Synthetic studies towards garsubellin A: synthesis of model systems and potential mimics by regioselective lithiation of bicyclo[3.3.1]nonane-2,4,9-trione derivatives from catechinic acid†

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Bridgehead lithiations have successfully been carried out on substrates derived from catechinic acid, which possess the core bicyclo[3.3.1]nonane-1,3,5-trione structure present in garsubellin A. Using an external quench method, various electrophiles have been incorporated at the C-5 bridgehead position in a one-step process that appears to be sensitive to the substitution pattern on the bicyclic system. Regioselective lithiation at the C-3 sp^2 centre was achieved by changing the base used from LDA to LTMP. Following the introduction of a prenyl substituent by bridgehead substitution, annulation of a THF ring, analogous to that in garsubellin A, was possible *via* an epoxidation–ring opening sequence. Oxidative modification of the catechol substituent of the catechinic acid core was possible to give systems with muconic acid, *ortho*-quinone or furan 2-carboxylic acid side chains.

Introduction

The natural products known as polyprenylated acylphloroglucinols (PPAPs) have emerged as an important class of compounds due to their broad range of biological activities.[1] These compounds, isolated from various plants and trees from the family Clusiaceae, are characterised by the presence of a common bicyclo[3.3.1]nonane-1,3,5-trione core, decorated with prenyl (or geranyl) and acyl groups. Important examples include garsubellin A, hyperforin and clusianone, Fig. 1.

These challenging structures, together with promising therapeutic potential have made these molecules attractive targets for total synthesis.[2] As a result, a number of research groups have described synthetic approaches to these compounds, and recently garsubellin A (**1**) has succumbed to total synthesis by the groups of Shibasaki, and Danishefsky.[3,4]

We recently described the first total synthesis of clusianone (**3**),[5] and also a formal synthesis of garsubellin A.[6] This work, inspired by a previous approach of Spessard and Stoltz,[7] employed a malonyl dichloride (**5**) annulation (Effenberger cyclisation)[8] of a cyclohexanone-derived enol ether **4** to set up the [3.3.1] trione core structure **6**, Scheme 1. Subsequent elaboration to the target natural product was then possible by regioselective metallation–substitution reactions at both the bridgehead C-5 and C-3 sp^2 hybridised positions.

Although this approach enabled a rapid access to clusianone, and has the potential to deliver other PPAPs, it has a number of deficiencies. First and foremost is the consistently modest efficiency of the type of annulation shown in Scheme 1 which, at least in our hands, rarely provides more than 25–30% yields.[9] Secondly, and in line with most other synthetic work in this area, the method has provided only racemic intermediates to date.[10]

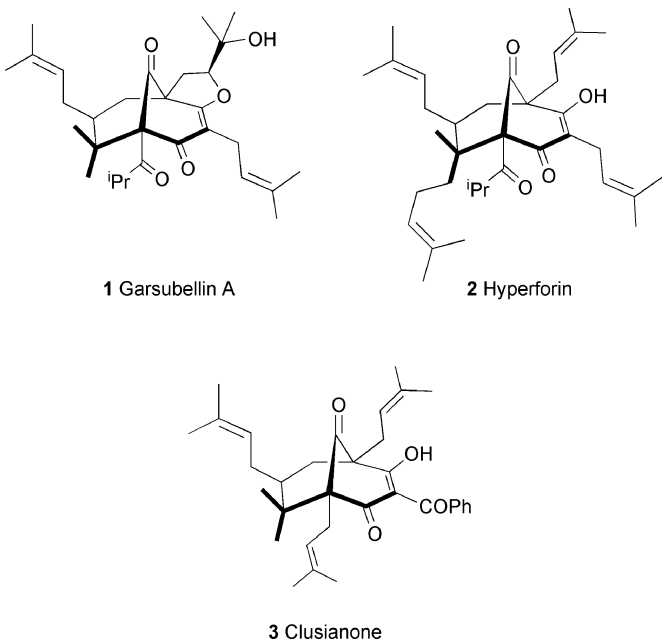

Fig. 1 Representative PPAP natural products.

In parallel with our synthetic investigations summarised above, we also surveyed the literature for alternative promising entries to enantiopure starting materials for PPAP synthesis. We identified a little-known, and remarkable, rearrangement of the naturally occurring, readily available, flavanoid (+)-catechin (**7**) into the bicyclo[3.3.1]nonane-1,3,5-trione derivative catechinic acid (**8**) under alkaline conditions (Scheme 2).[11]

Reported over thirty years ago by Sears *et al.* this highly stereoselective transformation has not attracted much interest

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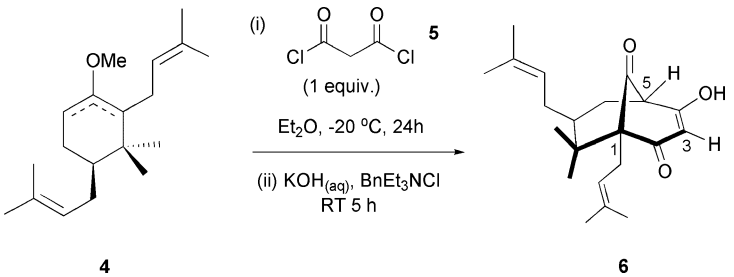
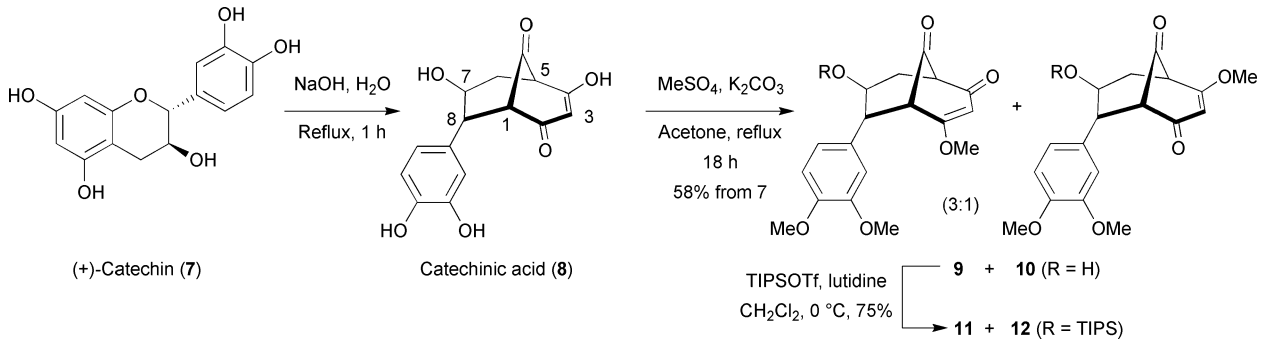
† Electronic supplementary information (ESI) available: Experimental procedures and/or full spectroscopic data for compounds **19–26**, **32–42**, **44**, **46–50**. See DOI: 10.1039/b704311b



Scheme 1 Access to the [3.3.1] core *via* Effenberger annulation.



Scheme 2 Preparation and protection of catechinic acid.

since. For our purpose, catechinic acid (**8**) constituted a promising, enantiopure entry into the bicyclic core of PPAP type structures, and might even constitute a chiral pool starting material for natural products such as garsubellin A.

As a prerequisite to a synthetic study towards **1** using **8** as a template, two key issues needed to be addressed: (i) the introduction of appropriate substituents at both bridgehead positions C-1 and C-5, as well as at position C-3; (ii) the conversion of the catechol ring at position C-8 of **8** into the *gem*-dimethyl group present in **1**.

The solution to the substitution problems at C-1, C-3 and C-5 were explored in parallel to our studies using the Effenberger derived materials (Scheme 1). In this regard the catechinic acid derived bicyclic systems could function as useful, and readily available, model systems to probe the scope and regiocontrol of substitution chemistry. Clearly, if the catechinic acid system was to provide access to the natural products themselves then degradation of the C-8 catechol unit was a key issue. In this regard the oxidative degradation of an aromatic ring into a carboxylic acid derivative is a well known transformation.[12] In turn, a C-8 carboxylic function would allow introduction of the desired *gem*-dimethyl through a methylation–reduction sequence. In order to address these issues, a systematic study was initiated on suitably protected derivatives of **8**.

In this paper we describe in full detail our results concerning the bridgehead substitution of catechinic acid derivatives through the selective formation of bridgehead enolates. Also reported is the selective introduction of various substituents at the C-3 sp^2 position of **8**. Additionally, the formation of the THF ring present in **1** is reported starting with a prenylated derivative, involving an epoxidation–ring opening sequence. Finally, some interesting results obtained by the oxidative degradation of the aromatic moiety of intermediates derived from **8** are described.

Results and discussion

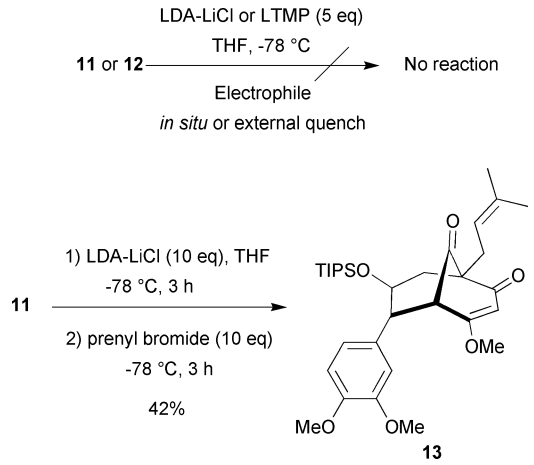
(i) Regioselective bridgehead substitution

Our study began with the protection of the acidic residues present in catechinic acid (**8**). Following literature precedent, methylation under basic conditions afforded regioisomers **9** and **10** in 58% overall yield from **7** (Scheme 2). The mixture of secondary alcohols was then treated with TIPSOTf and lutidine to afford the corresponding silylated vinylogous ester derivatives **11** and **12** in 75% yield (3 : 1 ratio), which were separated by column chromatography.

With suitable substrates in hand, initial studies of bridgehead substitution reactions were undertaken. Initial attempts to deprotonate major regioisomer **11** using excess LDA or LTMP (1 to 5 eq.) in THF at −78 °C in the presence of Me_3SiCl (*in situ* quench) failed to give any silylated product and starting material was recovered, Scheme 3.

Although previously this *in situ* quench technique had proved highly effective for bridgehead silylation of various substrates,[13] it proved singularly unsuccessful in this case, starting with either regioisomer **11** or **12**. Similar lack of product formation was also observed when more conventional external quenching reactions were attempted, using similar excess of base at low temperature for up to 3 hours, followed by addition of D_2O, or reactive alkyl halides. After some experimentation under these external quench conditions, we found that increasing the amount of LDA to 10 equivalents allowed the bridgehead deprotonation of **11** to occur, and after a quench with prenyl bromide, derivative **13** was isolated in 42% yield, Scheme 3.

Despite this preliminary success, the modest yield of **13** obtained, together with the fact that the reaction was less effective



Scheme 3 Initial metallation attempts.

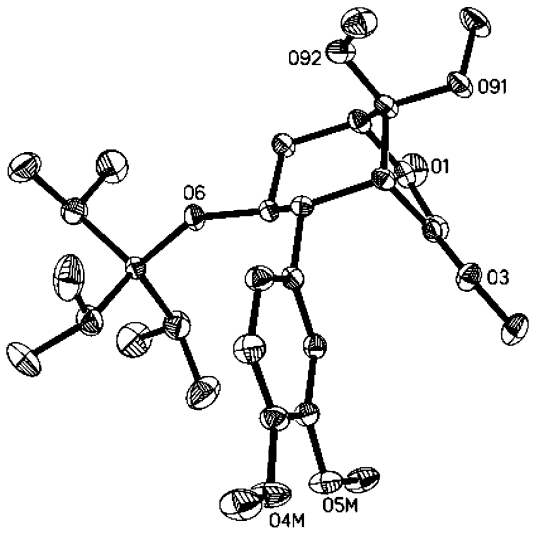


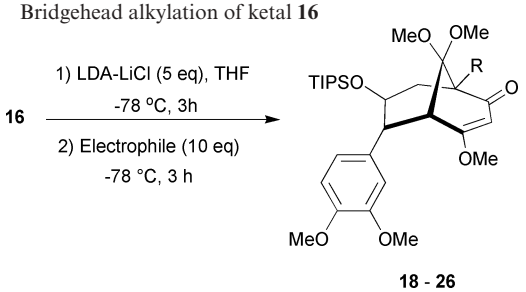
Fig. 2 X-Ray structure of **16** (ellipsoids are shown at 50% probability).

with a number of other electrophiles, prompted us to modify the structures of our substrates in order to make bridgehead lithiation more facile. We were interested to probe the effect of modifying the bridging ketone, especially since reduction or protection could generate slightly less rigid structures that might better accommodate the 'bridgehead enolate' character of the reactive intermediate. The first modification tested was to convert the bridgehead ketone into the corresponding dimethylketal. Thus, under acidic conditions, ketones **9** and **10** were converted into intermediate ketals, and the secondary alcohols were then directly silylated as previously described to afford the regioisomeric ketals **16** and **17** (Scheme 4).

We were able to clarify any regiochemical ambiguity as X-ray crystallography confirmed the structure of the major isomer **16** (Fig. 2).

Further studies focused on the lithiation of the major regioisomeric ketal **16**. As observed with ketone **11**, the use of an excess of LDA or LTMP under *in situ* quench conditions with various electrophiles failed to give any bridgehead substituted products when using ketal **16**. In contrast, the use of 5 equivalents of LDA–LiCl under external quench conditions (Scheme 3), enabled efficient bridgehead deprotonation–substitution of **16** to afford prenylated product **18** in a very acceptable 75% yield. The use of external quench conditions opened up the opportunity to use various electrophiles, and pleasingly, under our optimised conditions, various C-5 derivatives **18**–**26** were furnished in moderate to good yield (Table 1).

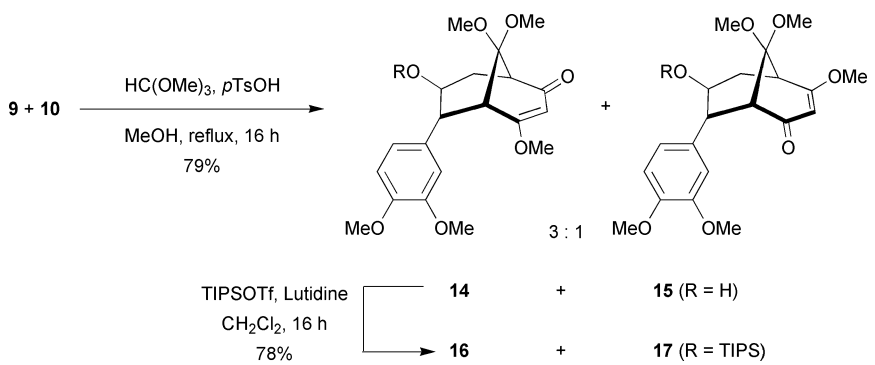
Table 1 Bridgehead alkylation of ketal **16**



18 - 26

Electrophile	R	Yield	Compound
Prenyl bromide	Prenyl	75 (89)[a]	**18**
Me_3SiCl	Me_3Si	46 (59)[a]	**19**
Allyl Br	Allyl	46	**20**
BnBr	Bn	56	**21**
MeI	Me	48 (55)[a]	**22**
PhCHO	PhCH(OH)	51 (1 : 1)[b]	**23**
^{i}PrCHO	^{i}PrCH(OH)	31 (42)[a]	**24**
Ph_2S_2	PhS	67	**25**
$^{n}Bu_3SnCl$	Bu_3Sn	63	**26**

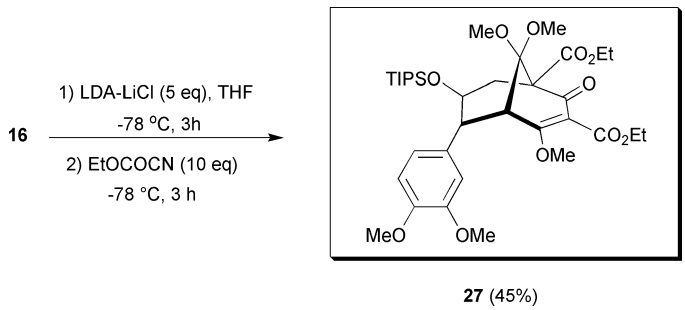
[a] Yield in parentheses is based on recovered starting material. [b] Diastereomeric ratio.



Scheme 4 Synthesis of [3.3.1] systems with bridging ketal functions.

The origin of the requirement for a large excess of base is unclear but lower yields of the products were obtained when fewer equivalents of base were employed. We saw no evidence for substitution at the alternative C-1 bridgehead position, and fortuitously for our planned natural product work quenching with prenyl bromide proved to be most effective. Heteroatom substituents such as Si, Sn or S groups could also be efficiently introduced at the bridgehead position, although attempted iodine quenching led to intractable mixtures, probably involving C-3 substitution. When benzaldehyde was used as electrophile, the aldol product **23** was isolated as an equimolar mixture of diastereoisomers, whereas the use of isobutyraldehyde resulted in a single isomer **24**, albeit in modest yield.

Surprisingly, reaction of **16** with the acylating agent EtOCOCN gave product **27**, in which substitution had occurred at both the C-3 and C-5 positions, Scheme 5. This behaviour appears unlikely to be due to dianion formation (little or no disubstituted product was observed in most other cases) and could be the result of activation of the system at C-3 following initial acylation at the bridgehead.



27 (45%)

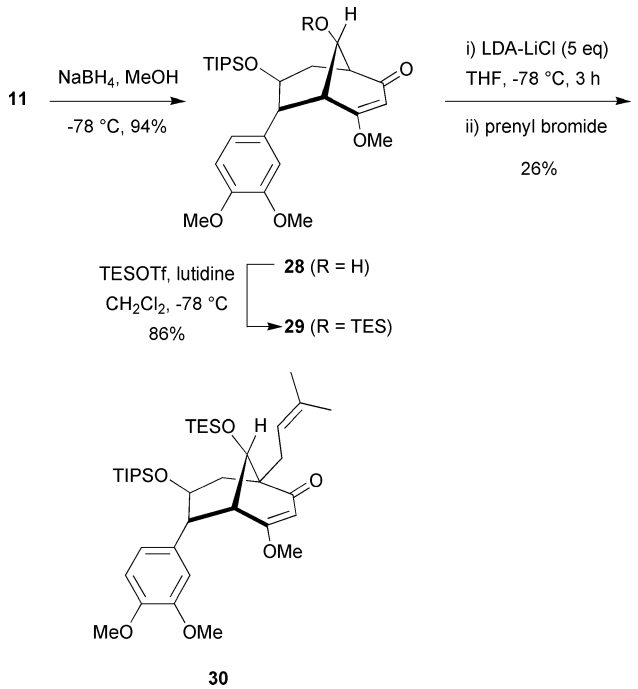
Scheme 5 Double acylation of **16**.

In order to further probe the metallation chemistry of these systems we also prepared a catechinic acid derivative in which the bridging ketone was converted into a protected alcohol. Thus, diastereoselective reduction of ketone **11**, using $NaBH_4$, provided alcohol **28**, which was then protected as the corresponding TES ether (Scheme 6).

In this case, our standard metallation–quenching conditions furnished the prenylated product **30** in a very modest 26% yield. This result contradicts our early hypothesis that an sp^3-hybridised bridging atom might prove superior to a more rigid bridging ketone. The bridgehead substitution is clearly viable in each of **11**, **16** and **29**, but the overall efficiency of the process is difficult to predict. It is possible that chelation with the ketal oxygen atoms plays a part in facilitating lithiation in the case of ketal derivative **16**, whereas steric effects may have the opposite effect in the bulky OTES compound **29**.

(ii) Regioselective sp^2 substitution

So far, our successful results relied on the use of LDA, and only bridgehead substitution was observed, with no isolable quantities of side products from substitution at either C-1 or C-3. It was interesting to study whether the nature of the base could allow us to modify this selectivity, and based on literature precedent it appeared that substitution of the vinylogous ester at C-3 should be possible.[14] When changing LDA for the more

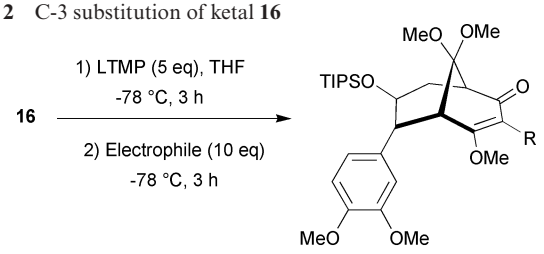


Scheme 6 Synthesis and lithiation of reduced derivative **29**.

sterically encumbered LTMP, ketal **16** failed to give any bridgehead substitution product when the lithiated intermediate was quenched with prenyl (or allyl) bromide. In contrast, the use of Me_3SiCl as electrophile gave a new product in a modest yield, which proved to be the vinyl silane **31**. Thus by using a bulkier lithium amide, the site of deprotonation on ketal **16** could be altered. This trend was further exemplified by reaction of the lithiated species with different electrophiles (Table 2).

Disappointingly, allyl or prenyl substituents could not be introduced at this position by this method (we later developed the use of cuprates to effect this type of substitution[6]). The use of iodine or diphenyl disulfide as the electrophile led to complex mixtures. In the case of benzoyl chloride, the benzoylated derivative **33** was isolated in 50% yield. Increasing the amount

Table 2 C-3 substitution of ketal **16**

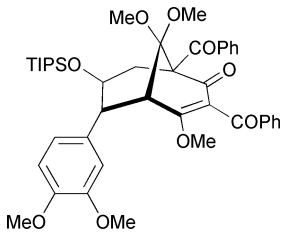


31- **34**

Electrophile	R	Yield	Compound
Me_3SiCl	Me_3Si	45	**31**
MeI	Me	36	**32**
PhCOCl	PhCO	50	**33**
$^nBu_3SnCl$	Bu_3Sn	61	**34**
Allyl bromide	Allyl	—[a]	—
Prenyl bromide	Prenyl	—[a]	—

[a] No reaction, starting material was recovered.

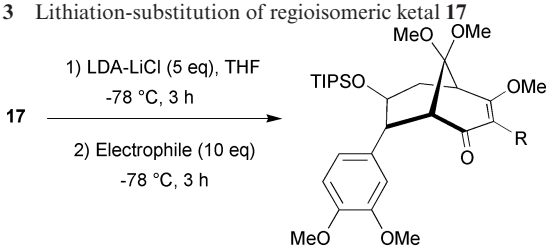
of LTMP to 10 equivalents resulted in the isolation of the di-substituted product **35** in 55% yield. As with the previously described acylation leading to **27** this last result could be due to sequential substitution or may indicate the intermediacy of a dianion. However, we were unable to provide further evidence that the reactive species may be a dianion in this system (for example quenching with D_2O did *not* give double incorporation).



35

Thus far, various substituents had been selectively introduced at positions C-3 and C-5 by altering the base employed. However, it was also of interest to introduce substituents at bridgehead position C-1, as most natural PPAPs have substituents at both their bridgehead positions. We thought that using the minor regioisomeric ketal **17** might allow lithiation to occur at position C-1 by analogy with previous results. Thus, isomer **17** was subjected to our optimised conditions. In this case, bridgehead substitution was not observed, only vinylic substitution (Table 3).

Table 3 Lithiation-substitution of regioisomeric ketal **17**



36 - 38

Electrophile	R	Base	Yield	Compound
Me_3SiCl	Me_3Si	LDA–LiCl	31 (34)[a]	**36**
MeI	Me	LDA–LiCl	60	**37**
Prenyl bromide	Prenyl	LDA–LiCl	25 (33)[a]	**38**
Prenyl bromide	Prenyl	LTMP	51	**38**

[a] Yields in parentheses based on recovered starting material.

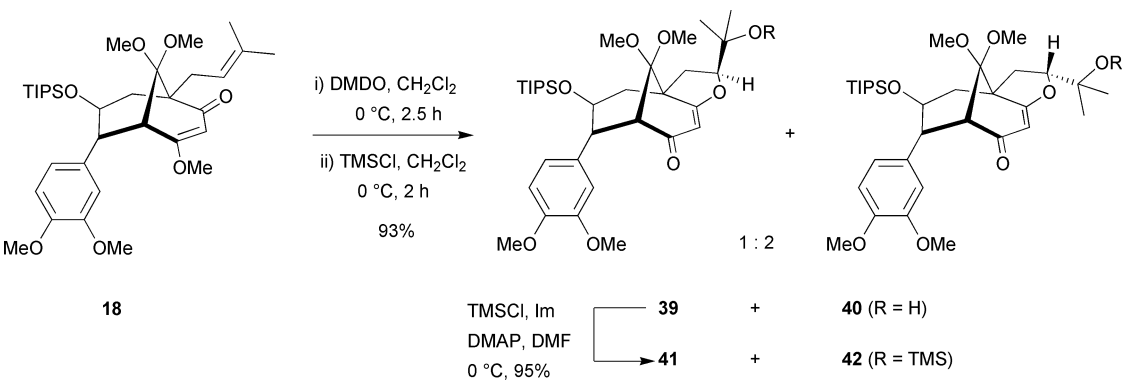
It is likely that the steric bulk of the aromatic residue at C-8 hinders deprotonation at C-1 in this case, although it should be noted that Danishefsky accomplished metallation at this position during the aforementioned garsubellin A synthesis.[4] Using TMSCl, MeI or prenyl bromide as electrophiles, derivatives **36**–**38** were isolated in moderate to good yields. It is worth noting that changing the base to LTMP did not change the selectivity, but allowed us to improve the yield of prenylation at the vinylic position. Having established that the selective introduction of substituents at the C-5 bridgehead and C-3 sp^2 positions was possible through the use of an appropriate base, we decided to further advance key intermediates by constructing the five-membered THF ring present in **1**.

(iii) Synthesis of the THF ring

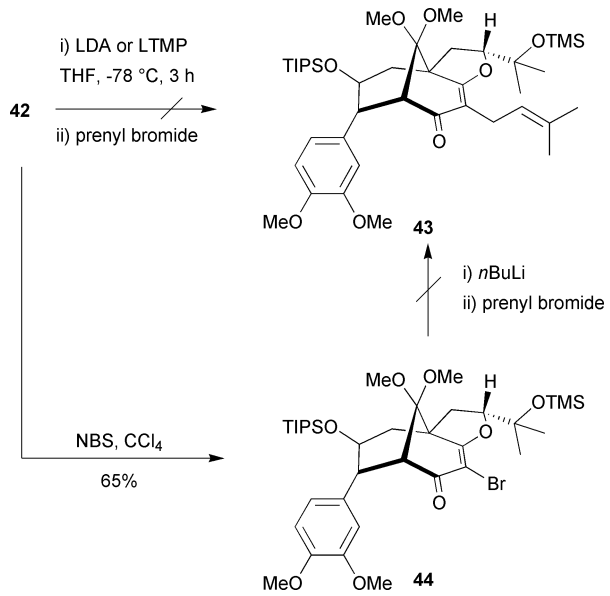
In contrast with the methodologies used previously by the groups of Danishefsky and Shibasaki during their total synthesis of **1**, we wanted to form the THF ring through the epoxidation of the C-5 bridgehead prenyl residue, followed by a *5-exo-tet* cyclisation involving the C-4 oxygen atom. This cyclisation would be accompanied by the cleavage of the vinylogous ester. Our first attempts to form the epoxide of **18** using *m*CPBA resulted in very low mass recovery. In contrast, the use of freshly prepared dimethyldioxirane (DMDO) allowed the epoxidation to proceed smoothly, affording a diastereomeric mixture of two epoxides. Due to instability of the epoxides on silica, we explored methods to directly cyclise the crude diastereomeric mixture, and we established that reaction with TMSCl effected their conversion into the separable THF derivatives **39** and **40** (Scheme 7).[15]

Trimethylsilyl chloride was found to be much more effective than the corresponding iodide for this cyclisation, which we assume proceeds *via* silicon-mediated activation of the epoxide. Surprisingly, however, we have not been able to directly isolate the silicon protected alcohol derivatives from this reaction.

The relative stereochemistry of the major diastereoisomer **40** was determined through NOE studies and proved to have the unnatural side chain configuration. The alcohols **39** and **40** were readily converted into the corresponding silyl ethers **41** and **42**. We decided to use the major silyl ether **42** to probe the feasibility of the direct installation of a prenyl residue at the C-3 sp^2 position, a result that had eluded us with compound **16**. Once again we were unable to effect C-3 allylation or prenylation using either LDA or LTMP under the conditions described previously, Scheme 8.



Scheme 7 Side chain epoxidation and cyclisation.

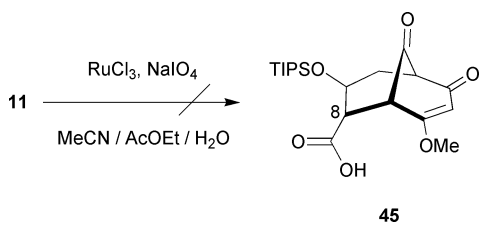


Scheme 8 Attempted C-3 prenylation of **42**.

The facile synthesis of vinyl bromide **44** enabled us to try the same type of substitution, originating with a halogen–metal transfer process, but again no product was obtained. The problem here is certainly one of poor reactivity of the intermediate organolithium and, as mentioned earlier, we eventually solved this problem by allylation of a mixed cuprate generated using thienyl copper cyanide.[6] This chemistry was not explored on the catechinic acid systems.

(iv) Oxidative degradation of the catechol ring

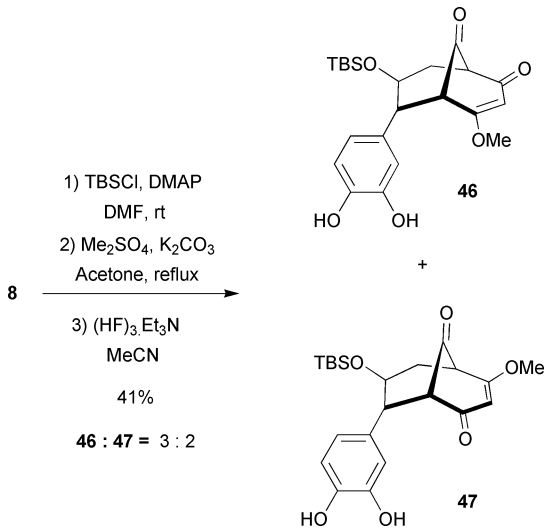
As shown before, in order to set up a synthesis of **1**, the aromatic moiety at position C-8 needed to be converted into the *gem*-dimethyl group present in **1**. The use of a ruthenium based oxidation on a suitably protected derivative of catechinic acid **8** was attempted to degrade the aromatic ring to a carboxylic acid (**11** → **45**, Scheme 9).



Scheme 9 Attempted oxidative cleavage of **11**.

In our case, however, a variety of conditions failed to provide any quantities of acid **45**. Use of Sharpless conditions rapidly led to decomposition of the starting material.[16] Alternative conditions for the *in situ* formation of the active species RuO_4 were tried, including the use of RuO_2 or the complex *cis*$[Ru(bpy)]_2Cl_2$ with $NaIO_4$ but in each case only decomposition was observed.[17,18] Ozonolysis of **11** followed by an acidic work up also failed to provide derivative **45**.[19]

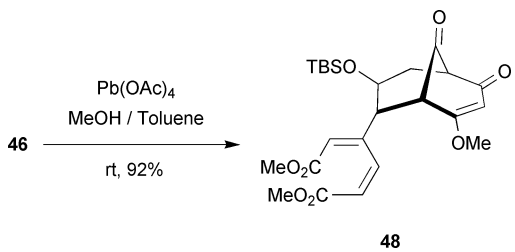
At this stage, a system bearing a free catechol unit was prepared as a means to make the aromatic moiety more easily oxidisable. Catechol derivatives **46** and **47** were prepared from **8** as depicted in Scheme 10.



Scheme 10 Synthesis of systems with a free catechol unit.

Initial silylation of the secondary alcohol as well as the two phenolic positions of **8** led, after methylation of the 1,3 diketone moiety to an inseparable mixture of tris-silylated derivatives. Selective deprotection of the phenolic hydroxyls was easily performed under acidic conditions to provide catechols **46** and **47** which were then separated by chromatography.

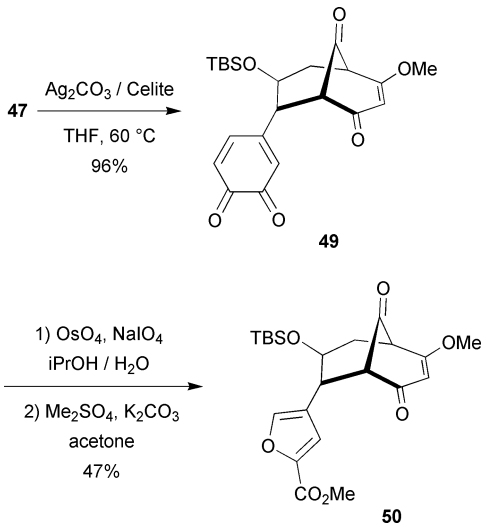
As seen for **11**, the use of RuO_4 based oxidation led to the rapid decomposition of the starting material. However, the presence of a free catechol function opened up the possibility of a more step-wise strategy, for example *via* muconic acid or quinone intermediates. To explore the first of these we followed the procedure of Gilheany,[20] which involved reaction of catechol **46** with $Pb(OAc)_4$ in MeOH, and were pleased to isolate the muconic acid diester derivative **48** in very high yield (Scheme 11).



Scheme 11 Oxidative cleavage of **46**.

With this new intermediate, we were hoping to be able to reach an acid derivative similar to **45** by the simultaneous oxidative cleavage of the two conjugated olefins in **48**. However, **48** proved to be completely inert towards dihydroxylation. In the case of ozonolysis, the substrate reacted with the initial cleavage of the disubstituted olefin but no products resulting from the cleavage of both C–C double bonds of the muconic acid moiety could be isolated.

Another potential route for the degradation of the aromatic part was explored using the minor regioisomer **47**, as depicted in Scheme 12.



Scheme 12 Formation of side chain quinone **49** and furan **50**.

Oxidation of **47** using Ag_2CO_3 on Celite (Fetizon's reagent)[21] resulted in an extremely clean conversion to the corresponding *ortho*-quinone **49**. Then, a one pot dihydroxylation–diol cleavage sequence was attempted, using a mixture of OsO_4 and $NaIO_4$.[22] To our surprise, under these conditions, **49** was converted into a furan carboxylic acid derivative, which was isolated as the corresponding methyl ester **50** after methylation under basic conditions. On further checking the literature we established a reasonable precedent for this transformation in the work of Gierer and Imsgard.[23]

Further attempts to cleave the furan ring using ozonolysis failed to give any usable products.[24]

Conclusions

In conclusion, the regioselective lithiation of derivatives of catechinic acid (**8**), possessing the bicyclo[3.3.1]nonane-1,3,5-trione core has been achieved. In the case of bridging ketal **16**, the use of LDA promoted selective bridgehead substitution, whilst LTMP enabled metallation–substitution at the C-3 sp^2 centre. With reactive electrophiles, such as acylating agents, we observed a tendency towards double substitution at both the C-3 and C-5 positions.

With regioisomer **17**, the use of either LDA or LTMP led to lithiation at the sp^2 center. These lithiations have been shown to be dependent on the nature of substitution at the bridging atom with the bridging dimethylketal proving superior to either a bridging ketone or a reduced and silicon protected variant.

A THF ring, resembling that present in garsubellin A, was appended to the catechinic acid system through an epoxidation–ring opening sequence. Oxidative degradation of the aryl group of our catechinic acid derivatives to give a carboxylic acid derivative did not succeed as predicted, although an interesting transformation of an *ortho*-quinone intermediate into a furan derivative was achieved. Although we have not yet been able to use catechinic acid to achieve an asymmetric synthesis of **1**, this template has provided us with a very rapid access to a wide range of enantiomerically pure bicyclo[3.3.1]nonane derivatives. Some of these new compounds have been tested for their biological properties; results will be reported in due course.

Experimental

General methods

All reactions were performed under an atmosphere of nitrogen in flame dried glassware unless otherwise stated. Organic solvents and reagents were dried by distillation from the following as required: THF (sodium–benzophenone), DCM, TMSCl (CaH_2). Allyl bromide, prenyl bromide, benzaldehyde, benzyl bromide, ethyl cyanoformate, iodomethane, and triethylamine were all distilled before use. Lead tetraacetate was freshly recrystallised before use from AcOH–Ac_2O. All other solvents and reagents were used as received from commercial suppliers unless otherwise stated. RT relates to the temperature range 20–25 °C. Reaction progress was monitored by thin layer chromatography (TLC) performed on Merck aluminium plates coated with kieselgel F_{254}. Visualisation was achieved by a combination of ultraviolet light (254 nm) and anisaldehyde or acidic potassium permanganate. Flash chromatography was performed using silica gel (Merck 7734 grade), eluted with the indicated solvent. Melting points were recorded on a Stuart Scientific SMP3 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer as dilute solutions in spectroscopic grade chloroform within a NaCl cell. NMR spectra were recorded on a Bruker AV400 or DRX500 machine, using $CDCl_3$ as solvent at 298 K. Chemical shifts are given in ppm downfield from tetramethylsilane, using residual protic solvent as an internal standard. *J* values are reported in Hz and rounded to the nearest 0.1 Hz. Where required, assignments were confirmed by two-dimensional homonuclear (^1H–^1H) and heteronuclear (^1H–^{13}C) correlation spectroscopy on a Brucker AV400 spectrometer. Mass spectra were obtained using a VG Micromass 70E spectrometer, using electron impact (EI) at 70 eV or chemical ionisation (CI) or electrospray ionisation (ESI). Optical rotations were recorded as dilute solutions in the indicated solvent in a 100 mm cell using a JASCO DIP370 digital polarimeter at a wavelength of 598 nm.

(1*S*,5*R*,7*S*,8*R*)-(+)-8-(3,4-Dimethoxyphenyl)-7-hydroxy-2-methoxybicyclo[3.3.1]non-2-ene-4,9-one 9 and (1*S*,5*R*,7*S*,8*R*)-(+)-8-(3,4-dimethoxyphenyl)-7-hydroxy-4-methoxy-bicyclo[3.3.1]non-3-ene-2,9-one 10

Solid KOH (600 mg, 6.90 mmol) was added to a solution of (+)-catechin (**7**) (2.00 g, 25.0 mmol) in water (80 ml) and the reaction mixture was then heated under reflux for 105 min. The reaction mixture was allowed to cool, filtered through a pad of Amberlite IR-120 and concentrated *in vacuo* to give a dark red solid (2.0 g, quantitative). Crude catechinic acid (**8**) was used without purification. Dimethyl sulfate (25.0 mL, 36.9 mmol, 7.7 eq.) and K_2CO_3 (15.7 g, 15.8 mmol, 3.3 eq.) were added to crude **8** (10.0 g, 4.8 mmol) in acetone (500 mL), and the solution was heated under reflux for 18 h. The reaction mixture was allowed to cool, diluted with H_2O (200 mL), and extracted with EtOAc (4 × 100 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a fluffy orange solid. Purification by column chromatography (petroleum

ether–EtOAc 3 : 7) gave regioisomers **9** and **10** in a 3 : 1 ratio (6.4 g, 58% over two steps) data for **9**; $[\alpha]_D^{27}$ +147 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 3463 (br), 2906, 1652, 1603, 1516, 1452, 1379, 1230, 1105, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89–1.97 (m, 1H, CH*H*), 2.23 (br s, 1H, O*H*), 2.57 (ddd, *J* 13.0, 8.8, 5.3, 1H, C*H*H), 3.08 (dd, *J* 11.0, 3.9, 1H, ArC*H*), 3.29 (m, 2H, 1-C*H*, 5-C*H*), 3.57 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.40 (ddd, *J* 11.0, 11.0, 5.3, 1H, C*H*OH), 5.70 (s, 1H, C=C*H*), 6.66 (d, *J* 2.0, 1H, Ar*H*), 6.69 (dd, *J* 8.2, 2.0, 1H, Ar*H*), 6.84 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2 (CH_2), 53.2 (CH), 56.5 (CH_3), 56.5 (CH_3), 57.1 (CH_3), 58.9 (CH), 59.4 (CH), 66.1 (CH), 105.1 (CH), 111.0 (CH), 111.3 (CH), 119.8 (CH), 129.7 (C), 148.7 (C), 149.2 (C), 174.5 (C), 194.9 (C), 203.9 (C); HRMS (EI) *m/z* 333.1362 $[M + H]^+$, $[C_{18}H_{21}O_6]^+$ requires 333.1338; **10**: $[\alpha]_D^{20}$ +67 (*c* 0.5 in $CHCl_3$); ν_{max} ($CHCl_3$) 2936, 1736, 1657, 1602, 1462, 1365, 1142, 908, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96–2.05 (m, 1H, C*H*H), 2.63 (ddd, *J* 13.4, 8.6, 5.3, 1H, CH*H*), 3.09 (dd, *J* 10.8, 4.0, 1H, ArC*H*), 3.33–3.40 (m, 2H, 1-C*H*, 5-C*H*), 3.86–3.89 (m, 9H, OCH_3, 2 × $ArOCH_3$), 4.46 (ddd, *J* 10.8, 10.8, 5.3, 1H, C*H*OH), 5.79 (s, 1H, C=C*H*), 6.67–6.72 (m, 2H, 2 × Ar*H*), 6.84–6.87 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3 (CH_2), 51.6 (CH), 53.3 (CH), 55.8 (CH_3), 55.9 (CH_3), 56.5 (CH_3), 57.1 (CH_3), 66.5 (CH), 66.8 (CH), 105.3 (CH), 111.3 (CH), 112.1 (CH), 120.1 (CH), 128.4 (C), 149.0 (C), 149.3 (C), 175.5 (C), 191.9 (C), 203.8 (C); HRMS (ESI) *m/z* 333.1316 $[M + H]^+$, $[C_{18}H_{21}O_6]^+$ requires 333.1338.

(1*S*,5*R*,7*S*,8*R*)-(+)-8-(3,4-Dimethoxyphenyl)-2-methoxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-ene-4,9-dione 11 and (1*S*,5*R*,7*S*,8*R*)-(+)-8-(3,4-dimethoxyphenyl)-4-methoxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-3-ene-2,9-dione 12

Triisopropylsilyl trifluoromethanesulfonate (2.06 mL, 7.68 mmol, 1.5 eq.) was added to a solution of bridged ketones **9** and **10** (1.70 g, 5.10 mmol) and 2,6-lutidine (1.79 mL, 15,4 mmol, 3 eq.) in dry CH_2Cl_2 (10.0 mL) at 0 °C. The mixture was allowed to warm to RT over 3 h, then stirred at RT for 16 h. After this period, the crude reaction mixture was washed with 2 M HCl (2 × 5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined and dried (Na_2CO_3), then concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 4 : 1) gave firstly **11** as a pale yellow solid (1.4 g, 56%); mp 128 °C; $[\alpha]_D^{22}$ +109 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 2939, 1736, 1657, 1604, 1374, 1118, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63–0.75 (m, 21H, $OSi(CH(CH_3)_2)_3$), 1.83–1.91 (m, 1H, CH*H*), 2.48–2.52 (m, 1H, C*H*H), 3.00 (dd, *J* 10.3, 3.8, 1H, ArC*H*), 3.17–3.22 (m, 2H, 1-C*H*, 5-C*H*), 3.54 (s, 3H, OCH_3), 3.73 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, $ArOCH_3$), 4.40 (ddd, *J* 10.3, 10.3, 5.2, 1H, C*H*OSi($CH(CH_3)_2)_3$), 5.67 (s, 1H, C=C*H*), 6.52–6.53 (m, 1H, Ar*H*), 6.55 (dd, *J* 8.2, 1.9, 1H, Ar*H*), 6.70 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8 (CH), 17.5 (CH_3), 39.0 (CH_2), 54.6 (CH), 55.8 (CH_3), 55.9 (CH_3), 56.4 (CH_3), 59.1 (CH), 59.4 (CH), 67.6 (CH), 105.1 (CH), 111.0 (CH), 111.6 (CH), 120.4 (CH), 131.5 (C), 148.5 (C), 148.7 (C), 174.9 (C), 194.8 (C), 204.1 (C); HRMS (CI, NH_3) *m/z* 489.2633 $[M + H]^+$, $[C_{27}H_{41}O_6Si]^+$ requires 489.2671 and secondly **12** as a yellow oil (0.42 g, 19%); $[\alpha]_D^{27}$ +6.0 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 2942, 1743, 1650, 1594, 1462, 1373, 1123 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.75–0.90 (m, 21H, $OSi(CH(CH_3)_2)_3$), 1.96–2.04 (m, 1H, CH*H*), 2.53–2.59 (m, 1H, C*H*H), 3.06 (dd, *J* 10.5, 4.1, 1H, ArC*H*), 3.24–3.26 (m, 1H, 5-C*H*), 3.34–3.37 (m, 1H, 1-C*H*), 3.83 (s, 9H, OCH_3, 2 × $ArOCH_3$), 4.54 (ddd, *J* 10.5, 10.5, 5.2, 1H, C*H*OSi($CH(CH_3)_2)_3$), 5.80 (s, 1H, C=C*H*), 6.60–6.65 (m, 2H, 2 × Ar*H*), 6.78 (d, *J* 8.0, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5 (CH), 17.5 (CH_3), 37.1 (CH_2), 51.6 (CH), 55.8 (CH_3), 55.9 (CH_3), 56.2 (CH_3), 57.0 (CH) 67.8 (CH), 68.3 (CH), 105.1 (CH), 110.9 (CH), 112.5 (CH), 120.9 (CH), 130.5 (C), 148.5 (C), 148.6 (C), 175.4 (C), 192.5 (C), 204.0 (C); HRMS (CI, NH_3) *m/z* 488.2585 $[M]^+$, $[C_{27}H_{40}O_6Si]^+$ requires 488.2594.

(1*S*,5*R*,7*S*,8*R*)-(+)-8-(3,4-Dimethoxyphenyl)-2-methoxy-1-(prenyl)-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-ene-4,9-dione 13

A solution of LDA·LiCl was prepared by treatment of a suspension of DIPA·HCl (256 mg, 2.04 mmol) in THF (4 mL) at −78 °C with ^{n}BuLi (1.6 M solution in hexanes; 2.56 mL, 4.08 mmol). The solution was allowed to warm to RT and after 10 min re-cooled to −78 °C. This LDA·LiCl solution was added dropwise *via* syringe to a solution of bridged ketone **11** (100 mg, 0.20 mmol) in THF (1 mL) at −78 °C resulting in a deep yellow-coloured solution. The solution was stirred at −78 °C for 3 h, followed by addition of prenyl bromide (0.25 mL, 2.04 mmol, 10 eq.) and stirring for a further 3 h at −78 °C. The reaction mixture was quenched after this period with H_2O (5 mL) followed by extraction with EtOAc (3 × 5 mL). The organic layers were combined and washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 4 : 1) gave the title compound **13** as a yellow oil (47 mg, 42%); $[\alpha]_D^{20}$ +82 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 2940, 2258, 1736, 1650, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (m, 21H, $OSi(CH(CH_3)_2)_3$), 1.64 (s, 3H, CH_3), 1.69 (s, 3H, OCH_3), 1.74–1.78 (m, 1H, 8-CH*H*), 2.32 (dd, *J* 12.7, 5.3, 1H, 8-C*H*H), 2.52 (dd, *J* 15.0, 7.0, 1H, CH*H*CH=C), 2.56 (dd, *J* 15.0, 7.0, 1H, C*H*HCH=C), 3.07 (dd, *J* 10.3, 4.3, 1H, ArC*H*), 3.33 (dd, *J* 4.3, 1H, 5-C*H*), 3.61 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.46 (ddd, *J* 10.3, 10.3, 5.3, 1H, C*H*OSi($CH(CH_3)_2)_3$), 4.95–5.01 (m, 1H, C*H*=$C(CH_3)_2$), 5.75 (s, 1H, C=C*H*), 6.63 (d, *J* 2.0, 1H, Ar*H*), 6.66 (dd, *J* 8.2, 2.0, 1H, Ar*H*), 6.80 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (CH), 17.8 (CH_3), 18.0 (CH_3), 25.9 (CH_3), 29.4 (CH_2), 45.8 (CH_2), 54.9 (CH_3), 55.8 (CH_3), 56.0 (CH), 56.2, (CH_3), 59.3 (CH_3), 62.6 (C), 68.2 (CH), 105.2 (CH), 110.0 (CH), 117.0 (CH), 119.1 (CH), 120.5 (CH), 122.2 (CH), 131.6 (C), 134.5 (C), 148.5 (C), 148.7 (C), 173.8 (C), 196.8 (C), 205.9 (C); HRMS (EI) *m/z* 557.3293 $[M + H]^+$, $[C_{32}H_{49}O_6Si]^+$ requires 557.3298.

(1*S*,5*S*,7*S*,8*R*)-(+)-8-(3,4-Dimethoxyphenyl)-7-hydroxy-2,9,9-trimethoxy-bicyclo[3.3.1]non-2-en-4-one 14 and (1*R*,5*R*,7*S*,8*R*)-(−)-8-(3,4-dimethoxyphenyl)-7-hydroxy-4,9,9-trimethoxy-bicyclo[3.3.1]non-3-en-2-one 15

Trimethyl orthoformate (0.50 mL, 4.50 mmol, 1.5 eq.) and *p*TsOH (57 mg, 0.30 mol, 0.1 eq.), were added to a solution of bridged ketones **9** and **10** (1.00 g, 3.0 mmol) in MeOH (20 mL), and the mixture was heated under reflux for 24 h. After this period, the solution was allowed to cool then concentrated *in vacuo*. Purification by column chromatography (EtOAc–petroleum ether 7 : 3) gave a mixture of ketals **14** and **15** in a 3 : 1 ratio (898 mg, 79%);

data for **14**: $[\alpha]_D^{30}$ +169 (*c* 0.9 in $CHCl_3$); ν_{max} ($CHCl_3$) 3463, 2906, 1652, 1603, 1516, 1230, 1105, 1068, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84–1.92 (m, 1H, CH*H*), 2.17 (ddd, *J* 12.8, 8.8, 5.6, 1H, C*H*H), 2.92 (m, 2H, 1-C*H*, 5-C*H*), 3.13 (s, 3H, OCH_3), 3.21 (dd, *J* 10.4, 3.6, 1H, ArC*H*), 3.31 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.86 (s, 3H, ArOCH_3), 3.87 (s, 3H, ArOCH_3), 4.17–4.29 (m, 1H, C*H*OH), 5.51 (s, IH, C=C*H*), 6.67 (d, *J* 2.0, 1H, Ar*H*), 6.70 (dd, *J* 8.0, 2.0, 1H, Ar*H*), 6.84 (d, *J* 8.0, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0 (CH_2), 47.4 (CH), 48.7 (CH_3), 48.8 (CH_3), 49.3 (CH), 49.8 (CH), 55.7 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 66.4 (CH), 101.3 (C), 103.4 (CH), 111.3 (CH), 111.6 (CH), 120.0 (CH), 131.4 (C), 148.4 (C), 149.2 (C), 175.7 (C), 190.0 (C); HRMS (ES) *m/z* 379.1768 $[M + H]^+$, $[C_{20}H_{27}O_7]^+$ requires 379.1757; data for **15**: $[\alpha]_D^{20}$ −5 (*c* 0.5 in $CHCl_3$); ν_{max} ($CHCl_3$) 2939, 1650, 1611, 1462, 1375, 1108, 1068, 1027, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94–2.00 (m, 1H, CH*H*), 2.21 (ddd, *J* 12.9, 8.8, 5.5, 1H, C*H*H), 2.94–2.99 (m, 2H, 1-C*H*, 5-C*H*), 3.12 (dd, *J* 10.9, 4.0, 1H, ArC*H*), 3.15 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, ArOCH_3), 3.87 (s, 3H, ArOCH_3), 4.24 (ddd, *J* 10.9, 10.9, 5.5, 1H, C*H*OH), 5.55 (s, 1H, C=C*H*), 6.65–6.67 (m, 2H, 2 × Ar*H*), 6.81–6.83 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (CH_2), 42.4 (CH), 47.2 (CH_3), 48.7 (CH_3), 48.7 (CH), 55.8 (CH_3), 55.8 (CH_3), 56.4 (CH_3), 56.5 (CH), 67.2 (CH), 101.0 (C), 103.1 (CH), 111.3 (CH), 112.5 (CH), 120.2 (CH), 130.3 (C), 148.4 (C), 149.1 (C), 176.9 (C), 196.5 (C); HRMS (ESI) *m/z* 379.1756 $[M + H]^+$, $[C_{20}H_{27}O_7]^+$ requires 379.1757.

(1*S*,5*S*,7*S*,8*R*)-(+)-8-(3,4-Dimethoxyphenyl)-2,9,9-trimethoxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-en-4-one 16 and (1*R*, 5*R*, 7*S*, 8*R*)-(+)-8-(3,4-dimethoxyphenyl)-4,9,9-trimethoxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-3-en-2-one 17

2,6-Lutidine (0.64 mL, 5.55 mmol, 3 eq.) and triisopropylsilyl trifluoromethanesulfonate (0.75 mL, 3.70 mmol, 1.5 eq.) were added to a solution of **14** and **15** (0.7 g, 1.85 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to RT over 1 h then stirred at RT overnight. The reaction mixture was washed with 2 M HCl (3 × 7 mL) and saturated aqueous NaCl (1 × 10 mL), extracted with CH_2Cl_2 (2 × 10 mL), dried ($MgSO_4$), then concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 85 : 15) gave firstly bridged ketal **16** as a white solid (480 mg, 56%); $[\alpha]_D^{26}$ +154 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 2941, 2865, 1650, 1604, 1462, 1379, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83–0.93 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$), 1.90–1.97 (m, 1H, CH*H*), 2.19 (ddd, *J* 12.8, 5.6, 3.7, 1H, C*H*H), 2.93–2.94 (m, 2H, 1-C*H*, 5-C*H*), 3.15 (s, 3H, OCH_3), 3.19 (dd, *J* 10.6, 3.7, 1H, ArC*H*), 3.35 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.87 (s, 3H, ArOCH_3), 3.39 (s, 3H, ArOCH_3), 4.33 (ddd, *J* 10.7, 10.7, 5.6, 1H, C*H*OSi(CH(CH_3)$_2$)$_3$), 5.58 (s, 1H, C=C*H*), 6.66 (d, *J* 1.8, 1H, Ar*H*), 6.68 (dd, *J* 8.2, 1.8, 1H, Ar*H*), 6.82 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8 (CH), 17.9 (CH_3), 34.0 (CH_2), 47.3 (CH_3), 48.3 (CH), 48.6 (CH_3), 49.5 (CH), 49.9 (CH), 55.6 (CH_3), 55.7 (CH_3), 55.9 (CH_3), 68.2 (CH), 101.3 (C), 103.12 (CH), 110.8 (CH), 111.9 (CH) 120.8 (CH), 133.2 (C), 147.9 (C), 148.5 (C), 176.6 (C), 198.9 (C); HRMS (ES) *m/z* 535.3069 $[M + H]^+$, $[C_{29}H_{47}O_7Si]^+$ requires 535.3091; and secondly bridged ketal **17** as a yellow oil (250 mg, 22%); $[\alpha]_D^{30}$ +81 (*c* 0.9 in $CHCl_3$); ν_{max} ($CHCl_3$) 2941, 2865, 1650, 1604, 1462, 1379, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77–0.87 (m, 21H, CHOSi(C*H*(CH_3)$_2$)$_3$), 1.93–1.99 (m, 1H, CH*H*), 2.13 (ddd, *J* 12.8, 5.4, 3.7, 1H, C*H*H), 2.89–2.92 (m, 2H, C*H*, C*H*), 3.06 (dd, *J* 10.7, 3.7, 1H, ArC*H*), 3.12 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, ArOCH_3), 3.82 (s, 3H, ArOCH_3), 4.31 (ddd, *J* 10.7, 10.7, 5.4, 1H, C*H*OSi(CH(CH_3)$_2$)$_3$), 5.56 (s, 1H, C=C*H*), 6.57–6.60 (m, 2H, 2 × Ar*H*), 6.75 (d, *J* 7.9, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6 (CH), 17.9 (CH_3), 32.4 (CH_2), 42.5 (CH), 47.2 (CH_3), 48.6 (CH_3), 49.3 (CH), 55.7 (CH_3), 55.9 (CH_3), 56.4 (CH_3), 57.0 (CH), 68.9 (CH), 100.9 (C), 103.0, (CH), 110.8 (CH), 112.9 (CH), 121.0 (CH), 132.3 (C), 147.9 (C), 148.4 (C), 176.6 (C), 197.4 (C); HRMS (ES) *m/z* 535.3086 $[M + H]^+$, $[C_{29}H_{47}O_7Si]^+$ requires 535.3091.

Crystal data for 16. $C_{29}H_{46}O_7Si$, $M = 534.75$, monoclinic, $a = 8.2824(6)$, $b = 13.7389(10)$, $c = 12.7110(10)$ Å, $\beta = 91.2840(10)°$, $U = 1446.04(19)$ Å^3, $T = 150$ K, space group $P2_1$ (no. 4), $Z = 2$, μ(Mo-Kα) = 0.124 mm^{-1}, 12515 reflections measured, 6307 unique ($R_{int} = 0.031$) which were used in all calculations. The final $wR(F^2)$ was 0.100 (all data) and the Flack parameter refined to 0.09(9) confirming the determination of the absolute configuration.‡

Typical procedure A for lithiation substitution using LDA (Table 1 and Table 3): (1*S*,5*S*,7*S*,8*R*)-(+)-8-(3,4-dimethoxyphenyl)-2,9,9-trimethoxy-5-(prenyl)-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-en-4-one 18

A solution of LDA·LiCl was prepared by treatment of a suspension of DIPA·HCl (180 mg, 1.31 mmol) in THF (2.5 mL) at −78 °C with ^{n}BuLi (1.64 mL, 2.62 mmol, 1.6 M solution in hexanes). The solution was allowed to warm to RT and after 10 min re-cooled to −78 °C. This LDA·LiCl solution was added dropwise *via* syringe to a solution of bridged ketone **16** (140 mg, 0.26 mmol) in THF (1.4 mL) at −78 °C resulting in a deep yellow-coloured solution. The solution was stirred at −78 °C for 3 h, followed by addition of prenyl bromide (0.30 mL, 2.62 mmol, 10 eq.) and stirring for a further 3 h at −78 °C. The reaction mixture was quenched after this period with H_2O (5 mL) followed by extraction with EtOAc (3 × 5 mL). The organic layers were combined and washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 4 : 1) gave the title compound **18** as a light brown oil (118 mg, 75%); $[\alpha]_D^{23}$ +150 (*c* 0.9 in $CHCl_3$); ν_{max} ($CHCl_3$) 2940, 2865, 1649, 1615, 1462, 1381, 1132, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77–0.88 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$), 1.62 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.82–1.84 (m, 2H, 8-CH_2), 2.47 (dd, *J* 15.0, 7.0, 1H, CH*H*CH=C(CH_3)$_2$), 2.60 (dd, *J* 15.0, 7.0, 1H, C*H*HCH=C(CH_3)$_2$), 2.92 (d, *J* 4.0, 1H, 5-C*H*), 3.07 (dd, *J* 10.4, 4.0, 1H, ArC*H*), 3.22 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.82 (s, 3H, ArOCH_3), 3.84 (s, 3H, ArOCH_3), 4.22 (ddd, *J* 10.4, 10.4, 7.0, 1H, C*H*OSi(CH(CH_3)$_2$)$_3$), 5.47–5.52 (m, 1H, (CH_3)$_2$C=C*H*), 5.53 (s, 1H, C=C*H*), 6.60 (d, *J* 1.9, 1H, Ar*H*), 6.64 (dd, *J* 8.2, 1.9, 1H, Ar*H*), 6.77 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6 (CH), 17.9 (CH_3), 25.9 (CH_3), 30.2 (CH_2), 41.1 (CH_2), 48.2 (CH), 49.7 (CH_3), 50.6 (CH), 51.1 (CH_3), 55.5 (CH_3), 55.7 (CH_3), 55.9 (CH_3), 57.1 (C), 68.7 (CH), 103.6 (CH), 103.9 (C), 110.8 (CH), 111.9 (CH), 121.0 (CH), 122.3 (CH), 131.5 (C), 133.2 (C), 147.9 (C), 148.4 (C), 174.7 (C), 201.2

‡ CCDC reference number 641180. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704311b

(C); HRMS (EI) m/z 603.3712 [M + H]$^+$, [$C_{34}H_{55}O_7Si$]$^+$ requires 603.3717.

(1*S*,5*R*,7*S*,8*R*)-(+)-8-(3,4-Dimethoxyphenyl)-4-oxo-2,9,9-trimethoxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-ene-3,5-dicarboxylic acid diethyl ester 27. Isolated as an amorphous yellow solid (55 mg, 45%); $[\alpha]_D^{30}$ +173 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75–0.90 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$), 1.29 (t, *J* 7.1, 3H, CH_3), 1.33 (t, *J* 7.1, 3H, CH_3), 2.26 (t, *J* 12.9, 1H, CH*H*), 2.39 (dd, *J* 12.9, 5.3, 1H, C*H*H), 3.15 (d, *J* 4.5, 1H, C*H*), 3.22 (s, 3H, OCH_3), 3.28 (dd, *J* 10.6, 4.5, 1H ArC*H*), 3.3 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.86 (s, 3H, ArOCH_3), 3.89 (s, 3H, ArOCH_3), 4.21–4.38 (m, 5H, C*H*OSi(CH(CH$_3$)$_2$)$_3$), OCH_2CH$_3$, OCH_2CH$_3$), 6.77–6.83 (m, 3H, Ar*H*, Ar*H*, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (CH_3), 14.2 (CH_3), 12.5 (CH), 18.0 (CH_3), 38.9 (CH_2), 48.8 (CH), 49.0 (CH_3), 49.3 (CH_3), 49.4 (CH), 55.8 (CH_3), 56.0 (CH_3), 56.8 (CH_3), 61.6 (CH_2), 61.7 (CH_2), 62.9 (C), 68.0 (CH), 101.8 (C), 111.0 (CH), 111.1 (CH), 115.1 (C), 121.6 (CH), 132.2 (C), 148.2 (C), 148.8 (C), 165.4 (C), 170.3 (C), 171.9 (C), 192.7 (C). IR ν_{max} 2913, 2847, 1729, 1614, 1463, 1373, 1249, 1089, 1051 cm^{-1}; HRMS (ES) m/z 679.3508 [M + H]$^+$, [$C_{35}H_{55}O_{11}Si$]$^+$ requires 679.3513.

(1*R*,5*S*,7*S*,8*R*,9*R*)-(+)-8-(3,4-Dimethoxyphenyl)-9-hydroxy-2-methoxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-en-4-one 28

Sodium borohydride (60.0 mg, 1.54 mmol, 1.5 eq.) in CH_3OH (4 mL) was added to a solution of **9** (500 mg, 1.02 mmol) in 2 : 1 CH_3OH : CH_2Cl_2 (15 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h. After this period the reaction was quenched with aqueous NaOH (2 mL, 2 M), extracted with EtOAc (3 × 5 mL). The organic extracts were combined and washed with saturated aqueous NaCl (aq.) (1 × 10 mL), dried ($MgSO_4$), then concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 3 : 7) gave the title compound **28** as a fluffy white solid (470 mg, 94%); mp 178–180 °C; $[\alpha]_D^{24}$ +163 (*c* 0.5 in $CHCl_3$); ν_{max} ($CHCl_3$) 3606, 2940, 1646, 1597, 1463, 1378, 1116, 1026, 882 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79–0.88 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$), 1.99–2.20 (m, 2H, 8-CH_2), 2.32 (d, *J* 3.5, 1H, O*H*), 2.78 (m, 2H, 1-C*H*, 5-C*H*), 3.29 (dd, *J* 10.2, 4.1, 1H, ArC*H*), 3.56 (s, 3H, OCH_3), 3.83 (s, 3H, ArOCH_3), 3.86 (s, 3H, ArOCH_3), 4.20–4.27 (m, 2H, C*H*OSi(CH(CH$_3$)$_2$)$_3$, C*H*OH), 5.55 (s, 1H, C=C*H*), 6.62–6.65 (m, 2H, 2 × Ar*H*), 6.78 (d, *J* 8.7, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6 (CH), 17.9 (CH_3), 18.1 (CH_3), 31.7 (CH_2), 45.7 (CH), 49.9 (CH), 50.4 (CH), 55.6 (CH_3), 55.7 (CH_3), 56.0 (CH_3), 68.3 (CH), 68.3 (CH), 104.0 (CH), 110.9 (CH), 112.2 (CH), 120.8 (CH), 133.6 (C), 147.8 (C), 148.5 (C), 178.7 (C), 200.2 (C); HRMS (ESI) m/z 491.2811 [M + H]$^+$, [$C_{27}H_{43}O_6Si$]$^+$ requires 491.2828.

(1*R*,5*S*,7*S*,8*R*,9*R*)-(−)-8-(3,4-Dimethoxyphenyl)-2-methoxy-9-triethylsilanyloxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-en-4-one 29

Triethylsilyl triflate (0.33 mL, 1.3 mmol, 1.5 eq.) was added to a solution of **28** (470 mg, 9.56 mmol) and 2,6-lutidine (0.33 mL, 2.6 mmol, 3 eq.) in dry CH_2Cl_2 (10 mL) at −78 °C and the solution stirred at −78 °C for 1 h. The reaction was quenched with aqueous HCl (10 mL, 2 M) and extracted with CH_2Cl_2 (3 × 8 mL). The organic extracts were combined and washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), then concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 8 : 2) gave the title compound **29** as a pale yellow oil (500 mg, 86%); $[\alpha]_D^{30}$ −50 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 2918, 1660, 1612, 1462, 1107, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (q, *J* 7.9, 6H, OSi(CH_2(CH$_3$)$_2$)$_3$), 0.77–0.89 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$), 1.01 (t, *J* 7.9, 9H, OSi(CH$_2$(CH_3)$_2$)$_3$), 2.04 (ddd, *J* 12.4, 8.6, 5.2, 1H, CH*H*), 2.14–2.18 (m, 1H, C*H*H), 2.61–2.67 (m, 2H, 1-C*H*, 5-C*H*), 3.28 (dd, *J* 10.5, 3.8, 1H, ArC*H*), 3.55 (s, 3H, OCH_3), 3.82 (s, 3H, ArOCH_3), 3.85 (s, 3H, ArOCH_3), 4.09 (t, *J* 3.6, 1H, C*H*OSi(CH$_2$CH$_3$)$_3$), 4.21 (ddd, *J* 10.5, 10.5, 5.2, 1H, C*H*OSi(CH(CH$_3$)$_2$)$_3$), 5.53 (s, 1H, C=C*H*), 6.59 (d, *J* 1.9, 1H, Ar*H*), 6.63 (dd, *J* 8.2, 1.9, 1H, Ar*H*), 6.78 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.8 (CH_2), 6.9 (CH_3), 12.7 (CH), 18.0 (CH_3), 18.1 (CH_3), 31.8 (CH_2), 45.7 (CH), 50.8 (CH), 51.3 (CH), 55.6 (CH_3), 55.7 (CH_3), 55.9 (CH_3), 68.2 (CH), 68.7 (CH), 104.1 (CH), 110.8 (CH), 111.9 (CH), 121.0 (CH), 134.0 (C), 147.7 (C), 148.4 (C), 178.8 (C), 200.7 (C); HRMS (ESI) m/z 605.3724 [M + H]$^+$, [$C_{33}H_{57}O_6Si_2$]$^+$ requires 605.3694.

(1*R*,5*S*,7*S*,8*R*,9*R*)-(+)-8-(3,4-Dimethoxyphenyl)-2-methoxy-5-(prenyl)-9-triethylsilanyloxy-7-triisopropylsilanyloxy-bicyclo[3.3.1]non-2-en-4-one 30

A solution of LDA·LiCl was prepared by treatment of a suspension of DIPA·HCl (141 mg, 1.03 mmol) in THF (2.5 mL) at −78 °C with ^{n}BuLi (1.28 mL, 2.05 mmol, 1.6 M solution in hexanes). The solution was allowed to warm to RT and after 10 min re-cooled to −78 °C. The LDA·LiCl solution was added dropwise *via* syringe to a solution of bicyclic compound **29** (124 mg, 0.20 mmol) in THF (2 mL) at −78 °C resulting in a yellow-coloured solution. The solution was stirred at −78 °C for 3 h, followed by addition of prenyl bromide (0.25 mL, 2.05 mmol, 10 eq.) and stirring for a further 4 h at −78 °C. The reaction mixture was quenched after this period with H_2O (5 mL) followed by extraction with EtOAc (3 × 5 mL). The organic layers were combined and washed with saturated aqueous NaCl (15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 4 : 1) gave the title compound **30** as a pale yellow oil (35 mg, 26%); $[\alpha]_D^{22}$ +73 (*c* 0.15 in $CHCl_3$); ν_{max} ($CHCl_3$) 2256, 1816, 1793, 1380, 1095, 947, 888, 641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66–0.74 (m, 6H, OSi(CH_2CH$_3$)$_3$), 0.78–0.88 (m, 21H, OSi(C*H*(CH_3)$_2$)$_3$), 1.06 (t, *J* 8.0, 9H, OSi(CH$_2$CH_3)$_3$), 1.64 (s, 3H, C=C(CH_3)$_2$), 1.65 (s, 3H, C=C(CH_3)$_2$), 1.74 (dd, *J* 12.0, 5.2, 1H, CH*H*), 1.93 (t, *J* 12.0, 10.3, 1H, C*H*H), 2.20 (dd, *J* 15.0, 7.0, 1H, CH*H*CH=C(CH$_3$)$_2$), 2.56 (dd, *J* 15.0, 7.0, 1H, C*H*HCH=C(CH$_3$)$_2$), 2.69 (dd, *J* 4.0, 4.0, 1H, 5-C*H*), 3.20 (dd, *J* 10.3, 4.0, 1H, ArC*H*), 3.54 (s, 3H, OCH_3), 3.81 (s, 3H, ArOCH_3), 3.85 (s, 3H, ArOCH_3), 4.07 (d, *J* 4.0, 1H, C*H*OSi(CH$_2$CH$_3$)$_3$), 4.16 (ddd, *J* 10.3, 10.3, 5.2, 1H, C*H*OSi(CH(CH$_3$)$_2$)$_3$), 4.91 (t, *J* 7.0, 1H, C*H*=C(CH$_3$)$_2$), 5.54 (s, 1H, C=C*H*), 6.60 (d, *J* 1.9, 1H, Ar*H*), 6.63 (dd, *J* 8.2, 1.9, 1H, Ar*H*), 6.78 (d, *J* 8.2, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1 (CH_2), 7.0 (CH_3), 12.7 (CH), 18.0 (CH_3), 18.2 (CH_3), 25.8 (CH_3), 26.9 (CH_3), 31.3 (CH_2), 39.4 (CH_2), 45.8 (CH), 51.2 (CH), 53.4 (CH), 55.4 (CH_3), 55.6 (CH_3), 55.9 (CH_3), 68.8 (CH), 70.0 (CH), 104.5 (CH), 110.9 (CH), 111.9 (CH), 119.7 (CH), 121.0 (CH), 133.5 (C), 147.7 (C), 148.4 (C), 177.0 (C), 201.4 (C); HRMS

(ESI) m/z 557.3293 $[M - OSi(CH_2CH_3)_3]^+$, $[C_{32}H_{49}O_6Si]^+$ requires 557.3298.

Typical procedure B for lithiation substitution using LTMP (Table 2): (1*S*,5*S*,7*S*,8*R*)-(+)-8-(3,4-dimethoxyphenyl)-2,9,9-trimethoxy-7-triisopropylsilanyloxy-3-trimethylsilanyl-bicyclo[3.3.1]non-2-en-4-one 31

A solution of LTMP was prepared by adding ^{n}BuLi (0.59 mL, 0.93 mmol, 1.6 M solution in hexanes) to tetramethylpiperidine (0.19 mL, 0.93 mmol, 5 eq.) in THF (1 mL) at −78 °C. The solution was allowed to warm to RT and after 10 min re-cooled to −78 °C. This LTMP–THF solution was added dropwise *via* syringe to a solution of bridged ketone **16** (100 mg, 0.19 mmol) in THF (1 mL) at −78 °C resulting in a deep yellow-coloured solution. The solution was stirred at −78 °C for 3 h, followed by addition of trimethylsilyl chloride (0.24 mL, mmol, 10 eq.) and stirring for a further 3 h at −78 °C. The reaction mixture was quenched after this period with H_2O (5 mL) followed by extraction with EtOAc (3 × 5 mL). The organic layers were combined and washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (petroleum ether–EtOAc 4 : 1) gave the title compound **31** as a clear viscous oil (53 mg, 45%); $[\alpha]_D^{22}$ +169 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 2941, 2866, 1634, 1565, 1462, 1366, 1141, 1108, 1027, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.22 (s, 9H, Si(C*H*$_3$)$_3$), 0.72–0.89 (m, 21H, OSi(C*H*(C*H*$_3$)$_2$)$_3$), 1.81–1.87 (m, 1H, CH*H*), 2.13 (ddd, *J* 12.5, 9.2, 5.3, 1H, C*H*H), 2.80–2.82 (m, 1H, 1-C*H*), 2.86 (s, 3H, OC*H*$_3$), 3.11 (s, 3H, OC*H*$_3$), 3.16 (dd, *J* 10.9, 3.0, 1H, ArC*H*), 3.22–3.24 (m, 1H, 5-C*H*), 3.31 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, ArOC*H*$_3$), 3.86 (s, 3H, ArOC*H*$_3$), 4.25 (ddd, *J* 10.9, 10.9, 5.3, 1H, C*H*OSi(CH(CH$_3$)$_2$)$_3$), 6.76–6.81 (m, 3H, 3 × Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.82 (CH_3), 12.6 (CH), 17.9 (CH_3), 18.1 (CH_3), 34.4 (CH_2), 44.3 (CH), 47.3 (CH_3), 48.5 (CH_3), 48.7 (CH), 49.7 (CH_3), 54.4 (CH_3), 55.7 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 68.1 (CH), 101.2 (C), 111.1 (CH), 116.8 (C), 132.9 (C), 148.2 (CH), 148.7 (C), 180.9 (C), 201.9 (C); HRMS (ES) m/z 607.3461 $[M + H]^+$, $[C_{32}H_{55}O_7Si_2]^+$ requires 607.3486.

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