Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5062

www.rsc.org/obc

PAPER

Studies on transannulation reactions across a nine-membered ring: the synthesis of natural product-like structures†

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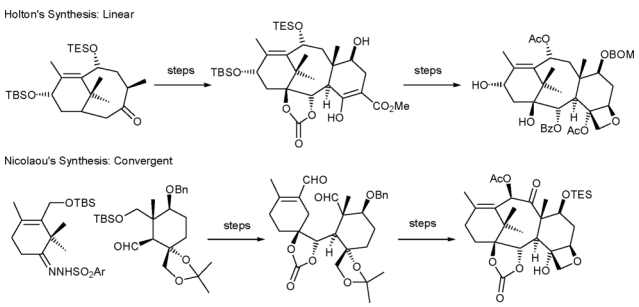
Received 21st March 2011, Accepted 11th April 2011
DOI: 10.1039/c1ob05448a

A series of diverse natural product-like structures have been synthesised by the use of a number of novel transannulation reactions across a cyclononene ring. Transannular cyclisations through oxygen functionality have generated a number of bicyclo[5.3.1]systems containing bridged cyclic ethers and bicyclo[5.2.2]lactones, as well as a tetrahydrofuran-containing bridged analogue of hexacyclinic acid. An unprecedented Brønsted acid mediated transannular cyclisation between proximal carbons generated bicyclo[4.3.0]nonanes which form the core of the pinguisane and austrodorane families of sesquiterpenoids. In all cases the key factor that determined the mode of reactivity was the conformation of the nine-membered ring and the distance between the reacting centres.

Introduction

Natural products containing multiple fused or bridged ring systems are regularly shown to exhibit biological activity against a wide variety of human diseases. Often studies to further investigate the activities of these compounds are hindered by the lack of availability of the compound. Even when quantities of these compounds are available, the difficulty in doing anything other than the most simple structural modifications and functional group manipulations means that analogues of interest, including truncated structures are unavailable for study. This dilemma was highlighted by the early days of Taxol chemistry, where the majority of the analogues generated involved manipulation of the side chain or hydroxyl groups.[1] One way to solve this problem is by the total synthesis of these ring systems in such a way as to provide for the production of analogues and truncated structures. Great advances have been made in the synthesis of natural products containing fused or bridged ring systems. Usually the strategies involve a linear iteration of ring additions or the coupling of two fragments to form a linking ring. Both of these strategies have been successfully demonstrated in the published total syntheses of Taxol (Scheme 1).[2,3]



Scheme 1 Linear and convergent literature approaches to Taxol.

Another strategy which can be as aesthetically pleasing as it is efficient is the use of transannulation reactions to 'fold' a larger ring into several smaller ones. In the case of Taxol this approach, which mimics its biosynthesis, has not been successfully applied, however, transannulation strategies have been used with success in a number of other natural product syntheses.[4] One drawback of this approach is that the transannulation precursor usually has to be constructed with appropriate functionality at specific points around the ring to allow for the desired transannulation reaction to occur. Thus a single transannulation precursor gives rise to a single specific product of a transannulation reaction. We desired to see if we could overcome the lack of diversification inherent in the transannulation strategies explored so far, and develop a transannulation precursor which could be elaborated into several different natural product-like structures by means of a diverse and novel set of transannulation reactions.

We have long had an interest in developing a total synthesis of the natural products hexacyclinic acid and FR182877 (Fig. 1), especially their DEF-rings, by means of transannulation reactions.[5] Indeed transannulative approaches to these molecules

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and CIF files for compounds **24** and **37**. CCDC reference numbers 611039 and 611040. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05448a

‡ Corresponding author for information concerning X-ray crystallographic data.

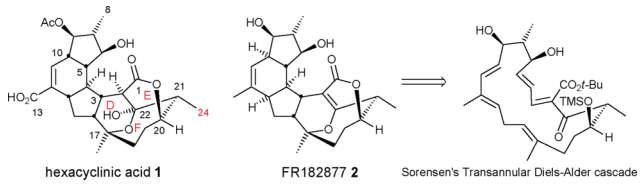
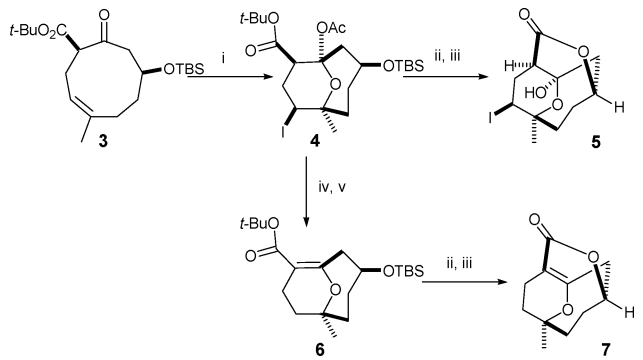


Fig. 1 Hexacyclinic acid and FR182877.

have proved popular, with two of the total syntheses of FR182877 relying on a series of transannular Diels–Alder and hetero-Diels–Alder reactions.[6] Our group has also demonstrated the utility of a novel transannular iodocyclisation reaction to form model DEF-rings of both hexacyclinic acid and FR182877 (Scheme 2).[5]



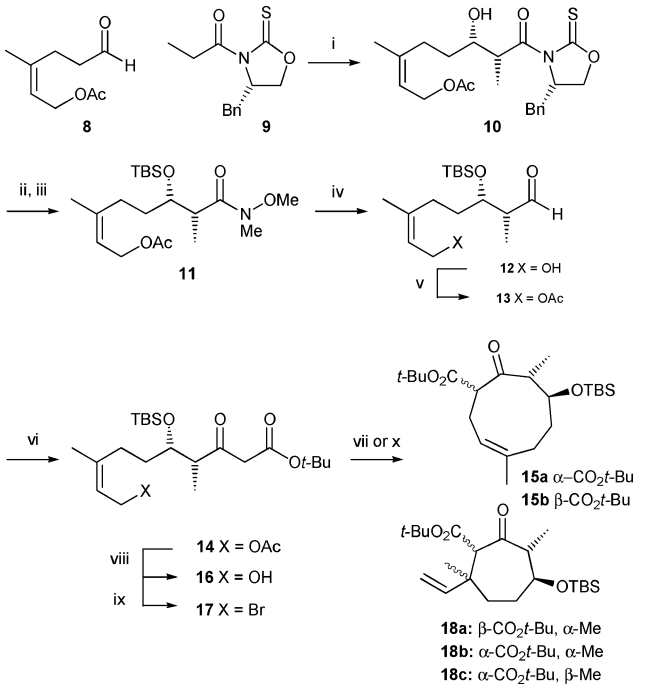
Scheme 2 Transannular iodocyclisation approaches to the DEF-rings of hexacyclinic acid and FR182877. *Reagents and conditions*: (i) I_2, AcOAg, AcOH, 61%; (ii) HF, MeCN, 97%; (iii) THF, CH_2Cl_2, 100%; (iv) $Pd(PPh_3)_4$, Bu_3N, HCO_2H, DMF, 23%; (v) DBU, MeCN, reflux, 93%.

In this earlier work, cyclononene **3** was treated with acetyl hypoiodite, a source of electrophilic iodine which had previously been used by Cambie *et al.* in the transannular iodoetherification of a cyclooctendiol.[7] Acetyl hypoiodite promoted the cyclisation of the ketone carbonyl onto the iodonium ion generated *in situ*, to form an oxocarbenium ion which was quenched by the acetic acid solvent to generate a model DF-ring core **4** of hexacyclinic acid.[5a] The DEF-rings of FR182877 were formed by elimination of acetic acid to generate the desired vinylogous carbonate unit found in the core of FR182877 **6**.[5b] However, while this strategy was a success, the resultant structures lacked the methyl group present in the natural product. It was decided to investigate the cyclononene ring system with the necessary methyl group with the aim of developing novel transannulation reactions that would yield, not only the DEF-ring system of hexacyclinic acid, but also other natural product-like structures.[8]

Results and discussion

Synthesis of the transannulation precursor

In order to study these transannulation reactions we needed to access cyclononene **15a/b**, with the additional methyl group. This was synthesised according to the route shown in Scheme 3. A Crimmins modification of an Evans' aldol reaction[9] between aldehyde **8**[5] and oxazolodinthione **9** generated the all *syn* aldol product **10** in 78% yield. Formation of the Weinreb amide and silyl protection of the hydroxyl group yielded **11** in 71% over the two steps. Reduction of the Weinreb amide to aldehyde

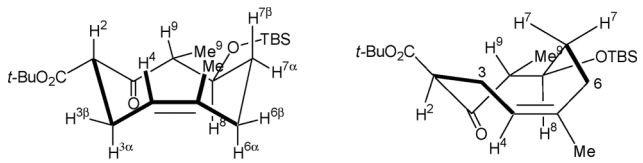


Scheme 3 Synthesis of transannulation precursor **15a/b**. *Reagents and conditions*: (i) $TiCl_4$, (–)-sparteine, CH_2Cl_2, –78 °C to 0 °C, 78%; (ii) MeNHOMe·HCl, Me_3Al, THF, –20 °C; (iii) TBSCl, imidazole, DMF, 71% (over two steps); (iv) DIBAL-H, THF, –78 °C, 48% (**12**) and 43% (**13**); (v) Ac_2O, Et_3N, CH_2Cl_2, $NaHCO_3$, 0 °C to rt, 90%; (vi) $SnCl_2$, *t*-BuO_2CCHN_2, CH_2Cl_2, 89%; (vii) **14**, NaH, $Pd(PPh_3)_4$, dppe, THF, reflux, 47% **15a** : **15b** (1 : 1.4), 53% **18**; (viii) K_2CO_3, $MeOH/H_2O$ (4 : 1), rt, 80%; (ix) NBS, Ph_3P, CH_2Cl_2, –30 °C; (x) **17**, Cs_2CO_3, DMF, –50 °C – rt, **15a** : **15b** (1 : 2), 64% over two steps.

13 in 48% yield also resulted in partial cleavage of the allylic acetate group **12** in 43% yield. The acetate was reinstalled by treatment with acetic anhydride and triethylamine in 90% yield. Roskamp homologation[10] with *tert*-butyl diazoacetate generated β-ketoester **14** in a yield of 89%. The cyclononene transannulation precursor **15a/b** was formed by use of an intramolecular Pd-π-allyl substitution reaction in a rather disappointing 47% yield, and as an inseparable 1 : 1.4 mixture of diastereomers **15a/b**. The remainder of the mass balance of this reaction was the product of allylic substitution at the more substituted end of the double bond to generate a cycloheptene ring as a mixture of three diastereomers **18a**, **18b** and **18c**. Trost and Verhoeven have reported that the competition between formation of the nine-membered ring and the seven-membered ring is very finely balanced and difficult to predict the outcome of. They found that bulkier nucleophiles tended to favor the formation of the nine-membered ring,[11] a result contrary to our observation in this case. The low yield in the cyclisation reaction to form cyclononene **15a/b** prompted us to examine alternative methods of cyclisation. The procedure that met with most success relied upon the conversion of acetate **14** to the bromide **17** *via* allylic alcohol **16**. It was found that treatment of **17** with caesium carbonate resulted in smooth 'S_N2-like' cyclisation to **15a/b** in 64% yield over the bromination and cyclisation steps. At first glance it may seem surprising that this cyclisation to form a nine-membered ring proceeds in such a high yield, as cyclisations to form nine-membered rings are usually hindered by severe destabilising transannular interactions in the

transition state. However, we believe that in the case of **17** cyclising to **15a/b**, these destabilising interactions are minimised by the number of sp^2-hybridised carbons in the molecule. Thus allowing the cyclisation to occur smoothly.

We realised that gaining an insight into the conformations of **15a/b** would be crucial in the understanding and designing of novel transannulation reactions. Analysis of the ^{1}H NMRs and their nOe difference spectra of the mixture **15a/b** showed that **15a** was in a chair-chair conformation while **15b** was in a boat-boat conformation (Fig. 2). Both of these conformations enable all the substituents around the nine-membered ring to adopt pseudo-equatorial positions.[12]



15a: α-CO_2*t*-Bu *chair-chair*

nOes
H^2 - H^4 1.3%
H^2 - H^9 4.8%
H^2 - Me^9 1.7%
$H^{3\alpha}$ - $H^{6\alpha}$ 4.7%
$H^{6\alpha}$ - H^8 2.2%
$H^{7\beta}$ - H^9 1.6%

15b: β-CO_2*t*-Bu *boat-boat*

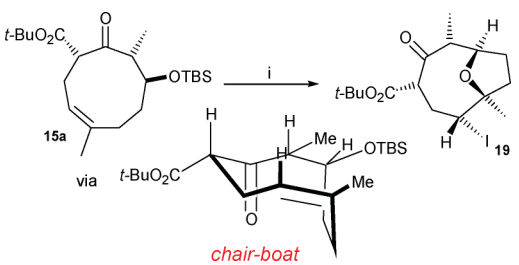
nOes
H^2 - H^4 1.2%
H^2 - H^8 3.0%
H^2 - Me^9 2.2%
$H^{3\beta}$ - $H^{6\beta}$ 7.8%
$H^{3\beta}$ - H^9 1.9%
$H^{6\beta}$ - H^9 3.4%

Fig. 2 Conformations of **15a/b** and diagnostic nOe enhancements.

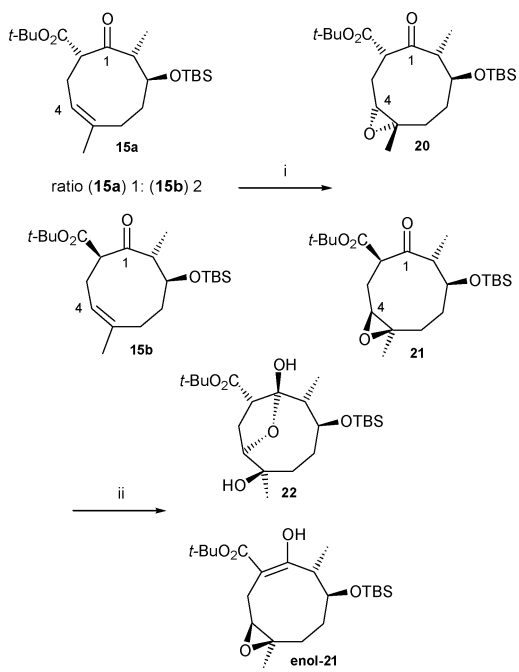
Cyclisations through oxygen

We anticipated that with **15b** in a boat-boat conformation iodocyclisation under our previously reported conditions would lead to the formation of a hexacyclinic acid DF-ring system, *via* the cyclisation of the ketone carbonyl on to the β-iodonium ion. However, when **15a/b** was subjected to our iodocyclisation conditions a new product, which was identified as **19** was formed in 11% yield (Scheme 4), as well as re-isolation of unreacted **15a/b**. We rationalise that the formation of **19** occurs from the reaction of **15a**, due to the loss of the TBS-ether and cyclisation of the resulting free hydroxyl group onto the α-iodonium ion *via* a chair-boat conformation. In order to understand this change in reactivity the conformations of **15a/b** were analysed using AM1 calculations (Spartan '04). For **15b** the global minimum was calculated to be the boat-boat conformation by at least 1.32 kcal mol^{-1}, although the same calculation also showed that the interatomic distance between the ketone oxygen and the tertiary olefinic carbon (C5) was 4.1 Å, which is significantly greater than the optimal distance for transannular reactions of 3.1 Å found by both D'Ambrosio *et al.*[13] and White *et al.*[14] It is interesting to note that **3**, which does cyclise also has an interactomic distance between the ketone oxygen and the tertiary olefinic carbon (C5) of 4.1 Å. However, in nine-membered ring **3** cyclisation to **4** lacks a key eclipsing interaction between the Me(9) and the OTBS group which will develop during cyclisation of **15b**. We believe that it is this interaction that inhibits the cyclisation of **15b** through the ketone carbonyl group. In the case of **15a** the observed chair-chair conformation was calculated to be the global minimum, with the interatomic distance between ketone oxygen and the tertiary olefinic carbon (C5) at 4.2 Å. The chair-boat conformation required for cyclisation to **19** was calculated to be only 2.82 kcal mol^{-1} above the chair-chair conformation, with an interatomic distance of 3.3 Å between the ether oxygen and the olefinic carbon (C5). With a difference in energy between the chair-chair and chair-boat conformations of **15a** of only 2.82 kcal mol^{-1}, which is accessible at r.t., and a reduced interatomic distance between the two reacting atoms it is possible to rationalise why **19** was formed.

Given the above result and the associated calculations we decided to examine other transannulation reactions with the aim of gaining a greater understanding of the factors effecting transannulation, as well as developing routes to other natural product-like bicyclic ring systems. With this goal in mind we next examined the epoxidation of **15a/b** with dimethyldioxirane (DMDO). We rationalised that the epoxide could act both as an electrophile and, after opening to the diol, as a nucleophile in other transannulation reactions. The mixture of **15a/b** was treated with 0.08 M DMDO, prepared according to the procedure of Adam *et al.*[15] As expected from the conformations of **15a/b**, **15a** was epoxidised from the α-face of the olefin to give **20** and **15b** was epoxidised from the β-face of the olefin to give **21** (Scheme 5).



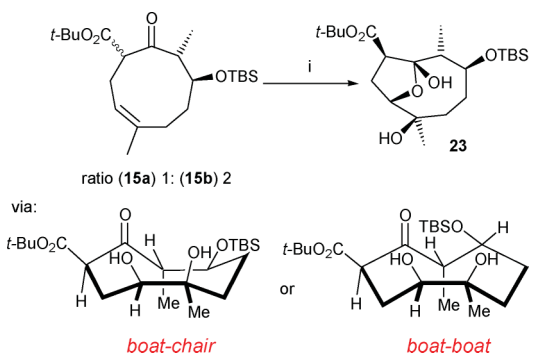
Scheme 4 Iodocyclisation of **15a**. *Reagents and conditions*: (i) I_2, AcOAg, AcOH, 11%.



Scheme 5 Epoxidation and cyclisation. *Reagents and conditions*: (i) DMDO, acetone, 100%; (ii) c.H_2SO_4, THF/H_2O 1 : 1, r.t., 24 h, **enol-21** 20%, **22** 32%.

We decided to treat the mixture of **20** and **21** with conc. sulfuric acid in THF/water, as we anticipated that this would provide a way to form products from both intramolecular opening of the epoxides as well as products resulting from the intramolecular cyclisation of any diols formed by intermolecular epoxide opening with aqueous acid. When the mixture of **20**/**21** was subjected to the proposed conditions two new products were formed. One of these products was identified as the enol tautomer of the β-epoxide **21** and the other was identified as the bicyclic hemiketal **22** (Scheme 5). On initial inspection it is quite remarkable that epoxide **21** is stable to these acidic conditions and that only enolisation occurs. Consideration of the consequences of **21** adopting a boat-boat conformation may provide some explanation for this. The alignment of the C(2)–H σ-bond with the C=O π*-orbital in the boat-boat conformation can justify why enolisation is so facile, while the lack of a viable standard S_N2 trajectory for any incoming nucleophile explains the epoxide's resilience to opening (Fig. 2). When more forcing conditions were investigated, including a greater amount of conc. sulfuric acid or heat, no recognisable products were returned. The formation of **22** can be explained by protonation of α-epoxide **20** and opening to give a tertiary carbocation, which is quenched by water from the β-face. The newly formed α-secondary hydroxyl is now in a position to cyclise onto the protonated ketone carbonyl to give **22**. No cyclisation of the ketone carbonyl onto the carbocation is observed and this is presumably due to the interatomic distance still being around 4.2 Å.

Interested by the cyclisation to form **22** we decided to investigate the formation and reactivity of α- and β-*syn* diols which we envisaged forming by the dihydroxylation of **15a**/**b** respectively (Scheme 6). As in the DMDO epoxidation reaction, we expected that the facial diastereoselectivity of the dihydroxylation would be controlled by the conformation of the nine-membered ring. That is **15a** would be dihydroxylated on the α-face of the olefin and **15b** would be dihydroxylated on the β-face of the olefin.

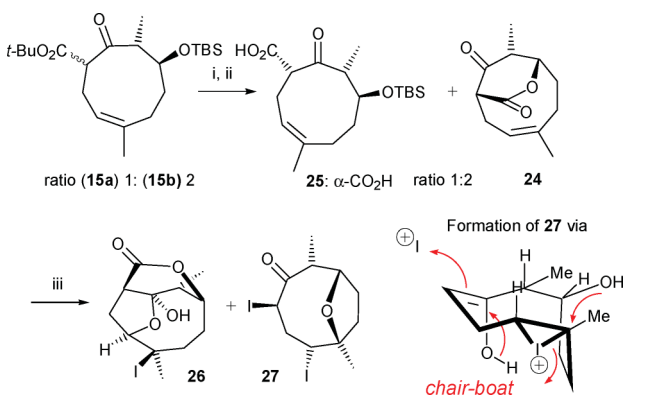


Scheme 6 Dihydroxylation of **15b**. *Reagents and conditions*: (i) OsO_4, NMO, acetone/H_2O, 23%.

Dihydroxylation was attempted by treating **15a**/**b** with catalytic osmium tetroxide and stoichiometric NMO reoxidant in an acetone/water mixture. While **15a**/**b** was consumed and several other products appeared to form, only one product was isolable and that was identified as having the structure **23**. The formation of **23** can be rationalised by assuming that dihydroxylation of **15b** occurred on the β-face of the olefin. Cyclisation to **23** can happen *in situ* if there is a conformational change from **15b**'s original boat-boat conformation to either a boat-chair or an alternative boat-boat conformation. This change in conformation will place the newly generated secondary hydroxyl group proximal to the ketone carbonyl and allow for hemi-ketalisation to occur.

Having gained a feeling for the reactivity of cyclononenes **15a**/**b** with respect to the transannulation reactions they undertook, we wondered if by making the nine-membered ring more rigid and hence restricting the conformations available to it, we could encourage other transannulation reactions. We decided that the formation of a lactone between the C2 carboxyl substituent and the C8 hydroxyl would achieve this goal. Modelling of the desired lactone **24** indicated that the distance between the ketone carbonyl and the tertiary olefinic carbon (C5) was around 3.8 Å compared to 3.2 Å between the carbonyl oxygen and the secondary olefinic carbon (C4). Even though the ketone oxygen is closer to C4, we felt that the greater stability of a tertiary cationic centre over a secondary one may bias the reaction and generate products of cyclisation onto C5 rather than C4.

To put this idea to the test lactone **24** was prepared by treating **15a**/**b** with aqueous hydrofluoric acid to remove the TBS-ether, followed by trifluoroacetic acid in order to remove the *tert*-butyl ester and promote lactonisation. These transformations proceeded without incident to give a 65% yield of lactone **24**. While the removal of the *tert*-butyl ester proceeded quantitatively, and we were able to see the free α-acid **25** in the ^{1}H NMR of the crude reaction mixture, we were never able to isolate it.



Scheme 7 Lactonisation of **15b** and iodocyclisation. *Reagents and conditions*: (i) aq. HF, MeCN, 0 °C, 99%; (ii) TFA, CH_2Cl_2, **24**, 65%; (iii) I_2, AcOAg, AcOH, rt, 24 h, **26** 38%, **27** 15%.

When lactone **24** was subjected to our iodocyclisation conditions two new products were formed in 38% and 15% yields, the structures of which were identified as being **26** and **27** respectively. In the case of **26**, it would seem that cyclisation of the ketone carbonyl had occurred, but onto the secondary olefinic carbon (C4) rather than the tertiary carbon (C5). This selectivity in the transannular cyclisations provided further evidence that it is the interatomic distance between the reacting centres, which are governed by the conformation of the nine-membered ring, that is the critical factor in understanding and predicting the mode of transannular cyclisation, rather than the relative stability of any presumed intermediates. The formation of **27** can be accounted for by hydrolysis of the lactone followed by decarboxylation and trapping of the resultant enol with the excess I^+ present. This is followed by cyclisation of the now unmasked hydroxyl group onto the α-iodonium ion through a chair-boat conformation

(Scheme 7). The presence of two iodines was confirmed by mass spectrometric analysis of **27**.

We had demonstrated that it was possible to initiate a number of novel transannulation reactions of a single nine-membered ring through any of its oxygen functionalities. This depended on the conformation of the cyclononene ring and the interatomic distances between the reacting centres. These reactions led to the formation of a number of bridged bi- and tri-cyclic ether systems which are natural product-like in structure. We next turned our attention to the more challenging task of transannular carbon–carbon bond formation, to see if we could increase the diversity of structures that can be accessed from a single nine-membered ring precursor.

Cyclisations through carbon

Our attention was drawn to two groups of sesquiterpenoid natural products; the pinguisanes[16] and the austrodoranes[17] (Fig. 3). Both of these families of natural products have a bicyclo[4.3.0]nonane ring system, a range of functionality around the bicyclo[4.3.0]nonane core. They also have a range of biological activities, including anticancer, antimicrobial and antifeedant activity.[18] Additionally, no member of either family of these natural products has had the bicyclo[4.3.0]nonane core constructed by a transannulation reaction.

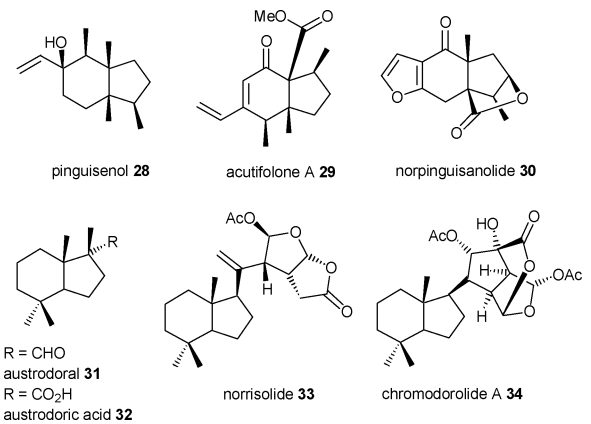
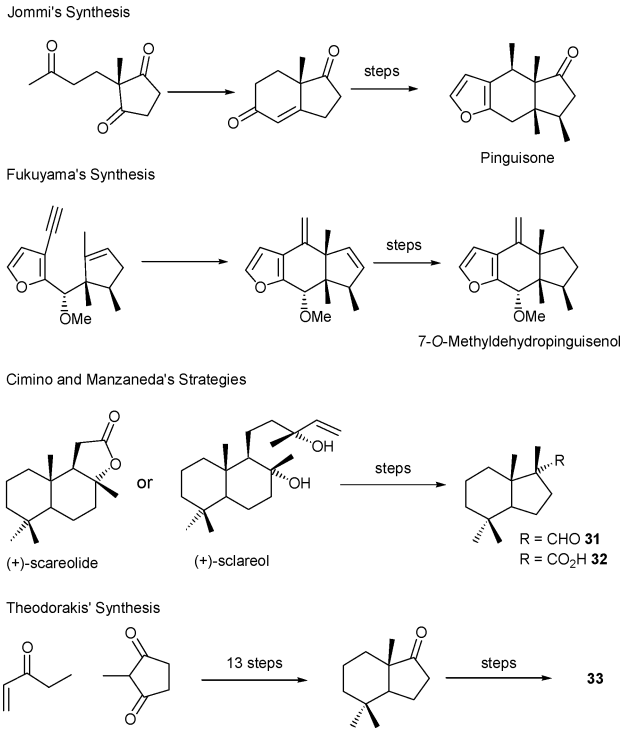


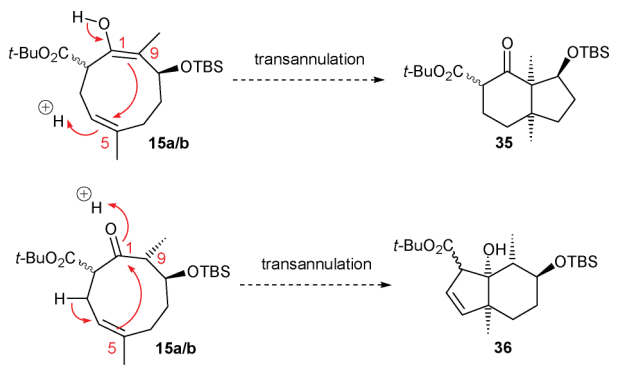
Fig. 3 The pinguisane and austrodorane sesquiterpenes.

Members of the pinguisanes have been constructed by several routes, both linear and convergent in nature (Scheme 8). These routes include annulation of the five-membered ring onto a pre-existing cyclohexanone,[19] intramolecular Diels–Alder reactions,[20] cycloisomerisations[21] and cationic cyclisations.[22] Members of the austrodanes have been synthesised by either the manipulation of the natural products (+)-scareolide[23] and (+)-sclareol[24] as well as by Robinson annulation[25] (Scheme 8).

In order to construct the bicyclo[4.3.0]nonane ring system we would have to form one of two possible bonds: either a bond between the C9 and C5 carbons of the nine-membered ring or a bond between the C1 and C5 carbons (Scheme 9). It is possible that the first of these strategies may be achieved by the cyclisation of a nucleophilic enol C9 onto an electrophilic C5. We thought that this might be achieved by the use of a Brønsted acid which would promote both enolisation and possible protonation of the double bond. The cyclisation of a nucleophilic C5 onto the electrophilic



Scheme 8 Illustrative routes to the pinguisanes and austrodoranes.



Scheme 9 Possible transannulation strategies for the formation of the bicyclo[4.3.0]nonane ring systems.

C1 would amount to a Prins cyclisation, which we reasoned may be achieved by the use of either a Brønsted or Lewis acid.

It did not escape our notice that there were problems with both of the strategies shown in Scheme 9. It is improbable that **15a/b** would be capable of cyclising to **35** under Brønsted acid mediated conditions for a number of reasons. Firstly, if enolisation did occur, it would most likely occur between C1 and C2 to form the more stable enol, rather than between C1 and C9, and secondly, the use of a Brønsted acid strong enough to protonate the double bond would almost certainly cause loss of the *tert*-butyl ester and possible decarboxylation. In the case of the transannular Prins cyclisation of **15a/b** to **36** it was unclear whether the double bond would be nucleophilic enough to attack the protonated carbonyl group. On top of all of these factors was the consideration of whether the nine-membered rings **15a/b** would adopt a conformation favourable for the desired modes of cyclisation. With these doubts in our mind we decided instead to

examine the possibility of using lactone **24** as our transannulation precursor.

A combination of molecular modelling and X-ray crystallography† heartened us to the potential of lactone **24** as a transannulation precursor. The X-ray crystal structure showed that the C9–H9 bond was aligned with the C═O π* orbital, thus making it reasonable to assume that enolisation could occur under appropriate conditions (Fig. 4). We rationalised that enolisation would not occur between C1 and C2 as this would generate an *anti*-Bredt bridgehead double bond. Additionally, molecular modelling indicated that the distance from the enol C9 to the olefin C5 was 3.36 Å and the distance from the olefin C5 to the carbonyl carbon C1 was 3.30 Å, both distances well within the range of transannular cyclisations we had previously witnessed.

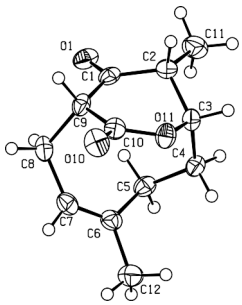
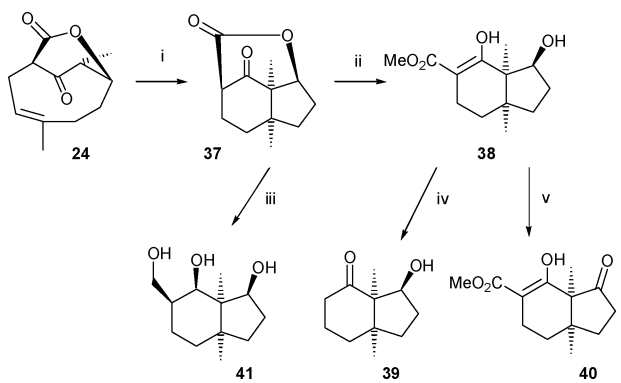


Fig. 4 X-ray crystal structure of lactone **24**.

We decided to investigate the use of tetrafluoroboric acid to promote the cyclisation as we rationalised that the non-nucleophilic counter ion would be unable to trap any carbocation generated by the protonation of the double bond.[26] To this end we treated **24** with 15 eq. of tetrafluoroboric acid and were delighted to witness the clean formation of a new product. After comprehensive characterisation attempts by NMR spectroscopy the structure was eventually revealed by single crystal X-ray crystallography† as **37**, which contained the desired bicyclo[4.3.0]nonane ring system present in the pinguisane family of sesquiterpenoids (Scheme 10 and Fig. 5). The lactone was opened with sodium methoxide in methanol to yield the bicyclo[4.3.0]nonane core **38**



Scheme 10 Formation of the bicyclo[4.3.0]nonane core of the pinguisane-type sesquiterpenoids. *Reagents and conditions*: (i) 54% HBF_4 in Et_2O, AcOH, 69%; (ii) NaOMe, MeOH, 70%; (iii) $NaBH_4$, MeOH, 0 °C to rt, 10% KOH, 63%; (iv) μ-wave, H_2O, DMF, 56%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 100%.

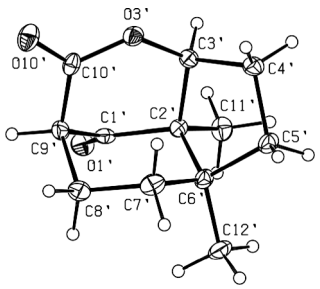
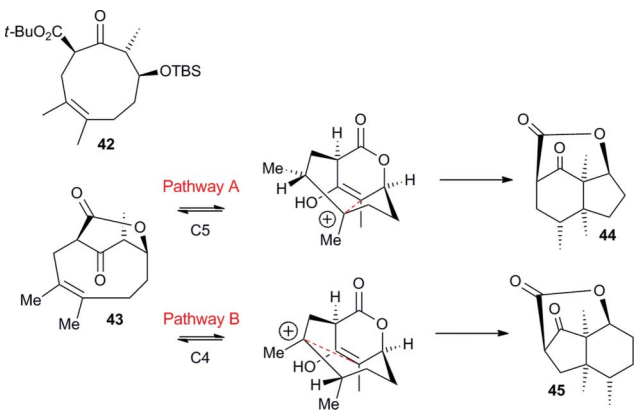


Fig. 5 X-ray crystal structure of compound **37**.

of the pinguisane-type sesquiterpenoids complete with the vicinal quaternary stereocentres at the ring junction.

We found that several functional group modifications could be made to **38**: demethyl decarboxylation to give **39** was achieved by heating **38** in wet dimethyl formamide in a microwave, and oxidation of the cyclopentanol to the cyclopentanone **40** occurred under Swern conditions. Additionally, lactone **37** could be reduced to the triol **41** by the action of sodium borohydride (Scheme 10). However, other modifications like formation of an enone from **39** by selenoxide elimination failed. While it is possible to envisage how the cyclopentanol could be converted into a methyl cyclopentane, it was less clear how the final methyl group could be installed. With this challenge in mind we decided to redesign our nine-membered ring transannulation precursor and install the required methyl group prior to transannulation. We therefore settled on cyclononone **42** as our new transannulation precursor, which differs from **15a/b** only in the fact that it has a *tetra*-substituted double bond (Scheme 11).[27]

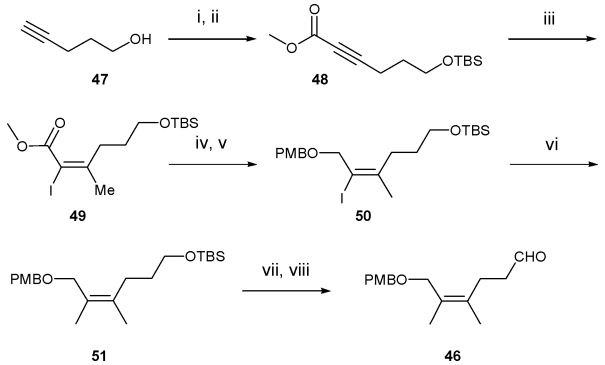


Scheme 11 Possible modes of transannular enol cyclisation on to the C4–C5 double bond.

Introduction of a *tetra*-substituted double bond required us to consider two possible eventualities. The first was that increasing the nucleophilicity of the double bond would lead to a change in reactivity, such that the Prins cyclisation would occur. We decided that this was not a concern as the bicyclo[4.3.0]nonane system generated should be able to be converted into either the pinguisanes or the austrodoranes. The second was that if cyclisation of the enol did occur, which end of the *tetra*-substituted double bond would it cyclise onto? In order to address this question molecular modelling was carried out on lactone **43**. This indicated that the cation generated at C5 was 2.033 kcal mol^{-1} lower in energy than the cation generated at C4, and that cyclisation

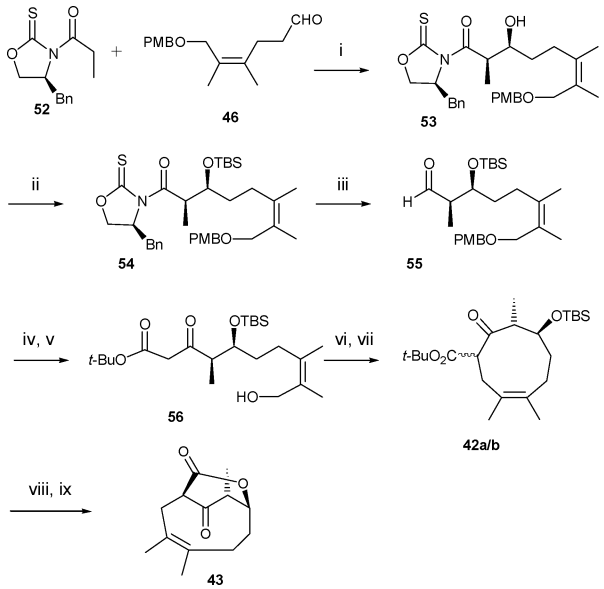
onto the C5 cation was 8.721 kcal mol^{-1} more exothermic than cyclisation onto the C4 cation. We were therefore optimistic that if lactone **43** could be synthesised, any enol cyclisation would occur in the desired manner (Scheme 11).

Our strategy for the synthesis of lactone **43** was similar to that already described for the synthesis of lactone **24**, although initially we required an aldehyde with a *tetra*-substituted double bond **46** to perform a Crimmins' aldol reaction on. The required aldehyde **46** was synthesised from pent-4-yne-1-ol according to Scheme 12.



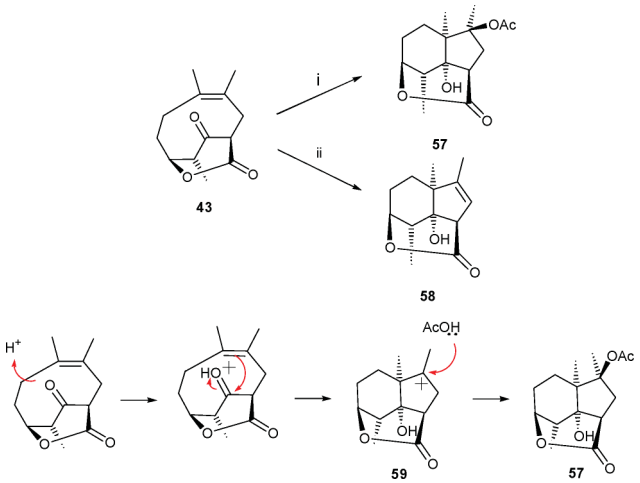
Scheme 12 Synthesis of aldehyde **46**. *Reagents and conditions*: (i) TBSCl, imidazole, DMF, 25 °C, 100%; (ii) BuLi, methyl chloroformate, THF, −78 °C, 100%; (iii) CuI, MeLi, then I_2, THF, −45 to 0 °C, 84%; (iv) DIBAL-H, CH_2Cl_2, −78 °C, 92%; (v) PMB-trichloroacetimidate, TfOH, cyclohexane, CH_2Cl_2, 25 °C, 77%; (vi) Pd(dppf)Cl_2, $ZnMe_2$, dioxane, 80 °C, 76%; (vii) TBAF, THF, 25 °C, 96%; (viii) DMP, CH_2Cl_2, 25 °C, 72%.

Pent-4-yne-1-ol was converted into ester **48** by protection as a TBS ether and subsequent acylation of the alkyne with BuLi and methyl chloroformate. Copper catalyzed conjugate addition of methyl lithium and trapping with iodine generated **49** in 84% yield.[28] Reduction of the ester with DIBAL-H and protection of the allylic alcohol as a PMB-ether gave **50** in 71% yield (two steps). A Negishi cross-coupling reaction added a methyl group and installed the *tetra*-substituted alkene as the single desired *Z*-isomer **51** in 76% yield.[29] Removal of the TBS ether with tetra-butylammonium fluoride (96% yield) and oxidation of the resultant alcohol with Dess–Martin periodinane gave aldehyde **46** in 72% yield. With aldehyde **46** in hand we were able to convert it into lactone **43** by reacting it with oxazolidinthione auxiliary **52** under the Crimmins' modification of the Evan's aldol conditions[9] to give **53** in 60% yield (Scheme 13). The secondary alcohol was protected as the TBS ether in 99% yield and the auxiliary was cleaved with DIBAL-H to give aldehyde **55** in 82% yield. A Roskamp homologation[10] with *tert*-butyl diazoacetate installed the β-ketoester unit in 67% yield. Removal of the PMB ether with DDQ generated the allylic alcohol **56** in 66% yield. Conversion to the bromide with *N*-bromosuccinimide and triphenylphosphine was immediately followed by cyclisation with caesium carbonate in DMF, which gave an inseparable mixture of nine-membered rings **42a/b** in 63% combined yield over the two steps. The TBS ether was removed in 100% yield by hydrofluoric acid in acetonitrile and the product was treated with trifluoroacetic acid to yield lactone **43** in 56% yield. As in the case of the conversion of **15a/b** to **24**, we were unable to isolate any of the deprotected α-acid diastereomer after work-up.



Scheme 13 Synthesis of lactone **43**. *Reagents and conditions*: (i) $TiCl_4$, (−)-sparteine, CH_2Cl_2, 0 °C to −78 °C, 60%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 99%; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 82%; (iv) $SnCl_2$, *t*-BuO_2CCHN_2, CH_2Cl_2, 25 °C, 67%; (v) DDQ, CH_2Cl_2 : H_2O 19 : 1, 25 °C, 66%; (vi) NBS, Ph_3P, CH_2Cl_2, −30 °C; (vii) Cs_2CO_3, DMF, 63% (over two steps); (viii) HF (48% aq), MeCN, 25 °C, 100%; (ix) TFA, CH_2Cl_2, 25 °C, 56%.

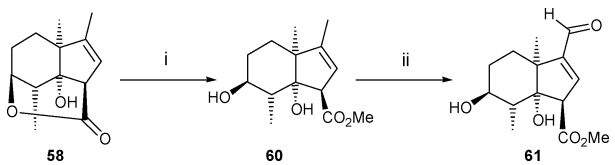
When lactone **43** was subjected to our tetrafluoroboric acid mediated transannulation conditions starting material was consumed and a new product was formed after 5 h.[27] The structure of this new product was determined to be **57**, which is the product of the alternative Prins cyclisation pathway and not the product of the expected enol cyclisation (Scheme 14). A mechanism for the formation of **57** is given in Scheme 14, where Prins cyclisation of the *tetra*-substituted double bond onto the protonated carbonyl group generated cation **59**, which is trapped by the acetic acid co-solvent to give the functionalised bicyclo[4.3.0]nonane core **57** of the austrodoranes. It would seem that simply changing the *tri*-substituted double bond to a *tetra*-substituted double bond



Scheme 14 Transannular Prins cyclisation of **43**. *Reagents and conditions*: (i) $HBF_4{\cdot}OEt_2$, AcOH, 25 °C, 57%; (ii) $HBF_4{\cdot}OEt_2$, Et_2O or C_6H_6, 25 °C, 61%.

increases the nucleophilicity of the double bond sufficiently for it to now become the nucleophilic component in the transannulation reaction rather than the electrophilic component. The reaction was repeated but this time without a nucleophilic co-solvent and **43** was smoothly transformed into **58**, by loss of a proton from cation **59**. Attempts to trap cation **59** with carbon nucleophiles such as anisole, cyanide and carbon monoxide all met with failure and returned **43** unchanged.

Further functionalisation was carried out on **58**, which was opened with sodium methoxide in methanol to yield methyl ester **60** in 71% yield (Scheme 15). Installation of an aldehyde group at the allylic methyl was achieved in 76% yield by treating **60** with selenium dioxide. The introduction of an aldehyde unit at this position provides a handle to attach other ring systems to the austrodorane core, like those found in **33** and **34** (Fig. 3).



Scheme 15 Allylic functionalisation of **58**. *Reagents and conditions*: (i) NaOMe/MeOH, 71%; (ii) SeO_2, dioxane, reflux, 76%.

Conclusions

We have investigated a number of novel transannulation reactions across a nine-membered ring system and generated a diverse array of natural product-like structures as single enantiomers. We have confirmed that the conformation of the nine-membered ring is of paramount importance to the success of any transannulation reaction, and that while transannulation reactions can occur over distances as great as 4 Å, the optimal distance is around 3 Å. Indeed, if the distance is too large then alternative transannulation reactions have been shown to occur from other energetically accessible conformations. We have also shown in the case of the nine-membered rings studied that the proximity of the reacting centres has a greater influence on the transannulation reaction than electronic bias with respect to cyclisation onto secondary or tertiary cationic centres. Additionally, we have also discovered that the difference in nucleophilicity between a *tri*- and a *tetra*-substituted double bond is sufficient to turn the double bond from an electrophilic component into a nucleophilic component. The results detailed contribute to our greater understanding of transannulation reactions and allow the prediction of which transannulation reactions may occur in a particular system.

Experimental

General methods

For general experimental details, including information on solvent purification and the spectrometers used in this research as well as for procedures, spectroscopic and crystallographic data not reported below, see the ESI.†

(4*S*)-4-Benzyl-3-[(2*R*,3*S*)-8-acetoxy-2,6-dimethyl-3-hydroxy-1-oxo-oct-6-enyl]-1,3-oxazolidine-2-thione (10). A 3 M solution of titanium tetrachloride in CH_2Cl_2 (11.0 mL, 33.0 mmol, 2.0 equivs) was added to a solution of **9**[9] (4.11 g, 16.5 mmol, 1 equiv) in dry CH_2Cl_2 (120 mL) at 0 °C. The resulting yellow slurry was stirred at 0 °C for 5 min after which time (−)-sparteine (4.17 mL, 18.2 mmol, 1.1 equivs) was added. The dark red titanium enolate was stirred at 0 °C for 30 min then cooled to −78 °C. A solution of **8**[5c] (3.09 g, 18.2 mmol, 1.1 equivs) in CH_2Cl_2 (20 mL) was drawn into a syringe and added at a rate of 20 mL h^{-1} *via* a syringe pump. The reaction mixture was stirred at −78 °C for 8 h and then quenched with a saturated aqueous NH_4Cl solution (100 mL) and the mixture was warmed to rt. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 300 mL). The combined organics were filtered through a pad of Celite® and washed with CH_2Cl_2 (4 × 100 mL). The filtrate was washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a viscous brown oil as the crude. The oil was purified *via* flash column chromatography eluting with pentane : Et_2O, 2 : 1 then 1 : 4, leaving **10** as an orange oil (5.6 g, 81%). $[\alpha]_D^{24}$ +58.1 (*c* 0.93, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 3520, 2939, 1735, 1453, 1354, 1193 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 7.36–7.22 (5 H, m), 5.39 (1 H, ddd, *J* = 7.3, 1.4, 0.8), 4.96 (1 H, dddd, *J* = 10.2, 6.7, 3.8, 2.9), 4.80 (1 H, dq, *J* = 7.0, 2.9), 4.67 (1 H, dd, *J* = 12.6, 7.3), 4.60 (1 H, dd, *J* = 12.6, 7.3), 4.33 (1 H, dd, *J* = 9.4, 2.9), 4.28 (1 H, dd, *J* = 9.4, 6.7), 4.04 (1 H, m), 3.30 (1 H, dd, *J* = 13.4, 3.7), 2.94 (1 H, d, *J* = 3.5), 2.77 (1 H, dd, *J* = 13.4, 10.2), 2.34 (1 H, m), 2.23 (1 H, m), 2.03 (3 H, s), 1.79 (3 H, d, *J* = 1.4), 1.73–1.55 (2 H, m), 1.24 (3 H, d, *J* = 7.0) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 185.2 (s), 177.5 (s), 171.5 (s), 140.8 (s), 135.1 (s), 129.3 (d), 127.3 (d), 119.8 (d), 70.3 (d), 70.1 (t), 60.8 (t), 59.9 (d), 42.2 (d), 37.7 (t), 31.6 (t), 28.2 (t), 23.2 (q), 21.2 (q), 10.3 (q) ppm. MS (ESI): *m*/*z* 420 ($M + H^+$), 401 ($M^+ - H_2O$), 360 (M^+ − OAc), 342 (M^+ − Ph), 284 ($M + H^+$ − Ph − OAc); HRMS (ESI): found (M + H)+: 420.1832, $C_{22}H_{29}NO_5S$ requires ($M + H^+$): 420.1845.

(2*R*,3*S*)-*N*-Methoxy-*N*-methyl-8-acetoxy-3-(*tert*-butyl,dimethylsilanyloxy)-2,6-dimethyl-oct-6-enamide (11). To a suspension of *N*,*O*-hydroxylamine hydrochloride (2.55 g, 26.1 mmol, 1.6 equivs) in dry THF (50 mL) was added a 2 M solution of trimethylaluminium in PhMe (12.3 mL, 24.5 mmol, 2.0 equivs) at 0 °C. Once gas evolution had ceased, the suspension was cooled to −78 °C and a solution of **10** (6.84 g, 16.3 mmol, 1 equiv) in THF (25 mL) was added *via* cannula. The reaction mixture was stored in a freezer at −18 °C for 24 h and then poured onto saturated aqueous NH_4Cl solution (200 mL). The biphasic mixture was rapidly stirred and acidified with a 1 M aqueous HCl solution (150 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 500 mL). The combined organics were washed successively with a 1 M aqueous HCl solution (150 mL), saturated aqueous $NaHCO_3$ solution (2 × 100 mL) and brine (150 mL), dried over $MgSO_4$, filtered and finally concentrated *in vacuo* leaving a mixture of the Weinreb amide and thiooxazolidinone as an orange oil (7.83 g). The oil was submitted unpurified to the next step, TBS protection of the secondary alcohol.

To a solution of an unpurified mixture of (2*R*,3*S*)-*N*-methoxy-*N*-methyl-8-acetoxy-2,6-dimethyl-3-hydroxy-oct-6-enamide and thiooxazolidinone (4.68 g of the Weinreb amide, 16.3 mmol, 1 equiv) in DMF (20 mL) was added imidazole (5.31 g, 78.0 mmol, 6.0 equivs) and *tert*-butyldimethylsilyl chloride (2.94 g, 19.5 mmol, 1.5 equivs) at rt. The reaction mixture was stirred at rt for 18 h,

diluted with Et_2O (500 mL) and poured onto H_2O (150 mL). The layers were separated and the organic phase was washed with H_2O (2 × 100 mL). The aqueous fractions were combined and extracted with Et_2O (3 × 500 mL). The combined organics were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving an orange oil. The oil was purified *via* flash column chromatography eluting with hexane : EtOAc, 2 : 1, leaving **11** as a yellow oil (5.76 g, 88% over 2 steps). $[\alpha]_D^{24}$ −1.2 (*c* 0.81, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 2932, 2884, 2858, 1737, 1659, 1462, 1383, 1233, 1109, 1043, 993 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 5.32 (1 H, dt, *J* = 7.3, 1.2), 4.55 (1 H, dd, *J* = 11.8, 7.3), 4.50 (1 H, dd, *J* = 11.8, 7.3), 3.95 (1 H, ddd, *J* = 8.5, 4.4, 4.1), 3.71 (3 H, s), 3.19 (3 H, s), 3.05 (1 H, m), 2.21–2.09 (2 H, m), 2.03 (3 H, s), 1.72 (3 H, d, *J* = 1.2), 1.61–1.45 (2 H, m), 1.18 (3 H, d, *J* = 7.0), 0.92 (9 H, s), 0.08 (3 H, s), 0.08 (3 H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4 (s), 171.1 (s), 143.2 (s), 118.9 (d), 73.5 (d), 61.6 (q), 61.1 (t), 40.1 (d), 34.1 (t), 32.1 (q), 26.4 (t), 26.0 (q), 23.6 (q), 21.1 (q), 18.2 (s), 15.4 (q), –4.1 (q), –4.5 (q) ppm. MS (ESI): *m/z* 402 (M + H^+), 342 (M^+ – OAc), 284 (M^+ – TBS), 228 (M^+ + HOAc – TBS); HRMS (ESI): found (M + Na^+): 424.2493, $C_{20}H_{39}NO_5Si$ requires (M + Na^+): 424.2490

(2*R*, 3*S*)-3-(*tert*-Butyl, dimethylsilanyloxy)-2, 6-dimethyl-8-hydroxy-oct-6-enal (12) and (2*R*, 3*S*)-8-acetoxy-3-(*tert*-butyl,dimethylsilanyloxy)-2,6-dimethyl-oct-6-enal (13). A 1 M solution of DIBAL-H in toluene (16.2 mL, 16.2 mmol) was added slowly to a solution of **11** (3.1 g, 7.72 mmol) in THF (80 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h after which a 10 M solution of acetic acid in THF (18.8 mL) was added and the reaction mixture was poured onto aqueous $NaHCO_3$ solution (200 mL). The layers were separated and aqueous phase was extracted with diethyl ether (3 × 250 mL). The organic fractions were combined and washed with 10% aqueous potassium sodium tartrate solution (3 × 80 mL), brine (300 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo* leaving pale yellow oil as a mixture of **12** and **13**. The mixture was submitted unpurified to next step, *i.e.* acetylation of primary alcohol of **12**. (2*R*,3*S*)-*3*-(*tert-Butyl*,*dimethylsilanyloxy*)-*2*,*6-dimethyl-8-hydroxy-oct-6-enal* **(12)** $[\alpha]_D^{24}$ −26.1 (*c* 0.98, $CHCl_3$). ν_{max} (NaCl) 3618, 2932, 2892, 2853, 1734, 1671, 1454, 1386, 1258, 1110 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 9.77 (1H, d, *J* = 0.9), 5.43 (1H, t, *J* = 7.3 Hz), 4.11 (2H, d, *J* = 7.3 Hz), 4.08 (1H, ddd, *J* = 6.4, 6.4, 4.1 Hz), 2.49 (1H, ddq, *J* = 6.7, 4.1, 0.9 Hz), 2.17(1H, m), 1.96(1H, m), 1.74 (3H, s), 1.64–1.48 (2H, m), 1.26 (1H, s), 1.08 (3H, d, *J* = 6.7 Hz), 0.87 (9H, s), 0.08 (3H, s), 0.04 (3H, s) ppm. δ_C (100 MHz; $CDCl_3$) 205.4 (s), 139.5 (s), 124.5 (d), 72.1 (d), 59.0 (t), 51.2 (d), 33.3 (t), 28.3 (t), 25.8 (q), 23.5 (q), 18.1 (s), 8.0 (q), –4.2 (q) ppm. LRMS (ESI+) *m/z* 301 (M+H)+, 323 (M+Na)+. HRMS (ESI+) *m/z* found 322.2018 (M+Na)+, requires 323.2109 (M+Na)+. (2*R*,3*S*)-*8-Acetoxy-3-*(*tert-butyl*,*dimethylsilanyloxy*)-*2*,*6-dimethyl-oct-6-enal* **(13)** $[\alpha]_D^{24}$ −30.1 (*c* 1.1, $CHCl_3$). ν_{max} (NaCl) 2951, 2931, 2862, 2724, 1721, 1677, 1460, 1376, 1312, 1276, 1043, 998 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 9.77 (1H, dd, *J* = 0.6 Hz), 5.36 (1H, t, *J* = 7.5 Hz), 4.53 (2H, d, *J* = 7.5 Hz), 4.09 (1H, ddd, *J* = 6.4, 5.9, 3.7 Hz), 2.49 (1H, ddq, *J* = 6.8, 3.7, 0.6 Hz), 2.18 (1H, m), 2.04 (3H, s), 1.98 (1H, m), 1.75 (3H, s), 1.63–1.48 (2H, m), 1.07 (3H, d, *J* = 6.8 Hz), 0.86 (9H, s), 0.07 (3H, s), 0.04 (3H, s) ppm. δ_C (100 MHz; $CDCl_3$) 205.0 (d), 171.0 (s), 142.3 (s), 119.5 (t), 72.2 (d), 60.8 (t), 51.3 (t), 33.3 (t), 28.5 (t), 25.8 (q), 23.5 (q), 21.1 (q), 18.1 (s), 8.0 (q), –4.2 (q), –4.5 (q) ppm. LRMS (ESI+) *m/z* 365 (M+Na)+. HRMS (ESI+) *m/z* found 365.2132 (M+Na)+, $C_{18}H_{34}NaO4Si$ requires 365.2119 (M+Na)+.

(2*R*,3*S*)-8-Acetoxy-3-(*tert*-butyl,dimethylsilanyloxy)-2,6-dimethyl-oct-6-enal (13). Acetic anhydride (0.13 mL, 1.37 mmol) was added to a solution of **12** and **13** (0.17 g of 12, 0.56 mmol), triethylamine (0.2 mL, 1.02 mmol) and solid $NaHCO_3$ (0.12 g, 1.43 mmol) in CH_2Cl_2 (6 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature and stirred for further 16 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), followed by addition of H_2O (5 mL) and the layers were separated. The organic phase was washed with water (2 × 10 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave yellow oil, the oil was purified by flash column chromatography (hexane : diethyl ether; 4 : 1) leaving **13** as a colourless oil (2.1 g, 81% over two steps). The proton NMR data was same as that already reported for **13**.

(4*R*,5*S*)-*tert*-Butyl-10-acetoxy-5-(*tert*-butyl,dimethylsilanyloxy)-4,8-dimethyl-3-oxodec-8-enoate (14). A solution of **13** (600 mg, 1.75 mmol) in CH_2Cl_2 (2.5 mL) was added to a suspension of $SnCl_2$ (32.7 mg, 0.17 mmol) and *tert*-butyl diazoacetate (0.29 mL, 2.12 mmol) in CH_2Cl_2 (3 mL) at room temperature. The reaction mixture was warmed to 35 °C and stirred for 3 h, after which 10 mol% of tin(II) chloride (32.7 mg, 0.17 mmol) and 0.6 eq of *tert*-butyl diazoacetate (0.14 mL, 1.02 mmol) were added and the reaction mixture was stirred for further 18 h at 35 °C, cooled to room temperature and diluted with CH_2Cl_2 (50 mL). The reaction mixture was poured onto H_2O (50 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics were washed with brine (100 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo* leaving a yellow oil. The oil was purified by flash column chromatography using TLC grade silica, (hexane : diethyl ether; 10 : 1–4 : 1) leaving **14** as a colourless oil (708 mg, 88%). $[\alpha]_D^{24}$ –41.2 (*c* 0.98, $CHCl_3$). ν_{max} (solution; CHCl3) 2922, 2853, 1741, 1715, 1645, 1449, 1366, 1232, 1156, 1023, 951, 913, 834 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 5.34 (1H, t, *J* = 7.1 Hz), 4.52(2H, d, *J* = 7.1 Hz), 3.86 (1H, ddd, *J* = 9.1, 4.7, 4.4 Hz), 3.52 (1H, d, *J* = 15.7 Hz), 3.46 (1H, d, *J* = 15.7 Hz), 2.85 (1H, dq, *J* = 7.0, 4.4 Hz), 2.18(1H, dt, *J* = 12.6, 5.0 Hz), 2.03 (3H, s), 1.98 (1H, dt, *J* = 12.6, 5.0 Hz), 1.73 (3H, s), 1.47 (2H, ddd, *J* = 9.1, 5.0, 4.7 Hz), 1.45 (9H, s), 1.08 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.08 (3H, s), 0.06 (3H, s) ppm. δ_C (100 MHz; $CDCl_3$) 205.8 (s), 171.1 (s), 166.8 (s), 142.6 (s), 119.3 (d), 81.8 (s), 74.0 (d), 60.8 (t), 51.7 (d), 50.8 (t), 32.9 (t), 28.6 (t), 28.1 (q), 25.9 (q), 23.6 (q), 21.1 (q), 18.1 (s), 12.1 (q), –4.3 (q), –4.4 (q) ppm. LRMS (ESI+) *m/z*, 479 (M+Na)+, 474 (M+NH_4)+, 457 (M+H)+, 341 (M-TBS)+. HRMS (ESI+) *m/z* found 479.2794 (M+Na)+, $C_{24}H_{44}NaO_6Si$ requires 479.2799 (M+Na)+.

(2*R*,8*S*,9*R*)-2-(*tert*-Butoxycarbonyl)-8-(*tert*-butyl,dimethylsilanyloxy)-5,9-dimethyl-cyclonon-4-enone (15) and (2*R*,3*S*,6*S*,7*R*)-2-(*tert*-butoxycarbonyl)-6-(*tert*-butyl,dimethylsilanyloxy)-3,7-dimethyl-3-ethenyl-cycloheptanone (18). A solution of **14** (110.4 mg, 0.24 mmol) in dry degassed THF (3.1 mL) was added to a flask containing sodium hydride (60% in mineral oil) (11.5 mg, 0.288 mmol) and stirred at room temperature for 15 min. The resulting yellow solution was drawn into the syringe and the syringe was equipped with a needle fitted with small

cotton wool plug. The solution was then added to a solution of tetrakis(triphenylphosphine) Pd (0) (13.86 mg, 0.012 mmol) and *bis*-diphenylphosphine ethylene (9.5 mg, 0.024 mmol) in dry degassed THF (2.3 mL) under reflux at a rate of 1.50 mL h^{-1} *via* syringe pump. The reaction mixture was maintained under reflux for further 2 h, after which the reaction was cooled to room temperature and filtered through a plug of silica and washed with diethyl ether. Filtrate was concentrated *in vacuo* leaving a yellow oil. The oil was purified by flash column chromatography on silver nitrate impregnated silica (TLC grade) using 1 : 12 diethyl ether–hexane elution giving nine-membered ring **15** (40 mg, 42%) as a diastereomeric mixture and seven-membered ring **18** (27 mg, 28%). (*2R**, 8*S*,9*R*)-*2*-(*tert-Butoxycarbonyl*)-*8*-(*tert-butyl*,*dimethylsilanyloxy*)-*5*,*9 dimethyl-cyclonon-4-enone* **(*15*) (*15b* = *d1*, *15a* = *d2*)** ν_{max}(film) 2955, 2926, 2857, 1740, 1706, 1624, 1459, 1252, 1144, 1078, 1067, 838 cm^{-1}. δ_H(400 MHz, $CDCl_3$) 5.37 (1H, t, *J* = 8.3 Hz, d2), 5.32 (1H, dt, *J* = 8.3, 1.2 Hz, d1), 4.05 (1H, dt, *J* = 8.6, 4.3 Hz, d1), 3.69 (1H, dt, *J* = 8.6, 3.0 Hz, d1), 3.61 (1H, dd, *J* = 9.4, 3.3 Hz, d2), 3.42 (1H, dd, *J* = 11.2, 2.1 Hz, d1), 2.87 (1H, dq, *J* = 8.6, 7.1 Hz, d2), 2.82 (1H, dq, *J* = 8.6, 7.0 Hz, d1), 2.71 (1H, ddd, *J* = 14.6, 11.2, 8.3 Hz, d1), 2.52 (1H, dd, *J* = 8.3, 3.3 Hz, d2), 2.49 (1H, app dd, *J* = 9.4, 8.3 Hz, d2), 2.47 (1H, ddd, *J* = 14.6, 8.3, 2.1 Hz, d1), 2.23 (1H, m, d1), 1.98–1.88 (3H, m, d2), 1.78–1.68 (3H, m, d1), 1.68 (3H, d, *J* = 1.2 Hz, d1), 1.68 (3H, s, d2), 1.58 (1H, m, d2), 1.43 (9H, s, d1), 1.42 (9H, s, d2), 1.20 (3H, d, *J* = 7.0 Hz, d1), 1.10 (3H, d, *J* = 7.1 Hz, d2), 0.89 (18H, s), 0.08 (3H, s), 0.07 (3H, s), 0.07 (3H, s), 0.06 (3H, s) ppm. δ_C(100 MHz; $CDCl_3$) 213.3 (s, d2), 212.1 (s, d1), 168.6 (s, d2), 168.5 (s, d1), 141.3 (s, d2), 139.6 (s, d1), 121.0 (d, d1), 120.4 (d, d2), 81.9 (s, d1), 81.1 (s, d2), 73.6 (d, d2), 71.0 (d, d1), 58.4 (d, d1), 57.7 (d, d2), 53.5 (d, d1), 52.7 (d, d2), 35.1 (t, d1), 34.2 (t, d2), 28.3 (t, d1), 28.0 (s, d1 and d2), 27.4 (t, d2), 26.6 (t, d1), 25.9 (q), 25.9 (q), 25.8 (t, d2), 23.4 (q, d2), 22.8 (q, d1), 18.1 (s), 18.0 (s), 16.2 (q, d1), 15.0 (q, d2), –4.2 (q), –4.3 (q), –4.4 (q), –4.7 (q) ppm. LRMS (ESI+) *m*/*z* 341 (M+NH_4–O^tBu), 397 (M+H)+, 419 (M+Na)+. HRMS (ESI+) *m*/*z* found 419.2584 (M+Na)+, $C_{22}H_{40}NaO_4Si$ requires 419.2588 (M+Na)+. (2*R*,3*S*,6*S*,7*R*)-*2*-(*tert-Butoxycarbonyl*)-*6*-(*tert-butyl*, *dimethylsilanyloxy*)-*3*,*7-dimethyl-3-ethenyl-cycloheptanone* **(*18*)** (*minor* = *d1*, *major* = *d2*) ν_{max} (film) 2931, 2857, 1744, 1699, 1639, 1462, 1369, 1129, 1078, 995 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 6.22 (1H, dd, *J* = 17.7, 11.0 Hz, d1), 5.85 (1H, dd, *J* = 17.4, 10.7 Hz, d2), 5.03 (1H, dd, *J* = 11.0, 1.1 Hz, d1), 5.02 (1H, dd, *J* = 17.4, 0.6 Hz, d2), 4.99 (1H, dd, *J* = 17.7, 1.1 Hz, d1), 4.98 (1H, dd, *J* = 10.7, 0.6 Hz, d2), 4.04 (1H, s, d1), 4.01 (1H, s, d2), 3.67 (1H, ddd, *J* = 8.1, 4.4, 1.9 Hz, d1), 3.52 (1H, dt, *J* = 8.7, 3.1 Hz, d1), 2.76 (1H, dq, *J* = 8.7, 7.0 Hz, d2), 2.61 (1H, dq, *J* = 7.1, 4.4 Hz, d1), 2.09 (1H, ddd, *J* = 14.3, 11.9, 2.3 Hz, d2), 1.91 (1H, ddd, *J* = 14.7, 7.0, 2.1 Hz, d1), 1.78 (1H, m, d2), 1.75 (1H, app ddd, *J* = 12.2, 3.1, 2.1 Hz, d1), 1.67 (1H, app ddd, *J* = 7.0, 3.1, 2.1 Hz, d1), 1.64 (1H, m, d2), 1.49 (1H, ddd, *J* = 14.7, 12.2, 2.1 Hz, d1), 1.40 (9H, s, d1), 1.39 (9H, s, d2), 1.22 (1H, m, d2), 1.20 (3H, s, d1), 1.18 (3H, d, *J* = 7.0 Hz, d2), 1.07 (3H, s, d2), 1.09 (3H, d, *J* = 7.1 Hz, d1), 0.93 (9H, s), 0.87 (9H, s), 0.08 (3H, s), 0.07 (3H, s), 0.04 (6H, s) ppm. δ_C (100 MHz, $CDCl_3$) 208.3 (s, d1), 207.4 (s, d2), 167.6 (s, d2), 167.6 (s, d1), 146.5 (d, d2), 142.7 (d, d1), 113.5 (t, d1), 112.1 (t, d2), 81.6 (s, d1), 80.9 (s, d2), 75.7 (d, d1), 73.2 (d, d2), 66.3 (d, d1), 64.6 (d, d2), 56.1 (d, d1), 56.0 (d, d2), 41.0 (s, d1), 40.5 (s, d2), 38.6 (t, d1), 35.1 (t, d2), 34.1 (t, d1), 28.9 (q, d2), 28.0 (t, d2), 28.1 (q, d1), 27.2 (q, d2), 25.9 (q), 25.8 (q), 20.3 (q, d1), 18.1 (s), 17.9 (s), 15.8 (q, d1), 14.5 (q, d2), –4.2 (q), –4.6 (q), –4.9 (q) ppm. LRMS (ESI+) *m*/*z* 341 (M+NH_4–O^tBu), 397 (M+H)+, 419 (M+Na). HRMS (ESI+) *m*/*z* found 397.2759 (M+H)+, $C_{22}H_{41}O_4Si$ requires 397.2769 (M+H)+.

(4*R*,5*S*)-*tert*-Butyl-10-hydroxy-5-(*tert*-butyl,dimethylsilanyloxy)-4,8-dimethyl-3-oxodec-8-enoate (16). To a solution of 14 (1.10 g, 2.40 mmol, 1 equiv) in MeOH : H_2O (30 mL, 4 : 1) at rt was added potassium carbonate (662 mg, 4.80 mmol, 2.0 equivs). The reaction was stirred for 1 h at rt before a saturated aqueous NH_4Cl solution (20 mL) was added and the mixture diluted with EtOAc (100 mL). After separation of the biphasic mixture, the aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organics were washed with a saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over $mgSO_4$. The extracts were filtered and concentrated *in vacuo* to give the crude as a bright yellow oil. The oil was purified *via* flash column chromatography eluting with petrol : EtOAc, 3 : 1 then 2 : 1, to afford alcohol **16** as a colourless oil (790 mg, 79%). $[\alpha]_D^{24}$ –46.1 (*c* 0.84, $CHCl_3$). ν_{max} (NaCl) 3420, 2930, 2857, 1734, 1717, 1645, 1472, 1456, 1318, 1253, 1152, 1027, 836, 775 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 5.41 (1H, t, *J* = 7.0 Hz), 4.08 (2H, m), 3.87 (1H, dd, *J* = 11.1, 4.7 Hz), 3.52 (1H, d, *J* = 15.7 Hz), 3.46 (1H, d, *J* = 15.7 Hz), 2.83 (1H, dq, *J* = 7.1, 4.7 Hz), 2.18 (1H, dt, *J* = 12.4, 5.4 Hz), 1.94 (1H, dt, *J* = 12.4, 4.7 Hz), 1.71 (3H, s), 1.60 – 1.50 (1H, m), 1.45 (9H, s), 1.43 –1.34 (1H, m), 1.09 (3H, d, *J* = 7.1 Hz), 0.90 (9H, s), 0.07 (6H, s) ppm. δ_C (125 MHz, $CDCl_3$) 205.8 (s), 166.7 (s), 139.4 (s), 124.5 (d), 81.7 (s), 73.7 (d), 58.8 (t), 51.5 (d), 50.5 (t), 33.0 (t), 28.3 (t), 28.1 (q), 25.8 (s), 23.3 (q), 11.9 (q), –4.4 (q), –4.4 (q), –4.9 (q) ppm. LRMS (ESI+) *m*/*z* 437 (M+Na)+, 432 (M+NH_4)+, 415 (M+H)+, 323 (M–TBS). HRMS (ESI+) *m*/*z* found 437.2690 (M+Na)+ $C_{22}H_{42}NaO_5Si$ requires 437.2694 (M+Na)+.

(2*R*,8*S*,9*R*)-2-(*tert*-Butoxycarbonyl)-8-(*tert*-butyl,dimethylsilanyloxy)-5,9-dimethyl-cyclonon-4-enone (15). To a solution of **16** (755 mg, 1.8 mmol) in CH_2Cl_2 (25 mL) was added triphenylphosphine (699 mg, 2.55 mmol) and *N*-bromosuccinimide (454 mg, 2.55 mmol) at –30 °C and stirred for 1 h. The flask was covered by aluminium foil. Once the starting material was consumed (TLC) the solvents were removed *in vacuo* at room temperature and crude was triturated using hot petrol. The solvent was removed *in vacuo* and the allylic bromide **17** as crude yellow oil (721 mg) was submitted to the cyclisation reaction.

To the solution of bromide **17** (721 mg) in DMF (15 mL) in a flask wrapped with aluminium foil at –50 °C was added caesium carbonate (739 mg, 2.2 mmol) and stirred for 16 h from –50 °C to room temperature. The reaction mixture was diluted with Et_2O (100 mL) and washed with water (3 × 15 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. A flash column chromatography furnished the product **15** as a colourless oil (381 mg, 64%) The data is identical to that stated previously.

(1*S*,2*R*,4*S*,6*R*,7*R*)-4-(*tert*-Butoxycarbonyl)-2,7-dimethyl-6-iodo-10-oxa-bicyclo[5.2.1]decan-3-one (19). Acetic acid (1.90 ml) was added to a flask containing iodine (65 mg, 0.26 mmol) and silver(I) acetate (43 mg, 0.26 mmol) at room temperature. The resulting mixture was stirred rapidly at 35 °C for 30 min during which time a white suspension in a dark orange solution had formed. The dark orange solution was transferred *via* syringe to a

solution of a mixture of diastereomers of **15** (34 mg, 0.09 mmol) in acetic acid (0.66 ml) at room temperature. The reaction mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (10 ml) and H_2O (3 ml) and neutralized with the addition of solid $NaHCO_3$. The resulting solution was saturated with solid NaCl and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 × 10 ml) and the combined organics were washed successively with saturated aqueous $Na_2S_2O_3$ solution (3 × 10 ml), saturated aqueous $NaHCO_3$ solution (2 × 10 ml), H_2O (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* leaving a colourless oil. The oil was purified by flash column chromatography (1 : 20 ether–hexane to neat ether elution) leaving **19** as a colourless oil (4 mg, 11%). $[\alpha]_D^{24}$ +37.4 (*c* 0.38, $CHCl_3$); ν_{max} (solution; $CHCl_3$) 2975, 2931, 1738 (C═O), 1709 (C═O), 1455, 1370, 1283, 1152, 1041 cm–1. δ_H (500 MHz; $CDCl_3$) 4.64 (1H, ddd, *J* = 8.8, 5.9, 3.4 Hz), 4.29 (1H, dd, *J* = 12.5, 4.9 Hz), 4.08 (1H, dd, *J* = 10.0, 1.0 Hz), 3.37 (1H, dq, *J* = 6.8, 5.9 Hz), 3.00 (1H, ddd, *J* = 15.6, 4.9, 1.0 Hz), 2.53 (1H, ddd, *J* = 15.6, 12.5, 10.0 Hz), 2.11 (1H, ddt, *J* = 12.2, 9.6, 8.8 Hz), 2.00 (1H, ddd, *J* = 13.3, 9.1, 8.8 Hz), 1.90 (1H, ddt, *J* = 12.2, 9.1, 3.4 Hz), 1.74 (1H, ddd, *J* = 13.3, 9.6, 3.4 Hz),1.58 (3H, s), 1.38 (9H, s), 0.92 (3H, d, *J* = 6.8 Hz) ppm. δ_C (100 MHz; $CDCl_3$) 212.9 (s), 168.1 (s), 87.9 (s), 85.1 (d), 81.6 (s), 60.3 (d), 52.5 (d), 39.2 (t), 37.9 (d), 31.5 (q), 30.9 (t),27.9 (q), 26.1 (t), 11.1 (q) ppm. MS (ES+) *m/z* 472 (M+Na+CH_3CN)+, 431 (M+Na)+, 352 (M+H–t-Bu)+, 308 (M+H–$CO_2{}^t$Bu)+; HRMS: found M+Na+CH_3CN 472.0961, $C_{18}H_{28}INNaO_4$ requires M+Na+CH_3CN 472.0961.

(2*R*,4*S*,5*R*,8*S*,9*R*)-2-(*tert*-Butoxycarbonyl)-8-(*tert*-butyl,dimethylsilanyloxy)-5,9-dimethyl-4-epoxy-cyclononanone (20) and (21). A precooled 0.09 M solution of DMDO in acetone (8.50 mL, 0.62 mmol) at –78 °C was added *via* cannula to a solution of a mixture of diastereomers of 15 (115 mg, 0.28 mmol) in CH_2Cl_2 (13.4 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h. The dimethyl sulfide (0.045 mL, 0.621 mmol) was added and the mixture was warmed to room temperature and then concentrated *in vacuo* leaving a colourless oil. The oil was purified by flash column chromatography (hexane : diethyl ether; 10 : 1–1 : 4) **20** and **21** as a colourless oil as a 2 : 3 mixture of inseparable diastereomers (d1 and d2). (*2R*, 4S*,5R*,8S,9R*)-*2*-(*tert-Butoxycarbonyl*)-*8*-(*tert-butyl,dimethylsilanyloxy*) -*5,9-dimethyl-4-epoxy-cyclononanone* **(*20*, *d2*)** *and* **(*21*, *d1*)** ν_{max}(film) 2956, 2931, 2858, 1738, 1708, 1462, 1370, 1310, 1280, 1151, 1055 cm^{-1}. δ_H(400 MHz, $CDCl_3$) 4.21 (1H, d, *J* = 9.6 Hz, d2), 4.01 (1H, dt, *J* = 6.8, 3.5 Hz, d2), 3.82 (1H, m, d1), 3.37 (1H, dd, *J* = 12.7, 2.2 Hz, d1), 3.05 (1H, dq, *J* = 6.6, 3.5 Hz, d1), 2.96 (1H, dq, *J* = 6.8, 3.5 Hz, d2), 2.91 (1H, dd, *J* = 6.0, 1.0 Hz, d2), 2.78 (1H, dd, *J* = 15.0, 6.0 Hz, d2), 2.66 (1H, dd, *J* = 10.5, 4.1 Hz, d1), 2.57 (1H, ddd, *J* = 15.0, 4.1, 2.2 Hz, d1), 2.09 (1H, ddd, *J* = 15.0, 12.7, 10.5 Hz, d1), 1.91 (1H, m, d2), 1.86–1.66 (5H, m, d1 and d2), 1.52–1.39 (2H, m, d1), 1.45 (9H, s, d1), 1.41 (9H, s, d2), 1.36 (3H, s, d2), 1.22 (3H, s, d1), 1.18 (3H, d, *J* = 6.6 Hz, d1), 1.11 (3H, d, *J* = 6.8 Hz, d2), 1.01 (1H, m, d2), 0.94 (9H, s), 0.87 (9H, s), 0.14 (3H, s), 0.12 (3H, s), 0.05 (6H, s) ppm. δ_C (100 MHz, $CDCl_3$) 212.0 (s, d2), 211.1 (s, d1), 168.1 (s, d2), 167.5 (s, d1), 82.8 (s, d1), 81.9 (s, d2), 74.5 (d, d2), 73.7 (d, d1), 63.3 (d, d2), 62.4 (s, d1), 61.4 (d, d1), 61.1 (s, d2), 58.8 (d, d1), 54.5 (d, d2), 53.7 (d, d2), 46.7 (d, d1), 30.4 (t, d2), 30.1 (t, d1), 29.8 (t, d1), 29.4 (t, d2), 28.0 (s, d1), 28.0 (s, d2), 27.5 (t, d2), 26.1 (s), 25.8 (s), 24.5 (t, d1), 22.9 (q, d2), 22.2 (q, d1), 18.3 (s), 18.1 (s), 17.7 (q, d1), 14.3 (q, d2), –4.2 (q), –4.4 (q), –4.6 (q), –5.1 (q) ppm. LRMS (ESI+) 435 (M+Na)+, 413 (M+H)+, 357 (M+NH_4 –O^{t}Bu). HMRS (ESI$^+$) *m/z* found 435.2541 (M+Na)+, $C_{22}H_{40}NaO_6Si$ requires 435.2537 (M+Na)+.

(4*S*,5*R*,8*S*,9*R*)-2-(*tert*-Butoxycarbonyl)-8-(*tert*-butyl,dimethylsilanyloxy)-5,9-dimethyl-4-epoxy-1-hydroxy-cyclonon-1-ene (enol 21) (1*S*,2*R*,3*S*,6*R*,7*S*,9*S*)-9-(*tert*-butoxycarbonyl)-3-(*tert*-butyl,dimethylsilanyloxy)-1,6-dihydroxy-2,6-dimethyl-10-oxa-bicyclo-[5.2.1]decane (22). One drop of conc. H_2SO_4 from the end of a disposable needle was added to a solution of a mixture of **15a** and **15b** (12 mg, 0.029 mmol) in THF (0.29 ml) and H_2O (0.29 ml) at room temperature. The reaction mixture was stirred at room temperature for 24 h, diluted with Et_2O (5 ml) and washed with saturated aqueous $NaHCO_3$ solution (1 ml). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution (2 × 1 ml). The aqueous washings were combined and extracted with Et_2O (3 × 5 ml). The combined organics were washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo* leaving a colourless oil. The oil was purified by flash column chromatography (1 : 1 to 4 : 1 ether–pentane elution) leaving **enol- 21** (20%) and **22** as a white solid (4 mg, 32%). (4*S*,5*R*,8*S*,9*R*)-*2*-(*tert-Butoxycarbonyl*)-*8*-(*tert-butyl*,*dimethylsilanyloxy*)-*5*,*9-dimethyl-4-epoxy-1-hydroxy-cyclonon-1-ene* **(*enol- 21*)** MP: 106–110 °C. $[\alpha]_D^{24}$ –22.3 (*c* 0.71, $CHCl_3$); ν_{max}(film) 3189, 2930, 2883, 2857, 1711, 1633, 1612, 1462, 1381, 1369, 1264, 1144, 1084, 838 cm^{-1}. δ_H(400 MHz, $CDCl_3$) 3.78 (1H, ddd, *J* = 8.9, 4.6, 1.7 Hz), 2.98 (1H, dd, *J* = 14.1, 4.6 Hz), 2.92 (1H, dd, *J* = 9.6, 4.6 Hz), 2.86 (1H, dq, *J* = 6.5, 1.6 Hz), 2.08 (1H, dd, *J* = 14.1, 9.6 Hz), 1.87–1.76 (2H, m), 1.53 (9H, s), 1.51–1.49 (1H, m), 1.37–1.33 (1H, m), 1.24 (3H, s), 1.17 (3H, d, *J* = 6.5 Hz), 0.88 (9H, s), 0.07 (3H, s), 0.06 (3H, s) ppm. δ_C(100 MHz; $CDCl_3$) 177.1 (s), 173.1 (s), 97.9 (s), 81.9 (s), 73.9 (d), 63.2 (d), 62.6 (s), 40.0 (d), 30.7 (t), 28.4 (q), 27.1 (t), 26.1 (t), 25.8 (q), 22.6 (q), 18.1 (s), 14.3 (q), –4.3 (q), –4.7 (q ppm. LRMS (ESI+) *m/z* 435 (M+Na)+. HRMS *m/z* (ESI+) found 435.2509 (M+Na)+, $C_{22}H_{40}NaO_5Si$ requires 435.2543 (M+Na)+. (1*S*,2*R*,3*S*,6*R*,7*S*,9*S*)-*9*-(*tert-Butoxycarbonyl*)-*3*-(*tert-butyl*,*dimethylsilanyloxy*)-*1*,*6-dihydroxy-2*,*6-dimethyl-10-oxa-bicyclo*[*5.2.1*]*decane* **(*22*)** MP: 124–125 °C; $[\alpha]_D^{24}$ +14.0 (*c* = 0.30, $CDCl_3$); ν_{max} (solution; $CDCl_3$) 3604, 2928, 2856, 1716, 1462, 1369, 1153, 1058 cm^{-1}. δ_H (500 MHz; CDCl3) 4.45 (1H, dd, *J* = 11.7, 9.7 Hz), 4.13 (1H, dd, *J* = 9.0, 1.6 Hz), 3.82 (1H, dd, *J* = 7.0, 2.3 Hz), 3.52 (1H, s), 2.46 (1H, ddd, *J* = 13.7, 11.7, 9.0 Hz), 2.36 (1H, ddd, *J* = 13.7, 9.7, 1.6 Hz), 2.16 (1H, dq, *J* = 7.3, 2.3 Hz), 2.03 (1H, dd, *J* = 15.3, 9.2 Hz), 1.89 (1H, dd, *J* = 15.1, 9.2 Hz), 1.74 (1H, ddd, *J* = 15.1, 10.5, 7.0 Hz), 1.54 (1H, s), 1.46 (9H, s), 1.35 (3H, s), 1.22 (2H, app dd, *J* = 15.3, 10.5 Hz), 1.05 (3H, d, *J* = 7.3 Hz), 0.92 (9H, s), 0.08 (3H, s), 0.05 (3H, s) ppm. δ_C (100 MHz; $CDCl_3$) 172.7 (s), 107.2 (s), 84.4 (d), 81.5 (s), 74.5 (d), 73.4 (s), 49.5 (d), 46.7 (d), 29.6 (t), 28.2 (q), 27.7, 27.7, 26.1 (q), 25.6 (t), 18.2 (s), 13.5 (q), –4.9 (q) ppm. MS (ES+) *m/z* 489 (M+NH_4+CH_3CN)+, 453 (M+Na)+, 413 (M+H–H_2O)+, 357 (M–O^{t}Bu)+; HRMS: found (M+Na)+ 453.2610, $C_{22}H_{42}NaO_6Si$ requires (M+Na)+ 453.2648.

(1*S*,2*R*,5*R*,6*R*,7*S*,8*S*)-8-(*tert*-Butoxycarbonyl)-5-(*tert*-butyl, dimethylsilyloxy)-2,7-dihydroxy-2,6-dimethyl-10-oxa-bicyclo-[5.2.1]decane-8-carboxylate (23). To a solution of **15** (44.7 mg, 0.133 mmol) in acetone/water (3 : 1) (2 mL) was added

N-methylmorpholine-*N*-oxide (13.2 mg, 0.113 mmol) and 4% aqueous solution of osmium tetraoxide (0.28 mL, 0.001 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was diluted with diethyl ether (25 mL), saturated aqueous Na_2SO_3 (5 mL) and saturated aqueous Na_2CO_3 (5 mL) and stirred for further 30 min before being extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (5 mL), 0.1 M aqueous HCl (6 mL), saturated Na_2CO_3 (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a brown oil, which was columned (petrol ether : EtOAc; 7 : 3) to leave a colourless oil. The mixture was crystallised from diethyl ether and hexane giving the diol **23** of major diastereomer (9 mg, 19%, 42%, corrected from NMR) as white crystals. MP: 111–113 °C. $[\alpha]_D^{24}$ −27.1 (*c* 0.265, $CHCl_3$). ν_{max} (solution, CH_2Cl_2) 3586, 2970, 2930, 2857, 1720, 1471.8, 1369, 1153, 1062 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 4.30 (1H, dd, *J* = 8.8, 4.1 Hz), 3.76 (1H, s), 3.31 (1H, app t, *J* = 9.1 Hz), 3.08 (1H, dd, *J* = 9.3, 8.7 Hz), 2.74 (1H, s), 2.51 (1H, ddd, *J* = 14.0, 8.8, 8.7, Hz), 2.20 (1H, ddd, *J* = 14.5, 9.8, 9.5, Hz), 2.01 (1H, dq, *J* = 9.1, 6.9 Hz), 1.88 (1H, ddd, *J* = 14.0, 9.3, 4.3 Hz), 1.81–1.67 (2H, m), 1.48 (9H, s), 1.45 (1H, m), 1.11 (3H, d, *J* = 6.9 Hz), 1.02 (3H, s), 0.89 (9H, s), 0.06 (6H, s) ppm. δ_C (125 MHz, $CDCl_3$) 172.3 (s), 108.7 (s), 85.7 (d), 82.3 (s), 78.4 (d), 73.2 (s), 51.1 (d), 48.8 (d), 35.0 (t), 33.3 (t), 31.1 (t), 28.0 (q), 25.9 (q), 24.8 (q), 18.0 (s), 15.2 (q), –4.1 (q), –4.5 (q) ppm. HMRS (ESI+) *m/z* found 253.2639 (M+Na)+ $C_{22}H_{42}NaO_6Si$ requires 453.2643 (M+Na)+.

(1*S*,7*R*,9*R*)-4,9-Dimethyl-10-oxa-bicyclo[5.2.2]undec-4-en-8,11-dione (24). To a solution of a mixture of diastereomers of **15** (150 mg, 0.38 mmol, 1 equiv) in MeCN (8 mL) was added HF (0.33 mL, 9.12 mmol, 24 equivs, 48% solution in H_2O) and the reaction mixture was stirred at rt. After 16 h a saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the mixture was diluted with Et_2O (100 mL) and the layers separated. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (2 × 10 mL) and H_2O (2 × 10 mL) and the combined aqueous washings were extracted with Et_2O (4 × 60 mL). The organic layers were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to leave the crude as an orange oil. The oil was purified *via* flash column chromatography eluting with hexane : Et_2O, 1 : 1, to afford alcohol as a colourless oil (99%) as a mixture of inseparable diastereomers which were submitted to the next step.

Trifluoroacetic acid (1.13 mL, 15.03 mmol, 15 equivs) was added to a solution of a diastereomeric mixture of alcohol (283 mg, 1.00 mmol, 1 equiv) in dry CH_2Cl_2 (7 mL) at rt. The reaction mixture was stirred at rt for 18 h and then concentrated *in vacuo* leaving the crude as a purple oil. The oil was purified *via* flash column chromatography eluting with pentane : Et_2O, 2 : 1, 1 : 3, and finally Et_2O, to give lactone **24** as a white solid (139 mg, 67%). $[\alpha]_D^{24}$ +77.6 (*c* 1.35, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 2970, 2937, 2868, 1732, 1711, 1450, 1389, 1335, 1244, 1031 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 5.41 (1 H, dt, *J* = 7.0, 1.3 Hz), 4.80 (1 H, ddd, *J* = 6.2, 3.3, 1.7 Hz), 3.48 (1 H, d, *J* = 10.3 Hz), 2.86 (1 H, dq, *J* = 6.6, 3.3 Hz), 2.80 (2 H, dd, *J* = 10.3, 7.0 Hz), 2.28 (1 H, dddd, *J* = 17.2, 13.0, 3.3, 1.7 Hz), 1.97–1.90 (2 H, m), 1.77 (1 H, m), 1.75 (3 H, d, *J* = 1.3 Hz), 1.20 (3 H, d, *J* = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 209.7 (s), 170.8 (s), 140.7 (s), 121.4 (d), 80.5 (d), 54.3 (d), 44.9 (d), 28.5 (t), 27.1 (t), 26.5 (t), 22.9 (q), 9.8 (q) ppm. MS (ES): *m/z* 226 (M + NH_4^+), 209 (M + H^+), 182 (M + NH_4^+ − CO_2), 165 (M + H^+ − CO_2); HRMS (ESI+): found (M + H^+): 209.1169, $C_{12}H_{16}O_3$ requires (M + H^+): 209.1172

(1*S*,4*R*,5*S*,7*R*,8*S*,9*R*)-8-Acetoxy-4,9-dimethyl-10,12-dioxa-4-iodo-tricyclo[5.2.2.15,8]undecan-11-one (26) and (1*R*,2*R*,4*R*,6*R*,7*S*)-1,6-dimethyl-2,4-*bis*(iodo)-10-oxa-bicyclo[5.2.1]decan-5-one (27). Acetic acid (8.8 ml) was added to a flask containing iodine (308 mg, 1.21 mmol) and silver(I) acetate (203 mg, 1.21 mmol) at room temperature. The resulting mixture was stirred at 35 °C for 30 min during which time a white suspension in a dark orange solution had formed. The dark orange solution was transferred *via* syringe to a solution of **24** (42 mg, 0.20 mmol) in acetic acid (1.6 ml) at room temperature. The reaction mixture was stirred at room temperature for 20 h, diluted with ether (30 ml) and H_2O (20 ml) and neutralized with the addition of solid $NaHCO_3$. The resulting solution was saturated with solid NaCl and the layers were separated. The aqueous phase was extracted with ether (5 × 20 ml) and the combined organics were washed successively with saturated aqueous $Na_2S_2O_3$ solution (3 × 40 ml), saturated aqueous $NaHCO_3$ solution (2 × 40 ml), H2O (2 × 40 ml) and brine (40 ml), dried ($MgSO_4$) and concentrated *in vacuo* leaving an orange oil. The oil was purified by flash column chromatography (1 : 10 ether–hexane to neat ether elution) leaving **26** as a colourless oil (30 mg, 38%) and 27 as an off-white solid (13 mg, 15%). (1*S*,4*R*,5*S*,7*R*,8*S*,9*R*)-*8-Acetoxy-4,9-dimethyl-10,12-dioxa-4-iodo-tricycle*[*5.2.2.15,8*]*undecan-11-one* **(26)** $[\alpha]_D^{24}$ −69.9 (*c* = 1.11, $CHCl_3$); ν_{max} (solution; $CHCl_3$) 2943, 1738, 1731,1464, 1386, 1370, 1338, 1139, 1065 cm^{-1}. δ_H (500 MHz; $CDCl_3$) 4.96 (1H, d, *J* = 8.9 Hz), 4.57 (1H, dd, *J* = 8.9, 5.1 Hz), 3.61 (1H, dd, *J* = 13.4, 2.4 Hz), 3.44 (1H, ddd, *J* = 14.3, 13.4, 8.9 Hz), 2.58 (1H, dt, *J* = 14.3, 2.4 Hz), 2.48 (1H, dq, *J* = 6.9, 5.1 Hz), 2.40–2.26 (2H, m), 2.15 (3H, s), 2.04 (1H, m), 2.04 (3H, s), 1.87 (1H, ddd, *J* = 15.9, 8.9, 2.0 Hz), 1.12 (3H, d, *J* = 6.9 Hz) ppm. δ_C (100 MHz; $CDCl_3$) 172.1 (s), 169.1 (s), 109.9 (s), 90.0 (d), 79.2 (d), 55.5 (s), 50.8 (d), 39.0 (d), 36.0 (t), 35.2 (t), 31.6 (q), 23.7 (t), 21.9 (q), 10.3 (q) ppm. MS (CI+) *m/z* 412 (M+NH_4)+, 352 (M+H–Ac)+, 226 (M+H–Ac–I)+, 209 (M–OAc–I)+; HRMS: (ES+) found M+$NH_4$412.0616, $C_{14}H_{23}INO_5$ requires M+$NH_4$412.0615. (1*S*,2*R*,4*R*,6*R*,7*S*)-*2,7-Dimethyl-4,6-bis*(*iodo*)*-10-oxa-bicyclo*[*5.2.1*]*decan-3-one* **(27)** MP: 108–110 °C; $[\alpha]_D^{24}$ −100.0 (*c* = 0.60, $CHCl_3$); ν_{max} (solution; $CHCl_3$) 2929, 1692, 1450, 1376, 1303 cm^{-1}. δ_H (500 MHz; $CDCl_3$) 4.99 (1H, dd, *J* = 12.6, 3.1 Hz), 4.33 (1H, dd, *J* = 6.9, 2.9 Hz), 4.20 (1H, dd, *J* = 4.6, 3.2 Hz), 3.61 (1H, dq, *J* = 6.9, 2.9 Hz), 3.45 (1H, ddd, *J* = 15.7, 12.6, 3.2 Hz), 2.46 (1H, ddd, *J* = 15.7, 4.6, 3.1 Hz), 1.95 (2H, app ddd, *J* = 8.0, 7.4, 6.9 Hz), 1.86 (1H, dd, *J* = 14.3, 7.4 Hz), 1.69 (1H, dd, *J* = 14.3, 8.0 Hz), 1.37 (3H, s), 1.10 (3H, d, *J* = 6.9 Hz) ppm. δ_C (125 MHz; $CDCl_3$) 208.0 (s), 85.4 (d), 84.5 (s), 45.2 (d), 43.2 (d), 42.0 (t), 38.2 (t), 33.2 (d), 28.2 (q), 26.6 (t), 15.1 (q) ppm. MS (CI+) *m/z* 452 (M+NH_4)+, 326 (M+NH_4–I)+, 307 (M–I)+, 198 (M+NH_4–I–I)+, 181 (M–I–I)+; HRMS: found M+NH_4 451.9586, $C_{11}H_{20}I_2NO_2$ requires M+NH_4 451.9578

(1*R*,3*R*,6*R*,9*S*)-1,6-Dimethyl-9-oxa-tricyclo[5.2.2.0]undecan-2,10-dione (37). To a solution of lactone **24** (897 mg, 4.31 mmol, 1 equiv) in glacial acetic acid (8 mL) at rt was added tetrafluoroboric acid Et_2O complex (2.37 mL, 17.2 mmol, 4.0 equivs). The solution was stirred for 12 h at rt, after which point the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL)

and stirred for 10 mins. The mixture was then diluted with Et_2O (150 mL) and poured onto H_2O (15 mL), solid $NaHCO_3$ and NaCl was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 150 mL), the combined organics were then washed with further portions of a saturated aqueous $NaHCO_3$ solution (2 × 10 mL) and brine (20 mL), before being dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a purple residue as the crude. Purification *via* flash column chromatography eluting on silica gel with pentane : Et_2O, 2 : 1, then 1 : 1, and finally Et_2O, gave **37** as a white solid (619 mg, 69%). $[\alpha]_D^{24}$ −1.5 (*c* 0.54, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 2952, 1746, 1715, 1456, 1376 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 4.50 (1H, dd, *J* = 7.2, 1.5 Hz), 3.38 (1H, t, *J* = 3.5 Hz), 2.47 (1H, dddd, *J* = 13.7, 10.6, 7.2, 2.9 Hz), 2.36 (1H, app. dddd, *J* = 13.7, 9.3, 8.2, 1.5 Hz), 2.36 (1H, app. dddd, *J* = 14.6, 5.0, 3.5, 1.9 Hz), 2.17 (1H, dddd, *J* = 14.6, 5.0, 4.4, 3.5 Hz), 1.91 (1H, dt, *J* = 14.9, 5.0 Hz), 1.80 (1H, ddd, *J* = 13.2, 9.3, 2.9 Hz), 1.70 (1H, ddd, *J* = 13.2, 10.6, 8.2 Hz), 1.56 (1H, ddd, *J* = 14.9, 4.4, 1.9 Hz), 1.05 (3H, s Hz), 1.01 (3H, s Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.2 (s), 170.8 (s), 89.0 (d), 58.0 (s), 56.0 (s), 55.0 (d), 37.6 (t), 33.5 (t), 32.2 (t), 20.6 (q), 13.8 (q) ppm. MS (ES): *m/z* 208 (M^+), 183 (M + H^+ + NH_4 − CO_2), 165 (M + H^+ − CO_2); HRMS (EI): found (M): 208.1096, $C_{12}H_{16}O_3$ requires (M) 208.1094.

(1*R*,6*R*,9*S*)-2,9-Dihydroxy-1,6-dimethyl-3-methoxycarbonyl-bicyclo[4.3.0]non-2-ene (38). To a solution of **37** (62 mg, 0.30 mmol, 1 equiv) in a mixture of dry MeOH (1.9 mL) and dry THF (1.9 mL) at −78 °C was added sodium methoxide (0.75 mL, 0.30 mmol, 25% w/w in MeOH, 1.0 equivs). The reaction was stirred for 4 h at −78 °C and then quenched with a saturated aqueous NH_4Cl solution (4 mL), and the solvents removed under reduced pressure. The aqueous residue was taken up in CH_2Cl_2 (20 mL) and the layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to leave the crude as a pale brown oil. The oil was purified *via* flash column chromatography eluting on silica gel with petrol : EtOAc, 10 : 1, then 6 : 1, 3 : 1, to give **38** as a clear oil (50 mg, 70%). $[\alpha]_D^{24}$ +60.5 (*c* 0.39, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 3518, 2952, 2873, 1743, 1692, 1650, 1616, 1443, 1363, 1325, 1289, 1131, 1075 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 4.09 (1H, ddd, *J* = 7.2, 6.3, 5.3 Hz), 3.77 (3H, s), 2.70 (1H, d, *J* = 5.3 Hz), 2.27 (1H, dt, *J* = 16.5, 5.7 Hz), 2.22 (1H, ddd, *J* = 16.5, 8.2, 5.7 Hz), 2.12 (1H, dddd, *J* = 13.1, 9.3, 7.2, 3.0 Hz), 1.75 (1H, ddd, *J* = 13.5, 8.2, 5.7 Hz), 1.68 (1H, dd, *J* = 12.7, 3.1 Hz), 1.59 (1H, ddd, *J* = 13.1, 8.4, 6.3 Hz), 1.48 (1H, ddd, *J* = 12.7, 9.3, 8.4 Hz), 1.35 (1H, dt, *J* = 13.5, 5.7 Hz), 1.16 (3H, s), 0.94 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0 (s), 173.4 (s), 99.5 (s), 81.7 (d), 52.4 (s), 51.7 (q), 42.0 (s), 35.1 (t), 31.7 (t), 31.1 (t), 24.3 (q), 19.6 (t), 18.8 (q) ppm. MS (ES): *m/z* 263 (M + Na^+), 191 (M^+ − H_2O − OMe); HRMS (ESI): found (M + Na^+): 263.1254, $C_{13}H_{20}O_4$ requires (M + Na^+): 263.1259

(1*R*,6*R*,9*S*)-9-Hydroxy-1,6-dimethyl-bicyclo[4.3.0]non-2-one (39). A solution of methyl ester **38** (10 mg, 0.042 mmol, 1 equiv) in DMF (0.80 mL) was heated in the microwave in the presence of H_2O (20 μL) under the following parameters: temperature 130 °C, pressure 100 psi, power 250 W, ramp time 20 min, hold time 15 min. Actual parameters from observation of reaction progression: temperature 120 °C, pressure 33 psi, power 250 W, a consequence of the cooling system present within the microwave. After this time the solvent was removed *in vacuo*, and the residue taken up in EtOAc (10 mL), and the layers separated. The aqueous phase was extracted with EtOAc (3 × 5 mL), organics were combined, washed with H_2O (2 mL) and brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give the crude as a colourless oil (8 mg). Purification *via* flash column chromatography on silica gel eluting with petrol : EtOAc, 8 : 1, then 4 : 1, and finally 2 : 1, afforded ketone **39** as colourless oil (4 mg, 56%). $[\alpha]_D^{24}$ +29.1 (*c* 0.50, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 3491, 2959, 1701, 1456, 1381, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.81 (1H, ddd, *J* = 8.5, 6.1, 1.5 Hz), 2.47 (1H, ddd, *J* = 13.5, 8.9, 5.5 Hz), 2.37 (1H, dt, 13.5, 6.1 Hz), 2.26 (1H, app. dddd, *J* = 13.6, 9.5, 6.1, 3.4 Hz), 1.87 (1H, ddd, *J* = 12.9, 8.9, 5.5, 1.9 Hz), 1.84–1.79 (1H, m), 1.77 (1H, ddd, *J* = 13.4, 9.5, 3.4 Hz), 1.66–1.59 (2H, m), 1.59 (1H, dt, *J* = 12.6, 5.5 Hz), 1.52 (1H, ddd, *J* = 12.6, 7.6, 1.9 Hz), 1.03 (3H, s), 1.03 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.1 (s), 77.1 (d), 61.9 (s), 47.9 (s), 37.5 (t), 36.0 (t), 35.2 (t), 30.9 (t), 23.4 (q), 22.2 (t), 11.9 (q) ppm. MS (ESI): *m/z* 205 (M^+ + Na^+), 183 (M^+ + H^+), 165 (M^+ − OH); HRMS: found (M + H^+): 183.1378, $C_{11}H_{18}O_2$ requires (M + H^+): 183.1380.

(1*R*,6*R*,9*S*)-2-Hydroxy-9-oxo-1,6-dimethyl-3-methoxycarbonyl-bicyclo[4.3.0]non-2-ene (40). To a solution of oxalyl chloride (18 μL, 0.21 mmol, 2.0 equivs) in dry CH_2Cl_2 (1 mL) at −78 °C was added DMSO (30 μL, 0.42 mmol, 4.0 equivs) and stirred for 30 min at −78 °C. At which point a solution of alcohol **38** (25 mg, 0.11 mmol, 1 equiv) in dry CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred for 1 h at −78 °C. After this time had elapsed, NEt_3 (0.22 mL, 1.56 mmol, 15.0 equivs) was added and the temperature was raised to rt. After 1 h at rt no starting material was visible by TLC analysis, therefore the mixture was poured onto H_2O (3 mL) and diluted with CH_2Cl_2 (30 mL) and layers separated. The organic phase was washed with 2 M HCl (2 × 2 mL), the aqueous phases were combined and extracted with CH_2Cl_2 (3 × 30 mL). The organics were combined and subsequently washed with a saturated aqueous solution of $NaHCO_3$ (2 × 3 mL) and brine (3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give the crude as a yellow oil (33 mg). Purification *via* flash column chromatography on silica gel eluting with petrol : EtOAc, 10 : 1, then 7 : 1, gave ketone **40** as white solid (25 mg, quant.). MP: 117–119 °C; $[\alpha]_D^{24}$ +46.3 (*c* 0.40, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 2949, 2938, 2878, 1738, 1715, 1449, 1435, 1256, 1239, 1112, 1050, 1021 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.77 (3H, s), 2.89 (1H, ddd, *J* = 14.3, 6.6, 3.7 Hz), 2.51 (1H, dt, *J* = 13.9, 4.4 Hz), 2.39 (1H, ddd, *J* = 13.9, 9.5, 4.4 Hz), 2.23 (1H, dt, *J* = 14.6, 3.7 Hz), 2.11 (1H, dt, *J* = 14.6, 4.4 Hz), 1.90 (1H, ddd, *J* = 13.2, 6.6, 3.7 Hz), 1.81 (1H, dt, *J* = 13.2, 6.6 Hz), 1.76 (1H, ddd, *J* = 14.6, 9.5, 4.4 Hz), 1.27 (3H, s), 1.08 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 213.1 (s), 196.6 (s), 171.2 (s), 166.8 (s), 71.9 (s), 60.5 (t), 54.1 (q), 46.8 (s), 35.2 (t), 32.4 (t), 21.6 (q), 21.1 (t), 16.8 (q) ppm. MS (ESI): *m/z* 261(M + Na^+); HRMS: found (M + Na^+): 261.1097, $C_{13}H_{18}O_4$ requires (M + Na^+): 261.1097.

(2*R*,3*S*,6*R*,9*S*)-2,9-Dihydroxy-3-hydroxymethyl-1,6-dimethyl-bicyclo[4.3.0]nonane (41). To a solution of the lactone **37** (15 mg, 0.072 mmol, 1.0 equiv) in dry MeOH (1 mL) at 0 °C was added $NaBH_4$ (11 mg, 0.29 mmol, 4.0 equiv) and the reaction mixture was stirred at 0 °C for 10 min before being raised to rt. After 4 h no starting material remained by TLC analysis, consequently the

reaction was quenched at 0 °C with a 10% aqueous solution of KOH (2.88 mL), stirred for 5 min and the solvent was removed *via* rotary evaporation. The off-white residue was redissolved in CH_2Cl_2 (20 mL), washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give the crude as a pale brown residue (14 mg). Purification *via* flash column chromatography on silica gel eluting with petrol : EtOAc, 1 : 1, then EtOAc, and finally EtOAc : MeOH, 4 : 1, gave triol **41** as a pale yellow oil (10 mg, 63%). $[\alpha]_D^{24}$ +48.9 (*c* 0.35, $CHCl_3$); ν_{max} (solution; $CDCl_3$): 3300br, 2945, 2929, 1059, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.64 (1H, app. dd, J = 9.6, 3.6 Hz), 4.10 (1H, d, J = 11.4 Hz), 3.71 (2H, m), 2.47 (1H, dddd, J = 13.4, 10.6, 8.9, 3.8 Hz), 2.15 (1H, ddd, J = 12.6, 8.9, 3.8 Hz), 2.06 (2H, m), 2.00 (1H, m), 1.84 (1H, app. dt, J = 13.9, 6.4 Hz), 1.62 (1H, ddd, J = 12.6, 9.2, 4.9 Hz), 1.46 (1H, ddd, J = 13.9, 9.5, 4.9 Hz), 1.38 (1H, dddd, J = 12.6, 9.5, 6.4, 4.4 Hz), 1.07 (3H, s), 0.91 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.0 (d), 76.8 (d), 45.6 (t), 45.0 (s), 44.7 (s), 36.5 (d), 31.7 (t), 30.7 (t), 28.6 (t), 25.2 (q), 24.0 (t), 11.9 (q) ppm. MS (ESI): 237 (M + Na^+), 215 (M + H^+), 179 (M+ – OH – OH); HRMS: found (M + H^+): 215.1645, $C_{12}H_{22}O_3$ requires (M + H^+): 215.1642.

Methyl-1-(*tert*-butyldimethylsilanyloxy)-4-hexynoate (48). ^{n}BuLi (2.6 M in hexanes, 33 mL, 78.7 mmol) was added to a solution of the alkyne (13 g, 65.6 mmol) in THF (250 mL) at –78 °C under an N_2 atmosphere and allowed to stir for 30 min. Methyl chloroformate (11 mL, 72.2 mmol) was added to the reaction flask which was then warmed to 25 °C and stirred for 5 h. The yellow solution was diluted with Et_2O (100 mL), washed with water (200 mL) and brine (200 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil **48** which did not require further purification (16.8 g, 100%). IR (film): ν_{max} 2954, 2857, 2237, 1717, 1471, 1435, 1388, 1256, 1107, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 3.72 (3H, s), 3.65 (2H, t, J = 5.9 Hz), 2.38 (2H, t, J = 7.0 Hz), 1.72 (2H, m), 0.84 (9H, s), 0.00 (6H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3 (s), 89.6 (s), 72.9 (s), 61.2 (t), 52.6 (q), 30.6 (t), 25.8 (q), 18.3 (s), 15.2 (t), –5.3 (q) ppm. HRMS (ESI): found (M + H^+): 257.1567, $C_{13}H_{25}O_3Si$ requires (M + H^+): 257.1571.

(*E*)-4,8-Dimethyl-5-iodo-(*tert*-butyldimethylsilanyloxy)-4-hexenoate (49). MeLi (1.6 M in Et_2O, 40.0 mL, 64.0 mmol) was added to a solution of CuI (6.22 g, 32.0 mmol) in THF (50 mL) 0 °C under a nitrogen atmosphere and stirred until the mixture turned colourless and all solids had dissolved. The mixture was cooled to –45 °C and treated with a solution of **48** (4.10 g, 16.0 mmol) in THF (10 mL) cooled to –78 °C *via* cannula transfer. The yellow solution was stirred for 1 h before a solution of iodine (12.2 g, 48.0 mmol) in THF (30 mL) cooled to –78 °C was added *via* cannula transfer. The dark brown solution was stirred at –45 °C for 1 h and then warmed to 0 °C and stirred for a further 2 h. The mixture was then washed with 10% aqueous NH_4OH solution (50 mL), saturated aqueous NH_4Cl solution (50 mL), saturated aqueous $Na_2S_2O_3$ (50 mL) and then brine (100 mL) before being dried over $MgSO_4$ and concentrated *in vacuo.* Purification *via* flash column chromatography on silica gel with a mobile phase of petroleum ether : EtOAc, 10 : 1, yielded a yellow oil **49** (5.35 g, 84%). IR (film): ν_{max} 2954, 2928, 2857, 2359, 2240, 2237, 1749, 1471, 1436, 1388, 1361, 1256, 1107, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 3.76 (3H, s), 3.59 (2H, t, J = 6.3 Hz), 2.48 (2H, t, J = 7.8 Hz), 2.05 (3H, s), 1.67 (2H, m), 0.87 (9H, s), 0.02 (6H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9 (s), 155.1 (s), 84.5 (s), 62.5 (t), 52.8 (q), 33.4 (t), 31.4 (t), 29.5 (q), 25.9 (q), 18.3 (s), –5.3 (q) ppm. MS (ESI): m/z 421 (M + Na^+), HRMS (ESI): found (M + H^+): 399.0847, $C_{14}H_{28}IO_3Si$ requires (M + H^+): 399.0843.

(*E*)-(*tert*-Butyldimethylsilanyloxy)-4-methyl-5-iodo-6-(*para*-methoxybenzyloxy)-hex-4-ene (50). Triflic acid (3.5 mL, 3.5 × 10^{-2} mmol) was added to a solution of the alcohol (4.3 g, 11.5 mmol) and the trichloroacetimidate (12.9 g, 46 mmol) in cyclohexane (20 mL) and dichloromethane (20 mL). The mixture was stirred for 4 h before being diluted with Et_2O (100 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo.* Purification *via* flash column chromatography on silica gel with a mobile phase of petroleum ether : EtOAc, 20 : 1, yielded a pale yellow oil **50** (4.36 g, 77%). IR (film): ν_{max} 2926, 2855, 2360, 2341, 1717, 1614, 1539, 1463, 1386, 1248, 1301, 1248, 1173, 1100, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.30–6.85 (4H, m), 4.41 (2H, s), 4.27 (2H, s), 3.79 (3H, s), 3.52 (2H, t, J = 6.0 Hz), 2.31 (2H, t, J = 7.6 Hz), 1.98 (3H, s), 1.57 (2H, dt, J = 7.7, 5.9 Hz), 0.89 (9H, s), 0.01 (6H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3 (s), 146.1 (s), 130.2 (s), 129.8 (d), 113.9 (d), 99.9 (s), 73.7 (t), 71.1 (t), 62.1 (t), 55.3 (q), 31.7 (t), 30.9 (t), 29.9 (q), 26.6 (t) 18.4 (s), –5.2 (q) ppm. HRMS (ESI): found (M + H^+): 491.1473, $C_{21}H_{36}IO_3Si$ requires (M + H^+): 491.1472.

(*Z*)-(*tert*-Butyldimethylsilanyloxy)-4,5-dimethyl-6-(*para*-methoxybenzyloxy)-hex-4-ene (51). Pd(dppf)·Cl_2 (98 mg, 0.12 mmol) and dimethyl zinc (2 M in toluene, 4.1 mL, 8.16 mmol) were added to a solution of **50** (2 g, 4.08 mmol) dissolved in 1,4-dioxane (20 mL) and stirred for 5 min with at 25 °C. The reaction was heated to 110 °C and stirred for 2 h then cooled to 0 °C, before being quenched with methanol (15 mL). The mixture was then diluted with Et_2O (100 mL) and washed with 1 M HCl (40 mL), water (40 mL) and brine (40 mL). The organic phase was then dried over $MgSO_4$, and concentrated *in vacuo.* Purification *via* flash column chromatography on silica gel with a mobile phase of petroleum ether : EtOAc, 40 : 1, yielded yellow oil **51** (1.15 g, 76%). IR (film): ν_{max} 2924, 2853, 2253, 1739, 1669, 1575, 1569, 1506, 1448, 1436, 1386 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–6.84 (4H, m), 4.36 (2H, s), 3.96 (2H, s), 3.79 (3H, s), 3.53 (2H, t, J = 6.2 Hz), 2.10 (2H, t, J = 7.9 Hz), 1.71 (3H, s), 1.68 (3H, s), 1.54 (2H, dt, J = 8.0, 6.2 Hz), 0.88 (9H, s), 0.03 (6H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2 (s), 133.9 (s), 131.0 (s), 129.8 (s), 129.8 (s), 129.4 (d), 113.9 (d), 71.6 (t), 70.4 (t), 62.9 (t), 55.3 (q), 32.1 (t), 30.5 (t), 26.0 (q), 18.9 (q), 18.4 (s), 16.9 (q), –5.2 (q) ppm. MS (ESI): m/z 401 (M + Na^+), HRMS (ESI): found (M + H^+): 379.2663, $C_{22}H_{39}O_3Si$ requires (M + H^+): 379.2665.

(*Z*)-4,5-Dimethyl-6-(*para*-methoxybenzyloxy)-hex-4-enal (46). DMP (1.18 g, 2.8 mmol, 2 equiv) was added to solution of the alcohol (365 mg, 1.4 mmol, 1 equiv) in CH_2Cl_2 (15 mL) under a nitrogen atmosphere at 25 °C. The mixture was stirred for 2 h before quenched with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and stirred for 10 min. The mixture was washed diluted with Et_2O (40 mL) and washed with saturated $NaHCO_3$ solution (30 mL). The aqueous phase was then extracted with Et_2O (3 × 30 mL). The organic extracts were combined and washed with

brine (70 mL) before being dried over $MgSO_4$, and concentrated *in vacuo.* Purification *via* flash column chromatography on silica gel with a mobile phase of petroleum ether : EtOAc, 10 : 1, yielded yellow oil **46** (263 mg, 72%). IR (film): ν_{max} 2927, 2866, 2359, 2243, 1725, 1633, 1627, 1496, 1444, 1436, 1375, 1350, 1243, 1212 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (1H, t, J = 1.2 Hz), 7.27–6.87 (4H, m), 4.39 (2H, s), 3.94 (2H, s), 3.80 (3H, s), 2.46 (2H, dt, J = 7.3, 1.5 Hz), 2.37 (2H, t, J = 7.3 Hz), 1.72 (3H, s), 1.68 (3H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.1 (d), 159.1 (s), 132.0 (s), 130.6 (s), 129.5 (d), 127.2 (s), 113.8 (d), 71.8 (t), 70.3 (t), 55.2 (q), 42.9 (t), 26.5 (t), 18.5 (q), 14.1 (q) ppm. HRMS (ESI): found (M + Na^+): 287.1618, $C_{16}H_{24}NaO_3$ requires (M + Na^+): 287.1619.

(2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxooxazolidin-3-yl)-8-(benzyloxy)-3-hydroxy-2,6,7-trimethyloct-6-en-1-one (53). Titanium tetrachloride (6.1 mL, 18.2 mmol, 2.0 equiv) was added to a solution of the thiooxazolidinone auxiliary (2.3 g, 9.1 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) at 0 °C. The resultant yellow slurry was stirred for 10 min at 0 °C, before (–)-sparteine (2.3 mL, 10.0 mmol, 1.1 equiv) was added. The now burgundy solution was maintained at this temperature for 25 min, before being cooled to −78 °C. A solution of aldehyde **46** (2.3 g, 10.0 mmol, 1.1 equiv) in a CH_2Cl_2 (20 mL) was added *via* syringe pump at a rate of 25 mL h^{-1} and the reaction was stirred at −78 °C for 4 h. The reaction was quenched with a saturated solution of aqueous NH_4Cl (40 mL), the temperature was then raised to 25 °C and diluted with CH_2Cl_2 (100 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were combined and filtered through a pad of Celite®, which was then washed with CH_2Cl_2 (3 × 30 mL). The organics were then washed with brine (100 mL), and dried over $MgSO_4$, to give after concentration *in vacuo*, the crude, as a viscous orange oil. Purification *via* flash column chromatography on silica gel eluting with petroleum ether : EtOAc, 10 : 1, then 6 : 1 and finally 3 : 1, gave the aldol adduct **53** as an orange oil (2.7 g, 60%). $[\alpha]_D^{24}$ −31.6 (*c* 0.50, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 3501, 2922, 2854, 1695, 1611, 1512, 1454, 1366, 1350, 1316, 1179 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–6.83 (11H, m), 4.96 (1 H, dddd, J = 10.3, 7.0, 3.7, 3.3 Hz), 4.75 (1H, dq, J = 7.0, 3.3 Hz), 4.45 (1H, d, J = 11.4 Hz), 4.40 (1H, d, J = 11.4 Hz), 4.30 (2H, m), 4.10 (1H, d, J = 10.3 Hz), 4.01 (1H, m), 3.87 (1H, d, J = 10.3 Hz), 3.76 (3H, s), 3.24 (1H, dd, J = 13.2, 3.3 Hz), 2.69 (1H, dd, J = 13.5, 10.3 Hz), 2.39 (1H, m), 2.17 (1H, m), 1.75 (3H, s), 1.72 (3H, s), 1.68–1.56 (2H, m), 1.22 (3 H, d, J = 7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 177.5, 159.2, 135.3, 134.2, 130.4, 129.6, 129.5, 129.1, 127.5, 126.5, 113.8, 72.1, 70.7, 70.5, 70.3, 60.1, 55.3, 42.6, 37.8, 32.5, 30.3, 18.6, 17.8, 10.6 ppm. HRMS (ESI): found (M + Na^+): 534.2285, $C_{29}H_{37}NNaO_5S$ requires (M + H^+): 534.2278.

(2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxooxazolidin-3-yl)-8-(benzyloxy)-3-(*tert*-butyldimethyl silyloxy)- 2,6,7-trimethyloct-6-en-1-one (54). Aldol adduct **53** (4.47 g, 8.74 mmol) was dissolved in dry CH_2Cl_2 (40 mL), at 25 °C, and treated with, TBSOTf (2.38 mL, 10.49 mmol, 1.2 equiv) and 2,6-lutidine (1.19 mL, 10.49 mmol, 1.2 equiv). The pale yellow solution was stirred for 2 h and the diluted with CH_2Cl_2 (40 mL) before being washed with a saturated solution of aqueous NH_4Cl (50 mL), water (50 mL) and brine (50 mL) before being dried over $MgSO_4$and concentrated *in vacuo.* Purification *via* flash column chromatography on silica gel eluting with petroleum ether: EtOAc, 20 : 1, yielded **54** as a yellow oil (5.43 g, 99%). $[\alpha]_D^{24}$ 29.6 (*c* 1.30, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 2929, 2856, 1694, 1512, 1455, 1364, 1311, 1248, 1182, 1151, 1060, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–6.86 (11H, m), 4.91 (1 H, m), 4.39 (2H, s), 4.27 (2H, m), 4.19 (1H, m), 4.00 (1H, d, J = 10.6 Hz), 3.97 (1H, d, J = 10.9 Hz), 3.80 (3H, s), 3.33 (1H, dd, J = 12.8, 3.3 Hz), 2.62 (1H, dd, J = 13.2, 10.9 Hz), 2.27 (1H, m), 2.18 (1H, m), 1.71 (3H, s), 1.69 (3H, s), 1.66–1.58 (2H, m), 1.24 (3 H, d, J = 7.0 Hz), 0.94 (9H, s), 0.11 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.2, 176.7, 159.1, 135.5, 133.8, 130.9, 129.5, 129.4, 129.1, 127.5, 125.9, 113.8, 73.2, 71.7, 70.4, 70.1, 60.3, 55.3, 42.6, 38.0, 35.0, 29.9, 26.1, 19.0, 18.3, 16.9, 13.9, –3.7, –4.2 ppm. MS (ESI): m/z 648 (M + Na^+), HRMS (ESI): found (M + H^+): 626.3330, $C_{35}H_{52}NO_5SSi$ requires (M + H^+): 626.3350.

(2*R*,3*S*)-8-(Benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-2,6,7-trimethyloct-6-enal (55). To a solution of the compound **54** (5.43 g, 8.67 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL), at −78 °C, was added DIBAL-H (1 M in toluene, 10.40 mL, 10.40 mmol, 1.2 equiv), and stirred for 20 min. The solution was treated saturated aqueous Rochelle's salt (1 M, 20 mL), CH_2Cl_2 (20 mL) and water (20 mL), then and allowed to stir for 1 h. The solution was extracted with CH_2Cl_2 and washed with brine before being dried over $MgSO_4$ and concentrated *in vacuo.* Purification *via* flash column chromatography on silica gel eluting with petroleum ether : EtOAc, 10 : 1, yielded **55** as a yellow oil (3.08 g, 82%). $[\alpha]_D^{24}$ –31.6 (*c* 0.5, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 2951, 2929, 2856, 2764, 1724, 1612, 1512, 1462, 1360, 1301, 1248, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (1H, d, J = 1.0 Hz), 7.27–6.86 (4H, m), 4.38 (2H, s), 4.02 (1H, dt, J = 6.6, 3.7 Hz), 3.90 (2H, s), 3.80 (3H, s), 2.38 (1H, ddq, J = 7.0, 3.7, 0.7 Hz), 2.14 (1H, dt, J = 12.5, 5.5 Hz), 1.90 (1H, dt, J = 12.1, 5.9 Hz), 1.72 (3H, s), 1.68 (3H, s), 1.58–1.43 (2H, m), 1.03 (3H, d, J = 7.0 Hz), 0.87 (9H, s), 0.03 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.1, 159.2, 133.6, 130.7, 129.5, 126.5, 113.8, 72.2, 71.8, 70.2, 55.3, 51.2, 33.8, 30.7, 25.9, 18.9, 18.1, 17.2, 7.8, –4.1, –4.5 ppm. MS (ESI): m/z 457 (M + Na^+), HRMS (ESI): found (M + H^+): 435.2925, $C_{25}H_{43}O_4Si$ requires (M + H^+): 435.2934.

(4*R*,5*S*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-10-hydroxy-4,8,9-trimethyl-3oxodec-8-enoate (56). To a solution of the β-ketoester (2.37 g, 4.32 mmol, 1 equiv.) in a 19 : 1 CH_2Cl_2–H_2O solution (40 mL) was carefully added DDQ (1.07 g, 4.73 mmol, 1.1 equiv). The reaction was stirred for 1 h at 25 °C, after which time the reaction was diluted with Et_2O (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), an aqueous solution of 10% $Na_2S_2O_5$ (20 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*, to give the crude as a dark brown oil. Purification *via* flash column chromatography on silica gel eluting with petroleum ether : EtOAc, 10 : 1, gave alcohol **56** as a pale yellow oil (1.20 g, 66%). $[\alpha]_D^{24}$ −20.0 (*c* 1.50, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 2976, 2951, 2930, 2857, 1731, 1709, 1643, 1461, 1368, 1252, 1148, 1003, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.09 (1H, d, J = 12.5 Hz), 4.02 (1H, d, J = 11.7 Hz), 3.82 (1H, m), 3.48 (2H, s), 2.82 (1H, dq, J = 7.0, 4.4 Hz), 2.20 (1H, dt, J = 12.5, 5.1 Hz), 1.92 (1H, dt, J = 12.1, 4.8 Hz), 1.70 (3H, s), 1.63 (3H, s), 1.55–1.51 (1H, m), 1.43 (9H, s), 1.35–1.27 (1H, m), 1.06 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.06 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.2, 166.9, 132.5, 128.5, 81.9, 74.1, 63.4, 51.8, 50.7, 33.6, 30.4, 28.1, 26.6, 18.9, 18.1, 16.8, 12.2, –4.4, –4.3

ppm. HRMS (ESI): found (M + Na^+): 451.2850, $C_{23}H_{44}NaNO_5Si$ requires (M + Na^+): 451.2850.

(2*R*,8*S*,9*R*)-2-(*tert*-Butoxycarbonyl)-8-(*tert*-butyl,dimethylsilanyloxy)-4,5,9 trimethyl-cyclonon-4-enone (42). To a solution of **56** (670 mg, 1.56 mmol) in CH_2Cl_2 (7 mL) was added *N*-bromosuccinimide (309 mg, 1.72 mmol, 1.1 equiv) and triphenylphosphine (453 mg, 1.72 mmol, 1.1 equiv) at −30 °C, the reaction was stirred for 1 h until no starting material was observed *via* TLC. The reaction mixture was concentrated *in vacuo* and triturated using copious amounts of hot hexane before being concentrated to yield a yellow oil (813 mg). This crude oil was dissolved in DMF (5 mL) and caesium carbonate (608 mg, 1.87 mmol, 1.2 equiv) was added at −78 °C. The reaction was warmed to 25 °C and stirred for 16 h. The reaction mixture was diluted with Et_2O (75 mL) and washed with H_2O (2 × 50 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The organic layers were combined together and washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* leaving a yellow oil. Purification *via* flash column chromatography on silica gel eluting with petroleum ether : EtOAc, 40 : 1, gave **42a/b** as a pale yellow oil (403 mg, 62% over two steps). $[\alpha]_D^{24}$ −19.6 (*c* 0.20, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 2929, 2857, 1736, 1702, 1613, 1513, 1460, 1368, 1251, 1148, 1368, 1251, 1148, 1119, 1098, 1005, 909, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (1H, dt, *J* = 9.0, 5.3 Hz, minor), 3.60 (2H, m, major + minor), 3.43 (1H, dd, *J* = 11.2, 2.0 Hz, major), 2.97 (1H, dd, *J* = 14.5, 11.4 Hz), 2.78 (2H, m, major + minor), 2.30 (1H, d, *J* = 14.5 Hz), 2.26 (1H, m), 1.99 (1H, m), 1.76 (2H, m), 1.73 (3H, s, minor), 1.68 (3H, s, major), 1.66 (3H, s, minor), 1.62 (3H, s, major), 1.44 (9H, s), 1.19 (3H, d, *J* = 7.0 Hz, major), 1.07 (3H, d, *J* = 7.1 Hz, minor), 0.89 (9H, s), 0.07 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.0, 169.2 (minor), 168.8 (major), 132.7 (minor), 130.7 (major), 125.9 (major), 125.2 (minor), 82.0 (major), 81.3 (minor), 74.0 (minor), 71.1 (major), 57.4 (minor), 56.8 (major), 53.6 (minor), 53.5 (major), 36.7 (major), 35.2 (major), 34.8 (minor), 34.7 (minor), 29.2 (major), 28.5 (minor), 28.0, 25.9, 20.3 (minor), 19.7 (major), 18.2 (minor), 18.2 (minor), 18.1 (major), 16.2 (major), 14.8 (major), 1.1, −4.1 (major) −4.3 (minor), −4.5 (major) −4.8 (minor) ppm. MS (ESI): *m/z* 433 (M + Na^+), HRMS (ESI): found (M + H^+): 411.2925, $C_{23}H_{43}O_4Si$ requires (M + H^+): 411.2926.

(1*S*,7*R*,9*R*)-4,5,9-Trimethyl-10-oxa-bicyclo[5.2.2]undec-4-en-8,11-dione (43). Trifluoroacetic acid (1.12 mL, 14.5 mmol, 15 equiv.) was added to a solution of a diastereomeric mixture of the alcohol (286 mg, 0.97 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at 25 °C for 16 h and concentrated *in vacuo* leaving the crude product as brown oil. The oil was purified by flash column chromatography eluting with pentane : Et_2O, 3 : 1 then 1 : 2, gave **43** as a white solid (120 mg, 56%).%). $[\alpha]_D^{24}$ −61.0 (*c* 1.80, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 2957, 2928, 2855, 1734, 1643, 1511, 1462, 1369, 1264, 1149, 1120, 836 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.79 (1H, m), 3.54 (1H, d, *J* = 11.7 Hz), 3.03 (1H, d, *J* = 14.6 Hz), 2.84 (1H, m), 2.69 (1H, dd, *J* = 14.6, 11.7 Hz), 2.21 (1H, m), 1.85 (3H, m), 1.69 (3H, s), 1.68 (3H, s), 1.18 (3H, d, *J* = 7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.7, 170.3, 131.1, 127.9, 80.4, 54.0, 45.1, 37.1, 28.8, 27.1, 23.1, 18.9, 9.9 ppm. HRMS: found M+H 296.2716, $C_{13}H_{18}O_3$ requires M+H 222.1397.

(1*S*,4*R*,5*S*,7*R*,8*R*,9*R*)-4,5,9-Trimethyl-5-acetoxy-8-hydroxy-10-oxa-tricyclo[3.4.2.0]undecane (57). To a solution of lactone **43** (7 mg, 0.03 mmol, 1.0 equiv) in glacial acetic acid (500 µL) stirring at rt under N_2 was added $HBF_4{\cdot}Et_2O$ (69 µL, 0.51 mmol, 16.0 equiv). The solution was stirred for 4 h at rt, after which point the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and stirred for 10 min. The mixture was diluted with Et_2O (8 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (4 mL) followed by water (4 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organics were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil as the crude compound. Purification *via* flash column chromatography with pentane : Et_2O, 2 : 1 gave **57** as a yellow oil (5 mg, 57%). $[\alpha]_D^{24}$ −60.4 (*c* 0.50, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 3552, 2928, 2856, 2254, 1735, 1460, 1379, 1251, 1115, 11093, 1033, 904, 727 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.58 (1H, m), 3.65 (1H, s), 3.30 (1H, dd, *J* = 17.0, 11.4 Hz), 2.90 (1H, dd, *J* = 11.5, 3.7 Hz), 2.39 (1H, dd, *J* = 17.0, 3.7 Hz), 2.35 (1H, m), 2.04 (3H, s), 1.88 (1H, m), 1.81 (1H, m), 1.52 (3H, s), 1.42 (1H, m), 1.17 (3H, d, *J* = 7.9 Hz), 1.16 (3H, s), 1.05 (1H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.9, 169.6, 97.3, 80.1, 79.2, 54.4, 50.7, 38.2, 37.1, 27.3, 22.7, 20.8, 17.0, 14.5, 11.4 ppm. MS (ESI): *m/z* 305 (M + Na^+), HRMS (ESI): found (M + H^+): 283.2329, $C_{15}H_{23}O_5$ requires (M + H^+): 283.2333.

(1*S*,4*R*,7*R*,8*R*,9*R*)-4,5,9-Trimethyl-8-hydroxy-10-oxa-tricyclo[3.4.2.0]undecan-5-ene (58). To a solution of lactone **43** (50 mg, 0.23 mmol, 1.0 equiv) in anhydrous Et_2O (500 µL) stirring at rt under N_2 was added $HBF_4{\cdot}Et_2O$ (494 µL, 3.68 mmol, 16.0 equiv). The solution was stirred for 4 h at rt, after which point the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and stirred for 10 min. The mixture was diluted with Et_2O (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL) followed by water (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil as the crude compound. Purification *via* flash column chromatography with petroleum ether : EtOAc, 10 : 1 then 5 : 1 gave **58** as a yellow oil (31 mg, 61%). $[\alpha]_D^{24}$ −30.6 (*c* 0.50, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 3446, 2936, 2857, 2359, 2340, 1761, 1733, 1669, 1662, 1489, 1472, 1318, 1252, 1153, 1032, 836.4 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 5.52 (1H, m), 4.66 (1H, dd, *J* = 6.7, 3.7 Hz), 3.19 (1H, m), 2.40 (1H, m), 1.93 (1H, m), 1.87 (1H, m), 1.69 (3H, t, *J* = 1.46 Hz), 1.34 (1H, m), 1.31 (1H, m), 1.19 (3H, d, *J* = 7.3 Hz), 1.18 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 153.6, 118.7, 80.4, 78.9, 60.5, 50.8, 37.4, 33.1, 21.4, 18.0, 13.1, 11.8 ppm. MS (ESI): *m/z* 245 (M + Na^+), HRMS (ESI): found (M + H^+): 223.1329, $C_{13}H_{19}O_3Si$ requires (M + H^+): 223.1336.

(1*S*,4*R*,7*R*,8*R*,9*R*)-1,8-Dihydroxy-4,5,9-trimethyl-7-methoxycarbonyl-bicyclo[4.3.0]undecan-5-ene (60). To a solution of **58** (9 mg, 0.05 mmol, 1 equiv) in a mixture of dry MeOH (200 µL) and dry THF (200 µL) at 0 °C was added sodium methoxide (200 µL, 25% w/w in MeOH). The reaction was stirred for 4 h at 0 °C and then quenched with a saturated aqueous NH_4Cl solution (200 µL). The mixture was diluted with Et_2O (5 mL) and washed with a saturated aqueous NH_4Cl solution (4 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated

in vacuo to give an orange oil as the crude compound. Purification *via* flash column chromatography with petroleum ether : EtOAc, 5 : 1 gave **60** as a yellow oil (5 mg, 71%). $[\alpha]_D^{24}$ −16.7 (*c* 0.50, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 3566, 2928, 2253, 1717, 1461, 1379, 1216, 1192, 909 731 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 5.34 (1H, dq, *J* = 1.6, 1.5 Hz), 4.33 (1H, s), 3.71 (3H, s), 3.48 (1H, m), 3.19 (1H, dq, *J* = 1.6, 1.5 Hz), 1.81 (1H, dddd, *J* = 12.3, 8.4, 8.2, 3.8 Hz), 1.71 (1H, m), 1.68 (3H, dd, *J* = 1.7, 1.7 Hz), 1.50 (1H, dq, *J* = 9.7, 6.8 Hz), 1.44 (1H, ddd, *J* = 14.5, 3.7, 2.9 Hz), 1.25 (1H, m), 1.14 (3H, d, *J* = 6.6 Hz), 0.91 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.4, 150.3, 119.6, 83.9, 72.1, 53.3, 52.1, 50.9, 46.1, 31.8, 29.8, 23.4, 13.7, 12.6 ppm. MS (ESI): *m/z* 277 (M + Na^+), HRMS (ESI): found (M + H^+): 255.1591, $C_{14}H_{23}O_4$ requires (M + H^+): 255.1558.

(1*S*,4*R*,7*R*,8*R*,9*R*)-1,8-Dihydroxy-4,9-dimethyl-7-methoxycarbonyl-bicyclo[4.3.0]undecan-5-enal (61). To a solution of **60** (6 mg, 0.03 mmol, 1 equiv) in anhydrous dioxane (600 μL) was added selenium oxide (4 mg, 0.04 mmol, 1.6 equiv). The reaction was heated under reflux and stirred for 3 h before being cooled to 25 °C. The mixture was diluted with Et_2O (5 mL) and filtered through a pad of Celite®, before being concentrated *in vacuo* to give an orange oil as the crude compound. Purification *via* flash column chromatography with petroleum ether : EtOAc, 3 : 1 gave **61** as a colourless oil (5 mg, 76%). $[\alpha]_D^{24}$ 14.8 (*c* 0.30, $CHCl_3$). ν_{max} (solution; $CDCl_3$): 3584, 3471, 3054, 2927, 2856, 2305, 1715, 1685, 1609, 1437, 1264, 1025, 896 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ = 9.75 (1H, s), 6.70 (1H, d, *J* = 3.7 Hz), 4.06 (1H, s), 3.76 (3H, s), 3.63 (1H, d, *J* = 3.7 Hz), 3.56 (1H, m), 2.39 (1H, dddd, *J* = 14.3, 9.2, 8.4, 3.3 Hz), 1.84 (1H, m), 1.55 (2H, m), 1.26 (1H, m), 1.15 (3H, d, *J* = 6.6 Hz), 1.09 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.0, 172.7, 153.3, 146.3, 84.5, 72.0, 54.5, 52.7, 50.5, 45.4, 31.0, 28.9, 23.3, 12.6 ppm. HRMS (ESI): found (M + Na^+): 291.1203, $C_{14}H_{20}NaO_5$ requires (M + Na^+): 291.1198.

Acknowledgements

We thank the Higher Education Commission of Pakistan and the Wild Fund of the Department of Chemistry, University of York (MI), the EPSRC (grant EP/F005970/1) (JW), The University of York/EPSRC DTA (ATR) and the University of Nottingham/EPSRC DTA and Pfizer Global Research, Sandwich (RJGB) for studentship funding, and the EPSRC National Mass Spectrometry Service, Swansea for accurate mass determination.

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