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A chemoenzymatic total synthesis of the hirsutene-type sesquiterpene (+)-connatusin B from toluene

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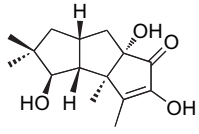
ABSTRACT

The first total synthesis of the hirsutene-type sesquiterpenoid natural product (+)-connatusin B (**2**) is reported. The *cis*-1,2-dihydrocatechol **3**, which is obtained in enantiomerically pure form via the enzymatic dihydroxylation of toluene, served as the starting material. Diels–Alder cycloaddition and oxa-di-π-methane rearrangement reactions represent key chemical steps in the reaction sequence leading to the cyclopropane ring-fused linear triquinane **14**. Reductive cleavage of the three-membered ring within this framework and various functional group interconversions then provide the title compound **2**.

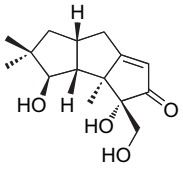
1. Introduction

In 2005 Rukachaisirikul and co-workers reported the isolation of the hirsutene-type sesquiterpenoids connatusins A and B, **1** and **2**, respectively, from the culture broth of the fungus *Lentinus connatus* BCC 8996.[1] The structures of these compounds were initially established using NMR techniques and that associated with connatusin A (**1**) was confirmed via single-crystal X-ray analysis. The assigned absolute configurations are consistent with those determined for related members of the linear triquinane family of natural products.[2] Compounds **1** and **2** were evaluated, alongside various co-metabolites, as antimalarial and cytotoxic agents but they proved to be inactive.[2]

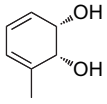
Recently, we have demonstrated that by using a combination of Diels–Alder cycloaddition and oxa-di-π-methane rearrangement reactions it is possible to convert the readily available, enantiomerically pure and toluene-derived *cis*-1,2-dihydrocatechol **3** into the linear triquinane-type sesquiterpenoids (−)-complicatic acid, (+)-hirsutic acid, and (−)-phellodonic acid.[3] We have also used analogous chemistry to prepare the non-natural enantiomeric form of the parent hydrocarbon hirsutene.[4] Herein, we detail the adaptation of such work to the first total synthesis of (+)-connatusin B (**2**) and thereby confirming the assigned structure, including absolute configuration, of this natural product.



(+)-connatusin A (**1**)



(+)-connatusin B (**2**)



3

2. Results and discussion

2.1. Retrosynthetic analysis

The retrosynthetic analysis employed in establishing the present synthesis of (+)-connatusin B (**2**) is shown in Figure 1 and follows from our earlier work in the area.[3,4] Thus, we anticipated that reductive cleavage of the carbonyl-conjugated cyclopropane ring together with various functional group interconversions (FGIs) would allow for the elaboration of the tetracyclic system **4** into the target **2**. Compound **4** would, in turn, be generated by a photochemically-promoted oxa-di-π-methane rearrangement of the cycopenta-fused bicyclo[2.2.2]octenone **5**,[5] itself the product of elaboration of the Diels–Alder adduct arising from the enantiomerically pure diene **3** and the dienophile **6**. Compounds **3** and **6** are both commercially available with the former being obtained, on large scale and in enantiomerically pure form, through the whole-cell biotransformation of toluene using micro-organisms that produce the responsible enzyme, namely toluene dioxygenase (TDO).[6] It is noteworthy that the carbonyl group within dienophile **6** acts in

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several different roles. First of all, it activates the cyclopentene residue in the cycloaddition reaction and assists in controlling the regiochemical outcome of this process. It then provides the means by which the *gem*-dimethyl group associated with target **2** is introduced and, finally, it serves as the progenitor to the isolated hydroxy group associated with connatusin B. The successful reaction sequence arising from this analysis is presented in the following sections.

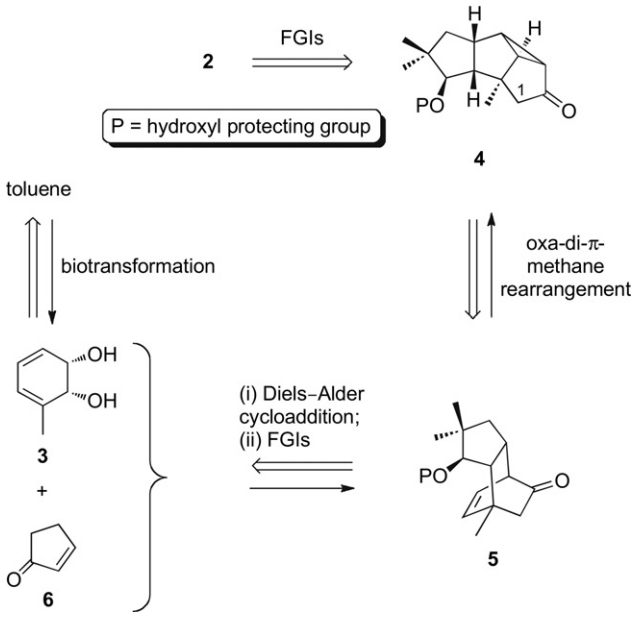
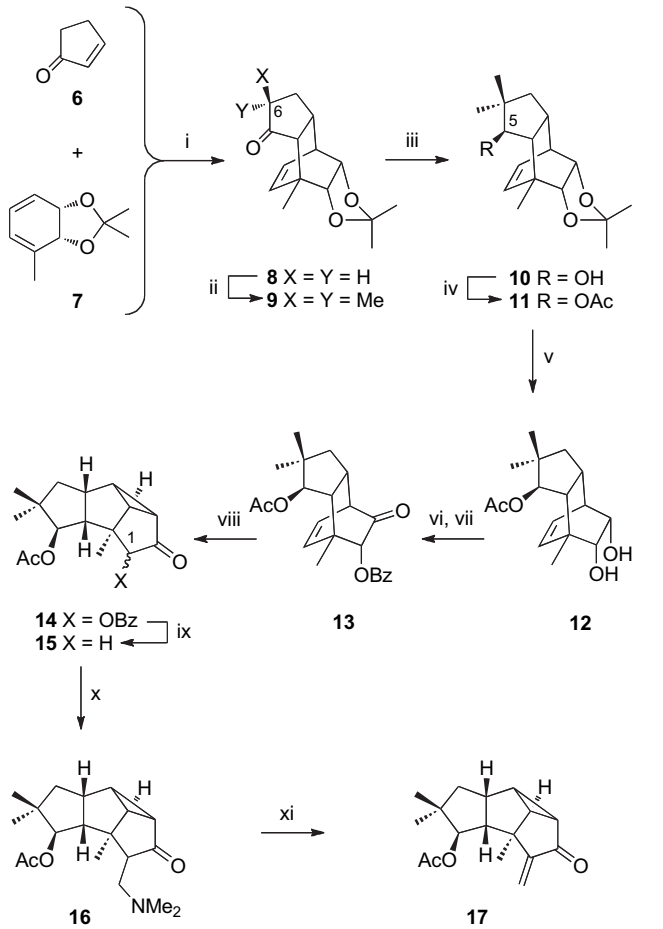


Figure 1. Retrosynthetic analysis of (+)-connatusin B (**2**).

2.2. The Diels–Alder cycloaddition and oxa-di-π-methane rearrangement steps

As a result of our earlier observations regarding the facial selectivity of Diels–Alder cycloaddition reactions involving diene **3** and its derivatives,[3,4,7] this compound was first converted into the corresponding and well-known[3b] acetonide **7** under standard conditions. Microwave irradiation of a 1:5 mixture of compounds **6** and **7** (no solvent) at 200 °C for 0.25 h using a reactor supplying ~200 W of power provided the required and previously reported Diels–Alder adduct **8** in 75% yield (Scheme 1).[8] Using conditions applied to a related compound,[4] adduct **8** was treated with lithium hexamethyldisilazide (LiHMDS) and the resulting enolate intercepted with methyl iodide. Repeating this deprotonation/methylation sequence on the mono-methylated ketone so formed gave the required *gem*-dimethylated ketone **9**, which was obtained in 56% yield. Reduction of compound **9** with lithium aluminum hydride in diethyl ether at −30 °C then afforded a chromatographically separable mixture of compound **10** (79%) and its epimer (19%). Various NOE experiments carried out on the former product suggested the correct stereochemistry had been established at the newly created stereogenic center and confirmation of this followed from single-crystal X-ray analyses of derivatives obtained after the photochemical rearrangement step. The origins of the reasonably high levels of stereoselectivity associated with the conversion **9**→**10** remain unclear at the present time. Given the nature of the conversions that had to be undertaken to complete the synthesis of target **2** from this point, protection of the newly introduced hydroxy group associated with compound **10** was necessary. Earlier work associated with the synthesis of (−)-phellodonic acid[3b] suggested that an ester group might serve the required purpose. Accordingly, compound **10** was treated with acetic anhydride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[9] and in this manner the expected acetate **11** was obtained in 99% yield. As has been the case with various closely related substrates,[3] hydrolysis of the acetonide unit within compound **11** proved difficult but could be accomplished by treating it with activated DOWEX-50 resin in refluxing methanol/water mixtures for 20 h. In this manner, diol **12** was obtained in 90% yield at 53% conversion. Selective oxidation of the hydroxyl group remote from the bridgehead methyl group within substrate **12** was effected using the sterically demanding oxammonium salt derived from reaction of 1-oxy-4-acetamido-2,2,6,6-tetramethylpiperidine (4-AcNH-TEMPO) with *p*-TsOH·H_2O[10] and the resulting acyloin was immediately subjected to *O*-benzoylation using benzoyl chloride in the presence of triethylamine and DMAP. By this means the substrate, **13**, required for the pivotal oxa-di-π-methane rearrangement was obtained in 86% yield (from **12**) and all the spectral data obtained on this compound were in accord with the assigned structure. In particular, the appearance of a one-proton singlet at δ 5.11 in the ^{1}H NMR spectrum of compound **13**, which is attributed to the oxymethine proton adjacent to the ketone unit, clearly indicated that the mono-oxidation of diol **12** had taken place in the anticipated manner.



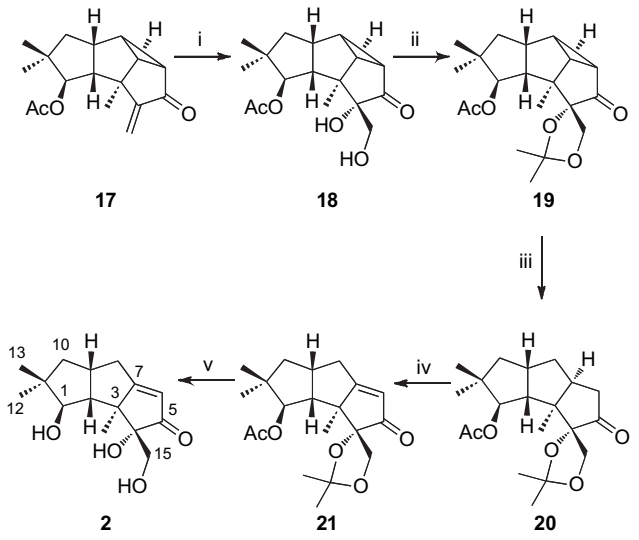
Scheme 1. Reagents and conditions: (i) see ref. 3b; (ii) LiHMDS (1.1 mol equiv), THF, −15→18→−15 °C, 1.25 h then MeI (1.2 mol equiv), 0.75 h then −15→18 °C (over 1.25 h) then repeat procedure; (iii) $LiAlH_4$ (1.5 mol equiv), Et_2O, −30→18 °C, 6.5 h; (iv) Ac_2O (3 mol equiv), DMAP (cat.), Et_3N, 0→18 °C, 16 h; (v) H^+-DOWEX-50, MeOH/H_2O, reflux, 20 h; (vi) 4-AcNH-TEMPO (2.2 mol equiv), *p*-TsOH·H_2O (2.2 mol equiv), CH_2Cl_2, 0→18 °C, 7 h; (vii) BzCl (2.5 mol equiv), DMAP (3.3 mol equiv), Et_3N (excess), CH_2Cl_2, 0→18 °C, 16 h; (viii) acetophenone (1.4 mol equiv), acetone, photolysis, 18 °C, 3.5 h; (ix) SmI_2 (2.2 mol equiv), THF/MeOH, −78 °C, 0.16 h; (x) LiHMDS (1.2 mol equiv), THF, −78 °C, 1 h then Eschenmoser's salt (3 mol equiv), −78→18 °C, 16 h; (xi) MeI (12 mol equiv), Et_2O/CH_2Cl_2, 18 °C, 16 h then Al_2O_3 (basic), CH_2Cl_2, 18 °C, 0.5 h.

A solution of compound **13** in acetone containing acetophenone was placed in Quartex™ immersion-well photo-reactor equipped with a Pyrex™ filter and irradiated with a 450 W medium-pressure mercury vapor lamp for 3.5 h. As a result, and in keeping with outcomes observed in related cases,[3] a ca. 1:1 mixture of the epimeric forms of compound **14** was obtained in 95% combined yield (at 76% conversion). While these epimers could be separated chromatographically and then characterized independently, for the purposes of continuing the synthesis a THF solution of the mixture was treated with samarium iodide at −78 °C in order to effect reductive removal of the benzoyloxy group. In this manner compound **15** was obtained in 81% yield and as a crystalline solid. While all of the spectral data obtained on this material were in full accord with the assigned structure, final confirmation of this was obtained by single-crystal X-ray analysis, details of which are provided in the Experimental section.

As a prelude to installing the vicinal diol unit associated with (+)-connatusin B (**2**), the enolate derived from ketone **15** was trapped with Eschenmoser's salt ($Me_2N{=}CH_2I$)[11] and the resulting tertiary amine **16** (71%) was subjected to a one-pot N-methylation/Hoffman elimination sequence using methyl iodide then basic alumina. By such means enone **17** was obtained in 87% yield. The final steps associated with the elaboration of this pivotal compound into target **2** are detailed in the following section.

2.3. The endgame: installation of the vicinal diol and enone moieties

Compound **17** would appear to contain all the functionality necessary for its elaboration into connatusin B (**2**). As the first step in such a process (Scheme 2), enone **17** was subjected to reaction with AD-mix-α containing added $K_2OsO_4{\cdot}2H_2O$.[12] After 16 h at 0 °C the reaction mixture worked up and after chromatographic purification diol **18** was obtained in 81% yield. The illustrated configuration was assigned to the newly created stereogenic center within product **18** on the basis that electrophilic attack at the double-bond within precursor **17** would take place at the more accessible convex face.



Scheme 2. Reagents and conditions: (i) AD-mix-α (excess), $K_2OsO_4{\cdot}2H_2O$ (excess), *tert*-BuOH/H_2O, $MeSO_2NH_2$ (excess), 0 °C, 16 h; (ii) $(MeO)_2CMe_2$ (5 mol equiv), *p*-TsOH·H_2O (cat.), THF, 0→18 °C, 18 h; (iii) *n*-Bu_3SnH (8 mol equiv), AIBN (cat.), C_6H_6, 80 °C, 6 h; (iv) (a) LiHMDS (1.05 mol equiv), THF, −78 °C, 1 h then *o*-$O_2NC_6H_4SeCN$ (1.05 mol equiv), −78→18 °C, 16 h; (b) *m*-CPBA (1 mol equiv), CH_2Cl_2, −78 °C, 0.5 h then Et_2NH, $^3O_2$, −78→18 °C, 3 h; (v) H^+-DOWEX-50, MeOH/H_2O, reflux, 16 h.

Confirmation of this assignment followed from a single-crystal X-ray analysis of the corresponding acetonide **19** that was obtained in 98% yield under standard conditions. Details of the X-ray analysis are presented in the Experimental section.

With the acetonide **19** in hand attention turned to the final requirement for completion of the synthesis, namely installation of the cyclopentenone subunit associated with connatusin B. While compound **19** is isomeric with the enone (**21**) being sought all attempts, including those involving various metal catalysts, to effect the relevant isomerization were unsuccessful. As a result a reduction/oxidation sequence was needed to effect the necessary conversion. Thus, treatment of a benzene solution of the carbonyl-conjugated cyclopropane **19** with 8 molar equivalents of tri-*n*-butyltin hydride and the free-radical initiator 1,1′-azobisisobutyronitrile (AIBN) and then heating the resulting mixture at reflux for 6 h resulted in the smooth cleavage of the three-membered ring and formation of the linear triquinane **20**, which was obtained in 98% yield as a white, crystalline solid. In order to install the required enone moiety, the enolate anion derived from ketone **20** using LiHMDS was trapped with *o*-nitrophenylselenocyanide.[13] The resulting α-arylselenoketone, which was obtained as a single diastereoisomer, was then subjected to reaction with *m*-chloroperbenzoic acid (*m*-CPBA) and the selenoxides so formed exposed to diethylamine and oxygen. In this manner the enone **21** was obtained in 75% overall yield from precursor **20**.[14] Finally, exposure of compound **21** to activated DOWEX-50 resin in refluxing methanol/water mixtures for 16 h afforded target **2** in 77% yield.

The spectroscopic data obtained on the synthetically-derived samples of compound **2** were in full accord with the assigned structure and in good agreement with those reported[1] for the natural product (+)-connatusin B. In particular, the specific rotations of the two materials were of the same sign and very similar in magnitude {$[\alpha]_D$ +12.3 (*c* 0.4, $CHCl_3$) (synthetic) vs $[\alpha]_D$ +14 (*c* 0.44, $CHCl_3$) (natural)[1]}. A comparison of the two sets of ^{13}C NMR spectroscopic data is shown in Table 1. The only minor discrepancy in chemical shifts ($\Delta\delta{>}0.2$ ppm) is observed for those resonances due to the carbonyl unit ($\Delta\delta{=}0.4$ ppm) and this could be attributed to the effects of intra- and/or inter-molecular hydrogen bonding in this polyhydroxylated compound. Certainly, when ^{13}C NMR spectra of synthetically derived connatusin B (**2**) were recorded at two different concentrations (ca. 1 mg/mL and 10 mg/mL) then variations in the chemical shifts of these signals of up to $\Delta\delta{=}0.4$ ppm were observed. The relevant comparison of the ^1H NMR spectral data sets is also shown in Table 1 and reveals an excellent match other than that the multiplet observed at δ 1.90 in the spectrum of the natural product (which is assigned to H-10β) is not seen in the one derived from the synthetic material. An inspection of the 300 MHz ^1H NMR spectrum of the natural product kindly provided to us by Professor Rukachaisirikul shows a doublet of doublets at δ 1.90 but no multiplet at this same position. Interestingly, while not reported in the original paper, a one-proton triplet can be seen at ca. δ 1.30 in the same spectrum. An equivalent signal is observed in the 800 MHz ^1H NMR spectrum of the synthetically-derived material (see Table 1). Accordingly, we believe that the multiplet reportedly appearing at δ 1.90 in the spectrum of the natural product is not real. Final confirmation of the structure of the synthetically-derived sample of connatusin B was secured through a single-crystal X-ray analysis of its mono-hydrate. The derived ORTEP is shown in Figure 2 while other details are provided in the Experimental section. The melting range recorded for the mono-hydrate of the synthetic material was 116–120 °C while that reported[1] for the natural product is 85.3–85.6 °C. Given the manner in which the natural product was isolated (extraction with methanol/dichloromethane) these varying melting ranges are probably attributable to differences in the degree of hydration of the two samples.

Table 1
Comparison of the ^{13}C and ^{1}H NMR data recorded for naturally-occurring and synthetically-derived (+)-connatusin B (**2**)

^{13}C NMR Data (δ_C)		^{1}H NMR Data (δ_H)	
Synthetic **2**[a]	Natural **2**[b]	Synthetic **2**[c]	Natural **2**[d]
209.4	209.0	5.79 (1H, d, *J*=2.1 Hz)	5.78 (1H, d, *J*=2.1 Hz)
194.1	194.2	3.83 (1H, d, *J*=7.8 Hz)	3.80 (1H, d, *J*=7.8 Hz)
119.2	119.2	3.69 (1H, d, *J*=12.0 Hz)	3.67 (1H, d, *J*=12.0 Hz)
84.4	84.6	3.50 (1H, d, *J*=12.0 Hz)	3.49 (1H, d, *J*=12.0 Hz)
79.6	79.5	2.83 (1H, dd, *J*=16.1 and 8.4 Hz)	2.83 (1H, dd, *J*=15.6 and 7.2 Hz)
65.9	65.8	2.77–2.70 (1H, m)	2.72 (1H, m)
54.4	54.5	2.50 (1H, dd, *J*=12.0 and 7.8 Hz)	2.51 (1H, dd, *J*=12.0 and 7.8 Hz)
51.5	51.1	2.31 (1H, ddd, *J*=16.1, 7.8 and 2.1 Hz)	2.30 (1H, ddd, *J*=15.6, 7.8 and 2.1 Hz)
47.2	47.2	1.91 (1H, dd, *J*=12.6 and 7.8 Hz)	1.90 (1H, dd, *J*=12.6 and 7.5 Hz)
45.9	45.8	Not observed	1.90 (1H, m)
38.9	38.9	1.30 (1H, t, *J*=12.0 Hz)	See text
32.9	33.1	1.19 (3H, s)	1.18 (3H, s)
26.8	26.8	1.09 (3H, s)	1.09 (3H, s)
22.6	22.6	0.98 (3H, s)	0.98 (3H, s)
20.3	20.3	—	—

[a] Data recorded in $CDCl_3$ at 100 MHz.
[b] Data obtained from ref. 1 and recorded in $CDCl_3$ at 75 MHz.
[c] Data recorded in $CDCl_3$ at 800 MHz.
[d] Data obtained from ref. 1 and recorded in $CDCl_3$ at 300 MHz.

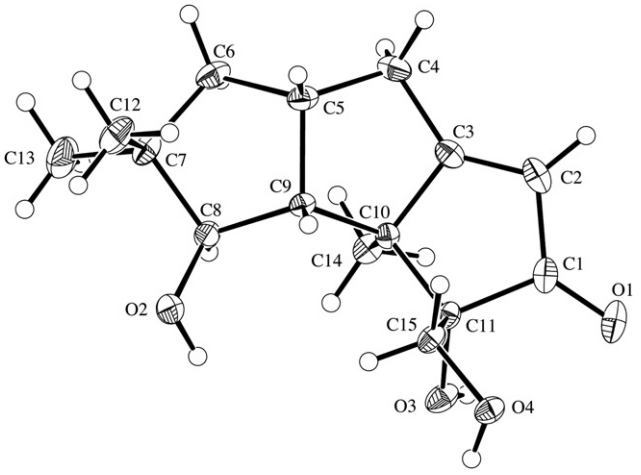


Figure 2. Molecular structure of compound **2** ($C_{15}H_{22}O_4$) with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Associated water molecule not shown.

3. Conclusions

The first total synthesis of the hirsutene-type sesquiterpene (+)-connatusin B (**2**) has been achieved and served to confirm the structure, including absolute configuration, originally assigned to this natural product. The reaction sequence used further emphasizes the utility of the starting material **3** in terpenoid synthesis and the effectiveness of combinations of Diels–Alder cycloaddition and oxa-di-π-methane rearrangement reactions in providing usefully functionalized linear triquinanes. Efforts are now focused on adapting the chemistry presented here to the development of a total synthesis of connatusin A (**1**).[1] Results will be reported in due course.

4. Experimental section

4.1. General experimental procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini machine operating at 300 or 75 MHz, respectively. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been stored over anhydrous sodium carbonate. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were normally recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as thin films on KBr plates (for liquids) or as a KBr disk (for solids). Low-resolution ESI mass spectra were recorded in positive-ion mode on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution EI mass spectra were recorded on a Fisons VG AUTOSPEC instrument. Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Optical rotations were measured at the sodium-D line (λ=589 nm) between 17 and 20 °C and at the concentrations (*c*, in g/100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included a mixture of vanillin:sulfuric acid:ethanol (1 g:1 g:18 mL) or phosphomolybdic acid:ceric sulfate:sulfuric acid (concd):water (37.5 g:7.5 g:37.5 g:720 mL). The retardation factor (R_f) values cited here have been rounded to the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[15] using silica gel 60 (0.040–0.0063 mm) as the stationary phase and 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 either used as supplied or, in the case of liquids, distilled when required. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, dichloromethane and benzene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[16] Spectroscopic grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

4.2. Specific chemical transformations

*4.2.1. Compound **9**.* Lithium hexamethyldisilazide (2.15 mL of a 1 M solution in THF, 2.15 mmol) was added, dropwise, to a magnetically stirred solution of compound **8**[3a] (485 mg, 1.95 mmol) in THF (15 mL) maintained at −15 °C under a nitrogen atmosphere. The

resulting mixture was stirred at −15 °C for 0.75 h then warmed to 18 °C over a period of 1.25 h. Iodomethane (134 μL, 2.15 mmol) was then added, dropwise, to the solution which had been re-cooled to −15 °C and the resulting mixture was stirred at this temperature for 0.75 h then warmed to 18 °C over a period of 1.25 h. This methylation process was then repeated once more and thereafter the reaction mixture left to stir at 18 °C overnight then quenched with ammonium chloride (20 mL of a saturated aqueous solution) and extracted with dichloromethane (3×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the light-yellow oil thus obtained was subjected to flash column chromatography (silica gel, 1:13.3→1:9 v/v ethyl acetate/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f=0.3 in 3:7 v/v ethyl acetate/hexane) gave compound **9**[3a] (300 mg, 56%) as a white, crystalline solid that was identical, in all respects, with an authentic sample.[3a]

Concentration of fraction B [R_f=0.2(5) in 3:7 v/v ethyl acetate/hexane] gave the previously reported[3a] mono-methylated derivative of compound **8** (109 mg, 21%) as a white, crystalline solid that was identical, in all respects, with an authentic sample.[3a]

*4.2.2. Compound **10**.* A magnetically stirred solution of ketone **9** (584 mg, 2.11 mmol) in diethyl ether (15 mL) was cooled to −30 °C then treated with lithium aluminum hydride (3.17 mL of a 1 M solution in THF, 3.17 mmol) over a period of 0.5 h. The ensuing mixture was left to stir at 18 °C for 6 h then treated with sodium sulfate (10 drops of a saturated aqueous solution), stirred at 18 °C for a further 16 h then filtered through Celite™, which was rinsed with ethyl acetate (15 mL). The combined filtrates were concentrated under reduced pressure to give a light-yellow oil and this was subjected to flash column chromatography (silica gel, 1:13.3→1:1 v/v ethyl acetate/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f=0.3 in 3:7 v/v ethyl acetate/hexane) gave *alcohol* ***10*** (464 mg, 79%) as a white, crystalline solid, mp=102–107 °C, $[\alpha]_D$ +32.1 (*c* 1.0, $CHCl_3$) [Found: $(M-H^{\bullet})^+$, 277.1804. $C_{17}H_{26}O_3$ requires $(M-H^{\bullet})^+$, 277.1804]. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.00 (t, *J*=8.1 Hz, 1H), 5.78 (d, *J*=8.1 Hz, 1H), 4.19 (dd, *J*=7.2 and 3.0 Hz, 1H), 3.80 (d, *J*=7.2 Hz, 1H), 3.27 (d, *J*=9.0 Hz, 1H), 2.68–2.60 (m, 1H), 2.24–2.08 (m, 1H), 1.57–1.42 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.38–1.18 (m, 1H), 1.25 (s, 3H), 1.04–0.92 (m, 1H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 131.1, 108.9, 83.4, 82.5, 79.8, 51.4, 41.9, 41.8, 41.0, 39.1, 37.8, 26.1, 25.7, 25.0, 21.2, 19.6; ν_{max} (KBr) 3491, 2957, 2897, 2870, 1457, 1377, 1255, 1207, 1165, 1080, 1057, 1025, 884, 734 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 ($M^{+\bullet}$, 5%), 277 $[(M-H^{\bullet})^+$, 10], 263 (20), 220 (35), 178 (55), 119 (65), 106 (75), 43 (100).

Concentration of fraction B (R_f=0.5 in 3:7 v/v ethyl acetate/hexane) afforded alcohol *C5*-epi-**10** (115 mg, 20%) as a white, crystalline solid, mp=113–117 °C, $[\alpha]_D$ −274 (*c* 1.0, $CHCl_3$) [Found: $(M-H^+)^-$, 277.1808. $C_{17}H_{26}O_3$ requires $(M-H^+)^-$, 277.1804]. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.08–5.99 (m, 2H), 4.22 (dd, *J*=7.2 and 2.8 Hz, 1H), 3.83 (d, *J*=7.6 Hz, 1H), 3.56–3.48 (m, 1H), 2.80–2.74 (m, 1H), 2.26–2.16 (m, 1H), 2.01 (dd, *J*=10.4 and 5.6 Hz, 1H), 1.45–1.36 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.28–1.22 (m, 1H), 1.10 (t, *J*=11.2 Hz, 1H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 130.3, 109.0, 83.8, 81.7, 80.3, 51.1, 45.0, 41.0, 40.9, 40.8, 38.4, 25.8, 25.6, 25.1, 22.6, 19.8; ν_{max} (KBr) 3552, 3043, 2958, 2935, 2901, 2857, 1462, 1383, 1369, 1256, 1160, 1078, 872 cm^{-1}; MS (ESI, −ve ion) *m*/*z* 277 $[(M-H^+)^-$, 10%], 255 (60), 161 (78), 145 (100).

*4.2.3. Compound **11**.* A magnetically stirred solution of alcohol **10** (73 mg, 0.27 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (3 mg, 0.02 mmol) in triethylamine (3 mL) was cooled to 0 °C then treated with acetic anhydride (75 μL, 0.80 mmol). The resulting mixture was allowed to warm to 18 °C, stirred at this temperature for 16 h then quenched with water (20 mL) and extracted with ethyl acetate (5×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *acetate* ***11*** (85 mg, 99%) as a white, crystalline solid, mp=77–78 °C, R_f=0.75 (in 3:7 v/v ethyl acetate/hexane), $[\alpha]_D$ +12.3 (*c* 1.1, $CHCl_3$) [Found: $(M-H^{\bullet})^+$, 319.1918. $C_{19}H_{28}O_4$ requires $(M-H^{\bullet})^+$, 319.1909]. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.08–6.02 (m, 1H), 5.86–5.82 (dm, *J*=8.4 Hz, 1H), 4.69 (d, *J*=8.4 Hz, 1H), 4.24–4.18 (m, 1H), 3.82–3.78 (dm, *J*=7.2 Hz, 1H), 2.72–2.66 (m, 1H), 2.30–2.18 (m, 1H), 2.05 (s, 3H), 1.80 (dd, *J*=10.8 and 8.8 Hz, 1H), 1.52 (dd, *J*=12.4 and 8.0 Hz, 1H), 1.31 (s, 3H) 1.27 (s, 3H), 1.14 (t, *J*=10.8 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 135.5, 130.9, 108.7, 82.8, 81.6, 79.4, 48.4, 41.9, 41.8, 40.6, 38.7, 37.5, 25.9, 25.4, 24.8, 22.1, 21.2, 18.5; ν_{max} (KBr) 2934, 1738, 1454, 1371, 1239, 1202, 1054, 1039, 878, 722 cm^{-1}; MS (EI, 70 eV) *m*/*z* 319 $[(M-H^{\bullet})^+$, 16%], 305 $[(M-CH_3^{\bullet})^+$, 16], 276 (27), 234 (21), 216 (49), 202 (49), 187 (59), 173 (22), 160 (48), 145 (50), 119 (42), 43 (100).

*4.2.4. Compound **12**.* A magnetically stirred solution of compound **11** (881 mg, 2.75 mmol) in methanol/water (30.6 mL of 5:1 v/v mixture) was treated with DOWEX-50 resin (1.38 g of material that had been rinsed successively with 1 M hydrochloric acid, water, saturated sodium bicarbonate solution and water). The resulting suspension was heated at reflux for 20 h then cooled and filtered. The solids thus retained were rinsed with dichloromethane (3×25 mL) and methanol (3×50 mL) and the combined filtrates concentrated under reduced pressure to give an off-white solid. Subjection of this material to flash column chromatography (silica gel, 1:1 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f=0.3) gave the *title diol* ***12*** (371 mg, 90% at 53% conversion) as an off-white and waxy solid, mp=59–62 °C, $[\alpha]_D$ +5 (*c* 1.0, $CHCl_3$) [Found: $(M+Na)^+$, 303.1563. $C_{16}H_{24}O_4$ requires $(M+Na)^+$, 303.1572]. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.16 (t, *J*=8.0 Hz, 1H), 5.91 (d, *J*=8.0 Hz, 1H), 4.61 (d, *J*=8.0, Hz, 1H), 3.84 (dd, *J*=7.2 and 2.4 Hz, 1H), 3.38 (d, *J*=7.2 Hz, 1H), 3.10 (br s, 1H), 2.98 (br s, 1H), 2.64–2.58 (m, 1H), 2.30–2.20 (m, 1H), 2.02 (s, 3H), 1.84–1.77 (m, 1H) 1.48 (dd, *J*=12.4 and 8.0 Hz, 1H), 1.09 (s, 3H), 1.10–1.00 (m, 1H), 0.84 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 136.8, 132.3, 82.2, 74.3, 71.3, 49.5, 42.1, 42.0, 41.7, 41.5, 38.2, 26.0, 22.3, 21.4, 18.3; ν_{max} (KBr) 2928, 2873, 1738, 1454, 1373, 1240, 1039, 740, 619 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 583 $[(2M+Na)^+$, 100%], 303 $[(M+Na)^+$, 48].

Concentration of fraction B (R_f=0.75 in 3:7 v/v ethyl acetate/hexane) gave the starting acetonide **11** (410 mg, 47% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

*4.2.5. Compound **13**. Step i*: A magnetically stirred solution of diol **12** (230 mg, 0.82 mmol) in dichloromethane (15 mL) was cooled to 0 °C then treated with *p*-toluenesulfonic acid monohydrate (343 mg, 1.81 mmol). 4-Acetamido-TEMPO (416 mg, 1.81 mmol) was then added, portionwise over 2 h, and the ensuing mixture stirred at 0 °C for 2 h then at 18 °C for 3 h before being quenched with sodium bicarbonate (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 light-orange/yellow oil that was subjected to flash column chromatography (silica gel, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f=0.6 in 1:1 v/v ethyl acetate/hexane) gave the expected *acyloin* (214 mg, 94%) as a white, crystalline solid, mp=96–97 °C, $[\alpha]_D$ +192.4 (*c* 0.7, $CHCl_3$) (Found: $M^{+\bullet}$, 278.1513. $C_{16}H_{22}O_4$ requires $M^{+\bullet}$, 278.1518). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.18–6.10 (m, 2H), 4.76 (d, *J*=8.8, Hz, 1H), 3.34 (s, 1H), 3.08–3.03 (m, 1H), 2.81 (br s, 1H),

2.73–2.63 (m, 1H), 2.22 (dd, *J*=11.2 and 8.8 Hz, 1H), 2.07 (s, 3H), 1.63 (dd, *J*=12.8 and 8.0 Hz, 1H), 1.19 (s, 3H) 1.19–1.08 (m, 1H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.4, 170.7, 140.3, 127.0, 81.5, 74.1, 50.9, 50.5, 44.2, 41.5, 41.3, 36.3, 25.8, 22.1, 21.2, 17.1; ν_{max} (KBr) 3401, 2961, 2873, 1736, 1464, 1373, 1241, 1036, 725 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 ($M^{+\bullet}$, 11%), 218 (73), 203 (67), 175 (42), 161 (68), 159 (55), 145 (74), 105 (67), 95 (60), 43 (100).

Step ii: A magnetically stirred solution of the acyloin (90 mg, 0.32 mmol, formed in step i), triethylamine (1 mL) and 4-(*N*,*N*-dimethylamino)pyridine (129 mg, 1.06 mmol) in dichloro-methane (5 mL) was cooled to 0 °C then treated with benzoyl chloride (92 μL, 0.79 mmol). The resulting mixture was allowed to warm to 18 °C, stirred at this temperature for 16 h then treated with HCl (20 mL of a 1 M aqueous solution) and extracted with dichloromethane (4×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil that was subjected to flash column chromatography (silica gel, 1:13.3→1:9 v/v ethyl acetate/hexane gradient elution). Concentration of the relevant fractions (R_f=0.4 in 1:4 v/v ethyl acetate/hexane) then gave the *keto-benzoate* ***13*** (111 mg, 91%) as a white, crystalline solid, mp=111–114 °C, $[\alpha]_D$ +170.4 (*c* 1.1, $CHCl_3$) (Found: $M^{+\bullet}$, 382.1772. $C_{23}H_{26}O_5$ requires $M^{+\bullet}$, 382.1780). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02–7.97 (m, 2H), 7.58–7.53 (tm, *J*=7.6 Hz, 1H), 7.45–7.39 (m, 2H), 6.30–6.20 (m, 2H), 5.11 (s, 1H), 4.80 (d, *J*=8.4 Hz, 1H), 3.20–3.14 (m, 1H), 2.86–2.76 (m, 1H), 2.44 (dd, *J*=10.8 and 8.8 Hz, 1H), 2.07 (s, 3H), 1.69 (dd, *J*=12.8 and 8.0 Hz, 1H), 1.27–1.18 (m, 1H), 1.10 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.1, 170.7, 166.2, 139.5, 133.4, 130.0, 129.3, 128.5, 127.8, 81.5, 73.7, 51.6, 50.3, 43.4, 41.6, 41.4, 36.7, 25.9, 22.2, 21.3, 17.2; ν_{max} (KBr) 2965, 2873, 1738, 1693, 1451, 1375, 1270, 1241, 1109, 1043, 771 cm^{-1}; MS (EI, 70 eV) *m*/*z* 382 ($M^{+\bullet}$, 4%), 226 (29), 200 (68), 198 (57), 160 (70), 145 (63), 122 (100), 121 (75), 106 (83), 105 (98), 77 (90), 51 (93), 50 (64), 43 (64).

4.2.6. Compound ***14***. A deoxygenated solution of compound **13** (428 mg, 1.12 mmol) and acetophenone (180 μL, 1.54 mmol) in acetone (200 mL) was placed in a Quartex™ immersion well photoreactor (500 mL reactor from Ace Glass Inc.) equipped with a Pyrex™ filter. The solution was subjected to irradiation with a Hanovia 450 W medium pressure mercury-vapor lamp for 3.5 h and then cooled and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica gel, 1:20→1:4 v/v ethyl acetate/hexane gradient elution) afforded three fractions, A, B and C.

Concentration of fraction A (R_f=0.25 in 1:4 v/v ethyl acetate/hexane) gave the *C1-β epimeric form of compound* ***14*** (165 mg, 51% at 76% conversion) as a white, crystalline solid, mp=135–136 °C, $[\alpha]_D$ +14.9 (*c* 1.0, $CHCl_3$) [Found: $(M+H)^+$, 383.1858. $C_{23}H_{26}O_5$ requires $(M+H)^+$, 383.1858]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.04 (m, 2H), 7.60 (t, *J*=8.0, Hz, 1H), 7.50–7.46 (m, 2H), 5.35 (d, *J*=4.0 Hz, 1H), 5.13 (d, *J*=12.0 Hz, 1H), 2.75 (dd, *J*=12.0 and 8.0 Hz, 1H), 2.58–2.50 (m, 1H), 2.35 (t, *J*=4.0 Hz, 1H), 2.06–2.00 (m, 1H), 2.01 (s, 3H), 1.98–1.94 (m, 1H), 1.82 (dd, *J*=12.0 and 8.0 Hz, 1H), 1.42 (dd, *J*=12.0 and 6.4 Hz, 1H), 1.36 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.6, 170.7, 165.4, 133.5, 130.0, 129.5, 128.6, 83.7, 80.0, 55.7, 49.4, 44.3, 43.1, 38.9, 36.0, 33.7, 32.1, 26.7, 21.8, 21.3, 19.6; ν_{max} (KBr) 2960, 2929, 2873, 1727, 1452, 1370, 1269, 1241, 1110, 1042, 710 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 405 [$(M+Na)^+$, 100%] 383 [$(M+H)^+$, 11].

Concentration of fraction B (R_f=0.35 in 1:4 v/v ethyl acetate/hexane) gave the *C1-α epimeric form of compound* ***14*** (143 mg, 44% at 76% conversion) as a white, crystalline solid, mp=139–150 °C, $[\alpha]_D$ +18.6 (*c* 1.0, $CHCl_3$) [Found: $(M+Na)^+$, 405.1671. $C_{23}H_{26}O_5$ requires $(M+Na)^+$, 405.1678]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06–8.02 (m, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.47–7.41 (m, 2H), 5.14 (d, *J*=9.6 Hz, 1H), 4.97 (s, 1H), 2.70–262 (m, 1H), 2.60–2.50 (m, 2H), 2.22 (dd, *J*=10.4 and 5.2 Hz, 1H), 2.05 (s, 3H), 2.06–1.97 (m, 1H), 1.84 (dd, *J*=10.0 and 6.0 Hz, 1H), 1.39 (dd, *J*=13.6 and 6.4 Hz, 1H), 1.17 (s, 3H), 1.02 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.5, 170.8, 165.7, 133.5, 130.0, 129.4, 128.6, 84.8, 80.1, 61.2, 50.8, 44.5, 43.5, 41.1, 39.7, 39.1, 38.7, 26.8, 22.0, 21.3, 14.1; ν_{max} (KBr) 2962, 1734, 1602, 1451, 1369, 1266, 1242, 1095, 711 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 787 [$(2\,M+Na)^+$, 8%], 405 [$(M+Na)^+$, 100%], 383 [$(M+H)^+$, 15], 173 (38).

Concentration of fraction C (R_f=0.4 in 1:4 v/v ethyl acetate/hexane) gave the starting keto-benzoate **13** (102 mg, 24% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

4.2.7. Compound ***15***. A magnetically stirred solution of either epimeric form of compound **14** (161 mg, 0.42 mmol), or a mixture thereof, in THF/methanol (8 mL of a 2:1 v/v mixture) was cooled to −78 °C and, while being maintained under an argon atmosphere, was treated with samarium(II) iodide (9.27 mL of a 0.1 M solution in THF, 0.93 mmol) by dropwise addition until a blue color persisted for ~10 min. After this time the reaction mixture was quenched with potassium carbonate (10 mL of saturated aqueous solution) and extracted with diethyl ether (3×2 mL). The combined organic extracts were then washed with water (1×5 mL) and brine (1×5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil that was subjected to flash column chromatography (silica gel, 1:4 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f=0.3 in 1:3 v/v ethyl acetate/hexane) then gave the *title compound* ***15*** (90 mg, 81%) as a white, crystalline solid, mp=126–129 °C, $[\alpha]_D$ +68.1 (*c* 0.8, $CHCl_3$) [Found: $(M+H)^+$, 263.1642. $C_{16}H_{22}O_3$ requires $(M+H)^+$, 263.1647]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.03 (d, *J*=10.0 Hz, 1H), 2.60–2.54 (m, 1H), 2.41 (t, *J*=5.2 Hz, 1H), 2.33 (dd, *J*=17.6 and 1.2 Hz, 1H), 2.26 (dd, *J*=10.0 and 7.6 Hz, 1H), 2.05 (s, 3H), 2.00–1.94 (m, 3H), 1.69–1.62 (m, 1H), 1.34 (dd, *J*=13.6 and 6.4 Hz, 1H), 1.25 (s, 3H), 0.98 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.3, 170.7, 80.5, 64.3, 57.7, 46.9, 44.7, 43.0, 39.7, 39.5, 38.9, 38.5, 26.9, 22.1, 21.3, 21.1; ν_{max} (KBr) 2942, 1716, 1378, 1244, 1041, 961, 886 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 285 [$(M+Na)^+$, 15%], 263 [$(M+H)^+$, <1], 102 (100).

4.2.8. Compound ***16***. A magnetically stirred solution of ketone **15** (86 mg, 0.33 mmol) in THF (4.4 mL) maintained at −78 °C under an argon atmosphere was treated, dropwise, with LiHMDS (394 μL of a 1 M THF solution, 0.39 mmol) and the resulting mixture left to stir at −78 °C for 1 h. After this time, Eschenmoser's salt (182 mg, 0.98 mmol) was added, in one portion, to the reaction mixture, which was then allowed to warm to 18 °C over 16 h before being quenched with HCl (10 mL of a 3 M aqueous solution) and, after 5 min., extracted with diethyl ether (3×10 mL). The separated aqueous phase was basified, to pH 14, then extracted with dichloromethane (3×10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the *title amine* ***16*** (75 mg, 71%) as a white, crystalline solid, mp=110–114 °C, R_f=0.7 in 1:3 v/v ethyl acetate/hexane, $[\alpha]_D$ −64.3 (*c* 1.0, $CHCl_3$) [Found: $(M+H)^+$, 320.2224. $C_{19}H_{29}NO_3$ requires $(M+H)^+$, 320.2226]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.04 (d, *J*=13.2 Hz, 1H), 2.60–2.52 (m, 1H), 2.46–2.35 (m, 2H), 2.28–2.20 (m, 2H), 2.18 (s, 6H), 2.08–1.98 (m, 1H), 2.03 (s, 3H), 1.96–1.86 (m, 2H), 1.63 (dd, *J*=10.4 and 6.0 Hz, 1H), 1.25 (dd, *J*=13.2 and 6.8 Hz, 1H), 1.16 (s, 3H), 0.95 (s, 3H) 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.7, 170.5, 80.2, 64.7, 62.2, 59.8, 49.6, 45.6, 44.2, 42.9, 38.6, 38.4, 37.7, 36.4, 26.6, 21.6, 21.2, 15.9; ν_{max} (KBr) 2960, 2866, 2822, 2768, 1732, 1455, 1369, 1241, 1040, 900, 819, 736 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 320 [$(M+H)^+$, 25%], 58 (97), 57 (100).

4.2.9. Compound ***17***. A magnetically stirred solution of tertiary amine **16** (195 mg, 0.61 mmol) in diethyl ether/dichloromethane

(15 mL of a 3:1 v/v mixture), maintained at 18 °C under a nitrogen atmosphere, was treated with iodomethane (456 μL, 7.33 mmol) and the resulting solution stirred at the same temperature for 16 h then concentrated under reduced pressure to give a yellow oil. This oil was dissolved in dichloromethane (15 mL) and the solution so-obtained treated with basic alumina (ca. 500 mg of 0.063–0.200 mesh material, activity grade 1). The resulting suspension was stirred at 18 °C for 0.5 h then concentrated under reduced pressure. The ensuing solid was loaded onto the top of a column of TLC-grade alumina and this was eluted with dichloromethane. Concentration of the relevant fractions (R_f=0.6 in 1:3 v/v ethyl acetate/hexane) gave the *title compound* ***17*** (146 mg, 87%) as a white, crystalline solid, mp=122–127 °C, $[\alpha]_D$ −61.0 (*c* 1.0, $CHCl_3$) (Found: M^{+}•, 274.1566. $C_{17}H_{22}O_3$ requires M^{+}•, 274.1569). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (d, *J*=1.6 Hz, 1H), 5.12–5.06 (m, 2H), 2.50–2.40 (m, 2H), 2.28–2.20 (m, 1H), 2.16–2.10 (m, 1H), 2.10 (s, 3H), 1.95 (dd, *J*=13.2 and 9.6 Hz, 1H), 1.85 (dd, *J*=10.0 and 6.0 Hz, 1H), 1.35 (dd, *J*=14.0 and 6.0 Hz, 1H), 1.30 (s, 3H), 1.00 (s, 3H) 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.2, 170.8, 156.6, 114.0, 80.4, 66.3, 50.8, 44.6, 43.3, 42.1, 39.5, 38.6, 38.1, 27.1, 22.2, 21.4, 18.4; ν_{max} (KBr) 2925, 2853, 1739, 1715, 1633, 1464, 1374, 1322, 1240, 1093, 1043, 956, 852, 801 cm^{-1}; MS (EI, 70 eV) *m*/*z* 274 (M^{+}•, 4%), 259 (11), 214 (78), 199 (81), 171 (54), 145 (58), 43 (100).

4.2.10. Compound ***18****.* A magnetically stirred solution of enone **17** (74 mg, 0.27 mmol) in toluene (3 mL) and *tert*-butanol/water (2.7 mL of a 1:1 v/v mixture) maintained at 0 °C was treated with methane sulfonamide (13 mg, 13 mmol) and AD mix-α (378 mg with added $K_2OsO_4 \cdot 2H_2O$ such that the total osmium tetroxide content was 1 mg). The resulting solution was left to stir at 0 °C for 16 h then subjected to flash column chromatography (silica gel, 1:1 v/v ethyl acetate/hexane). Concentration of the relevant fractions (R_f=0.4) gave the *title compound* ***18*** (67 mg, 81%) as a clear, colorless oil, $[\alpha]_D$ −68.1 (*c* 1.1, $CHCl_3$) (Found: M^{+}•, 308.1623. $C_{17}H_{24}O_5$ requires M^{+}•, 308.1624). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.06 (d, *J*=9.6 Hz, 1H), 3.84 (d, *J*=12.0 Hz, 1H), 3.74 (br s, 1H), 3.35 (d, *J*=12.0 Hz, 1H), 2.94 (br s, 1H), 2.44 (t, *J*=5.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.18–2.14 (m, 1H), 2.14–2.08 (m, 1H), 2.09 (s, 3H), 1.97–1.88 (m, 1H), 1.76 (dd, *J*=10.4 and 6.0 Hz, 1H) 1.35 (dd, *J*=13.6 and 6.0 Hz, 1H), 1.22 (s, 3H), 0.98 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.2, 170.6, 81.8, 80.3, 61.7, 55.7, 52.7, 44.4, 43.1, 39.8, 38.8, 38.5, 34.9, 26.9, 22.2, 21.3, 12.5; ν_{max} (KBr) 3460, 2959, 2927, 2871, 1731, 1465, 1370, 1241, 1042 cm^{-1}; MS (EI, 70 eV) *m*/*z* 308 (M^{+}•, 7%), 279 (30), 167 (35), 149 (100), 71 (34), 57 (51), 43 (73).

4.2.11. Compound ***19****.* A magnetically stirred solution of diol **18** (67 mg, 0.22 mmol) in THF (5 mL) maintained at 0 °C was treated with 2,2′-dimethoxypropane (133 μL, 1.09 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol) and the resulting solution was stirred at 0 °C for 2 h before being allowed to warm to 18 °C and then left to stand at this temperature for 16 h. The ensuing mixture was quenched with sodium hydrogen carbonate (5 mL of a saturated aqueous solution) and extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (1×10 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the *acetonide* ***19*** (74 mg, 98%) as a colorless, crystalline solid, mp=145–152 °C, R_f=0.5 in 1:3 v/v ethyl acetate/hexane, $[\alpha]_D$ −38.6 (*c* 1.0, $CHCl_3$) [Found: $(M+Na)^{+}$, 371.1829. $C_{20}H_{28}O_5$ requires $(M+Na)^{+}$, 371.1834]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.08 (d, *J*=9.6 Hz, 1H), 4.11 (d, *J*=9.2 Hz, 1H), 3.64 (d, *J*=9.2 Hz, 1H), 2.44–2.35 (m, 2H), 2.13 (dd, *J*=10.0 and 4.8 Hz, 1H), 2.06 (s, 3H), 1.90–1.78 (m, 2H), 1.75 (dd, *J*=10.4 and 6.0 Hz, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.42–1.30 (m, 1H), 1.22 (s, 3H), 0.97 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 170.5, 111.2, 93.4, 80.4, 64.3, 57.0, 51.3, 44.1, 43.5, 39.4, 39.2, 37.3, 34.0, 26.6, 26.4, 26.1, 21.6, 21.3, 13.0; ν_{max} (KBr) 2930, 2858, 1738, 1462, 1379, 1238, 1158, 1043, 946, 867 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 371 [$(M+Na)^{+}$, 100%], 331 (97).

4.2.12. Compound ***20****.* A magnetically stirred solution of cyclopropyl ketone **19** (118 mg, 0.34 mmol) in benzene (10 mL) maintained at 18 °C under an argon atmosphere was treated with AIBN (1 mg, 0.003 mmol) and tri-*n*-butyltin hydride (197 μL, 0.68 mmol). The resulting solution was heated at reflux for 1.5 h then allowed to cool to 18 °C. The addition of further aliquots of AIBN and tri-*n*-butyltin hydride and subsequent heating of resulting solution at reflux was repeated three times and with the result that all of the starting material was then consumed. The cooled reaction mixture was concentrated under reduced pressure and the residue subjected to flash column chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f=0.6 in 1:3 v/v ethyl acetate/hexane) gave *compound* ***20*** (117 mg, 98%) as a white, crystalline solid, mp=58–61 °C, $[\alpha]_D$ +42.4 (*c* 1.0, $CHCl_3$) [Found: $(M+Na)^{+}$, 373.1997. $C_{20}H_{30}O_5$ requires $(M+Na)^{+}$, 373.1991]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.11 (d, *J*=8.8 Hz, 1H), 4.13 (d, *J*=8.8 Hz, 1H), 3.60 (d, *J*=8.8 Hz, 1H), 2.76–2.60 (m, 2H), 2.60–2.50 (m, 1H), 2.05 (s, 3H), 2.02–1.92 (m, 1H), 1.86–1.68 (m, 3H), 1.58–1.48 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 1.25–1.17 (m, 1H), 1.14 (s, 3H), 0.96 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.7, 170.4, 111.3, 89.6, 80.4, 65.2, 51.6, 51.5, 47.9, 46.8, 45.8, 39.6, 39.4, 36.7, 26.9, 26.5, 25.9, 21.3, 21.2, 16.3; ν_{max} (KBr) 2927, 2855, 1742, 1464, 1378, 1233, 1031 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 373 [$(M+Na)^{+}$, 100%].

4.2.13. Compound ***21****. Step i*: A magnetically stirred solution of triquinane **20** (55 mg, 0.16 mmol) in THF (5 mL) maintained at −78 °C under a nitrogen atmosphere, was treated, dropwise, with LiHMDS (173 μL of a 1.0 M solution in THF, 0.17 mmol) and the resulting solution was stirred at this temperature for 1 h. After this time *o*-nitrophenyl selenocyanate (39 mg, 0.17 mmol) was added and the ensuing mixture allowed to warm to 18 °C and stirred for at this temperature for 16 h then quenched with ammonium chloride (5 mL of a saturated aqueous solution) and extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil that was subjected to flash column chromatography (silica gel, 1: 9 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f=0.3 in 1:3 v/v ethyl acetate/hexane) gave the expected o-*nitrophenylselenide* (25 mg, 76% at 38% conversion) as a waxy, yellow oil, $[\alpha]_D$ −150.0 (*c* 1.0, $CHCl_3$) [Found: $(M+Na)^{+}$, 574.1320. $C_{26}H_{33}NO_7Se$ requires $(M+Na)^{+}$, 574.1320]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30–8.20 (m, 2H), 7.60–7.50 (m, 1H), 7.40–7.30 (m, 1H), 5.16 (d, *J*=8.0 Hz, 1H), 4.23 (d, *J*=8.8 Hz, 1H), 3.59 (d, *J*=8.8 Hz, 1H), 3.44 (d, *J*=6.8 Hz, 1H), 2.86–2.76 (m, 1H), 2.54 (t, *J*=6.4 Hz, 1H), 2.08 (s, 3H), 2.11–2.02 (m, 1H), 1.98–1.91 (m, 1H), 1.82–1.74 (m, 1H), 168–1.57 (m, 2H), 1.40 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.7, 170.4, 146.4, 134.5, 134.2, 131.2, 126.4, 126.2, 112.1, 89.6, 80.1, 64.7, 56.1, 51.8, 50.7, 47.2, 46.0, 44.3, 39.9, 35.3, 26.8, 26.5, 25.8, 21.3, 21.1, 16.0; ν_{max} (KBr) 2925, 2854, 1741, 1591, 1567, 1514, 1463, 1379, 1332, 1306, 1232, 1035, 853, 730 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 574 [$(M+Na)^{+}$, 26%], 373 (39), 357 (100).

Concentration of fraction B (R_f=0.6 in 1:3 v/v ethyl acetate/hexane) gave the starting ketone **20** (34 mg, 62% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

Step ii: A magnetically stirred solution of the selenide (25 mg, 0.05 mmol) prepared via step i in dichloromethane (3 mL) maintained under argon at −78 °C was treated with *m*-CPBA (12 mg of ca. 70% technical grade material, 0.05 mmol) and the resulting

solution was stirred at this temperature for 0.5 h. After this time diethylamine (100 μL, 0.97 mmol) was added and the resulting mixture allowed to warm to 18 °C then stirred at this temperature in the presence of atmospheric oxygen for 3 h. The reaction mixture was quenched with sodium bicarbonate (5 mL of a saturated aqueous solution) then extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (1×5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.7 in 1:1 v/v ethyl acetate/hexane) afford *enone* ***21*** (15 mg, 95%) as a white, crystalline solid, $[\alpha]_D$ +2.9 (*c* 0.5, $CHCl_3$) [Found: $(M+Na)^+$, 371.1834. $C_{20}H_{28}O_5$ requires $(M+Na)^+$, 371.1834]. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.82 (d, *J*=2.0 Hz, 1H), 5.24 (d, *J*=8.0 Hz, 1H), 3.98 (d, *J*=8.8 Hz, 1H), 3.79 (d, *J*=8.8 Hz, 1H), 2.86–2.62 (m, 3H), 2.33 (ddd, *J*=15.6, 8.4 and 2.0 Hz, 1H), 2.06 (s, 3H), 1.97 (dd, *J*=12.8 and 8.0 Hz, 1H), 1.55 (s, 3H), 1.43 (s, 3H), 1.28–1.22 (m, 1H), 1.19 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 170.6, 120.8, 111.7, 92.1, 80.2, 70.2, 54.0, 48.1, 46.5, 46.2, 39.6, 34.9, 29.9, 27.1, 26.6, 25.7, 23.8, 21.8, 21.4; ν_{max} (KBr) 2929, 1729, 1708, 1629, 1369, 1248, 1048 cm^{-1}; MS (ESI, +ve ion) *m*/*z* 371 [$(M+Na)^+$, 28%], 74 (100).

4.2.14. Compound ***2****.* A magnetically stirred solution of enone **21** (12 mg, 0.03 mmol) in methanol/water (1 mL of a 5:1 v/v mixture) was treated with DOWEX-50 resin [24 mg of material that had been rinsed successively with 1 M hydrochloric acid, water, saturated sodium bicarbonate solution and water] and the resulting suspension was heated at reflux for 16 h. The cooled reaction mixture was filtered and the solids thus retained were rinsed with dichloromethane (3×10 mL) and methanol (3×25 mL). The combined filtrates were concentrated under reduced pressure to give an off-white solid. Subjection of this material to flash column chromatography (silica gel, ethyl acetate elution) and concentration of the appropriate fractions (R_f=0.4) afforded connatusin B (**2**) (7 mg, 77%) as a white, crystalline solid, mp=116–120 °C, $[\alpha]_D$ +12.3 (*c* 0.4, $CHCl_3$), [Found $(M+Na)^+$, 289.1417. $C_{15}H_{22}O_4$ requires $(M+Na)^+$, 289.1416]. ^1H NMR ($CDCl_3$, 800 MHz) δ see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 1; ν_{max} (KBr) 3397, 2922, 2853, 1705, 1630, 1463, 1119 cm^{-1}; MS (ESI, +ve) *m*/*z* 331 [$(M+Na)^+$, 8%], 289 (100).

4.3. Single-crystal X-ray analyses of compounds 15, 19 and 2

4.3.1. Data for Compound ***15****.* $C_{16}H_{22}O_3$, *M*=262.35, *T*=200 K, orthorhombic, space group $P2_12_12_1$, *Z*=4, *a*=6.7923(1), *b*=12.3722(4), *c*=17.4495(5) Å, *V*=1466.38(7) $Å^3$, D_x=1.188 g cm^{-3}, 1934 unique data ($2\theta_{max}$=55°), *R*=0.037 [for 1399 reflections with $I>2.0\sigma(I)$]; *R*w=0.091 (all data), *S*=0.86.

4.3.2. Data for Compound ***19****.* $C_{20}H_{28}O_5$, *M*=348.44, *T*=200 K, orthorhombic, space group $P2_12_12_1$, *Z*=4, *a*=7.6564(1), *b*=11.6410(2), *c*=21.4772(3) Å, *V*=1914.22(5) $Å^3$, D_x=1.209 g cm^{-3}, 3157 unique data ($2\theta_{max}$=60°), *R*=0.035 [for 2537 reflections with $I>2.0\sigma(I)$]; *R*w=0.088 (all data), *S*=0.89.

4.3.3. Data for Compound ***2****·H_2O.* $C_{15}H_{22}O_4\cdot H_2O$ *M*=284.35, *T*=200 K, monoclinic, space group *C*2, *Z*=4, *a*=10.0661(2), *b*=8.9993(2), *c*=16.7001(4) Å, β=105.6552(16)°, *V*=1456.70(6) $Å^3$, D_x=1.296 g cm^{-3}, 1766 unique data ($2\theta_{max}$=55°), *R*=0.030 [for 1688 reflections with $I>2.0\sigma(I)$]; *R*w=0.080 (all data), *S*=1.01.

4.3.4. Structure determinations. Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[17] Structure solution was by direct methods (SIR92).[18] The structures of compounds **15**, **19** and **2** were refined using the CRYSTALS program package.[19] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Center (CCDC nos. 775438, 775439 and 775437 for **15**, **19** and **2**, respectively). 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 Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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