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Chemoenzymatic Syntheses of Some Analogues of the Tricarbocyclic Core of the Anti-Bacterial Agent Platencin and the Biological Evaluation of Certain of their *N*-Arylpropionamide Derivatives*

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A range of structural variations on the tricarbocyclic core **2** of the anti-bacterial agent platencin **1**, including those represented by compounds **14**, **15**, and **27**, have been prepared and certain of these elaborated, through substrate-controlled enolate alkylation reactions, to analogues of the natural product. Preliminary biological evaluation of these analogues revealed that they are only weakly active anti-infective agents.

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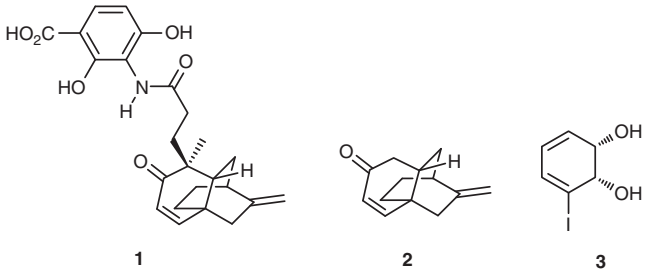
Introduction

The emergence of drug-resistant bacteria has been described as one of the most significant threats facing humankind at the present time.[1] In seeking to address this profound challenge through the identification of new anti-bacterial agents possessing novel modes of action, scientists at Merck & Co. isolated platencin **1** from a strain of the soil bacterium *Streptomyces platensis*.[2] It was established that this natural product inhibited certain enzymes associated with bacterial fatty acid biosynthesis and thus interfered with the assembly of their cell walls.[2] As a result, compound **1** acts against a wide range of bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Mycobacterium tuberculosis*. Such features, together with its lack of toxicity to mammalian systems, have created significant interest in platencin as a lead for the development of new generation anti-bacterial agents.[2,3] Accordingly, extensive efforts have been directed towards its synthesis and a range of approaches has been reported and reviewed.[1,4]

In 2008 we detailed[5] an enantioselective synthesis of compound **2** that embodies the tricarbocyclic core of platencin and that has been elaborated, by Nicolaou and-co-workers,[6] to platencin itself. The starting material used in our work was the *cis*-1,2-dihydrocatechol **3**. This is obtained in homochiral form through the whole-cell biotransformation of iodobenzene using the genetically engineered microorganism *E. coli* JM109 (pDTG601) that overexpresses the responsible enzyme, namely toluene dioxygenase (Chart 1).[7]



1 2 3

Chart 1.

The key features of our reaction sequence[5] leading to enone **2** are shown in Scheme 1. Thus, the readily obtained acetonide derivative **4** of diol **3**, was subjected to a Negishi-type cross-coupling with the racemic organozinc species **5** and so formed the triene **6** as a ~1 : 1 mixture of diastereoisomers in 85 % combined yield. Despite the absence of an activating group, the side-chain double bond within compound **6** engaged in a remarkably facile, thermally induced, and diastereoselective Type 1 intramolecular Diels–Alder (IMDA) cycloaddition reaction with the diene moiety embedded in the *cis*-1,2-dihydrocatechol residue and thus affording adduct **7** in 89 % yield. A series of twelve relatively conventional functional group interconversions then allowed for the completion of the synthesis of compound **2**.

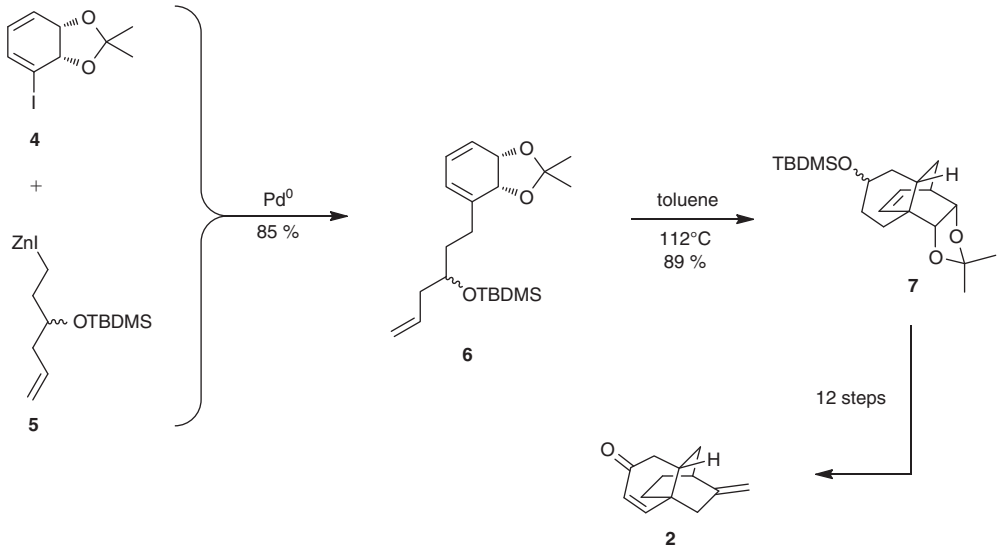
In an effort to establish a shorter route to platencin, the pathway shown in Scheme 2 was developed.[8] Thus, acetonide **4** was engaged in a Stille cross-coupling reaction with a more elaborate side-chain, namely the *Z*-configured alkenylstannane **8** wherein the associated stereogenic centre was constructed using a chiral auxiliary-based approach. While the so-formed

*Dedicated to the memory of Professor Sir Derek Barton and in recognition of his seminal contributions to so many aspects of organic chemistry.

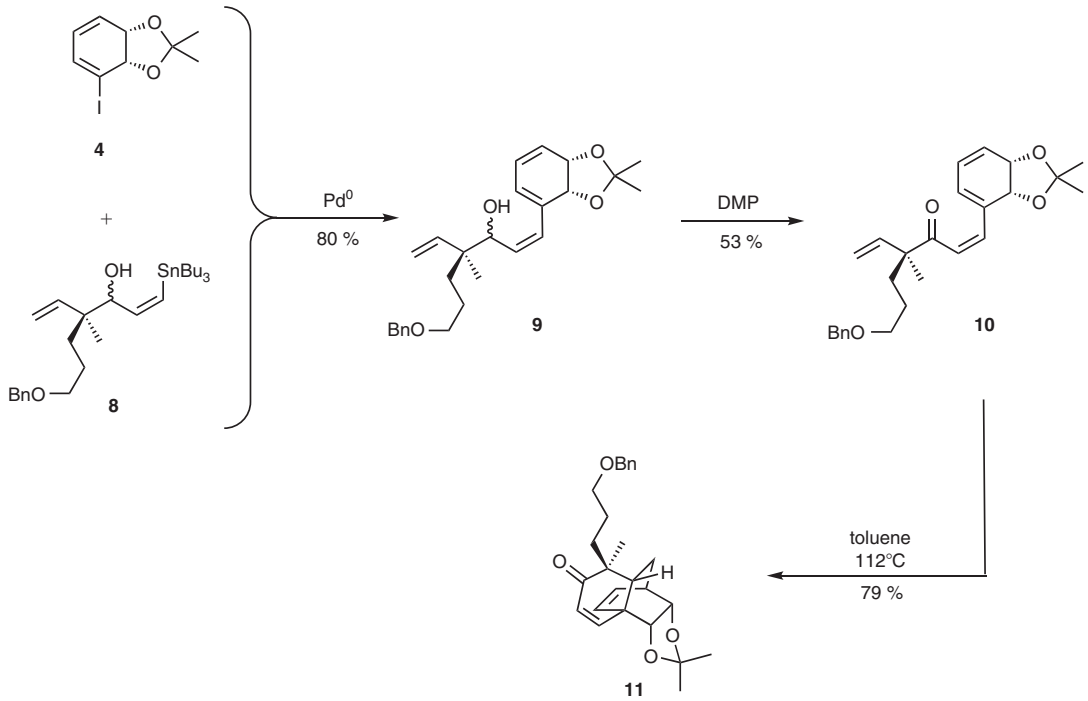
tetra-ene **9** (80 %) failed to engage in the hoped-for IMDA cycloaddition reaction, the readily derived ketone **10** (53 %) did so and thus produced adduct **11** in 79 % yield. The differing behaviours of compounds **9** and **10** towards this critical cycloaddition process may reflect the conformational preferences within the latter substrate that predispose it, through pre-organisational effects, towards reaction. Adduct **11** could be elaborated to platencin over 13-steps, although on exposing this compound to hydrogen in the presence of Pd on C not only did cleavage of the benzyl ether and hydrogenation of the isolated C=C double bond take place (both desired processes) but the double bond of the enone moiety was also reduced (an undesired process). As a result, two additional steps were required to reinstate the latter bond.

In another study, the outcomes of which we reported recently,[9] compound **2** was elaborated, including via substrate-controlled enolate alkylation reactions, into platencin and by a slightly shorter route than that involving the manipulation of the IMDA adduct **11**.

In an effort to improve the pharmacokinetic properties of platencin, considerable effort has been directed towards the synthesis of analogues.[2b] Structure–activity relationship studies in this domain have revealed that modest variations in the tricarbocyclic core **2** of platencin can be tolerated but that even minor modifications to the 3-amino-2,4-dihydroxybenzoic acid residue are deleterious. The impact of varying the nature of the propionamide linker between these two motifs remains to be established.



Scheme 1.



Scheme 2.

In this report we now detail efforts to apply the 'intelligence' gathered during the above-mentioned total synthesis studies on compound **1** to the production of various analogues of the tricarbocyclic core of the natural product as well as the elaboration of certain of these to 'fully fledged' variants of platencin for the purposes of subjecting them to biological evaluation. Among the various analogues of enone **2** targeted in preliminary synthetic studies were compounds **12**–**15** (Chart 2). These were sought because of their anticipated ease of access using our established chemical protocols and the lack of any prior studies on most of them. The approaches to these compounds are detailed in the following section, as are the outcomes of studies on the conversion of certain of these into *N*-arylpropionamide derivatives for the purposes of assessing their anti-bacterial effects.

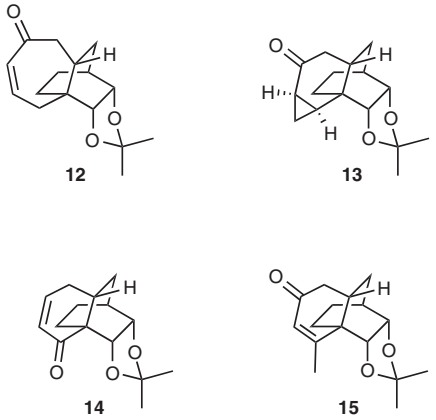


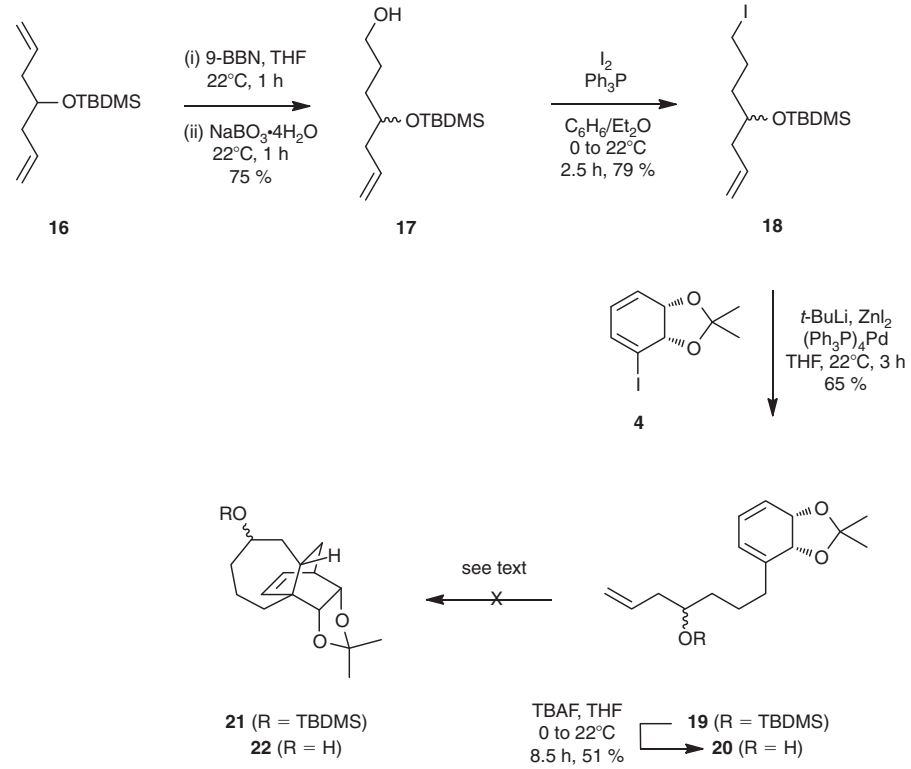
Chart 2.

Results and Discussion

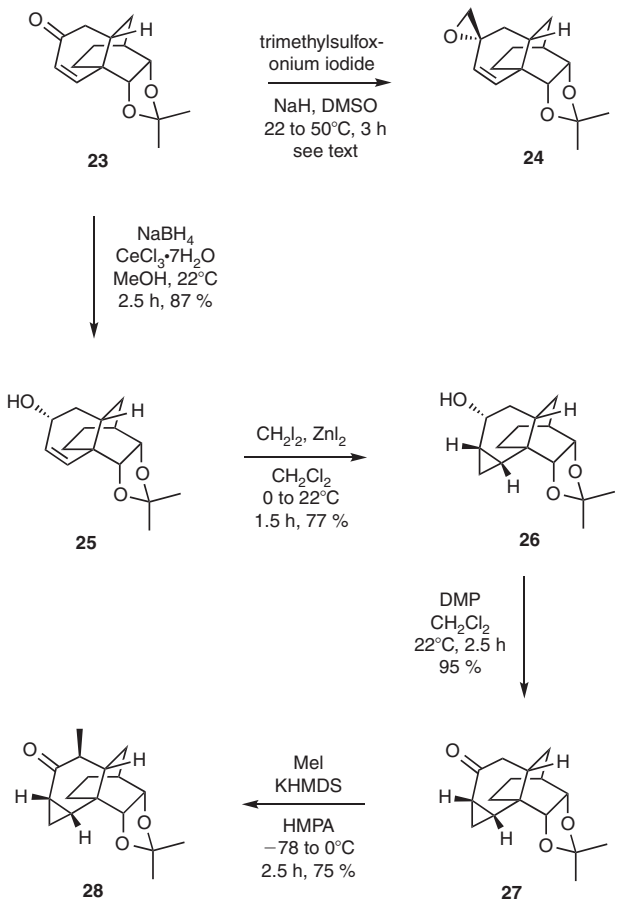
Synthetic Studies

The approach taken in efforts to prepare our initial target compound **12** is shown in Scheme 3 and involved attempting to implement an IMDA reaction analogous to that employed in obtaining compound **2** (Scheme 1). Thus, the previously reported[5] diene **16** was subjected to mono-hydroboration using 9-borabicyclo[3.3.1]nonane (9-BBN) and the ensuing organoborane oxidised in situ to give, in racemic form, the 1° alcohol **17**[10] in 75 % yield. The reaction of compound **17** with triphenylphosphine in the presence of molecular iodine gave the anticipated Appel-type product **18** (79 %) and the organozinc species derived from this was cross-coupled with the iododiene **4** to give the triene **19** (65 %) as a ~1 : 1 mixture of diasteroisomers. Treatment of this last compound with tetra-*n*-butylammonium fluoride (TBAF) then afforded the corresponding alcohol **20**. Disappointingly, and despite examining a range of conditions, neither ether **19** nor the corresponding alcohol **20** participated in IMDA cycloaddition reactions to give the hoped-for adducts **21** and **22**, respectively. Such outcomes are attributed to adverse entropic effects arising from the longer linker (relative to congeners **6** and **10**) joining the diene and dienophilic residues in compounds **19** and **20**. Accordingly, alternate routes to such seven-membered ring-containing compounds were pursued.

Our failure to establish a direct route to seven-membered ring homologues of compound **2** prompted exploration of an approach wherein cyclopropanated derivatives of the parent framework would be assembled with the intention of subjecting these to ring-expansion processes. In a first attempt to implement such ideas, the previously reported[9] cyclohexenone **23** (Scheme 4), and a readily obtained derivative of compound **7**, was subjected to reaction with the Corey–Chaykovsky ylide[11] in the hope of effecting a nucleophilic cyclopropanation



Scheme 3.



Scheme 4.

reaction. However, this did not occur. Rather, a complex reaction mixture was obtained and spectroscopic analysis of this indicated the presence of olefinic protons and the absence of a carbonyl group suggesting the spirocyclic epoxide **24** may have been formed (the illustrated configuration at the spirocyclic centre is suggested on the basis that nucleophilic additions to substrates such as **23** take place preferentially from the sterically more accessible β-face). However, pure samples of compound **24** could not be obtained and so exhaustive characterisation of this product was not possible.

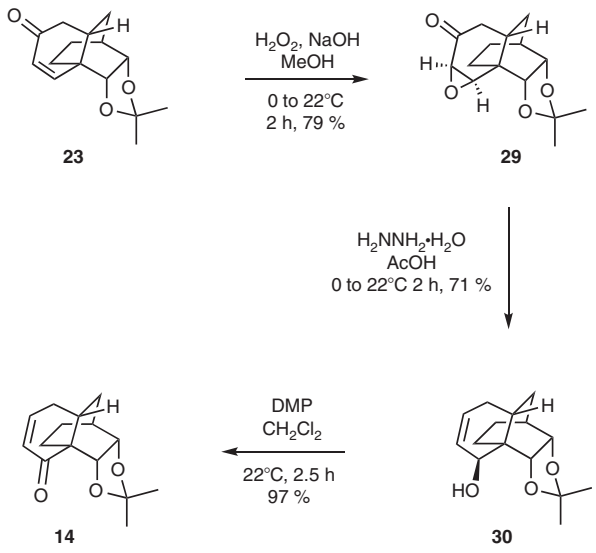
A directed electrophilic cyclopropanation pathway (Scheme 4) was also pursued in efforts to obtain the target ring system. Thus, Luche reduction[12] of enone **23** afforded the α-configured allylic alcohol **25** (87 %) stereoselectively and on subjecting this to a Furukawa-modified Simmons–Smith cyclopropanation reaction[13] compound **26** was obtained as a single diastereoisomer in 77 % yield. Oxidation of alcohol **26** with the Dess–Martin periodinane (DMP)[14] then gave the corresponding cyclopropyl ketone **27** (95 %) and on treatment of the derived enolate with methyl iodide the mono-methylated ketone **28** (75 %) was obtained as a crystalline solid. A single-crystal X-ray analysis of this material served to confirm the illustrated structure. Details of this analysis, including the derived *ORTEP* diagram, are provided in the Supplementary Material.

The outcomes of the conversions **23** → **25** and **27** → **28** shown in Scheme 4 serve to emphasise that while β-face attack on such substrates tends to be favoured, α-face addition processes (such as **25** → **26**) can still be effected through reagent complexation by appropriately (α) configured directing groups.

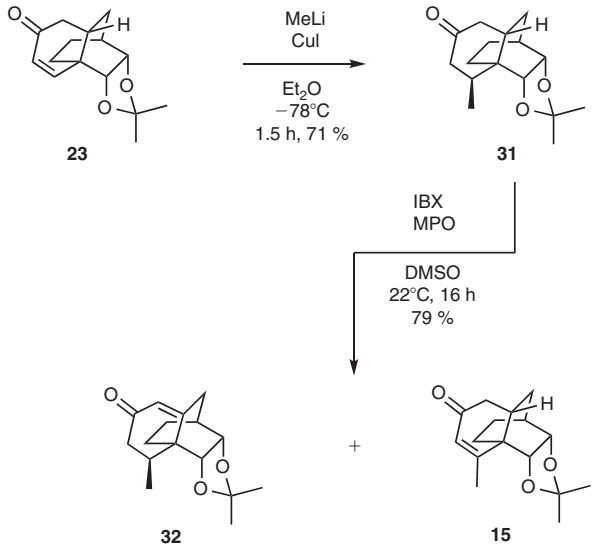
Various efforts, involving the use of both Brønsted–Lowry and Lewis acids, were made to effect the ring-expansion of compounds **26**, **27**, and **28** but these either returned the starting materials or produced complex mixtures of products. As such, attempts to convert these cyclopropannulated cyclohexanes into seven-membered ring-containing systems such as **22** were abandoned.

In seeking to obtain the rearranged enone **14**, another of our original targets, the nucleophilic epoxidation of enone **23** (Scheme 5) was explored. This proceeded effectively on exposure of the substrate to alkaline hydrogen peroxide and thus afforded compound **29** in 79 % yield. While the configuration of this epoxide proved to be of little consequence in terms of the outcomes of the subsequent Wharton rearrangement,[15] it is presumed to possesses the illustrated stereochemistry as a result of preferential β-face addition of the hydroperoxy anion to the enone moiety of the substrate. That said, inspection of the ^{13}C NMR spectrum of this product suggested that small amounts (~10 %) of the other diastereoisomer were also likely to have been formed in the reaction. On treating this epoxy-ketone with hydrazine in the presence of acetic acid the anticipated reaction took place and so afforded the allylic alcohol **30** in 71 % yield. DMP-mediated oxidation of this last compound then gave the rearranged enone **14** (97 %), the spectroscopic features of which were similar but not identical with those of precursor **23**. Perhaps the most notable difference was evident in the ^{1}H NMR spectra. In the spectrum of compound **14** the resonance due to the β-proton of the enone moiety appeared at δ 6.83 as a doublet of doublet of doublets (J 10.2, 5.8, and 2.2) while for precursor **23** this resonated at δ 6.89 as a doublet (J 10.1).[9]

In another conjugate addition process (Scheme 6), compound **23** was treated with the Gilman reagent and thus afforded the β-methylated cyclohexanone **31** in 71 % yield. On exposing this compound to a mixture of 2-iodoxybenzoic acid (IBX) and 4-methoxypyridine *N*-oxide (MPO), under conditions defined by Nicolaou and co-workers,[16] a chromatographically inseparable 2 : 3 mixture of the methylated and regioisomeric cyclohexenones **15** and **32** was obtained in 79 % yield. Interestingly, this mixture of compounds proved to be crystalline and an X-ray analysis revealed the presence of one molecule of each of compounds **15** and **32** in the unit cell. Once again, details of this



Scheme 5.



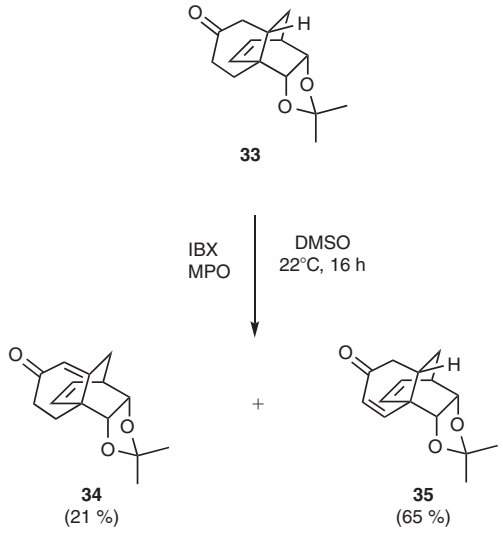
Scheme 6.

analysis are provided in the Experimental section and the Supplementary Material.

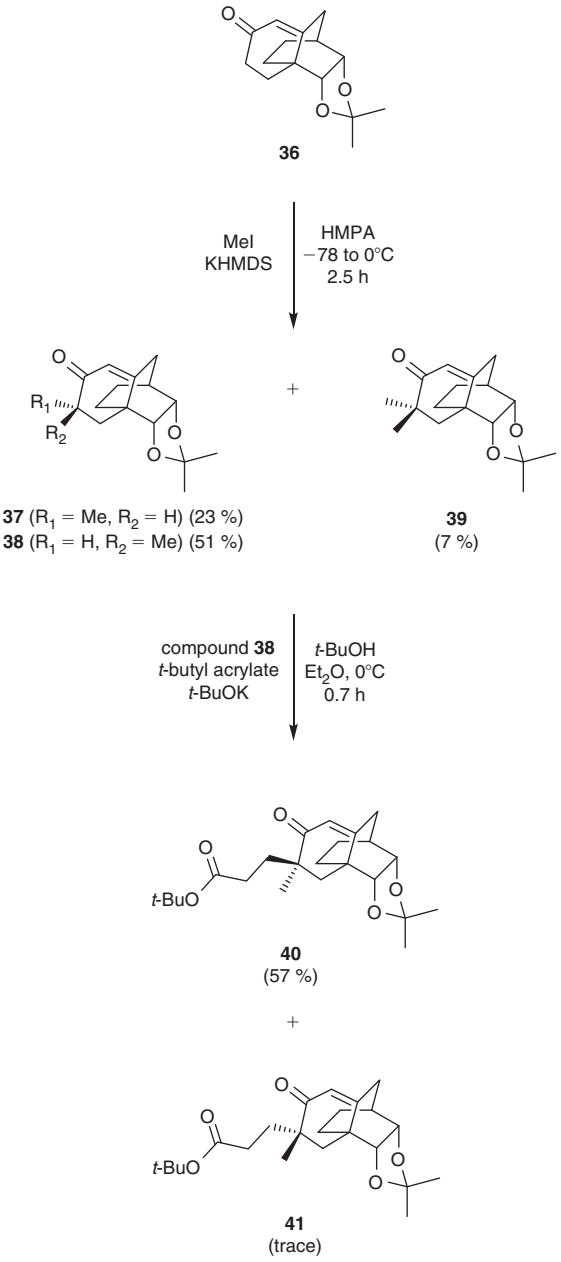
In an effort to establish the effect that other, adjacent functionalities might have on the regioselectivities of these types of dehydrogenation reactions, the unsaturated cyclohexanone **33** (Scheme 7), which is readily prepared from IMDA adduct **7** (see Experimental for details), was also subjected to reaction with IBX and MPO. Under such conditions essentially the same outcome was observed, namely a 1 : 3 mixture of the regioisomeric dienones **34** and **35** was formed in 86 % combined yield. Gratifyingly, these could be separated chromatographically and each was subjected to single-crystal X-ray analysis, details of which are provided in the Supplementary Material.

Having established various protocols for manipulating the cyclohexenone-containing core of platencin, our attention turned to the application of enolate alkylation protocols so as to determine how readily the α-methyl and propionic acid 'side-chain' groups seen in platencin could be installed in a stereoselective manner. The protocols developed for this purpose were, of course, informed by our earlier study[9] on the total synthesis of platencin and a representative set of outcomes is shown in Scheme 8.

Thus, the enolate obtained on treating enone **36** with potassium hexamethyldisilazide (KHMDS) at −78°C was treated with methyl iodide and the ensuing mixture allowed to warm to 0°C over 2.5 h. After work-up and chromatography three products, namely the mono-methylated compounds **37** (23 %) and **38** (51 %) together with the *gem*-dimethylated congener **39** (7 %), were obtained and the structure of the first of these was confirmed by single-crystal X-ray analysis. On treating the mono-methylated system **38** with *t*-butyl acrylate in the presence of potassium *t*-butoxide, the anticipated Michael addition reaction took place and so produced propionate ester **40** (57 %) as the major reaction product. NMR analysis of the crude reaction product also suggested the presence of traces of epimer **41** but this could not be isolated in pure form in sufficient quantities to allow for its independent spectroscopic characterisation. The illustrated



Scheme 7.

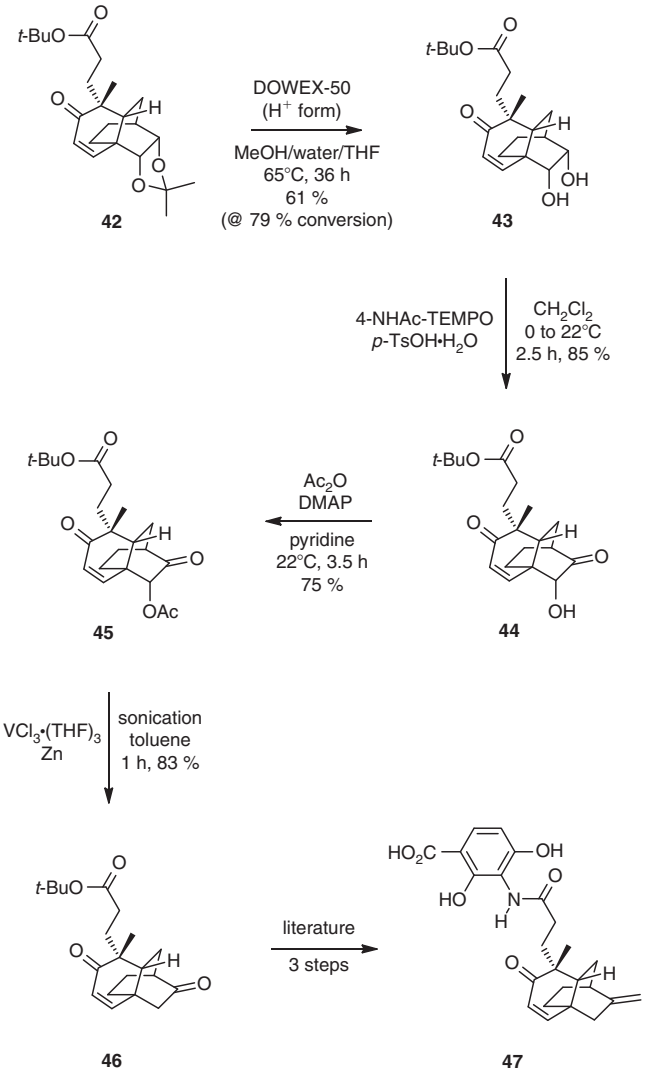


Scheme 8.

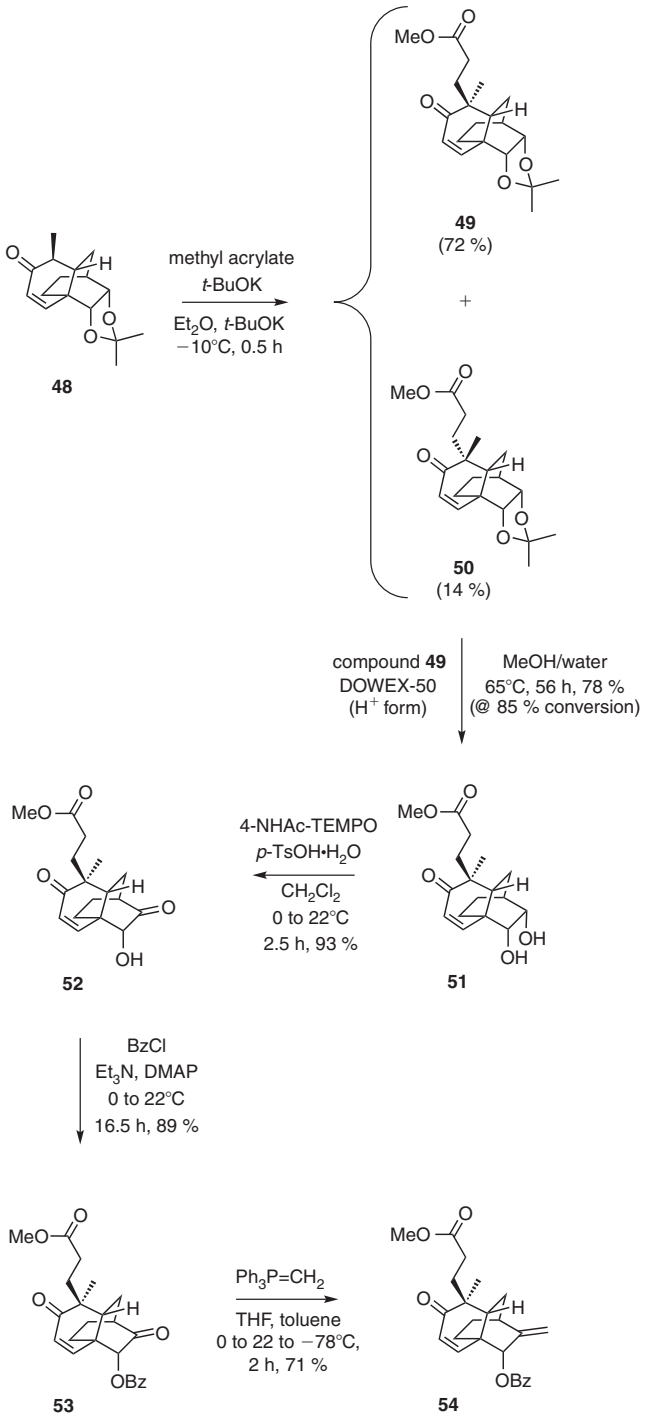
configurations of the newly established quaternary carbons in these esters are assigned on the basis that the major product of reaction should be that in which the acrylate reacts preferentially at the β-face of the enolate.

Another aspect of our intelligence gathering activities in the area was an investigation of the capacity to effect selective manipulations of the acetonide moiety in systems incorporating cyclohexenone and propionate residues using the repertoire of transformations that we had employed earlier.[8,9] The substrate we chose for such purposes was compound **42** (Scheme 9) that had been obtained previously as a minor product from successive methylation and propionylation reactions of enone **23** using the same conditions as described immediately above. Thus, treating acetonide **42** with acidified DOWEX-50 resin in methanol/THF/water at 65°C for 36 h afforded diol **43** in 61 % yield (at 79 % conversion). Gratifyingly, there was little evidence for the competing cleavage of the *t*-butyl ester moiety under these conditions. The selective oxidation of the hydroxy group remote from the fully substituted bridgehead carbon of the bicyclo[2.2.2] octane framework within compound **43** could be achieved using Bobbitt's reagent,[17] namely the sterically demanding oxammonium salt derived from the *p*-toluenesulfonic acid-promoted disproportionation of 4-NHAc-(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO). By such means the acyloin **44** was obtained in 85 % yield and with no evidence for the co-production of its regio-isomer. Acetylation of compound **44** was achieved under conventional conditions and the resulting ester **45** (75 %) was subjected to reductive deoxygenation using Torii's low-valent vanadium reagent[18] to afford the ketone **46** in 85 % yield. Chen and co-workers have reported[19] the elaboration of compound **46**, over three steps, into amide **47**, the C-4 epimer of platencin and a compound that displays somewhat weaker antibacterial activity than the natural product.

In a series of related transformations, as shown in Scheme 10, the enolate anion obtained by deprotonation of the previously



Scheme 9.



Scheme 10.

reported[9] mono-methylated enone **48** was reacted with methyl acrylate and thus afforded a 5 : 1 mixture of the epimeric propionic acid methyl esters **49** (72 %) and **50** (14 %). The acetonide residue associated with the major product, which is assumed to possess the illustrated β-configuration of the propionoate side-chain at C-4, could be cleaved under standard conditions and the resulting diol **51** (78 % at 85 % conversion) selectively oxidised using Bobbitt's reagent[17] and thus afforded acyloin **52** (93 %) that was itself esterified using benzoyl chloride in the presence of 4-(*N*,*N*-dimethylamino) pyridine (DMAP) and triethyamine to yield compound **53** (89 %). Selective Wittig methylenation of the non-conjugated ketone residue within this last compound could be accomplished under relatively conventional conditions and gave the allylic ester **54** in 71 % yield.

The final focus of the present study was the conversion of certain propionic acid ester derivatives of the tricarbocyclic core framework, namely those incorporating an acetonide protecting group, into the corresponding *N*-aryl amides for the purposes of evaluating these as anti-infective agents. To such ends the reaction sequence shown in Scheme 11 was pursued wherein ester **49** was saponified using lithium hydroxide in aqueous THF and the free-acid **55** (97 %) obtained on work-up coupled, under conditions defined by Chen,[19] with the protected aminobenzoic acid derivative **56**[19] in the presence of 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophos-phate (HATU)[20] to form the amide **57** (32 %). Finally, treatment of this TMSE-ester-containing compound with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[21] resulted in the formation of target **58**, although repeated chromatographic purification was required to obtain material of appropriate quality and as a consequence this compound was only obtained in 21 % yield.

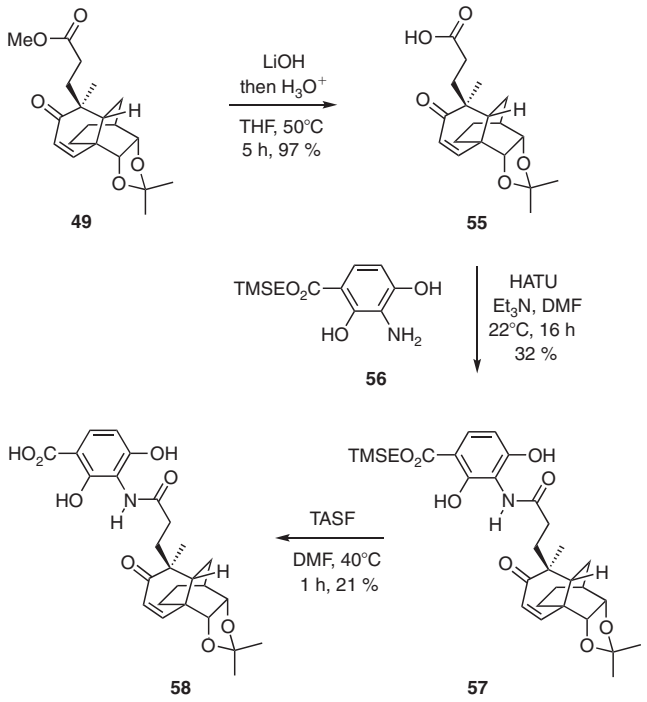
The C-4 epimer of compound **58** was prepared in a slightly more direct manner as shown in Scheme 12. Thus, ester **50** was saponified in the same way as congener **49** and the resulting free-acid **59** (95 %) obtained after acidic work-up was coupled with the unprotected aminobenzoic acid **60** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to provide the target *N*-aryl amide **61** (27 %). The lack of a clean reaction associated with this coupling reaction led us to conclude that despite the need to employ an extra step (viz. a deprotection reaction) in the reaction sequence, couplings involving the protected aminobenzoic acid **56** (rather than congener **60**) lead to superior outcomes.

There are some modest differences in the spectroscopic data sets derived from the epimeric platencin analogues **58** and **61**, perhaps the most conspicuous being in the high-field regions of the ^{13}C NMR spectra with the signals due to certain of the sp^3-hybridised carbons in the latter compound being more shielded by the 'overhanging' *N*-aryl amide residue.

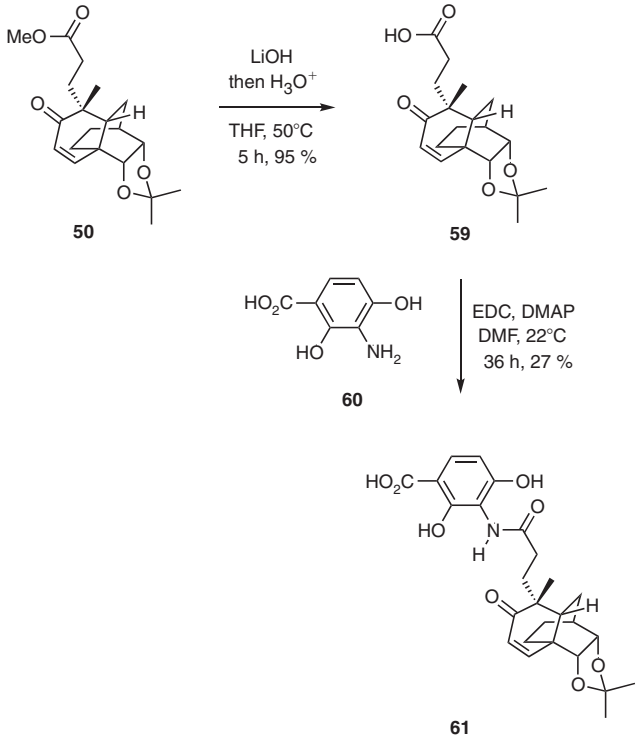
The final, acetonide-containing platencin analogue to be prepared was the saturated equivalent of compound **58**. This was obtained by the simple route shown in Scheme 13. Specifically, the previously reported[8] acid **62** was coupled with aniline **56** to afford amide **63** (14 %) that was deprotected with TASF and delivered the third target analogue, namely compound **64**, in 15 % yield. Once again, the low yields observed in this sequence derived from the need to subject each product to extensive flash column chromatography so as to secure material of adequate purity.

Biological Studies

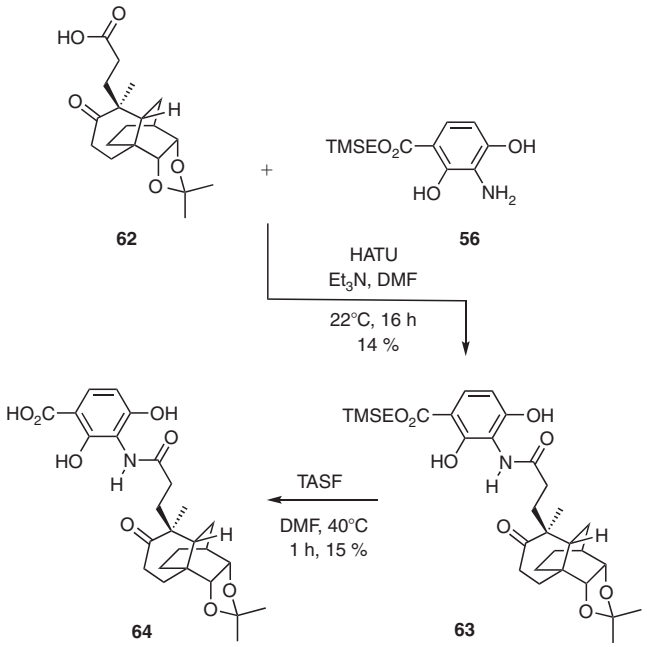
The acetonide-containing platencin analogues **58**, **61**, and **64** were evaluated against a panel of Gram-positive bacteria including *Streptococcus pynogens* ATCC 51339, *Staphylococcus aureus* ATCC 19636, *Enterococcus faecium* ATCC 19434, and *Haemophilus influenzae* ATCC 49247. Commercially available platencin **1** and chloramphenicol were used as positive controls. Such evaluations established that these analogues displayed the same activity against *S. pynogens* and *E. faecium*



Scheme 11.



Scheme 12.



Scheme 13.

as that observed for platencin, namely that they were only weakly active materials ($>16\ \mu g\ mL^{-1}$). In contrast, platencin inhibited the growth of *S. aureus* and *H. influenzae* at $4\ \mu g\ mL^{-1}$ but analogues **58**, **61**, and **64** proved ineffective against all four of these same pathogens as revealed by their anti-bacterial activities being above $16\ \mu g\ mL^{-1}$. These biological data are summarised in Table 1.

Conclusion

The work detailed above has provided the capacity to generate a range of analogues of the tricarbocyclic core of platencin. While previous studies have established that modest variations in this core allow for the retention of anti-bacterial activity,[2b] the incorporation of an acetonide residue into such a framework (as seen in compounds **58**, **61**, and **64**) at the expense of the exocyclic double bond (as seen in the natural product) clearly has adverse impacts. Nevertheless, other opportunities for variations within this framework are likely to be available through the transformations reported here and these are now being pursued. The outcomes of such studies will be reported in due course.

Experimental

General Experimental Procedures

Unless otherwise specified, ^1H and ^{13}C NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^1H NMR data are recorded as follows: chemical shift (δ) (multiplicity, coupling constant(s) J (Hz), relative integral) where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ 'triplet' appearing at δ_C 77.0 were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analysed as thin films on KBr plates. Low-resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass LC-ZMD single quadrupole liquid chromatography–mass spectrometer while high-resolution measurements were conducted on an LCT Premier time-of-flight instrument. Low- and high-resolution electron impact (EI) mass spectra were recorded on an Autospec Premier Micromass magnetic-sector machine. Optical rotations were recorded in $CHCl_3$ at 20°C on a Perkin Elmer Model 343 Polarimeter. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL) or potassium permanganate/potassium carbonate/5 % sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[22] with silica gel 60 (40–63 μm) (silica) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol, and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[23] Where necessary, reactions were performed under an inert atmosphere. Semi-preparative HPLC separations were carried out using a $10 \times 250\ mm^2$ i.d. Daicel Chiral Pak 1A

Table 1. Comparison of the anti-bacterial properties of compounds 58, 61, and 64 with a naturally derived sample of platencin and with chloramphenicol

Compound[A]	Minimal inhibitory concentration[B] [$\mu g\ mL^{-1}$]			
	Streptococcus pynogens ATCC 51339	*Staphylococcus aureus* ATCC 19636	*Enterococcus faecium* ATCC 19434	*Haemophilus influenzae* ATCC 49247
58	>16	>16	>16	>16
61	>16	>16	>16	>16
64	>16	>16	>16	>16
Platencin (**1**)	4	>16	4	>16
Chloroamphenicol	≤2.0	≤2.0	≤2.0	≤2.0

[A]Compounds were tested in doubling dilutions over the concentration range 0.008–16 $\mu g\ mL^{-1}$.
[B]The minimal inhibitory concentration is the lowest compound concentration needed to inhibit visible bacterial growth or to inhibit growth based on absorbance readings.

column packed with amylose tris(3,5-dimethylphenyl carbamate) immobilised on 5 μm silica gel. An eluting solvent of 9 : 90 : 1 v/v/v *iso*-propyl alcohol/hexane/TFA was used at a flow rate of 4.5 mL min^{-1}.

Specific Synthetic Transformations

*Compound **16***

A magnetically stirred solution of commercially available hepta-1,6-dien-4-ol (13.45 g, 0.12 mol) in dry CH_3CN (50 mL) maintained under nitrogen atmosphere at 22°C was treated with *t*-butyldimethylsilyl chloride (TBDMS-Cl) (19.6 g, 0.13 mol) and the resulting mixture stirred for a further 0.25 h before being treated, in portions, with imidazole (250 mg, 1.0 mmol). The reaction mixture thus obtained was left to stir for 16 h before being diluted with hexane (90 mL), washed with water (1 × 35 mL) and brine (1 × 35 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting viscous light-yellow oil was subjected to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f 0.8 in 3 : 7 v/v ethyl acetate/hexane), compound **16** (24.7 g, 91 %) as a clear, colourless oil. δ_H (400 MHz, $CDCl_3$) 5.90–5.74 (complex m, 2H), 5.05 (m, 2H), 5.02 (s, 2H), 3.75 (p, *J* 5.9, 1H), 2.33–2.10 (complex m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). These data matched those reported previously.[5]

*Compound **17***

A magnetically stirred solution of diene **16**[5] (226 mg, 1.0 mmol) in dry THF (19.0 mL) maintained at 22°C under an atmosphere of nitrogen was treated, via syringe, with 9-borabicyclo[3.3.1]nonane (2.56 mL of a 0.43 M solution in THF, 1.1 mmol). The ensuing mixture was stirred for 1 h and then treated with water (7.5 mL) and $NaBO_3{\cdot}4H_2O$ (5 equiv.) (CAUTION: exothermic reaction). The ensuing heterogeneous mixture was stirred vigorously for an additional 1 h and then treated with NH_4Cl (10 mL of a saturated aq. solution) before being extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. Subjection of this material to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.5 in 1 : 4 v/v ethyl acetate/hexane), the title alcohol **17**[10] (183 mg, 75 %) as a clear, colourless liquid. δ_H (400 MHz, $CDCl_3$) 5.78 (m, 1H), 5.08–5.00 (complex m, 2H), 3.79 (m, 1H), 3.62 (m, 2H), 2.25 (m, 2H), 1.98 (br. s, 1H), 1.69–1.50 (complex m, 4H), 0.89 (s, 9H), 0.06 (s, 6H). δ_C (101 MHz, $CDCl_3$) 135.2, 117.1, 71.9, 63.3, 41.7, 33.2, 28.4, 26.0, 18.3, −4.3, −4.4. ν_{max} (KBr)/cm^{-1} 3352, 3077, 2955, 2930, 2887, 2858, 1641, 1472, 1463, 1434, 1412, 1388, 1361, 1328, 1255, 1187, 1071, 1028, 1005, 969, 938, 912, 869, 836, 775, 665. *m/z* (ESI, +ve) 267 ($[M + Na]^+$, 20 %), 70 (100). HRMS *m/z* 267.1756; $C_{13}H_{28}O_2Si$ $[M + H]^+$ requires 267.1756.

*Compound **18***

A magnetically stirred solution of alcohol **17** (122 mg, 0.5 mmol) in anhydrous diethyl ether (10 mL) maintained under an atmosphere of nitrogen was cooled to 0°C and then treated with imidazole (72 mg, 1.05 mmol), triphenylphosphine (262 mg, 1.0 mmol), and molecular iodine (255 mg, 1.05 mmol). The ensuing mixture was allowed to warm to 22°C and stirred at this temperature for a further 2 h. After this time, the now dark-coloured reaction mixture was diluted with diethyl ether (25 mL) and $Na_2S_2O_3$ (7.5 mL of a 10 % w/v aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions were washed with brine (1 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. Subjection of this material to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) and concentration of appropriate fractions (R_f 0.5), afforded iodide **18** (140 mg, 79 %) as a clear, colourless oil. δ_H (400 MHz, $CDCl_3$) 5.79 (m, 1H), 5.06 (m, 1H), 5.02 (s, 1H), 3.74 (m, 1H), 3.18 (t, *J* 7.0, 2H), 2.21 (m, 2H), 1.99–1.76 (complex m, 2H), 1.63–1.44 (complex m, 2H), 0.88 (s, 9H), 0.05 (s, 6H). δ_C (101 MHz, $CDCl_3$) 134.9, 117.2, 71.1, 42.0, 37.5, 29.6, 26.0, 18.2, 7.4, −4.2, −4.4. ν_{max} (KBr)/cm^{-1} 2955, 2928, 2850, 1641, 1471, 1462, 1436, 1361, 1255, 1071 1004, 913, 835, 774, 719. *m/z* (ESI, +ve) 377 ($[M + Na]^+$, 100 %). HRMS *m/z* 377.0774; $C_{13}H_{27}IOSi$ $[M + H]^+$ requires 377.0774.

*Compound **19***

A magnetically stirred solution of iodide **18** (179 mg, 0.50 mmol) in diethyl ether (5 mL) maintained under a nitrogen atmosphere at −78°C was treated dropwise with *t*-BuLi (617 μL of a 1.7 M solution in pentane, 1.05 mmol) over 3 min and then stirred at this temperature for a further 5 min After this time a solution of anhydrous ZnI_2 (175 mg, 0.55 mmol) in dry THF (750 μL) was added to the reaction mixture and stirring continued for a further 10 min before it was warmed to 22°C over 1 h. At this point, a solution of freshly prepared iodide **4** (140 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.08 mmol) in THF (750 μL) was added, dropwise, and stirring continued for 2 h. After this time the reaction mixture was quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) and the separated aqueous phase extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine (1 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. This was subjected to flash column chromatography (1 : 99 to 1 : 19 v/v ethyl acetate/hexane gradient elution) to afford, after concentration of the relevant fractions (R_f 0.4 in 1 : 4 v/v ethyl acetate/hexane), a ~1 : 1 mixture of the diastereoisomeric forms of compound **19** (123 mg, 65 %) as a clear, colourless oil. δ_H (400 MHz, $CDCl_3$) 5.98 (m, 1H), 5.84–5.75 (complex m, 2H), 5.72 (m, 1H), 5.05 (m, 2H), 4.64 (m, 1H), 4.52 (dd, *J* 8.7 and 2.5, 1H), 3.71 (m, 1H), 2.27–2.18 (complex m, 4H), 1.43–144 (complex m, 4H), 1.41 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.05 (br s, 6H). δ_C (101 MHz, $CDCl_3$) 138.5, 135.9, 135.5, 128.4, 125.7, 124.9, 124.8, 122.7, 118.4, 116.8, 105.4, 86.1, 73.5, 71.9, 71.5, 42.2, 42.1, 36.6, 34.4, 33.8, 30.5, 27.1, 26.1, 25.2, 23.0(4), 22.9(7), 21.3, 18.3, −4.21, −4.4 (ten resonances obscured or overlapping). ν_{max} (KBr)/cm^{-1} 3047, 2986, 2933, 2891, 1644, 1570, 1454, 1394, 1379, 1371, 1302, 1233, 1210, 1157, 1060, 1033, 982, 869, 787, 723, 622. *m/z* (ESI, +ve) 401 ($[M + Na]^+$, 20 %), 147 (100). HRMS *m/z* 401.2487; $C_{22}H_{38}O_3Si$ $[M + H]^+$ requires 401.2488.

*Compound **20***

A magnetically stirred solution of silyl ether **19** (135 mg, 0.357 mmol) in THF (7.5 mL) maintained at 0°C was treated with TBAF (750 μL of a 1.0 M solution in THF, 0.75 mmol). Stirring was continued for 0.25 h and then the reaction mixture was warmed to 22°C and stirring continued for further for 8 h at this temperature. After this time the reaction mixture was

concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f 0.3 in 1 : 1 v/v ethyl acetate/hexane), a ~1 : 1 mixture of the diastereoisomeric forms of compound **20** (47.6 mg, 51 %) as a clear, colourless oil. δ_C (101 MHz, $CDCl_3$) 143.5, 140.2, 139.1, 133.6, 128.9, 125.3, 124.7, 109.4, 108.8, 106.0, 104.0, 101.5, 84.9, 79.2, 78.7, 77.9, 75.4, 71.7, 48.4, 45.7, 38.5, 35.4, 28.0, 26.9, 26.8, 25.6, 25.3 (five resonances obscured or overlapping). ν_{max} (KBr)/cm^{-1} 3415, 3047, 2983, 2932, 1640, 1443, 1375, 1370, 1259, 1210, 1158, 1046, 914, 884, 747, 667. *m/z* (EI, 70 eV) 264 ($M^{+\bullet}$, < 1 %), 263 ($[M - H\bullet]^+$, 3), 249 ($[M - CH_3\bullet]^+$, 100). HRMS *m/z* 264.1726; $C_{16}H_{24}O_3$ $M^{+\bullet}$ requires 264.1725.

Attempted Nucleophilic Cyclopropanation of Enone ***23***

A magnetically stirred suspension of sodium hydride (40 mg, 1.01 mmol) in DMSO (1.0 mL) was treated with trimethylsulfoxonium iodide (334 mg, 1.52 mmol) and the ensuing mixture stirred at 22°C for 0.5 h. A solution of enone **23**[9] (24.8 mg, 0.10 mol) in DMSO (1.0 mL) was then added to the reaction mixture that was then stirred for a further 2.5 h. After this time the reaction temperature was raised to 50°C and stirring continued at this temperature for 0.5 h. The cooled reaction mixture was then treated with diethyl ether (5 mL) followed by pH 7 aqueous buffer (5 mL). The separated aqueous phase was extracted with diethyl ether (5 × 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil (21 mg). NMR spectroscopic and TLC analyses of this material suggested it was a mixture of products. The presence of olefinic proton resonances in the ^1H NMR spectrum of the crude reaction mixture and the absence of a carbonyl absorption band in the infrared spectrum of this material suggested that spiro-epoxidation (leading, at least in part, to compound **24**), rather than nucleophilic cyclopropanation, had taken place.

Compound ***25***

A magnetically stirred solution of enone **23** (1.24 g, 5.0 mmol) and $CeCl_3{\cdot}7H_2O$ (3.71 g, 10.0 mmol) in methanol (19 mL) was cooled to 0°C and then treated, in portions over 0.5 h, with $NaBH_4$ (375 mg, 10.0 mmol). The ensuing mixture was allowed to warm to 22°C and then stirred at this temperature for a further 2.5 h before water (10 mL) was slowly added. After hydrogen gas evolution had ceased the reaction mixture was concentrated under reduced pressure and the residue thus obtained extracted with dichloromethane (5 × 15 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white, crystalline solid. Recrystallisation (hexane/methanol) of this material gave alcohol **25** (1.09 g, 87 %) as a white solid, mp 108–116°C, $[\alpha]_D$ −31.2 (*c* 1.0, $CHCl_3$) (R_f 0.3 in 3 : 7 v/v ethyl acetate/hexane). δ_H (400 MHz, $CDCl_3$) 5.69 (dd, *J* 10.1 and 2.0, 1H), 5.58 (m, 1H), 4.23 (m, 1H), 4.12 (m, 1H), 3.71 (dd, *J* 8.1 and 1.4, 1H), 2.04 (m, 1H), 1.88–1.74 (complex m, 3H), 1.70–1.59 (complex m, 2H), 1.52 (s, 3H), 1.47 (m, 1H), 1.33 (s, 4H), 1.30 (m, 1H), 1.26–1.14 (complex m, 2H). δ_C (101 MHz, $CDCl_3$) 134.0, 130.8, 108.7, 79.4, 75.9, 68.1, 36.3, 35.3, 31.8, 30.0, 29.9, 26.0, 24.4, 20.9, 19.5. ν_{max} (KBr)/cm^{-1} 3407, 2987, 2932, 2868, 1463, 1373, 1277, 1260, 1207, 1163, 1063, 1013, 994, 968, 931, 894, 876, 732, 647, 522. *m/z* (EI, 70 eV) 250 ($M^{+\bullet}$, 18 %), 235 ($[M - CH_3\bullet]^+$, 100), 192 (85), 157 (66), 148 (93), 130 (88), 105 (80), 91 (75). HRMS *m/z* 250.1568; $C_{15}H_{22}O_3$ $M^{+\bullet}$ requires 250.1569.

Compound ***26***

A magnetically stirred solution of allylic alcohol **25** (1.14 g, 4.5 mmol) in dry toluene (21 mL) maintained under an argon atmosphere and protected from light was cooled to 0°C before being treated, dropwise over 0.5 h, with diethyl zinc (13.5 mL of a 1 M solution in hexane, 13.5 mmol) and diiodomethane (1.01 mL, 13.1 mmol). After 0.5 h the reaction mixture was allowed to warm to 22°C and stirred at this temperature for 1.5 h. NH_4Cl (40 mL of a saturated aqueous solution) was then carefully added to the reaction mixture which was then extracted with dichloromethane (5 × 25 mL). The combined organic phases were washed successively with $NaHCO_3$ (1 × 15 mL of a saturated aqueous solution) and water (1 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.25 in 1 : 4 v/v ethyl acetate/hexane), compound **26** (920 mg, 77 %) as a white, crystalline solid, mp 146–148°C, $[\alpha]_D$ −63.1 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 4.17–4.08 (complex m, 2H), 3.99 (dd, *J* 8.0 and 1.3, 1H), 1.80 (m, 1H), 1.73–1.53 (complex m, 6H), 1.57 (s, 3H), 1.37 (s, 3H), 1.31–0.97 (complex m, 6H), 0.41 (td, *J* 8.9 and 5.3, 1H), 0.32 (q, *J* 5.5, 1H). δ_C (101 MHz, $CDCl_3$) 108.5, 82.2, 76.2, 69.1, 35.1, 32.0, 31.5, 30.3, 29.3, 26.1, 24.4, 22.1, 19.9, 19.7, 18.6, 3.1. ν_{max} (KBr)/cm^{-1} 3402, 2987, 2930, 2865, 1469, 1380, 1371, 1283, 1259, 1207, 1164, 1143, 1098, 1085, 1065, 1031, 1009, 911, 876, 732. *m/z* (EI, 70 eV) 249 ($[M - CH_3\bullet]^+$, 100 %). HRMS *m/z* 249.1498; $C_{16}H_{24}O_3$ $[M - CH_3\bullet]^+$ requires 249.1491.

Compound ***27***

A magnetically stirred solution of alcohol **26** (501 mg, 1.90 mmol)) and DMP (481 mg, 2.85 mmol) in dry dichloromethane (25.0 mL) was stirred at 22°C for 0.25 h and then concentrated under reduced pressure. The residue thus obtained was redissolved in a minimum volume of diethyl ether and the resulting solution washed with $Na_2S_2O_3/NaHCO_3$ (1 × 35 mL of a 1 : 1 v/v mixture of 10 % w/v solution and a saturated aqueous solution, respectively), water (1 × 20 mL), and brine (1 × 20 mL). The combined aqueous washings were extracted with diethyl ether (1 × 40 mL) and the combined organic layers then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of the residue thus obtained to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.4), ketone **27** (474 mg, 95 %) as a white, crystalline solid, mp 151–154, $[\alpha]_D$ −51.7 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 4.26 (m, 1H), 4.07 (m, 1H), 2.21 (t, *J* 13.8, 1H), 2.00 (m, 1H), 1.93–1.61 (complex m, 7H), 1.53 (s, 3H), 1.36 (s, 3H), 1.30–1.09 (complex m, 3H), 1.06 (m, 1H), 0.95 (m, 1H). δ_C (101 MHz, $CDCl_3$) 209.5, 108.7, 81.6, 76.0, 40.0, 38.6, 32.3, 30.4, 29.7, 28.7, 26.0, 25.5, 24.4, 19.7, 19.5, 13.5. ν_{max} (KBr)/cm^{-1} 2993, 2985, 2954, 2896, 1693, 1453, 1380, 1372, 1271, 1256, 1209, 1130, 1068, 1038, 1025, 994, 948, 910, 862, 805, 778, 733, 644, 516. *m/z* (ESI, +ve) 317 (73 %), 301 (100), 285 ($[M + Na]^+$, 50), 263 (18). HRMS *m/z* 285.1467; $C_{16}H_{22}O_3$ $[M + H]^+$ requires 285.1467.

*Compound **28***

A magnetically stirred solution of compound **27** (263 mg, 1.00 mmol) in dry THF/HMPA (10 mL of a 3 : 1 v/v mixture) and maintained under nitrogen at −78°C was treated, dropwise, with KHMDS (2.5 mL of a 0.5 M solution in toluene, 1.25 mmol). The ensuing mixture was stirred at −78°C for 0.5 h then treated, dropwise, with iodomethane (449 μL of material freshly filtered through anhydrous K_2CO_3, 7.00 mmol). The ensuing mixture was stirred for 0.5 h and then allowed to warm to 0°C over a period of 1 h before being treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.5), compound **28** (197 mg, 75 %) as a white, crystalline solid, mp 176–182, $[\alpha]_D$ −32.1 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 4.15 (m, 1H), 4.07 (dd, *J* 7.9 and 1.4, 1H), 2.20 (m, 1H), 1.97–1.58 (complex m, 7H), 1.54 (s, 3H), 1.37 (s, 3H), 1.32–1.21 (complex m, 3H), 1.05 (m, 1H), 0.98 (t, *J* 3.3, 1H), 0.95 (d, *J* 6.6, 3H). δ_C (101 MHz, $CDCl_3$) 211.2, 108.9, 81.6, 75.8, 46.0, 38.7, 32.7, 30.5, 28.7, 28.4, 26.0, 25.5, 24.4, 20.4, 19.7, 13.8, 10.8. ν_{max} (KBr)/cm^{-1} 2985, 2937, 2897, 1688, 1456, 1374, 1354, 1285, 1257, 1208, 1161, 1130, 1086, 1064, 1044, 970, 935, 876, 829, 807, 738, 640, 509. *m/z* (ESI, +ve) 331 (100 %), 299 ($[M + Na]^+$, 48), 277 (15). HRMS *m/z* 299.1623; $C_{17}H_{24}O_3$ $[M + H]^+$ requires 299.1623.

*Compound **29***

A magnetically stirred solution of enone **23** (150 mg, 0.60 mmol) in methanol (25 mL) was cooled to 0°C and then treated, successively, with hydrogen peroxide (217 μL of a 35 % w/v aqueous solution, 2.1 mmol) and sodium hydroxide (109 μL of 6 M aqueous solution, 0.65 mmol). The ensuing mixture was warmed to 22°C, stirred at this temperature for 1.5 h and then poured into a mixture of ethyl acetate (25 mL) and NH_4Cl (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (4 × 15 mL) and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light-yellow residue thus obtained was subjected to flash column chromatography (silica, 3 : 7 : 0.1 v/v/v ethyl acetate/hexane/acetic acid elution) to afford, after concentration of the appropriate fractions (R_f 0.5 in 3 : 7 : 0.1 v/v/v ethyl acetate/hexane/acetic acid) compound **29** (127 mg, 79 %) as a white, crystalline solid mp 79–80°C, $[\alpha]_D$ +9.45 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 4.21–4.11 (complex m, 2H), 3.43 (d, *J* 3.9, 1H), 3.25 (d, *J* 3.9, 1H), 2.61 (m, 1H), 2.08 (m, 1H), 2.00–1.08 (complex m, 6H), 1.54 (s, 3H), 1.39 (s, 3H), 1.20 (m, 1H), 1.05 (m, 1H). δ_C (101 MHz, $CDCl_3$) 204.7, 109.1, 75.4, 59.1, 55.1, 41.8, 35.1, 31.1, 29.4, 25.9, 25.0, 24.3, 18.2, 16.2 (one resonance obscured or overlapping). ν_{max} (KBr)/cm^{-1} 2935, 2925, 1710, 1467, 1406, 1380, 1260, 1207, 1163, 1115, 1067, 1031, 982, 918, 877, 854, 822, 803. *m/z* (EI, 70 eV) 249 ($[M - CH_3\bullet]^+$, 100 %). HRMS *m/z* 249.1130; $C_{15}H_{20}O_4$ $[M - CH_3\bullet]^+$ requires 249.1127.

*Compound **30***

A magnetically stirred solution of epoxy-ketone **29** (105 mg, 0.4 mmol) in anhydrous methanol (5 mL) was cooled to 0°C and then treated, dropwise, with hydrazine hydrate (75 mg, 1.50 mmol). The ensuing mixture was stirred at 0°C for 0.5 h before being warmed to 22°C and treated, dropwise via syringe, with acetic acid (90 mg, 1.50 mmol). The ensuing mixture was stirred for a further 1.5 h at this temperature and then diluted with dichloromethane (15 mL) and quenched (CAUTION: exothermic reaction with accompanying gas evolution) with $NaHCO_3$ (10 mL of a saturated aqueous solution). The ensuing mixture was extracted with dichloromethane (4 × 15 mL) and the combined organic phases washed with brine (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexanes elution) to afford, after concentration of the relevant fractions (R_f 0.5 in 1 : 1 v/v ethyl acetate/hexane), compound **30** (71 mg, 71 %) as a white, crystalline solid, mp 95–96°C, $[\alpha]_D$ +37.2 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 5.87 (m, 1H), 5.78 (m, 1H), 4.24 (dd, *J* 8.4 and 1.9, 1H), 4.18 (m, 1H), 3.67 (dd, *J* 4.9 and 1.4, 1H), 2.28 (m, 1H), 1.94–1.83 (complex m, 4H), 1.68 (m, 2H), 1.54 (s, 3H), 1.45 (m, 1H), 1.39 (s, 3H), 1.35–1.15 (complex m, 3H). δ_C (101 MHz, $CDCl_3$) 131.3, 127.2, 108.5, 76.0, 75.8, 67.8, 37.8, 32.6, 30.6, 28.6, 26.0, 25.5, 24.5, 19.3, 17.2. ν_{max} (KBr)/cm^{-1} 3399, 2925, 2862, 1469, 1380, 1259, 1207, 1164, 1064, 1031, 876, 807, 518. *m/z* (EI, 70 eV) 250 ($M^{+\bullet}$, 5 %), 235 ($[M - CH_3\bullet]^+$, 85), 149 (100). HRMS *m/z* 250.1562; $C_{15}H_{22}O_3$ $M^{+\bullet}$ requires 250.1569.

*Compound **14***

A magnetically stirred solution of allylic alcohol **30** (71 mg, 0.28 mmol) in anhydrous dichloromethane (7.0 mL) maintained at 22°C under a nitrogen atmosphere was treated with molecular sieves (75 mg of powered, anhydrous 4 Å material), pyridinium dichromate (PDC 117 mg, 0.31 mmol), and then acetic acid (95 μL, 16.6 mmol). The resulting mixture was stirred at 22°C for 1.5 h and then treated with Celite (1.50 g) before being filtered through a sintered-glass funnel. The filtrate thus obtained was concentrated under reduced pressure and the ensuing residue subjected to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.5 in 3 : 7 v/v ethyl acetate/hexane), enone **14** (67 mg, 97 %) as a white, crystalline solid, mp 104–107°C, $[\alpha]_D$ + 59.05 (*c* 1.0, $CHCl_3$). δ_H (800 MHz, $CDCl_3$) 6.83 (ddd, *J* 10.2, 5.8, and 2.2, 1H), 5.94 (m, 1H), 4.15 (dd, *J* 8.1 and 1.7, 1H), 4.10 (ddd, *J* 8.1, 3.3 and 1.4, 1H), 2.55 (m, 1H), 2.32 (m, 1H), 1.96 (m, 2H), 1.87–1.78 (complex m, 3H), 1.58 (s, 3H), 1.42 (s, 3H), 1.35–1.20 (complex m, 3H). δ_C (201 MHz, $CDCl_3$) 202.6, 147.6, 129.5, 108.9, 76.1, 76.0, 46.0, 32.5, 30.5, 29.9, 28.8, 26.2, 24.3, 18.9, 17.0. ν_{max} (KBr)/cm^{-1} 2923, 2852, 1737, 1673, 1465, 1379, 1263, 1207, 1166, 1121, 1074, 1015, 963, 918, 879, 797, 745, 646. *m/z* (EI, 70 eV) 248 ($M^{+\bullet}$, 22 %), 233 ($[M - CH_3\bullet]^+$, 100). HRMS *m/z* 233.1179; $C_{15}H_{20}O_3$ $[M - CH_3\bullet]^+$ requires 233.1178.

*Compound **31***

A magnetically stirred slurry of dry copper(I) iodide (389 mg, 2.0 mmol) in distilled diethyl ether (17 mL) maintained at −78°C under nitrogen was treated, dropwise, with methyl lithium (2.5 mL of a 1.6 M solution in diethyl ether, 4.0 mmol). The resulting light-tan coloured solution was stirred for 0.33 h at this temperature and then a solution of the enone **23** (248 mg, 1.0 mmol) in diethyl ether (3.5 mL) was added, via syringe pump, over 0.17 h. The ensuing bright-yellow reaction mixture was stirred for 1 h at −78°C and then quenched with NH_4Cl solution (15 mL of a saturated aqueous solution). The separated aqueous

layer was extracted with diethyl ether (3 × 25 mL) and the combined organic phases washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. Subjection of this oil to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f 0.5) afforded compound **31** (187 mg, 71 %) as a white, crystalline solid, mp 147–154°C, $[\alpha]_D$ +19.5 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 4.13 (ddd, *J* 8.4, 3.8, and 1.3, 1H), 3.98 (dd, *J* 8.4 and 2.0, 1H), 2.67 (dd, *J* 14.3 and 6.2, 1H), 2.42–2.26 (complex m, 2H), 2.12–1.59 (complex m, 9H), 1.51 (s, 3H), 1.35 (s, 3H), 1.14 (m, 1H), 0.94 (d, *J* 7.3, 3H). δ_C (101 MHz, $CDCl_3$) 211.5, 108.4, 76.7, 75.7, 46.2, 45.0, 36.3, 36.2, 31.1, 31.0, 28.8, 25.9, 24.3, 19.3, 19.1, 15.8. ν_{max} (KBr)/cm^{-1} 2998, 2973, 2960, 2925, 2863, 1705, 1466, 1454, 1430, 1417, 1382, 1374, 1288, 1266, 1203, 1145, 1080, 1064, 1025, 993, 972, 939, 908, 878, 832, 733, 671, 648, 601, 515. *m/z* (EI, 70 eV) 249 ($[M - CH_3\bullet]^+$, 100 %). HRMS *m/z* 249.1491; $C_{16}H_{24}O_3$ $[M - CH_3\bullet]^+$ requires 249.1491.

*Compounds **15** and **32***

Step i. A magnetically stirred solution of ketone **31** (157 mg, 0.59 mmol) in dry dichloromethane (7.5 mL) maintained under an atmosphere of nitrogen was cooled to 0°C then treated with trimethylamine (660 μL, 7.1 mmol) and TMSOTf (600 μL, 3.54 mmol). The resulting mixture was stirred at 0°C for 1.5 h, after which time it was warmed to 22°C and stirred for a further 0.5 h before being diluted with hexane (65 mL). The resulting solution was washed with $NaHCO_3$ (1 × 15 mL of a saturated aqueous solution) and brine (1 × 10 mL), dried ($MgSO_4$) then filtered, and concentrated under reduced pressure to give a clear, colourless oil that is presumed to be comprising of the anticipated mixture of silyl enol ethers.

Step ii. The oil obtained from *step i* was dissolved in DMSO (500 mL) and the resulting solution treated with IBX (2.21 mL of a 0.4 M solution in DMSO, 0.89 mmol) and MPO (2.21 mL of a 0.4 M solution in DMSO, 0.89 mmol). The ensuing mixture was stirred at 22°C for 16 h while being protected from light and then quenched with $NaHCO_3$ (7.5 mL of a saturated aqueous solution) before being extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$) then filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. Subjection of this material to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) gave, after concentration of the relevant fractions (R_f 0.5 in 2 : 8 v/v ethyl acetate/hexane), a ~2 : 3 mixture of enones **15** and **32** (122 mg, 79 % combined yield) as a white, crystalline and chromatographically inseparable solid, mp 80–116°C. δ_H (400 MHz, $CDCl_3$) 5.93 (m, 2/5H), 5.80 (br s, 3/5H), 4.15–4.10 (complex m, 1H), 3.90 (m, 3/5H), 3.48 (br s, 2/5H), 2.55–2.20 (complex m, 4H), 2.10 (m, 1H), 2.02 (s, 1.8H), 2.00–1.75 (complex m, 4H), 1.57 (s, 4.2H), 1.50–1.15 (complex m, 3.8H), 1.08 (d, *J* 8.0, 1.2H). δ_C (101 MHz, $CDCl_3$) 198.8, 198.6, 167.4, 165.5, 127.6, 126.4, 109.4, 108.6, 78.1, 76.0, 75.9, 73.0, 42.3, 41.7, 40.9, 40.6, 35.1, 33.4, 32.6, 31.0, 30.5, 29.4, 26.2, 26.1, 24.5, 24.4, 22.7, 22.3, 19.1, 18.3, 16.8 (one resonance obscured or overlapping). ν_{max} (KBr)/cm^{-1} 2939, 2882, 1713, 1675, 1372, 1259, 1203, 1063, 875, 514. *m/z* (EI, 70 eV) 262 ($M^{+\bullet}$, 60), 247 (45), 85 (95), 83 (92), 51 (100). HRMS *m/z* 262.1565; $C_{16}H_{22}O_3$ $M^{+\bullet}$ requires 262.1569.

*Compound **33***

A magnetically stirred solution of the previously reported and epimeric mixture of alcohols[5] derived from compound **7** (187.6 mg, 0.75 mmol) in dichloromethane (10 mL) maintained at 22°C was treated, in portions, with DMP (353 mg, 0.83 mmol). The ensuing mixture was stirred for 2.5 h before being diluted with dichloromethane (10 mL) and the resulting solution washed with $Na_2S_2O_3$ (1 × 15 mL of a saturated aqueous solution) and $NaHCO_3$ (1 × 15 mL of a saturated aqueous solution). The combined aqueous phases were extracted with dichloromethane (3 × 15 mL) and the combined organic phases were washed with brine (1 × 15 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of appropriate fractions (R_f 0.4) afforded compound **33** (140 mg, 75 %) as a white, crystalline solid, mp 122–124°C, $[\alpha]_D$ +42.5 (*c* 1.0, $CDCl_3$). δ_H (400 MHz, $CDCl_3$) 6.26 (m, 1H), 6.04 (m, 1H), 4.20 (m, 1H), 3.77 (m, 1H), 2.82 (br s, 1H), 2.52–2.28 (complex m, 3H), 2.19 (m, 1H), 1.99 (m, 1H), 1.77–1.60 (complex m, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 0.85 (m, 1H). δ_C (101 MHz, $CDCl_3$) 211.1, 132.4, 130.9, 108.8, 83.5, 79.3, 47.1, 41.7, 38.1, 36.7, 34.7, 31.9, 29.6, 25.6, 25.1. ν_{max} (KBr)/cm^{-1} 2986, 2938, 2869, 1714, 1455, 1431, 1379, 1366, 1266, 1245, 1206, 1110, 1165, 1065, 1042, 1009, 986, 954, 879, 841, 726, 699, 525, 514. *m/z* (ESI, +ve) 303 (98 %), 271 ($[M + Na]^+$, 100). HRMS *m/z* 271.1312; $C_{15}H_2O_3$ $[M + H]^+$ requires 271.1310.

*Compounds **34** and **35***

A magnetically stirred solution of ketone **33** (248 mg, 1.0 mmol) in dry dichloromethane (13.0 mL) maintained under an atmosphere of nitrogen was cooled to 0°C then treated with trimethylamine (975 μL, 10.5 mmol) and TMSOTf (1.03 mL, 6.0 mmol). The mixture thus obtained was stirred at 0°C for 1 h then warmed to 22°C and stirred at this temperature for a further 0.5 h before being diluted with hexane (125 mL), washed with $NaHCO_3$ (1 × 25 mL of a saturated aqueous solution) and brine (1 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. This oil was dissolved in DMSO (1.0 mL) and the resulting solution treated with a solution of IBX (3.95 mL of 0.4 M solution in DMSO, 1.58 mmol) and MPO (3.95 mL of 0.4 M solution in DMSO, 1.58 mmol) then stirred at 22°C for 16 h while being protected from light. After this time the reaction mixture was quenched with $NaHCO_3$ (15 mL of a saturated aqueous solution) and extracted with ethyl acetate (5 × 15 mL). The combined organic extracts were washed with brine (1 × 25 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, light-yellow oil. Subjection of this oil to flash column chromatography (silica 1 : 9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.3(7) in 3 : 7 v/v ethyl acetate/hexane) afforded compound **34** (54 mg, 21 %) as a white, crystalline solid, mp 146–148°C, $[\alpha]_D$ +10.7 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.31 (t, *J* 7.2, 1H), 5.96 (d, *J* 2.0, 1H), 5.83 (d, *J* 7.2, 1H), 4.33 (m, 1H), 4.19 (dd, *J* 7.2 and 1.3, 1H), 3.07 (m, 1H), 2.53–2.22 (complex m, 6H), 1.35 (s, 3H), 1.29 (s, 3H). δ_C (101 MHz, $CDCl_3$) 197.9, 162.3, 133.2, 132.2, 125.9, 109.9, 78.9, 78.6, 44.5, 35.8, 33.7, 31.5, 27.1, 25.6, 25.2. ν_{max} (KBr)/cm^{-1} 2989, 2937, 2901, 1670, 1629, 1452, 1423, 1380, 1331, 1266, 1207, 1162, 1075, 1045, 974, 918, 875, 793, 726, 703. *m/z* (ESI, +ve) 269 ($[M + Na]^+$, 100 %), 247 ($[M + H]^+$, 22). HRMS *m/z* 247.1327; $C_{15}H_{18}O_3$ $[M + H]^+$ requires 247.1334.

Concentration of fraction B (R_f 0.3(5) in 3 : 7 v/v ethyl acetate/hexane) afforded compound **35** (162 mg, 65 %) as a white, crystalline solid, mp 133–135°C, $[\alpha]_D$ +13.9 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 7.29 (dd, *J* 10.0 and 1.5, 1H), 6.33 (t, *J* 8.0, 1H), 6.09 (d, *J* 10.0, 1H), 5.75 (d, *J* 8.0, 1H), 4.27 (m, 1H), 3.93 (dd, *J* 8.0 and 1.8, 1H), 2.90 (broad s, 1H), 2.36 (dd, *J* 16.2 and 4.3, 1H), 2.09 (ddd, *J* 16.2, 13.8, and 1.5, 1H), 1.93 (m, 1H), 1.73 (m, 1H), 1.36 (d, *J* 1.5, 3H), 1.29 (d, *J* 1.5, 3H), 0.95–0.88 (complex m, 1H). δ_C (101 MHz, $CDCl_3$) 199.5, 152.0, 133.1, 129.7, 128.6, 109.1, 80.8, 78.6, 44.3, 43.4, 34.9, 33.7, 28.7, 25.6, 25.1. ν_{max} (KBr)/cm^{-1} 2979, 2937, 2892, 1681, 1456, 1415, 1381, 1373, 1265, 1207, 1165, 1094, 1066, 996, 884, 828, 778, 726, 703, 647, 542, 514. *m/z* (ESI, +ve) 301 (100 %), 269 ($[M + Na]^+$, 50), 247 ($[M + H]^+$, 51). HRMS *m/z* 247.1330; $C_{15}H_{18}O_3$ $[M + H]^+$ requires 247.1334.

*Compounds **37**, **38**, and **39***

A magnetically stirred solution of enone **36** (125 mg, 0.5 mmol) in THF/HMPA (7.5 mL of a 4 : 1 v/v mixture) maintained under an argon atmosphere was cooled to −78°C and then treated, dropwise, with KHMDS (1.25 mL of a 0.5 M solution in toluene, 0.63 mmol). The ensuing mixture was allowed to stir at −78°C for 0.3 h before being treated, dropwise, with iodomethane (225 μL, 3.5 mmol) then stirred at −78°C for 0.3 h. The ensuing mixture was allowed to warm to 0°C over a period of 0.5 h before being quenched with $NaHCO_3$ (10 mL of saturated aqueous solution) and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the clear, light-yellow oil thus obtained subjected to semi-preparative HPLC (see General Experimental Procedures above for details) to afford three fractions, A–C.

Concentration of fraction A (R_t 6.3 min) afforded compound **38** (66 mg, 51 %) as a white, crystalline solid, mp 118–121°C, $[\alpha]_D$ +66.9 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 5.93 (t, *J* 2.0, 1H), 4.23 (dd, *J* 8.1 and 1.5, 1H), 4.13 (m, 1H), 2.60–2.46 (complex m, 2H), 2.35 (m, 1H), 2.15 (dd, *J* 14.0 and 5.4, 1H), 2.11–1.99 (complex m, 2H), 1.91 (m, 1H), 1.55 (s, 3H), 1.44 (s, 3H), 1.40–1.23 (complex m, 3H), 1.11 (d, *J* 6.6, 3H). δ_C (101 MHz, $CDCl_3$) 200.5, 164.7, 126.3, 109.6, 75.5, 73.9, 38.3, 37.6, 36.7, 31.4, 30.4, 26.0, 25.3, 24.5, 18.9, 14.8. ν_{max} (KBr)/cm^{-1} 2963, 2937, 2920, 2872, 1668, 1631, 1460, 1374, 1261, 1209, 1164, 1078, 1059, 1028, 921, 879, 848, 830, 518. *m/z* (EI, 70 eV) 263 (25 %), 262 ($M^{+\bullet}$, 75), 249 (43), 248 (92), 247 (51), 233 (100). HRMS *m/z* 262.1566; $C_{16}H_{22}O_3$ $M^{+\bullet}$ requires 262.1569.

Concentration of fraction B (R_t 6.7 min) afforded compound **37** (30 mg, 23 %) as a white, crystalline solid, mp 153–159°C, $[\alpha]_D$ +31.5 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 5.96 (t, *J* 2.0, 1H), 4.28 (dd, *J* 8.2 and 4.2, 1H), 3.80 (dd, *J* 8.2 and 1.9, 1H), 2.52 (m, 1H), 2.41 (m, 1H), 2.34–2.18 (complex m, 2H), 2.01–1.87 (complex m, 3H), 1.62–1.59 (complex m, 3H), 1.57 (s, 3H), 1.38 (s, 3H), 1.10 (d, *J* 6.7, 3H). δ_C (101 MHz, $CDCl_3$) 200.8, 163.8, 126.0, 109.4, 79.3, 75.8, 39.3, 39.0, 36.6, 32.6, 30.1, 25.9, 24.4, 21.8, 18.8, 14.8. ν_{max} (KBr)/cm^{-1} 2963, 2932, 2907, 2872, 1673, 1634, 1459, 1375, 1263, 1205, 1152, 1068, 1047, 978, 945, 877, 848. *m/z* (ESI, +ve) 547 (47 %), 317 (50), 285 (100), 263 (70). HRMS *m/z* 262.1568; $C_{16}H_{22}O_3$ $M^{+\bullet}$ requires 262.1569.

Concentration of fraction C (R_t 7.1 min) gave compound **39** (9 mg, 7 %) as a white, crystalline solid, mp 160–162°C, $[\alpha]_D$ +15.4 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.05 (d, *J* 6.9, 1H), 4.04 (m, 1H), 3.87 (dd, *J* 8.4 and 1.7, 1H), 2.77 (m, 1H), 2.50–2.39 (complex m, 2H), 2.17–2.01 (complex m, 2H), 1.95–1.83 (complex m, 2H), 1.51 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H), 1.05 (complex m, 2H). δ_C (101 MHz, $CDCl_3$) 213.9, 149.7, 125.8, 112.1, 78.2, 75.5, 48.5, 40.7, 35.4, 35.2, 26.8, 26.6, 26.2, 25.5, 24.9, 24.7, 19.2. ν_{max} (KBr)/cm^{-1} 2978, 2937, 2902, 2871, 1713, 1462, 1379, 1263, 1207, 1162, 1064, 1088, 973, 877, 836. *m/z* (ESI, +ve) 413 (100 %), 331 (75), 299 (52), 277 (39). HRMS *m/z* 299.1622. $C_{17}H_{24}O_3$ $[M + Na]^+$ requires 299.1623.

*Compound **40***

A magnetically stirred solution of enone **38** (195 mg, 0.75 mmol) in diethyl ether/*t*-butanol (5.0 mL of a 1 : 1 v/v mixture) maintained at 0°C under a nitrogen atmosphere was treated, dropwise, with *t*-BuOK (1.5 mL of a 1.0 M solution in *t*-butanol, 1.5 mmol). The resulting mixture was stirred at 0°C for 0.33 h before being treated, dropwise, with a solution of *t*-butyl acrylate (223 μL, 1.49 mmol) in dry diethyl ether (4.5 mL). The ensuing mixture was allowed to stir for another 0.4 h at 0°C before being quenched with NH_4Cl (15 mL of a saturated aqueous solution) and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 7 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f 0.5 in 3 : 7 v/v ethyl acetate/hexane), a clear, colourless oil. ^1H NMR spectroscopic analysis of this material suggested it comprised a > 6 : 1 mixture of esters **40** and **41**. Subjection of this material to semi-preparative HPLC (see General Experimental Procedures above for details) and concentration of the appropriate fractions (R_t 10.7 min) afforded compound **40** (167 mg, 57 %) as a white foam, $[\alpha]_D$ +10.3 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 4.14 (dd, *J* 8.2 and 3.7, 1H), 3.97 (d, *J* 8.2, 1H), 2.64–1.60 (complex m, 12H), 1.53 (s, 1H), 1.42 (s, 9H), 1.42–1.24 (complex m, 9H) (one resonance obscured or overlapping). δ_C (101 MHz, $CDCl_3$) 201.9, 173.0, 156.5, 132.6, 109.2, 80.3, 78.4, 75.5, 42.6, 39.9, 37.4, 34.2, 33.8, 31.1, 30.5, 30.0, 28.3, 26.1, 25.9, 25.1, 24.3. ν_{max} (KBr)/cm^{-1} 2977, 2934, 1728, 1674, 1458, 1368, 1296, 1260, 1207, 1153, 1119, 1066, 975, 876, 848, 756. *m/z* (EI, 70 eV) 390 ($M^{+\bullet}$, 5 %), 375 (25), 334 (90), 317 (56), 203 (95), 159 (80), 57 (100). HRMS *m/z* 391.2489; $C_{23}H_{34}O_5$ $[M + H]^+$ requires 391.2484.

*Compound **43***

A magnetically stirred solution of acetonide **42** (285 mg, 0.72 mmol) in THF/methanol/water (9 mL of 3:1:3 v/v/v mixture) was treated with DOWEX-50 resin (350 mg of material that had been rinsed successively with 1 M aqueous hydrochloric acid, water, saturated sodium bicarbonate solution, and water). The resulting suspension was heated at 65°C for 36 h and then cooled, filtered, and the solids thus retained rinsed with dichloromethane (3 × 25 mL) and then methanol (3 × 15 mL). The combined filtrates were dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the resulting clear, colourless oil was subjected to flash column chromatography (silica, 1 : 9 → 3 : 7 v/v ethyl acetate/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.6 in 3 : 7 v/v ethyl acetate/hexane) afforded the starting acetonide **42** (59 mg, 21 % recovery) as a clear, colourless oil that was identical, in all respects, with authentic material.

Concentration of fraction B (R_f 0.4 in 1 : 1 : 0.1 v/v ethyl acetate/hexane/acetic acid) afforded diol **43** (154 mg, 61 %

at 79% conversion) as a thick, white foam, $[\alpha]_D$ +3.5 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.82 (d, *J* 10.2, 1H), 5.88 (d, *J* 10.2, 1H), 3.95 (m, 1H), 3.40 (m, 1H), 3.22 (br s, 1H), 2.63 (br s, 1H), 2.17 (m, 1H), 2.06–1.85 (complex m, 6H), 1.79–1.59 (complex m, 5H), 1.41 (s, 9H), 1.01 (s, 3H). δ_C (101 MHz, $CDCl_3$) 203.7, 173.2, 152.6, 126.4, 80.6, 72.6, 67.5, 47.3, 42.1, 39.0, 32.8, 30.6, 28.2, 27.2, 25.1, 19.8, 18.2(3), 18.1(9). ν_{max} (KBr)/cm^{-1} 3280, 2929, 2912, 1725, 1671, 1450, 1376, 1366, 1293, 1155, 1143, 1109, 1072, 1054, 1018, 967, 873, 844, 829, 700. *m/z* (ESI, +ve) 723 (35%), 373 ($[M + Na]^+$, 75), 351 ($[M + H]^+$, 52), 295 (60), 242 (100). HRMS *m/z* 373. 1991; $C_{20}H_{30}O_5$ $[M + H]^+$ requires 373. 1991.

Compound ***44***

A magnetically stirred solution of diol **43** (127 mg, 0.55 mmol) in dichloromethane (9 mL) was cooled to 0°C then treated with *p*-TsOH·H_2O (260 mg, 1.37 mmol). 4-Acetamido-TEMPO (315 mg, 1.37 mmol) was then added, in portions over 0.5 h, to the reaction mixture that was stirred at 0°C for 1 h and then at 22°C for 1 h before being quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with dichloromethane (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a clear, light-orange oil. Subjection of this material to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.6 in 3 : 7 v/v ethyl acetate/hexane) afforded acyloin **44** (163 mg, 85%) as thick, yellow foam, $[\alpha]_D$ +95.3 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.87 (d, *J* 10.3, 1H), 5.95 (d, *J* 10.3, 1H), 3.31 (s, 1H), 3.28 (s, 1H), 2.60 (br s, 1H), 2.23 (m, 1H), 2.12–1.81 (complex m, 10H), 1.41 (s, 9H), 1.04 (s, 3H). δ_C (101 MHz, $CDCl_3$) 216.5, 202.6, 173.0, 149.3, 127.1, 80.7, 79.0, 47.4, 44.1, 42.4, 41.9, 30.3, 28.2, 26.4, 25.6, 24.3, 20.5, 18.3. ν_{max} (KBr)/cm^{-1} 3437, 2987, 2949, 2873, 1728, 1670, 1439, 1386, 1360, 1294, 1233, 1197, 1173, 1062, 1035, 993, 954, 851, 827, 732, 706. *m/z* (ESI, +ve) 371 ($[M + Na]^+$, 100%). HRMS *m/z* 371.1835; $C_{20}H_{28}O_5$ $[M + H]^+$ requires 371.1834.

Compound ***45***

A magnetically stirred solution of acyloin **44** (159 mg, 0.45 mmol) in anhydrous dichloromethane (3.5 mL) was treated with DMAP (25 mg, 0.2 mmol) and then acetic anhydride (51 μL, 0.54 mmol) and the ensuing mixture stirred at 22°C for 3.5 h. The reaction mixture was then diluted with dichloromethane (10 mL) before being washed with brine (1 × 7 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane) to afford, after concentration of the appropriate fractions (R_f 0.5 in 2 : 3 v/v ethyl acetate/hexane), compound **45** (133 mg, 75%) as a clear, colourless foam, $[\alpha]_D$ +105.0 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.87 (d, *J* 10.3, 1H), 5.95 (d, *J* 10.3, 1H), 4.74 (s, 1H), 2.57 (br s, 1H), 2.23 (m, 1H), 2.19 (s, 3H), 2.12–1.81 (complex m, 7H), 1.41 (s, 9H), 1.04 (s, 3H). δ_C (101 MHz, $CDCl_3$) 209.6, 201.8, 172.9, 169.9, 146.9, 127.6, 80.7, 47.4, 43.7, 42.8, 41.0, 30.2, 29.8, 28.3, 26.4, 24.7, 24.4, 21.3, 20.8, 18.3. ν_{max} (KBr)/cm^{-1} 2929, 1754, 1729, 1675, 1369, 1219, 1152, 1112, 1050, 977, 849. *m/z* (ESI, +ve) 445 (100%), 413 ($[M + Na]^+$, 50). HRMS *m/z* 413.1940; $C_{22}H_{30}O_6$ $[M + H]^+$ requires 413.1940.

Compound ***46***

A solution of freshly prepared VCl_3·$(THF)_3$ (188 mg, 0.50 mmol) in dry toluene (2.5 mL) maintained at 22°C was treated with activated[24] zinc dust (33 mg, 0.50 mmol) and the resulting mixture irradiated in an ultrasonic bath (Branson Model B2500R-DTH). After 0.33 h a solution of acetate **45** (97 mg, 0.25 mmol) in toluene (1.5 mL) was added to the reaction mixture and sonication continued for 0.66 h. The reaction mixture was then cooled to 22°C before being diluted with ethyl acetate (5.0 mL) and the resulting mixture passed through a short plug of TLC grade silica that was then washed with ethyl acetate (3 × 5 mL). The combined filtrates were washed with water (1 × 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f 0.4), compound **46**[19] (70 mg, 83%) as a thick, white foam, $[\alpha]_D$ +19.1 (*c* 0.5, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.48 (d, *J* 10.1, 1H), 5.90 (d, *J* 10.1, 1H), 2.52 (br s, 1H), 2.31 (d, *J* 18.1, 1H), 2.22 (m, 2H), 2.10–1.92 (complex m, 9H), 1.67 (m, 1H), 1.43 (s, 9H), 1.03 (s, 3H). δ_C (101 MHz, $CDCl_3$) 213.6, 202.8, 172.8, 151.1, 126.5, 80.5, 52.6, 47.2, 46.0, 43.2, 38.1, 30.1, 28.1, 26.1, 26.0, 25.6, 23.0, 18.0. ν_{max} (KBr)/cm^{-1} 2975, 2937, 2875, 2850, 1724, 1673, 1455, 1367, 1257, 1147, 917, 849, 830, 732, 648, 532. *m/z* (ESI, +ve) 355 ($[M + Na]^+$, 100%). HRMS *m/z* 355.1883; $C_{20}H_{28}O_4$ $[M + Na]^+$ requires 355.1885.

Compounds ***49*** *and* ***50***

A magnetically stirred solution of enone **48** (551 mg, 2.10 mmol) in distilled diethyl ether and *t*-butanol (21 mL of 2 : 1 v/v mixture) maintained at −10°C under an argon atmosphere was treated, dropwise, with *t*-BuOK (5.25 mL of a 1.0 M solution in *t*-butanol, 5.25 mmol). The ensuing mixture was stirred at −10°C for 0.2 h before being treated, via syringe pump, with a solution of methyl acrylate (1.42 mL, 15.75 mmol) in diethyl ether (15 mL). The mixture thus obtained was allowed to stir for 0.3 h and then treated with NH_4Cl (15 mL of a saturated aqueous solution) before being extracted with diethyl ether (5 × 15 mL). The combined organic fractions were washed with brine (1 × 15 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f 0.4 in 3 : 7 v/v ethyl acetate/hexane), a clear colourless oil. Subjection of this material to semi-preparative HPLC (see General Experimental Procedures above for details) afforded two fractions, A and B.

Concentration of fraction A (R_t 7.5 min) afforded compound **49** (526 mg, 72%) as a clear, colourless oil, $[\alpha]_D$ +19.5 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.73 (d, *J* 10.2, 1H), 5.88 (d, *J* 10.2, 1H), 4.18 (m, 1H), 3.68 (dd, *J* 8.1 and 1.6, 1H), 3.65 (s, 3H), 2.29–2.12 (complex m, 3H), 2.05–1.81 (complex m, 3H), 1.74 (td, *J* 9.6 and 1.4, 1H), 1.68–1.60 (complex m, 3H), 1.54 (s, 3H), 1.35 (s, 3H), 1.33–1.23 (complex m, 2H), 1.19 (s, 3H). δ_C (101 MHz, $CDCl_3$) 203.3, 174.0, 152.3, 127.0, 109.4, 79.4, 75.5, 51.8, 47.3, 37.6, 36.6, 30.5, 29.5(9), 29.5(6), 25.9, 24.4, 23.7, 21.3, 19.4, 18.5. ν_{max} (KBr)/cm^{-1} 3025, 2976, 2933, 2873, 1738, 1673, 1469, 1454, 1438, 1381, 1306, 1260, 1207, 1166, 1131, 1116, 1086, 1067, 1033, 992, 931, 875, 826, 811, 709. *m/z* (EI, 70 eV) 348 ($M^{+\bullet}$, 20%), 333(32), 261 (42), 203 (100),

175 (68), 159 (85). HRMS *m/z* 348.1937; $C_{20}H_{28}O_5$ $M^{+\bullet}$ requires 348.1937.

Concentration of fraction B (R_t 9.7 min) afforded compound **50** (100 mg, 14 %) as a clear, colourless and viscous oil, $[\alpha]_D$ +11.7 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.72 (d, *J* 10.2, 1H), 5.87 (d, *J* 10.2, 1H), 4.19 (m, 1H), 3.66 (m, 1H), 3.64 (s, 3H), 2.30 (m, 1H), 2.14 (m, 1H), 2.06–1.75 (complex m, 6H), 1.65 (m, 4H), 1.55 (s, 3H), 1.25 (s, 3H), 1.05 (s, 3H). δ_C (101 MHz, $CDCl_3$) 203.2, 174.2, 152.1, 126.4, 109.4, 79.7, 75.6, 51.8, 47.3, 42.8, 37.7, 29.9, 29.3, 26.9, 25.9, 24.4, 24.1, 19.8, 18.6, 18.5. ν_{max} (KBr)/cm^{-1} 2925, 2873, 1738, 1673, 1461, 1375, 1294, 1260, 1206, 1170, 1118, 1067, 974, 931, 877, 824, 806, 704.

*Compound **51***

A magnetically stirred solution of acetonide **49** (501 mg, 1.44 mmol) in methanol/water (21 mL of a 4 : 1 v/v mixture) was treated with DOWEX-50 resin (575 mg of acidified material). The ensuing mixture was heated at 65°C for 56 h then cooled to 22°C, and the DOWEX-50 resin removed by filtration and washed with methanol (3 × 15 mL). The combined filtrates were concentrated under reduced pressure and the aqueous residue diluted with brine (15 mL) and extracted with dichloromethane (5 × 30 mL). The combined organic fractions were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.4 in 3 : 7 v/v ethyl acetate/hexane) afforded the starting ester **49** (75 mg, 15 % recovery) as a clear, colourless oil that was identical, in all respects, to authentic material.

Concentration of fraction B (R_f 0.4 in 4 : 1 v/v ethyl acetate/hexane) afforded diol **51** (345 mg, 78 % at 85 % conversion) as a thick, white foam, $[\alpha]_D$ +2.4 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.84 (d, *J* 10.2, 1H), 5.89 (d, *J* 10.2, 1H), 3.96 (m, 1H), 3.66 (s, 3H), 3.43 (m, 1H), 3.22 (d, *J* 4.3, 1H), 2.58 (br s, 1H), 2.31–2.08 (complex m, 3H), 1.94–1.85 (complex m, 3H), 1.78–1.40 (complex m, 6H), 1.18 (s, 3H). δ_C (101 MHz, $CDCl_3$) 203.5, 174.2, 152.8, 126.9, 72.4, 67.4, 51.8, 47.2, 38.8, 36.1, 32.6, 30.0, 29.5, 24.7, 21.7, 19.3, 18.2. ν_{max} (KBr)/cm^{-1} 3297, 2924, 2869, 1737, 1668, 1450, 1435, 1417, 1376, 1294, 1263, 1192, 1092, 1069, 1055, 1013, 970, 944, 903, 868, 827, 795, 762,. *m/z* (ESI, +ve) 639 (100 %), 331 ([M + Na]$^+$, 80). HRMS *m/z* 331.1516; $C_{17}H_{24}O_5$ $[M + H]^+$ requires 331.1521.

*Compound **52***

A magnetically stirred mixture of *p*-TsOH·H_2O (390 mg, 2.1 mmol) and 4-acetamido-TEMPO (466 mg, 1.5 mmol) in dichloromethane (25 mL) was maintained at 22°C for 0.5 h and the resulting suspension added, in portions, to a magnetically stirred solution of compound **51** (308 mg, 1.0 mmol) in dichloromethane (25 mL) maintained at 0°C. The resulting mixture was stirred at 0°C for a further 2 h before being treated with $NaHCO_3$ (25 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (4 × 75 mL) and the combined organic fractions washed with water (1 × 15 mL) and brine (1 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting clear, light-yellow oil was subjected to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.4), acyloin **52** (285 mg, 93 %) as a thick, light-yellow coloured foam, $[\alpha]_D$ +15.9 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.92 (d, *J* 10.3, 1H), 5.98 (d, *J* 10.3, 1H), 3.64 (s, 3H), 3.38 (s, 1H), 3.17 (s, 1H), 2.57 (m, 1H), 2.24–2.14 (complex m, 2H), 2.10–1.59 (complex m, 8H), 1.42 (m, 1H), 1.25 (s, 3H). δ_C (101 MHz, $CDCl_3$) 216.2, 202.6, 173.8, 149.6, 127.7, 78.8, 51.8, 47.5, 41.9(3), 41.9(0), 38.2, 30.3, 29.4, 25.8, 23.7, 21.1, 20.4. ν_{max} (KBr)/cm^{-1} 3450, 2950, 2875, 1731, 1671, 1469, 1439, 1387, 1364, 1295, 1232, 1198, 1175, 1103, 1061, 993, 929, 851, 828, 752, 707, 577. *m/z* (ESI, +ve) 361 (100 %), 329 ([M + Na]$^+$, 61), 307 (60), 275 (70). HRMS *m/z* 329.1363; $C_{17}H_{22}O_5$ $[M + Na]^+$ requires 329.1365.

*Compound **53***

A magnetically stirred solution of acyloin **52** (125 mg, 0.41 mmol), triethylamine (1.7 mL), and DMAP (124 mg, 1.02 mmol) in dichloromethane (7 mL) was cooled to 0°C and then treated with benzoyl chloride (119 μL, 1.02 mmol). The resulting mixture was allowed to warm to 22°C, stirred vigorously at this temperature for 16 h, and then treated with HCl (15 mL of a 1 M aqueous solution) before being extracted with dichloromethane (5 × 15 mL). The combined organic phases were washed with brine (1 × 15 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.6 in 3 : 7 v/v ethyl acetate/hexane) gave compound **53** (147 mg, 89 %) as a clear, colourless foam, $[\alpha]_D$ +91.5 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 8.11–8.02 (complex m, 2H), 7.62 (m, 1H), 7.51–7.45 (complex m, 2H), 6.51 (d, *J* 10.3, 1H), 5.96 (d, *J* 10.3, 1H), 5.04 (s, 1H), 3.66 (s, 3H), 2.67 (s, 1H), 2.33–1.98 (complex m, 9H), 1.84 (m, 1H), 1.96 (m, 1H), 1.28 (s, 3H). δ_C (101 MHz, $CDCl_3$) 209.2, 202.0, 173.7, 165.6, 147.4, 133.9, 130.1, 129.0, 128.8, 128.1, 77.1, 51.9, 47.5, 42.5, 41.3, 37.7, 30.1, 29.3, 24.8, 23.9, 21.3, 21.2. ν_{max} (KBr)/cm^{-1} 2948, 2874, 1729, 1674, 1601, 1468, 1451, 1390, 1314, 1253, 1197, 1176, 1108, 1069, 1026, 988, 803, 710. *m/z* (ESI, +ve) 465 (63 %), 433 ([M + Na]$^+$, 100), 411 (35). HRMS *m/z* 433.1629; $C_{24}H_{26}O_6$ $[M + H]^+$ requires 433.1627.

*Compound **54***

A vigorously stirred solution of methyl triphenylphosphonium bromide (89 mg, 0.25 mmol) in freshly distilled THF (5 mL) maintained at 0°C was treated, dropwise via syringe, with KHMDS (650 μL of a 0.5 M solution in toluene). The resulting yellow solution was stirred for 0.5 h, warmed to 22°C over 0.5 h, and then cooled to −78°C. A solution of keto-ester **53** (55 mg, 0.13 mmol) in THF (2.5 mL) was then added, dropwise, to the reaction mixture after which it was stirred at −78°C for a further 1.5 h before being quenched with NH_4Cl (10 mL of saturated aqueous solution). After warming the mixture was extracted with diethyl ether (5 × 5 mL) and the combined organic phases were washed with brine (1 × 5 mL), dried (Na_2SO_4) then filtered, and concentrated under a stream of nitrogen. Subjection of the ensuing light-yellow oil to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.6), compound **54** (37.8 mg, 71 %) as a clear, colourless foam, $[\alpha]_D$ +21.3 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 8.07 (m, 2H), 7.60 (m, 1H), 7.48 (t, *J* 7.6, 2H), 6.55 (d, *J* 10.3, 1H), 5.90 (d, *J* 10.3, 1H), 5.38 (s, 1H), 5.21 (s, 1H), 5.12 (s, 1H), 3.66 (s, 3H), 2.59 (s, 1H), 2.32–2.05 (complex m, 4H), 2.01–1.25 (complex m, 7H), 1.23

(s, 3H). δ_C (101 MHz, $CDCl_3$) 203.0, 174.1, 166.5, 149.8, 148.5, 133.4, 130.3, 129.9, 128.7, 127.6, 114.6, 76.0, 51.8, 47.3, 39.1, 37.1, 35.5, 30.0, 29.4, 27.5, 25.9, 22.0, 21.0. ν_{max} (KBr)/cm^{-1} 2956, 2929, 2854, 1740, 1720, 1677, 1464, 1452, 1442, 1377, 1261, 1179, 1110, 1072, 1027, 975, 804, 711. *m/z* (ESI, +ve) 431 ($[M + Na]^+$, 100 %), 409 (42). HRMS *m/z* 431.1844; $C_{25}H_{28}O_5$ $[M + H]^+$ requires 431.1834.

Compound ***55***

A magnetically stirred solution of ester **49** (87 mg, 0.25 mmol) in THF (10 mL) maintained at 50°C was treated with LiOH (10 mL of a 1 M aqueous solution) and the ensuing mixture stirred at this temperature for 5 h. The cooled reaction mixture was treated with water (15 mL) and brine (10 mL) before being washed with diethyl ether (1 × 20 mL). The separated aqueous layer was then acidified with HCl (15 mL of a 1 M aqueous solution) and extracted with diethyl ether (10 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 55 : 45 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f 0.2 in 1 : 1 v/v ethyl acetate/hexane) gave acid **55** (81 mg, 97 %) as a clear, colourless and viscous foam, $[\alpha]_D$ +6.1 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.74 (d, *J* 10.1, 1H), 5.89 (d, *J* 10.1, 1H), 4.19 (m, 1H), 3.69 (d, 1H), 2.34–2.12 (complex m, 3H), 2.03 (m, 1H), 1.96–1.81 (complex m, 2H), 1.77–1.55 (complex m, 5H), 1.52 (s, 3H), 1.35 (s, 3H), 1.33–1.23 (complex m, 2H), 1.19 (s, 3H). δ_C (101 MHz, $CDCl_3$) 203.5, 179.1, 152.5, 126.9, 109.4, 79.4, 75.4, 47.3, 37.6, 36.7, 30.2, 29.6, 29.5, 25.9, 24.4, 23.7, 21.2, 19.4, 18.5. ν_{max} (KBr)/cm^{-1} 2978, 2934, 1708, 1673, 1469, 1454, 1440, 1381, 1311, 1280, 1260, 1208, 1164, 1131, 1116, 1087, 1066, 1033, 970, 931, 874, 826, 754. *m/z* (EI, 70 eV) 334 ($M^{+\bullet}$, <1 %), 318 (90), 260 (40), 207 (100). HRMS *m/z* 334.1767; $C_{19}H_{26}O_5$ $M^{+\bullet}$ requires 334.1780.

Compound ***56***

A magnetically stirred solution of 2-(trimethylsilyl)ethyl 2,4-dihydroxy-3-nitrobenzoate[19] (1.00 g, 3.34 mmol) in ethyl acetate/methanol (65 mL of a 5 : 1 v/v mixture) was treated with acetic acid (190 μL) and 10 % palladium on carbon (185 mg). The resulting suspension was stirred at 22°C under a hydrogen atmosphere for 16 h after which time it was filtered through a pad of Celite that was washed with ethyl acetate (50 mL). The combined filtrates were concentrated under reduced pressure to afford a dark solid, recrystallisation (hexane) of which afforded aniline **56**[19] (710 mg, 79 %) as a grey solid, mp 107°C. δ_H (400 MHz, $CDCl_3$) 11.19 (s, 1H), 7.33 (d, *J* 8.3, 1H), 6.35 (d, *J* 8.3, 1H), 4.51–4.37 (complex m, 3H), 1.12 (m, 2H), 0.11 (s, 9H) (resonances due to OH group protons not observed). δ_C (101 MHz, $CDCl_3$) 170.8, 153.0, 151.3, 122.0, 121.1, 106.9, 106.2, 63.6, 17.5, −1.30. ν_{max} (KBr)/cm^{-1} 3381, 3310, 3110, 2954, 2900, 1661, 1625, 1506, 1468, 1387, 1288, 1250, 1217, 1175, 1143, 1062, 1044, 941, 860, 837, 778, 694. *m/z* (EI, 70 eV) 269 ($M^{+\bullet}$, 5 %), 267 (8), 241 (21), 226 (19), 152 (31), 151 (100), 73 (41). HRMS *m/z* 269.1084; $C_{12}H_{19}NO_4$ $M^{+\bullet}$ requires 269.1083.

Compound ***57***

A magnetically stirred solution of compound **55** (70 mg, 0.21 mmol) and aniline **56** (117 mg, 0.69 mmol) in DMF (750 μL) maintained at 22°C under an argon atmosphere was treated with dry triethylamine (120 μL, 0.88 mmol) and HATU (263 mg, 0.69 mmol). After 16 h the reaction mixture was quenched with brine (1.9 mL) and then extracted with chloroform (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing dark residue was subjected to flash column chromatography (silica, 1 : 10 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f 0.6 in 3 : 7 v/v ethyl acetate/hexane) afforded amide **57** (39.2 mg, 32 %) as light-yellow and viscous film, $[\alpha]_D$ −5.9 (*c* 0.1, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 11.84 (s, 1H), 11.01 (br s, 1H), 8.12 (s, 1H), 7.56 (d, *J* 9.0, 1H), 6.75 (d, *J* 10.2, 1H), 6.50 (d, *J* 9.0, 1H), 5.94 (d, *J* 10.2, 1H), 4.42 (m, 2H), 4.19 (m, 1H), 3.70 (dd, *J* 8.0 and 1.6, 1H), 2.41 (m, 2H), 2.22 (m, 1H), 2.09–1.27 (complex m, 9H), 1.55 (s, 3H), 1.35 (s, 3H), 1.24 (s, 3H), 1.16–1.09 (complex m, 2H), 0.08 (s, 9H). δ_C (101 MHz, $CDCl_3$) 203.9, 174.0, 170.6, 154.8, 154.1, 152.9, 127.6, 126.9, 114.5, 111.3, 109.5, 104.6, 79.4, 75.4, 63.9, 47.8, 37.7, 36.9, 32.7, 31.6, 29.6, 25.9, 24.4, 23.8, 21.1, 19.4, 18.5, 17.5, −1.3. ν_{max} (KBr)/cm^{-1} 3319, 2924, 2807, 1654, 1597, 1535, 1467, 1385, 1331, 1292, 1259, 1208, 1147, 1115, 1087, 1064, 969, 932, 859, 837, 789. *m/z* (EI, 70 eV) 585 ($M^{+\bullet}$, 5 %), 570 (5), 317 (100), 259 (38), 241 (42), 204 (31), 151 (42), 73 (48). HRMS *m/z* 585.2755; $C_{31}H_{43}NO_8Si$ $M^{+\bullet}$ requires 585.2758.

Compound ***58***

A magnetically stirred solution of compound **57** (29 mg, 0.05 mmol) in DMF (500 μL) maintained under a nitrogen atmosphere at 22°C was treated with TASF (28 mg, 0.10 mmol). The ensuing mixture was heated at 40°C for 1 h then cooled, and quenched with brine (4 mL). The separated aqueous phase was extracted with chloroform (5 × 5 mL) and the combined organic fractions were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 8 : 12 : 0.1 : 0.1 : 0.1 v/v ethyl acetate/hexane/acetic acid/methanol/water elution) and concentration of the relevant fractions (R_f 0.3 in 80 : 20 : 0.5 : 1.0 : 0.5 v/v ethyl acetate/ hexane/acetic acid/methanol/water) afforded compound **58** (5 mg, 21 %) as a light-brown foam, $[\alpha]_D$ −29.0 (*c* 0.1, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 11.86 (s, 1H), 11.12 (s, 1H), 8.20 (s, 1H), 7.63 (dd, *J* 8.9 and 0.8, 1H), 6.82 (d, *J* 10.1, 1H), 6.52 (dd, *J* 8.9 and 0.7, 1H), 5.96 (dd, *J* 10.1 and 0.7, 1H), 4.21 (m, 1H), 3.71 (m, 1H), 2.51–2.35 (complex m, 2H), 2.21 (m, 1H), 2.12–1.29 (complex m, 6H), 1.55 (s, 3H), 1.36 (s, 3H), 1.27 (m, 3H), 1.26 (s, 3H) (resonance due to amide or OH group proton not observed). δ_C (101 MHz, $CDCl_3$) 205.2, 174.0, 172.8, 155.5, 154.6, 154.3, 128.5, 126.7, 114.5, 111.4, 109.5, 103.6, 79.3, 75.4, 47.8, 37.8, 36.7, 32.5, 31.8, 29.5, 25.9, 24.4, 23.7, 21.4, 19.5, 18.5. ν_{max} (KBr)/cm^{-1} 2928, 2859, 1654, 1537, 1451, 1379, 1259, 1064, 875, 795. *m/z* (ESI, −ve) 484 ($[M - H^+]^-$, 53 %), 96 (100). HRMS *m/z* 484.1971; $C_{26}H_{31}NO_8$ $[M - H^+]^-$ requires 484.1971.

Compound ***59***

A magnetically stirred solution of ester **50** (53 mg, 0.15 mmol) in THF (5 mL) maintained at 50°C was treated with LiOH (5 mL of a 1 M aqueous solution) and the ensuing mixture stirred at this temperature for 5 h. After this time the reaction mixture was cooled and treated with water (7 mL) and brine (5 mL) before being washed with dichloromethane (2 × 10 mL). The separated aqueous layer was acidified to pH 2 (with 1 M aqueous HCl) and extracted with dichloromethane (7 × 4 mL).

The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 55 : 45 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.2 in 1 : 1 v/v ethyl acetate/hexane) gave acid **59** (48 mg, 95 %) as a clear, colourless foam, $[\alpha]_D$ +61.3 (*c* 1.0, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 6.72 (d, *J* 10.2, 1H), 5.88 (d, *J* 10.2, 1H), 4.19 (m, 1H), 3.65 (dd, *J* 8.1 and 1.6, 1H), 2.35 (m, 1H), 2.18 (m, 1H), 2.07–1.35 (complex m, 11H), 1.43 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H). δ_C (101 MHz, $CDCl_3$) 203.2, 178.5, 152.3, 126.3, 109.5, 79.7, 75.6, 47.2, 42.7, 37.7, 30.5, 29.2, 26.7, 25.9, 24.4, 24.1, 19.9, 18.6, 18.5. ν_{max} (KBr)/cm^{-1} 2977, 2934, 2872, 1728, 1674, 1458, 1368, 1296, 1260, 1153, 1119, 1066, 975, 876, 848, 755. *m/z* (EI, 70 eV) 334 ($M^{+\bullet}$, 11 %), 319 (30), 233 (75), 190 (70), 146 (100), 121 (80). HRMS *m/z* 334.1799; $C_{19}H_{26}O_5$ $M^{+\bullet}$ requires 334.1780.

*Compound **61***

Method i. A magnetically stirred solution of compound **59** (50 mg, 0.15 mmol) in acetonitrile (1.5 mL) maintained at 22°C was treated with dry triethylamine (62 μL, 0.45 mmol), DMAP (37 mg, 0.30 mmol), and DCC (230 μL of a 1.0 M solution in freshly distilled dichloromethane, 0.23 mmol). After 5 h a solution of 3-amino-2,4-dihydroxybenzoic acid (**60**) (49.5 mg, 0.30 mmol) in DMF (350 μL) was added to the reaction mixture and stirring continued for another 36 h. The resulting mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 80 : 20 : 1 : 0.5 : 0.5 v/v ethyl acetate/hexane/methanol/acetic acid/water elution) to afford, after concentration of the relevant fractions (R_f = 0.3 in 80 : 20 : 0.5 : 1.0 : 0.5 v/v ethyl acetate/hexane/methanol/acetic acid/water), compound **61** (15 mg, 21 %) as a light-orange foam, $[\alpha]_D$ −9.2 (*c* 0.1, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 11.90 (s, 1H), 11.31 (s, 1H), 8.09 (s, 1H), 7.63 (d, *J* 8.9, 1H), 6.85 (d, *J* 10.1, 1H), 6.51 (d, *J* 8.9, 1H), 5.97 (d, *J* 10.1, 1H), 4.22 (m, 1H), 3.68 (d, *J* 7.9, 1H), 2.52–1.26 (complex m, 12H), 1.36 (s, 6H), 1.15 (s, 3H) (resonance due to amide or OH group proton not observed). δ_C (101 MHz, $CDCl_3$) 205.5, 173.4, 172.4, 155.0, 154.6, 154.2, 128.2, 125.7, 114.2, 111.1, 109.4, 103.4, 79.3, 75.4, 47.5, 42.5, 37.9, 31.8, 29.7, 27.6, 25.8, 24.3, 23.9, 19.7, 18.5, 18.2. ν_{max} (KBr)/cm^{-1} 3307, 2924, 2853, 1658, 1647, 1535, 1456, 1379, 1260, 1208, 1154, 1119, 1065, 910, 874, 799, 733, 608. *m/z* (ESI, −ve) 484 ($[M - H^+]^-$, 18 %), 134 (100), 105 (38). HRMS *m/z* 484.1970; $C_{26}H_{31}NO_8$ $[M - H^+]^-$ requires 484.1971.

Method ii. A magnetically stirred solution of compound **59** (21 mg, 0.063 mmol) in DMF (1.0 mL) maintained at 22°C was treated with DMAP (5 mg, 0.164 mmol) and EDC (15.4 mg, 0.081 mmol). After 5 h a solution of 3-amino-2,4-dihydroxybenzoic acid (**60**) (21.9 mg, 0.13 mmol) in DMF (250 μL) was added to the reaction mixture and stirring continued for 36 h at which point water (7 mL) was added and the pH of the ensuing mixture was adjusted to 4 using HCl (1 M aqueous solution) and then extracted with dichloromethane (5 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash column chromatography (silica, 75 : 25 : 1 : 0.5 : 0.5 v/v ethyl acetate/hexane/methanol/acetic acid/water elution) to afford, after concentration of the relevant fractions (R_f 0.3 in 80 : 20 : 0.5 : 1.0 : 0.5 v/v ethyl acetate/hexane/methanol/acetic acid/water), compound **61** (8.2 mg, 27 %) as a thick foam. This material was identical, in all respects, with that obtained by *Method i* described immediately above.

*Compound **63***

A magnetically stirred solution of compound **62**[8] (63 mg, 0.19 mmol) and aniline **56** (101 mg, 0.60 mmol) in DMF (0.67 mL) maintained at 22°C under a nitrogen atmosphere was treated with triethylamine (110 μL, 0.81 mmol) and HATU (228 mg, 0.60 mmol). After 16 h the reaction mixture was quenched with brine (1 mL) and extracted with chloroform (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The dark-coloured residue thus obtained was subjected to flash column chromatography (silica, 1 : 10 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f = 0.6 in 3 : 7 v/v ethyl acetate/hexane) afforded amide **63** (16 mg, 14 %) as a white film. This material was immediately subjected to treatment with TASF as described below.

*Compound **64***

A magnetically stirred solution of TMSE amide **63** (12 mg, 0.02 mmol) in DMF (0.18 mL) maintained under a nitrogen atmosphere at 22°C was treated with TASF (11.2 mg, 0.04 mmol). The ensuing mixture was heated at 40°C for 1 h and then cooled and quenched with brine (2 mL). The separated aqueous phase was extracted with chloroform (5 × 2 mL) and the combined organic fractions were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 8 : 12 : 0.1 : 0.1 : 0.1 v/v ethyl acetate/hexane/acetic acid/methanol/water elution) and concentration of the relevant fractions (R_f 0.3 in 80 : 20 : 0.5 : 1.0 : 0.5 v/v ethyl acetate/hexane/acetic acid/methanol/water) afforded compound **64** (1.5 mg, 15 %) as a white film, $[\alpha]_D$ −24.0 (*c* 0.1, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 11.52 (s, 1H), 11.24 (s, 1H), 8.32 (s, 1H), 7.63 (d, *J* 9.2, 1H), 6.54 (d, *J* 9.2, 1H), 4.20 (m, 1H), 3.64 (m, 1H), 2.68 (m, 1H), 2.48 (m, 2H), 2.27 (m, 1H), 2.04–1.73 (complex m, 6H), 1.63–1.51 (complex m, 3H), 1.52 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H) (resonances due to amide and OH group protons not observed). δ_C (200 MHz, $CDCl_3$) 217.4 (C), 174.3 (C), 172.9 (C), 155.7 (C), 154.5 (C), 128.3 (CH), 114.5 (C), 111.6 (CH), 108.8 (C), 103.1 (C), 82.2 (CH), 75.9 (CH), 51.0 (C), 41.0 (CH), 34.7 (C), 34.0 (CH_2), 33.5 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 29.0 (CH), 25.8 (CH_3), 24.2 (CH_3), 20.4 (CH_3), 19.7 (CH_2), 19.1 (CH_2) (one resonance obscured or overlapping). ν_{max} (KBr)/cm^{-1} 3292, 3072, 2933, 2619, 1696, 1654, 1597, 1534, 1453, 1380, 1260, 1241, 1209, 1153, 1062, 1038, 910, 875, 794, 732. *m/z* (ESI, −ve) 486 ($[M - H^+]^-$, 100 %), 168 (10), 59 (24). HRMS *m/z* 486.2129; $C_{26}H_{33}NO_8$ $[M - H^+]^-$ requires 486.2128.

X-Ray Crystallographic Studies

Crystallographic Data

*Crystallographic Data for the Admixture of Compounds **15** and **32***

$C_{16}H_{22}O_3$, *M* 262.34, *T* 150 K, monoclinic, space group $P2_1$, *Z* 4, *a* 6.34903(17), *b* 9.1348(2), *c* 23.8101(7) Å; β 95.882(3)°; *V* 1373.65(6) $Å^3$, D_x 1.269 g cm^{-3}, 5468 unique data ($2\theta_{max}$ 148.2°), *R* 0.039 [for 4880 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.095 (all data), *S* 1.01.

Crystallographic Data for Compound ***28***

$C_{17}H_{24}O_3$, M 276.38, T 150 K, orthorhombic, space group $P2_12_12_1$, Z 4, a 6.4901(1), b 11.7812(1), c 18.7583(2) Å; V 1434.28(3) Å^3, D_x 1.280 g cm^{-3}, 2831 unique data ($2\theta_{max}$ 144.6°), R 0.028 [for 2753 reflections with $I > 2.0\sigma(I)$]; Rw 0.069 (all data), S 1.00.

Crystallographic Data for Compound ***34***

$C_{15}H_{18}O_3$, M 246.31, T 150 K, monoclinic, space group $P2_1$, Z 6, a 12.1619(3), b 8.3569(2), c 18.7928(4) Å; β 97.273(2)°; V 1894.65(8) Å^3, D_x 1.295 g cm^{-3}, 6248 unique data ($2\theta_{max}$ 144.8°), R 0.033 [for 5917 reflections with $I > 2.0\sigma(I)$]; Rw 0.081 (all data), S 1.00.

Crystallographic Data for Compound ***35***

$C_{15}H_{18}O_3$, M 246.31, T 150 K, monoclinic, space group $P2_1$, Z 4, a 6.2911(4), b 35.4329(15), c 6.4453(4) Å; β 118.271(8)°; V 1265.36(16) Å^3, D_x 1.293 g cm^{-3}, 2533 unique data ($2\theta_{max}$ 144.6°), R 0.064 [for 2454 reflections with $I > 2.0\sigma(I)$]; Rw 0.166 (all data), S 1.01.

Crystallographic Data for Compound ***37***

$C_{16}H_{22}O_3$, M 262.35, T 150 K, orthorhombic, space group $P2_12_12_1$, Z 4, a 8.0668(2), b 9.8097(3), c 18.1236(6) Å; V 1434.17(7) Å^3, D_x 1.215 g cm^{-3}, 2830 unique data ($2\theta_{max}$ 145.4°), R 0.032 [for 2698 reflections with $I > 2.0\sigma(I)$]; Rw 0.088 (all data), S 1.00.

Structure Determinations

Images were measured on a diffractometer (Cu Kα, mirror monochromator, λ 1.54184 Å) fitted with an area detector and the data extracted using the *CrysAlis* package.[25] The structure solutions for all four compounds were solved by direct methods (*SIR92*)[26] and then refined using the *CRYSTALS* program package.[27] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1832710, 1827734, 1827735, 1827736 and 1827737). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Supplementary Material

The anisotropic displacement ellipsoid plot derived from the single-crystal X-ray structures of compounds **15/32**, **28**, **34**, **35**, and **37** together with the ^{1}H and/or ^{13}C NMR spectra of compounds **14**–**20**, **25**–**40**, **43**–**59**, **61**, and **64** are available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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