

Enantioselective total synthesis of the novel tricyclic sesquiterpene (–)-sulcatine G. Absolute configuration of the natural product

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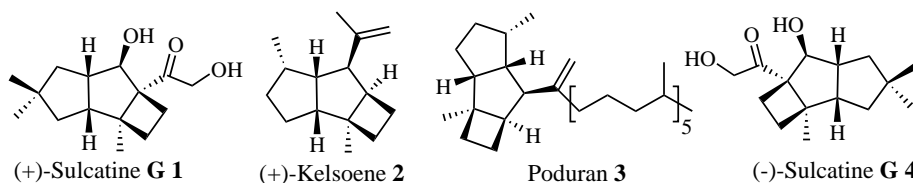
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Abstract—An enantioselective total synthesis of (–)-sulcatine G **4** from the readily available (+)-diquinane diol **6** has been accomplished. This leads to the establishment of the absolute configuration of the natural product (+)-sulcatine G as **1**.

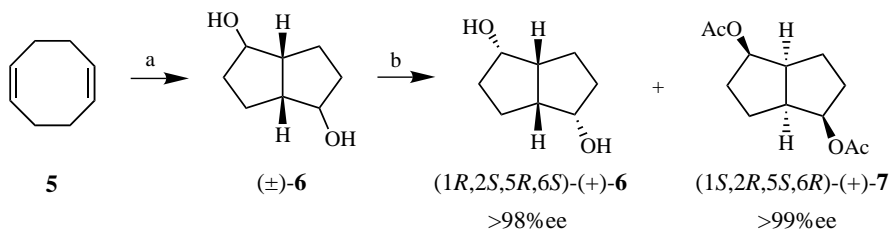
During the past decade, novel terpene skeleta embodying the 4-5-5 ring fused tricyclic core have been encountered in Nature from diverse sources. Among the very few known examples of terpenoid natural products bearing this ring system are sulcatine G **1** from a *Basidiomycetes* fungi,¹ kelsoene **2** from a tropical marine sponge *Cymbastela hooperi*,^{2a} liverworts *Ptychanthus striatus*,^{2b,c} *Calypogeia muelleriana*^{2d} and *Tritomaria quinquedentata*^{2e} and poduran **3** from the springtail *Podura aquatica*.³ The structural novelty and interesting biosynthetic origin of these natural products have aroused considerable synthetic interest in the past few years.^{4,5} We too have been enticed by these natural products and have accomplished the total synthesis of racemic, (+)- and (–)-kelsoene **2**.^{4a–c} Continuing our efforts in the area, a total synthesis of racemic sulcatine G **1** has been reported recently by us,⁵ fully securing its formulation which had been earlier deduced¹ mainly from the analysis of the NMR data. However, the absolute configuration of sulcatine G remains unknown as the functionality profile of the natural product does not permit ready recourse to chiro-optical methods of absolute configuration determination. Herein, we wish to describe an enantioselective synthesis of (–)-sulcatine G **4**, which establishes the absolute configuration of the naturally occurring (+)-sulcatine G as **1**.

We have recently shown that *endo,endo-cis*-bicyclo[3.3.0]octane-2,6-diol *rac*-**6**, obtained in two steps from commercially available 1,5-cyclooctadiene **5** via Pd²⁺-mediated transannular diacetoxylation and hydrolysis,⁶ on lipase-catalyzed enantiomer selective transesterification in an organic medium furnished diol (+)-**6** (>98% ee) and diacetate (+)-**7** (>99% ee) in preparatively useful yields (Scheme 1).^{4c} For our projected enantioselective synthesis of sulcatine G, diol (+)-**6** was employed and elaborated to diquinane ketone (–)-**9**, through the intermediacy of (–)-**8**, as described by us recently⁵ (Scheme 2).⁷ This is the first enantioselective preparation of (–)-**9**, which in racemic form has been previously employed in the synthesis of triquinane natural products⁸ and may find further applications in chiral synthesis of terpenoid natural products.

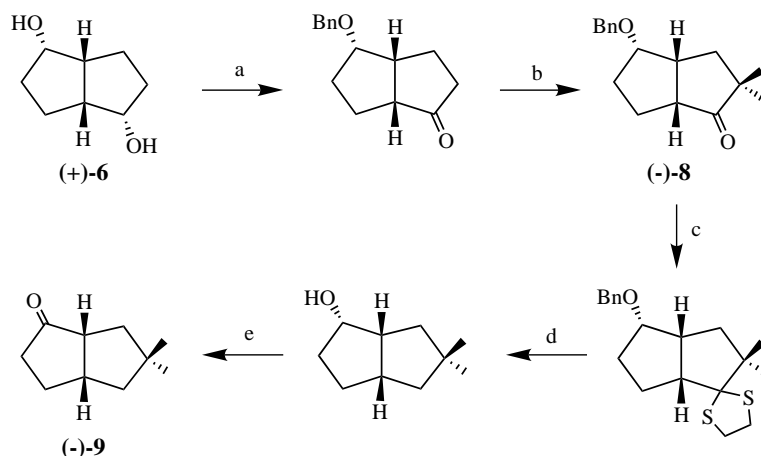
Diquinane (–)-**9** was further elaborated to the α -carbomethoxycyclopentenone (–)-**10** as shown in Scheme 3.⁷ Further evolution of (–)-**10** to the tricyclic bridgehead vinyl compound (–)-**11**, involved [2+2]-photocycloaddition as a pivotal step to append the cyclobutane ring and generate the desired 4-5-5 fused tricyclic framework. With tricyclic (–)-**11** having all the 15-carbons of the natural product in hand, the remaining task was to harness the vinyl group to access the oxy-func-



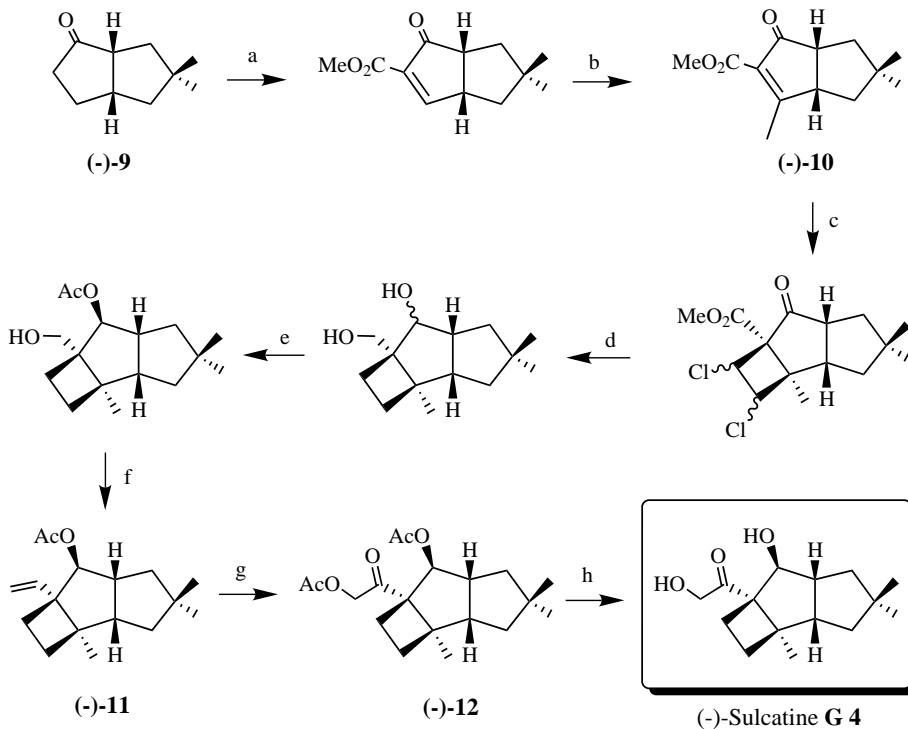
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Scheme 1. Reagents and conditions: (a) i. PdCl₂, Pb(OAc)₄, AcOH, rt, 72 h, 70%; ii. KOH, MeOH, rt, 3 h, 95%; (b) vinyl acetate, Amano lipase PS-30, ^tBuOMe, rt, 6 days, 82%.



Scheme 2. Reagents and conditions: (a) i. NaH, BnBr, Bu₄N⁺I⁻, THF, rt, 12 h, 87%; ii. PCC, DCM, rt, 94%; (b) KO^tBu, ^tBuOH, MeI, 0°C–rt, 8 h, 91%; (c) i. (CH₂SH)₂, PTSA, benzene, 96%; (d) Raney-Ni, EtOH, reflux, 6 h, 92%; (e) PCC, DCM, rt, 3 h, 90%.



Scheme 3. Reagents and conditions: (a) i. NaH, (MeO)₂CO, benzene, reflux, 5 h, 85%; ii. NaH, PhSeCl, THF, 0°C, 15 min; iii. 30% H₂O₂, DCM, 0°C, 15 min, 82% (two steps); (b) i. MeMgI, CuI, Et₂O, -10°C, 2 h, 96%; ii. NaH, PhSeCl, THF, 0°C, 15 min; iii. 30% H₂O₂, DCM, 0°C, 15 min, 50%, (two steps); (c) *trans*-1,2-dichloroethylene, C₆H₁₂, *hv*, Pyrex, rt, 6 h, 95%; (d) i. DIBAL-H, DCM, rt, 3 h, ii. sodium naphthalenide, DME, rt, 1 h; iii. H₂, PtO₂, EtOAc, 1 h, 60% (three steps); (e) i. ^tBDMS-Cl, imidazole, DMAP, DCM, 8 h, rt, 92%; ii. Ac₂O, DMAP, DCM, rt, 20 h, 100%; iii. 2*N* H₂SO₄, MeOH–H₂O (4:1), rt, 2 h, 90%; (f) i. PCC, DCM, rt, 2 h, 91%; ii. MePPh₃I, KO^tBu, THF, 0°C, 10 min, 92%; (g) i. OsO₄, NMMO, Me₂CO–H₂O (4:1), rt, 2 h, 86%; ii. Ac₂O, DMAP, DCM, 0°C, 30 min, 100%; iii. PCC, DCM, rt, 6 h, 77%; (h) i. Sc(OTf)₃, MeOH–H₂O (4:1), 47°C, 8 h; ii. 8% KOH–MeOH, -10°C, 3 h, 61% (two steps).

tionalization present in the natural product and sulcatine G diacetate (-)-**12** was readily realized, Scheme 3.⁷ Finally, acetate hydrolysis as reported previously⁵ furnished (-)-sulcatine G **4**, $[\alpha]_D -40$ (*c* 0.25, CHCl₃), which was spectroscopically identical with the natural product but had opposite specific rotation to that reported for the naturally occurring sulcatine G **1** $[\alpha]_D +44.5$ (*c* 0.15, CHCl₃).¹ This established the absolute configuration of the natural product as **1**.

In summary, we have outlined a stereo- and enantiocontrolled synthesis of the sesquiterpene (-)-sulcatine G **4** from a readily available chiral diquinane diol (+)-**6**, which unambiguously establishes the absolute configuration of the natural product as depicted in **1**. Since, sulcatine G (+)-**1** is biogenetically related to illudins and related sesquiterpenoids which are also found in *Basidiomycetes* fungi, determination of the absolute configuration of **1** has a bearing on the absolute configuration of other members of this group.

Acknowledgements

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