DOI: 10.1002/chem.200701567

Synthesis of (+)-Obtusenyne

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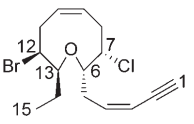
Abstract: An enantioselective synthesis of the halogenated medium-ring ether natural product (+)-obtusenyne is reported which uses the ring expansion of a seven-membered ketene acetal by means of a Claisen rearrangement to construct the core nine-membered oxygen heterocycle. The *trans* substituents across the ether linkage were established by using a transition-metal-catalyzed intramolecular hydrosilation reaction of an *exo*-cyclic enol ether. In addition, a formal synthesis of *ent*-obtusenyne from 2-deoxy-D-ribose is reported. A number of interesting points regarding the chemistry of medium-ring oxygen heterocycles are highlighted.

Keywords: Claisen rearrangement · hydrosilation · medium rings · natural products · total synthesis

Introduction

Medium-ring oxacycles constitute important structural features present in many biologically active natural products and have generated tremendous interest in the synthetic organic chemistry community.[1] A plethora of methods have been developed to construct these systems which are difficult to synthesize by "classical" methods due the unfavourable entropy and enthalpy of activation associated with the forming medium ring.[2] The development of these new synthetic methods is duly reflected by a number of elegant syntheses of marine natural products containing medium-ring ethers.[1] The C_{15}-halogenated acetogenins isolated from the *Laurencia* species of red algae, and those marine organisms which feed on *L.* sp., have frequently been used as a testing ground for new methods developed for the construction of medium-ring ethers.[3] Our own strategy towards medium-ring oxacycles has involved exploitation of the Claisen rearrangement of a vinyl-substituted ketene–acetal to deliver a medium-ring lactone,[4] a reaction first reported by Petrzilka for the synthesis of a 10-membered lactone.[5] The medium-ring lactone is subsequently converted into the corresponding medium-ring ether by methylenation followed by elaboration of the so-formed *exo*-cyclic enol ether. This strategy has successfully been employed in the synthesis of (+)-laurencin[6] and in the preparation of fused bicyclic medium-ring ethers and lactones.[7] To test the scope of this Claisen rearrangement/methylenation methodology in the synthesis of other marine-ether natural products we selected (+)-obtusenyne as our synthetic target.[8]

(+)-Obtusenyne ((+)-**1**) was independently isolated from *L. obtusa* by Imre[9] and Fenical and Clardy[10] and their respective co-workers. The structure and absolute configuration of (+)-**1** were assigned by a combination of spectroscopic analysis and X-ray crystallography. The total synthesis of (+)-obtusenyne (+)-**1** was first accomplished by Murai and co-workers in 1999.[11] The core nine-membered oxacycle was constructed by



(+)-obtusenyne ((+)-**1**)

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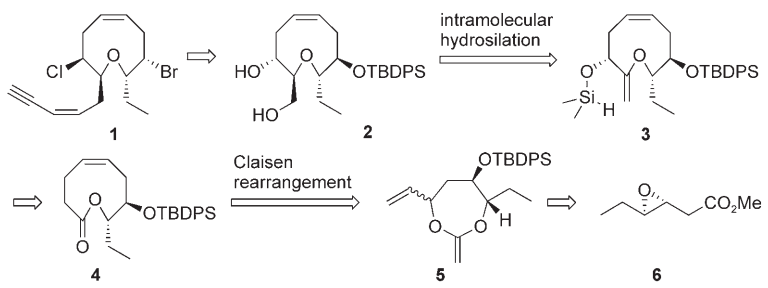
using a Keck lactonisation,[12] and the resulting lactone was converted into the 9-membered ether by means of a sequence involving formation of an enol triflate, coupling of the enol triflate with an ethyl cuprate, epoxidation of the resulting *endo*-cyclic enol ether and reduction of the so-formed epoxide. In 2003, the second enantioselective synthesis of (+)-obtusenyne was reported by Crimmins and co-workers.[13] In their synthesis, the core nine-membered ether was directly synthesised from an acyclic precursor by means of a highly efficient ring-closing metathesis. Herein, we report a full account[8] of our synthetic efforts towards this marine natural product which has culminated in the total synthesis of (+)-obtusenyne. Additionally we disclose a formal synthesis of the enantiomer of the natural product (−)-obtusenyne and highlight some of the interesting chemistry exhibited by medium-ring ethers. During the preparation of this manuscript, Suzuki and co-workers disclosed the fourth total synthesis of (+)-obtusenyne which involved the cyclisation of a linear hydroxy epoxide to form the core nine-membered ether directly.[14]

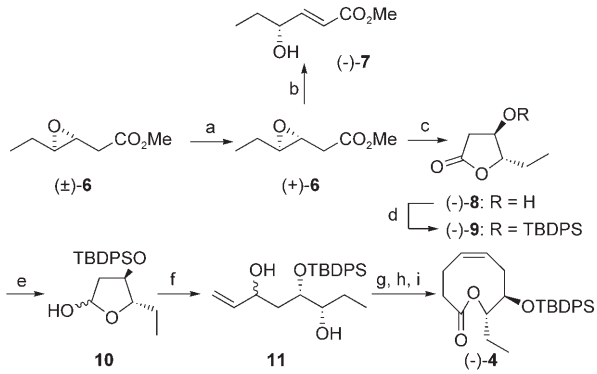
Results and Discussion

First generation approach to natural (+)-obtusenyne: Our retrosynthetic analysis of (+)-obtusenyne ((+)-**1**) is outlined in Scheme 1. We envisioned that the Δ^5-hexahydrooxonine **2** would serve as a key late-stage intermediate. Subsequent stereospecific halogenations and introduction of the (*Z*)-enyne side chain would complete the synthesis of (+)-**1**. The thermodynamically less-favoured "*trans*" relationship of the two substituents across the ether linkage in **2**[15,16] was to be established by a diastereoselective intramolecular hydrosilation of the enol ether **3**,[17] which would be readily prepared from the lactone **4**. Claisen rearrangement of the seven-membered vinyl-substituted ketene acetal **5** was considered to be the method of choice for the preparation of the lactone **4**, based upon much precedent.[4] The ketene acetal **5** was to be prepared in an enantioenriched form from the chiral non-racemic methyl *trans*-3,4-epoxyhexanoate **6**. The success of this strategy hinges on the late-stage stereospecific halogenation of the medium-ring ether derived from **2**. It should be noted that such an operation remained relatively unexplored when we initiated our synthetic program towards **1** and some interesting aspects of the displacement reactions using medium-ring ether substrates came to light as the project progressed.



Scheme 1. First-generation retrosynthetic analysis of (+)-obtusenyne ((+)-**1**).

Full details of the preparation of the racemic lactone (±)-**4** have been reported previously, starting with the racemic epoxide (±)-**6**.[8a] Our synthesis of the enantioenriched lactone (−)-**4** closely followed the route to racemic (±)-**4**, and began with a pig liver esterase-catalysed kinetic resolution of racemic *trans*-methyl 3,4-epoxyhexanoate (±)-**6**[18] by following the method of Tamm and co-workers[19] (Scheme 2). Thus, the racemic epoxide was suspended in

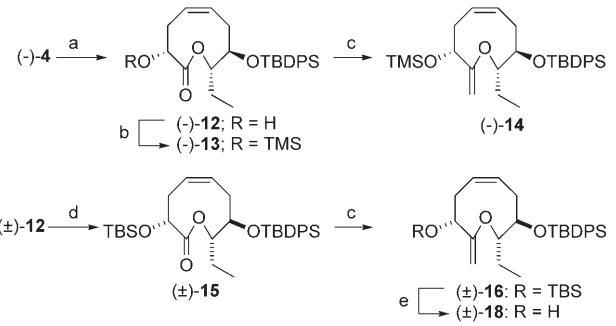


Scheme 2. Enantioselective synthesis of the lactone (−)-**4**. a) Crude pig-liver esterase, pH 7.2 phosphate buffer, 31%; b) DBU, CH_2Cl_2, 86%; c) 3% aqueous H_2SO_4, 85%; d) TBDPSCl, imidazole, DMF, 96%; e) DIBAL, THF, −78°C, RT, 90%; f) CH_2=CHMgBr, THF, 91%; g) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 90%; h) $NaIO_4$, CH_2Cl_2, MeOH, H_2O, 100%; i) DBU, toluene, reflux, 85%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL = diisobutylaluminium hydride; TBDPS = *tert*-butyldiphenylsilyl; PPTS = pyridinium *p*-toluene sulfate.

pH 7.2 phosphate buffer and pig liver esterase was added. The pH of the reaction mixture was monitored (pH meter) and maintained at pH 7.2 by the addition of 1 M sodium hydroxide solution which provided a convenient measure of conversion. At approximately 60% conversion, the enantioenriched epoxide (+)-**6** ($[\alpha]_D^{21} = +26.6$ ($c = 0.64$ in CH_2Cl_2), 96% *ee*; *ee* = enantiomeric excess) could be isolated in 31% yield. The formation of emulsions at times made isolation of the epoxide problematic, but emulsion formation could be minimised by repeated filtering of the reaction mixture through Celite. This procedure allowed the preparation of multigram quantities of the enantioenriched epoxide (+)-**6**. The enantiomeric excess of the epoxide was determined on a derivative. Thus, exposure of (+)-**6** to DBU caused isomerization to the allylic alcohol (−)-**7** ($[\alpha]_D^{21} = -25.8$ ($c = 2.9$ in $CHCl_3$)). The enantiomeric excess of the allylic alcohol (−)-**7**, and hence of the epoxide (+)-**6**, was determined by ^{1}H NMR spectroscopy by using the chiral-shift reagent [(+)-Eu(hfc)$_3$] (hfc = 3-(heptafluoropropylhydroxymeth-

ylene)camphorate); the enantiomeric excess was confirmed by Mosher's ester analysis of a later synthetic intermediate, the lactone (−)-**8** (vide infra). By analogy with Tamm's observations,[19] the epoxide (+)-**6** was presumed to have the (3*R*,4*R*)-configuration which was confirmed by comparison of the optical rotation of the allylic alcohol (−)-**7** with the known antipode[20] (Scheme 2). The chiral non-racemic epoxide (+)-**6** was readily converted into the lactone (−)-**4** with yields similar to those reported for the racemic series.[8a] Thus, exposure of the enantioenriched epoxide to aqueous acid gave the butyro-lactone (−)-**8** ($[\alpha]_D^{22} = -24.1$ ($c = 1.4$ in $CHCl_3$)}. The enantioenriched lactone (−)-**8** and the corresponding racemic lactone (±)-**8** were derivatised with (*R*)-(+)-methoxy-α-(trifluoromethyl)phenylacetic acid. ^{1}H NMR spectroscopic analysis of the derived Mosher's esters indicated that the lactone was of high enantiomeric purity (>95%). The enantioenriched lactone (−)-**8** was readily converted into the crystalline silyl ether (−)-**9** (m.p. (hexane) 64–65 °C; $[\alpha]_D^{22} = -17.3$ ($c = 1.5$ in $CHCl_3$)) which on reduction with diisobutylaluminium hydride yielded the corresponding lactols **10** as a mixture of anomers (ca. 4:1). The purified lactols **10** were exposed to an excess of vinylmagnesium bromide in THF at −78 °C to give a mixture of the allylic diols **11** in 85% yield. The diols **11** were converted into the seven-membered seleno-acetals, which on oxidation gave the corresponding selenoxides. Heating the selenoxides in toluene under reflux in the presence of DBU delivered the desired enantioenriched nine-membered lactone (−)-**4** in excellent yield ($[\alpha]_D^{20} = -11.6$ ($c = 1.0$ in $CHCl_3$)) as a clear and colourless oil.

Conversion of the lactone (−)-4 into the diol (−)-2: Enolate oxidation of the lactone (−)-**4** was achieved by using KHMDS and the Davis oxaziridine,[21] as in the racemic series[8b] (Scheme 3). This delivered the hydroxy lactone (−)-**12** as a single diastereomer of unknown configuration ($[\alpha]_D^{23} = -36.5$ ($c = 2.7$ in $CHCl_3$)) in 79% yield after extensive chromatography. The extensive chromatography could be avoided by rapid chromatography of the crude reaction mixture followed by silylation to give the α-silyloxy lactone (−)-**13** in 55% yield from the lactone (−)-**4**.



Scheme 3. Enolate oxidation and methylenation. a) KHMDS, THF, −78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, then (±)-camphor-10-sulfonic acid, 79%; b) TMSCl, Et_3N, THF, 98%; c) Tebbe reagent, DMAP, THF, −40 °C, RT, 90% (−)-**14**, 94% (±)-**16**; d) TBSCl, imidazole, DMF, 98%; e) TBAF, THF, 29–38%. DMAP = 4-dimethylaminopyridine; KHMDS = potassium hexamethyl disilazide; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl.

Molecular modelling,[22] of the enol **17**-TMS as a model for the enolate derived from the lactone (−)-**4** was conducted and the global minimum is shown in Figure 1. The global minimum conformation clearly shows that the *Re* face of the enol is exposed (and all conformations within 10 kJ mol^{-1} of the global minimum had the *Re* face of the enolate more accessible than the *Si* face) which would give rise to the hydroxy-lactone (−)-**12** with the configuration shown. Proof of the relative stereochemistry of (−)-**12** was provided by X-ray crystallographic analysis of a rearranged derivative from the enolate oxidation of (±)-**4** in the racemic series; the configuration of (−)-**12** was further confirmed by the synthesis of the natural product (+)-**1**.

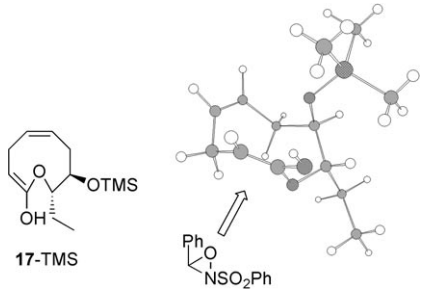
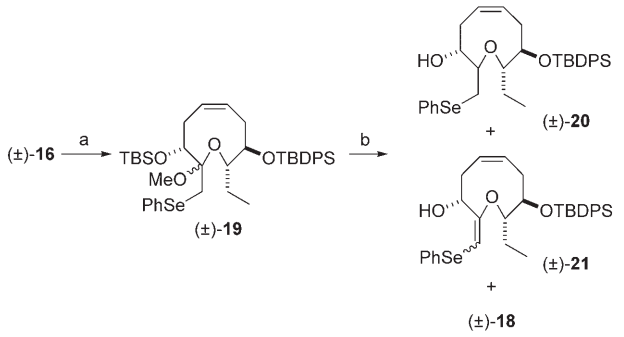
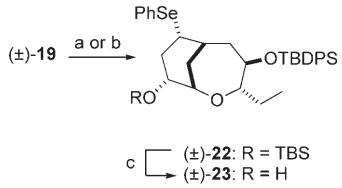


Figure 1. Global minimum conformation for **17**-TMS corresponding to the enolate derived from **4**.

The protected lactone (−)-**13** was methylenated by using the Tebbe reagent,[23] giving the *exo*-cyclic enol ether (−)-**14** in 90% yield (we also prepared the corresponding TBS-protected enol ether (±)-**16** in a similar manner—see Scheme 3). We initially investigated the elaboraton of the *exo*-cyclic enol ethers in the *racemic* series. It had been expected that hydroboration of the more nucleophilic enol ether in racemic (±)-**16** would proceed faster than the hydroboration of the *endo*-cyclic olefin. In practice, the development of an efficient and selective hydroboration was not achieved. Under a variety of conditions, hydroboration of the racemic enol ether (±)-**16** caused ring opening, competitive hydroboration of the *endo*-cyclic double bond,[24] hydrolysis of the enol ether and other unwanted reactions.[25] Our attention, therefore, was turned to the addition of selenenic electrophiles to the *exo*-cyclic enol ether by using methodology which we had developed during studies on the synthesis of (+)-laurencin[6] and used latterly in the synthesis of eunicellin analogues.[26] The protected racemic enol ether (±)-**16** was exposed to phenylselenyl chloride and *N,N*-diisopropylethylamine in a mixed solvent system (Scheme 4). Under optimised conditions, a 15:1 mixture of the selenoacetals (±)-**19** was obtained in 55% yield. The next step required the reduction of the acetals (±)-**19** to deliver the required Δ^5-hexahydrooxonine. We had previously used alane for the reduction of medium-ring methoxy-acetals;[6] howev-



Scheme 4. Methoxy selenation and reduction. a) PhSeCl, iPr$_2$EtN, MeOH, CH_2Cl_2, 55%; b) DIBAL, CH_2Cl_2, RT, 20% (±)-**20**, 24% (±)-**21**, 12% (±)-**18**.



Scheme 5. Formation of the 2-oxabicyclo[4.3.1]decane (±)-**23**. a) $TiCl_4$, Et_3SiH, −78 °C, then MeOH, 59% (±)-**23**; b) $TiCl_4$, Et_3SiH, −78 °C, then NH_4Cl, 79% (±)-**22**; c) TBAF, THF, RT, 68%.

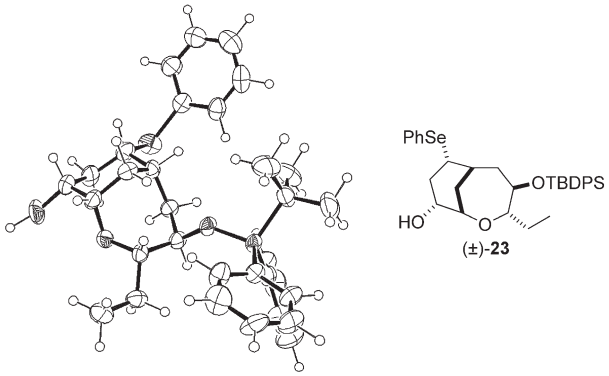


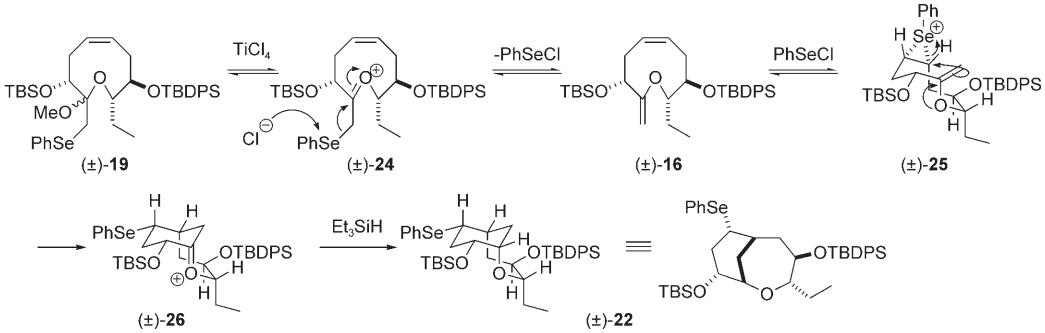
Figure 2. X-ray crystal structure of the 2-oxabicyclo[4.3.1]decane (±)-**23**.

er, these conditions were deemed incompatible with the silyl-protecting groups. Independent reports from the groups of Yamamoto[27] and Kotsuki[28,29] suggested that diisobutylaluminium hydride would be a suitable reagent to effect the reduction of the acetals (±)-**19**. Exposure of the acetals (±)-**19** to diisobutylaluminium hydride in dichloromethane resulted in the required reduction (with concomitant loss of the *tert*-butyldimethylsilyl protecting group) to deliver the Δ^5-hexahydrooxonine (±)-**20** in poor yield along with the elimination products (±)-**21** and (±)-**18**; the stereochemistry at C-2 of the Δ^5-hexahydrooxonine (±)-**20** was not assigned.

The combination of a titanium Lewis acid and triethylsilane has been used for the reduction of bicyclic ketals.[27,28] Exposure of the acetals (±)-**19** to titanium tetrachloride and triethylsilane at low temperature, followed by quenching with methanol, did not deliver the desired reduced Δ^5-hexahydrooxonine (±)-**20** but rather the crystalline [4.3.1]bicyclic ether (±)-**23** (m.p. (ether/hexane) 131–132 °C) in 59% yield (Scheme 5).

The bicyclic skeleton of (±)-**23** (Figure 2) was initially deduced by a ^{1}H NMR COSY experiment and was firmly established by X-ray crystallography,[30,31] thus confirming the relative configuration of the α-hydroxy lactone (±)-**12**.

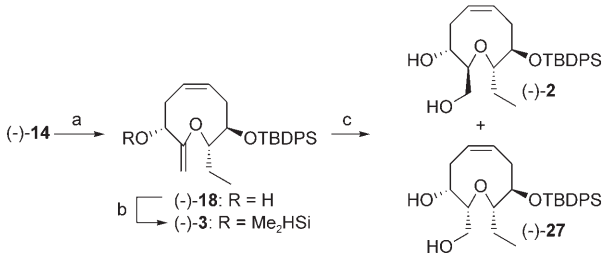
Workup of the silane reduction reaction with ammonium chloride in place of methanol enabled retention of the silyl protecting group to afford (±)-**22**. Conversion of (±)-**22** to (±)-**23** could be readily effected on exposure of (±)-**22** to tetrabutylammonium fluoride. A possible mechanism for this novel rearrangement is outlined in Scheme 6. Lewis acid mediated *exo*-cyclic cleavage of the acetal (±)-**19** gives the oxocarbenium ion (±)-**24**, which on loss of phenylselenyl chloride delivers the enol ether (±)-**16**. Addition of phenylselenyl chloride to either double bond of the enol ether (±)-**16** is possible, although attack at the enol ether double bond would be expected to be favoured. Nevertheless selenirenium-ion formation on the *endo*-cyclic double bond will occur to give (±)-**25**, and (irreversible) formation of the bicyclic oxocarbenium ion (±)-**26** can then occur. Irreversible reduction of the oxonium ion (±)-**26** then delivers the [4.3.1]-bicyclic ether (±)-**22**. The postulated mechanism involves the enol ether (±)-**16** and two pieces of circumstantial evidence support this proposal. Firstly, diisobutylaluminium hydride reduction of the methoxy-acetal (±)-**19** produced the enol ether (±)-**18**. Secondly, exposure of the enol



Scheme 6. Proposed mechanism for formation of the 2-oxabicyclo[4.3.1]decane (±)-**22**.

ether (±)-**16** to phenylselenyl chloride, titanium(IV) chloride and triethylsilane gave the same oxabicyclic-[4.3.1]decane (±)-**22**.

Returning to the synthesis of natural (+)-obtusenyne, the formation of the diol (−)-**2** was ultimately achieved by intramolecular hydrosilation of the silane (−)-**3** derived from the enol ether (−)-**14**, a reaction first reported by Tamao[17] (Scheme 7). The intramolecular hydrosilation of the racemic



Scheme 7. Hydrosilation of the enol ether (−)-**3**. a) TBAF, THF, 99%; b) $(Me_2SiH)_2NH$, NH_4Cl, 100%; c) $[RhCl(Ph_3P)_3]$, THF, reflux then H_2O_2, KOH, THF, MeOH, H_2O, see Table 1.

enol ether (±)-**3** has been discussed at length.[8c] However, further studies of this powerful reaction were made in light of the work of Evans[32] and Burgess[33] who have demonstrated that the age of rhodium catalysts used in catecholborane-mediated hydroborations has some bearing on the diastereoselectivity of these reactions. Upon reinvestigation of the hydrosilation of the enol ether (−)-**3** catalysed by Wilkinson's catalyst, we found that the diastereoselectivity changed depending on the level of oxidation of the catalyst (Table 1). Exposure of the enol ether (−)-**3** to Wilkinson's catalyst (ex-Aldrich) in THF at reflux gave the diols (−)-**2** and (−)-**27** in a 10:1 ratio after Tamao–Fleming oxidation.[34,35] Oxidation of Wilkinson's catalyst with oxygen, by using Evans's conditions,[32] prior to addition of the enol ether, improved this ratio to 21:1. The diastereoselectivity of this process is, therefore, markedly influenced by the degree of oxidation of the catalyst. Remarkably, pre-treatment of Wilkinson's catalyst with two molar equivalents of triphenylphosphane (relative to catalyst),[32] followed by addition to the enol ether (−)-**3** gave the diols (−)-**2** and (−)-**27** in a >12:1 ratio after oxidation and in very good yield. This pre-treatment of the catalyst with triphenylphosphane presumably replaces any ligand that has been lost from the coordination sphere of the rhodium by means of an oxidation mechanism.[32] Hydrosilation/oxidation of the enol ether (−)-**3** by using the pre-reduced catalyst proved to be a robust procedure which gave the diols

Table 1. Hydrosilation of the enol ether (−)-**3**.

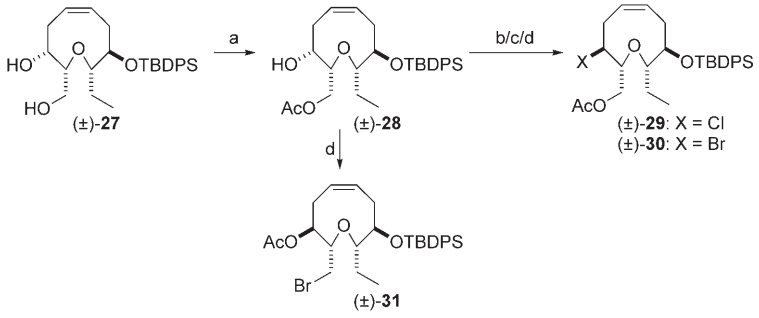
Catalyst	Ratio of diols[a]	Isolated yield of *trans*-diol (−)-**2** [%][b]	Isolated yield of *cis*-diol (−)-**27** [%][b]
$[(Ph_3P)_3RhCl]$[c]	9.9:1	64	6
$[(Ph_3P)_3RhCl]+O_2$[d]	21:1	58	8
$[(Ph_3P)_3RhCl]+2PPh_3$[e]	12.8:1	78	6

[a] Determined by HPLC. [b] After preparative HPLC. [c] As supplied. [d] Oxygen passed through a dichloromethane solution of the catalyst followed by exhaustive evaporation and redisolution in THF. [e] Catalyst and triphenylphosphane dissolved in dichloromethane, evaporated and redissolved in THF.

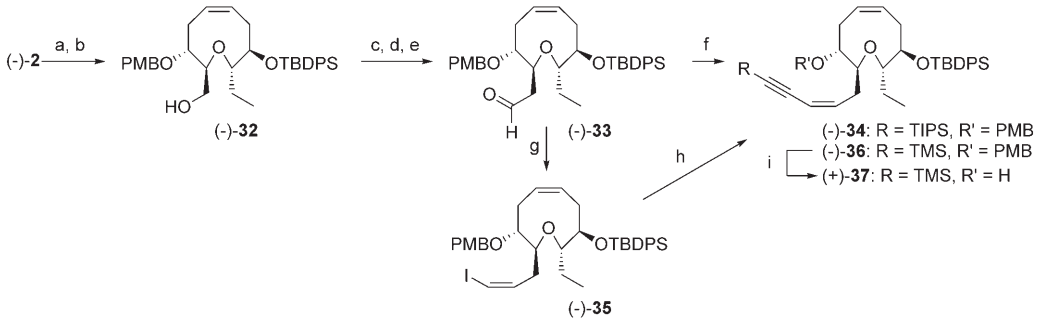
(−)-**2** and (−)-**27** in the highest isolated yield. On a preparative scale, the diols (−)-**2** and (−)-**27** could be separated by HPLC; however, it generally proved more convenient to separate the diols after further derivatization. The relative stereochemistry of the racemic diols (±)-**2** and (±)-**27** had been proven by ^1H NMR spectroscopic analysis of the derived acetonides as previously discussed.[8c]

In the racemic series, a trace amount of the *cis*-diol (±)-**27** was isolated from the intramolecular hydrosilation and we decided to make use of this diol as a model system for the late-stage stereospecific halogenations. Selective mono-acylation of the primary hydroxyl group of the *cis*-diol (±)-**27** furnished the acetate (±)-**28** (Scheme 8). We have reported the bromination and chlorination of the secondary alcohol (±)-**28** with the Ghosez reagents, 1-(halo-2-methylpropenyl)dimethylamines.[36,37] Interestingly, bromination of the alcohol (±)-**28** with carbon tetrabromide and trioctylphosphane[38] delivered a mixture of the bromides (±)-**30** and (±)-**31** presumably by means of neighbouring-group participation of acetate involving the corresponding six-membered acetoxonium ion. Having demonstrated, in the racemic series, that it was indeed possible to introduce halogen atoms stereospecifically onto a medium-ring ether system that closely resembles the core structure of (+)-obtusenyne (**1**), we turned our attention to the elaboration of the *trans*-diol (−)-**2**.

Returning to the natural series, the *trans*-diol (−)-**2** was converted into the corresponding *p*-methoxybenzylidene acetal and selective reductive cleavage with diisobutylalumi-



Scheme 8. Model halogenation study. a) Ac_2O, DMAP, CH_2Cl_2, 78%; b) $Me_2C{=}CClNMe_2$, 4 Å MS, CH_2Cl_2, (±)-propylene oxide, 71% (±)-**29**; c) $Me_2C{=}CBrNMe_2$, 4 Å MS, CH_2Cl_2, (±)-propylene oxide, 42% (±)-**30**; d) CBr_4, $P(Oct)_3$, toluene, reflux, 50% (±)-**30**, 50% (±)-**31**.



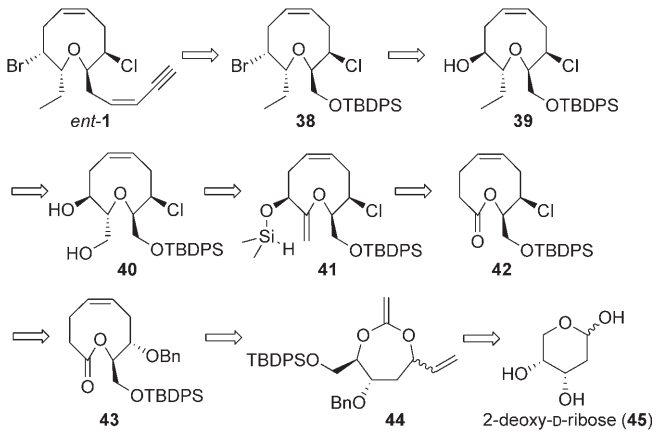
Scheme 9. Completion of the carbon skeleton of (+)-**1**. a) *p*-methoxybenzaldehyde, PPTS, benzene, reflux, 95%; b) DIBAL, CH_2Cl_2, −78→−15°C, 1 h, 86%; c) MsCl, Et_3N, CH_2Cl_2, 99%; d) NaCN, DMF, 60°C, 99%; e) DIBAL, toluene, −78→−15°C, 100%; f) TIPSC≡CCH_2TIPS, *n*BuLi, THF, −78°C→RT, 50%; g) $Ph_3P^+CH_2I\ I^-$, NaHMDS, THF, DMPU, −78°C→RT, 73%; h) TMSC≡CH, CuI, $[Pd(PPh_3)_4]$, Et_2NH, RT, 97%; i) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 92%. DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propylene urea.

nium hydride[39,40] released the primary alcohol (−)-**32** (Scheme 9). Mesylation of (−)-**32** and subsequent cyanide displacement delivered the corresponding nitrile in excellent yield. Careful nitrile reduction with diisobutylaluminium hydride furnished the relatively unstable aldehyde (−)-**33**, in readiness for the incorporation of the (*Z*)-enyne side chain. We first examined the Peterson-type olefination of Corey for the selective introduction of the enyne.[41] The aldehyde (−)-**33** was treated with lithiated 1,3-bis(triisopropylsilyl)-propyne at −78°C to furnish the desired (*Z*)-enyne (−)-**34** in moderate yield (50%), along with the corresponding (*E*)-enyne (separable). Alternatively, the Stork–Wittig[42] reaction of the aldehyde (−)-**33** delivered the corresponding (*Z*)-vinyl iodide (−)-**35** exclusively. Subsequent Sonogashira[43] coupling of (−)-**35** with trimethylsilylacetylene furnished the (*Z*)-enyne (−)-**36** in good overall yield (71% over two steps).

On the basis of the chlorination studies on the secondary alcohol (±)-**28**, we decided to introduce the chlorine substitutent prior to the bromine substituent. The PMB (PMB = *p*-methoxybenzyl) ether in (−)-**36** was readily removed with borontrichloride-dimethyl sulfide complex[44] to provide the secondary alcohol (+)-**37** in readiness for chlorination (Scheme 9). However, we were disappointed to find that attempted chlorination of the secondary alcohol (+)-**37** under a wide variety of conditions, [1-(chloro-2-methylpropenyl)dimethylamine,[36,37] carbon tetrachloride and trioctylphosphane,[45] triflate followed by benzyltriethylammonium chloride,[46] failed to yield any products containing a chlorine substituent.

The difficulty which we experienced with introducing the chlorine atom onto late-stage intermediates en route to (+)-obtusenyne led us to believe that it would be necessary to introduce the chlorine substitutent as early as possible in the synthetic sequence. This belief was reinforced when the first synthesis of obtusenyne was published by Murai and co-workers.[11] In this elegant synthesis, the chlorine atom was introduced prior to medium-ring ether formation with the bromine atom being introduced as early as possible after the formation of the Δ^5-hexahydrooxonine. Subsequently Crimmins[13] demonstrated the successful introduction of both halogen atoms at a very late stage in the synthetic route and hence "early-stage" halogenation is not a prerequisite for synthesis of the natural product. However, our synthetic endeavours pre-dated the Crimmins publication, and our own and Murai's results indicated that "early-stage" halogenation may be required. We, therefore, revised our original approach to **1** and attempted to introduce the chlorine and bromine atoms at an earlier stage in the synthesis. This strategy was based upon the well-known rate suppression of nucleophilic substitution at carbon atoms carrying a β-oxygen.[47]

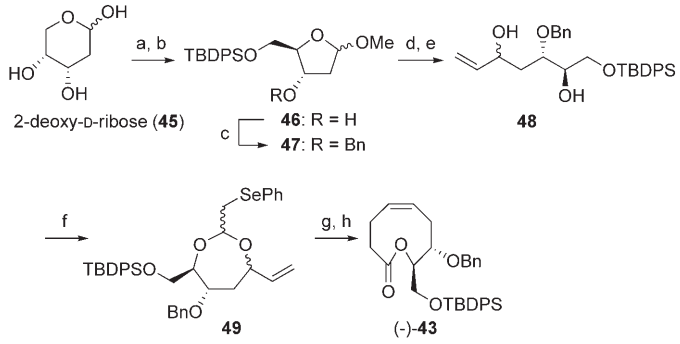
The second-generation approach: the non-natural series: Our second-generation approach to obtusenyne involved introducing the chlorine atom as early as possible in the synthetic sequence due to difficulties we had encountered in the late-stage chlorination of a secondary alcohol attached to a medium-ring ether. We have previously developed a highly efficient synthesis of nine-membered lactones from 2-deoxy-D-ribose and we decided to use this methodology for our second-generation approach to obtusenyne and for further model studies.[48,49] In part, this decision was taken because of the time-consuming kinetic resolution of the racemic epoxide (±)-**6** discussed above. The use of 2-deoxy-D-ribose as a starting material would ultimately give rise to a synthesis of non-natural (−)-obtusenyne *ent*-**1**; however, we pursued this synthetic route knowing that a number of efficient preparations of 2-deoxy-L-ribose have been reported, which would subsequently allow the synthesis of the natural enantiomer of **1**.[50] Our second-generation retrosynthetic analysis of non-natural (−)-obtusenyne *ent*-**1** is outlined in Scheme 10. We envisioned that the chloro-alcohol **39** would be smoothly brominated based upon a precedent from Murai's synthesis of obtusenyne[11] to give the bishalogenated Δ^5-hexahydrooxonine **38**. Subsequent (*Z*)-enyne side-chain installation would complete the synthesis of (−)-obtusenyne *ent*-**1**. The ethyl substituent in the chloro alcohol **39** would, in turn, be installed by a cuprate addition upon the activated primary hydroxyl group of the *trans*-diol **40**, which could be readily prepared from the chloro lactone **42**, by means of an intramolecular hydrosilation of the enol ether



Scheme 10. Second-generation retrosynthetic analysis of non-natural (−)-obtusenyne, *ent*-**1**.

41. The differentially protected lactone **43** would be prepared by the Claisen rearrangement of the ketene acetal **44** derived from the corresponding selenoxides which would, in turn, be available from 2-deoxy-D-ribose (**45**). We have previously reported the preparation of the chlorolactone (−)-**42**[48] from **45**, in which we had introduced the chlorine atom prior to medium-ring lactone formation. However, this route was not amenable to the production of gram quantities of the lactone (−)-**42**. Hence the decision was made to develop an efficient route to the nine-membered lactone **43** and subsequently to introduce the chlorine atom as soon as possible thereafter.

An efficient synthesis of the bis-*tert*-butyldiphenylsilyl-protected lactone, corresponding to **43**, from **45**, has previously been disclosed[48,49] and the synthesis of the differentially protected lactone (−)-**43** closely followed this route (Scheme 11).



Scheme 11. Preparation of the lactone (−)-**43**. a) HCl, Et_2O, MeOH; b) TBDPSCl, imidazole, DMF, 78% from **45**; c) NaH, BnBr, TBAI, THF, 72%; d) $BCl_3{\cdot}SMe_2$, THF, then Na_2CO_3, water, 83%; e) $CH_2{=}CHMgBr$, THF, 91%; f) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 90%; g) $NaIO_4$, CH_2Cl_2, MeOH, water, 100%; h) DBU, toluene, reflux, 85%.

Thus treatment of **45** with acidic methanol followed by silylation provided the methyl glycosides **46** in 78% yield.[48,49] Benzylation of the separated glycosides **46** (or a mixture of glycosides) provided the benzylethers **47** in 72% yield. The benzylethers **47** were hydrolysed to the corresponding lactols on treatment with boron trichloride–dimethyl sulfide complex. To obtain a high yield of the lactols, it was found to be imperative that the reaction mixture was rapidly quenched by the addition of saturated aqueous sodium carbonate and THF, followed by vigorous stirring and rapid chromatography. If this protocol was not followed, then the yield of the lactols was greatly diminished. Addition of vinylmagnesium bromide to the pre-dried (azeotropic distillation with toluene) lactols provided the allylic alcohols **48** as a mixture of diastereomers. Conversion of diols **48** into the corresponding selenoacetals **49** was readily achieved on treatment with phenylselanylacetaldehyde diethylacetal and PPTS in toluene at reflux under Dean–Stark conditions. The desired selenides **49** (isolated as a mixture of diastereomers) were oxidised to the corresponding selenoxides and then pyrolysed in toluene at reflux to provide the nine-membered lactone (−)-**43** in excellent yield. The nine-membered lactone was readily prepared in multigram quantities from **45** in 32% overall yield and in six synthetic steps.

The use of microwaves in organic synthesis has rapidly increased over the past decade and microwave reactors are now regarded as routine equipment for the synthetic organic chemist.[51] The selenoxide elimination/Claisen rearrangement for the formation of medium-ring lactones is generally conducted at high temperature (>100 °C) in a non-polar solvent at reflux for many hours and could be potentially conducted more efficiently under microwave irradiation.[52] We have conducted a brief survey of conditions of the selenoxide elimination/Claisen rearrangement for the formation of the lactone (−)-**43** under microwave irradiation (Table 2).

Table 2. Formation of the lactone (−)-**43** by using microwave irradiation.

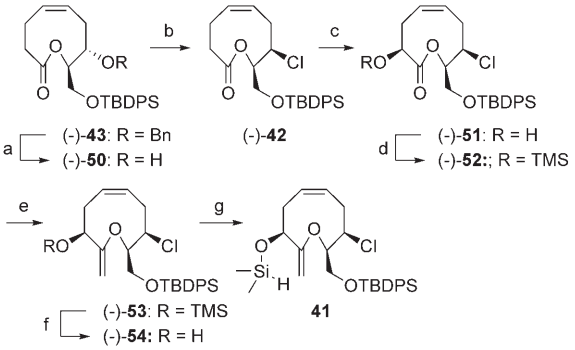
Entry	Solvent	$Bmim/BF_4$ [%][a]	T [°C]	t [min][b]	Yield [%][c]
1	toluene	–	160	30	55
2	toluene	–	160	45	95
3	*p*-xylene	–	160	45	95
4	1,2-dichlorobenzene	–	160	40	95
5	1,2-dichlorobenzene	–	200	9	96
6	*p*-xylene	–	180	12	86
7	*p*-xylene	1	180	12	95
8	*p*-xylene	–	180	9	55
9	*p*-xylene	1	180	9	82
10	*p*-xylene	2	180	9	92

[a] Percentage by volume with respect to the solvent. [b] Time under irradiation. [c] Isolated yield after column chromatography.

Initial experiments indicated that the rearrangement could be readily performed in toluene or xylene at 160 °C with microwave irradiation for 45 minutes, and gave the lactone (−)-**43** in excellent yield after column chromatography (Table 2, entries 1–3). Moving to a more polar solvent (1,2-dichlorobenzene), to increase the rate of dielectric heating, decreased the reaction time and further raising the tempera-

ture to 200 °C allowed the reaction to be completed in only nine minutes with the lactone being isolated in 95 % yield (Table 2, entry 5). We also examined the influence of ionic liquids on the Claisen rearrangement as they are known to increase the dielectric heating rates of non-polar solvents, such as toluene and xylene, but the polarity of the bulk solvent remains effectively unchanged.[53] The use of 1-butyl-3-methylimidazolium tetrafluoroborate ($BminBF_4$) as an additive (2 % by volume) to the rearrangements conducted in xylene and with a reaction temperature of 180 °C provided the desired lactone (−)-**43** in 92 % yield after only nine minutes of irradiation (Table 2, entry 10). These reaction conditions provided the lactone (−)-**43** in an improved yield compared with the standard reaction conditions (heating at reflux in toluene). The microwave conditions were excellent for the rapid production of small quantities (ca. 100 mg) of material. Nevertheless the standard reaction conditions were more convenient for the processing of 20 g batches of material.

Debenzylation of the lactone (−)-**43** was smoothly accomplished by the use of boron trichloride–dimethyl sulfide complex,[44] yielding the secondary alcohol (−)-**50** (Scheme 12). The debenzylation of secondary benzylethers



Scheme 12. Preparation of the silane **41**. a) BCl_3·SMe_2, CH_2Cl_2, 65 %; b) $Cl_2C{=}NMe_2^+$ Cl^-, pyridine, CH_2Cl_2, 0 °C→RT, 100 %; c) KHMDS, toluene, −78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, followed by (±)-camphor-10-sulfonic acid 79 %; d) TMSCl, Et_3N, THF, 90 %; e) Tebbe reagent, DMAP, THF, −40 °C→RT; f) K_2CO_3, MeOH, 71 % from (−)-**52**; g) $(Me_2SiH)_2NH$, NH_4Cl, 100 %.

with this Lewis acid is known to be sluggish and the above reaction took three days to reach completion. The stage was now set for introduction of the chlorine substituent. Thus, stirring the hydroxy lactone (−)-**50** in dichloromethane, containing 4 Å molecular sieves for 20 minutes, followed by the addition of the freshly distilled Ghosez reagent, 1-(chloro-2-methylpropenyl)dimethylamine,[36,37] and stirring at room temperature for four days provided the desired chlorinated Δ^5-oxonene (−)-**42** in excellent yield (91 %). If the reaction is quenched before reaching completion, then the *iso*-butyric acid ester derived from the alcohol (−)-**50** may be isolated. We have reported[37] that (±)-propylene oxide can suppress the formation of such esters; however, it is now clear that extended reaction times, rather than the addition of epoxides, are much more efficient at preventing formation of such side products at least in the case of the alcohol (−)-**50**. The rate of the previous two reactions meant that bringing through stocks of material proved time consuming. Gratifyingly, conversion of the secondary alcohol into the chloro-lactone (−)-**42** could be achieved in 3 h and with quantitative yield by using phosgene iminium chloride.[54] The chloro-lactone (−)-**42** was α-hydroxylated by using the protocol developed for the α-hydroxylation of the lactone (−)-**4**. This procedure provided the α-hydroxy lactone (−)-**51** in 79 % yield as a single diastereomer of unknown configuration. Molecular modelling[22] of the enol **55**-TMS, as a model for the enolate derived from the lactone (−)-**42** was conducted. The global-minimum conformation is shown in Figure 3 and indicates that the *Si* face of the enol

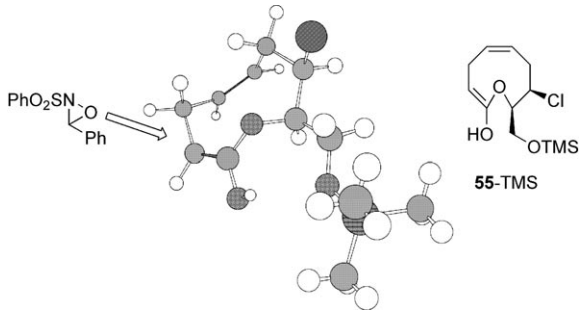


Figure 3. Global minimum structure for **55**-TMS.

is exposed, which would give rise to the hydroxy-lactone (−)-**51** with the 3(*S*)-configuration; the configuration of the hydroxy-lactone (−)-**51** was confirmed by X-ray crystallographic analysis of a later intermediate (vide infra).

Having introduced the chlorine atom and an appropriately oriented hydroxy group for the late-stage bromination, we turned our attention to the functionalization of the lactone moiety through the methylenation/intramolecular hydrosilation sequence. We have used dimethyl titanocene[55,56] for the methylenation of numerous medium-ring lactones and chlorine-containing substrates.[6,7,48] However, exposure of the lactone (−)-**52** to dimethyl titanocene in toluene at reflux provided the desired enol ether (−)-**53** in rather low yield (17 %). Fortunately methylenation of the lactone (−)-**52** could be achieved in good yield on treatment with the Tebbe reagent in THF at −50 °C (Scheme 12).[23] Removal of all the titanium residues from the crude enol ether (−)-**53** required two chromatographic purifications and it was, therefore, more practical to remove the trimethylsilyl group from (−)-**53** which allowed the hydroxy-enol ether (−)-**54** to be readily purified. The hydroxy-enol ether (−)-**54** occasionally crystallized when prepared on a 300 mg scale. A single crystal X-ray structure of the alcohol (−)-**54** (Figure 4)[57] confirmed that the chlorination of the lactone (−)-**50** had proceeded with inversion of configuration at the reacting centre and that the hydroxy group had been introduced into the lactone (−)-**42** with the desired stereochemis-

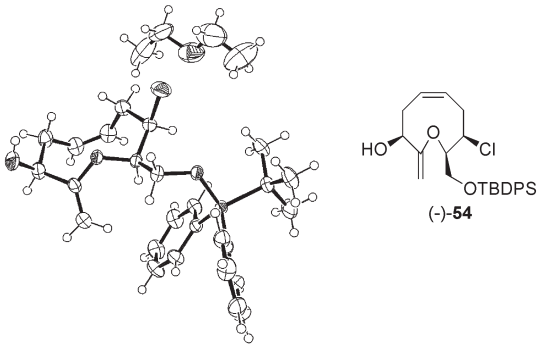
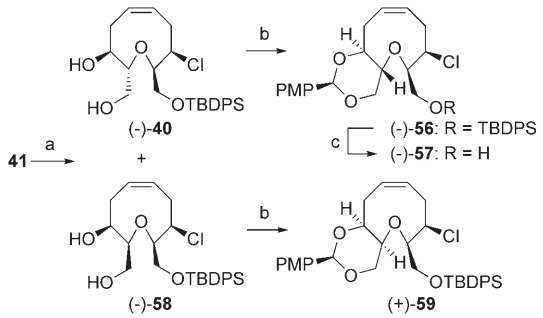


Figure 4. X-ray crystal structure of the enol ether (−)-**54** showing the ether of crystallisation.



Scheme 13. Hydrosilation of the enol ether **41**. a) 10 mol% (bicyclo-[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate, THF, reflux, then H_2O_2, KOH, THF, MeOH, 57% (−)-**40**, 28% (−)-**58**; b) *p*-methoxybenzaldehyde, PPTS, benzene, reflux, 98% (−)-**56**, 77% (+)-**59**; c) HF·pyridine, pyridine, THF, 94%.

try for the synthesis of non-natural *ent*-obtusenyne (−)-**1**. The alcohol (−)-**54** was converted into the silane **41** in readiness for the intramolecular hydrosilation reaction.

We screened a wide variety of catalysts (similar to the hydrosilation study for the enol ether **3**) for the hydrosilation of **41**. Surprisingly, hydrosilation by using Wilkinson's catalyst, followed by Tamao–Fleming oxidation,[34,35] delivered the diols (−)-**40** and (−)-**58** in moderate yield and without any selectivity (Scheme 13). The best catalyst proved to be (bicyclo[2.2.1]hepta-2,5-diene)-[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate, which delivered the diols (−)-**40** and (−)-**58** in 85% yield as a 2:1 mixture favouring the *trans*-diol (−)-**40**; the diols could be separated by preparative thin-layer chromatography but it was generally more convenient to separate them at a later stage in the synthetic sequence.

The stereochemistry of the diols (−)-**40** and (−)-**58** was assigned on the basis of ^{1}H NMR spectroscopic experiments conducted on the corresponding *p*-methoxybenzylidene acetals. The acetals (−)-**56** and (+)-**59** were formed in good yield on treatment of the corresponding diols (−)-**40** and (−)-**58** with *p*-methoxybenzaldehyde and PPTS in toluene at reflux (Scheme 13). ^{1}H NMR COSY and NOESY experiments coupled with molecular modelling analysis[22] indicated that the structure of the *p*-methoxybenzylidene acetal (+)-**59** is as shown (Figure 5), thus the configuration of C-4a and
C-11a of (+)-**59** had been established. It is noteworthy that the ^{1}H NMR NOESY data for (+)-**59** and the molecular modelling data for **59**-TMS were in close agreement. Furthermore, analysis of the ^{1}H NMR spectra of (+)-**59** indicated that the coupling between H-4a and H-11a was small and hence H-4a and H-11 were in a *cis* relationship.

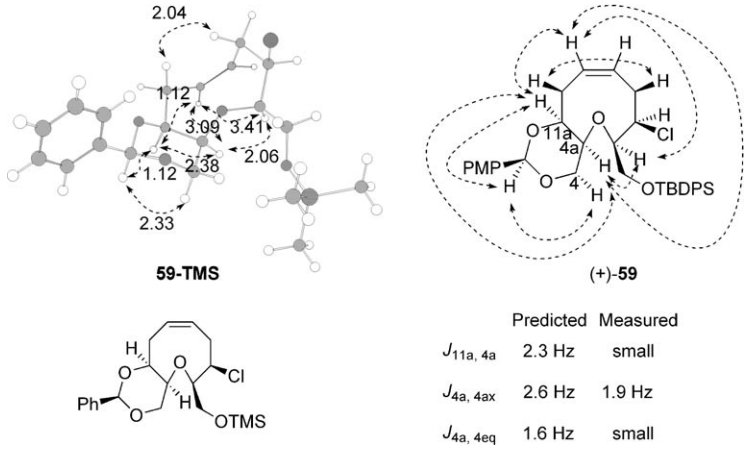


Figure 5. Global minimum conformation for **59**-TMS corresponding to the acetal (+)-**59**. The distances on the molecular model are in Ångstroms (Å). Selected ^{1}H NMR NOEs are shown on structure (+)-**59**. Coupling constants were calculated by using the Altona equation.

^{1}H NMR spectroscopic analysis of the *p*-methoxybenzylidene acetal (−)-**56** coupled with molecular modelling of **56**-TMS[22] indicated that the *p*-methoxybenzylidene acetal (−)-**56** had the stereochemistry shown. More specifically, ^{1}H NMR NOESY data were in excellent agreement with a low-energy conformation (0.94 kJ mol^{-1} above the global minimum) of the acetal **56**-TMS found by molecular modelling (Figure 6). The ^{1}H NMR NOESY data for (−)-**56** does not fit the global minimum conformation for **56**-TMS. However, a weak NOE is observed between H-11α and H-8α in (−)-**56**, indicating that the conformation corresponding to **56**-TMS is accessible to the bicyclic structure.

The stereochemistry of the *trans*-diol (−)-**40** was confirmed by X-ray crystallographic analysis of the primary alcohol (−)-**57**[58–62] formed by removal of the silyl protecting group from (−)-**56** (Scheme 13). Interestingly, the X-ray crystal structure of (−)-**57** (Figure 7) corresponds very well with the fourth lowest-energy conformation of **56**-TMS, which best fits the ^{1}H NMR NOE data.

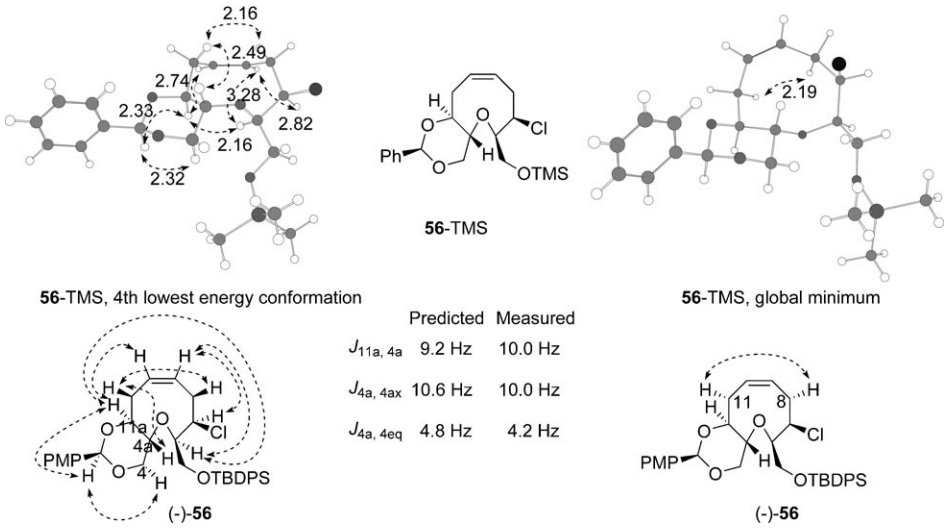


Figure 6. Conformations of **56**-TMS corresponding to the acetal (−)-**56**. The distances on the molecular model are in Ångstroms (Å). Selected ^{1}H NMR NOEs are shown on structure (−)-**56**. Coupling constants were calculated by using the Altona equation.

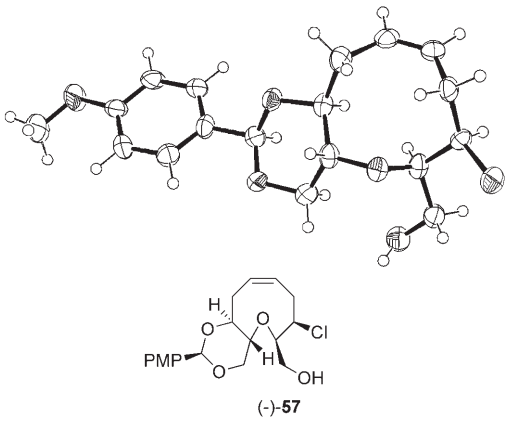
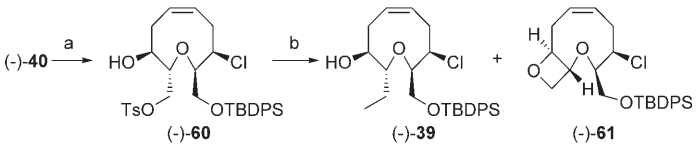


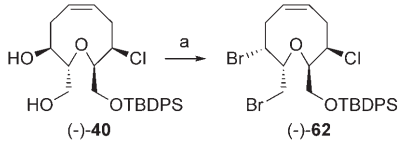
Figure 7. X-ray crystal structure of the acetal (−)-**57**. The X-ray crystal structure of (−)-**57** has two different conformers in the unit cell. One of the conformers shows some disorder in the hydroxymethyl side chain (see the Supporting Information for details).

With the stereochemistry of the diols (−)-**40** and (−)-**58** secured, the next step involved the conversion of the C-2 hydroxymethyl group into an ethyl group. Following precedent from our recent synthesis of (+)-laurencin,[6] the ethyl side-chain of obtusenyne was to be introduced by displacement of a sulfonate ester by an organocuprate. Monotosylation of the diol (−)-**40** proceeded in moderate yield to provide the hydroxy-tosylate (−)-**60** (Scheme 14). In our synthesis of (+)-laurencin, cuprate displacement on a 1,3-*trans*-hydroxy-tosylate occurred in excellent yield on exposure of the substrate to the cuprate derived from methyllithium and copper(I) cyanide. However, treatment of the tosylate (−)-**60** with the cuprate derived from methyllithium and copper(I) cyanide provided the *trans*-oxetane (−)-**61** as well as the desired ethyl-substituted oxonane (−)-**39**. The opening of oxetanes with both organolithiums[63] and organocuprates[64] has been reported. Unfortunately, exposure of (−)-**61** to the cuprate derived from methyllithium and copper(I) cyanide in the presence of boron trifluoride etherate resulted only in the recovery of the starting substrate.

The reaction of alkyl bromides with organocuprates is a well-documented procedure for the formation of carbon–carbon sigma bonds.[65] We, therefore, reasoned that conversion of the diol (−)-**40** into the dibromide (−)-**62** would simultaneously introduce the secondary bromide required for obtusenyne and activate the primary hydroxyl in readiness for carbon–carbon bond formation. In the event, exposure of the diol (−)-**40** to freshly purified carbon tetrabromide and freshly distilled trioctylphosphane in hot toluene[38] provided the requisite dibromide (−)-**62** in 90% yield (Scheme 15). Attempted coupling of the dibromide (−)-**62** with various methylcuprates under a variety of conditions resulted either in no reaction, or in the formation of ring-opened products.



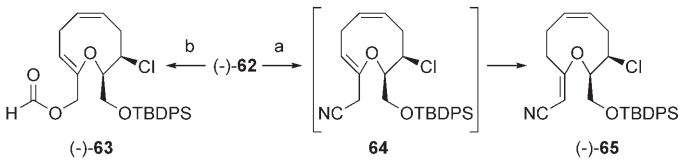
Scheme 14. Synthesis of the Δ^5-hexahydrooxonines (−)-**39** and (−)-**61**. a) TsCl, DMAP, Et_3N, CH_2Cl_2, 51% (−)-**60**, 24% (−)-**40**; b) $Me_2CuLi{\cdot}LiCN$, Et_2O, −78°C→RT, 30% (−)-**39**, 70% (−)-**61**.



Scheme 15. Synthesis of the dibromide (−)-**62**. a) CBr_4, $P(Oct)_3$, toluene, 70°C, 90%.

Further methods for the chemoselective differentiation of the dibromide (−)-**62** were attempted. We initially investigated the displacement of the dibromide (−)-**62** with cyanide with the aim of subsequently converting the introduced nitrile into the requisite C-2 ethyl group. Unfortunately, exposure of the dibromide (−)-**62** to sodium cyanide under a variety of conditions resulted in recovery of the dibromide or conversion of the dibromide into the α,β-unsaturated ni-

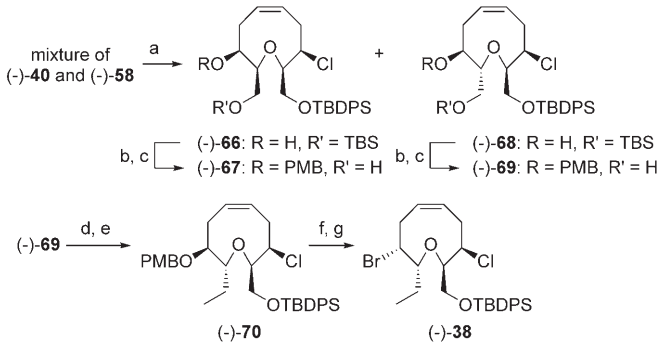
trile (−)-**65** (Scheme 16). The nitrile (−)-**65** presumably arises by an elimination/substitution sequence to give **64**, followed by conjugation of the enol ether double bond with



Scheme 16. Reactions of the dibromide (−)-**62**. a) NaCN, HMPA, 65%; b) $Cs(O_2CCF_3)$, DMF, 100°C, 78%. HMPA = hexamethylphosphoramide.

the installed nitrile functionality giving (−)-**65**. Similarly, treatment of the dibromide (−)-**62** with cesium trifluoroacetate in DMF,[66] resulted in another elimination/substitution sequence to give the formate (−)-**63**.

The installation of the ethyl group at C-13 of non-natural *ent*-obtusenyne proved problematic. Attempts to convert the tosyloxymethyl group of (−)-**60** and the bromomethyl group of (−)-**62** into ethyl groups were not fruitful and it was, therefore, decided to adopt the more pedestrian route of protecting the secondary hydroxyl group in (−)-**40** to leave the primary hydroxyl group available for conversion into a methyl group. We have achieved monoprotection of 1,3-diols by cleavage of the corresponding *p*-methoxybenzylidene acetals with diisobutylaluminium hydride (see earlier).[6,7] Unfortunately, attempted regioselective cleavage of the acetal (−)-**56** with diisobutylaluminium hydride only furnished the desired primary alcohol ((−)-**69** see Scheme 17) in low yield (17%); the primary silicon protecting group in (−)-**56** was found to be labile under the reaction conditions, resulting in a poor yield of the desired primary alcohol. Subsequently, an orthogonal protection–deprotection strategy was employed to furnish the desired primary alcohol (−)-**69** in good overall yield. A mixture of the diols (−)-**40** and (−)-**58** was converted into the corresponding, readily separable, bis-silyl ethers (−)-**68** and (−)-**66** (Scheme 17).[67] The separated bis-silyl ethers were further protected[68] and then the *tert*-butyldimethylsilyl protecting group was chemoselectively removed on treatment with mild acid,[69] to give the differentially protected triol derivatives (−)-**69** and (−)-**67**.



Scheme 17. Elaboration of the diols (−)-**40** and (−)-**58**. a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C→RT, 77% (−)-**68**, 16% (−)-**66**; b) *p*-methoxylbenzyl trichloroacetimidate, $Sc(OTf)_3$ (5 mol%), toluene, 30 min; c) PPTS, MeOH, 3 d, 82% (−)-**69** from (−)-**68**, 56% (−)-**67** from (−)-**66**; d) Tf_2O, pyridine, CH_2Cl_2, −20°C; e) Me_2CuLi, Et_2O, 0°C, 62% from (−)-**69**; f) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 97%; g) CBr_4, $P(Oct)_3$, toluene, 80°C, 70%.

The *trans*-triol-derivative (−)-**69** was esterified and the resulting unstable triflate was immediately exposed to an excess of dimethylcopper lithium in ether to give the ethyl-substituted Δ^5-hexahydrooxonine (−)-**70** (Scheme 17).[6] The *p*-methoxybenzyl ether in (−)-**70** was removed by using borontrichloride–dimethyl sulfide complex[44] to reveal the secondary alcohol in excellent yield. Exposure of the alcohol to carbon tetrabromide and trioctylphosphane[38] provided the corresponding bromide (−)-**38** in 70% yield. The structure of the bromide (−)-**38** was confirmed by single-crystal X-ray analysis, indicating that the bromination had occurred with inversion of configuration at C-3 (Figure 8);[70] Murai has reported that the introduction of bromine in medium-ring ethers can occur with inversion or retention of configuration at the reacting centre depending on the conditions employed.[71]

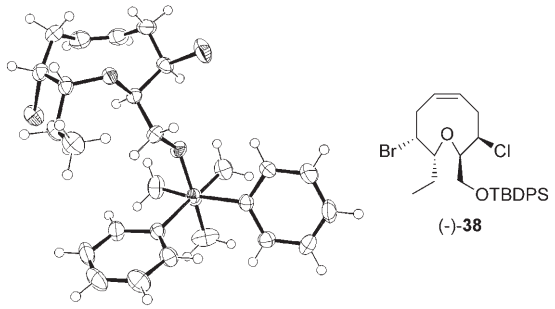
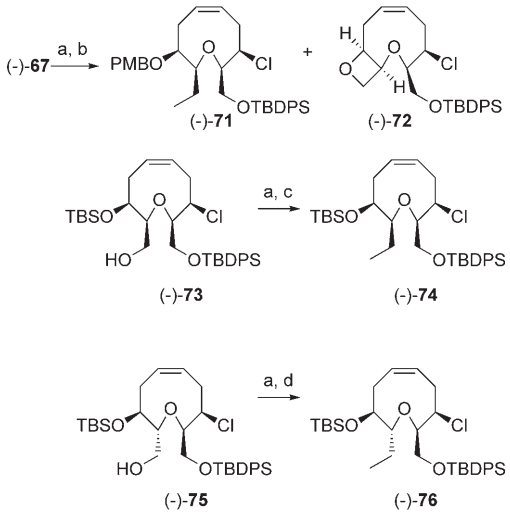


Figure 8. X-ray crystal structure of the Δ^5-hexahydrooxonine (−)-**38**.

Although the synthesis of the fully substituted core of (−)-obtusenyne *ent*-**1** had been completed, we encountered difficulties in bringing through sufficient quantities of material because the cuprate displacement of the triflate derived from the alcohol (−)-**69** proved to be capricious. The use of dimethylcopper lithium occasionally gave the desired ethyl-substituted Δ^5-hexahydrooxonine in reasonable yield (65%), although sometimes none of the desired product was formed and, more frequently, the Δ^5-hexahydrooxonine (−)-**70** was formed in low yield (ca. 30%) along with significant quantities of the alcohol (−)-**69**, which arises from attack of the cuprate at sulfur;[72] use of the cuprate derived from methyllithium and copper(I) cyanide again gave the ethyl-substituted Δ^5-hexahydrooxonine (−)-**70** in low yield (34%). We used derivatives of the *cis* alcohol (−)-**58** as model substrates when attempting to optimize this cuprate displacement reaction. Conversion of the primary alcohol (−)-**67** derived from the *cis*-diol (−)-**58**, into the corresponding triflate, and treatment with dimethylcopper lithium resulted in the formation of the desired Δ^5-hexahydrooxonine (−)-**71** in low yield in tandem with formation of the bicyclic oxetane

(−)-**72** (Scheme 18). The loss of the *p*-methoxybenzyl group during the formation of the oxetane (−)-**72** prompted us to explore the compatibility of other protecting groups with

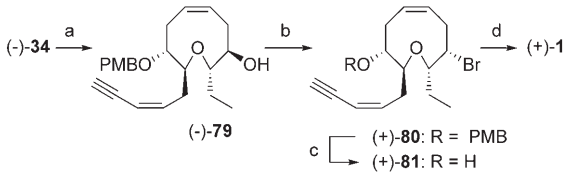


Scheme 18. Cuprate displacement studies. a) Tf_2O, pyridine, CH_2Cl_2, −20 °C; b) Me_2CuLi, Et_2O, 0 °C, 34 % (−)-**71**, 34 % (−)-**72**; c) Me_2CuLi, Et_2O, 0 °C, 65–73 % from (−)-**73**; d) $Me_2CuLi{\cdot}LiCN$, Et_2O, 0 °C, 36 % from (−)-**75**.

the cuprate displacement reactions. A mixture of the *cis*- and *trans*-diols (−)-**40** and (−)-**58** were readily converted into the corresponding (separable) primary alcohols (−)-**73** and (−)-**75** in an analogous manner to the preparation of (−)-**67** and (−)-**69** (Scheme 18).[67,69] Conversion of the *cis*-alcohol (−)-**73** into the corresponding triflate and subsequent treatment with dimethylcopper lithium, gave the ethyl-substituted Δ-hexahydrooxonine (−)-**74** in 65–73 % yield; no oxetane was formed in this reaction. In contrast, the triflate derived from the *trans*-alcohol (−)-**75**, on exposure to the cuprate derived from methyllithium and copper(I) cyanide gave the ethyl-substituted Δ-hexahydrooxonine (−)-**76** in 36 % yield; the use of dimethylcopper lithium gave only trace amounts of the desired product (−)-**76**.

Not only are these cuprate reactions sensitive to the nature of the protecting groups within the molecule but they are also very sensitive to the stereochemistry of the substituents adorning the medium ring. The stereochemistry of the ring substituents is also clearly important for the success of the displacement reactions necessary for the introduction of the requisite halogen atoms.

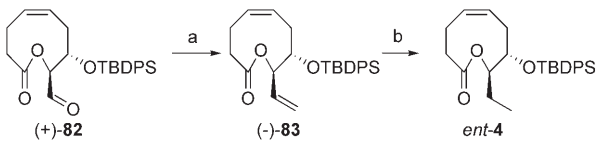
Completion of the synthesis of (+)-obtusenyne and formal synthesis of (−)-obtusenyne: While we were exploring alternative strategies for the installation of the ethyl substituent in the non-natural series towards (−)-obtusenyne *ent*-**1**, Crimmins and co-workers[13] reported their elegant total synthesis of (+)-obtusenyne (+)-**1**, featuring two late-stage halogenations of a fully substituted Δ^5-hexahydrooxonine not dissimilar to the advanced intermediates we already had in hand. We, therefore, decided to turn our attention back to the synthesis of natural (+)-obtusenyne (+)-**1** and it was envisaged that a late-stage bromination of the secondary alcohol (−)-**79** would install the required bromine atom onto the Δ^5-hexahydrooxonine system of natural (+)-obtusenyne **1**. In the event, the secondary alcohol (−)-**79** was obtained by global desilylation of the Δ^5-hexahydrooxonine (−)-**34** (Scheme 19) which had been prepared by means of the first-



Scheme 19. Synthesis of (+)-obtusenyne (+)-**1**. a) TBAF, THF, 96 %; b) CBr_4, $P(Oct)_3$, toluene, 80 °C, 67 %; c) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 70 %; d) CCl_4, $P(Oct)_3$, toluene, 80 °C, 50 %.

generation route from the racemic epoxide (±)-**6**. Gratifyingly, upon treatment of the secondary alcohol (−)-**79** with freshly purified carbon tetrabromide and freshly distilled trioctylphosphane in hot toluene,[38] the desired bromide (+)-**80** was obtained in 67 % yield. Subsequent removal of the remaining hydroxyl protecting group furnished the bromo-alcohol (+)-**81**, an intermediate in Crimmins's synthesis of (+)-obtusenyne ((+)-**1**).[13] The data for our synthetic bromo-alcohol (+)-**81** were in close agreement with the data kindly provided by M. Crimmins resulting in a formal synthesis of (+)-**1**. Chlorination of the secondary alcohol (+)-**81** by using Crimmins procedure[13] delivered natural (+)-obtusenyne (+)-**1** as a clear and colourless oil ($[\alpha]_D^{24} = +142.5$ ($c = 0.03$ in $CHCl_3$)). Our synthetic sample had characteristics (^1H and ^{13}C NMR, IR, $[\alpha]_D$ and MS data) in accordance with the data for both the natural product and synthetically prepared material.[9–11,13]

Having completed a total synthesis of natural (+)-**1** from the ethyl-substituted lactone (−)-**4**, we became interested in the preparation of the enantiomer of the lactone *ent*-**4** as this would constitute a formal synthesis of *ent*-**1** and conclude our studies towards the synthesis of unnatural *ent*-obtusenyne. In the event, the required lactone *ent*-**4** was readily synthesized from the previously reported lactone (+)-**82**.[49] Wittig methylenation of the lactone-aldehyde (+)-**82** furnished the vinyl-substituted lactone (−)-**83** (Scheme 20). Careful reaction monitoring allowed the selective hydrogenation of the vinyl group in (−)-**83** under stan-



Scheme 20. Synthesis of the lactone *ent*-**4**—formal synthesis of non-natural (−)-obtusenyne *ent*-**1**. a) $MePPh_3Br$, KHMDS, THF 98 %; b) Pd/C, H_2, EtOH, 67 %.

dard conditions (Pd/C, H_2 atmosphere),[73] to give the ethyl-substituted lactone *ent*-**4** in 67% yield along with the fully saturated ethyl-substituted lactone as a minor side product (17%). The lactone *ent*-**4** ($[\alpha]_D^{24} = +14.5$ ($c = 0.35$ in $CHCl_3$)) had spectroscopic characteristics (^1H and ^{13}C NMR, IR and MS data) in accordance with its enantiomer (−)-**4** ($[\alpha]_D^{24} = -11.6$ ($c = 1.00$ in $CHCl_3$)).

Conclusion

We have developed an efficient twenty-four step, enantioselective synthesis of the halogenated marine natural product (+)-obtusenyne ((+)-**1**) by using the Claisen rearrangement/intramolecular hydrosilation approach to medium-ring ethers. Studies towards the synthesis of non-natural *ent*-obtusenyne (*ent*-**1**) were conducted, which eventually led to a formal synthesis of *ent*-obtusenyne.

The stereochemistry of the substituents adorning the medium-ring has a profound effect on the conformation of the medium-ring and hence on the reactivity of those substituents. While molecular modelling has proven to be very useful in rationalizing (and predicting) the selectivity of certain reactions involving the Δ^5-hexahydrooxonine moiety (e.g. enolate hydroxylation) we are currently unable to predict the catalyst dependence and general selectivity of the hydrosilation reactions (most probably due to the highly complex nature of the system); furthermore, we are unable to rationalize the substrate-dependent nature of the success of both the cuprate displacement reactions and the halogenation reactions.[74] The chemistry of medium-ring ether synthesis is both challenging and exciting and this work highlights some of the interesting reactivity displayed by medium-ring oxygen heterocycles in addition to demonstrating the limits of current synthetic methodology towards the synthesis of this class of natural products.

Experimental Section

General information: See the Supporting Information.

(3*R*,4*R*)-Methyl-3,4-epoxyhexanoate ((+)-6): This synthesis was carried out according to the method of Tamm and co-workers.[19] Pig-liver esterase powder (5.22 g) was added to a rapidly stirred suspension of the racemic epoxy ester (±)-**6**[18] (10.46 g, 72.6 mmol) in 0.1 M phosphate buffer (360 mL) at pH 7.2. Sodium hydroxide solution (143.5 mL, 60% conversion) was added over a 2 h period to maintain the pH at 7.2 (pH meter). Ice was added and the reaction mixture was filtered through a Celite pad washing with ether. The filtrate was separated and the aqueous phase extracted three times with ether. During the extraction, an emulsion forms which can be dispersed by filtering twice through Celite. The separated organic extracts were combined and dried (Na_2SO_4). The solvent was removed in vacuo and purification by flash chromatography (ether/hexane, 1:2→1:1) gave the resolved epoxide (+)-**6** (3.27 g, 22.7 mmol, 31%). R_f = 0.4 (ether/hexane 1:1); $[\alpha]_D^{21} = +26.6$ ($c = 0.64$ in CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.71$ (s, 3H; CH_3O), 3.03 (dt, J(H,H) = 6, 2 Hz, 1H; 3-H or 4-H), 2.73 (dt, J(H,H) = 6, 2 Hz, 1H; 3-H or 4-H), 2.59 (dd, J(H,H) = 2, 16 Hz, 1H; 2-H), 2.51 (dd, J(H,H) = 6, 16 Hz, 1H; 2-H′), 1.59 (m, 2H; CH_2), 0.99 ppm (t, J(H,H) = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.9$ (1-C), 59.6, 53.6, 51.8, 37.5 (2-C), 24.7 (5-C), 9.7 ppm (6-C); IR (CCl_4): $\nu = 1745\ cm^{-1}$; HRMS (EI): m/z: calcd for $C_7H_{12}O_3$: 144.0786; found: 144.0779 (0.1) $[M]^+$.

(*Z*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-3-hydroxy-4,7,8,9-tetrahydro-3*H*-oxonin-2-one ((−)-12): A solution of the lactone (−)-**4** (183 mg, 0.434 mmol) in THF (4 mL) was added to a solution of KHMDS (0.91 mL of a 0.5 M solution in toluene, 0.455 mmol) in THF (5 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min and then a solution of (±)-phenylsulfonyloxaziridine (227 mg, 0.879 mmol) in THF (4 mL) was added dropwise. After stirring at −78 °C for 30 min, (±)-camphor-10-sulfonic acid (312 mg, 1.343 mmol) in THF (3 mL) was added to quench the reaction. The cooling bath was removed to allow the mixture to warm to room temperature. The mixture was poured into water (20 mL) and the aqueous layer was extracted with ether (3× 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash column chromatography (hexane/ether 2:1) yielded the impure hydroxy lactone (−)-**12** (159 mg). For characterisation purposes, further purification by flash chromatography (CH_2Cl_2), gave analytically pure material. $R_f = 0.31$ (hexane/ether 1:1); $[\alpha]_D^{21} = -41.6$ ($c = 0.25$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.68$–7.71 (m, 4H; Ar), 7.40–7.49 (m, 6H; Ar), 5.29–5.35 (m, 1H; C*H*=CH), 5.09–5.20 (m, 1H; CH=C*H*), 4.91–4.95 (m, 1H; 8-H or 9-H), 4.35 (ddd, J(H,H) = 0.3, 6.0, 2.5 Hz, 1H; 3-H), 3.70 (dd, J(H,H) = 8.7, 8.7 Hz, 1H; H-8 or H-9), 2.45–2.49 (m, 2H; ring CH_2), 2.24–2.31 (m, 1H; ring C*H*H), 2.12 (d, J(H,H) = 10.3 Hz, 1H; OH), 1.98–2.04 (m, 2H; ring CH*H*, C*H*HCH$_3$), 1.57–1.68 (m, 1H; CH*H*CH$_3$), 1.07 (s, 9H; C(C*H*$_3$)$_3$), 0.92 ppm (t, J(H,H) = 7.4 Hz, 3H; CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.8$ (2-C) 135.9, 135.89, 133.8, 133.1, 133.0, 130.0, 129.9, 127.9, 127.7, 122.0, 82.7, 75.7, 70.9, 35.3 (CH_2), 32.1, 27.0 (SiC(*C*H$_3$)$_3$), 25.2 (CH_2, Si*C*(CH$_3$)$_3$—accidental equivalence), 19.3, 9.8 ppm (CH_2CH_3); IR (film): $\tilde{\nu} = 1732\ cm^{-1}$; MS (CI, NH_3): m/z (%): 439 (20) $[M+H]^+$, 246 (100); HRMS (CI, NH_3): m/z: calcd for $C_{26}H_{35}O_4Si$: 439.2305; found: 439.2305; elemental analysis calcd (%) for $C_{26}H_{34}O_4Si$: C 71.19, H 7.81; found: C 71.1, H 7.9.

(*Z*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-3-trimethylsilanyloxy-4,7,8,9-tetrahydro-3*H*-oxonin-2-one ((−)-13): Chlorotrimethylsilane (0.22 mL, 1.73 mmol) was added to a solution of the impure hydroxy lactone (−)-**12** (150 mg) in THF (7 mL) and triethylamine (0.30 mL, 2.15 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with water (10 mL). The aqueous layer was extracted with ether (3×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (hexane/ether 9:1) furnished the TMS-ether (−)-**13** (122 mg, 53% over two steps) as a pale-yellow oil. $R_f = 0.39$ (hexane/ether 9:1); $[\alpha]_D^{24} = -36.7$ ($c = 0.33$ in $CHCl_3$); ^1H NMR (500 MHz, C_6D_6); $\delta = 7.81$–7.85 (m, 4H; Ar), 7.26–7.31 (m, 6H; Ar), 5.72 (m, 1H; C*H*=CH), 5.59 (dt, J(H,H) = 9.3, 8.0 Hz, 1H; 8-H or 9-H), 5.31 (brs, 1H; CH=C*H*), 4.48 (dd, J(H,H) = 7.8, 4.1 Hz, 1H; H-3), 4.03 (dt, J(H,H) = 2.0, 8.0 Hz, 1H; 8-H or 9-H), 2.61 (brs, 1H; ring C*H*H), 2.51 (brs, 1H; ring CH*H*), 2.38–2.43 (m, 2H; ring CH_2), 2.00 (brs, 1H; C*H*HCH$_3$), 1.58–1.65 (m, 1H; CH*H*CH$_3$), 1.23 (s, 9H; C(C*H*$_3$)$_3$), 1.05 (t, J(H,H) = 7.4 Hz, 3H; CH$_2$C*H*$_3$), 0.18 ppm (s, 9H; Si(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, C_6D_6); $\delta = 173.4$ (2-C), 136.25, 136.21, 134.12, 133.65, 130.6, 130.2, 130.1, 128.1, 125.3, 80.9, 76.6, 72.9, 33.9 (br, CH_2), 33.5, 27.2 (SiC(*C*H$_3$)$_3$), 26.2, 19.5 (CH_2, Si*C*(CH$_3$)$_3$), 9.7 (CH_2CH_3), −0.3 ppm (Si(CH$_3$)$_3$); IR (film): $\nu = 1730\ cm^{-1}$; MS (CI, NH_3): m/z (%): 511 (30) $[M+H]^+$, 90 (100); HRMS (CI, NH_3): m/z: calcd for $C_{29}H_{43}O_4Si_2$: 511.2700; found: 511.2700; elemental analysis calcd (%) for $C_{29}H_{42}O_4Si_2$: C 68.18, H 8.29; found: C 68.4, H 8.4.

(*Z*,2*S*,3*R*,8*R*)-3-*tert*-Butyldiphenylsilanyloxy-2-ethyl-9-methylene-8-trimethylsilanyloxy-2,3,4,7,8,9-hexahydrooxonine ((−)-14): The bis-silylether (−)-**13** (280 mg, 0.55 mmol) and DMAP (239 mg, 2.20 mmol) were dissolved in THF (15 mL). The solution was freeze–thaw degassed (three cycles) and cooled to −40 °C. Tebbe reagent (4.0 mL of a 0.5 M solution in toluene, 2.00 mmol) was then added to this mixture and the resulting dark-red solution was stirred at −40 °C for 0.5 h and then warmed to room temperature and stirred for a further 45 min. The reaction mixture was re-cooled to −10 °C and a 2.5 M aqueous solution of NaOH (1.5 mL)

was added to quench the reaction. The reaction mixture was then warmed to room temperature and poured into ether (30 mL) over anhydrous sodium sulphate. The supernatant was filtered through a short plug of Celite and the filtrate was concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane/ether 20:1) furnished the enol ether (−)-**14** (225 mg, 80%) as a clear and colourless oil. $R_f = 0.57$ (hexane/ether 9:1); $[\alpha]_D^{24} = -23.7$ ($c = 0.27$ in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6); $\delta = 7.83$–7.86 (m, 4H; Ar), 7.28–7.34 (m, 6H; Ar), 6.06 (dt, J(H,H) = 10.7, 5.9 Hz, 1H; C*H*=CH), 5.65 (dt, J(H,H) = 10.7, 5.9 Hz, 1H; CH=C*H*), 4.34 (d, J(H,H) = 1.4 Hz, 1H; OC=C*H*H), 4.27 (dd, J(H,H) = 9.4, 5.9 Hz, 1H; 8-H), 4.19 (d, J(H,H) = 1.4 Hz, 1H; OC=CH*H*), 4.16–4.17 (m, 1H; 2-H or 3-H), 4.03 (ddd, J(H,H) = 8.4, 5.2, 3.0 Hz, 1H; 2-H or 3-H), 2.99 (dt, J(H,H) = 11.5, 10.2 Hz, 1H; ring C*H*H), 2.86 (dt, J(H,H) = 13.5, 3.5 Hz, 1H; ring CH*H*), 2.34 (dt, J(H,H) = 11.5, 5.9 Hz, 1H; ring C*H*H), 2.24 (dt, J(H,H) = 13.5, 4.3 Hz, 1H; ring CH*H*), 1.93 (dqn, J(H,H) = 14.3, 7.4 Hz, 1H; C*H*HCH$_3$), 1.78 (dqn, J(H,H) = 14.3, 7.4 Hz, 1H; CH*H*CH$_3$), 1.26 (s, 9H; C(C*H*$_3$)$_3$), 0.93 (t, J(H,H) = 7.4 Hz, 3H; CH$_2$C*H*$_3$), 0.27 ppm (s, 9H; Si(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 166.9$ (9-C), 136.3, 136.3, 134.4, 133.9, 130.4, 130.1, 128.6, 127.9, 89.8 (C=*C*H$_2$), 85.8, 76.0, 74.6, 33.8 (CH$_2$), 32.4, 27.3 (SiC(*C*H$_3$)$_3$), 26.0, 19.5 (CH$_2$, Si*C*(CH$_3$)$_3$), 8.7 (CH$_2$*C*H$_3$), 0.5 ppm (Si(CH$_3$)$_3$); IR (film): $\tilde{\nu} = 1631$ cm^{-1}; MS (CI, NH$_3$): m/z (%): 509 (30) $[M+H]^+$, 90 (100); HRMS (CI, NH$_3$): m/z: calcd for $C_{30}H_{45}O_3Si_2$: 509.2907; found: 509.2910; elemental analysis calcd (%) for $C_{30}H_{44}O_3Si_2$: C 70.81, H 8.72; found: C 71.0, H 8.7.

(*Z*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-3-hydroxy-2-methylene-2,3,4,7,8,9-hexahydrooxonine ((−)-18): TBAF (0.19 mL of a 1.0 M solution in THF, 0.190 mmol) was added to a solution of the enol ether (−)-**14** (92 mg, 0.181 mmol) in THF (3.5 mL) at −10 °C. The reaction mixture was stirred at this temperature for 15 min and was then quenched by the addition of a saturated solution of aqueous NaHCO$_3$ (5 mL), followed by the addition of ether (5 mL). The aqueous layer was separated, extracted with ether (3×15 mL) and the combined organic extracts were washed with brine (10 mL), dried (MgSO$_4$) and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography (hexane/ether 3:1) to give the hydroxy enol ether (−)-**18** as a colourless oil (72 mg, 89%). $R_f = 0.55$ (hexane/ether 3:1); $[\alpha]_D^{24} = 31.3$ ($c = 0.60$ in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.83$–7.89 (m, 4H; Ar), 7.26–7.35 (m, 6H; Ar), 4.73–5.79 (m, 1H; C*H*=CH), 5.51 (dt, J(H,H) = 10.2, 6.8 Hz, 1H; CH=C*H*), 4.25 (d, J(H,H) = 1.9 Hz, 1H; OC=C*H*H), 4.13 (d, J(H,H) = 1.9 Hz, 1H; OC=CH*H*), 4.05–4.11 (m, 2H; 3-H, 8-H or 9-H), 4.01 (ddd, J(H,H) = 8.0, 5.5, 2.4 Hz, 1H; 8-H or 9-H), 2.54–2.60 (m, 2H; ring C*H*$_2$), 2.38 (dt, J(H,H) = 13.2, 6.5 Hz, 1H; ring C*H*H), 2.30 (ddd, J(H,H) = 11.9, 6.2, 5.0 Hz, 1H; ring CH$_2$), 1.97 (dqn, J(H,H) = 14.7, 7.3 Hz, 1H; C*H*HCH$_3$), 1.68–1.73 (m, 2H; CH*H*CH$_3$, O*H*), 1.25 (s, 9H; C(C*H*$_3$)$_3$), 0.94 ppm (t, J(H,H) = 7.3 Hz, 3H; CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 166.9$ (2-C), 136.3, 136.3, 134.4, 133.8, 130.2, 130.1, 129.9, 128.0, 126.6, 87.7 (C=*C*H$_2$), 86.2, 75.8, 73.0, 33.5 (2×CH$_2$), 27.2 (SiC(*C*H$_3$)$_3$), 26.3, 19.5 (CH$_2$, Si*C*(CH$_3$)$_3$), 9.1 ppm (CH$_2$*C*H$_3$); IR (film): $\tilde{\nu} = 3389$, 1633 cm^{-1}; MS (CI, NH$_3$): m/z (%): 437 (23) $[M+H]^+$, 181 (100); HRMS (CI, NH$_3$): m/z: calcd for $C_{27}H_{37}O_3Si$: 437.2512; found: 437.2512.

(*Z*,2*S*,3*R*,8*R*)-3-*tert*-Butyldiphenylsilanyloxy-8-dimethylsilanyloxy-2-ethyl-9-methylene-2,3,4,7,8,9-hexahydrooxonine ((−)-3): The hydroxy enol ether (−)-**18** (72.3 mg, 0.166 mmol), 1,1,3,3-tetramethyldisilazane (0.30 mL, 2.10 mmol) and NH$_4$Cl (ca. 2 mg) were stirred at 60 °C for 18 h. The mixture was diluted with hexane (10 mL) and the NH$_4$Cl was then filtered off. The solvent was removed in vacuo to give the silane (−)-**3** (79.4 mg, 100%) as a colourless oil. $R_f = 0.55$ (hexane/ether 3:1); $[\alpha]_D^{25} = -27.6$ ($c = 0.29$ in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.82$–7.86 (m, 4H; Ar), 7.27–7.33 (m, 6H; Ar), 6.03 (dt, J(H,H) = 10.9, 5.0 Hz, 1H; C*H*=CH), 5.62 (dt, J(H,H) = 10.9, 5.7 Hz, 1H; CH=C*H*), 5.05 (sp, J(H,H) = 2.8 Hz, 1H; SiMe$_2$*H*), 4.36 (d, J(H,H) = 1.6 Hz, 1H; RORC=C*H*H), 4.26 (dd, J(H,H) = 9.5, 5.8 Hz, 1H; 8-H), 4.23 (d, J(H,H) = 1.6 Hz, 1H; RORC=CH*H*), 4.17 (ddd, J(H,H) = 11.0, 8.0, 4.0 Hz, 1H; 3-H), 4.03 (ddd, J(H,H) = 9.1, 5.3, 4.0 Hz, 1H; 2-H), 2.98 (q, J(H,H) = 10.7 Hz, 1H; 7-H), 2.85 (ddd, J(H,H) = 13.5, 11.0, 2.5 Hz, 1H; 4-H), 2.36 (ddd, J(H,H) = 12.0, 5.8, 5.8 Hz, 1H; 7-H′), 2.24 (ddd, J(H,H) = 13.5, 4.4, 4.4 Hz, 1H; 4-H′), 1.90 (dqn, J(H,H) = 14.3, 7.4 Hz, 1H; C*H*HCH$_3$), 1.74 (dqn, J(H,H) = 14.3, 7.4 Hz, 1H; CH*H*CH$_3$), 1.25 (s, 9H; C(C*H*$_3$)$_3$), 0.92 (t, J(H,H) = 7.4 Hz, 3H; CH$_2$C*H*$_3$), 0.28–0.30 ppm (m, 6H; Si(C*H*$_3$)$_2$H); ^{13}C NMR (100 MHz, C_6D_6); $\delta = 166.1$ (2-C), 136.3, 136.3, 134.4, 133.9, 130.10, 130.08, 128.7, 128.3, 128.0, 90.2 (C=*C*H$_2$), 85.9, 76.0, 33.4, 32.4, 27.3 (SiC(*C*H$_3$)$_3$), 26.0 (CH$_2$), 19.5 (Si*C*(CH$_3$)$_3$), 8.7 (CH$_2$*C*H$_3$), −0.6 (Si(CH$_3$)$_2$), −0.7 ppm (Si(CH$_3$)$_2$); IR (film): $\tilde{\nu} = 2120$, 1632 cm^{-1}; MS (CI, NH$_3$): m/z (%): 495 (12) $[M+H]^+$, 181 (100); HRMS (EI): m/z: calcd for $C_{29}H_{42}O_3Si_2$: 494.2673 $[M]^+$; found: 494.2673.

(*Z*,2*S*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-3-hydroxy-2-hydroxymethyl-2,3,4,7,8,9-hexahydro-oxonine ((−)-2) and (*Z*,2*R*,3*R*,8*R*,9*S*)-8-*tert*-butyldiphenylsilanyloxy-9-ethyl-3-hydroxy-2-hydroxymethyl-2,3,4,7,8,9-hexahydrooxonine ((−)-27): Wilkinson's catalyst (10.3 mg) and triphenylphosphane (5.3 mg) were mixed in CH_2Cl_2 (1 mL) and the solvent was removed in vacuo. The residue was dissolved in THF (1 mL) and put to one side under a nitrogen atmosphere. The silane (−)-**3** (79 mg, 0.160 mmol) was dissolved in THF (4 mL) and was freeze–thaw degassed (3 cycles). A portion of the catalyst solution (0.12 mL) was then added to the solution of the silane (−)-**3** and the reaction mixture was heated under reflux for 16 h. The mixture was allowed to cool, diluted with ether (10 mL) and passed through a short pad of Florisil washing with ether. The solvent was removed in vacuo to give a pale-brown oil, which was subsequently dissolved in THF (1 mL) and MeOH (1 mL). A 15% aqueous solution of KOH (0.10 mL) and 27.5% aqueous solution of H_2O_2 (0.16 mL) were then sequentially added. The resultant suspension was stirred at room temperature for 1.5 h. Powdered anhydrous sodium sulphate (ca. 20 mg) was added (exothermic). The mixture was stirred for 20 min, diluted with CH_2Cl_2 (15 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (CH_2Cl_2/MeOH 95:5) furnished the 1,3-*trans* diol (−)-**2** (60.1 mg, 83%) contaminated with a trace amount of the 1,3-*cis* diol (−)-**27**. For characterisation purposes the diols (−)-**2** and (−)-**27** could be readily separated by HPLC or could be separated later in the synthetic route.

*Data for (−)-**2***: $R_f = 0.22$ (CH_2Cl_2/MeOH 95:5); m.p. 68–69 °C (from hexane); $[\alpha]_D^{25} = -24.0$ ($c = 0.20$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.68$–7.72 (m, 4H; Ar), 7.40–7.48 (m, 6H; Ar), 5.44 (dt, J(H,H) = 10.2, 6.8 Hz, 1H; C*H*=CH), 5.02 (dt, J(H,H) = 10.3, 8.0 Hz, 1H; CH=C*H*), 3.91 (ddd, J(H,H) = 9.2, 4.5, 2.5 Hz, 1H; 8-H or 9-H), 3.87 (dd, J(H,H) = 11.0, 1.5 Hz, 1H; C*H*HOH), 3.74 (dd, J(H,H) = 11.0, 5.3 Hz, 1H; CH*H*OH), 3.65 (t, J(H,H) = 8.5 Hz, 1H; 8-H or 9-H), 3.52 (dt, J(H,H) = 9.3, 1.5 Hz, 1H; 2-H or 3-H), 3.20 (ddd, J(H,H) = 8.5, 5.3, 2.5 Hz, 1H; 2-H or 3-H), 2.61–2.71 (m, 2H; ring CH$_2$), 2.13–2.19 (m, 2H; ring CH$_2$, OH), 2.09 (ddd, J(H,H) = 13.6, 7.6, 7.6 Hz, 1H; ring CH$_2$), 1.97–2.05 (m, 2H; C*H*HCH$_3$, OH), 1.50 (dqn, J(H,H) = 14.4, 7.4 Hz, 1H; CH*H*CH$_3$), 1.06 (s, 9H; C(C*H*$_3$)$_3$), 0.97 ppm (t, J(H,H) = 7.3 Hz, 3H; CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.01$, 135.95, 134.2, 133.4, 129.7, 129.9, 129.4, 127.8, 127.6, 125.0, 84.4, 74.0, 73.8, 70.8, 64.1 (CH$_2$OH), 33.5 (CH$_2$), 30.6, 27.0 (SiC(*C*H$_3$)$_3$), 24.2 (CH$_2$), 19.4 (Si*C*(CH$_3$)$_3$), 10.3 ppm (CH$_2$*C*H$_3$); IR (film): $\tilde{\nu} = 3617$ cm^{-1}; MS (CI, NH$_3$): m/z (%): 455 (4) $[M+H]^+$, 199 (100); HRMS (CI, NH$_3$): m/z: calcd for $C_{27}H_{39}O_4Si$: 455.2618; found: 455.2618.

*Data for (−)-**27***: $R_f = 0.26$ (CH_2Cl_2/MeOH 95:5); m.p. 89–91 °C (from hexane); $[\alpha]_D^{22} = -72.2$ ($c = 4.0$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.68$–7.63 (m, 4H; Ar), 7.47–7.35 (m, 6H; Ar), 5.75–5.68 (m, 1H; C*H*=CH), 5.58–5.50 (m, 1H; CH=C*H*), 4.01–3.85 (m, 2H), 3.90 (dd, J(H,H) = 11.5, 5.9 Hz, 1H; C*H*HOH), 3.76 (dd, J(H,H) = 11.5, 2.9 Hz, 1H; CH*H*OH), 3.67 (dt, J(H,H) = 5.7, 2.7 Hz, 1H), 3.28 (dt, J(H,H) = 5.4, 5.0 Hz, 1H), 2.70–2.59 (m, 2H; allylic CH$_2$), 2.30–2.03 (m, 4H; allylic CH$_2$, 2×OH), 1.50–1.28 (m, 2H; C*H*$_2$CH$_3$), 1.05 (s, 9H; C(C*H*$_3$)$_3$), 0.62 ppm (t, J(H,H) = 7.3 Hz, 3H; CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.0$, 135.9, 134.0, 133.6, 130.2, 129.8, 129.76, 127.7, 127.6, 126.1, 85.6, 80.4, 74.7, 72.8, 63.3 (CH$_2$OH), 32.5, 30.1, 27.0 (SiC(*C*H$_3$)$_3$), 25.8 (CH$_2$), 19.3, (Si*C*(CH$_3$)$_3$)), 8.7 ppm (CH$_2$*C*H$_3$); IR (CCl_4): $\tilde{\nu} = 3517$ cm^{-1}; MS (CI, NH$_3$): m/z (%): 455 (8) $[M+H]^+$, 199 cm^{-1} (100); HRMS (CI, NH$_3$): m/z: calcd for $C_{27}H_{39}O_4Si$: 455.2618; found: 455.2618.

(*Z*,2*S*,4a*S*,6*S*,7*R*,11a*R*)-7-*tert*-Butyldiphenylsilanyloxy-6-ethyl-2-(4-methoxyphenyl)-4a,6,7,8,11,11a-hexahydro-4*H*-1,3,5-trioxabenzocyclonon-

ene and (*Z*,2*S*,4a*R*,6*S*,7*R*,11a*R*)-7-*tert*-butyldiphenylsilanyloxy-6-ethyl-2-(4-methoxyphenyl)-4a,6,7,8,11,11a-hexahydro-4*H*-1,3,5-trioxabenzocyclononene: Freshly distilled *p*-anisaldehyde (24 μL, 0.197 mmol), anhydrous $MgSO_4$ (ca. 10 mg) and PPTS (4 mg, 0.016 mmol) were added to a mixture of the diols (−)-**2** and (−)-**27** (58 mg, 0.132 mmol) in dry benzene (3.5 mL). The mixture was heated at reflux for 2 h. The mixture was allowed to cool and was concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane/ether 4:1) furnished the *trans*-PMP acetal (*Z*,2*S*,4a*S*,6*S*,7*R*,11a*R*)-7-*tert*-butyldiphenylsilanyloxy-6-ethyl-2-(4-methoxyphenyl)-4a,6,7,8,11,11a-hexahydro-4*H*-1,3,5-trioxabenzocyclononene (59.4 mg, 83%) and the *cis*-PMP acetal (*Z*,2*S*,4a*R*,6*S*,7*R*,11a*R*)-7-*tert*-butyldiphenylsilanyloxy-6-ethyl-2-(4-methoxyphenyl)-4a,6,7,8,11,11a-hexahydro-4*H*-1,3,5-trioxabenzocyclononene (4.4 mg, 6%), both as clear and colourless oils.

Data for the trans-*PMP acetal*: $R_f = 0.34$ (hexane/ether 4:1); $[\alpha]_D^{25} = -39.1$ ($c = 0.34$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.69$–7.72 (m, 4H; Ar), 7.41–7.50 (m, 6H; Ar), 7.35–7.37 (m, 2H; Ar), 6.86–6.88 (m, 2H; Ar), 5.36–5.46 (br m, 1H; C*H*=CH), 5.40 (s, 1H; ArC*H*O_2), 4.86–4.97 (br m, 1H; CH=C*H*), 4.27 (dd, J(H,H) = 10.5, 4.4 Hz, 1H; C*H*HO), 3.80 (s, 3H; OCH_3), 3.66–3.74 (m, 3H; 3×OCH), 3.48 (td, J(H,H) = 10.5, 2.5 Hz, 1H; OCH), 3.30–3.37 (m, 1H; OC*H*), 2.69–2.88 (m, 2H; ring CH_2), 1.97–2.22 (m, 3H; ring CH_2, C*H*HCH$_3$), 1.32–1.43 (m, 1H; CH*H*CH$_3$), 1.06 (s, 9H; C(CH_3)$_3$), 0.97 ppm (t, J(H,H) = 7.6 Hz, 3H; CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.1$, 136.0, 135.9, 134.2, 133.4, 130.3, 129.9, 129.7, 129.6, 127.8, 127.6, 127.4, 125.2, 113.6, 101.3, 84.8, 79.7, 74.6, 71.8 (CH_2), 66.1, 55.3 (OCH_3), 33.4 (CH_2), 28.2, 27.0 (SiC(*C*H$_3$)$_3$), 25.4 (CH_2), 19.5, (Si*C*(CH$_3$)$_3$), 10.5 ppm (CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.1$, 136.0, 135.9, 134.2, 133.4, 130.3, 129.9, 129.7, 129.6, 127.8, 127.6, 127.4, 125.2, 113.6, 101.3, 84.8 (OCH), 79.7 (OCH), 74.6, 71.8 (CH_2), 66.1 (OCH), 55.3 (OCH_3), 33.4 (CH_2), 28.1, 27.0 (SiC(*C*H$_3$)$_3$), 25.4 (CH_2), 19.5 (Si*C*(CH$_3$)$_3$), 10.5 ppm; IR (CCl_4): $\tilde{\nu} = 3072$ cm^{-1}; MS (CI, NH_3): m/z (%): 573 (10) $[M+H]^+$, 137 (100); HRMS (CI, NH_3): m/z: calcd for $C_{35}H_{45}O_5Si$: 573.3036; found: 573.3040; elemental analysis calcd (%) for $C_{35}H_{44}O_5Si$: C 73.39, H 7.74; found: C 73.2, H 7.8.

Data for the cis-*PMP acetal*: $R_f = 0.26$ (hexane/ether 4:1); $[\alpha]_D^{25} = 87.0$ ($c = 0.22$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$–7.69 (m, 4H; Ar), 7.38–7.47 (m, 8H; Ar), 6.86–6.88 (m, 2H; Ar), 5.87 (dt, J(H,H) = 10.8, 5.8 Hz, 1H; C*H*=CH), 5.57 (dt, J(H,H) = 10.8, 5.8 Hz, 1H; CH=C*H*), 5.46 (s, 1H; ArC*H*O_2), 4.26 (d, J(H,H) = 12.4 Hz, 1H; C*H*HO), 3.99–4.20 (m, 2H), 3.95 (dd, J(H,H) = 12.4, 1.7 Hz, 1H; CH*H*O), 3.80 (s, 3H; OCH_3), 3.43–3.44 (m, 1H; OC*H*CH_2O), 3.21 (dd, J(H,H) = 10.0, 5.2 Hz, 1H), 2.94 (q, J(H,H) = 11.3 Hz, 1H; ring CH_2), 2.76–2.81 (m, 1H; ring CH_2), 2.24 (dt, J(H,H) = 12.0, 5.8 Hz, 1H; ring CH_2), 2.07 (dt, J(H,H) = 12.0, 5.8 Hz, 1H; ring CH_2), 1.45–1.54 (m, 1H; C*H*HCH$_3$), 1.26–1.33 (m, 1H; CH*H*CH$_3$), 1.09 (s, 9H; C(CH_3)$_3$), 0.72 ppm (t, J(H,H) = 7.4 Hz, 3H; CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.8$, 135.9, 135.8, 133.9, 133.7, 130.9, 130.7, 129.8, 129.7, 127.7, 127.6, 127.5, 125.1, 113.5, 85.7 (OCH), 77.6 (OCH), 75.0 (OCH), 73.2 (OCH), 70.5 (O*C*H_2Ar), 55.3 (OCH_3), 29.3 (CH_2), 27.0 (SiC(*C*H$_3$)$_3$), 26.9 (CH_2), 25.5 (CH_2), 19.3 (Si*C*-(CH$_3$)$_3$), 8.8 ppm (CH_2CH_3); IR (film): $\tilde{\nu} = 2961$ cm^{-1}; MS (CI, NH_3): m/z (%): 590 (10) $[M+NH_4]^+$, 573 $[M+H]^+$ (100); HRMS (ES): m/z: calcd for $C_{35}H_{45}O_5Si$: 573.3036; found: 573.3033.

(*Z*,2*S*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-2-hydroxymethyl-3-(4-methoxybenzyloxy)-2,3,4,7,8,9-hexahydro-oxonine ((−)-32): DIBAL-H (0.28 mL of a 1.5 M solution in toluene, 0.420 mmol) was added to a solution of the *trans*-PMP acetal described above (50 mg, 0.087 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The reaction mixture was stirred at this temperature for 10 min and was then warmed to −15 °C and stirred for another 45 min. The reaction was quenched with MeOH (1 mL) at −78 °C. A saturated solution of aqueous NH_4Cl (1 mL) was then added and the reaction mixture was warmed to room temperature. Water (5 mL) was added to the resultant suspension and the aqueous layer was extracted with ether (5×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by column chromatography (hexane/ether 1:1) furnished the alcohol (−)-**32** as a colourless oil (44 mg, 88%). $R_f = 0.31$ (hexane/ether 1:1); $[\alpha]_D^{25} = -55.4$ ($c = 0.34$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.68–7.71 (m, 4H; Ar), 7.38–7.47 (m, 6H; Ar), 7.23–7.25 (m, 2H; Ar), 7.23–7.25 (m, 2H; Ar), 5.38–5.43 (m, 1H; C*H*=CH), 5.00–5.05 (m, 1H; CH=C*H*), 4.59 (d, J(H,H) = 11.0 Hz, 1H; C*H*HAr), 4.37 (d, J(H,H) = 11.0 Hz, 1H; CH*H*Ar), 3.81 (s, 3H; OCH_3), 3.71–3.77 (m, 1H), 3.62–3.68 (m, 3H), 3.51 (dt, J(H,H) = 2.7, 9.0 Hz; 1H), 3.26–3.28 (m, 1H), 2.52–2.64 (m, ring C*H*H, 2H; CH_2O*H*), 2.31–2.38 (m, 1H; ring CH*H*), 2.01–2.16 (m, 2H; ring CH_2), 1.92–2.01 (m, 1H; C*H*HCH$_3$), 1.46–1.56 (m, 1H; CH*H*CH$_3$), 1.06 (s, 9H; C(CH_3)$_3$), 0.95 ppm (t, J(H,H) = 7.2 Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.4$, 135.99, 135.95, 125.6, 114.0, 83.8 (CH), 76.9 (CH), 74.0 (CH), 73.7 (CH), 71.0 (CH_2), 63.5, 55.3 (OCH_3), 33.2 (CH_2), 27.0 (SiC(*C*H$_3$)$_3$), 26.0 (CH_2), 24.1, 19.4 (Si*C*(CH$_3$)$_3$), 10.1 ppm (CH_2CH_3); IR (film): $\tilde{\nu} = 3617$ cm^{-1}; MS (CI, NH_3): m/z (%): 575 (10) $[M+H]^+$, 319 (100); HRMS (CI, NH_3): m/z: calcd for $C_{35}H_{47}O_5Si$: 575.319; found: 575.319; elemental analysis calcd (%) for $C_{35}H_{46}O_5Si$: C 73.13, H 8.04; found: C 73.1, H 8.3.

(*Z*,2*S*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-2-methansulfonyloxymethyl-3-(4-methoxybenzyloxy)-2,3,4,7,8,9-hexahydrooxonine: Methanesulfonyl chloride (50 μL, 0.646 mmol) was slowly added to a solution of the alcohol (−)-**32** (44 mg, 0.073 mmol), DMAP (40 mg, 0.368 mmol) and triethylamine (0.25 mL, 1.79 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 1 h at room temperature and was then quenched by the addition of a saturated solution of aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane/ether 1:1) furnished the title compound as a colourless oil (49 mg, 100%). $R_f = 0.31$ (hexane/ether 1:1); $[\alpha]_D^{25} = 41.1$ ($c = 0.51$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$ (m, 4H; Ar), 7.38–7.47 (m, 6H; Ar), 7.26–7.28 (m, 2H; Ar), 6.87–6.88 (m, 2H; Ar), 5.37–5.45 (m, 1H; C*H*=CH), 5.03–5.13 (m, 1H; CH=C*H*), 4.56 (d, J(H,H) = 10.5 Hz, 1H; C*H*HAr), 4.50 (dd, J(H,H) = 10.5, 2.8 Hz, 1H; C*H*HOMs), 4.37 (d, J(H,H) = 10.5 Hz, 1H; CH*H*Ar), 4.26 (dd, J(H,H) = 10.5, 1.3 Hz, 1H; CH*H*OMs), 3.81 (s, 3H; OCH_3), 3.61–3.66 (m, 2H), 3.57 (dt, J(H,H) = 8.6, 3.0 Hz, 1H), 3.46–3.51 (m, 1H), 3.00 (s, 3H; SO_2CH_3), 2.53–2.58 (m, 2H; ring CH_2), 2.39–2.42 (m, 1H; ring C*H*H), 2.15–2.20 (m, 1H; ring CH*H*), 1.95–2.00 (m, 1H; C*H*HCH$_3$), 1.42–1.47 (m, 1H; CH*H*CH$_3$), 1.05 (s, 9H; C(CH_3)$_3$), 0.97–0.98 ppm (m, 3H; CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.3$, 135.99, 135.95, 134.1, 133.3, 129.9, 129.8, 129.75, 128.85, 127.78, 127.6, 125.6, 114.0, 84.0 (CH), 75.1 (CH), 73.3, 72.7 (CH), 71.1 (CH_2), 68.8, 55.3 (OCH_3), 37.5, 33.1, 27.0 (SiC(*C*H$_3$)$_3$), 25.9 (CH_2), 23.9 (CH_2), 19.4 (Si*C*(CH$_3$)$_3$), 9.6 ppm (CH_2CH_3); IR (film): $\tilde{\nu} =$ 3095 cm^{-1}; MS (CI, NH_3): m/z (%): 670, 80 $[M+NH_4]^+$, 121 (100); HRMS (CI, NH_3): m/z: calcd for $C_{36}H_{32}NO_7SSi$: 670.3234; found: 670.3230; elemental analysis calcd (%) for $C_{36}H_{48}O_7SSi$: C 66.23, H 7.41; found: C 66.3, H 7.4.

(*Z*,2*S*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-2-cyanomethyl-9-ethyl-3-(4-methoxybenzyloxy)-2,3,4,7,8,9-hexahydrooxonine: The mesylate, prepared above, (49 mg, 0.075 mmol) was mixed with sodium cyanide (13 mg, 0.265 mmol) and then dry DMF (0.3 mL) was added. The mixture was heated at 60 °C for 6 h. The solution was then diluted with water (10 mL) and extracted with CH_2Cl_2 (5×15 mL) and ether (5×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane/ether 2:1) furnished the title compound as a colourless oil (43 mg, 99%). $R_f = 0.60$ (hexane/ether 1:1); $[\alpha]_D^{25} = -27.1$ ($c = 0.43$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$–7.70 (m, 4H; Ar), 7.39–7.47 (m, 6H; Ar), 7.22–7.25 (m, 2H; Ar), 6.87–6.90 (m, 2H; Ar), 5.33–5.39 (m, 1H; C*H*=CH), 4.96–5.04 (m, 1H; CH=C*H*), 4.60 (d, J(H,H) = 10.7 Hz, 1H; C*H*HAr), 4.37 (d, J(H,H) = 10.7 Hz, 1H; CH*H*Ar), 3.81 (s, 3H; OCH_3), 3.57–3.62 (m, 3H), 3.36–3.41 (m, 1H), 2.78 (dd, J(H,H) = 17.0, 3.2 Hz, 1H; C*H*HCN), 2.62–2.66 (m, 2H; ring CH_2), 2.57 (dd, J(H,H) = 17.0, 3.9 Hz, 1H; CH*H*CN), 2.33–2.36 (m, 1H; ring C*H*H), 2.04–2.10 (m, 2H; ring CH*H*, C*H*HCH$_3$), 1.34–1.43 (m, 1H; CH*H*CH$_3$), 1.05 ppm (m, 12H; CH_2CH_3, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 159.5, 135.9, 134.1, 133.2, 129.9, 129.7, 129.2, 127.8, 127.6, 125.1, 117.9, 114.0, 108.8, 84.5 (CH), 78.4 (CH), 73.7 (CH), 71.4 (CH_2), 69.7 (CH), 55.3 (OCH_3), 33.3 (CH_2), 27.0 (SiC(*C*H$_3$)$_3$), 25.4 (CH_2), 24.4, 19.4 (Si*C*-(CH$_3$)$_3$), 10.2 ppm (CH_2CH_3); IR (film): $\tilde{\nu} = 2260$ cm^{-1}; MS (CI, NH_3): m/z (%): 601 (95) $[M+NH_4]^+$, 584 (70) $[M+H]^+$, 121 (100); HRMS (CI,

NH_3): *m/z*: calcd for $C_{36}H_{49}N_2O_4Si$: 601.3462; found: 601.3460 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{36}H_{45}NO_4Si$: C 74.06, H 7.77; found: C 73.9, H 7.7.

(*Z*,2*S*,3*R*,8*R*,9*S*)-8-*tert*-Butyldiphenylsilanyloxy-9-ethyl-2-formylmethyl-3-(4-methoxybenzyloxy)-2,3,4,7,8,9-hexahydrooxonine ((−)-33): DIBAL-H (33 μL of a 1.5 M solution in toluene, 0.050 mmol) was added to a solution of the nitrile, prepared above, (12.3 mg, 0.021 mmol) in toluene (1.1 mL) at −78 °C. The reaction mixture was stirred at this temperature for 15 min and was then warmed to −15 °C. Stirring was continued for another 1.5 h at this temperature. The reaction was quenched by the addition of MeOH (1 mL) at −78 °C. A saturated solution of aqueous NH_4Cl was then added and the reaction mixture allowed to warm to room temperature, followed by the addition of water (10 mL). The aqueous layer was extracted with ether (4×15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by column chromatography (hexane/ether 2:1) furnished the aldehyde (−)-**33** (12.3 mg, 100%) as a colourless oil. R_f=0.61 (hexane/ether 1:1); $[\alpha]_D^{25}=-55.9$ (c=2.6 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.57 (dd, J(H,H)=1.6, 3.5 Hz, 1H; C*H*O), 7.68–7.70 (m, 4H; Ar), 7.39–7.47 (m, 6H; Ar), 7.20–7.22 (m, 2H; Ar), 6.86–6.89 (m, 2H; Ar), 5.48–5.53 (m, 1H; C*H*=CH), 5.24–5.29 (m, 1H; CH=C*H*), 4.47 (d, J(H,H)=10.8 Hz, 1H; C*H*HAr), 4.26 (d, J(H,H)=10.8 Hz, 1H; CH*H*Ar), 3.86–3.89 (m, 1H), 3.81 (s, 3H; OCH_3), 3.70–3.72 (m; 1H), 3.48 (ddd, J(H,H)=9.5, 6.2, 3.5 Hz, 1H), 3.34 (ddd, J(H,H)=9.5, 9.5, 3.5 Hz; 1H), 2.71 (ddd, J(H,H)=15.5, 4.7, 1.6 Hz, 1H; C*H*HCHO), 2.62 (ddd, J(H,H)=15.5, 7.7, 3.5 Hz, 1H; CH*H*CHO), 2.29–2.47 (m, 4H; 2× ring CH_2), 1.75–1.85 (br m, 1H; C*H*HCH$_3$), 1.55–1.63 (m, 1H; CH*H*CH$_3$), 1.06 (s, 9H; C(CH_3)$_3$), 0.74 ppm (t, J(H,H)=7.0 Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=199.5 (CO), 159.4, 136.1, 136.0, 134.1, 133.3, 130.1, 129.8, 129.4, 128.1, 127.8, 127.6, 126.7, 113.9, 80.0, 72.4 (CH), 70.6 (CH_2), 55.3 (OCH_3), 49.1 (CH_2), 31.9 (CH_2), 27.5 (CH_2), 27.1 (SiC(CH_3)$_3$), 23.4 (CH_2), 19.5 (Si*C*(CH_3)$_3$), 8.7 ppm (CH_2CH_3); IR (film): $\tilde{\nu}$=1718 cm^{-1}; MS (CI, NH_3): *m/z* (%): 604 (30) $[M+NH_4]^+$, 587 (35) $[M+H]^+$, 121 (100); HRMS (CI, NH_3): *m/z*: calcd for $C_{36}H_{47}O_5Si$: 587.3193 $[M+H]^+$; found: 587.3190.

(*Z*,2*S*,3*R*,8*R*,9*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-ethyl-8-(4-methoxybenzyloxy)-9-((*Z*)-5-triisopropylsilanylpent-2-en-4-ynyl)-2,3,4,7,8,9-hexahydrooxonine ((−)-34): *n*BuLi (50 μL of a 1.6 M solution, 0.080 mmol) was added to a stirred solution of the 1,3-bistriisopropylsilanylpropyne (32.9 mg, 0.093 mmol) in THF (1 mL) at −20 °C. The resultant yellow solution was stirred at this temperature for 15 min and then a portion of this solution (0.65 mL) was added to a stirred solution of the aldehyde (−)-**33** (11.9 mg, 0.020 mmol) in THF (1 mL) at −78 °C. The reaction mixture was stirred at this temperature for 30 min, then warmed to room temperature and stirred for another 30 min. The reaction was quenched with a saturated solution of aqueous NH_4Cl (3 mL) and water (10 mL). The aqueous layer was extracted with ether (4×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane/ether 10:1) furnished the (*Z*)-enyne (−)-**34** (8.0 mg, 50% yield). R_f=0.49 (hexane/ether 4:1); $[\alpha]_D^{24}=-7.3$ (c=0.15 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.68–7.70 (m, 4H; Ar), 7.37–7.46 (m, 6H; Ar), 7.22–7.24 (m, 2H; Ar), 6.86 (m, 2H; Ar), 6.07 (dt, J(H,H)=11.1, 6.2 Hz, 1H; CH_2CH=CH), 5.57 (d, J(H,H)=11.1 Hz, 1H; CH_2CH=C*H*), 5.45–5.53 (m, 1H; 5-H or 6-H), 5.18–5.29 (m, 1H; 5-H or 6-H), 4.49 (d, J(H,H)=11.1 Hz, 1H; C*H*HAr), 4.38 (d, J(H,H)=11.1 Hz, 1H; CH*H*Ar), 3.80 (s, 3H; OCH_3), 3.66–3.72 (m, 1H), 3.43–3.57 (m, 2H), 3.29–3.35 (m, 1H), 2.71–2.86 (m, 2H; allylic CH_2), 2.20–2.47 (m, 4H; 2×allylic CH_2), 1.82–1.93 (m, 1H; C*H*HMe), 1.54–1.64 (m, 1H; CH*H*Me), 1.10–1.11 (m, 21H; TIPS), 1.06 (s, 9H; C(CH_3)$_3$), 0.70–0.78 ppm (m, 3H; CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=159.2, 136.0, 135.9, 134.3, 133.4, 130.2, 129.7, 129.6, 127.6, 127.5, 113.7, 110.2, 104.0, 95.6, 71.1 (OCH_2Ar), 55.2 (OCH_3), 33.7, 29.7 (ring CH_2), 26.8 (SiC(*C*H$_3$)$_3$), 23.7 (*C*H$_2$CH$_3$), 19.4 (Si*C*(CH_3)$_3$), 18.6 (*C*(CH_3)$_2$), 11.3 ppm (CH_2CH_3); IR (film): $\tilde{\nu}$=1613 cm^{-1}; MS (ES): *m/z* (%): 787 (100) $[M+Na]^+$; HRMS (ES): *m/z*: calcd for $C_{48}H_{68}O_4Si_2Na$: 787.4554; found: 787.4566.

(*Z*,2*S*,3*R*,8*R*,9*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-ethyl-9-((*Z*)-3-iodoprop-3-enyl)-8-(4-methoxybenzyloxy)-)-2,3,4,7,8,9-hexahydrooxonine ((−)-35): Iodomethyltriphenylphosphonium iodide (183 mg, 0.343 mmol) was suspended in dry THF (5.2 mL) and NaHMDS (0.343 mL of a 1.0 M solution in THF) was added dropwise. The orange solution was stirred for 1 min and then cooled to −78 °C. DMPU (0.173 mL) was added and the resultant solution was cooled to −90 °C. The aldehyde (−)-**33** (162 mg, 0.276 mmol) was added as a solution in THF (5 mL, 2 mL rinse) via cannula. The mixture was stirred at −90 °C for 10 min and was then gradually allowed to warm to room temperature. After stirring for a further 30 min, the mixture was poured onto saturated $NaHCO_3$ (15 mL) and the aqueous phase was extracted with ether (6×20 mL). The organics were dried (Na_2SO_4), evaporated and purification by flash chromatography (hexane/ether, 3:1) gave the vinyl iodide (−)-**35** as a colourless gum (144 mg, 73%). *Note the vinyl iodide should be used immediately in the next reaction as it is prone to isomerisation.* R_f=0.4 (hexane/ether 4:1); $[\alpha]_D^{22}=-30.6$ (c=2.9 in $CHCl_3$); ^{1}H NMR (200 MHz, C_6D_6): δ=7.95–7.82 (m, 4H; Ar), 7.40–7.22 (m, 8H; Ar), 6.96–6.88 (m, 2H; Ar), 6.41 (dt, J(H,H)=4.6, 7.4 Hz, 1H; C*H*=CHI), 6.08 (dm, J(H,H)=7.4 Hz, 1H; CH=C*H*I), 5.74–5.39 (m, 2H; 5-H, 6-H), 4.44 (d, J(H,H)=11.0 Hz, 1H; C*H*HAr), 4.26 (d, J(H,H)=11.0, 1H; CH*H*Ar), 3.97–3.86 (m, 1H; CHO), 3.73 (td, J(H,H)=6.8, 3.0 Hz, 1H; CHO), 3.61 (dd, J(H,H)=10.5, 4.2 Hz, 1H; CHO), 3.42 (s, 3H; OCH_3), 3.34–3.27 (m, 1H; OCH), 2.85–2.40 (m, 6H; allylic CH_2), 2.10–1.92 (m, 1H; C*H*HMe), 1.77–1.62 (m, 1H; CH*H*Me), 1.25 (s, 9H; C(CH_3)$_3$), 0.97 ppm (t, J(H,H)=7.1 Hz, 3H; CH_2CH_3); IR ($CHCl_3$): $\tilde{\nu}$=2959 cm^{-1}; MS (CI, NH_3): *m/z* (%): 711 (45) $[M+H]^+$, 121 (100); HRMS (CI, NH_3): *m/z*: calcd for $C_{37}H_{48}O_4Isi$: 711.2366 $[M+H]^+$; found: 711.2370.

(*Z*,2*S*,3*R*,8*R*,9*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-ethyl-8-(4-methoxybenzyloxy)-9-((*Z*)-5-trimethylsilanylpent-2-en-4-ynyl)-2,3,4,7,8,9-hexahydrooxonine ((−)-36): Copper(I) iodide (cat.) was added to diethylamine (2 mL). TMS-acetylene (70 μL) was then added and the mixture stirred at room temperature for 5 min. The vinyl iodide (−)-**35** (174 mg, 0.245 mmol) and [Pd(Ph$_3$P)$_4$] (cat.) were dissolved in diethylamine (1 mL) and stirred for 2 min. This mixture was then rapidly added via cannula to the pre-complexed acetylene mixture (diethylamine rinse, 1 mL). This mixture was stirred overnight in the dark. The resultant black solution was diluted with ether (10 mL), poured into 10% NH_4OH (10 mL) and saturated NH_4Cl (10 mL) was added. The mixture was extracted with ether (5×15 mL) and the organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane/ether 9:1) to give the enyne (−)-**36** as a colourless gum (161 mg, 97%) as a single isomer. R_f=0.4 (hexane/ether 4:1); $[\alpha]_D^{21}=-3.7$ (c=2.12 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.73–7.68 (m, 4H; Ar), 7.44–7.37 (m, 6H; Ar), 7.28–7.24 (m, 2H; Ar), 6.89–6.84 (m, 2H; Ar), 6.16 (ddd, J(H,H)=11.1, 8.1, 5.1 Hz, 1H; CH_2C*H*=CH), 5.58 (d, J(H,H)=11.1 Hz, 1H; CH_2CH=C*H*), 5.54–5.37 (m, 1H; 5-H or 6-H), 5.23–5.04 (m, 1H; 5-H or 6-H), 4.50 (d, J(H,H)=10.8 Hz, 1H; C*H*HAr), 4.38 (d, J(H,H)=10.8 Hz, 1H; CH*H*Ar), 3.79 (s, 3H; OCH_3), 3.75–3.29 (m, 4H; 4×OCH), 2.98–2.15 (m, 6H), 2.05–1.85 (m 1H; C*H*HMe), 1.70–1.51 (m, 1H; CH*H*Me), 1.07 (s, 9H; C(CH_3)$_3$), 0.85 (t, J(H,H)=7.1, 3H; CH_2CH_3), 0.20 ppm (s, 9H; (CH_3)$_3$Si); ^{13}C NMR (50 MHz, $CDCl_3$):δ= 159.2, 141.9, 135.97, 135.92, 134.3, 133.4, 130.3, 129.7, 129.6, 128.1, 127.7, 127.5, 126.5, 113.8, 110.2, 102.4, 99.1, 78.9, 74.1, 73.2, 71.2, 55.2, 33.5, 32.6, 27.0, 23.9, 19.4, 9.7, 0.01 ppm; IR ($CHCl_3$): $\tilde{\nu}$=1612 cm^{-1}; MS (CI, NH_3): *m/z* (%): 681 (1) $[M+H]^+$, 121 (100); HRMS (CI, NH_3): *m/z*: calcd for $C_{42}H_{57}O_4Si$: 681.3795; found: 681.3795.

(*Z*,2*S*,3*R*,8*R*,9*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-ethyl-8-hydroxy-9-[(*Z*)-5-trimethylsilanylpent-2-en-4-ynyl]-2,3,4,7,8,9-hexahydrooxonine ((+)-37): BCl_3•SMe_2 (0.16 mL of a 2.0 M solution in CH_2Cl_2, 0.320 mmol) was added to the ether (−)-**36** (108 mg, 0.159 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 10 min and then poured onto saturated aqueous $NaHCO_3$ (15 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (5×20 mL). The combined organic extracts were dried (Na_2SO_4) and purification by flash chromatography (hexane/ether 6:1) gave the title compound (+)-**37** as a colourless gum (82 mg, 92%). R_f=0.2 (hexane/ether 4:1); $[\alpha]_D^{21}=+51.3$ (c=1.6 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ=7.71–7.64 (m, 4H; Ar), 7.47–7.34 (m, 6H; Ar), 6.18 (dt, J(H,H)=10.1, 5.5 Hz, 1H; CH_2C*H*=CH), 5.64 (d, J(H,H)=11.0 Hz, 1H; CH_2CH=C*H*), 5.41 (td, J(H,H)=10.1, 7.0 Hz, 1H; 5-H or 6-H), 4.97 (td, J(H,H)=10.1, 7.0 Hz, 1H; 5-H or 6-H), 3.68–

3.29 (m, 4H; 4×OCH), 2.95–2.48 (m, 8H), 1.62–1.49 (m, 1H; CH*H*Me), 1.03 (s, 9H; C(CH_3)$_3$), 0.97 (t, J(H,H) = 7.3 Hz, 3H; CH_2CH_3), 0.17 ppm (s, 9H; (CH_3)$_3$Si)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 136.0, 135.96, 134.3, 133.2, 129.8, 129.7, 129.1, 127.8, 127.6, 125.4, 111.5, 102.1, 99.8, 84.4, 73.98, 73.97, 71.2, 33.7, 33.3, 29.9, 27.1, 24.4, 19.4, 10.6, −0.01 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3563 cm^{-1}; HRMS (CI, NH_3): m/z (%): calcd for $C_{34}H_{49}O_3Si_2$: 561.322; found: 561.322 $[M+H]^+$; elemental analysis calcd (%) for $C_{34}H_{48}O_3Si_2$: C 72.86, H 8.73; found: C 72.8, H 8.63.

(*Z*,2*S*,3*R*,8*R*,9*S*)-2-Ethyl-3-hydroxy-8-(4-methoxybenzyloxy)-9-((*Z*)-9-pent-2-en-4-ynyl)-2,3,4,7,8,9-hexahydrooxonine ((−)-79): TBAF (52 μL of a 1.0 M solution in THF, 52 μmol) was added to a solution of the (*Z*)-enyne (−)-**34** (5.2 mg, 6.8 μmol) in THF (0.35 mL) at 0 °C. The reaction mixture was stirred at this temperature for 10 min, then warmed to room temperature and stirred for another 1.5 h. The reaction mixture was purified directly by flash chromatography (hexane/ether 1:1), furnishing the alcohol (−)-**79** (2.4 mg, 95 %). R_f = 0.22 (hexane/ether 1:1); $[\alpha]_D^{24}$ = −8.0 (c = 0.23 in $CHCl_3$); IR (film): $\tilde{\nu}$ = 3287 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.30 (m, 2H; Ar), 6.88–6.90 (m, 2H; Ar), 6.22 (dt, J(H,H) = 11.0, 7.2 Hz, 1H; CH_2CH=CH), 5.67–5.76 (m, 2H; 5-H, 6-H), 5.57 (dd, J(H,H) = 11.0, ^4J(H,H) = 1.8 Hz, 1H; CH_2CH=C*H*), 4.58 (d, J(H, H) = 10.9 Hz, 1H; C*H*HAr), 4.41 (d, J(H,H) = 10.9 Hz, 1H; CH*H*Ar), 3.82 (s, 3H; OCH_3), 3.62–3.68 (m, 2H), 3.33–3.39 (m, 2H), 3.11 (d, ^4J(H,H) = 1.8 Hz, 1H; C=CH), 2.79–2.85 (m, 1H; allylic CH_2), 2.72–2.75 (m, 1H; allylic CH_2), 2.45–2.61 (m, 4H; allylic CH_2), 1.79 (dqn, J(H,H) = 14.8, 7.4 Hz, 1H; C*H*HCH$_3$), 1.68–1.76 (m, 1H; CH*H*CH$_3$), 0.98 ppm (t, J(H,H) = 7.4 Hz, 3H; CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 142.7 (CH_2CH=CH), 135.7, 130.1, 129.7, 125.5, 113.8, 109.3, 81.9 (C=CH), 80.7 (C=CH), 79.0, 69.0, 71.1 (OCH_2Ar), 55.3 (OCH_3), 34.2, 33.6, 32.0 (allylic CH_2), 29.7 (CH_2CH_3), 9.2 ppm (CH_2CH_3), owing to the conformational mobility of (−)-**79**, two of the carbon atoms adjacent to oxygen are broadened to the baseline; IR (film): $\tilde{\nu}$ = 3287 cm^{-1}; MS (ES): m/z (%): 393 (10) $[M+Na]^+$; HRMS (ES): m/z: calcd for $C_{23}H_{30}O_4Na$: 393.2042; found: 393.2046.

(*Z*,2*S*,3*S*,8*R*,9*S*)-3-Bromo-2-ethyl-8-(4-methoxybenzyloxy)-9-((*Z*)-pent-2-en-4-ynyl)-2,3,4,7,8,9-hexahydrooxonine ((+)-80): The alcohol (−)-**79** (3.1 mg, 8.4 μmol) was mixed with CBr_4 (55.0 mg, 0.165 mmol; previously purified by sublimation and neutralisation by passage through a short pad of basic alumina) and toluene (0.5 mL) was added to the mixture. To this stirred solution at room temperature was added freshly distilled trioctylphosphane (74 μL, 0.166 mmol). The reaction mixture was heated at 80 °C for 2 h and the resultant yellow solution was subjected directly to column chromatography (hexane/ether 3:1), furnishing the bromide (+)-**80** (2.3 mg, 63 % yield) as a colourless oil. R_f = 0.69 (hexane/ether 1:1); $[\alpha]_D^{24}$ = +47.5 (c = 0.04 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.30 (m, 2H; Ar), 6.89–6.91 (m, 2H; Ar), 6.23 (dt, J(H,H) = 11.0, 6.1 Hz, 1H; CH_2CH=CH), 5.76 (dt, J(H,H) = 10.5, 7.4 Hz, 1H; 5-H or 6-H), 5.54 (dd, J(H,H) = 11.0, ^4J(H,H) = 1.9 Hz, 1H; CH_2CH=C*H*), 5.45 (dt, J(H,H) = 10.5, 6.5 Hz, 1H; 5-H or 6-H), 4.60 (d, J(H,H) = 11.0 Hz, 1H; C*H*HAr), 4.40 (d, J(H,H) = 11.0 Hz, 1H; CH*H*Ar), 4.04–4.06 (m, 1H), 3.88 (dt, J(H,H) = 9.8, 3.8 Hz, 1H; 3-H), 3.83 (s, 3H; OCH_3), 3.48–3.35 (m, 3H; 2×OC*H*, allylic CH_2), 3.13 (d, ^4J(H,H) = 1.9 Hz, 1H; C=CH), 2.95–3.03 (m, 2H; allylic CH_2), 2.54–2.61 (m, 2H; allylic CH_2), 2.21 (dd, J(H,H) = 14.0, 7.4 Hz, 1H; allylic CH_2), 1.78–1.89 (m, 2H; CH_2CH$_3$), 0.80 ppm (t, J(H,H) = 7.5 Hz, 3H; CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.4 (CH_2CH=CH), 130.9, 129.9, 129.7, 127.0, 113.9, 109.0 (CH_2CH=C*H*), 81.9 (C=CH), 79.8 (C=CH), 71.1 (OCH_2Ar), 55.7 (C-3), 55.3 (OCH_3), 34.0, 31.6, 30.0 (allylic CH_2), 28.5 (CH_2CH$_3$), 9.8 ppm (CH_2CH_3); IR (film): $\tilde{\nu}$ = 3291 cm^{-1}; MS (ES): m/z (%): 457 (50) $[M+Na]^+$, 455 (50) $[M+Na]^+$, 435 (10) $[M+H]^+$, 433 (10) $[M+H]^+$; HRMS (ES): m/z: calcd for $C_{23}H_{29}O_3Na^{79}Br$: 455.1198; found: 455.1200.

(*Z*,2*S*,3*R*,8*S*,9*S*)-8-Bromo-9-ethyl-3-hydroxy-2-((*Z*)-pent-2-en-4-ynyl)-2,3,4,7,8,9-hexahydrooxonine ((+)-81): BCl_3·SMe_2 complex solution (21 μL of a 2.0 M solution in CH_2Cl_2, 42 μmol) was added to a stirred solution of the bromide (+)-**80** (3.0 mg, 6.9 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for another 10 min. The reaction was quenched by the addition of a saturated solution of aqueous $NaHCO_3$ (ca. 0.2 mL). The reaction mixture was dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by column chromatography (hexane/ether 2:1) furnished the alcohol (+)-**81** (1.5 mg, 70 %) as a colourless oil. R_f = 0.29 (hexane/ether 1:1); $[\alpha]_D^{24}$ = +46.7 (c = 0.06 in $CHCl_3$) (lit.[13] $[\alpha]_D^{24}$ = +105.8 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.26 (dt, J(H,H) = 10.9, 6.9 Hz, 1H; CH_2CH=CH), 5.87 (dt, J(H,H) = 10.0, 8.2 Hz, 1H; 5-H or 6-H), 5.60 (dd, J(H,H) = 10.9, ^4J(H,H) = 1.8 Hz, 1H; CH_2CH=C*H*), 5.50 (dt, J(H,H) = 10.0, 6.8 Hz, 1H; 5-H or 6-H), 4.12 (br d, J(H,H) = 11.2 Hz, 1H; 2-H), 3.80–3.84 (m, 1H; 3-H), 3.64–3.68 (m, 1H), 3.37–3.40 (m, 1H), 3.20–3.28 (m, 1H; allylic CH_2), 3.16 (d, ^4J(H,H) = 1.8 Hz, 1H; C=CH), 2.94–2.98 (m, 2H; allylic CH_2), 2.70 (dt, J(H,H) = 15.8, 7.0 Hz, 1H; allylic CH_2), 2.59 (ddd, J(H,H) = 10.8, 6.3, 4.1 Hz, 1H; allylic CH_2), 2.15–2.20 (br m, 1H; allylic CH_2), 1.85–1.89 (m, 2H; CH_2CH$_3$), 1.69 (d, J(H,H) = 6.3 Hz, 1H; O*H*), 0.84 ppm (t, J(H,H) = 7.5 Hz, 3H; CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.7 (CH_2CH=CH), 129.8 (5-C), 127.5 (6-C), 109.6 (CH_2CH=*C*H), 82.4 (C=CH), 80.4 (C=CH), 81.5, 72.9, 55.7 (3-C), 34.1, 33.5, 33.2 (allylic CH_2), 28.5 (CH_2CH$_3$), 9.8 ppm (CH_2CH_3); IR (film): $\tilde{\nu}$ = 3409 cm^{-1}; MS (ES): m/z (%): 337 (50) $[M+Na]^+$, 335 (50) $[M+Na]^+$, 315 (10) $[M+H]^+$, 313 (10) $[M+H]^+$; HRMS (ES): m/z: calcd for $C_{15}H_{21}O_2Na^{79}Br$: 335.0623; found: 335.0622.

(*Z*,2*S*,3*S*,8*S*,9*S*)-3-Bromo-8-chloro-2-ethyl-((*Z*)-pent-2-en-4-ynyl)-2,3,4,7,8,9-hexahydrooxonine, (+)-obtusenyne (1): Freshly distilled trioctylphosphane (34 μL, 0.076 mmol) was added to a stirred solution of the alcohol (+)-**81** (2.2 mg, 7.05 μmmol) and CCl_4 (7 μL, 0.073 mmol) in toluene (0.5 mL) at room temperature. The reaction mixture was heated at 80 °C for 4 h and the resultant pale-yellow solution was subjected directly to column chromatography (hexane/ether 3:1), furnishing (+)-**1** as a crude product. Further purification of this crude residue by column chromatography (hexane/CH_2Cl_2 1:1) afforded a pure sample (+)-obtusenyne **1** (1.2 mg, 51 %) as a colourless oil. R_f = 0.33 (hexane/CH_2Cl_2 1:1); $[\alpha]_D^{24}$ = +142.5 (c = 0.03 in $CHCl_3$) (lit.[13] $[\alpha]_D^{24}$ = +151 (c = 0.13 in $CHCl_3$)); ^{1}H NMR (500 MHz, 50 °C, C_6D_6): δ = 5.92 (dt, J(H,H) = 10.8, 7.3 Hz, 1H; CH_2CH=CH), 5.33–5.43 (m, 3H; CH_2CH=C*H*, 5-H, 6-H), 4.13–4.20 (m, 1H; 9-H), 3.90 (dt, J(H,H) = 10.8, 2.8 Hz, 1H; 3-H), 3.77 (dt, J(H,H) = 10.8, 3.0 Hz, 1H; 8-H), 3.68–3.74 (m, 1H; 2-H), 3.02 (ddt, J(H,H) = 14.2, 7.1, 1.2 Hz, 1H; C*H*HCH=CH), 2.92 (d, ^4J(H,H) = 2.0 Hz, 1H; C=CH), 2.87 (dt, J(H,H) = 14.7, 7.0 Hz, 1H; CH*H*CH=CH), 2.78–2.62 (m, 2H; 7-H, 4-H), 2.52 (ddd, J(H,H) = 12.9, 6.5, 3.0 Hz, 1H; 4-H′), 2.40 (ddd, J(H,H) = 13.2, 6.6, 2.9 Hz, 1H; 7-H′), 1.91 (dq, J(H,H) = 14.2, 7.4 Hz, 1H; C*H*HCH$_3$), 1.74 (dq, J(H,H) = 14.2, 7.4 Hz, 1H; CH*H*CH$_3$), 0.85 ppm (t, J(H,H) = 7.4, 1H; CH_2CH_3); ^{13}C NMR (125 MHz, 34 °C, C_6D_6): δ = 140.7 (CH_2CH=CH), 110.7 (CH_2CH=*C*H), 82.8 (C=CH), 80.1 (C=CH), 63.3 (8-C), 56.6 (3-C), 35.3 (*C*H$_2$CH=CH), 32.0 (7-C), 31.2 (4-C), 28.7 (*C*H$_2$CH$_3$), 10.1 ppm (CH_2CH_3); owing to the conformational mobility of the natural product the signals due to 6-C and C-13 were broadened to the baseline; signals assignable to C-9 and C-10 were obscured by solvent; IR (film): $\tilde{\nu}$ = 3290 cm^{-1}; MS (ES): m/z (%): 357 (25) $[M+Na]^+$, 355 (100) $[M+Na]^+$, 353 (80) $[M+Na]^+$; HRMS (ES): m/z: calcd for $C_{15}H_{20}ONa^{79}Br^{35}Cl$: 353.0278; found: 353.0278.

Acknowledgements

We thank the Royal Society for the award of University Research Fellowships (JWB, SIP), Universities UK and the Cambridge Commonwealth Trust (studentship to S.Y.F.M.), Merck Sharp & Dohme (CASE award to A.J.W.) and the EPSRC for generous financial support, including financial assistance towards the purchase of the Nonius CCD diffractometer and provision of the Swansea National Mass Spectrometry Service. We are grateful to Professor M.T. Crimmins for supplying spectroscopic data of (+)-**81** and (+)-**1**. We thank the ARC, VESKI and CSIRO for support.

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Received: October 5, 2007
Published online: January 29, 2008

