evaporated and the viscous red semisolid heated in an acidic buffer according to the reported procedure for **12a**. The oil obtained was purified by column chromatography on silica gel (pentane:EtOAc, 10:1) to provide **12a** (30 mg, 40% yield, 18% ee) and (1S,2R,4S)-methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **12b** (31 mg, 41% yield, 60% ee). NMR spectroscopic data was consistent with the reported values for **12b**[25]. **12b** was then crystallized from Et_2O at -18^{o}C until the supernatant solution was enriched to enantiomeric purity as indicated by chiral GC-MS. The Et_2O was evaporated to dryness to leave pure **(1S,2R,4S)-(+)-12b** (14.5 mg, 19% yield from **9b**, >99 % ee) [α] = + 1.72° (*c* = 1.45, chloroform).

An identical procedure was used for the reaction of **9a** under aqueous conditions.

Preparation of 13 for X-Ray Crystal Structure Analysis.

$NaBH_4$ (0.87 g, 23.0 mmol) was added portion-wise to glacial acetic acid (35 mL) with cooling in an ice bath and the mixture stirred until the evolution of hydrogen ceased. The heptane carboxylate **11a** (2.55 g, 7.7 mmol) in glacial acetic acid (17 mL) was added drop-wise, followed by additional $NaBH_4$ (0.50 g, 13.2 mmol) portion-wise over 30 min.

The solution was allowed to stir for 4 h at ambient temperature then poured into distilled H_2O (200 mL) and carefully neutralized with $NaHCO_3$. The neutral solution was extracted with DCM (3 x 75 mL) and the combined extracts dried over Na_2SO_4. Evaporation under vacuum gave a red resin which was bulb distilled (150°C @ 0.1 mmHg) to yield *(1S,2S,4S,5S)-methyl 5-(N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylamino)-1-methyl-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate* **13** as a viscous yellow resin (1.8 g, 70% yield, d.r. 10:1, >98% pure GCMS). ^{1}H (300MHz; $CDCl_3$) δ 7.35-7.22 (5H, arom. m, H-2'', H-3'', H-4'', H-5'', H-6''), 4.40 (1H, m, H-4), 4.27 (1H, d, J = 9.6 Hz, H-1'), 3.78 (3H, s, H-10), 3.12 (1H, m, H-5), 2.78 (1H, m, H-2), 2.76 (1H, m, H-3_A), 2.64 (1H, m, H-2'), 2.10 (3H, s, $NC\underline{H}_3$), 2.03 (1H, m, H-3_B), 1.64 (2H, m, H-6), 1.57 (3H, s, H-9), 0.66 (3H, d, J = 6.7 Hz, H-3').

^{13}C (75MHz; $CDCl_3$) δ 172.7 (C-8), 142.3 (C-1''), 128.4 (C-5'', C-3''), 127.8 (C-6'', C-2''), 127.5 (C-4''), 87.0 (C-1), 79.4 (C-4), 74.5 (C-1'), 64.9 (C-5), 63.2 (C-2'), 53.3 (C-2), 52.5 (C-10), 38.3 (C-6), 33.2 ($N\underline{C}H_3$), 28.0 (C-3), 21.6 (C-9), 7.5 (C-3'). *(1R,2R,4R,5R)-Diastereoisomer*: ^{13}C (75MHz; $CDCl_3$) δ172.7, 142.3, 128.4, 127.9, 127.5, 87.1, 78.6, 75.1, 65.1, 63.2, 53.1, 52.2, 38.9, 33.2, 28.7, 21.7, 6.7. Mass Spectrum *m/z* 333 ($M^{+\cdot}$ not observed), 227 (21.0), 226 (100), 140 (10.0), 137 (5.9), 124 (4.1), 109 (4.0), 84 (3.9), 81 (6.1), 79 (4.7), 58 (11.6). HRESI Found $[M]^{+\cdot}$, 334.2013. $[C_{19}H_{28}NO_4]^+$ $[M]^{+\cdot}$ requires 334.2018.

*Crystallization of **13**.*

To a solution of **13** (1.0 g, 30.0 mmol) in dry Et_2O was bubbled $HCl_{(g)}$. A white hygroscopic salt precipitated and was quickly filtered and dried in a vacuum desiccator over drying silica. The hydrochloride salt was dissolved in ACN (20 mL) and silver perchlorate (620 mg, 30.0 mmol) was added as the solution was gently warmed (50°C). After 10 min, the solution was filtered and the salt crystallized by slow evaporation of solvent. Recrystallization from hot EtOH gave colourless needles that showed only a single diastereoisomer by ^{13}C NMR analysis. One final crystallization was performed from ACN by the slow diffusion of Et_2O to give pure *(1S,2S,4S,5S)-methyl 5-(N-*

((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylamino)-1-methyl-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate perchlorate salt as colourless plates (m.p. 227°C). ^{1}H (300MHz; CD_3CN) δ 7.27 (5H, arom. br. s., H-2'', H-3'', H-4'', H-5'', H-6''), 4.76 (1H, s, OH), 4.75 (1H, m, H-4), 4.74 (1H, d, J = 10.1 Hz, H-1'), 3.91 (1H, m, J = 5.3 Hz, H-5), 3.78 (3H, s, H-10), 3.47 (1H, m, H-2'), 2.95 (1H, apparent t., H-2), 2.87 (3H, s, N$\underline{C}H_3$), 2.30 (2H, m, H-3), 1.95 (2H, m, H-6), 1.54 (3H, s, H-9), 1.02 (3H, d, J = 6.8 Hz, H-3'). ^{13}C (75MHz; CD_3CN) δ 174.8 (C-8), 140.1 (C-1''), 130.0 (C-4''), 129.7 (C-3'', C-5''), 128.3 (C-2'', C-6''), 88.4 (C-1), 77.0 (C-4), 72.5 (C-1'), 67.8 (C-2'), 65.3 (C-5), 53.5 (C-10), 52.5 (C-2), 35.6 (C-6), 35.1 (N$\underline{C}H_3$), 30.7 (C-3), 20.8 (C-9), 8.7 (C-3').

Crystal Data for **13**. $C_{19}H_{28}ClNO_8$, MW = 433.87, T = 293(2) K, λ = 1.54180 Å, orthorhombic, space group P-$2_12_12_1$, a = 8.511(2), b = 15.356(5), c = 15.839(3) Å, $\alpha = 90.00^o$, $\beta = 90.00^o$, $\gamma = 90.00^o$, V = 2070.1(9) Å^3, Z = 4, D_c = 1.392 Mg/m^3, μ(Cu Kα) = 2.025 mm^{-1}, F(000) = 920, crystal size 0.20 x 0.10 x 0.02, 2462 reflections measured, 2365 independent reflections (R_{int} = 0.0230); the final wR(F^2) was 0.1371 (all data) and final R was 0.0496 for 2006 unique data [$I > 2\sigma(I)$]. Goodness of fit on F^2 = 1.071.
Crystallographic data for the structure reported has been deposited with the Cambridge Crystallographic Data Centre as deposition No. 288601. Copies of the data can be obtained, free of charge, via www.ccdc.ca.ac.uk or on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB@ 1EZ, UK (fax: +44 1233 336033).

Ether cleavage of 12.

Preparation of ***14***.

To **12a** (100 mg, 0.54 mmol) in dry benzene (1.0 mL) under a dry (N_2) atmosphere was added a solution of CF_3SO_3(t-Bu)Me_2 (0.43 g, 1.63 mmol) and triethylamine (0.21 g, 2.12 mmol) in benzene (1.5 mL) over 1.5 h. The solution was stirred at ambient temperature for 4 hours then poured into Et_2O (15 mL) and washed with 1M HCl (10 mL) followed by 5% $NaHCO_3$ solution (10 mL). The organic phase was evaporated under reduced pressure and the resin subject to column chromatography on silica gel to afford *3-[(3-tert-butyl-dimethyl-silanyloxy)-5-methyl-furan-2-yl]-propionic acid methyl ester* **14** as a yellow oil (111 mg, 69% yield). ^{1}H (300MHz; $CDCl_3$) δ5.66 (1H, s, H-4'), 3.70 (3H, s, H-4), 2.85 (2H, apparent t, J = 8.5 Hz, H-2), 2.60 (2H, apparent t, J = 8.5 Hz, H-3), 2.16 (3H, s, H-6'), 0.96 (9H, s, H-3''), 0.14 (6H, s, H-2''). ^{13}C (75MHz; $CDCl_3$) δ173.6 (C-1), 148.2 (C-2'), 138.4 (C-3'), 136.9 (C-5'), 103.2 (C-4'), 51.8 (C-4), 32.8 (C-2), 25.8 (C-3''), 20.7 (C-3), 18.2 (C-2''), 14.2 (C-6'), -4.5 (C-1''). Mass Spectrum *m/z* 298 ($M^{+\cdot}$, 18.3), 242 (10.3), 241 (60.3), 226 (15.1), 225 (81.0), 199 (19.0), 169 (9.5), 167 (25.4), 135 (31.7), 131 (37.3), 111 (27.0), 90 (7.9), 89 (98.4), 75 (23.8), 74 (9.5), 73 (100), 59 (34.9), 55 (7.1), 45 (10.3), 43 (18.3).

*Preparation of **15**.*

Under an inert (N_2) atmosphere a solution of **12b** (100 mg, 0.54 mmol) in dry THF (2.5 mL) was cooled to -78°C in a dry ice/acetone bath. LHMDS (1.35 mmol, 1.35 mL, 1M in THF) was then added dropwise and the solution stirred at –50°C for 1.5 hours. An additional volume of LHMDS (0.95 mmol, 0.95 mL, 1M in THF) was added and the solution stirred at -45°C for 30 min. The mixture was then quenched with saturated NH_4Cl (10 mL), and extracted with DCM (3 x 15 mL). The combined organic layers were evaporated and the product was subject to column chromatography on silica gel (pentane:EtOAc, 5:3) to give *methyl 3-(2,3-dihydro-5-methyl-3-oxofuran-2-yl)propanoate* **15** (63 mg, 63% yield). ^{1}H (300MHz; $CDCl_3$) δ 5.44 (1H, s, H-4'), 4.49 (1H, dd, $J1$ = 4.9 Hz, $J2$ = 7.7 Hz, H-2'), 3.67 (3H, s, H-4), 2.46 (2H, m, H-2), 2.27 (1H, m, H-3_A), 2.23 (3H, s, H-6'), 2.02 (1H, apparent sextet, J = 7.7 Hz, H-3_B). ^{13}C (75MHz; $CDCl_3$) δ 204.3 (s, C-3'), 190.5 (s, C-5'), 173.1 (s, C-1), 104.6 (d, C-4'), 85.0 (d, C-2'), 52.0 (q, C-4), 29.2 (t, C-2), 26.4 (t, C-3), 17.0 (q, C-6'). Mass Spectrum m/z 184 ($M^{+\cdot}$, 26.2), 153 (33.3), 152 (34.9), 125 (14.3), 124 (19.0), 112 (7.1), 111 (100), 110 (15.9), 98 (42.9), 85 (20.6), 71 (11.9), 69 (14.3), 68 (58.7), 59 (13.5), 57 (11.9), 55 (81.0), 43 (42.9), 42 (11.1).

Preparation of ***16***

To a racemic solution of **12b** (75 mg, 0.41 mmol) in dry DCM (100 mL) at -1°C was added BBr_3 (0.3 mL, 0.30 mmol, 1M in DCM) at once under dry N_2. The solution was stirred at -1°C for 10 min then quickly poured into a well stirred quenching solution of 2,4,6-collidine (3 g) in DCM (25 mL, LR). The solution was stirred at ambient temperature for 35 min, then extracted with HCl (3 x 75 mL, 1M aq.). The organic phase was evaporated to give a mixture of compounds as a yellow/brown resin. The sample was purified by semi preparative HPLC (t_R = 5.1 min, λ_{max} = 235 nm) to give *(1R, 5S)/(1S, 5R)-methyl-5-hydroxy-2-methyl-4-oxocyclohex-2-enecarboxylate* **16** as a colourless oil (46 mg, 61% yield). IR (neat)/cm^{-1} 3452m, 2956w, 2922w, 2856w, 1735s, 1683s, 1438m, 1379w, 1261m, 1197m, 1164m, 1106s. ^1H (300MHz; $CDCl_3$) δ 6.00 (1H, s, H-3), 4.05 (1H, dd, J1 = 13.5 Hz, J2 = 5.5 Hz, H-5), 3.75 (3H, s, H-9), 3.55 (1H, m, H-1), 2.52 (1H, dt, J1 = 13.4 Hz, J2 = 5.5 Hz, H-6_A), 2.07 (1H, apparent quartet, J = 13.4 Hz, H-6_B), 1.98 (3H, s, H-8). ^{13}C (75MHz; $CDCl_3$) δ 198.4 (C-4), 172.0 (C-7), 158.9 (C-2), 125.9 (C-3), 71.2 (C-5), 52.7 (C-9), 47.4 (C-1), 34.4 (C-6), 22.2 (C-10). Mass Spectrum *m/z* 184 ($M^{+\cdot}$, 1.4%), 140 (72.5), 112 (100), 109 (7.2), 97 (66.7), 95 (9.4), 67 (8.7), 53 (11.6), 41 (13.0). High Resolution Mass Spectrum (HRESI) Found [$M^{+\cdot}$], 207.0627. $C_9H_{12}O_4Na$ [$M^{+\cdot}$] requires 207.0633.

Preparation of ***17***

To a racemic solution of **12b** (75 mg, 0.41 mmol) in dry DCM (100 mL) at -1°C was added BBr_3 (0.3 mL, 0.30 mmol, 1M in DCM) at once under dry N_2. The solution was stirred at -1°C for 10 min, then immediately poured into a well stirred quenching solution of collidine (3 g) in DCM (25 mL, LR). The solution was stirred at ambient temperature for 35 min then acetyl chloride (2 mL) was added and the mixture stirred for an additional 35 min. The solution was then extracted with HCl (3 x 75 mL, 1M) and the organic layer evaporated to leave a brown viscous resin. The sample was purified by semi preparative HPLC (t_R = 7.2 min, λ_{max} = 235 nm) to afford *(1R, 5S)/(1S, 5R)-methyl 5-acetoxy-2-methyl-4-oxocyclohex-2-enecarboxylate* **17** as a pale yellow oil (37 mg, 40%

yield). IR (neat)/cm^{-1} 2925m, 2857w, 1742s, 1692s, 1634m, 1442m, 1379m, 1222s, 1169s, 1078s. ^1H (300MHz; $CDCl_3$) δ 6.02 (1H, s, H-3), 5.32 (1H, dd, $J1$ = 11.1 Hz, $J2$ = 6.2 Hz, H-5), 3.77 (3H, s, H-11), 3.58 (1H, m, H-1), 2.44 (2H, m, H-6), 2.17 (3H, s, H-11), 1.98 (3H, s, H-10). ^{13}C (75MHz; $CDCl_3$) δ 192.2 (C-1), 171.8 (C-7), 170.3 (C-8), 157.1 (C-2), 127.7 (C-3), 71.8 (C-5), 52.8 (C-11), 47.1 (C-1), 31.7 (C-6), 22.2 (C-10), 21.0 (C-9). Mass Spectrum *m/z* 226 ($M^{+\cdot}$, 0.1%), 153 (10.1), 151 (5.8), 141 (8.0), 140 (89.9), 123 (13.0), 112 (100), 109 (8.7), 97 (20.3), 95 (16.7), 79 (7.2), 67 (13.0), 43 (35.5). High Resolution Mass Spectrum (HRESI) Found $[M + Na]^{+\cdot}$, 249.0734. $C_{11}H_{14}O_5Na$ $[M + Na]^{+\cdot}$ requires 249.0739.

***Preparation of Ring C*.**

Preparation of ***19***

To a solution of 3-furaldehyde (1.0g, 10.4 mmol) in acetone (18 mL) was added a 1% NaOH solution (2.5 mL) drop-wise between –6 to -9°C. Stirring was continued for 40min, before neutralization with 0.5M HCl. The solution was concentrated *in vacuo* and the residue dissolved in water (100 mL) then extracted with ether (3 x 75 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated to leave *4-(Furan-3-yl)-4-hydroxybutan-2-one* **19** as a colourless oil (1.55g, 97% yield). Mass Spectrum *m/z* 154 ($M^{+\cdot}$, 16.9), 111 (16.2), 97 (53.1), 96 (56.9), 95 (28.5), 94 (15.4), 93 (10.8), 83 (6.1), 69 (64.6), 68 (12.3), 65 (10.0), 58 (15.4), 55 (9.2), 43 (100), 42 (18.5), 41 (51.5).

Preparation of ***21***[35].

Compound **19** (1.0 g, 6.5 mmol) was added to dry Et_2O (6 mL) then cooled to -78°C in a dry ice/acetone bath under inert atmosphere (N_2). Dry triethylamine (2.1 g, 21 mmol) was then added, followed by a solution of **20** (1.9 g, 10 mmol) in Et_2O (3 mL) drop-wise with overhead stirring. An additional volume of Et_2O (3 mL) was added then the mixture was allowed to stir at -78°C for 45 min followed by vacuum filtration. The filter cake was washed with Et_2O (2 x 25 mL, LR), and the solution was allowed to stand until all precipitate had formed, then filtered under suction once more. The ethereal solution was washed with HCl (3 x 20 mL, 1M), dried with Na_2SO_4 then evaporated to leave *1-(furan-3-yl)-3-oxobutyl 2-bromobut-3-enoate* **21** (1.8 g, 92% yield) as a 10:1 mixture of β-γ- and α,β-unsaturated esters. The β,γ- ester was present as a 1:1 mixture of diastereoisomers. IR (neat)/cm^{-1} 3136w, 2985w, 2917w, 1741s, 1724s, 1624m, 1504m, 1419m, 1369m, 1315m, 1289m, 1252s, 1201s, 1148s, 1092m, 1037s. ^{1}H (300MHz; $CDCl_3$) δ 7.48 (2H, arom. m, H-5’’), 7.38 (2H, arom. m, H-2’’), 6.40 (2H, arom. m, H-4’’), 6.26 (2H, dd, *J*1 = 8.1 Hz, *J*2 = 5.2 Hz, H-1’), 6.10 (2H, m, H-3), 5.37 (2H, dd, *J*1 = 16.9 Hz , *J*2 = 4.5 Hz, H-4_A), 5.27 (2H, dd, *J*1 = 10.1 Hz, *J*2 = 3.3 Hz, H-4_B), 4.73 (2H, d, *J* = 9.4 Hz, H-2), 3.16 (2H, dd, *J*1 = 16.9 Hz, *J*2 = 8.1 Hz, H-2_A’), 2.89 (1H, dd, *J*1 = 16.9 Hz, *J*2 = 5.4 Hz, H-2_B’, *isomer 1*), 2.88 (1H, dd, *J*1 = 16.9 Hz, *J*2 = 5.2 Hz, H-2_B’, *isomer 2*), 2.18 (6H, s, H-4’). ^{13}C (75MHz; $CDCl_3$) δ 204.0 (C-3’), 204.0 (C-3’), 167.0 (C-1), 166.9 (C-1), 143.0 (C-5’’), 143.0 (C-5’’), 140.7 (C-2’’), 140.6 (C-2’’), 132.5 (C-3), 132.5 (C-3), 123.2 (C-3’’), 123.2 (C-3’’), 120.6 (C-4), 120.6 (C-4), 108.6 (C-4’’), 108.6 (C-4’’), 66.3 (C-1’), 66.2 (C-1’), 48.0 (C-2’), 47.9 (C-2’), 45.4 (C-2), 45.3 (C-2), 30.5 (C-4’), 30.5 (C-4’). Mass Spectrum *m/z* 302 (1.0%), 300 ($M^{+\cdot}$, 1.0), 221 (4.6), 161 (6.1), 155 (3.8), 154 (50.0), 153 (30.0), 149 (4.6), 147 (4.6), 137 (9.2), 136 (9.2), 121 (22.3), 119 (15.4), 112 (7.7), 111 (7.7), 96 (6.9), 95 (46.2), 94 (72.3), 93 (12.3), 68 (21.5), 65 (9.2), 43 (100), 38 (20.8).

Preparation of ***22***

A solution of **21** (1.0 g, 6.0 mmol) in dry THF (40 mL) was cooled to 0°C and Rieke Zinc (120 mg, 18.0 mmol) suspension in THF (2.5 mL) was added in one portion. The solution was heated to reflux for 5 hours then cooled before quenching in HCl (30 mL, 2M) and allowed to stir for 1 h. Distilled H_2O (50 mL) was added and the solution extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 then concentrated to leave *6-(furan-3-yl)-5,6-dihydro-4-methyl-3-vinylpyran-2-one* **22** (1.4 g, 92% yield via GCMS) as a deep yellow resin. IR (neat)/cm^{-1} 3147w, 2972w, 2933w, 1713s, 1629s, 1505m, 1430m, 1376m, 1260s, 1162s, 1122m, 1098m, 1061m, 1034s. ^{1}H (300MHz; $CDCl_3$) δ 7.49 (1H, arom. m, H-5’), 7.42 (1H, arom. m, H-2’), 6.55

(1H, dd, *J*1 = 17.7 Hz, *J*2 = 11.5 Hz, H-7), 6.45 (1H, arom. m, H-4'), 5.72 (1H, d, *J* = 17.7 Hz, H-8_A), 5.47 (1H, d, *J* = 11.5 Hz, H-8_B), 5.35 (1H, dd, *J*1 = 11.5 Hz, *J*2 = 3.8 Hz, H-6), 2.78 (1H, dd, *J*1 = 18.2 Hz, *J*2 = 11.5 Hz, H-5_A), 2.54 (1H, dd, *J*1 = 18.2 Hz, *J*2 = 3.8 Hz, H-5_B), 2.11 (3H, s, H-9). ^{13}C (75MHz; $CDCl_3$) δ 164.2 (C-2), 150.3 (C-4), 143.9 (C-5'), 140.2 (C-2'), 128.9 (C-7), 125.4 (C-3), 124.1 (C-3'), 121.0 (C-4), 108.8 (C-4'), 70.8 (C-6), 37.7 (C-5), 21.1 (C-9). EIMS *m/z* (relative intensity) 204 (M^+ 41.5), 189 (46.2), 160 (9.2), 159 (33.1), 158 (13.8), 145 (13.8), 131 (25.4), 129 (20.0), 128 (8.5), 127 (10.0), 117 (18.5), 116 (13.1), 115 (29.2), 95 (20.8), 94 (22.3), 93 (7.7), 91 (30.0), 82 (13.1), 81 (88.5), 80 (42.3), 79 (100), 78 (6.1), 77 (27.7), 75 (7.7), 67 (7.7), 66 (17.7), 65 (27.7), 63 (11.5), 53 (13.8), 51 (13.1), 41 (8.5), 40 (10.8), 39 (36.2). High Resolution Mass Spectrum (HRESI) Found $[M + Na]^{+\cdot}$, 227.0677. $C_{12}H_{12}O_3Na$ $[M + Na]^{+\cdot}$ requires 227.0684.

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