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Total synthesis of the novel tricyclic sesquiterpene sulcatine G

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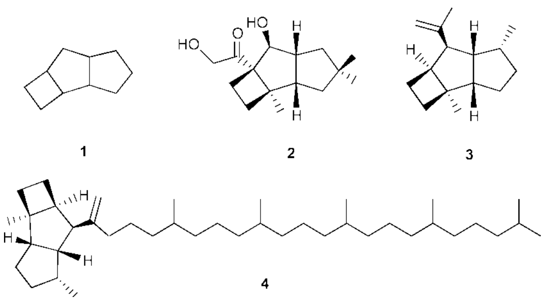
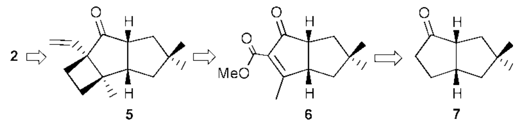
A synthetic approach to the tricyclic sesquiterpene sulcatine G, 2, bearing a novel tricyclo[6.2.0.0^{2,6}]decane framework, from commercially available 1,5-cod and leading to the first total synthesis of the natural product is described.

The tricyclo[6.2.0.0^{2,6}]decane framework **1**, constituted through the linear fusion of 4-5-5-membered carbocyclic rings, has been encountered only sporadically among the natural products. Among the very few known examples of terpenoid natural products based on this ring system are sulcatine G, **2**, from a *Basidiomycetes* fungi,[1] kelsoene **3** from a tropical marine sponge *Cymbastela hooperi*[2a] and liverwort *Ptychanthus striatus*[2b] and poduran **4** from the springtail *Podura aquatica*.[3]

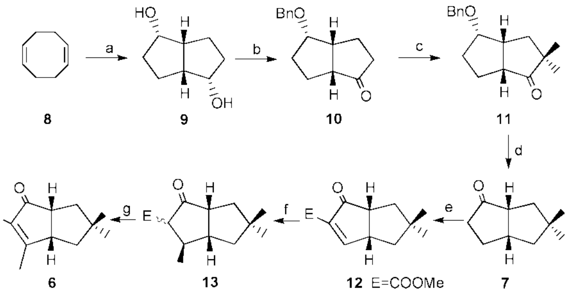


While these terpenes share the common *cis, anti, cis*-fused tricarbocyclic framework, they differ in the distribution of alkyl substitution and the level of functionalization. In an effort directed towards the synthesis of these novel natural products, we have recently accomplished the total synthesis of the hydrocarbon kelsoene **3** and established its absolute configuration.[4,5] Continuing our efforts in the area, we have turned our attention towards the uniquely functionalized, 4-5-5-fused tricarbocyclic sesquiterpene sulcatine G, **2**, which has also been shown to exhibit antifungal activity on *Cladosporium cladosporioides* and *C. cucumerinum*.[1] Herein, we report the *first* total synthesis of sulcatine G, **2** which fully confirms the stereostructure of the natural product established earlier[1] on the basis of NMR data.

Our synthetic approach to **2** was delineated through the retrosynthetic analysis indicated in Scheme 1. Accordingly, C_{15}-tricyclic vinyl ketone **5** or an equivalent compound, embodying the entire skeleton of **2** and the two adjacent bridgehead quaternary cabon centres, emerged as the advanced precursor in which key functional group transformations could be effected *en route* to the natural product. The tricyclic ketone **5** in turn could be accessed from the diquinane **7**[6] *via* the intermediacy of the bicyclic enone–ester **6**. The bicyclic ketone **7** has been prepared in a new sequence[7] emanating from the commercially available cycloocta-1,5-diene **8** (1,5-cod), Scheme 2.



Scheme 1



Scheme 2 *Reagents*: (a) i. $PdCl_2$, $Pb(OAc)_4$, AcOH, 70%, ii. KOH–MeOH, 95%; (b) i. NaH, BnBr, $Bu_4N^+I^-$, THF, 85%, ii. PCC, DCM, 92%; (c) $K^+{}^-O^tBu$, ^tBuOH, MeI, 90%; (d) i. $(CH_2SH)_2$, toluene-*p*-sulfonic acid, benzene, 96%, ii. Raney-Ni, EtOH, 90%, iii. PCC, DCM, 90%; (e) i. NaH, $(MeO)_2CO$, benzene, ii. NaH, PhSeCl, THF, iii. 30%H_2O_2, DCM, 66% (3 steps); (f) MeMgI, CuI, Et_2O, 96%; (g) i. NaH, PhSeCl, THF, ii. 30%H_2O_2, DCM, 50%.

C_2-Symmetric diquinane diol **9** was obtained from 1,5-cod in two steps involving Pd^{2+}-mediated transannular cyclization and base hydrolysis as reported previously.[8] Mono-protection of the hydroxy group and PCC oxidation in **9** led to **10**. α-*gem*-Dimethylation of **10** furnished **11**[9] in which the carbonyl group was deoxygenated *via* thioketal formation and Raney-Ni desulfurization to furnish the debenzylated bicyclic alcohol in excellent yield which was further oxidized with PCC to give **7**,[7,9] our main building-block for the synthesis of **2**, Scheme 2. A three step sequence from **7** involving α-carbomethoxylation, phenylselenation–selenoxide elimination delivered the enone–ester **12**.[9] 1,4-Addition of methylmagnesium iodide to **12** in the presence of Cu(I) installed the third methyl group and led to a diastereomeric mixture **13** (80:20)[10] which was directly transformed to the enone–ester **6**[9] by repeating the phenylselenation–selenoxide elimination sequence, Scheme 2.

The diquinane enone–ester **6**† had been crafted for the annulation of a four membered ring through the olefin-enone [2 + 2]-photocycloaddition protocol. Irradiation of a mixture of **6** and (*E*)-1,2-dichloroethylene furnished the [2 + 2]-addition product **14**[9] as a mixture (30:70) of *cis*- and *trans*-1,2-dichloro isomers, respectively, in excellent yield. The two stereoisomers could be separated for characterization purposes but it was not necessary for the further transformations. The photocycloaddition to **6** proceeded exclusively from the *exo*-face of the diquinane moiety to generate the requisite *cis, anti, cis* ring junction stereochemistry in the natual product **2**. DIBAL-H reduction of **14** followed by eliminative dehalogenation with sodium naphthalenide furnished an epimeric mixture of tricyclic cyclobutene diols **15a,b** (55:45), Scheme 3.[9] The major isomer **15a** has the hydroxy group stereochemistry as in the natural product and is derived from the vicinal coupling (J = 8.4 Hz) between the *trans* disposed H6–H7 protons (*cf.* J = 9 Hz in sulcatine G, **2**).[1] In the minor isomer **15b**, coupling between *cis* disposed H6–H7 protons was 6.3 Hz. Catalytic hydrogenation of **15a,b** readily furnished **16a,b**.[9] At this stage, the two hydroxy groups in the required epimer **16a** needed to be differentiated. This was achieved through sequential protection of the primary and secondary hydroxy groups as the ^{t}butyldimethylsilyl (TBDMS) ether and acetate groups, respectively, and

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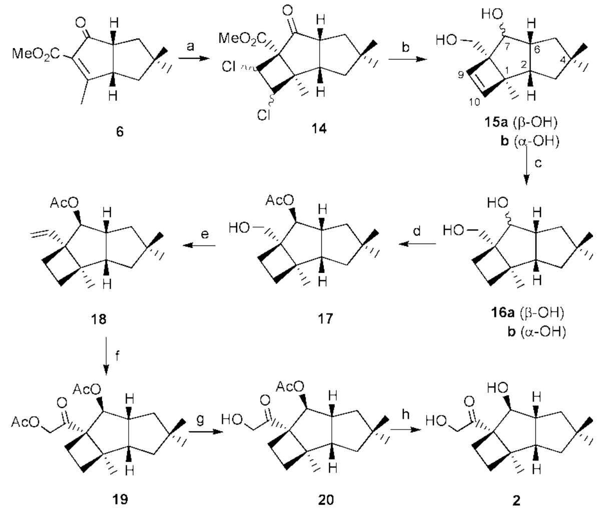

Scheme 3 *Reagents*: (a) (*E*)-1,2-dichloroethylene, C_6H_{12}, $h\nu$, pyrex, 94%; (b) i. DIBAL-H, DCM, ii. sodium naphthalenide, DME, (**15a**:**15b** = 55:45), 63% (2 steps); (c) H_2, 10% Pd/C, EtOAc, 92%; (d) i. ${}^tBDMS$-Cl, imidazole, DMAP, DCM, 91%; ii. Ac_2O, DMAP, DCM, 100%; iii. 2N H_2SO_4, MeOH–H_2O, 87%; (e) i. PCC, DCM, 90%, ii. $MePPh_3I$, KO^tBu, THF, 92%; (f) i. OsO_4, *N*-methylmorpholine oxide Me_2CO–H_2O, 85%; ii. Ac_2O, DMAP, 100%; iii. PCC, DCM, 75%; (g) $Sc(OTf)_3$, MeOH–H_2O, 80%; (h) KOH–MeOH, 70%.

further deprotection of the TBDMS group delivered the hydroxy–acetate **17**.[9] Oxidation of the primary hydroxy group in **17** with PCC to the aldehyde functionality and Wittig methylenation delivered **18**, Scheme 3. Although **18** could be readily elaborated to the targeted advanced precursor **5**[9] (Scheme 1) of sulcatine G, **2**, tactical considerations at this stage required further processing through **18**. Consequently, **18** was dihydroxylated and the primary hydroxy group in the resulting diol was selectively protected as the acetate. Further oxidation of the secondary hydroxy group delivered sulcatine G diacetate **19**, spectroscopically identical with the diacetate reported from the natural product **2**.[1,9] Transformation of **19** to the natural product presented some problems but could be accomplished in two steps involving $Sc(OTf)_3$ mediated hydrolysis of the α-ketoacetoxy group[11] to monoacetate **20** and further exposure to base furnished sulcatine G, **2**, Scheme 3.[9] Our synthetic **2** was found to be exactly identical with the natural product spectroscopically (IR, ^{1}H and ^{13}C NMR).[1]

In summary, we have outlined a stereocontrolled synthesis of the sesquiterpene sulcatine G, **2**, from a readily available starting material (1,5-cod), which also unambiguously secures the stereostructure of the natural product.

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Notes and references

† The IUPAC name for diquinane is bicyclo[3.3.0]octane.

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6 For a recent review on the synthesis of polyquinane natural products, see: G. Mehta and A. Srikrishna, *Chem. Rev.*, 1997, **97**, 671.
7 For an earlier synthesis of diquinane **7**, see: J. Cossy, D. Belotti and J.-P. Pete, *Tetrahedron Lett.*, 1987, **28**, 4547.
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9 All new compounds reported here were duly characterized on the basis of spectral (IR, ^{1}H and ^{13}C NMR) and analytical data. *J* values are measured in Hz. Selected spectral data: **15a**: IR (neat) ν_{max} 3313, 3047, 1652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26 (d, *J* 2.7, 1H), 6.19 (d, *J* 3.0, 1H) 3.84 (d, *J* 8.4, 1H), 3.81 (br s, 2H), 2.48–2.23 (m, 2H), 1.93 (m, 2H), 1.76 (dd, J_1 13.5, J_2 8.1, 1H), 1.60 (d, *J* 13.5, 1H), 1.40–1.30 (m, 1H), 1.13 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 146.1, 133.7, 82.8, 66.2, 62.9, 55.8, 49.3, 46.9, 44.0, 43.9, 40.8, 31.5, 30.6, 16.1; EIMS (20 eV) *m*/*z* 204 (M^+ − 18); **15b**: IR (neat) ν_{max} 3365, 3032, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.10 (d, *J* 3.0, 1H), 5.92 (d, *J* 3.0, 1H), 3.97 ($\frac{1}{2}$ ABq, *J* 11.7, 1H), 3.92 ($\frac{1}{2}$ ABq, *J* 11.7, 1H), 3.97 (d, *J* 6.3, 1H), 2.85–2.75 (m, 1H), 2.47–2.38 (m, 1H), 1.67–1.22 (series of m, 4H), 1.18 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 145.9, 135.8, 77.3, 65.1, 64.9, 57.3, 50.7, 48.2, 43.8, 40.7, 38.4, 30.9, 29.5, 16.4; EIMS (20 eV) *m*/*z* 204 (M^+ − 18); **16a**: IR (neat) ν_{max} 3326 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (d, *J* 9.3, 1H), 3.81 ($\frac{1}{2}$ ABq, *J* 10.2, 1H), 3.73 ($\frac{1}{2}$ ABq, *J* 10.8, 1H), 2.61–2.52 (m, 1H), 2.23–2.00 (series of m, 2H), 1.90–1.52 (series of m, 6H), 1.35 (dd, J_1 12.6, J_2 7.2, 1H), 1.12 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 85.4, 68.5, 54.7, 52.6, 49.4, 45.4, 45.0, 44.0, 40.5, 31.8, 31.6, 30.6, 19.2, 17.0; EIMS (20 eV) *m*/*z* 206 (M^+ − 18); **16b**: IR (neat) ν_{max} 3366 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 ($\frac{1}{2}$ ABq, *J* 11.4, 1H), 3.85 ($\frac{1}{2}$ ABq, *J* 11.4, 1H), 3.82 (d, *J* 5.7, 1H), 2.99–2.90 (m, 1H), 2.42–2.32 (m, 1H), 1.81–1.17 (series of m, 8H), 1.12 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 83.1, 66.1, 58.0, 55.0, 48.1, 46.1, 44.1, 40.2, 38.7, 31.1, 30.4, 29.1, 23.1, 20.1; EIMS (20 eV) *m*/*z* 206 (M^+ − 18); **18**: IR (neat) ν_{max} 3082, 1738, 1635 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (AB*X*, J_1 17.2, J_2 10.8, 1H), 5.16 (d, *J* 9.3, 1H), 5.10 (*A*BX, J_1 10.8, J_2 1.5, 1H), 4.98 (*A*BX, J_1 17.1, J_2 1.2, 1H), 2.86–2.76 (m, 1H), 2.33–2.23 (m, 1H), 2.10–1.66 (series of m, 6H), 2.01 (s, 3H), 1.39 (dd, J_1 12.3, J_2 7, 1H), 1.20–1.10 (m, 1H), 1.14 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 170.9, 141.9, 113.5, 86.2, 55.3, 54.5, 49.0, 48.5, 44.8, 43.8, 40.5, 31.7, 31.5, 30.6, 21.2, 20.4, 17.1; EIMS (20 eV) *m*/*z* 262 (M^+); **19**: IR (neat) ν_{max} 1736, 1715; ^{1}H NMR (300 MHz, acetone-d_6): δ 5.23 (d, *J* 16.8, 1H), 4.97 (d, *J* 8.7, 1H), 4.66 (d, *J* 16.8, 1H), 3.03–2.94 (m, 1H), 2.50–2.39 (m, 1H), 2.34–2.25 (m, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 2.01–1.78 (series of m, 4H), 1.65 (dd, J_1 13.8, J_2 2.4, 1H), 1.53 (t, *J* 12.6, 1H), 1.40–1.31 (m, 1H), 1.15 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75.0 MHz, acetone-d_6): δ 203.8, 171.5, 170.3, 88.2, 68.3, 63.0, 55.4, 53.9, 50.3, 45.5, 44.0, 41.0, 31.8, 31.3, 30.8, 21.0, 20.6, 20.4, 14.5.
10 The major isomer in **13** is expected to have β-methyl and α-carbomethoxy groups in *trans* disposition through sequential addition and protonation from the convex face. However, the stereochemistry of **13** is inconsequential in the context of the further steps in the synthesis.
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