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The total synthesis of (−)-connatusin A, a hirsutane-type sesquiterpene isolated from the fungus *Lentinus connatus* BCC8996

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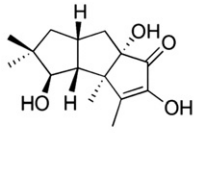
ABSTRACT

The title sesquiterpenoid natural product **1** has been prepared for the first time using the enantiomerically pure *cis*-1,2-dihydrocatechol **3** as starting material. Key steps associated with the synthesis include a Diels–Alder cycloaddition reaction of the acetonide **5** with cyclopentenone (**4**) and an oxa-di-π-methane rearrangement of bicylco[2.2.2]octenone **6** derived from the initial adduct. The product of this sequence, the cyclopropannulated triquinane **7**, was elaborated, over a further eight steps including those involving Upjohn dihydroxylation and Swern oxidation protocols, to the target **1**. A single-crystal X-ray analysis served to confirm the structure of this synthetically derived material.

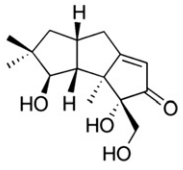
1. Introduction

The natural product (−)-connatusin A (**1**) was obtained together with congener **2** [(+)-connatusin B] from the ethyl acetate extracts of the crude culture broth of the fungus *Lentinus connatus* BCC8996 by Rukachaisirikul et al. in 2005.[1] The illustrated structures were initially established through detailed NMR spectroscopic studies and that of compound **1** was confirmed by single-crystal X-ray analytical techniques. The two compounds differ significantly in terms of the oxygenation patterns incorporated within the right-hand part of the linear triquinane ring system.[2] While several other metabolites isolated from the above-mentioned extracts displayed significant anti-malarial and cytotoxic activities, sesquiterpenoids **1** and **2** did not.[1]

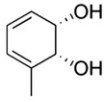
Recently we detailed[3] the first total synthesis of (+)-connatusin B (**2**) using the enantiomerically pure *cis*-1,2-dihydrocatechol **3** as starting material.[4] The key features associated with this approach had been validated during the course of earlier work on the synthesis of related triquinane natural products[5] and involved the initial engagement of the acetonide derivative of diene **3** in a Diels–Alder reaction with cyclopentenone. Manipulation of the resulting cycloaddend ultimately provided a cyclopentannulated bicyclo[2.2.2]octenone that could be engaged in a photochemically-promoted oxa-di-π-methane rearrangement[6] and thereby generating the linear triquinane framework associated with the target compound. Straightforward manipulations of this photoproduct allowed for the completion of the synthesis. Herein we report the adaptation of this work to the synthesis of (−)-connatusin A (**1**).



(−)-connatusin A (**1**)



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



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2. Results and discussion

The reaction sequence implemented during the course of the present work is shown in Scheme 1 and the first eight steps are the same as the ones used to prepare congener **2**. Thus, the reaction sequence starts with a Diels–Alder reaction between cyclopentenone (**4**) and the known[7] and readily obtained acetonide derivative, **5**, of diene **3**. The adduct so-formed was then elaborated, using well-established procedures,[3,5] into the ring-fused bicyclo[2.2.2]octenone **6**,[3] the substrate for the pivotal and photochemically-promoted oxa-di-π-methane rearrangement.

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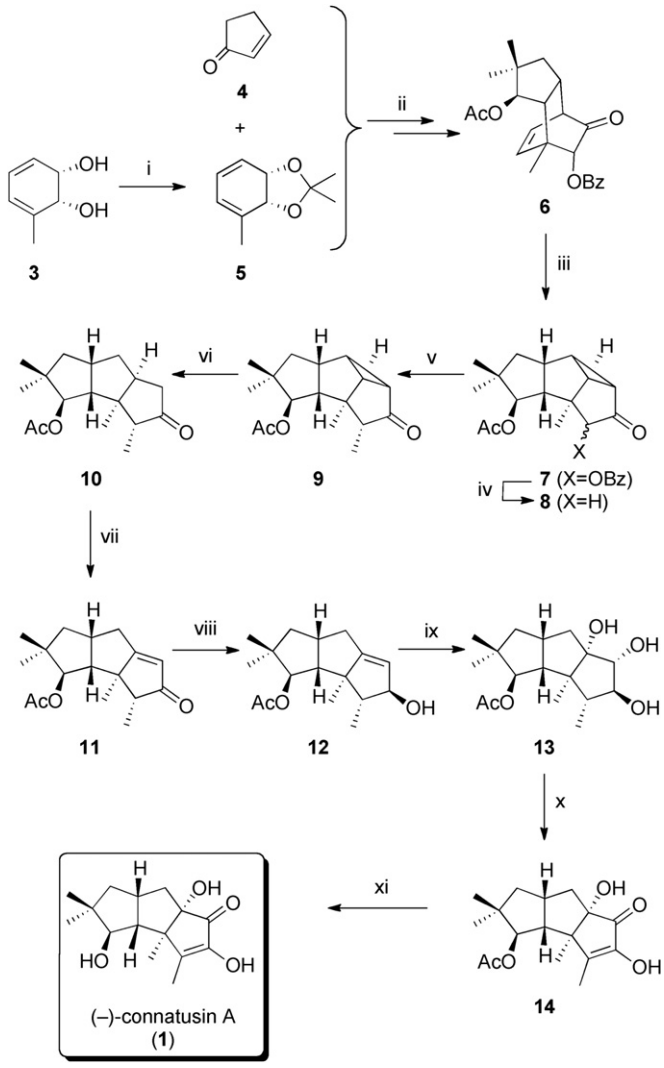
Irradiation of an acetone solution of compound **6** containing acetophenone with a medium pressure mercury vapor lamp effected the required rearrangement and the ca. 1:1 epimeric mixture of ketobenzoates **7**[3] so-formed (95% at 76% conversion) was subjected to samarium iodide-mediated reduction and thereby forming the previously reported[3] ketone **8** (81%). Reaction of compound **8** with lithium hexamethyldisilazide (LiHMDS) at −78 °C and trapping of the resulting kinetic enolate with methyl iodide afforded, in a completely stereoselective manner, a new, mono-methylated derivative in 75% yield that was assigned structure **9** based on the derived ^{1}H NMR spectral data.



Scheme 1. Reagents and conditions: (i) 2,2-DMP, *p*-TsOH·H_2O, 18 °C, 1 h; (ii) see Ref. 3; (iii) acetophenone, acetone, hν, 18 °C, 24 h; (iv) SmI_2, MeOH, THF, −78 °C, 0.25 h; (v) LiHMDS, THF, −78 °C, 1 h then MeI, 18 °C, 16 h; (vi) Bu_3SnH, AIBN, C_6H_6, 80 °C, 10 h; (vii) TMSOTf, 2,6-lutidine, 0 °C, 5 h then $Pd(OAc)_2$, *p*-benzoquinone, MeCN, 18 °C, 18 h; (viii) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 0–18 °C, 3 h; (ix) OsO_4, NMO, *t*-BuOH, THF, H_2O, 18 °C, 15 h; (x) $(COCl)_2$, DMSO, DCM, −60 °C, 0.17 h then compound **13**, −60 °C, 1 h then Et_3N, −60 °C, 0.5 h; (xi) DOWEX-50WX-100 resin, MeOH/H_2O, 65 °C, 16 h.

Treatment of the cyclopropane ring-fused triquinane **9** with tri-*n*-butyltin hydride in refluxing benzene containing catalytic quantities of the free-radical initiator azobisisobutyronitrile (AIBN) under conditions originally defined by Singh et al.[8] resulting in cleavage of the three-membered ring and formation of compound **10** (52% at 65% conversion or 80% based on recovered starting material). The derived spectral data were in full accord with the assigned structure but final confirmation of this was obtained by X-ray analysis of its co-crystal with 2,2,3,3-tetramethylsuccinonitrile (the by-product arising from fragmentation of AIBN). The resulting ORTEP is shown in Fig. 1 and further details of this analysis are presented in the Experimental section.

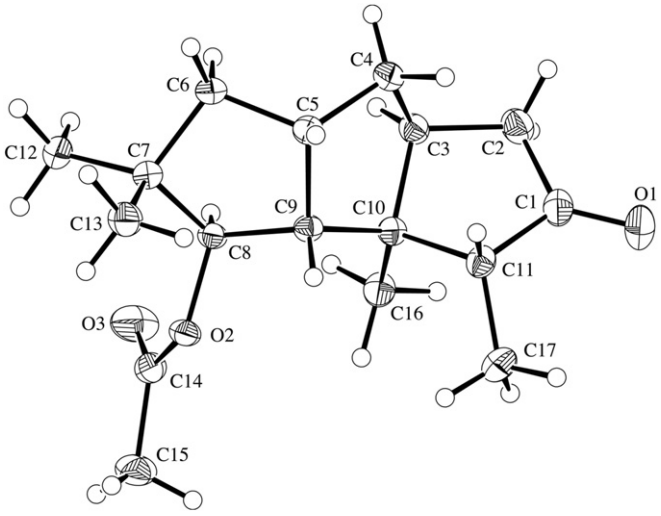


Fig. 1. ORTEP derived from the single-crystal X-ray analysis of compound **10** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles of an arbitrarily small radius. The structure of the co-crystallized 2,2,3,3-tetramethylsuccinonitrile has been omitted for clarity.

In order to establish the required oxygenation pattern within the right-hand five-membered ring of compound **10** it was subjected to a Saegusa oxidation[9] by treatment with trimethylsilyl triflate (TMSOTf) in the presence of 2,6-lutidine and reacting the resulting silyl enol ether with palladium(II) acetate and *p*-benzoquinone. The enone **11** thus obtained (in 77% yield) was subjected to a Luche-type reduction[10] using sodium borohydride in the presence of $CeCl_3\cdot 7H_2O$ and thereby forming, in 99% yield, a single diastereoisomeric form of the anticipated allylic alcohol. On the basis of the derived NMR spectral data this is tentatively assigned structure **12** incorporating a β-orientated hydroxyl group. Dihydroxylation of compound **12** under the Upjohn conditions (and using *N*-methylmorpholine-*N*-oxide or NMO as the stoichiometric oxidant)[11] was readily effected, with full stereochemical control, at ambient temperatures and the resulting and rather polar triol **13** (69%) was then subjected to Swern oxidation[12] in dichloromethane (DCM) and so giving the α-hydroxy-β-methylcyclopent-2-en-1-one **14** in 52% yield. The ^{1}H and ^{13}C NMR spectral data obtained on this acetate derivative of (−)-connatusin A were in complete accord with the structure shown. In particular, the single set of signals apparent in each spectrum suggests that the compound exists in a single tautomeric form and most likely the illustrated one. The final step of the reaction sequence required cleaving the acetate residue within compound **14** so as to reveal the corresponding alcohol and this proved somewhat troublesome in terms of securing good yields of the final product. Ultimately, and after considerable experimentation, the use of acidified DOWEX-50WX-100 resin in 5:1 v/v methanol at 65 °C for 18 h proved most effective and provided a crystalline sample of (−)-connatusin A in 84% yield.

The ^{13}C NMR spectral data obtained on synthetically derived (−)-connatusin A (**1**) compared rather well (Table 1) with those reported by Rukachaisirikul et al.[1] for the natural product. The ^{1}H NMR data for the two materials did not compare quite so favorably (see Table 1), perhaps because of proton exchange and variations in the concentrations of the three possible tautomeric and stereoisomeric forms of the compound. However, comparison of the

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

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
Synthetic **1**[a]	Natural **1**[b]	Synthetic **1**[c]	Natural **1**[d]
202.3	202.8	2.45, 1H, br s[e]	5.99, 1H, br s
151.3	152.2	5.18, 1H, br s[e]	5.32, 1H, br s
145.3	145.5	3.89, 1H, d, J=10.2 Hz	3.90, 1H, d, J=10.2 Hz
85.5	85.5	2.36, 1H, dd, J=14.0 and 8.4 Hz	2.37, 1H, dd, J=13.8 and 8.7 Hz
81.0	81.0	2.26, 1H, t, J=10.0 Hz	2.28, 1H, dd, J=10.2 and 9.9 Hz
55.0	55.0	2.11–2.06, 1H, m	2.13, 1H, m
54.2	54.1	1.97, 3H, s	1.99, 3H, s
46.6	46.6	1.79, 1H, dd, J=14.0 and 8.4 Hz	1.80, 1H, dd, J=13.8 and 8.7 Hz
44.2	44.2	1.60–1.53, 1H, m	1.59, 1H, dd, J=13.8 and 9.9 Hz
43.2	43.2	1.30, 3H, s	1.31, 3H, s
34.6	34.6	1.30, 1H, m	1.29, 1H, m
28.5	28.5	1.10, 3H, s	1.11, 3H, s
22.6	22.6	0.90, 3H, s[f]	0.91, 3H, s[f]
16.5	16.6	—	—
10.2	10.3	—	—

[a] Data recorded in $CDCl_3$ at 400 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.
[e] The chemical shift of these signals varied somewhat from run to run.
[f] The resonance due to one proton not observed.

various other spectral data acquired on the synthetic material with those reported[1] for (−)-connatusin A (**1**) suggested they were one and the same compound. In particular, the IR, MS, and UV spectra proved good matches. However, final confirmation of the structure of the synthetic material was obtained by single-crystal X-ray analysis (see Experimental section for details). This revealed that the compound exists in the illustrated tautomeric form in the solid state. Furthermore, the specific rotation of this material was in good agreement with that reported for the natural product and thus confirming the illustrated absolute configuration for this sesquiterpenoid.

3. Conclusions

The first total synthesis of the hirsutene-type sesquiterpene (−)-connatusin A (**1**) has been achieved and serves 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 the extended biological evaluation of compounds **1** and **2**. 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 machine operating at 400 or 100 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 F_{254} 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.[13] with silica gel 60 (40–63 μm) 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 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 (DCM), acetonitrile, and benzene were dried using a Glass Contour solvent purification system, that is, based upon a technology originally described by Grubbs et al.[14] 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**.* A magnetically stirred solution of ketone **8**[3] (297 mg, 1.13 mol) in THF (3 mL) maintained at −78 °C was treated with LiHMDS (1.25 mL of a 1.0 M solution in THF, 1.25 mmol) and the resulting solution stirred at this temperature for 1 h. After this time the reaction mixture was allowed to warm to 18 °C and kept at this temperature for 0.25 h then re-cooled to −78 °C. Iodomethane (78 μL, 1.25 mmol) was then added to the reaction mixture and the ensuing solution was again allowed to warm to 18 °C, stirred at this temperature for 16 h then quenched with ammonium chloride (15 mL of a saturated aqueous solution) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an off-white solid. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.4 in 1:3 v/v ethyl acetate/hexane) then gave the *title compound **9*** (236 mg, 75%) as a white, crystalline solid, mp=131 °C; $[\alpha]_D$ −60.3 (c 1.0, $CHCl_3$); [found: $(M+Na)^+$, 299.1620. $C_{17}H_{24}O_3$ requires: $(M+Na)^+$, 299.1623]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.07 (d, J=10.0 Hz, 1H), 2.56 (q, J=7.6 Hz, 1H), 2.29–2.21 (m, 2H), 2.05 (s, 3H), 1.97–1.86 (m, 3H), 1.67 (dd, J=10.0 and 6.0 Hz, 1H), 1.33 (dd, J=13.6 and 6.8 Hz, 1H), 1.10 (s, 3H), 1.05 (d, J=8.0 Hz, 3H), 0.97 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 218.1, 170.7, 80.6, 65.0, 58.9, 49.4, 44.6, 43.1, 38.7, 38.6, 37.9, 36.8, 26.9, 21.9, 21.4, 16.1, 15.1; ν_{max} (KBr) 2969, 2871, 1718, 1448, 1366, 1245, 1039 cm^{-1}; MS (ESI) 299 [$(M+Na)^+$, 100%].

*4.2.2. Compound **10**.* A magnetically stirred solution of cyclopropane **9** (72 mg, 0.26 mmol) in benzene (8 mL) maintained at 18 °C was treated with AIBN (4 mg, 0.03 mmol) and Bu_3SnH (138 μL, 0.52 mmol). The resulting solution was heated at reflux for 1.5 h, cooled to 18 °C and treated with additional aliquots of AIBN (4 mg,

0.03 mmol) and Bu_3SnH (138 μL, 0.52 mmol) then reheated at reflux for 1.5 h. This process was repeated twice more then the reaction mixture was cooled and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f=0.5 in 1:3 v/v ethyl acetate/hexane) afforded the *title compound* ***10*** (36 mg, 80% at 65% conversion) as a white, crystalline solid, mp=77–78 °C; $[\alpha]_D$ −53.8 (*c* 1.1, $CHCl_3$); [found: $(M+Na)^+$, 301.1778. $C_{17}H_{26}O_3$ requires: $(M+Na)^+$, 301.1780]; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.93 (d, *J*=9.2 Hz, 1H), 2.76 (pentet, *J*=11.2 Hz, 1H), 2.50 (t, *J*=9.2 Hz, 1H), 2.42 (m, 1H), 2.31 (dd, *J*=18.8 and 7.2 Hz, 1H), 2.07 (s, 3H), 1.97 (dd, *J*=14.0 and 7.2 Hz, 1H), 1.85 (dd, *J*=13.2 and 9.2 Hz, 1H), 1.72 (ddd, *J*=14.0, 8.4 and 1.2 Hz, 1H), 1.62–1.54 (m, 2H), 1.17 (dd, *J*=13.6 and 10.0 Hz, 1H), 0.97 (s, 3H), 0.93 (d, *J*=6.4 Hz, 3H), 0.91 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.7, 170.6, 81.3, 54.4, 51.9, 51.5, 46.0, 43.3, 41.3, 39.3, 37.5, 26.5, 21.4, 20.7, 16.2, 8.0 (one signal obscured or overlapping); ν_{max} (KBr) 2931, 2872, 1740, 1463, 1374, 1240, 1035 cm^{-1}; MS (ESI) 301 [$(M+Na)^+$, 100%].

Concentration of fraction B (R_f=0.4 in 1:3 v/v ethyl acetate/hexane) afforded the starting cyclopropane **9** (25 mg, 35% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

4.2.3. Compound ***11****. Step i*: A magnetically stirred solution of ketone **10** (52 mg, 0.19 mmol) and 2,6-lutidine (206 μL, 1.14 mmol) in DCM (3 mL) maintained at 0 °C under nitrogen atmosphere was treated, dropwise, with TMSOTf (87 μL, 0.75 mmol). The ensuing mixture was left to stir at this temperature for 5 h before being warmed to 18 °C and quenched with deionized water (5 mL) then extracted with DCM (3×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the silyl enol ether derived from compound **10**. This material was used immediately in the next step of the sequence.

Step ii: A solution of silyl enol ether (66 mg, 0.19 mmol), obtained as described immediately above, in MeCN (1.5 mL) was added to a slurry of palladium(II) acetate (85 mg, 0.38 mmol) and *p*-benzoquinone (20 mg, 0.19 mmol) in MeCN (0.5 mL). The ensuing mixture was stirred at 18 °C for 18 h then diluted with Et_2O (15 mL) and filtered through a thin pad of Celite™ contained in a sintered glass funnel. The solids thus retained were washed with additional Et_2O (3×5 mL) and the combined filtrates concentrated under reduced pressure to give an orange-yellow oil. Subjection of this material to flash column chromatography (silica, 19:1 v/v DCM/ethyl acetate elution) and concentration of the relevant fractions (R_f=0.3 in 1:3 v/v ethyl acetate/hexane) then gave the *title product* ***11*** (40 mg, 77%) as a white, crystalline solid, mp=73–74 °C; $[\alpha]_D$ −18.0 (*c* 1.1, $CHCl_3$); [found: $(M+Na)^+$, 299.1621. $C_{17}H_{24}O_3$ requires: $(M+Na)^+$, 299.1623]; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72 (d, *J*=2.0 Hz, 1H), 5.08 (d, *J*=8.0 Hz, 1H), 2.91–2.77 (m, 2H), 2.34–2.26 (m, 2H), 2.13 (q, *J*=7.6 Hz, 1H), 2.08 (s, 3H), 1.97 (dd, *J*=12.8 and 8.0 Hz, 1H), 1.37 (q, *J*=6.8 Hz, 1H), 1.09 (s, 3H), 1.03 (d, *J*=6.8 Hz, 3H), 1.03 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.2, 192.4, 170.7, 121.6, 81.0, 56.9, 56.5, 52.1, 47.4, 45.9, 40.9, 33.0, 26.7, 21.7, 21.5, 21.2, 9.7; ν_{max} (KBr) 2925, 1736, 1709, 1640, 1383, 1237, 1047 cm^{-1}; MS (ESI) 299 [$(M+Na)^+$, 100%].

4.2.4. Compound ***12****.* A magnetically stirred solution of enone **11** (12 mg, 0.04 mmol) and $CeCl_3{\cdot}7H_2O$ (33 mg, 0.09 mmol) in methanol (1.5 mL) maintained at 0 °C under nitrogen atmosphere was treated with $NaBH_4$ (2 mg, 0.05 mmol). The ensuing mixture was left to stir for 3 h at 0 °C before being allowed to warm to 18 °C then slowly treated with deionized water (5 mL). After hydrogen evolution had ceased the reaction mixture was concentrated under reduced pressure and the residue extracted with DCM (4×10 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give compound ***12*** (12 mg, 99%) as a waxy solid, R_f=0.2 in 1:3 v/v ethyl acetate/hexane, $[\alpha]_D$ −52.3 (*c* 1.0, $CHCl_3$); [found: $(M+Na)^+$, 301.1785. $C_{17}H_{26}O_3$ requires: $(M+Na)^+$, 301.1780]; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.18 (s, 1H), 5.03 (d, *J*=8.8 Hz, 1H), 4.51 (dd, *J*=7.6 and 3.6 Hz, 1H), 2.84–2.72 (m, 1H), 2.44 (dd, *J*=15.2 and 8.4 Hz, 1H), 2.28 (dd, *J*=12.0 and 8.4 Hz, 1H), 2.07 (s, 3H), 1.87–1.79 (m, 2H), 1.64–1.57 (m, 2H), 1.01 (d, *J*=7.6 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 161.1, 120.6, 86.1, 80.9, 59.9, 57.4, 54.1, 47.0, 45.7, 41.0, 32.3, 26.8, 21.4, 21.3, 18.4, 11.7; ν_{max} (KBr) 3401, 2955, 2920, 2849, 1738, 1462, 1376, 1245, 1233, 1023 cm^{-1}; MS (ESI) 301 [$(M+Na)^+$, 98%], 201 (100).

4.2.5. Compound ***13****.* A magnetically stirred solution of allyl alcohol **12** (46 mg, 0.17 mmol) in THF (200 μL) containing deionized water (40 μL) was treated with osmium tetroxide (15 μL of a 0.2 μM solution in *tert*-butanol, 1 μmol) and NMO (4 mg, 0.07 mmol) and the resulting mixture stirred at 18 °C for 5 h then treated with Na_2SO_3 (5 mL of a saturated aqueous solution) and left to stir for 0.17 h before being extracted with ethyl acetate (4×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.4 in 3:1 v/v ethyl acetate/hexane) gave compound ***13*** (36 mg, 69%) as a white, crystalline solid, mp=68–71 °C; $[\alpha]_D$ +6.4 (*c* 1.0, $CHCl_3$); [found: $(M+Na)^+$, 335.1834. $C_{17}H_{28}O_5$ requires $(M+Na)^+$, 335.1834]; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.19 (d, *J*=9.2 Hz, 1H), 3.69 (dd, *J*=9.6 and 3.2 Hz, 1H), 3.60 (d, *J*=3.2 Hz, 1H), 3.50 (br s, 1H), 2.92 (br s, 1H), 2.64 (m, 1H), 2.37 (t, *J*=9.2 Hz, 1H), 2.10 (dd, *J*=14.4 and 9.6 Hz, 1H), 2.05 (s, 3H), 1.85 (br s, 1H), 1.79 (dd, *J*=12.8 and 9.2 Hz, 1H), 1.63 (dd, *J*=14.4 and 3.6 Hz, 1H), 1.49–1.42 (m, 1H), 1.39–1.33 (m, 1H), 0.99–0.97 (m, 6H), 0.88 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 88.0, 84.7, 81.9, 81.5, 55.7, 54.2, 46.8, 46.0, 45.6, 43.6, 36.0, 27.0, 21.4 (2), 21.3 (9), 12.2, 11.6; ν_{max} (KBr) 3441, 2960, 2919, 2872, 2850, 1738, 1717, 1463, 1368, 1243, 1093, 1033, 1004 cm^{-1}; MS (ESI) 335 [$(M+Na)^+$, 10%], 118 (100), 101 (60).

4.2.6. Compound ***14****.* A magnetically stirred solution of oxalyl chloride (24 μL, 0.28 mmol) in DCM (1.5 mL) maintained under argon atmosphere at −60 °C was treated, dropwise, with DMSO (44 μL, 0.61 mmol). The resulting solution was stirred at −60 °C for 0.17 h then treated, dropwise, with a solution of triol **13** (29 mg, 0.09 mmol) in DCM (1.5 mL). The ensuing mixture was stirred at −60 °C for 1 h, treated with Et_3N (129 μL, 0.93 mmol) and, after 0.5 h, warmed to ca. 5 °C before being poured in HCl (5 mL of a 2 M aqueous solution) and extracted with DCM (3×5 mL). The combined organic extracts were washed with water (1×5 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to a light-yellow oil. Subjection of this material to flash chromatography (silica, 3:1 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.7 in 3:1 v/v ethyl acetate/hexane) gave *compound* ***14*** (15 mg, 52%) as a white, crystalline solid, mp=137–138 °C; $[\alpha]_D$ −30.2 (*c* 1.0, $CHCl_3$); [found: $(M+Na)^+$, 331.1525. $C_{17}H_{24}O_5$ requires: $(M+Na)^+$, 331.1521]; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.23 (d, *J*=10.8 Hz, 1H), 2.84 (br s, 1H), 2.52 (t, *J*=10.0 Hz, 1H), 2.35 (dd, *J*=14.0 and 8.4 Hz, 1H), 2.18–2.02 (m, 1H), 2.10 (s, 3H), 1.95 (s, 3H), 1.79 (dd, *J*=13.6 and 9.2 Hz, 1H), 1.68 (dd, *J*=14.0 and 10.8 Hz, 1H), 1.39 (dd, *J*=13.6 and 3.6 Hz, 1H), 1.09 (s, 6H), 0.89 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.6, 170.6, 151.5, 145.9, 85.3, 81.2, 54.8, 52.2, 45.9, 44.2, 43.5, 35.0, 29.2, 24.2, 21.4, 16.1, 10.4; ν_{max} (KBr) 3369,

2918, 2850, 1738, 1713, 1653, 1455, 1368, 1239, 1083, 1040 cm^{-1}; MS (ESI) 331 [$(M+Na)^+$, 100%].

4.2.7. Compound ***1****.* A magnetically stirred solution of acetate **14** (18 mg, 0.06 mmol) in methanol/water (2.4 mL of a 5:1 v/v mixture) was treated with DOWEX-50WX-100 resin [~250 mg of material that had been rinsed successively with HCl (1 M aqueous solution), 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, ethyl acetate elution) and concentration of the appropriate fractions (R_f=0.4 in 3:1 v/v ethyl acetate/hexane) afforded (−)-connatusin A (**1**) (13 mg, 84%) as a white, crystalline solid, no mp, decomposition above 200 °C (lit.[1] mp=84–84 °C); $[\alpha]_D$−34.6 (*c* 1.0, $CHCl_3$) {lit.[1] $[\alpha]_D$ −36.0 (*c* 0.47, $CHCl_3$)}; [found: $(M-H)^-$, 265.1447. $C_{15}H_{22}O_4$ requires: $(M-H)^-$, 265.1440]; UV (MeOH) λ_{max} 269; ^{1}H NMR ($CDCl_3$, 400 MHz) δ see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 1; ν_{max} (KBr) 3392, 2957, 2924, 2853, 1740, 1707, 1647, 1463, 1378, 1081 cm^{-1}; MS (ESI) 265 [$(M-H)^-$, 25%], 247 (22), 59 (100).

4.3. Single-crystal X-ray analyses of compounds 1 and 10

4.3.1. Data for compound ***1****.* $C_{15}H_{22}O_4$, *M*=266.34, *T*=200 K, monoclinic, space group $P2_1$, *Z*=2, *a*=9.6924 (4), *b*=5.7342 (2), *c*=12.0831 (5) Å, β=94.738 (2)°; *V*=669.26 (5) $Å^3$, D_x=1.322 g cm^{-3}, 1309 unique data ($2\theta_{max}$=50°), *R*=0.027 [for 1241 reflections with $I>2.0\sigma(I)$]; *Rw*=0.069 (all data), *S*=1.00.

4.3.2. Data for compound ***10****.* $C_{17}H_{26}O_3\cdot C_8H_{12}N_2$, *M*=414.59, *T*=200 K, orthorhombic, space group $P2_12_12_1$, *Z*=4, *a*=7.6083 (1), *b*=12.7312 (2), *c*=24.8746 (3) Å; *V*=2409.42 (6) $Å^3$, D_x=1.143 g cm^{-3}, 3141 unique data ($2\theta_{max}$=55°), *R*=0.035 [for 2678 reflections with $I>2.0\sigma(I)$]; *Rw*=0.089 (all data), *S*=0.98.

4.3.3. Structure determination. Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[15] Structure solution was by direct methods (SIR92).[16] The structures of compounds **1** and **10** were refined using the CRYSTALS program package.[17]

The structure of compound **1** has been determined previously.[1] The present data were recorded at 200 K (rather than at room temperature) and the resultant $R[F^2>2\sigma(F^2)]$ value is 2.7% rather than 7.4%. The standard uncertainties in bond distances and angles are less than half of those reported previously.[1] The structure described here has considerably improved agreement factors and substantially better precision.

Crystallographic data (excluding structure factors) for compounds **1** and **10** have been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 827001 and 827000 for **1** and **10**, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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