The Claisen rearrangement approach to fused bicyclic medium-ring oxacycles†‡§

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The synthesis of five fused-bicyclic medium-ring lactones carrying identical ring-fusion to that in the polyether toxins is described using an enolate hydroxylation, intramolecular hydrosilation, Claisen rearrangement sequence.

Introduction

The *trans*-fused polyether toxins, exemplified by the brevetoxins, are a growing class of natural products of marine origin.[1] Their diverse and potent biological activities coupled with their unprecedented molecular architectures have caught the imagination of the synthetic organic chemistry community. The total synthesis of brevetoxins A (**1**) and B (**2**) by Nicolaou[2,3] and co-workers stands as a landmark in modern total synthesis. Since these groundbreaking reports there have been a number of other total syntheses of, and approaches to, the "ladder toxins" which are summarised in a series of review articles.[4] Perhaps the greatest challenge for the synthesis of these molecules involves the construction of the fused medium-ring ethers, often embedded in the natural product core, and a large number of elegant methods have been invented and developed to synthesise these structural motifs. Our own approach to the synthesis of medium-ring ethers involves the synthesis of a medium-ring lactone *via* Claisen rearrangement of a ketene acetal,[5,6] and subsequent conversion of these lactones into the corresponding medium-ring ethers by a methylenation–hydrosilation sequence,[7] a strategy which we have successfully employed in the total synthesis of (+)-laurencin[8] and (+)-obtusenyne.[9] Herein we report the full details[10] of the extension of this methodology to the synthesis of five fused-bicyclic medium-ring lactones carrying identical ring-fusion to that found in the polyether toxins.

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§ The HTML version of this article has been enhanced with colour images.

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Strategy

Our strategy for the synthesis of fused bicyclic medium-ring lactones is shown in Scheme 1. Thus, the first-generation monocyclic medium-ring lactone **3** will be transformed into a 1,3-diol **4** by a methylenation–hydrosilation sequence. Transformation of the resultant 1,3-diol into a vinyl-substituted ketene acetal **5**, *via* selenoxide elimination or carbonate methylenation,[11] will provide the desired fused bicyclic medium-ring lactone **6** after Claisen rearrangement. The preparation of medium-ring lactones by conversion of a selenide into a vinyl-substituted ketene acetal followed by subsequent Claisen rearrangement was first reported by Petrzilka[12] for the preparation of a ten-membered lactone and subsequently developed by us,[8,9,13] and others,[14,15] for the synthesis of a number of medium-ring ether and lactone-containing natural products.

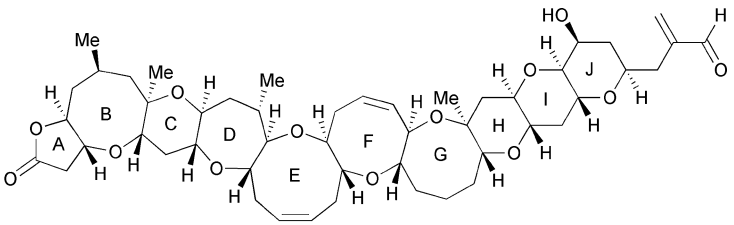
Results and discussion

Synthesis of three [6.6.0]-bicyclic lactones

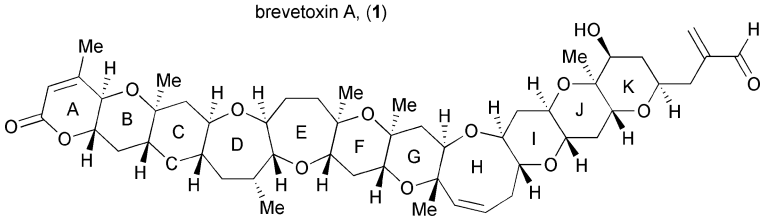
The conversion of the medium-ring lactones **7**, **8** and **9** into the corresponding [6.6.0]-bicyclic lactones was to follow a methylenation–hydrosilation sequence which we had previously developed for the synthesis of monocyclic medium-ring lactones.[7–9] The first task therefore involved the conversion of the medium-ring lactone into the corresponding *exo*-cyclic enol ether. We have used both the Tebbe reagent[16,17] and Petasis reagent (dimethyltitanocene)[18,19] to effect this transformation,[8,9] however, where possible, we favour the use of the Petasis reagent for the methylenation of medium-ring lactones because of its ease of preparation[20] and extended shelf-life.

Preparation of the [6.6.0]-bicyclic lactone 26

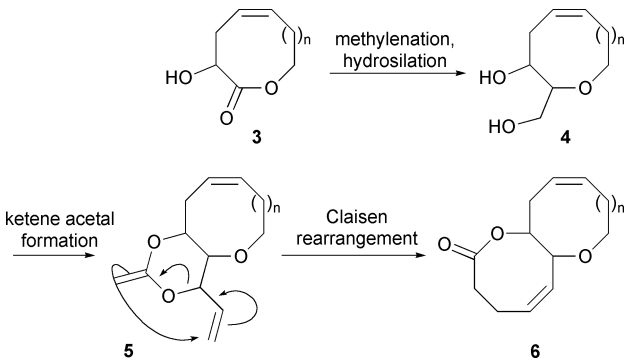
The lactone **7**[21] was efficiently converted into the *exo*-cyclic enol ether **10** on exposure to dimethyltitanocene[18] (71%) and the BOM protecting group was removed on treatment of **10** with LiDBB[22] giving **11** (94%) (Scheme 2). In our synthesis of (+)-laurencin[8] we had converted a similar eight-membered lactone (*ent*-**7** with TBPDS in place of TIPS) into the corresponding α-hydroxy enol ether using a four step procedure: replacement of the BOM group by a TMS ether (2 steps), methylenation of the lactone, removal of the TMS group.



brevetoxin A, (**1**)

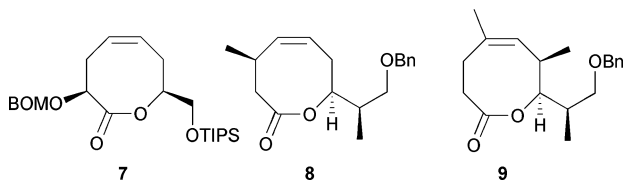


brevetoxin B, (**2**)



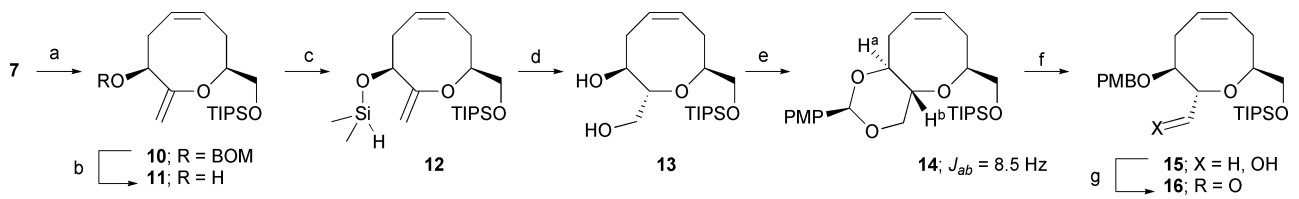
3 **4** **5** **6**

Scheme 1 Claisen rearrangement approach to bicyclic medium-ring lactones.



7 **8** **9**

We have frequently found that in order to completely remove the titanium residues from the methylenation of a medium-ring lactone with dimethyltitanocene, it is necessary to perform at least two chromatographic separations. The use of LiDBB to cleave the BOM group in **10** also acts to reduce any titanium residues remaining from the previous reaction, thereby facilitating purification of the α-hydroxy enol ether **11**. This enol ether was readily converted into the silane **12** in readiness for the key intramolecular hydrosilation reaction which would set the required *trans*-stereochemistry of the ring fusion. We have previously reported on the hydrosilation of a closely related silane (*ent*-**12**, with TBDPS in place of TIPS)[8] using platinum bis(1,3-divinyl-1,1,3,3-tetramethylsiloxane)[23] and had isolated the corresponding diols in good yield (86%) but with poor diastereocontrol. Moreover, larger scale hydrosilation reactions under these conditions had been capricious. We had also investigated the use of Wilkinson's catalyst in the hydrosilation of the same substrate, which had given the diols in low yield but with reasonable selectivity for the *trans*-diol. We were pleased to find that exposure of the silane **12** to a catalytic quantity of (bicyclo[2.2.1]hepta-2,5-diene)[1,4-(diphenylphosphino)butane]rhodium(I) tetrafluoroborate[24] followed by Tamao–Fleming oxidation,[25,26] delivered the desired *trans*-diol **13** as a single diastereomer in good yield. The stereochemistry of the *trans*-diol **13** was assigned by comparison with the spectroscopic data of a closely related *trans*-diol (*ent*-**13**, with TBDPS instead of TIPS)[8] and was proven by X-ray crystallography of a later intermediate. Monoprotection of the secondary alcohol in the diol **13** was achieved using a two step procedure. Exposure of the diol **13** to *p*-anisaldehyde and PPTS under Dean–Stark conditions in benzene at reflux provided the corresponding benzylidene acetal **14** in excellent yield (85%). The ^{1}H NMR coupling constant of the bridgehead protons H^a and H^b ($J_{a,b}$ = 8.5 Hz) confirmed that they were disposed *trans* to one another. Reduction of the benzylidene acetal **14** with DIBAL-H[27] in dichloromethane and toluene provided the mono-protected crystalline diol **15** in 80% yield. The advantages of using the robust



12 **13** **14**; J_{ab} = 8.5 Hz

Scheme 2 Synthesis of the aldehyde **16**. *Reagents and conditions:* (a) Cp_2TiMe_2, toluene, reflux, 71%; (b) LiDBB, THF, −78 °C, 94%; (c) $(Me_2SiH)_2NH$, NH_4Cl, 99%; (d) 3 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, 86%; (e) *p*-methoxybenzaldehyde, PPTS, benzene, reflux, 85%; (f) DIBAL-H, CH_2Cl_2, −50 → −30 °C, 80%; (g) IBX, Me_2SO, RT. BOM = benzyloxymethyl; TIPS = triisopropylsilyl; LiDBB = lithium di-*tert*-butylbiphenylide; IBX = *o*-iodoxybenzoic acid.

TIPS group to protect the primary alcohol were again evident in this transformation, as reduction of the corresponding TBDPS protected acetal (*ent*-**14**, with TBDPS instead of TIPS)[8] with DIBAL-H had resulted in extensive loss of the silicon protecting group with the desired product being isolated in only 51% yield. Recrystallisation of the alcohol **15** from hot hexane provided crystals suitable for X-ray analysis (mp 121–121.5 °C).‡ The X-ray crystal structure established the relative stereochemistry of **15**[28] and confirmed that the hydrosilation had occurred in the desired sense to provide the *trans*-diol **13** (Fig. 1). The primary alcohol in **15** was readily oxidised to the corresponding aldehyde **16** using IBX.[29]

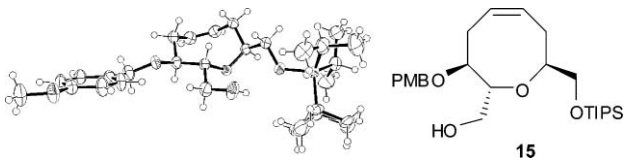


Fig. 1 X-Ray crystal structure of the alcohol **15** showing 50% probability ellipsoids.

The next stage in the synthetic plan involved the addition of a vinylmetal to the aldehyde **16**. Due to the possibility of epimerisation at C-2 in **16**, coupled with the possibility of elimination to provide the corresponding α,β-unsaturated aldehyde, it was deemed necessary to use a vinylmetal of low basicity. We had previously used Imamoto's organocerium reagents[30] to add a vinyl unit to a base sensitive aldehyde,[8] and this procedure proved to be successful with the aldehyde **16**. Thus, exposure of the aldehyde to a mixture of vinylmagnesium bromide and thoroughly dried cerium(III) chloride[31] provided the desired allylic alcohols **17** and **18** as a 5 : 1 mixture of diastereomers (Scheme 3). The major diastereomer **17** was readily crystallised from hot hexane and an X-ray crystal structure established the relative stereochemistry[28] (Fig. 2).‡ The X-ray structure of **17** (mp 99–100 °C) shows that the vinylmetal addition to the aldehyde **16** had occurred in accord with both the polar Felkin–Anh[32,33] and Cornforth[34,35] models for the addition of nucleophiles to α-chiral aldehydes,[36] and not surprisingly, that the conformation of the medium-ring was virtually identical to that of the primary alcohol **15** (Fig. 1).

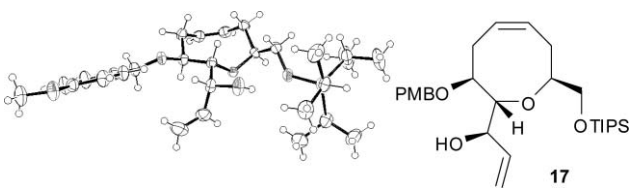
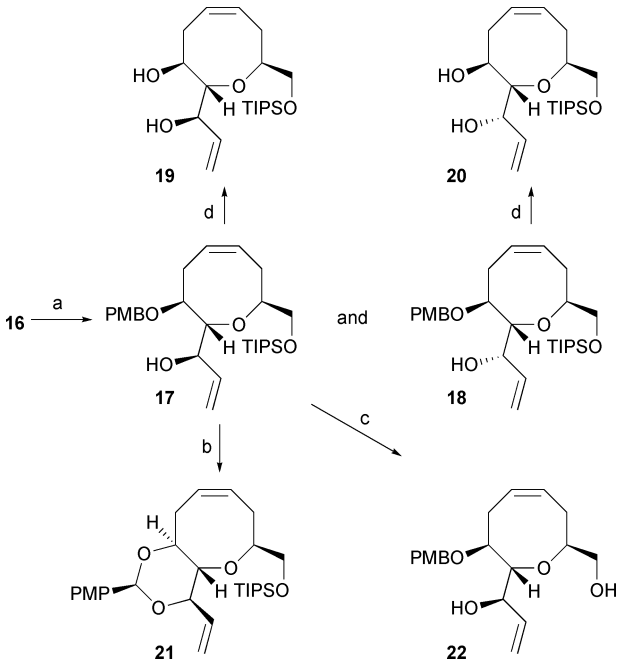


Fig. 2 X-Ray crystal structure of the allylic alcohol **17** showing 50% probability ellipsoids.

The next step required removal of the *p*-methoxybenzyl protecting group from **17**. The use of standard reagents such as DDQ or CAN to effect this transformation resulted in other reaction pathways. Attempted removal of the PMB group from the major diastereomer **17** using CAN resulted in isolation of the diol **22** in 86% yield where the triisopropylsilyl group instead of the PMB group had been removed.[37] Similarly, exposure of the allylic alcohol **17** to DDQ in wet dichloromethane did not result



Scheme 3 Formation of the allylic alcohols **19** and **20**. *Reagents and conditions:* (a) CH_2=CHMgBr, $CeCl_3$, THF, −78 °C → RT, **17** 74%, **18** 15%; (b) DDQ, CH_2Cl_2, water, 78%; (c) CAN, MeCN, water, 86%; (d) TFA, CH_2Cl_2, −20 °C, 90%. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; CAN = ammonium cerium(IV) nitrate; TFA = trifluoroacetic acid.

in removal of the PMB group, even after prolonged reaction times, but instead resulted in oxidation of the PMB group to provide the benzylidene acetal **21** (78%). Finally it was found that exposure of either of the pure diastereomers **17** or **18**, or a mixture of the two, to a solution of TFA in dichloromethane at −20 °C resulted in clean removal of the PMB group, with the diols **19** and **20** being isolated in excellent yield (90%) (Scheme 3).

Either of the diastereomeric diols **19** or **20** could be readily transformed into the corresponding selenoacetals on treatment with phenylselanylacetaldehyde diethyl acetal and catalytic PPTS in toluene at reflux (Scheme 4). The diol **19** provided the selenides **23** as a 13 : 1 mixture of diastereomers at the centre indicated. The major diastereomer **23maj** was assigned as having the $PhSeCH_2$ group in the less sterically demanding equatorial position on the basis of the upfield shift of the proton H* ($\delta_{H^*} = 4.83$) compared with the corresponding proton in the minor diastereomer ($\delta_{H^*} = 5.27$); axial protons on six-membered rings generally come into resonance at lower chemical shifts than the corresponding equatorial protons (Fig. 3).[38] The corresponding selenide **24** synthesised from the diol **20** was isolated as a single diastereomer, presumably with the $PhSeCH_2$ group in the thermodynamically more favourable equatorial position.

Oxidation of the selenides (**23** or **24**) with sodium periodate furnished the corresponding selenoxides, which on pyrolysis under reflux in xylene in the presence of DBU, provided the desired [6.6.0]-bicyclic lactone **26** in excellent yield. The stereochemistry at the ring fusion was readily confirmed to be *trans* by ^{1}H NMR coupling constant analysis (Scheme 4, $J_{a,b} = 9.2$ Hz). It also proved possible to synthesise the bicyclic lactone **26** from the carbonate **25**, which was prepared by exposure of the diol **19** to triphosgene in dichloromethane.[11,39] Treatment of the carbonate **25**

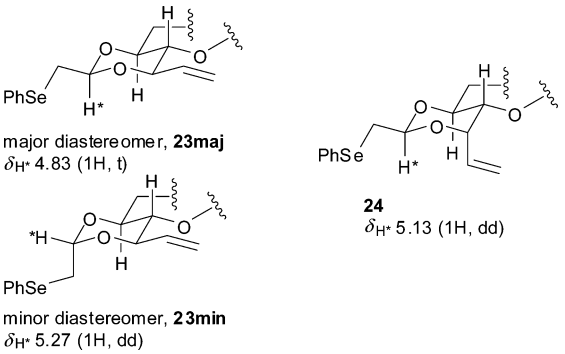
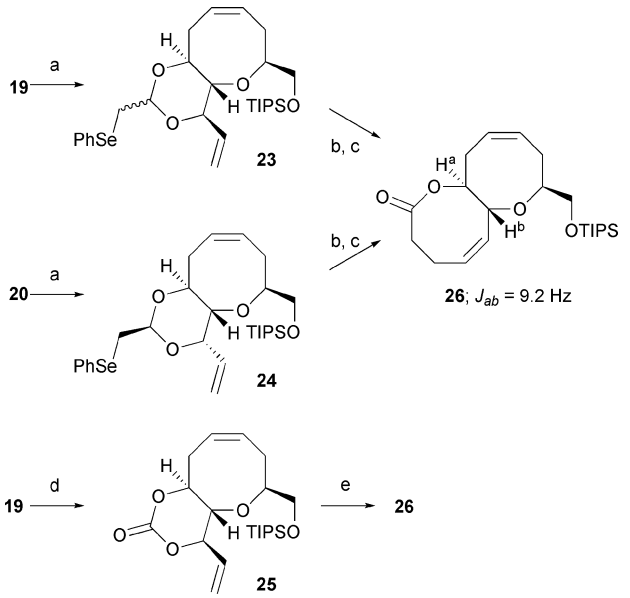


Fig. 3 Structures of the selenoacetals **23** and **24**.



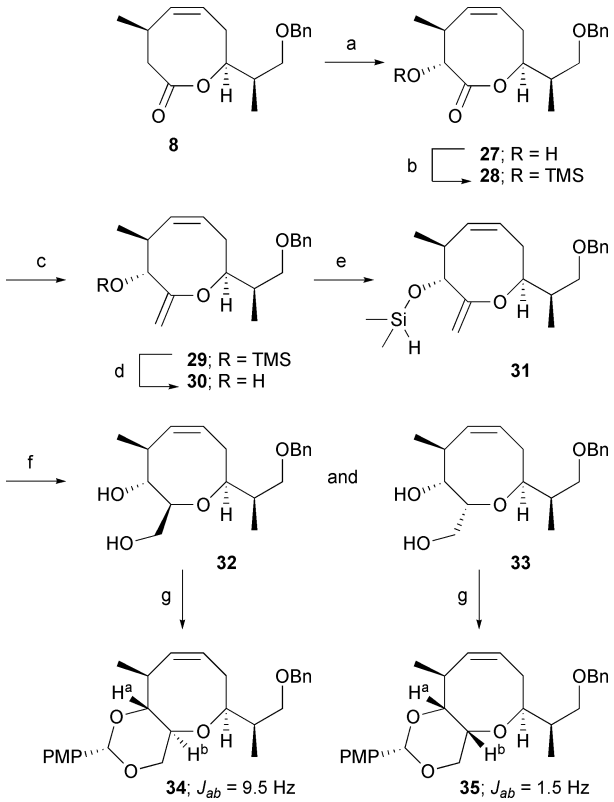
Scheme 4 Formation of the fused bicyclic lactone **26**. *Reagents and conditions:* (a) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 90% from **19**, 60% from **20**; (b) $NaIO_4$, CH_2Cl_2, MeOH, water, 100%; (c) DBU, xylene, reflux, 90% from **23** or **24**; (d) $(Cl_3CO)_2CO$, pyridine, Et_3N, CH_2Cl_2, −78 °C → RT, 89%; (e) Cp_2TiMe_2, toluene, reflux, 63%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

with dimethyltitanocene in toluene at reflux[11] provided the desired bicyclic lactone **26** in 63% yield.

Having established an efficient method for the annulation of an eight-membered lactone onto an existing medium-ring lactone, we sought to verify the generality of the method with the synthesis of a number of other bicyclic medium-ring lactones.

Preparation of the [6.6.0]-bicyclic lactone 40

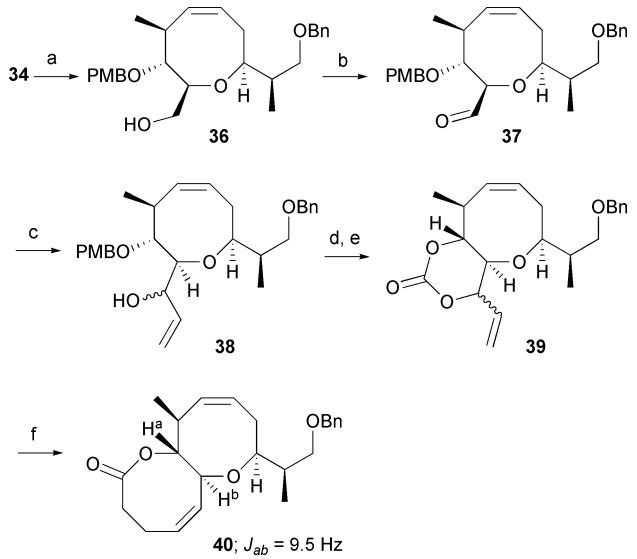
The synthesis of the remaining [6.6.0]-bicyclic lactones followed synthetic routes analogous to the one described above for the synthesis of **26** (Scheme 5). Thus, the lactone **8**[11] was converted into the α-hydroxy lactone **27** in excellent yield and as a single diastereomer, by oxidation of the derived potassium enolate with the Davis oxaziridine.[40] The α-hydroxy lactone was protected, methylenated, deprotected and silylated to give the dimethylsilane **31**. Hydrosilation of the enol ether **31** using the same catalyst as for the enol ether **12** delivered the diols (1.34 : 1, **32** : **33**) in reasonable yield (57%). The poor diastereoselectivity in the formation of



Scheme 5 Elaboration of the lactone **8**. *Reagents and conditions:* (a) KHMDS, toluene, −78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, then (±)-camphor-10-sulfonic acid, 91%; (b) Me_3SiCl, Et_3N, THF, 99%; (c) Cp_2TiMe_2, toluene, reflux, 2 h; (d) K_2CO_3, MeOH, 76% from **28**; (e) $(Me_2SiH)_2NH$, NH_4Cl, 98%; (f) 3 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, **32** 33%, **33** 24%; (g) *p*-methoxybenzaldehyde, PPTS, benzene, reflux, **34** 100%, **35** 100%.

the diols **32** and **33** was disappointing. Attempts to improve the proportion of the desired *trans*-diol **32** proved fruitless: conducting the hydrosilation in the presence of tetramethyldisilazane (which had previously been used to increase the proportion of *trans*-diol)[7] merely increased the proportion of the undesired *cis*-diol **33**, and using platinum bis(1,3-divinyl-1,1,3,3-tetramethylsiloxane)[23] gave the *cis*-diol **33** as the sole product after Tamao–Fleming oxidation.[25,26]

Conversion of both diols **32** and **33** into the corresponding *p*-methoxybenzylidene acetals **34** and **35** was readily achieved in quantitative yields and the stereochemistry of the ring junctions of the acetals **34** and **35** was determined using ^{1}H NMR coupling constant analysis (**34**, $J_{a,b}$ = 9.5 Hz; **35**, $J_{a,b}$ = 1.5 Hz). The *trans*-acetal **34** was elaborated to the [6.6.0]-bicyclic lactone **39** as illustrated in Scheme 6. Exposure of the acetal to DIBAL-H delivered the primary alcohol **36**[27] which was readily oxidised to the corresponding aldehyde **37** using IBX.[29] Exposure of the aldehyde **37** to vinylmagnesium bromide gave a complex mixture of degradation products. Disappointingly the use of the less basic organocerium reagent only returned the alcohol **36**. There is some precedent for the reduction of carbonyl substrates with certain organocerium reagents,[30] although in those examples, the organocerium compound is more usually aliphatic and contains



Scheme 6 Synthesis of the fused bicyclic lactone **40**. *Reagents and conditions:* (a) DIBAL-H, toluene, CH_2Cl_2, −78 → −5 °C, 90%; (b) IBX, Me_2SO, RT, 90%; (c) vinyl iodide, $CrCl_2$ (1% $NiCl_2$), Me_2SO, RT, 40%; (d) TFA, CH_2Cl_2, −20 °C, 75%; (e) triphosgene, Et_3N, pyridine, CH_2Cl_2, −78 → −10 °C, 90%; (f) Cp_2TiMe_2, toluene, reflux, 46%.

β-hydrogens which can eliminate with release of hydride (the reducing agent). This pathway is less likely for a vinylcerium reagent, and reduction in these cases may occur *via* a single electron transfer process.[30] Addition of a vinyl nucleophile to the aldehyde **37** was eventually achieved using the Nozaki–Hiyama–Kishi reaction.[41] Thus, exposure of a mixture of the aldehyde **37** and vinyl iodide to excess chromium(II) chloride (1% nickel(II) chloride) in dimethylsulfoxide, provided the desired allylic alcohols **38** in 40% yield as a 2 : 1 mixture of diastereoisomers. The stereochemistry of the diastereomers was assigned by ^{1}H NMR coupling constant analysis of later intermediates (the carbonates **39**). The major diastereomer has the (*R*)-stereochemistry at the newly installed stereocentre, which is consistent with both the polar Felkin–Anh[32,33] and Cornforth[34] models for the addition of nucleophiles to α-chiral aldehydes.

The allylic alcohols **38** were readily converted into the corresponding cyclic carbonates **39** by deprotection (TFA) followed by exposure of the resultant diols to triphosgene.[39] The relative stereochemistry of the two carbonates **39** was determined by ^{1}H NMR coupling constant analysis (Fig. 4) which consequently allowed the assignment of the relative stereochemistry of the allylic alcohols **38**. Exposure of the carbonates **39** to dimethyltitanocene in toluene at reflux[11] in the absence of light effected methylenation of the carbonyl group and subsequent Claisen rearrangement to afford the bicyclic lactone **40** in 46% yield. As before the ring-fusion stereochemistry was confirmed to be *trans* by ^{1}H NMR coupling constant analysis (Scheme 6, $J_{a,b} = 9.5$ Hz).

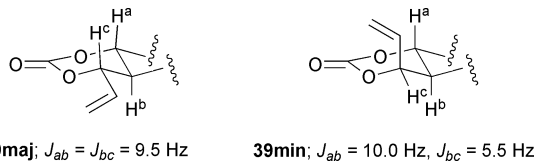
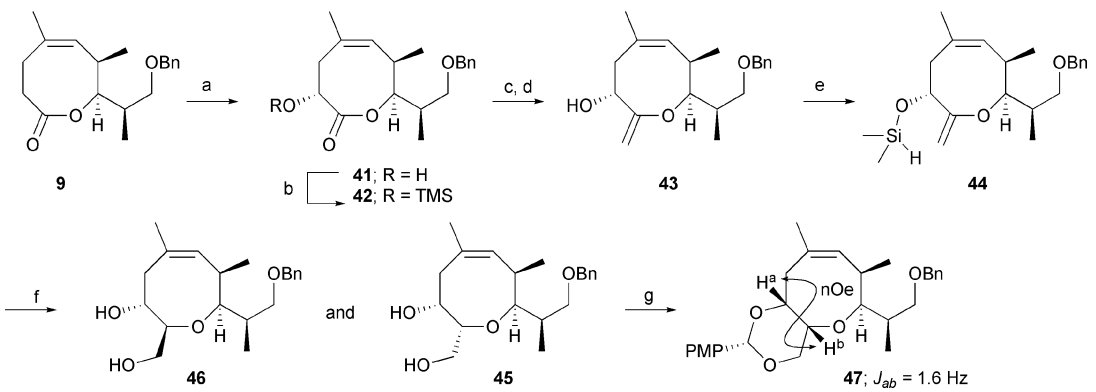


Fig. 4 Structures of the carbonates **39**.

Preparation of the [6.6.0]-bicyclic lactone 54

The final [6.6.0]-bicyclic lactone was synthesised in an analogous manner to the previous two, beginning from the lactone **9**.[11] Formation of the potassium enolate of the lactone **9** (KHMDS) in toluene followed by the addition of three equivalents of the Davis oxaziridine[40] delivered the desired α-hydroxy lactone **41** in 88% yield as a 20 : 1 mixture of diastereomers as judged by ^{1}H NMR (Scheme 7). After extensive purification by repeated flash chromatography the major diastereomeric α-hydroxy lactone **41** was isolated pure as a white crystalline solid (mp 102–104 °C). The relative stereochemistry of the major diastereomer was proven by X-ray crystal structure analysis and the X-ray structure is shown in Fig. 5.[28]‡ The α-hydroxy lactone **41** was converted into the dimethylsilane **44** in readiness for the hydrosilation reaction.

Treatment of the silane **44** with the previously used cationic rhodium catalyst followed by Tamao–Fleming oxidation[25,26] delivered the corresponding diols **45** and **46** isolated as a 6.4 : 1 mixture of inseparable diastereomers. The mixture of diols was readily converted into the corresponding *p*-methoxybenzylidene



Scheme 7 Preparation of the diols **45** and **46**. *Reagents and conditions:* (a) KHMDS, toluene, −78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, then (±)-camphor-10-sulfonic acid, 88%; (b) Me_3SiCl, Et_3N, THF, 86%; (c) Cp_2TiMe_2, toluene, reflux, 98%; (d) K_2CO_3, MeOH, 87%; (e) $(Me_2SiH)_2NH$, NH_4Cl, 99%; (f) 3 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, 61%, 6.4 : 1 mixture of **45** : **46**; (g) *p*-methoxybenzaldehyde, PPTS, benzene, reflux, 81% from mixture of **45** and **46**.

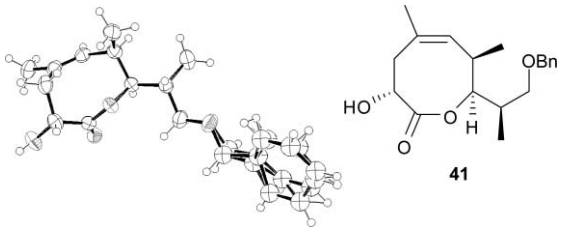


Fig. 5 X-Ray crystal structure of the α-hydroxy lactone **41** showing disorder in the benzyl group (50% probability ellipsoids).

acetals from which the major diastereomer **47** could be isolated in 81% yield.

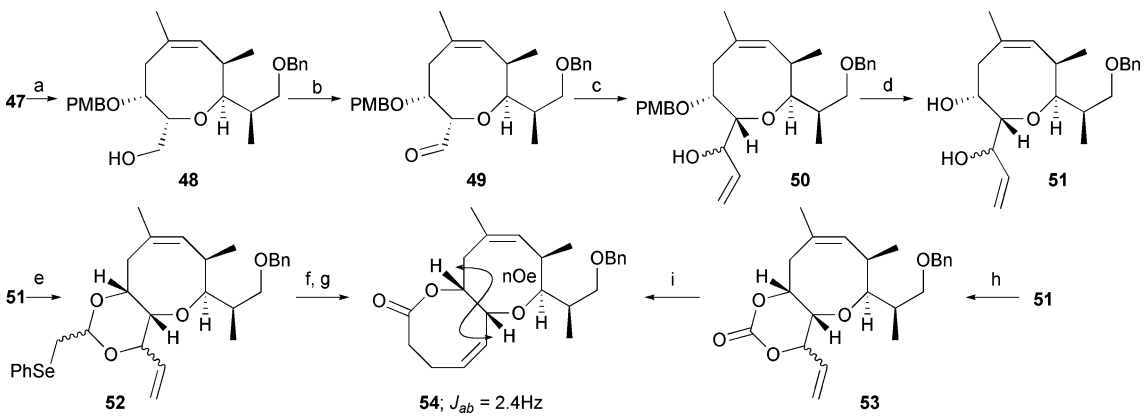
The room temperature ^{1}H NMR spectrum (400 MHz) of **47** contained a number of broad peaks, while the room temperature ^{13}C NMR spectrum (100 MHz) of **47** was missing a number of key resonances. This indicated that the acetal existed as an interconverting mixture of conformers which were in intermediate exchange on the NMR timescale. A number of spectra were taken at varying temperatures (see ESI†) and the stereochemistry of the bridgehead protons could be assigned as *cis* on the basis of ^{1}H NMR (55 °C, $CDCl_3$) coupling constant analysis (Scheme 7, $J_{a,b} = 1.6$ Hz). The *cis* ring fusion in **47** was further verified by the observation of a large ^{1}H NMR nOe between these protons. As before the *p*-methoxybenzylidene acetal **47** was cleaved with DIBAL-H[27] and the released primary alcohol **48** was oxidised[29] to the corresponding aldehyde **49** (Scheme 8). Addition of the vinylcerium reagent[30] derived from vinylmagnesium bromide and thoroughly dried cerium(III) chloride[31] to the aldehyde **49** gave the allylic alcohols **50** as a 3 : 1 mixture of diastereomers. The *p*-methoxybenzyl protecting group was then cleaved as before using TFA. The resultant diols **51** were converted into the corresponding selenoacetals **52** as a mixture of one major and two minor diastereomers; the full stereochemistry of the selenoacetals was not assigned. The selenoacetals **52** were oxidised to the corresponding selenoxides, which were heated in xylene in the presence of DBU to deliver the bicyclic lactone **54** in 60% yield. The diols **51** could also be converted into the corresponding carbonates,[39] which on heating with dimethyltitanocene[11] in toluene delivered the same bicyclic lactone **54** in 47% yield. Akin to several intermediates in the above synthetic sequence, the ^{1}H NMR spectrum of **54** measured at 27 °C contained many broad unidentifiable peaks, while the ^{13}C NMR spectrum was found to be missing several carbon peaks. This problem was again easily solved by measuring both spectra above 50 °C, affording mostly distinct sharp peaks in the ^{1}H NMR spectrum and all of the expected carbon resonances in the ^{13}C NMR spectrum (see ESI†). The *cis*-ring fusion of **54** was confirmed by ^{1}H NMR nOe and coupling constant analysis (Scheme 8, $J_{a,b} = 2.4$ Hz).

Synthesis of the [7.6.0]-bicyclic lactones

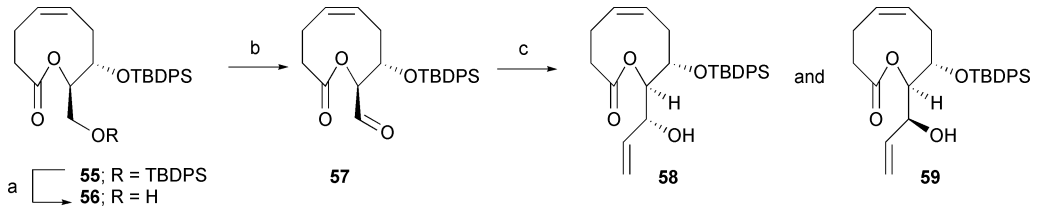
Synthesis of the dilactone 63

The synthesis of the first of the two [7.6.0]-bicyclic lactones began with the nine-membered lactone **55**, a literature compound that is readily available from 2-deoxy-D-ribose.[11,42] Monodeprotection of the lactone **55** using the conditions initially described by Congreve[42] (HF·pyridine, pyridine, THF in glassware) proved capricious. However, when the reaction was executed in a polypropylene vessel a reproducibly high yield of the alcohol **56** could be obtained (80%) (Scheme 9). Oxidation of the alcohol **56** was readily achieved using the procedure of Swern *et al*.[43] to provide **57**. For the next step in the synthetic sequence it was necessary to introduce a vinylmetal equivalent which would react chemoselectively with the aldehyde in the presence of the lactone, and we elected to use the Nozaki–Hiyama–Kishi reaction[41] for this purpose. Addition of vinyl bromide to the aldehyde **57** in the presence of $CrCl_2$ containing 1% $NiCl_2$ provided the desired allylic alcohols **58** and **59** as a 1 : 2 mixture of diastereomers. X-Ray crystal structure analysis of later intermediates (the lactone **61** and the carbonate **62**) indicated that the addition of the vinylchromium species onto the aldehyde **57** had occurred according to both the polar Felkin–Anh[32,33] and Cornforth[34] models. Vinyl iodide could also be used in the above addition process with no detriment to the yield.

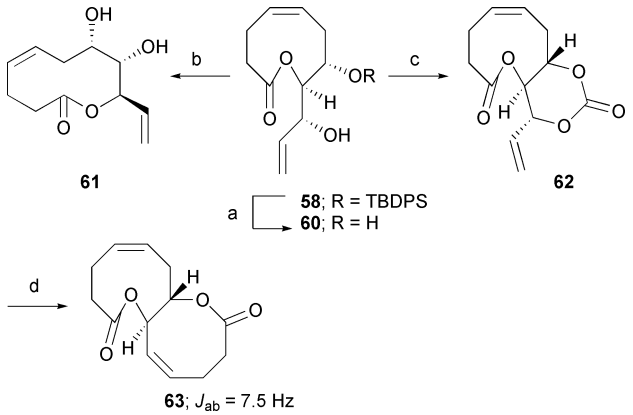
Desilylation of the lactone **58** using HF·pyridine occurred in reasonable yield to provide the nine-membered diol **60** (71%) (Scheme 10). The quenching procedure for this reaction proved to be important for the attainment of high yields of **60**. Quenching



Scheme 8 Synthesis of the bicyclic lactone **54**. *Reagents and conditions:* (a) DIBAL-H, CH_2Cl_2, −78 → −5 °C, 97%; (b) IBX, Me_2SO, RT, 100%; (c) CH_2=CHMgBr, $CeCl_3$, THF, −78 °C → RT, 80%, 3 : 1 mixture of diastereomers; (d) TFA, CH_2Cl_2, −15 °C, 86%; (e) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 97%; (f) $NaIO_4$, CH_2Cl_2, MeOH, water, 100%; (g) DBU, xylene, reflux, 60%; (h) triphosgene, Et_3N, pyridine, CH_2Cl_2, −78 → −10 °C, 81%; (i) Cp_2TiMe_2, toluene, reflux, 47%.



Scheme 9 Synthesis of the allylic alcohols **58** and **59**. *Reagents and conditions:* (a) HF·pyridine, pyridine, THF, 80%; (b) $(COCl)_2$, Me_2SO, **55**, −78 °C then Et_3N, −78 °C → RT, 78%; (c) vinyl bromide, $CrCl_2$ (1% $NiCl_2$), Me_2SO, RT, 63%.



Scheme 10 Synthesis of the bicyclic dilactone **63**. *Reagents and conditions:* (a) HF·pyridine, pyridine, THF, 71%; (b) HF MeCN; (c) triphosgene, Et_3N, pyridine, CH_2Cl_2, −78 °C → RT, 78%; (d) Cp_2TiMe_2, toluene, reflux, 31%.

the reaction with either aqueous sodium bicarbonate or aqueous hydrochloric acid resulted in the isolation of significant quantities of the ten-membered lactone **61**. However, quenching the reaction with water followed by washing with aqueous copper(II) sulfate provided solely the nine-membered diol **60** in acceptable yield. When the deprotection of the silylether **58** was attempted with aqueous HF in acetonitrile the ten-membered diol **61** was the sole product.

The ten-membered diol **61** was isolated as a white crystalline solid that provided crystals suitable for X-ray analysis after recrystallisation from hexane and ether (mp 112–114 °C). The X-ray crystal structure (Fig. 6) established the relative stereochemistry of **61**[28] and confirmed that the addition of the vinylmetal species to the aldehyde **57** had occurred in accord with both the polar Felkin–Anh and Cornforth models.[32–35]‡ We have noted this ring expansion previously,[13,42] and it is likely driven by the release of strain when moving from a nine-membered lactone to a ten-membered lactone.[44] Due to the ease of this ring expansion, the formation of the carbonate **62** was approached with some concern. In the event, exposure of the diol **60** to triphosgene, triethylamine and pyridine provided the desired carbonate **62** in good yield (78%). The carbonate **62** was isolated as a white crystalline solid which was recrystallised from hexane (mp 126–127 °C) and provided crystals suitable for X-ray analysis. The X-ray crystal structure confirmed the relative stereochemistry of **62** (Fig. 7)[28] and established that no undesired ring expansion had occurred under the reaction conditions.‡

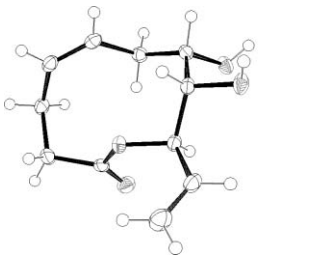


Fig. 6 X-Ray crystal structure of the lactone **61** showing 50% probability ellipsoids.

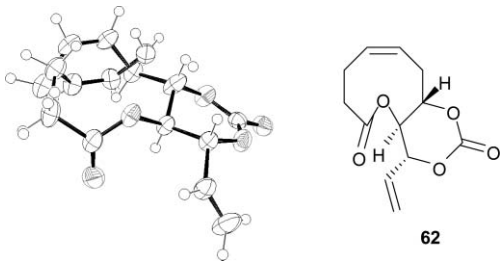


Fig. 7 X-Ray crystal structure of the carbonate **62** showing disorder in the medium ring (50% probability ellipsoids).

Exposure of the carbonate **62** to dimethyltitanocene in toluene at reflux[11] provided the dilactone **63** as a white crystalline solid (31%, mp 109–111 °C). The mass-balance from this reaction was made up of material possessing the [7.6.0]-bicyclic skeleton with either one of the lactone carbonyl groups having been competitively methylenated. Recrystallisation of the dilactone **63** from hot hexane provided crystals suitable for X-ray analysis which established the relative stereochemistry (Fig. 8).[28]‡ Attempted synthesis of the corresponding selenoacetals from the nine-membered lactone **60** under our standard conditions [$PhSeCH_2CH(OEt)_2$, PPTS] resulted in the formation of a myriad of products most probably due to translactonisation of **60** under the reaction conditions and subsequent formation of acetals from both the nine- and ten-membered lactones **60** and **61**.

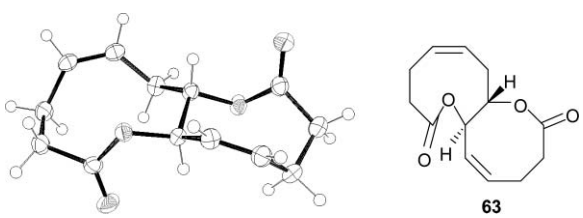
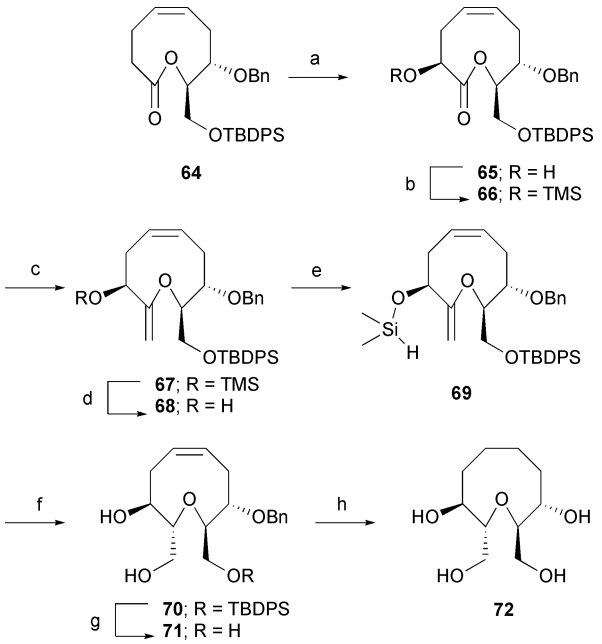


Fig. 8 X-Ray crystal structure of the dilactone **63** showing 50% probability ellipsoids.

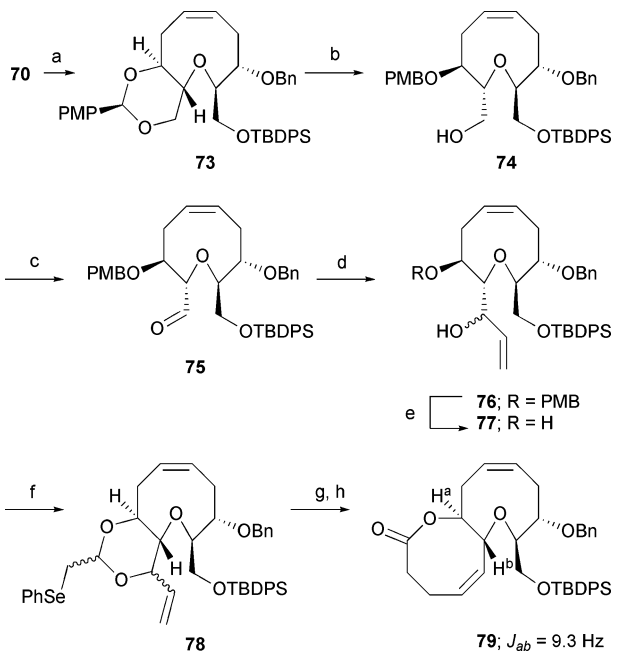
Synthesis of the [7.6.0]-bicyclic lactone 79

The second [7.6.0]-bicyclic lactone was synthesised beginning with the related nine-membered lactone **64** prepared in a similar manner from 2-deoxy-D-ribose.[11,42] The lactone **64** was converted into the α-hydroxy lactone **65** by oxidation of the derived potassium enolate with the Davis oxaziridine[40] to give the product **65** in good yield as a single diastereomer (Scheme 11). The stereochemistry of the newly introduced hydroxy group was confirmed on a later intermediate and was in keeping with the selectivity observed for the α-oxidation of a closely related nine-membered lactone which we used in our recent synthesis of obtusenyne.[9] Surprisingly the enolate oxidation was very sensitive to the nature of the protecting groups on the hydroxy and hydroxymethyl groups adorning the nine-membered lactone. The bis-TBDPS-protected lactone **55** was completely unreactive under these reaction conditions whereas the corresponding bis-TES-protected lactone (**55** with TES in place of TBDPS) was readily hydroxylated under the same conditions as for the lactone **64**.



Scheme 11 Synthesis of the diol **70**. *Reagents and conditions:* (a) KHMDS, toluene, −78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, then (±)-camphor-10-sulfonic acid, 78%; (b) Me_3SiCl, Et_3N, THF, 87%; (c) Cp_2TiMe_2, toluene, reflux; (d) K_2CO_3, MeOH, 60% from **65**; (e) $(Me_2SiH)_2NH$, NH_4Cl, 100%; (f) 3 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, 61%; (g) HF·pyridine, pyridine, THF, 97%; (h) H_2, Pd/C, EtOH, 88%.

The α-hydroxy lactone **65** was converted into the silane **69** in readiness for the intramolecular hydrosilation reaction. Exposure of the silane **69** to catalytic (bicyclo[2.2.1]hepta-2,5-diene)[1,4(diphenylphosphino)butane]rhodium(I) tetrafluoroborate followed by Tamao–Fleming oxidation[25,26] gave the *trans*-diol **70** exclusively after oxidation as well as returning some of the enol ether **68** (Scheme 11). All efforts to improve this yield have so far failed. The enol ether **68** is most probably formed from oxidative cross-coupling of the silane **69** with loss of dihydrogen followed by deprotection of the so formed disilane on work up; a known side reaction in hydrosilation reactions.[45] The structure of the diol **70** was established by using the latent C_2 symmetry of the molecule. Deprotection of the silyl group in **70**, giving **71**, followed by hydrogenolysis of the benzyl group and hydrogenation of the alkene provided the tetrol **72** in excellent yield. The ^{13}C NMR spectrum of **72** contained only five resonances indicating that it was either C_2 or C_S-symmetric. However, the tetrol **72** had a non-zero optical rotation {$[\alpha]_D^{20}$ +26 (*c* 0.05 in EtOH)} and therefore must be C_2-symmetric having the structure indicated. The diol **70** was converted into the corresponding *p*-methoxybenzylidene acetal **73**, which was reduced with DIBAL-H[27] to provide the desired primary alcohol **74** in low yield (45%) along with the diol corresponding to loss of the silyl group from **74** (Scheme 12). This side reaction has been noted in other systems[8] and may be avoided by the use of the TIPS protecting group (see above). The primary alcohol **74** was oxidised (IBX)[29] to the corresponding aldehyde **75** and addition of vinylmagnesium bromide provided the allylic alcohols **76** as a 6 : 1 mixture of diastereomers in excellent yield. Deprotection of the mixture of diastereomers with TFA provided a separable mixture of diols **77** (88%). The major diastereomer was converted into the selenides **78** which were oxidised with sodium periodate to the corresponding selenoxides. Pyrolysis of the selenoxides in toluene at reflux provided the bicyclic lactone **79** in good yield. The stereochemistry across the ring fusion was once again confirmed as being *trans* by ^1H NMR coupling constant analysis (Scheme 12, $J_{a,b} = 9.3$ Hz).



Scheme 12 Synthesis of the bicyclic lactone **79**. *Reagents and conditions:* (a) *p*-methoxybenzaldehyde, PPTS, benzene, reflux, 80%; (b) DIBAL-H, CH_2Cl_2, −78 → −30 °C, 45%; (c) IBX, Me_2SO, RT, 100%; (d) CH_2=CHMgBr, THF, 0 °C, 94%, 6 : 1 mixture of diastereomers; (e) TFA, CH_2Cl_2, −20 °C, 88%; (f) $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 91%; (g) $NaIO_4$, CH_2Cl_2, MeOH, water; (h) DBU, toluene, reflux, 73% from **77**.

Discussion

The general procedure for the annulation of an eight-membered lactone onto a medium-ring lactone follows an enolate oxidation, hydrosilation, Claisen rearrangement route. During the course of these studies and in the synthesis of both (+)-obtusenyne[9] and (+)-laurencin[8] we have investigated the intramolecular hydrosilation of a number of medium-ring *exo*-cyclic enol ethers. Due to the complexity of the systems, we are currently unable to predict with any certainty what the diastereoselectivity of this process will be. Nevertheless, it is generally the case that either the *cis*- or the *trans* diol can be selected as the major product from the reaction after screening a number of catalysts and reaction conditions.

The annulated medium-ring lactones are all formed by Claisen rearrangement of the corresponding ketene acetals, which, in turn, are prepared by selenoxide elimination or methylenation of a cyclic carbonate. We,[11] and others,[46–48] have previously demonstrated that it is possible to perform chemoselective methylenations of carbonyl groups using titanium-based reagents. The yields for the synthesis of the bicyclic lactones *via* methylenation of a carbonate and subsequent Claisen rearrangement, and for the formation of monocyclic medium-ring lactones *via* an analogous route, demonstrate that methylenation of a cyclic carbonate with dimethyltitanocene is frequently faster than methylenation of an ester[13] or a medium-ring lactone. The methylenation of carbonyl groups with the Petasis reagent has been demonstrated to occur *via* formation of a titanium carbene.[49,50] The chemoselectivity observed in the preferential methylenation of a six- or seven-membered ring cyclic carbonate over an acetate or medium-ring lactone, may relate to the nucleophilicity of the lone pairs of the carbonyl group oxygen atom, which presumably coordinate to the titanium carbene to initiate the methylenation process. Wiberg and Waldron[51] have studied the basicities of a number of esters and lactones as well as that of diethyl carbonate. Furthermore, they have shown that the rate of reaction of a set of carbonyl compounds with triethyloxonium tetrafluoroborate follows the order: valerolactone (fastest), butyrolactone, diethyl carbonate and ethyl acetate (slowest), which mirrors the basicities of these compounds towards triethyloxonium tetrafluoroborate.[51] They conclude that (*E*)-esters are more basic than (*Z*)-esters from dipole–dipole interaction arguments. From their work it is reasonable to assume that six- and seven-membered cyclic carbonates would be more basic than diethyl carbonate. Huisgen and Ott[52] have reported that eight- and nine-membered lactones exist as an equilibrium mixture of (*Z*)- and (*E*)-forms whereas ten-membered lactones adopt the (*Z*)-configuration; a search of the Cambridge Crystallographic Data Centre (CCDC) confirms that eight- and nine-membered lactones can exist in either (*E*)- or (*Z*)-forms whereas ten-membered lactones invariably adopt the (*Z*)-form. Since diethyl carbonate is more basic than (*Z*)-esters[51] the chemoselective methylenation of a carbonate in the presence of an enol-acetate[13] is readily accounted for. The chemoselectivity in the methylenation of a carbonate in the presence of a medium-ring lactone may be related to the (*E*) : (*Z*)-conformer ratio of the lactone, and may therefore account for the moderate yields sometimes encountered in the formation of medium-ring lactones derived from methylenation and subsequent Claisen rearrangement of the corresponding cyclic carbonates.

Conclusion

We have developed a procedure for the annulation of an eight-membered lactone onto an existing medium-ring lactone which utilises an enolate oxidation, enol ether hydrosilation, Claisen rearrangement sequence. The preparation of five fused-bicyclic medium-ring lactones containing the precise structural features present in the medium-ring fused polyether segments of brevetoxin A and ciguatoxin has been achieved.

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