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A formal total synthesis of (+)-apicularen A: base-induced conversion of apicularen-derived intermediates into salicylihalamide-like products

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A synthesis of apicularen precursor (−)-**6** in 18 steps from D-glucal is reported. As (+)-**6** has been converted into the potent, naturally occurring salicylate anti-cancer agent, (−)-apicularen A in 8 steps, this study constitutes a formal total synthesis of (+)-apicularen A. Key steps in the synthetic route include: (i) useful D-glucal elaboration processes, (ii) organometallic displacements at carbohydrate C-6 triflates using Knochel-type and related functionalised, aromatic Grignard reagents, (iii) stereoselective allyltrimethylsilane–acetal reactions generating *C*-allyl systems, (iv) stereocontrolled aldehyde allylation processes from both substrate and reagent, and (v) a novel Keck-type macrolactonisation. In addition, preliminary studies are reported in which a procedure has been devised to convert apicularen-derived intermediates into salicylihalamide-like products.

Introduction

Apicularen A (**1**) (Fig. 1) was originally isolated from the myxobacterial genus *Chondromyces* by Jansen *et al.* in 1998.[1] Apicularen B (**2**), a glycosylated co-metabolite of apicularen A was isolated from the same source. Biological screening indicated that apicularen B showed weak antimicrobial activity against some Gram-positive bacteria, *e.g. Micrococcus luteus* (MIC 12.5 μg ml^{-1}), and moderate cytotoxic activity with IC_{50} values ranging between 0.2 and 1.2 μg ml^{-1}. Apicularen A did not show any antibiotic activity but exhibited remarkably high cytostatic activity (IC_{50} values between 0.3 and 3 ng ml^{-1} against nine different human cancer cell lines). Furthermore, Sasse[2] observed several abnormal effects in tumour cells suggesting a novel mode of action.

Other related salicylate anti-tumour natural products are known,[3] including salicylihalamide A (**3**),[3a] lobatamide C (**4**),[3b] CJ-12950[3c] and oximidine I (**5**).[3d] These families of compounds were tested in the NCI 60 cell-line tumour screen and it was found that as well as acting *via* a novel mode of action they all share the same (or similar) molecular target. Recent studies have established that these compounds are selective inhibitors of mammalian vacuolar (H^+)-ATPase.[4]

The potent biological activity, structural novelty and limited availability of these salicylate anti-tumour natural products has resulted in the development of numerous synthetic approaches[5] culminating in recent total syntheses of salicylihalamide A by De Brabander *et al.*,[6a] Fürstner *et al.*,[6b] Labrecque *et al.*,[6c] Smith and Zheng[6d] and Snider and Song,[6e] of lobatamide C by Porco *et al.*,[6f] and of apicularen A by De Brabander's group,[6g] together with a formal total synthesis of the latter compound.[7]

This paper details the formal total synthesis of apicularen A using a carbohydrate based route.[7] D-Glucal is used to prepare the protected, side-chain truncated macrolide (−)-**6** (Scheme 1); (+)-**6** has been utilised by De Brabander *et al.* during their total synthesis of apicularen A.[5d,6g] We also report our findings concerning the base-induced ring opening of the tetrahydropyran ring in an apicularen intermediate. This kind of process may be

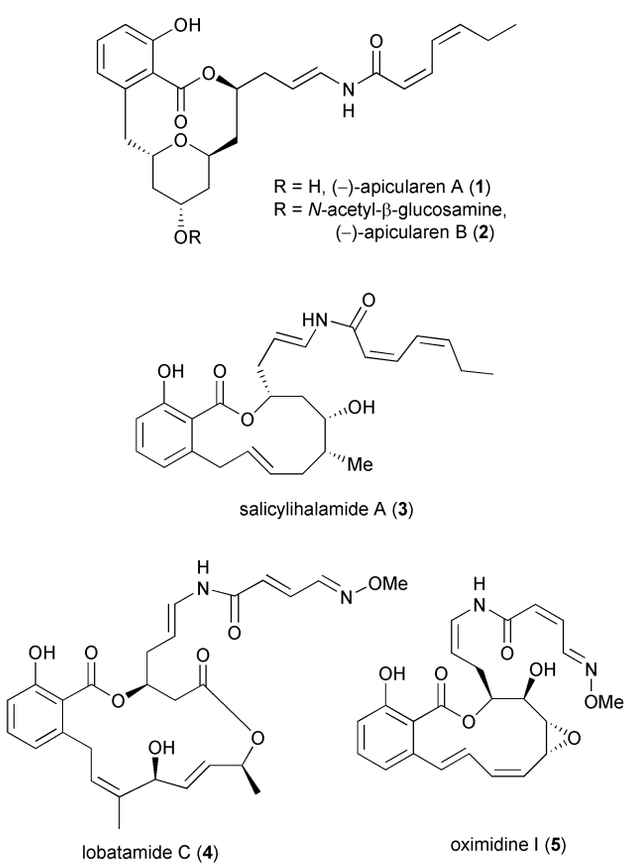
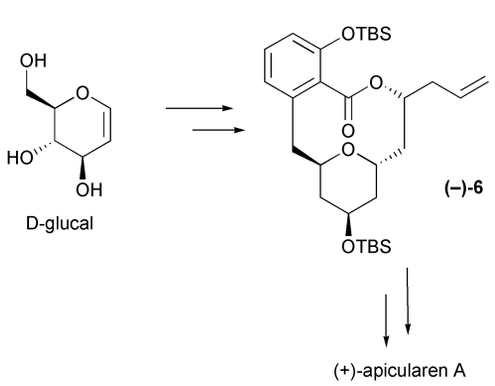


Fig. 1



Scheme 1

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involved in the biosynthetic conversion of apicularens into other members of the salicylate family (or *vice versa*).[5p,r]

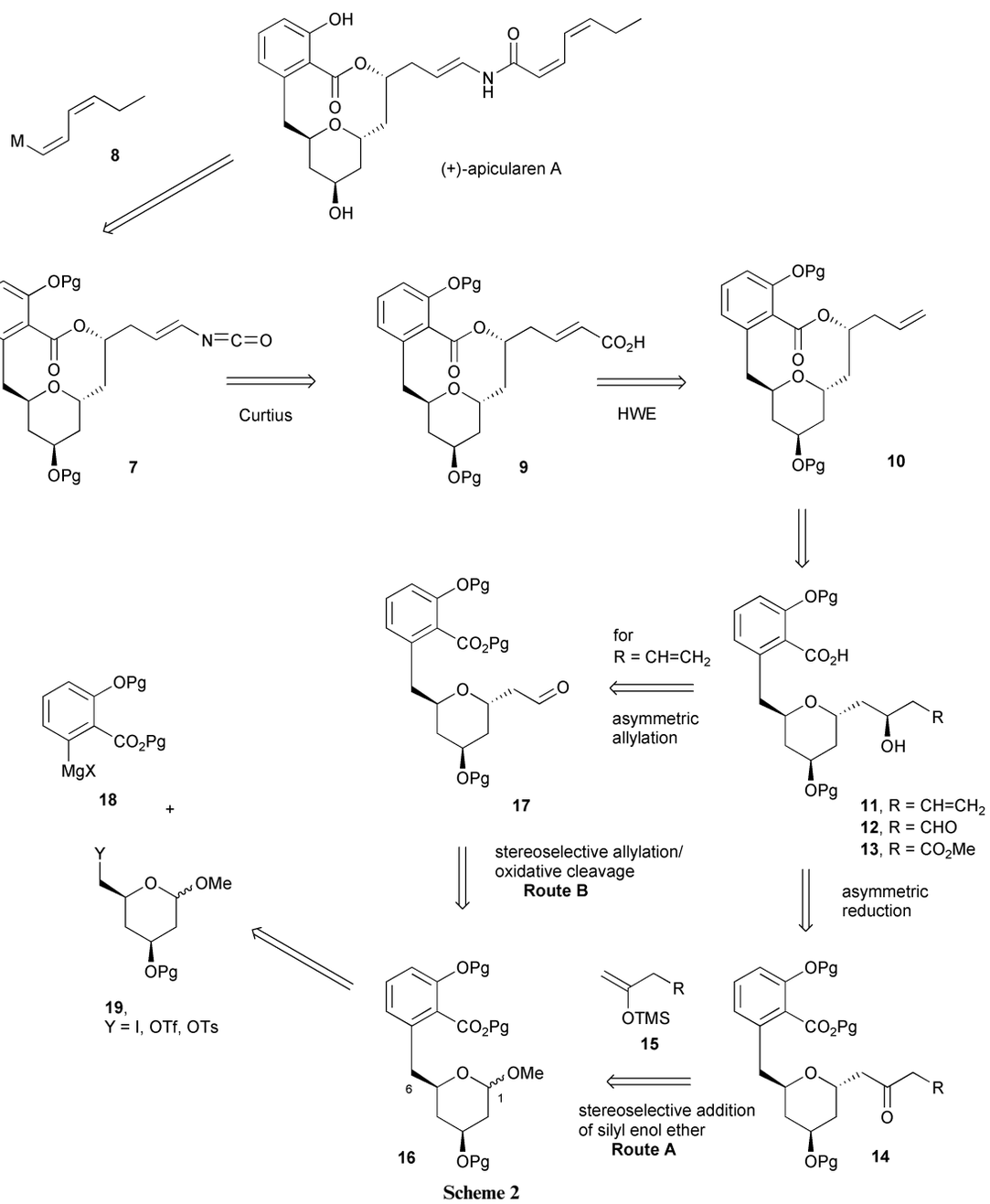
(i) Formal total synthesis of (+)-apicularen A

The absolute stereochemistry of apicularen A was mis-assigned in the original publication[1a] and was subsequently revised to the enantiomeric form.[1c] As we commenced our study before the publication of the structural revision, we concentrated our efforts on the synthesis of the enantiomer of the natural product.

The unsaturated enamide side chains are characteristic structural features of the salicylate anti-tumour natural products, and provide a significant synthetic challenge. We decided to construct these side chains *via* vinyl organometallic addition to unsaturated isocyanates, and in model studies successfully developed this methodology for the preparation of enamide side chains of the apicularen/salicylihalamide (hydrocarbon terminated),[5g] and lobatamide/oximidine (oxime terminated)[5h] types.

Retrosynthetic analysis of (+)-apicularen A **1** therefore suggested disconnection of the *Z,Z*-enamide to give isocyanate **7** and organometallic reagent **8** (Scheme 2). We have previously described the preparation of reagent **8** (M = Cu) by a double acetylene carbocupration process,[8] and indeed this methodology has been successfully employed in the total syntheses of salicylihalamide A reported by the groups of Smith[6d] and Snider.[6e] Isocyanate **7** should be available by Curtius rearrangement of the acyl azide derived from carboxylic acid **9**, and again we carried out model studies[5g,h] to establish the viability of this approach. Horner–Wadsworth–Emmons alkene formation and functional group interconversion lead back to the allylic intermediate **10**, itself obtained by macrolactonisation of hydroxy-acid **11**. Alternatively, functionalised intermediates **12** and **13** were also considered viable at this stage.

We envisaged two possible strategies for incorporation of the appendage at C-1 of the tetrahydropyran (Routes A and B, Scheme 2). The chiral alcohol could be produced by β-alkoxy- or reagent-directed asymmetric reduction of a ketone **14**. Side-chains containing ketone functionalities have been introduced at C-1 of sugar derivatives with good α-selectivity by reaction of silyl enol ethers **15** with acetals of type **16**[9] and we were keen to establish whether functionalised silyl enol ethers were

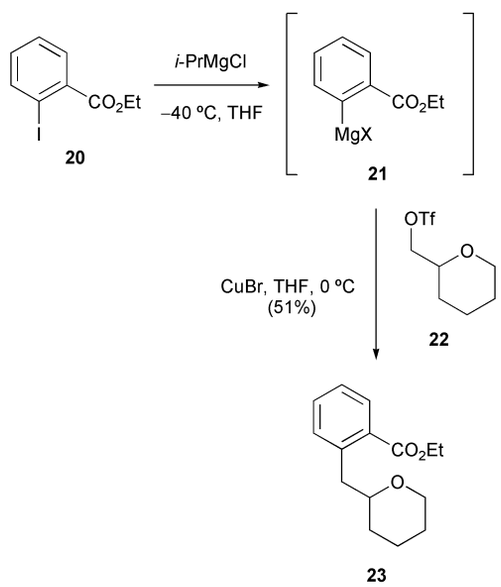


Scheme 2

applicable to this type of reaction (Route A). An alternative methodology involved the use of an allyl group as a masked aldehyde (Route B). In this second route, the asymmetric allylation of aldehyde **17** would be employed to install the secondary alcohol in the side chain with the appropriate stereocontrol. Lewis acid-promoted reactions of acetals of type **16** with allyltrimethylsilane are well-established for the generation of *C*-glycosides possessing the required α-stereochemistry.[10]

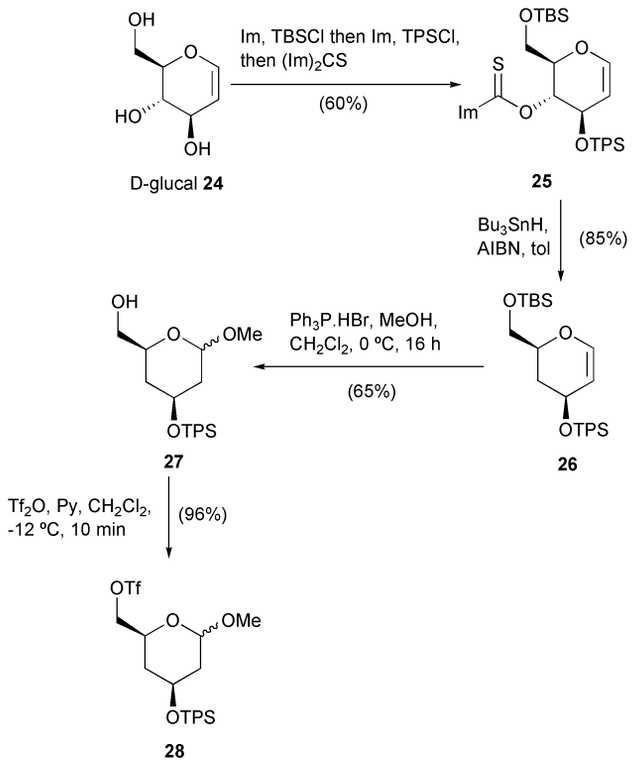
Construction of the sp^2–sp^3 bond of **16** at C-6 was considered possible by reaction of a functionalised organometallic of type **18** with a suitable electrophile **19** (Scheme 2). Although Grignard or organolithium reagents incorporating esters are generally considered to be synthetically non-viable, recent work by Knochel[11] and Oshima[12] and their co-workers indicates that reagents **18** should be accessible. We were aware, however, that β-oxygenated electrophiles such as **19** are known to possess reduced electrophilicity.[13] We therefore set out to explore the synthesis of system **16** from precursors such as **18** and **19** as the first part of this study.

Knochel *et al.* have shown that a range of functionalised aryl iodides can be converted into the corresponding Grignard reagents at low temperature by use of an iodine–magnesium exchange reaction.[11] As a model system, we initially examined whether Grignard reagent **21** could be derived from ethyl *o*-iodobenzoate **20** and then coupled with triflate **22** to produce adduct **23** (Scheme 3).



Scheme 3

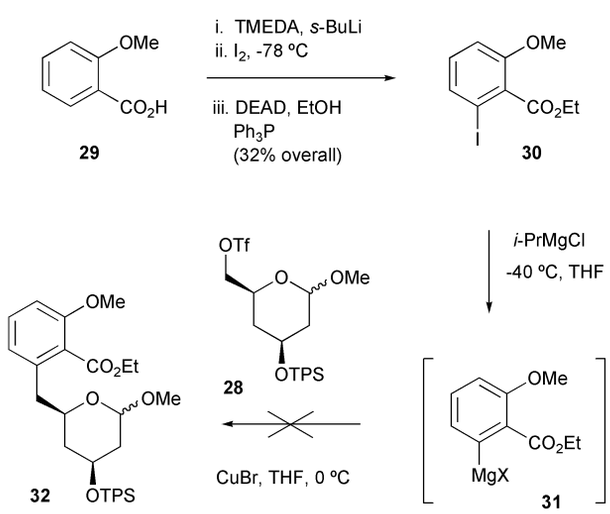
After generation of the Grignard reagent **21** using Knochel's conditions (^{i}PrMgCl, THF, −40 °C), copper(I)-catalysed coupling with triflate **22** at the same temperature failed to produce adduct **23**. However, by allowing the reaction temperature to warm to 0 °C, the required coupling proceeded in reasonable yield (51%) to produce **23**. Encouraged by this result, we embarked upon construction of the core tetrahydropyran-ring system **28** required in our synthesis (Scheme 4). Derivatisation of each hydroxy of D-glucal **24** in a one-pot procedure using a three reagent sequence (successively TBSCl, TPSCl then thiocarbonyldiimidazole) gave the protected derivative **25** in 60% overall yield after chromatography. The tri-protected D-glucal **25** then underwent Bu_3SnH-mediated deoxygenation *via* a Barton–McCombie type process[14] to give dihydropyran **26**. Acid-catalysed addition of methanol to the enol ether moiety,[15] together with concomitant deprotection of the primary TBS group, was then achieved using triphenylphosphine hydrobromide in dichloromethane–methanol giving primary alcohol **27** as a mixture of anomers. Reaction with triflic anhydride then



Scheme 4

gave the unstable triflate derivative **28** which was used immediately in the subsequent coupling reaction.

Meanwhile, the aryl iodide coupling partner **30** was successfully prepared from *o*-anisic acid **29** *via* *o*-lithiation and iodination,[16] followed by Mitsunobu esterification (Scheme 5).

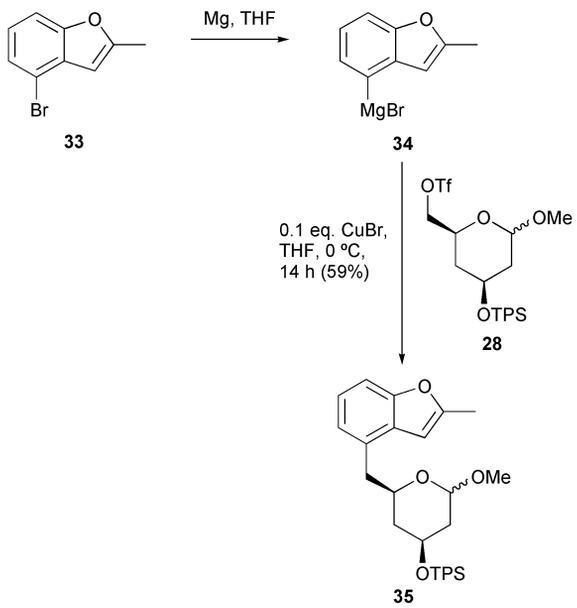


Scheme 5

Disappointingly, none of the desired product **32** could be isolated following treatment of iodide **30** with triflate **28** under the previously-devised conditions for Grignard formation and copper-catalysed coupling. Presumably the intermediate Grignard reagent **31** was less stable than the model version **21** and failed to survive the elevated reaction temperatures required for reaction with the relatively unreactive electrophile **28**.

We therefore looked for a more stable alternative to Grignard reagent **31** and examined Kotsuki's benzofuryl reagent **34**, which has been designed as a masked nucleophilic *o*-hydroxybenzoic acid synthon: the latent functionality can be revealed by oxidative furan cleavage (see later).[17] The starting material required for this procedure, 4-bromo-2-methylbenzofuran **33**,

was prepared using the method published by Kotsuki *et al.*,[17] and after some experimentation with reaction conditions, we discovered that it was possible to couple Grignard reagent **34** to triflate **28** using Cu(I)-catalysis producing adduct **35** in 59% yield (Scheme 6).

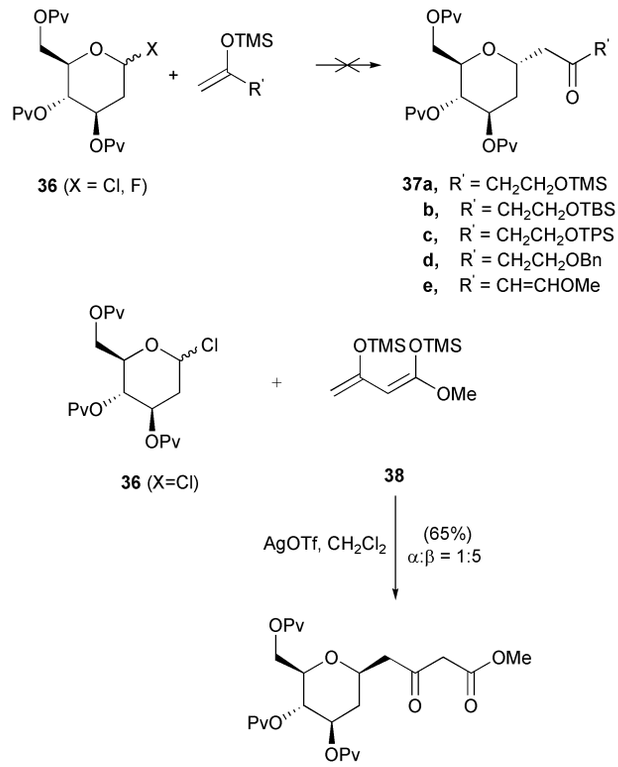


Scheme 6

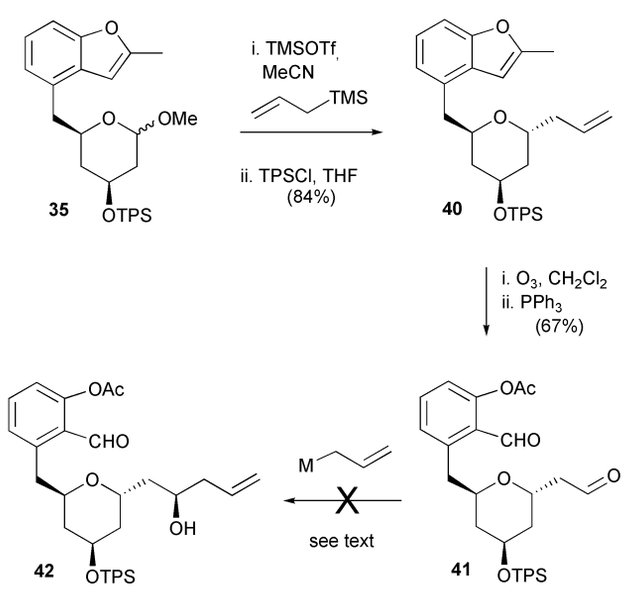
Having established a procedure for the introduction of the C-6 substituent, we turned our attention towards the introduction of a suitably functionalised side-chain at the C-1 position. Initial studies utilised the model compounds **36** (X = Cl, F) and focused on the incorporation of a 4-carbon fragment by use of silyl enol ether methodology (Scheme 2, Route A). Reactions of simple silyl enol ethers with sugar-derived electrophiles are well-documented,[9] but extension of this technique to functionalised nucleophiles has seen little attention to date. We required a 4-carbon oxygenated silyl enol ether for later elaboration. To this end we examined a series of functionalised silyl enol ethers **37a**–**e** prepared by LDA deprotonation of the corresponding ketones followed by enolate trapping using chlorotrimethylsilane.[18] Unfortunately, this methodology gave a mixture of regioisomeric enol ethers, despite the use of hindered alcohol protecting groups, and all of the silyl enol ethers proved to be unstable to the coupling conditions. However, the known bis-silyl enol ether **38**[19] possesses higher stability, and reaction of this with a model deoxyglycosyl chloride **36** (X = Cl), mediated by silver triflate in dichloromethane, successfully generated the *C*-glycoside **39**, in good yield but with the undesired β-stereochemistry predominating (Scheme 7). Efforts to bias the stereoselectivity of the reaction towards the α-anomer by use of boron trifluoride–diethyl ether in acetonitrile[20] gave a poor yield of a mixture of anomers (<30%, α : β >5:1) which were difficult to separate and purify.

These disappointing results led us to examine the more stereochemically reliable reactions of allyltrimethylsilane as outlined in Scheme 2, Route B. We decided to retain the benzofuryl group during the anomeric coupling procedure and therefore investigated the allylation of methyl acetal **35** (Scheme 8). Treatment of acetal **35** with allyltrimethylsilane–TMSOTf–MeCN, conditions known[10] to promote α-allylation, produced exclusively the required *C*-allylated adduct **40**, after resilylation to restore the protection lost by partial cleavage during the Lewis acid-mediated coupling conditions. Adduct **40** was isolated in 84% yield over these two steps with complete α-stereocontrol (as deduced from anomeric coupling constants).

Subsequent ozonolysis of **40** resulted in the cleavage of both the terminal alkene and the benzofuran giving dialdehyde **41** in



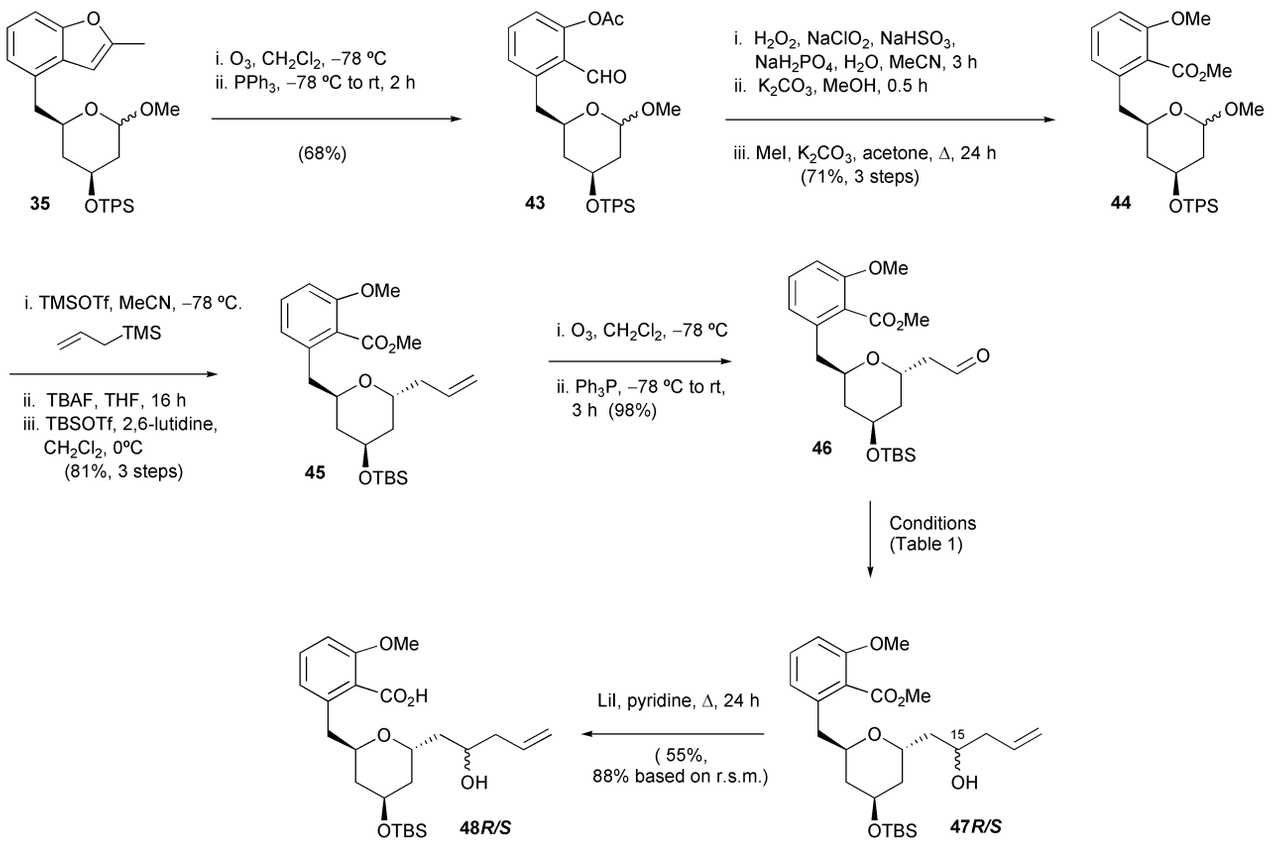
Scheme 7



Scheme 8

67% yield. Given the expected lower reactivity of the aromatic aldehyde of **41**, we had hoped to perform a regio- and stereoselective allylation reaction at the aliphatic aldehydic centre. However, subjection of compound **41** to several allylation conditions [allylmagnesium bromide, allyltrimethylsilane–dimethylaluminium chloride,[21] allyl(diisopinocampheyl)borane[22]] failed to give any of the desired allyl compound **42**.

The inability to discriminate between the two aldehydes in compound **41** encouraged us to carry out these oxidative cleavage processes in a sequential manner (Scheme 9). Thus, intermediate **35**, described earlier, was subjected to benzofuranyl ozonolytic cleavage to give mono-aldehyde **43**. Subsequent aldehyde oxidation and acetyl saponification followed by concomitant methylation of both of the resultant benzoic



Scheme 9

acid and phenol groups led us to the required salicylate core **44** (Scheme 9).

Reaction of allyltrimethylsilane with acetal **44** using the allyltrimethylsilane–TMSOTf–MeCN conditions described above again gave the desired α-*C*-allylated product, this time with a significant amount of TPS group cleavage. Unfortunately, the resultant secondary alcohol could not be reprotected using TPSCl, presumably for steric reasons. Therefore, complete removal of the TPS group was carried out using fluoride and then the product was treated with the more reactive silylating agent TBSOTf to give the TBS ether **45** in 81% yield over the three steps (Scheme 9). The next step in this revised synthetic strategy was the oxidative cleavage of the terminal double bond of alkene **45**. This was again achieved using ozone, with a reductive work up, giving a quantitative yield of aldehyde **46** (Scheme 9).

We were then ready for a second attempt at stereoselective allylation (*cf.* Scheme 8), this time without the problem of regioselectivity. Initial attempts (Scheme 9, and Table 1) with aldehyde **46**, utilised allyltrimethylsilane in the presence of chelating Lewis acids, with a view to obtaining the 15*S*-diastereomer of product **47** for subsequent Mitsunobu lactonisation.[23] The best result (entry i) was obtained using dimethylaluminium chloride giving the 1,3-*anti* and 1,3-*syn* addition products **47*S*** and **47*R*** in a ratio of 85 : 15.[21] The structure of the major isomer was assigned with the help of Mosher ester studies.[24] Interestingly (entry ii), the use of titanium(IV) chloride in this reaction lead to no diastereoselective bias at the C-15 centre, which is unusual, although a similar result was reported by De Brabander during his total synthesis of apicularen A.[5d]

The use of reagent control was also successful (entry iii), Brown's allyl(diisopinocampheyl)borane[22] reacting with aldehyde **46** to give a 90 : 10 predominance of the required 1,3-*syn* addition product **47*R*** in good yield.

Cleavage of the methyl ester in **47** was then attempted using hydrolytic conditions [*e.g.* LiOH, $Ba(OH)_2$] but without success. However, we were pleased to find that lithium iodide-induced *O*-alkyl ester cleavage allowed access to the macrocyclisation precursors **48*R*** and **48*S*** (90 : 10) in good yield.

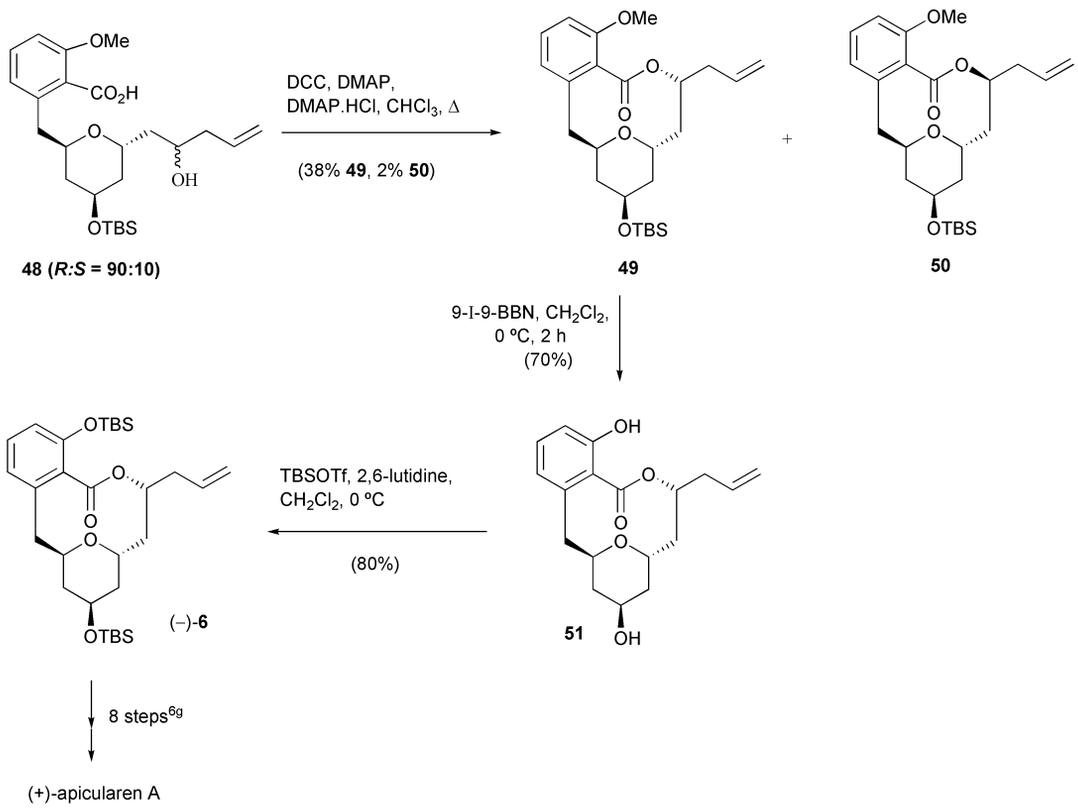
Several different lactonisation methods were assessed in order to close the macrocyclic ring-system. Whilst the procedures of Mitsunobu[23] and Yamaguchi and co-workers[25] gave none of the desired lactone, the DCC–DMAP procedure developed by Boden and Keck[26] successfully afforded the lactone **49**, together with a small amount of the C-15 epimer **50**, which was easily separated by chromatography (Scheme 10).

Finally, silyl and methyl group deprotection of **49** with iodo-9-BBN[27] gave the diol **51**, which was fully characterised and found to have comparable spectroscopic/analytical data to those reported by De Brabander *et al.* for the enantiomeric compound.[5d,6g] For example, the ^{13}C NMR data for **51** are compared to published data[5d] in Table 2.

Silylation of both the phenolic and secondary hydroxy groups then gave the corresponding bis-TBS ether (−)-**6**. The enantiomeric compound, (+)-**6**, has been converted into (−)-apicularen A by De Brabander *et al.*[5d,6g] The chemistry described herein, by preparation of the advanced apicularen intermediate (−)-**6**, thus constitutes a formal total synthesis of (+)-apicularen A.

Table 1 Stereoselectivity in the conversion of **46** into **47*R/S***

	Conditions	Yield **47**(%)	Ratio of 15*S* : 15*R*
(i)	Allyltrimethylsilane, −78 °C, Me_2AlCl, 30 min	85	85 : 15
(ii)	$TiCl_4$, −78 °C, allyltrimethylsilane, 1 h	35	50 : 50
(iii)	(−)-*B*-Allyl-β-(diisopinocampheyl)borane, Et_2O, −78 °C, 3 h	77	10 : 90



Scheme 10

Table 2 Key comparative data for apicularen precursor **51** (published[5d] values in brackets)[a]

δ_C (125 MHz, acetone-d_6): 169.28 (169.3), 154.31 (154.3), 140.23 (139.6), 135.32 (135.4), 130.38 (130.3), 125.47 (125.5),[b] 122.34 (122.4), 117.48 (117.5), 114.43 (114.4), 73.65 (73.7), 73.61 (73.6), 68.08 (68.1), 64.91 (64.9), 40.36 (40.4), 40.10 (40.1), 39.96 (40.0), 39.72 (39.8), 39.13 (39.1).

[a] Corrected for calibration at acetone, 29.84 (rather than 30.38[5d]). [b] The peak at δ 125.5 was not reported in the original paper[5d] where an erroneous peak at δ 160.7 was included. In a personal communication Professor De Brabander confirmed the revised data shown above.

(ii) Tetrahydropyran-ring cleavage: conversion of the apicularen nucleus into salicylihalamide-type products

As a brief extension to our apicularen synthetic studies, we decided to explore the ring-opening of the tetrahydropyran ring, possibly leading to salicylihalamide-type products, and then, if successful, the re-closure of the tetrahydroyran ring system returning to the apicularen nucleus. We felt that such studies would be valuable in terms of evaluating the possibility of devising a unified approach to both types of natural products, and could provide information concerning possible biosynthetic pathways.

We decided to attempt this interconversion *via* tetrahydropyranone **52**, which we aimed to subject to ring-opening conditions (Scheme 11). The regioselectivity in this proposed enolate β-elimination process would obviously be of interest, but we were hoping to observe at least partial conversion into enone **53** which possesses a salicylihalamide-like nucleus. In turn, we hoped to investigate the ring closure of hydroxy enone **53** to return to the apicularen nucleus **52** in what appears to be a likely biosynthetic sequence.[5p,r]

The key pyranone **52** was readily prepared from silyl ether **49** in 94% overall yield by fluoride-mediated deprotection followed by Dess–Martin oxidation. Initial attempts to ring-open the tetrahydropyran moiety of **52** involved the use of weak acids and bases but were not successful. However, when pyranone **52** was treated with an excess of LDA a hydroxy-alkene was formed in 20% yield. To our initial surprise, the product was not enone **53**, nor the regioisomeric enone, but the styrene **54**. The identity of compound **54** was confirmed unambiguously by X-ray crystallography.[28] It is possible that pyranone **52** is first converted into enone **53** which subsequently undergoes isomerisation to give styrene **54**: however, it seems more likely that styrene **54** is generated directly from **52** by benzylic deprotonation. We next attempted to recyclise **54** by treatment with base, but unfortunately without success. Lack of material precluded further studies such as the base-mediated ring-opening of **49** and the acid-catalysed ring-closure of **54**. Although further research is obviously required, these preliminary experiments demonstrate the first conversion of the apicularen nucleus into a salicylihalamide-type product thus suggesting an alternative synthetic approach to the salicylihalamides, and may be instructive in terms of biosynthetic studies.

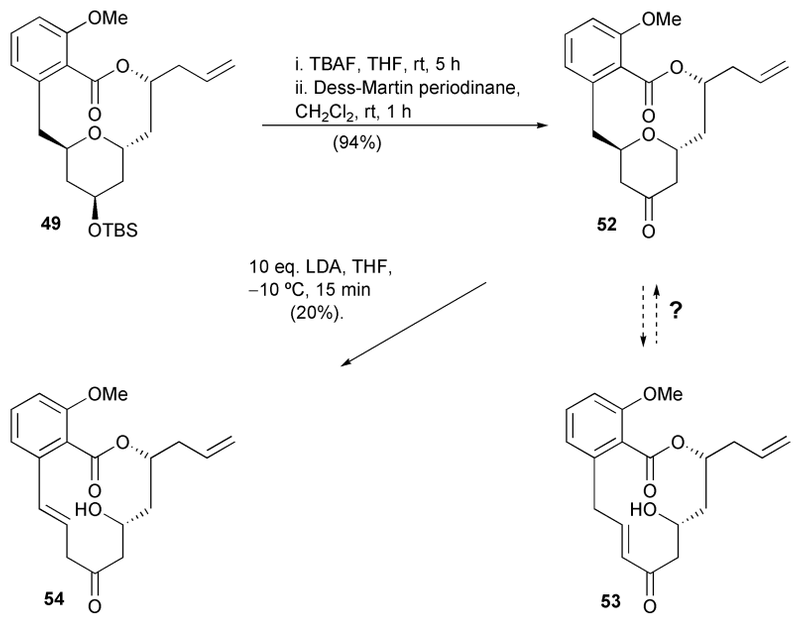
Conclusions

Compound (+)-**6** has been converted into (−)-apicularen A in 8 steps (4% overall yield) by a published procedure.[6a,5a] The synthetic studies described herein therefore constitute a formal total synthesis of (+)-apicularen A. Tetrahydropyran ring opening has been achieved using pyranone **52**, providing interesting mechanistic and biosynthetic insights.

Experimental

General

All reactions were carried out under a nitrogen atmosphere. THF and diethyl ether (Et_2O) were dried over Na–benzophenone ketyl; CH_2Cl_2 was dried over CaH_2 and distilled immediately before use. Where necessary, acetonitrile and toluene were purchased in anhydrous form. Column chromatography was carried out using 70–200 or 33–63 micron (60 Å) silica gel. NMR spectra were recorded using JEOL GX-270 or Bruker



Scheme 11

AMX-500 instruments in the solvents indicated; chemical shifts (δ) in ppm are given relative to Me_4Si, coupling constants (J) in Hz. Infra-red spectra were recorded on an API Mattson Genesis FT-IR. Melting points were obtained using an Electrothermal IA9100 digital apparatus (uncorrected). Optical rotations: JASCO DIP-370 digital polarimeter at 20 °C (Na-D line, 589 nm). Mass spectra were obtained on a Fisons analytical (VG) autospec instrument. CuBr was purified by precipitation from conc. HBr.[29] Tf_2O was re-distilled from P_2O_5 before use. All other commercially available compounds were used as received.

Ethyl 2-(tetrahydro-2*H*-pyran-2-ylmethyl)benzoate (23)

To a stirred solution of ester **20** (750 mg, 2.66 mmol) in THF (5 mL) at −40 °C was added isopropylmagnesium chloride (1.5 mL, 3.0 mmol, 2 M in diethyl ether) dropwise. The mixture was stirred at this temperature for 40 min then copper(I) bromide (85 mg, 0.59 mmol) was added followed by a solution of triflate **22**[13] (400 mg, 1.61 mmol) in THF (3 mL). The mixture was warmed to 0 °C over 30 min, stirred at this temperature for 5 h then quenched with sat. NH_4Cl(aq) and extracted with diethyl ether. The organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give an oil which was purified by flash chromatography (petroleum ether : EtOAc, 8 : 1) to give the *title compound* **23** (202 mg, 51%) as a colourless oil; R_f 0.50 (petroleum ether : EtOAc, 7 : 1); ν_{max}/cm^{-1} (thin film) 2980, 2636, 2848, 1717, 1601, 1447, 1365, 1256, 1088, 1047; δ_H (270 MHz, $CDCl_3$): 7.89 (dd, 1 H, J = 8.0, 1.5 Hz), 7.42 (ddd, 1 H, J = 8.0, 8.0, 1.5 Hz), 7.32–7.24 (m, 2 H), 4.37 (q, 2 H, J = 7.0 Hz), 3.98–3.91 (m, 1 H), 3.58–3.48 (m, 1 H), 3.35 (ddd, 1 H, J 11.5, 11.5, 2.5 Hz), 3.17 (dd, 1 H, J = 13.0, 5.0 Hz), 3.09 (dd, 1 H, J = 13.0, 7.5 Hz), 1.85–1.79 (m, 1 H), 1.65–1.27 (m, 5 H), 1.41 (t, 3 H, J = 7.0 Hz); δ_C (67.9 MHz, $CDCl_3$): 168.3, 140.8, 132.8, 131.9, 130.9, 130.8, 126.6, 79.0, 68.9, 61.2, 41.7, 32.2, 26.5, 24.0, 14.7. Found: C, 72.54; H, 8.37%. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%. Found (CI): 249.1489 [MH]$^+$, $C_{15}H_{20}O_3$ requires 249.1491 (0.7 ppm error); *m*/*z* (CI) 249 (100%, [MH]$^+$), 203 (15).

1,5-Anhydro-6-*O*-[*tert*-butyl(dimethyl)silyl]-3-*O*-[*tert*-butyl-(diphenyl)silyl]-2-deoxy-4-*O*-(1*H*-imidazol-1-ylthiocarbonyl-oxy)-D-*arabino*-hex-1-enitol (25)

To a stirred solution of D-glucal **24** (8.98 g, 61.4 mmol) in THF (180 mL) at rt was added imidazole (4.60 g, 68.0 mmol) followed by the slow addition of a solution of *tert*-butyldimethylsilyl choride (9.53 g, 61.4 mmol) in THF (10 mL). After 4.5 h another portion of imidazole (4.60 g, 68.0 mmol) and a solution of *tert*-butyldiphenylsilyl chloride (15.4 mL, 16.5 g, 58.9 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 24 h then filtered and thiocarbonyldiimidazole (14.1 g, 71.8 mmol) added to the filtrate. After 20 h at rt the solvent was evaporated under reduced pressure and the residue purified by column chromatography (petroleum ether : EtOAc, 9 : 1) to give the *title compound* **25** (22.5 g, 60%) as a pale yellow gum; R_f 0.56 (petroleum ether : EtOAc, 4 : 1); $[\alpha]_D$ +23.7 (*c* 2.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2953, 2932, 2858, 1646, 1391, 1247, 1112; δ_H (270 MHz, $CDCl_3$): 8.20 (1 H, s), 7.72–7.66 (4 H, m), 7.51–7.32 (7 H, m), 7.00–6.98 (1 H, m), 6.40 (1 H, d, J = 6.5 Hz), 5.94 (1 H, td, J = 4.0, 1.0 Hz), 4.63 (1 H, ddd, J = 6.5, 4.5, 1.0 Hz), 4.41–4.34 (1 H, m), 4.24–4.21 (1 H, m), 4.14 (1 H, dd, J = 7.0, 11.5 Hz), 4.03 (1 H, dd, J = 4.5, 11.5 Hz), 1.08 (9 H, s), 0.93 (9 H, s), 0.11 (3 H, s), 0.09 (3 H, s); δ_C (67.9 MHz, $CDCl_3$): 182.4, 143.5, 136.8, 135.8, 133.3, 132.5, 130.7, 130.0, 129.9, 127.8, 127.7, 117.9, 101.1, 78.5, 76.3, 63.4, 61.5, 26.8, 25.9, 19.1, 18.3, −5.3, −5.4. Found (CI): 609.2631 [MH]$^+$, $C_{32}H_{45}N_2O_4SSi_2$ requires 609.2639 (1.3 ppm error); *m*/*z* (CI) 609 (25%, [MH]$^+$), 69 (100).

2,6-Anhydro-1-*O*-[*tert*-butyl(dimethyl)silyl]-4-*O*-[*tert*-butyl-(diphenyl)silyl]-3,5-dideoxy-D-*threo*-hex-5-enitol (26)

A stirred solution of D-glucal derivative **25** (1.40 g, 2.23 mmol) in toluene (40 mL) was degassed by the successive evacuation of the reaction flask (water pump), then flushing with Ar (3 times). The mixture was heated to reflux then a solution of tributyltin hydride (1.26 mL, 1.36 g, 4.68 mmol) and AIBN (95 mg) in toluene (10 mL) was added dropwise over 30 min. Heating was continued for a further 30 min then the reaction was cooled to rt and the solvent evaporated under reduced pressure to give an orange oil. This was purified by column chromatography (petroleum ether to petroleum ether : EtOAc, 9 : 1) to give the *title compound* **26** (920 mg, 85%, containing a small amount of tributyltin-derived impurity) as a pale yellow gum; R_f 0.83 (petroleum ether : EtOAc, 4 : 1); ν_{max}/cm^{-1} (thin film) 2957, 2931, 2856, 1644, 1471, 1427, 1251, 1110, 840, 701; δ_H (270 MHz, $CDCl_3$): 7.70–7.62 (4 H, m), 7.47–7.34 (6 H, m), 6.28 (1 H, dd, J = 6.5, 1.0 Hz), 4.67 (1 H, ddd, J = 6.5, 2.5, 1.5 Hz), 4.44–4.38 (1 H, m), 3.92–3.80 (2 H, m), 3.64–3.59 (1 H, m), 1.98–1.90 (1 H, m), 1.81–1.75 (1 H, m), 1.07 (9 H, s), 0.89 (9 H, s), 0.05 (6 H, s);

δ_C (67.9 MHz, $CDCl_3$): 144.3, 136.1, 136.1, 134.5, 134.4, 130.0, 127.9, 105.9, 75.5, 65.6, 63.9, 34.4, 27.3, 26.3, 19.4, 18.7, −4.3, −5.0. Found (CI): 500.3016 $[MNH_4]^+$, $C_{28}H_{42}O_3Si_2$ requires 500.3016 (0.1 ppm error); *m/z* (CI) 500 (<1%, $[MNH_4]^+$), 483 (<1), 425 (1), 244 (6), 227 (100), 196 (6).

Methyl 3-*O*-[*tert*-butyl(diphenyl)silyl]-2,4-dideoxy-D-threo-hexopyranoside (27)

To an ice-cooled, stirred solution of compound **26** (3.04 g, 6.30 mmol) and methanol (300 mg, 9.4 mmol) in dichloromethane (25 mL) was added triphenylphosphine hydrobromide (110 mg, 0.32 mmol). After 3 h at 0 °C, methanol (0.9 mL) and triphenylphosphine hydrobromide (290 mg) were added and the mixture was allowed to warm to rt then stirred for 2 h. Sat. $NaHCO_3$(aq) (15 mL) was then added and the mixture extracted with dichloromethane. The organic layers were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether : EtOAc, 4 : 1) to give the *title compound* **27** (1.44 mg, 65%, mixture of anomers) as a colourless gum; R_f 0.17 (petroleum ether : EtOAc, 4 : 1); ν_{max}/cm^{-1} (thin film) 3466, 2931, 1428, 1112, 1047, 703; δ_H (270 MHz, $CDCl_3$): 7.69–7.63 (4 H, m), 7.45–7.33 (6 H, m), 4.78 (1 H, d, J = 3.5 Hz), 4.23–4.08 (1 H, m), 3.64–3.42 (3 H, m) 3.20 (3 H, s), 2.02–1.95 (1 H, m), 1.89 (1 H, dd, J = 7.5, 5.5 Hz), 1.67–1.57 (2 H, m), 1.49–1.36 (1 H, dt, J = 11.5. 11.5 Hz), 1.04 (9 H, s); δ_C (67.9 MHz, $CDCl_3$): 136.0, 134.6, 134.5, 129.9, 127.9, 127.9, 99.5, 68.6, 65.9, 65.4, 54.2, 39.7, 37.0, 27.2, 19.4. Found (CI): 401.2157 $[MH]^+$, $C_{23}H_{32}O_4Si$ requires 401.2148 (2.1 ppm error); *m/z* (CI) 401 (1%, $[MH]^+$), 386 (3), 291 (59), 207 (67), 187 (100), 133 (67).

Ethyl 2-iodo-6-methoxybenzoate (30)

(a) To a stirred solution of TMEDA (3.40 mL, 22.5 mmol) in THF (50 mL) was added *sec*-butyllithium (1.4 M in cyclohexane, 16.0 mL, 22.4 mmol) at *ca.* −60 °C under N_2. The resultant yellow solution was cooled to *ca.* −100 °C (EtOH/liq. N_2 cooling bath) and a solution of 2-methoxybenzoic acid **29** (1.45 g, 9.53 mmol) in THF (10 mL) was added dropwise over 30 min. The orange–yellow mixture was stirred for a further 30 min at this temperature then warmed to −78 °C over 30 min. A solution of iodine (9.00 g, 35.4 mmol) in THF (10 mL) was then added until the brown colour persisted and the mixture was warmed to −60 °C then stirred at this temperature for a further 1 h. Sat. NH_4Cl(aq) (5 mL) was then added slowly followed by sat. Na_2SO_3(aq) until the brown colour had dissipated. The solution was then extracted with diethyl ether (100 mL) and the organic extract washed with 1 M NaOH (10 mL). The aqueous layers were then combined and acidified (10% HCl) and extracted with dichloromethane (4 × 100 mL), these organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product as a yellow oil containing unreacted 2-methoxybenzoic acid. This mixture was re-dissolved in methanol (15 mL) and conc. H_2SO_4 (0.75 mL), then stirred at reflux for 4 h. After cooling to rt, water (50 mL), then diethyl ether (50 mL) were added and the mixture was made alkaline with 1 M NaOH. The organic layer was separated and the aqueous phase further extracted with diethyl ether (50 mL). The aqueous layer was then acidified (10% HCl) and extracted with dichloromethane (3 × 50 mL). These organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give 2-iodo-6-methoxybenzoic acid (1.01 g, 39%) as colourless crystals; R_f 0.22 (EtOAc); mp 128–130 °C (lit.[30] mp 131.5–132 °C).

(b) To a stirred solution of the acid from (a) (526 mg, 1.91 mmol), triphenylphosphine (650 mg, 2.48 mmol) and ethanol (0.17 mL, 2.90 mmol) in THF (15 mL) at 0 °C was added dropwise diethyl azodicarboxylate (0.39 mL, 2.48 mmol). After 4 h, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether : EtOAc, 30 : 1) to give the *title compound* **30** (485 mg, 83%) as a colourless oil; R_f 0.84 (petroleum ether : EtOAc, 1 : 1); ν_{max}/cm^{-1} (thin film) 2979, 2940, 1731, 1584, 1567, 1461, 1430, 1264, 1104; δ_H (270 MHz, $CDCl_3$): 7.37 (dd, 1 H, J = 8.0, 0.5 Hz), 7.03 (t, 1 H, J = 8.0 Hz), 6.87 (d, 1 H, J = 8.0 Hz), 4.41 (q, 2 H, J = 7.0 Hz), 3.79 (s, 3 H), 1.40 (t, 3 H, J = 7.0 Hz); δ_C (67.9 MHz, $CDCl_3$): 167.7, 157.0, 131.7, 131.1, 130.6, 111.0, 92.7, 62.2, 56.7, 14.4. Found: C, 39.63; H, 3.55%. $C_{10}H_{11}IO_3$ requires C, 39.24; H, 3.62%). Found (EI): 305.9756 (M^+), $C_{10}H_{11}IO_3$ requires 305.9753 (1.0 ppm error); *m/z* (EI) 306 (40%, M^+), 261 (100), 218 (13), 203 (10), 151 (5).

{(4*S*,6*R*)-2-Methoxy-6-[(2-methyl-1-benzofuran-4-yl)methyl]-tetrahydro-2*H*-pyran-4-yloxy}(*tert*-butyl)diphenylsilane (35)

(a) Formation of Grignard reagent **34**: to a suspension of magnesium turnings (180 mg, 7.40 mmol) in THF (2 mL) was added catalytic iodine and the mixture stirred at rt, under N_2 until the iodine colour had been consumed. A solution of 4-bromo-2-methylbenzofuran **33**[17] (1.04 g, 4.91 mmol) in THF (5 mL) was then added over 6 h *via* syringe pump and the mixture stirred for a further 1 h giving the Grignard reagent **34** as a grey–green cloudy solution which was used immediately.

(b) Synthesis of triflate **28**: to a stirred solution of alcohol **27** (1.12 g, 2.80 mmol) and pyridine (0.68 mL, 660 mg, 8.4 mmol) in dichloromethane (10 mL) at −12 °C (ice–salt) under N_2 was added triflic anhydride (0.60 mL, 1.0 g, 3.6 mmol) in dichloromethane (2 mL) over 2 min. After a further 15 min at this temperature the mixture was diluted with dichloromethane (5 mL) and washed with sat. $NaHCO_3$(aq) (5 mL). The aqueous layer was then extracted with dichloromethane (2 × 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$), and filtered through a short plug of silica, eluting with dichloromethane (15 mL). The solvent was evaporated under reduced pressure (below 20 °C), azeotroping the remaining pyridine with toluene (1 mL), at 0.1 mmHg to give triflate **28** (1.07 g, 96%, mixture of anomers) as a colourless oil. (This material darkened in colour upon standing and was dried for no more than 30 min at rt, then used immediately.) R_f 0.37 (dichloromethane : petroleum ether, 1 : 1); δ_H (270 MHz, C_6D_6): 7.75–7.69 (4 H, m), 7.26–7.19 (6 H, m), 4.39 (1 H, d, J = 3.0 Hz), 4.28–4.15 (1 H, m), 3.81 (1 H, dd, J = 7.5, 10.5 Hz), 3.55 (1 H, dd, J = 2.5, 10.5 Hz), 3.23 (1 H, ddt, J = 12.0, 7.5, 2.5 Hz), 1.91 (1 H, ddt, J = 13.0, 5.0, 1.5 Hz), 1.44 (1 H, ddd, J = 13.0, 10.5, 3.0 Hz), 1.34–1.27 (1 H, m), 1.16 (10 H, m).

(c) The Grignard reagent **34**, freshly prepared, was cooled to 0 °C, then copper(I) bromide (140 mg, 1.00 mmol) was added and the mixture stirred for 2 min under N_2. Triflate **28** was then dissolved in THF (10 mL) and added to the Grignard reagent dropwise over 5 min. The resultant mixture was stirred overnight at 0 °C then quenched with sat. NH_4Cl(aq) : NH_4OH(aq) (10 : 1, 2 mL) and the mixture filtered through Celite and the filtrate extracted with EtOAc. The organic extract was then dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. Flash chromatography (petroleum ether : dichloromethane, 2 : 1) gave the *title compound* **35** (852 mg, 59% from alcohol **27**, mixture of anomers) as a pale brown oil; R_f 0.26 (dichloromethane : petroleum ether, 1 : 1); ν_{max}/cm^{-1} (thin film) 2932, 1428, 1113, 1070, 1048, 702; δ_H (270 MHz, $CDCl_3$): 7.63–7.57 (4 H, m), 7.41–7.23 (7 H, m), 7.08 (1 H, t, J = 8.0 Hz), 6.91 (1 H, dd, J = 8.0, 0.5 Hz), 6.30 (1 H, t, J = 1.0 Hz), 4.72 (1 H, d, J = 2.5 Hz), 4.12–4.01 (1 H, m), 3.69–3.79 (1 H, m), 2.99 (3 H, s), 2.97 (1 H, dd, J = 13.5, 6.5 Hz), 2.76 (1 H, dd, J = 13.5, 6.5 Hz), 2.44 (3 H, d, J = 1.0 Hz), 1.95 (1 H, ddt, J = 13.0, 4.5, 1.5 Hz), 1.63–1.71 (2 H, m), 1.35 (1 H, dt, J = 11.5, 11.5 Hz), 1.02 (9 H, s); δ_C (67.9 MHz, $CDCl_3$): 155.0, 154.8, 136.1, 134.5, 129.9, 129.8, 128.0, 127.9, 127.7, 155.0, 154.8, 130.7, 129.2, 123.4, 123.1, 108.9, 101.7, 99.5, 68.3, 66.0, 54.5, 41.3, 39.8, 39.7, 27.2, 19.3, 14.4. Found (CI): 532.2878 $[MNH_4]^+$, $C_{32}H_{38}O_4Si$

requires 532.2883 (1.0 ppm error); *m/z* (CI) 532 (3%, $[MNH4]^+$), 500 (2), 483 (9), 457 (3), 405 (4), 274 (17), 227 (100), 216 (30), 196 (42), 183 (17).

{(2*S*,4*R*,6*R*)-2-Allyl-6-[(2-methyl-1-benzofuran-4-yl)methyl]-tetrahydro-2*H*-pyran-4-yloxy}(*tert*-butyl)diphenylsilane (40)

To a stirred solution of acetal **35** (420 mg, 0.760 mmol) and allyltrimethylsilane (0.43 mL, 2.7 mmol) in acetonitrile (4 mL) at −35 °C was added trimethylsilyl triflate (60 μL, 0.34 mmol) dropwise. The reaction mixture was warmed to *ca.* −25 °C, stirred for 40 min then sat. $NaHCO_3$ (6 mL) was added and the mixture extracted with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give an oil which was re-dissolved in DMF (3 mL).

The resultant solution was cooled to 0 °C then imidazole (50 mg, 0.73 mmol) and *tert*-butyldiphenylsilyl chloride (200 mg, 0.73 mmol) were added. The mixture was allowed to warm to rt and stirred for 15 h. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 30 : 1) to give the *title compound* **40** (337 mg, 84%) as a colourless gum; R_f 0.52 (petroleum ether : EtOAc, 9 : 1); $[\alpha]_D$ +59.3 (*c* 0.750, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3071, 2932, 2857, 1589, 1428, 1251, 1111, 1073; δ_H (270 MHz, $CDCl_3$): 7.67–7.60 (m, 4 H), 7.44–7.26 (m, 7 H), 7.11 (t, 1 H, *J* = 8.0 Hz), 6.96 (d, 1 H, *J* = 8.0 Hz), 6.35 (s, 1 H), 5.60–5.47 (m, 1 H), 4.92 (dd, 1 H, *J* = 10.0, 2.0 Hz), 4.85 (dd, 1 H, *J* = 17.0, 1.5 Hz), 4.10–3.90 (m, 2 H), 3.81–3.70 (m, 1 H), 3.18 (dd, 1 H, *J* = 13.5, 6.5 Hz), 2.86 (dd, 1 H, *J* = 13.5, 7.0 Hz), 2.46 (s, 3 H), 2.25–2.14 (m, 1 H), 2.20 (ddd, 1 H, *J* = 14.0, 7.0, 7.0 Hz), 1.99–1.88 (ddd, 1 H, *J* = 14.0, 7.0, 7.0 Hz), 1.79–1.72 (m, 1 H), 1.70–1.58 (m, 2 H), 1.51–1.40 (m, 1 H), 1.07 (s, 9 H); δ_C (67.9 MHz, $CDCl_3$): 154.9, 154.7, 136.1, 135.3, 134.5, 131.1, 130.0, 129.2, 127.9, 123.4, 123.2, 116.9, 109.0, 101.7, 71.7, 70.3, 66.4, 40.4, 40.0, 37.6, 37.1, 27.3, 19.4, 14.5. Found: C, 77.92; H, 7.37%. $C_{34}H_{40}O_3Si$ requires C, 77.82; H, 7.68%. Found (CI): 542.3097 $[MNH_4]^+$, $C_{34}H_{40}O_3Si$ requires 542.3090 (1.2 ppm error); *m/z* (CI) 542 (12%, $[MNH_4]^+$), 525 (2, $[MH]^+$), 467 (15), 447 (18), 379 (15), 269 (50), 251 (30), 227 (20), 199 (100), 185 (24), 145 (30).

3-{(2*R*,4*S*,6*R*)-4-[*tert*-Butyl(diphenyl)silyloxy]-6-(2-oxoethyl)-tetrahydro-2*H*-pyran-2-ylmethyl}-2-formylphenyl acetate (41)

Ozone was bubbled through a stirred solution of benzofuran **40** (195 mg, 0.372 mmol) in dichloromethane (6.5 mL) at −78 °C for *ca.* 20 min, until a pale blue colour appeared. Oxygen was then bubbled through the solution for a further 5 min and triphenylphosphine (420 mg, 1.60 mmol) was added. The reaction mixture was allowed to warm to 4 °C then stirred for a further 15 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 3 : 1) to give the *title compound* **41** (140 mg, 67%) as a colourless gum; R_f 0.12 (petroleum ether : EtOAc, 4 : 1); $[\alpha]_D$ +54.6 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2930, 2857, 1768, 1723, 1695, 1603, 1468, 1427, 1368, 1188, 1110, 1059; δ_H (270 MHz, $CDCl_3$): 10.31 (s, 1 H), 9.38 (t, 1 H, *J* = 3.0 Hz), 7.69–7.60 (m, 4 H), 7.51–7.35 (m, 7 H), 7.13 (d, 1 H, *J* = 7.5 Hz), 7.03 (d, 1 H, *J* = 7.5 Hz), 4.63–4.53 (m, 1 H), 4.02–3.92 (m, 1 H), 3.73–3.65 (m, 1 H), 3.33 (dd, 1 H, *J* = 14.0, 8.5 Hz), 3.17 (dd, 1 H, *J* = 14.0, 4.0 Hz), 2.41 (ddd, 1 H, *J* = 16.0, 9.0, 3.0 Hz), 2.37 (s, 3 H), 2.06 (ddd, 1 H, *J* = 16.0, 5.5, 3.0 Hz), 1.95–1.87 (m, 1 H), 1.74–1.50 (m, 2 H), 1.50–1.41 (m, 1 H), 1.09 (s, 9 H); δ_C (67.9 MHz, $CDCl_3$): 200.9, 190.3, 169.7, 152.9, 143.2, 136.0, 136.0, 134.2, 134.1, 130.2, 130.1, 128.0, 126.6, 122.0, 71.2, 66.3, 66.0, 46.5, 39.6, 38.7, 38.2, 27.2, 19.3. Found (CI): 576.2772 $[MNH_4]^+$, $C_{33}H_{38}O_6Si$ requires 576.2784 (1.6 ppm error); *m/z* (CI) 576 (80%, $[MNH_4]^+$), 559 (25, $[MH]^+$), 517 (65), 303 (37), 274 (35), 261 (30), 216 (37), 196 (100).

3-{(2*R*,4*S*)-4-[*tert*-Butyl(diphenyl)silyloxy]-6-methoxytetrahydro-2*H*-pyran-2-ylmethyl}-2-formylphenyl acetate (43)

Oxygen was bubbled through a stirred solution of benzofuran **35** (403 mg, 0.783 mmol) in dichloromethane (15 mL) for 10 min, with cooling to −78 °C. Ozone in oxygen was then bubbled through the solution for *ca.* 30 min until a pale blue colour appeared. Oxygen was then bubbled through the solution for a further 10 min after which time triphenylphosphine (637 mg, 2.43 mmol) was added. The cooling bath was then removed and the reaction mixture allowed to warm to rt over 3 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 9 : 1) to give the *title compound* **43** (280 mg, 68%, mixture of anomers) as a yellowish gum; R_f 0.18 (petroleum ether : EtOAc, 9 : 1); ν_{max}/cm^{-1} (thin film) 2933, 1773, 1697, 1197, 1112; δ_H (270 MHz, $CDCl_3$): 10.34 (1 H, s), 7.75–7.65 (4 H, m), 7.51–7.34 (7 H, m), 7.14 (1 H, d, *J* = 7.0 Hz), 7.03 (1 H, dd, *J* = 8.0, 1.0 Hz), 4.68 (1 H, d, *J* = 3.0 Hz), 4.20–4.08 (1 H, m), 3.68–3.55 (1 H, m), 3.18 (1 H, dd, *J* = 14.0, 8.0 Hz), 3.01 (1 H, dd, *J* = 14.0, 4.5 Hz), 2.87 (3 H, s), 2.38 (3 H, s), 2.00–1.94 (1 H, m), 1.89–1.82 (1 H, m), 1.64 (1 H, ddd, *J* = 13.0, 11.0, 3.5 Hz), 1.45 (1 H, dd, *J* =11.5, 11.5 Hz), 1.09 (9 H, s); δ_C (67.9 MHz, $CDCl_3$): 190.0, 169.5, 151.9, 143.0, 135.8, 134.5, 134.4, 133.8, 129.7, 127.7, 126.8, 121.9, 99.0, 68.3, 65.6, 54.2, 41.1, 39.4, 38.6, 27.0, 21.0, 19.2. Found (CI): 564.2790 $[MNH_4]^+$, $C_{32}H_{38}O_6Si$ requires 564.2781 (1.5 ppm error); *m/z* (CI) 564 (12%, $[MNH_4]^+$), 529 (6), 515 (100), 473 (10), 259 (25), 196 (8).

Methyl 2-{(2*R*,4*S*)-4-[*tert*-butyl(diphenyl)silyloxy]-6-methoxytetrahydro-2*H*-pyran-2-ylmethyl}-6-methoxybenzoate (44)

(a) To a solution of sodium chlorite (83 mg, 0.91 mmol), sodium dihydrogen orthophosphate (176 mg, 1.47 mmol) and hydrogen peroxide (30% v/v in water, 75 mg) in water (2 mL) at 0 °C was added sodium hydrogen sulfite (48 mg, 0.40 mmol) portion-wise. This mixture was slowly added to a stirred solution of aldehyde **43** (230 mg, 0.409 mmol) in acetonitrile (5 mL) at rt. After 1.5 h a mixture of sodium chlorite (40 mg), sodium dihydrogen orthophosphate (85 mg), hydrogen peroxide (30% v/v in water, 35 mg) and sodium hydrogen sulfite (25 mg) was again prepared and added to the aldehyde mixture. After a further 2 h, sat. sodium sulfite (2 mL) was added cautiously and the reaction mixture extracted with EtOAc (4 × 20 mL). The organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give 2-(acetyloxy)-6-{(2*R*,4*S*)-4-[*tert*-butyl(diphenyl)silyloxy]-6-methoxytetrahydro-2*H*-pyran-2-ylmethyl}benzoic acid (222 mg, 94%, mixture of anomers) as a colourless oil; R_f 0.19 (petroleum ether : EtOAc, 2 : 1); ν_{max}/cm^{-1} (thin film) 3070, 2930, 2858, 1771, 1730, 1702, 1472, 1427, 1371, 1198, 1112; δ_H (270 MHz, $CDCl_3$): 8.50 (1 H, br s), 7.70–7.62 (4 H, m), 7.48–7.33 (7 H, m), 7.05 (1 H, d, *J* = 8.0 Hz), 7.00 (1 H, dd, *J* = 8.0, 1.0 Hz), 4.71 (1 H, d, *J* = 3.5 Hz), 4.20–4.07 (1 H, m), 3.80–3.68 (1 H, m), 2.93 (1 H, dd, *J* = 14.0, 9.0 Hz), 2.81 (1 H, dd, *J* = 14.0, 4.0 Hz), 2.77 (3 H, s), 2.27 (3 H, s), 1.99–1.84 (2 H, m), 1.65 (1 H, ddd, *J* = 12.0, 11.0, 4.0 Hz), 1.53 (1 H, dt, *J* = 12.0, 12.0 Hz), 1.05 (9 H, s); δ_C (67.9 MHz, $CDCl_3$): 169.6, 167.0, 148.7, 135.8, 134.3, 134.1, 131.2, 129.8, 127.9, 127.7, 121.8, 99.4, 69.8, 65.1, 54.5, 40.9, 40.6, 39.2, 27.0, 21.0, 19.2. Found (CI): 580.2726 $[MNH_4]^+$, $C_{32}H_{38}O_7Si$ requires 580.2731 (0.8 ppm error); *m/z* (CI) 580 (22%, $[MNH_4]^+$), 453 (75), 247 (75), 196 (100).

(b) To a stirred solution of the acid from (a) (222 mg, 0.395 mmol) in methanol (6 mL) was added potassium carbonate (290 mg, 2.10 mmol) at rt. After 1 h, the basic reaction mixture was neutralised with 1 M HCl and extracted with EtOAc. The aqueous layer was then acidified to pH 2.0 and again extracted with EtOAc. The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give crude hydroxy-acid as a pale brown gum (203 mg). This was re-dissolved in acetone (5 mL) and

potassium carbonate (216 mg, 1.56 mmol) added, followed by methyl iodide (0.49 mL, 1.1 g, 7.8 mmol). The mixture was stirred under N_2 at reflux for 2 d. After cooling to rt the reaction mixture was filtered, the solvent evaporated under reduced pressure and the crude product purified by flash chromatography (petroleum ether : EtOAc, 6 : 1) to give the *title compound* **44** (161 mg, 75%, mixture of anomers) as a yellowish gum; R_f 0.26 (petroleum ether : EtOAc, 6 : 1); ν_{max}/cm^{-1} (thin film) 2932, 1726, 1472, 1279, 1113; δ_H (270 MHz, $CDCl_3$): 7.77–7.60 (4 H, m), 7.43–7.30 (6 H, m), 7.22 (1 H, t, J = 8.0 Hz), 6.77 (1 H, d, J = 8.0 Hz), 6.76 (1 H, d, J = 8.0 Hz), 4.68 (1 H, d, J = 3.0 Hz), 4.05–4.14 (1 H, m), 3.81 (3 H, s), 3.80 (3 H, s), 3.67–3.57 (1 H, m), 2.99 (3 H, s), 2.77 (1 H, dd, J = 14.0, 7.5 Hz), 2.57 (1 H, dd, J = 14.0, 6.0 Hz), 1.96 (1 H, dd, J = 12.5, 5.0 Hz), 1.73–1.56 (2 H, m), 1.32 (1 H, dt, J = 11.5, 11.5 Hz), 1.04 (9 H, s); δ_C (67.9 MHz, $CDCl_3$): 168.7, 156.5, 137.3, 135.8, 134.6, 134.5, 130.1, 129.8, 129.6, 127.6, 127.0, 122.8, 109.1, 99.2, 67.9, 65.7, 56.0, 56.3, 52.1, 41.1, 39.5, 39.5, 27.0, 19.2. Found (CI): 566.2963 $[MNH_4]^+$, $C_{32}H_{40}O_6Si$ requires 566.2938 (4.4 ppm error); m/z (CI) 566 (3%, $[MNH_4]^+$), 517 (95), 491 (100), 261 (95).

Methyl 2-{(2*R*,4*R*,6*S*)-6-allyl-4-[*tert*-butyl(dimethyl)silyloxy]-tetrahydro-2*H*-pyran-2-ylmethyl}-6-methoxybenzoate (45)

To a stirred solution of acetal **44** (139 mg, 0.253 mmol) in acetonitrile (1.5 mL) at −20 °C, under N_2, was added allyltrimethylsilane (0.20 mL, 150 mg, 1.3 mmol) followed by trimethylsilyl triflate (46 μL 57 mg, 0.26 mmol) dropwise over 10 min. The reaction mixture was warmed to 0 °C over 45 min then quenched with sat. $NaHCO_3$(aq) and extracted with EtOAc (2 × 10 mL). The organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a colourless gum. This was re-dissolved in THF (1.0 mL) and TBAF (1 M in THF + 5 wt% water, 0.75 mL, 0.75 mmol) added. This was stirred overnight at rt. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 1 : 1) to give the corresponding alcohol (83 mg) as a colourless gum. This was re-dissolved in dichloromethane (2.0 mL), cooled to 0 °C and 2,6-lutidine (56 μL, 51 mg, 0.48 mmol) followed by *tert*-butyl-(dimethyl)silyl triflate (52 μL, 61 mg, 0.23 mmol) were added with stirring. After 45 min, a further portion of *tert*-butyl-(dimethyl)silyl triflate (5 μL, 6 mg, 0.02 mmol) was added and stirring continued for a further 45 min. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 6 : 1) to give the *title compound* **45** (89 mg, 81%) as a colourless gum; R_f 0.69 (petroleum ether : EtOAc, 2 : 1); $[\alpha]_D$ +35.2 (*c* 1.34, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2950, 2855, 1733, 1585, 1472, 1268, 1114, 1073; δ_H (270 MHz, $CDCl_3$): 7.27 (1 H, t, J = 8.0 Hz), 6.90 (1 H, d, J = 8.0 Hz), 6.80 (1 H, d, J = 8.0 Hz), 5.70 (1 H, dddd, J = 17.0, 10.0, 7.5, 6.5 Hz), 5.08–4.98 (2 H, m), 4.05–3.98 (1 H, m), 3.97–3.90 (1 H), 3.91 (3 H, s), 3.91–3.84 (1 H, m), 3.82 (3 H, s), 3.00 (1 H, dd, J = 14.0, 7.5 Hz), 2.67 (1 H, dd, J = 14.0, 6.0 Hz), 2.45–2.33 (1 H, m), 2.23–2.13 (1 H, m), 1.87–1.78 (1 H, m), 1.76–1.54 (2 H, m), 1.34 (1 H, dt, J = 13.0, 9.0 Hz), 0.89 (9 H, s), 0.05 (6 H, s); δ_C (67.9 MHz, $CDCl_3$): 168.9, 156.5, 137.7, 135.2, 130.2, 124.1, 123.0, 116.8, 109.0, 70.8, 70.4, 65.1, 56.0, 52.3, 40.1, 39.5, 37.8, 37.3, 25.9, 18.2, −4.5, −4.6. Found (CI): 435.2568 $[MH]^+$, $C_{24}H_{38}O_5Si$ requires 435.2567 (0.3 ppm error); m/z (CI) 435 (100%, $[MH]^+$), 403 (50), 377 (18), 255 (20).

Methyl 2-{(2*R*,4*S*,6*S*)-4-[*tert*-butyl(dimethyl)silyloxy]-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-ylmethyl}-6-methoxybenzoate (46)

Oxygen was bubbled through a stirred solution of ester **45** (136 mg, 0.313 mmol) in dichloromethane (10 mL) at −78 °C for 10 min. Ozone in oxygen was then bubbled through the solution for *ca.* 25 min until a pale blue colour appeared. Oxygen was bubbled through the solution for a further 10 min then triphenylphosphine (246 mg, 0.939 mmol) was added. The cooling bath was then removed and the reaction mixture allowed to warm to rt over 3 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 4 : 1) to give the *title compound* **46** (133 mg, 98%) as a colourless gum; R_f 0.52 (petroleum ether : EtOAc, 2 : 1); $[\alpha]_D$ +36.3 (*c* 2.20, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2951, 2935, 2856, 1738, 1585, 1471, 1267, 1247, 1074; δ_H (270 MHz, C_6D_6): 9.36 (1 H, dd, J = 3.0, 2.0 Hz), 7.05 (1 H, t, J = 8.0 Hz), 6.87 (1 H, dd, J = 8.0, 1.0 Hz), 6.64 (1 H, dd, J = 8.0, 1.0 Hz), 4.40 (1 H, m), 4.01–3.85 (1 H, m), 3.73 (1 H, m), 3.65 (3 H, s), 3.25–3.15 (4 H, m), 2.76 (1 H, dd, J = 14.0, 5.0 Hz), 2.37 (1 H, ddd, J = 16.0, 9.0, 3.0 Hz), 1.81 (1 H, ddd, J = 16.0, 5.5, 2.0 Hz), 1.85–1.72 (1 H, m), 1.53 (1 H, ddd, J = 13.0, 8.5, 5.0 Hz), 1.40–1.30 (2 H, m), 0.94 (9 H, s), 0.00 (3 H, s), −0.01 (3 H, s); δ_C (67.9 MHz, C_6D_6): 199.7, 168.6, 157.0, 138.1, 130.1, 125.2, 122.9, 109.3, 71.0, 65.9, 65.3, 55.3, 51.8, 46.7, 39.9, 39.5, 38.7, 26.1, 18.2, −4.5, −4.6. Found (CI): 437.2374 $[MH]^+$, $C_{23}H_{36}O_6Si$ requires 437.2359 (3.2 ppm error); m/z (CI) 437 (1, $[MH]^+$), 401 (6), 379 (100), 257 (46).

Methyl 2-{(2*R*,4*S*,6*R*)-4-[*tert*-butyl(dimethyl)silyloxy]-6-[(2*S*)-2-hydroxypent-4-enyl]tetrahydro-2*H*-pyran-2-ylmethyl}-6-methoxybenzoate (47)

(a) To a solution of aldehyde **46** (334 mg, 0.765 mmol) in dichloromethane (15 mL) at −78 °C was added allyltrimethylsilane (0.36 mL, 2.3 mmol) followed by dimethylaluminium chloride (1 M in hexane, 4.59 mL, 4.59 mmol) with stirring under N_2. After 30 min, sat. NH_4Cl(aq) (0.5 mL) was added and the reaction allowed to warm to rt. Brine (5 mL) was added and the mixture extracted with dichloromethane (4 × 10 mL). The organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product as a cloudy gum. Flash chromatography (petroleum ether : EtOAc, 2 : 1) gave the *title compound* **47** (310 mg, 85%, 15*S* : 15*R* = 85 : 15) as a colourless oil; R_f 0.34 (petroleum ether : EtOAc, 2 : 1); $[\alpha]_D$ +18.0 (*c* 1.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3460, 2927, 2853, 1721, 1583, 1468, 1433, 1264, 1104, 1070; δ_H (270 MHz, $CDCl_3$): 7.28 (1 H, t, J = 8.0 Hz), 6.87 (1 H, d, J = 8.0 Hz), 6.80 (1 H, d, J = 8.0 Hz), 5.76–5.61 (1 H, m), 5.05–4.96 (2 H, m), 4.34–4.25 (1 H, m), 4.02–3.93 (1 H, m), 3.89 (3 H, s), 3.82 (3 H, s), 3.82–3.73 (1 H, m), 3.43–3.34 (1 H, m), 3.06 (1 H, dd, J = 14.0, 8.5), 2.66 (1 H, dd, J = 14.0, 4.5), 2.09 (2 H, t, J = 7.0 Hz), 1.84 (1 H, dt, J = 13.0, 3.5 Hz), 1.75 (1 H, ddd, J = 14.0, 11.0, 3.0 Hz), 1.62 (2 H, t, J = 5.0 Hz), 1.45–1.26 (2 H, m), 0.89 (9 H, s), 0.05 (6 H, 2 × s); δ_C (67.9 MHz, $CDCl_3$): 168.9, 156.6, 138.2, 135.3, 130.2, 124.0, 122.7, 117.0, 109.2, 70.6, 67.0, 66.8, 65.2, 55.9, 52.2, 41.6, 39.8, 39.2, 38.8, 38.7, 25.8, 18.1, −4.7, −4.7. Found (CI): 479.2825 $[MH]^+$, $C_{26}H_{42}O_6Si$ requires 479.2829 (0.9 ppm error); m/z (CI) 479 (100%, $[MH]^+$), 447 (42), 429 (47), 167 (33).

(b) To a stirred solution of (+)-*B*-methoxydiisopinocampheyl borane (475 mg, 1.50 mmol) in Et_2O (10 mL) was added allylmagnesium bromide (1 M in Et_2O, 1.5 mL, 1.50 mmol) at −78 °C under N_2. After 15 min, the mixture was allowed to warm to rt and stirred for 2 h. The mixture was again cooled to −78 °C and aldehyde **46** (437 mg, 1.5 mmol) in Et_2O (5 mL) was added dropwise. After 3 h at −78 °C, the mixture was allowed to warm to rt and 1 M NaOH (5 mL) then 30% H_2O_2 (5 mL) was added; stirring was continued for a further 45 min. Sat. Na_2SO_3(aq) (2 mL) was then added and the reaction mixture extracted with EtOAc (3 × 100 mL). The organic extracts were combined and dried ($MgSO_4$), filtered and evaporated under reduced pressure. Flash chromatography (petroleum ether : EtOAc, 4 : 1) gave the *title compound* **47** (416 mg, 77%, 15*R* : 15*S* = 90 : 10) as a colourless oil; R_f 0.35 (petroleum ether : EtOAc, 2 : 1); $[\alpha]_D$ +28.0 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3496, 2949, 2929, 2856, 1732, 1585, 1471, 1267, 1074; δ_H (270 MHz, $CDCl_3$): 7.28 (1 H, t, J = 8.0 Hz), 6.87 (1 H, d, J = 8.0

Hz), 6.80 (1 H, d, J = 8.0 Hz), 5.86–5.70 (1 H, m), 5.10–5.00 (2 H, m), 4.30–4.19 (1 H, m), 4.04–3.94 (2 H, m), 3.89 (3 H, s), 3.81 (3 H, s), 3.80–3.68 (1 H, m), 3.10 (1 H, dd, J = 14.0, 8.0 Hz), 2.75 (1 H, dd, J = 14.0, 5.5 Hz), 2.20–2.13 (2 H, m), 1.82 (1 H, dt, J = 13.0, 4.0 Hz), 1.75–1.66 (1 H, m), 1.59 (2 H, t, J = 6.0 Hz), 1.43–1.36 (2 H, m), 0.88 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s); δ_C (67.9 MHz, $CDCl_3$): 168.9, 156.7, 137.6, 135.2, 130.4, 124.1, 122.8, 117.3, 109.4, 71.1, 71.0, 69.8, 64.9, 56.1, 52.4, 41.7, 39.7, 39.4, 38.9, 38.6, 26.0, 18.2, −4.5, −4.6. Found (CI): 479.2818 $[MH]^+$, $C_{26}H_{42}O_6Si$ requires 479.2829 (2.2 ppm error); *m*/*z* (CI) 479 (100%, $[MH]^+$), 447 (15), 421 (10), 180 (15), 167 (18).

2-{(2*R*,4*S*,6*R*)-4-[*tert*-Butyl(dimethyl)silyloxy]-6-[(2*R*)-2-hydroxypent-4-enyl]tetrahydro-2*H*-pyran-2-ylmethyl}-6-methoxybenzoic acid (48)

To a stirred solution of ester **47** (15*R* : 15*S* = 90 : 10, 32 mg, 0.067 mmol) in pyridine (2 mL) was added lithium iodide (105 mg, 0.784 mmol), and the solution was heated at 100 °C under N_2 for 24 h. The mixture was cooled to rt and diluted with EtOAc (5 mL) and 0.5 M HCl (1 mL). This was extracted with EtOAc (6 × 5 mL) and the organic extracts dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. Flash chromatography (petroleum ether : EtOAc, 2 : 1 to EtOAc + 1% AcOH) gave first, recovered starting material **47** (12 mg) and then the *title compound* **48** (17 mg, 55%, 88% with respect to the recovered starting material, 15*R* : 15*S* = 90 : 10) as a yellowish gum; R_f 0.45 (EtOAc + 1% AcOH); $[\alpha]_D$ +64.4 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3440, 2951, 2929, 2856, 1726, 1585, 1471, 1263, 1074; δ_H (270 MHz, $CDCl_3$): 7.29 (1 H, dd, J = 7.5, 8.5 Hz), 6.84 (1 H, d, J = 8.5 Hz), 6.82 (1 H, d, J = 7.5 Hz), 5.76–5.59 (1 H, m), 5.08–5.00 (2 H, m), 4.28–4.18 (1 H, m), 4.11–4.01 (1 H, m), 4.01–3.88 (1 H, m), 3.85 (3 H, s), 3.67–3.58 (1 H, m), 3.07 (1 H, dd, J = 14.0, 4.0 Hz), 2.86 (1 H, dd, J = 14.0, 10.0 Hz), 2.20–2.10 (2 H, m), 2.00–1.62 (2 H, m), 1.69–1.63 (2 H, m), 1.47–1.26 (2 H, m), 0.88 (9 H, s), 0.06 (3 H, s), 0.05 (3 H, s); δ_C (67.9 MHz, $CDCl_3$): 156.7, 137.0, 134.3, 130.7, 123.6, 117.8, 109.8, 72.3, 71.8, 70.1, 64.6, 56.1, 41.2, 40.5, 39.9, 39.6, 37.3, 25.9, 18.1, −4.8, −4.9. Found (CI): 465.2664 $[MH^+]$, $C_{25}H_{40}O_6Si$ requires 465.2672 (1.8 ppm); *m*/*z* (CI) 465 (100%, $[MH]^+$), 447 (30), 421 (25), 184 (30), 167 (35).

(1*R*,11*R*,13*R*,15*S*)-11-Allyl-15-[*tert*-butyl(dimethyl)silyloxy]-7-methoxy-10,17-dioxatricyclo[11.3.1.0^{3,8}]heptadeca-3,5,7-trien-9-one (49)

To a solution of DCC (365 mg, 1.77 mmol), DMAP (252 mg, 2.07 mmol) and DMAP·HCl (280 mg, 1.77 mmol) in $CHCl_3$ (spectrophotometric grade 99.8%, 105 mL) at reflux with stirring under N_2 was added carboxylic acid **48** (15*R* : 15*S* = 90 : 10, 137 mg, 0.295 mmol) *via* syringe pump over 5 h. This was stirred for a further 16 h at reflux then cooled to rt and methanol (2 mL) and acetic acid (0.2 mL) were added. After stirring for a further 30 min at rt the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 6 : 1) giving first the cyclised compound **49** (50 mg, 38%) as a white solid; R_f 0.40 (petroleum ether : EtOAc, 4 : 1); mp 149–150 °C (EtOAc); $[\alpha]_D$ −6.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2928, 2913, 1719, 1583, 1471, 1276, 1252, 1117; δ_H (500 MHz, $CHCl_3$): 7.22 (1 H, t, J = 8.0 Hz), 6.76 (1 H, d, J = 8.0 Hz), 6.73 (1 H, d, J = 8.0 Hz), 5.87 (1 H, dddd, J = 16.0, 10.0, 6.0, 6.0 Hz), 5.61–5.55 (1 H, m), 5.13 (1 H, dd, J = 16.0, 2.0), 5.09 (1 H, d, J = 10.0), 4.56–4.49 (1 H, m), 4.08–4.01 (1 H, m), 4.00–3.93 (1 H, m), 3.78 (3 H, s), 3.54 (1 H, dd, J = 15.0, 10.5 Hz), 2.37 (1 H, dd, J = 15.0, 1.5 Hz), 2.47–2.43 (1 H, m), 2.36–2.28 (1 H, m), 1.87 (1 H, ddd, J = 13.5, 5.5, 4.0 Hz), 1.82 (1 H, ddd, J = 11.0, 11.0, 14.5), 1.66–1.48 (4 H, m), 0.91 (9 H, s), 0.06 (6 H, s); δ_C (125 MHz, $CHCl_3$): 169.59, 156.01, 139.31, 133.92, 130.02, 125.92, 122.90, 117.66, 109.50, 74.06, 73.12, 65.87, 65.69, 55.98, 39.77, 39.43, 39.32, 39.11, 39.44, 25.97, 18.18, −4.74. Found (CI): 447.2566 $[MH]^+$, $C_{25}H_{38}O_5Si$ requires 447.2567 (0.1 ppm error); *m*/*z* (FAB) 469 (100%, $[MNa]^+$), 176 (45), 149 (17).

Further elution gave a trace of diastereomer **50** (2 mg, 2%) as a white solid; R_f 0.31 (petroleum ether : EtOAc, 4 : 1); mp 93–95 °C; $[\alpha]_D$ +7.9 (*c* 0.20, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2951, 2924, 2856, 1718, 1585, 1471, 1458, 1263, 1110, 1070; δ_H (500 MHz, $CDCl_3$): 7.29 (1 H, t, J = 8.0 Hz), 6.82 (1 H, d, J = 8.0 Hz), 6.74 (1 H, d, J = 8.0 Hz), 5.83–5.74 (1 H, m), 5.06 (1 H, dd, J = 17.0, 1.5 Hz), 5.05 (1 H, d, J = 11.0 Hz), 4.66 (1 H, m), 4.24 (1 H, t, J = 10.5 Hz), 4.14 (1 H, m), 3.99–3.92 (1 H, m), 3.81 (3 H, s), 3.61 (1 H, t, J = 13.0 Hz), 2.56–2.50 (2 H, m), 2.44 (1 H, dt, J = 7.5, 7.5 Hz), 1.95 (1 H, ddd, J = 13.5, 6.5, 4.0 Hz), 1.67–1.60 (3 H, m), 1.55–1.50 (1 H, m), 1.47 (1 H, dt, J = 9.5, 3.5 Hz), 0.92 (9 H, s), 0.06 (6 H, s); δ_C (125 MHz, $CDCl_3$): 170.22, 155.64, 140.23, 133.80, 130.64, 124.52, 122.66, 117.75, 108.28, 74.20, 74.06, 65.72, 60.67, 55.71, 39.77, 38.98, 37.37, 36.73, 25.95, 18.11, −4.64, −4.78. Found (CI): 447.2565 $[MH]^+$, $C_{25}H_{38}O_5Si$ requires 447.2567 (0.3 ppm error); *m*/*z* (CI) 447 (100%, $[MH]^+$), 429 (32), 389 (13), 297 (10), 148 (10).

(1*R*,11*R* ,13*R*,15*S*)-11-Allyl-7,15-dihydroxy-10,17-dioxatricyclo[11.3.1.0^{3,8}]heptadeca-3,5,7-trien-9-one (51)

To a stirred solution of methyl ether **49** (8 mg, 0.018 mmol) in dichloromethane (1 mL) was added 9-iodo-9-BBN (1 M in hexanes, 40 μL, 0.040 mmol) at 0 °C under N_2. After 1 h a further portion of 9-iodo-9-BBN (1 M in hexanes, 10 μL, 0.010 mmol) was added and the reaction was stirred for a further 1 h. Water (2 drops) was added, stirring continued for 15 min, then the mixture extracted with EtOAc. The organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane : EtOH, 20 : 1) to give the *title compound* **51** (4 mg, 70%) as a pale brown gum; R_f 0.30 (dichloromethane : EtOH, 20 : 1); $[\alpha]_D$ −4.5 (*c* 0.15, MeOH); lit. (enantiomer)[5d] $[\alpha]_D$ +6.8 (*c* 0.16, MeOH); ν_{max}/cm^{-1} (thin film) 3262, 2924, 1716, 1583, 1464, 1294; δ_H (500 MHz, acetone-d_6) 8.39 (1 H, s), 7.11 (1 H, dd, J = 8.0, 7.7 Hz), 6.77 (1 H, d, J = 8.0 Hz), 6.69 (1 H, d, J = 7.7 Hz), 5.92 (1 H, dddd, J = 6.4, 7.6, 10.2, 17.2 Hz), 5.48 (1 H, dddd, J = 2.4, 5.6, 5.6, 10.0 Hz), 5.13 (1 H, dddd, J = 1.6, 1.6, 2.4, 17.2 Hz), 5.03 (1 H, dddd, J = 1.6, 1.6, 2.4, 10.2 Hz), 4.24–4.30 (1 H, m), 3.96–4.03 (1 H, m), 3.85–3.91 (1 H, m), 3.77–3.81 (1 H, m), 3.34 (1 H, dd, J = 9.8, 15.0 Hz), 2.44 (1 H, dd, J = 1.0, 15.0 Hz), 2.30–2.41 (2 H, m), 1.93 (1 H, ddd, J = 4.5, 4.5, 12.7 Hz), 1.77–1.86 (1 H, m), 1.40–1.71 (4 H, m); δ_C (125 MHz, acetone-d_6) 169.28, 154.31, 140.23, 135.32, 130.38, 125.47, 122.34, 117.48, 114.43, 73.65, 73.61, 68.08, 64.91, 40.36, 40.10, 39.96, 39.72, 39.13. Found (CI): 319.1545 $[MH]^+$, $C_{18}H_{22}O_5$ requires 319.1546 (0.1 ppm error); *m*/*z* (CI) 336 (20%, $[MNH_4]^+$), 319 (100, $[MH]^+$), 301 (70), 283 (20), 162 (20), 134 (25).

^1H NMR, ^{13}C NMR and IR spectroscopic data were in agreement with published values (see Table 2).[5d]

(1*R*,11*R*,13*R*,15*S*)-11-Allyl-7,15-bis[*tert*-butyl(dimethyl)-silyloxy]-10,17-dioxatricyclo[11.3.1.0^{3,8}]heptadeca-3,5,7-trien-9-one [(−)-6]

To a solution of diol **51** (3 mg, 0.009 mmol) in dichloromethane (0.5 mL) was added 2,6-lutidine (0.2 mL) and *tert*-butyl-(dimethyl)silyl triflate (10 μL 12 mg, 0.044 mmol) with stirring at 0 °C under N_2. After 2 h a further portion of *tert*-butyl-(dimethyl)silyl triflate (10 μL, 12 mg, 0.044 mmol) was added and stirring was continued for a further 2 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 9 : 1) to give the *title compound* (−)-**6** (3 mg, 80%) as a colourless oil; R_f 0.71 (petroleum ether : EtOAc, 2 : 1); $[\alpha]_D$ −20 (*c* 0.10, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2927, 2856, 1722, 1579, 1463, 1285, 1255, 1106; δ_H (500 MHz, acetone-d_6): 7.18 (1 H, t, J = 8.0 Hz), 6.83

(1 H, d, J = 8.0 Hz), 6.79 (1 H, d, J = 8.0 Hz), 5.90 (1 H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.58–5.52 (1 H, m), 5.14 (1 H, dd, J = 17.0, 1.0 Hz), 5.07 (1 H, dt, J = 10.0, 1.0 Hz), 4.33–5.28 (1 H, m), 4.18–4.13 (1 H, m), 3.93–3.88 (1 H, m), 3.46 (1 H, dd, J = 15.0, 10.5 Hz), 2.44 (1 H, J = 15.0, 1.5 Hz), 2.48–2.35 (2 H, m), 1.92 (1 H, ddd, J = 13.5, 5.0, 5.0 Hz), 1.81 (1 H, dt, J = 14.5, 10.5 Hz), 1.65–1.58 (1 H, m), 1.60 (1 H, dt, J = 14.5, 2.0 Hz), 1.56–1.47 (2 H, m), 0.99 (9 H, s), 0.92 (9 H, s), 0.26 (3 H, s), 0.20 (3 H, s), 0.10 (3 H, s), 0.09 (3 H, s); δ_C (125 MHz, acetone-d_6): 169.54, 152.45, 140.94, 134.98, 130.17, 129.85, 124.08, 117.98, 117.67, 74.20, 73.75, 66.75, 66.55, 40.22, 40.10, 39.97, 39.47, 38.87, 26.25, 26.16, 18.88, 18.55, −3.79, −4.22, −4.61, −4.64. Found (CI): 547.3275 $[MH]^+$, $C_{30}H_{50}O_5Si_2$ requires 547.3275 (0.0 ppm error); m/z (CI) 564 (12%, $[MNH_4]^+$), 547 (85, $[MH]^+$), 529 (100), 489 (14), 428 (30), 261 (25), 137 (30).

(1*R*,11*R*,13*R*)-11-Allyl-7-methoxy-10,17-dioxatricyclo-[11.3.1.0^{3,8}]heptadeca-3,5,7-triene-9,15-dione (52)

(a) To a solution of lactone **49** (50 mg, 0.11 mmol) in THF (2 mL) was added TBAF (1 M in THF, 0.22 mL, 0.22 mmol) with stirring at rt. After 5 h the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 4 : 1 to EtOAc) to give (1*R*,11*R*,13*R*,15*S*)-11-allyl-15-hydroxy-7-methoxy-10,17-dioxatricyclo[11.3.1.0^{3,8}]heptadeca-3,5,7-trien-9-one (36 mg, 97%) as a colourless oil; R_f 0.50 (EtOAc); $[a]_D$ −10.6 (c 1.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3460, 2946, 2923, 2841, 1732, 1598, 1581, 1470, 1272, 1119, 1089, 1071; δ_H (270 MHz, $CDCl_3$): 7.21 (1 H, t, J = 8.0 Hz), 6.77 (1 H, d, J = 8.0 Hz), 6.72 (1 H, d, J = 8.0 Hz), 5.86 (1 H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.62–5.52 (1 H, m), 5.18–5.08 (2 H, m), 4.34–4.25 (1 H, m), 4.05–3.93 (2 H, m, 9-H), 3.77 (3 H, s), 3.37 (1 H, dd, J = 15.0, 10.0 Hz), 2.50–2.27 (2 H, m), 2.44 (1 H, d, J = 14.5 Hz), 2.08 (1 H, broad s), 2.00–182 (2 H, m), 1.77–1.70 (1 H, dt, J = 13.0, 6.0 Hz), 1.58–1.46 (3 H, m); δ_C (67.9 MHz, $CDCl_3$): 169.2, 156.1, 138.5, 133.7, 130.0, 125.5, 122.9, 117.8, 109.5, 73.0, 72.7, 67.6, 65.1, 55.9, 39.7, 39.5, 38.9, 38.7, 38.2. Found (CI): 333.1701 $[MH]^+$, $C_{19}H_{24}O_5$ requires 333.1702 (0.4 ppm error); m/z (CI) 350 (10%, $[MNH_4]^+$), 333 (100, $[MH]^+$), 315 (63), 245 (10), 148 (25).

(b) To a solution of the alcohol from (a) (30 mg, 0.090 mmol) in dichloromethane (2 mL) was added Dess–Martin periodinane (42 mg, 0.099 mmol) with stirring under N_2 at rt. After 1 h the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether : EtOAc, 1 : 1) to give the *title compound* **52** (29 mg, 97%) as a white crystalline solid; R_f 0.40 (EtOAc); mp 184–185 °C; $[a]_D$ −140 (c 0.60, $CHCl_3$); ν_{max}/cm^{-1} (thin deposit) 2934, 2908, 1709, 1598, 1470, 1355, 1278, 1254, 1116, 1071; δ_H (270 MHz, $CDCl_3$): 7.28 (1 H, t, J = 8.0 Hz), 6.84 (1 H, d, J = 8.0 Hz), 6.79 (1 H, d, J = 8.0 Hz), 5.88 (1 H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.68–5.58 (1 H, m), 5.17 (1 H, ddd, J = 17.0, 3.0, 1.5 Hz), 5.17–5.12 (1 H, m), 4.50 (1 H, tddd, J = 10.0, 3.5, 1.5, 0.5), 4.25 (1 H, dddd, J = 11.0, 8.5, 6.5, 2.0), 3.81 (3 H, s), 3.46 (1 H, dd, J = 14.0, 11.0 Hz), 2.67 (1 H, ddd, J = 15.5, 6.5, 0.5 Hz), 2.52 (1 H, dd, J = 15.5, 8.5 Hz), 2.51–2.31 (4 H, m), 2.22 (1 H, dd, J = 17.0, 10.0 Hz), 1.85 (1 H, ddd, J = 15.0, 11.0, 10.0 Hz), 1.71 (1 H, ddd, J = 15.0, 3.5, 1.5 Hz); δ_C (67.9 MHz, $CDCl_3$): 207.2, 169.9, 156.1, 137.1, 133.5, 130.6, 125.8, 122.7, 118.1, 110.2, 74.2, 72.2, 68.3, 55.9, 47.2, 45.2, 40.2, 39.1, 39.0. Found (CI): 331.1546 $[MH]^+$, $C_{19}H_{22}O_5$ requires 331.1545 (0.2 ppm error); m/z (CI) 348 (11%, $[MNH_4]^+$), 331 (100, $[MH]^+$), 313 (63), 177 (12), 148 (24).

(3*R*,5*R*)-3-Allyl-5-hydroxy-14-methoxy-3,4,5,6-tetrahydro-1*H*-2-oxabenzocyclododecene-1,7(8*H*)-dione (54)

To a freshly prepared stirred solution of LDA (0.1 M in THF, 3.0 mL, 0.30 mmol) was added a solution of pyranone **52** (10 mg, 0.030 mmol) in THF (0.6 mL) under N_2 at −10 °C. After 15 min the reaction mixture had darkened considerably. Sat. NH_4Cl(aq) (0.1 mL) was then added, the mixture stirred at −10 °C for a further 10 min, then the solvent evaporated under reduced pressure. Flash chromatography (petroleum ether: EtOAc, 3 : 1 to 1 : 1) gave first recovered starting material **52** (2 mg, 20%), then the *title compound* **54** (2 mg, 20%) as a yellowish oil, which was recrystallised from ether to give a yellowish solid; R_f 0.27 (petroleum ether : EtOAc, 1 : 1); mp 123–124 °C; $[a]_D$ −110 (c 0.20, MeOH); ν_{max}/cm^{-1} (thin deposit): 3448, 2941, 1707, 1644, 1575, 1467, 1268, 1110; δ_H (500 MHz, acetone-d_6): 7.37 (1 H, t, J = 8.0 Hz), 7.01 (1 H, d, J = 8.0 Hz), 6.86 (1 H, d, J = 8.0 Hz), 6.71 (1 H, d, J = 16.0 Hz), 6.00 (1 H, ddd, J = 16.0, 8.0, 6.5 Hz), 5.87 (1 H, dddd, J = 16.0, 10.0, 6.5, 6.5 Hz), 5.31 (1 H, m), 5.11 (1 H, dq, J = 17.0, 1.5 Hz), 5.08 (1 H, ddt, J = 10.0, 2.5, 1.0 Hz), 4.46 (1 H, m), 3.81 (1 H, d, J = 6.0 Hz), 3.23 (2 H, m), 2.99 (1 H, dd, J = 13.5, 3.5 Hz), 2.43 (2 H, tq, J = 6.0, 1.5 Hz), 2.26 (1 H, dd, J = 13.5, 9.5 Hz), 1.99 (1 H, ddd, J = 14.0, 11.0, 5.0 Hz), 1.76 (1 H, ddd, J = 14.0, 9.5, 3.5 Hz); δ_C (125 MHz, acetone-d_6): 206.75, 167.87, 157.29, 136.96, 134.60, 134.04, 131.06, 128.85, 124.16, 121.23, 118.05, 111.13, 71.78, 65.21, 56.33, 50.15, 47.93, 41.77, 40.36. Found (CI): 348.1812 $[MNH_4]^+$, $C_{19}H_{22}O_5$ requires 348.1811 (0.2 ppm error); m/z (CI) 348 (10%, $[MNH_4]^+$), 331 (100, $[MH]^+$), 313 (85), 295 (15), 234 (15), 217 (35), 174 (20), 148 (15).

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