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

Goverdhan Mehta* and K. Sreenivas

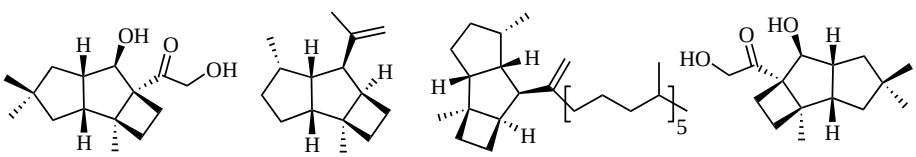
*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

**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 tricarbocyclic 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 deduced[1] 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**.

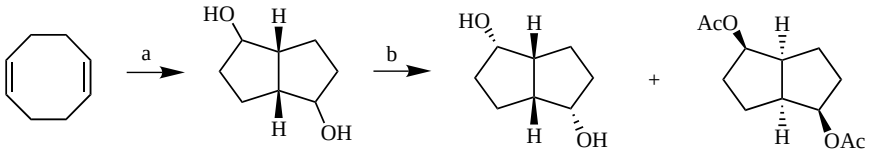
We have recently shown that *endo*,*endo*-*cis*-bicyclo[3.3.0]octane-2,6-diol *rac*-**6**, obtained in two steps from commercially available 1,5-cyclooctadiene **5** via $Pd^{2+}$-mediated transannular diacetoxylation and hydrolysis,[6] on lipase-catalyzed enantiomer selective transesterification in 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 recently[5] (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 products[8] 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-



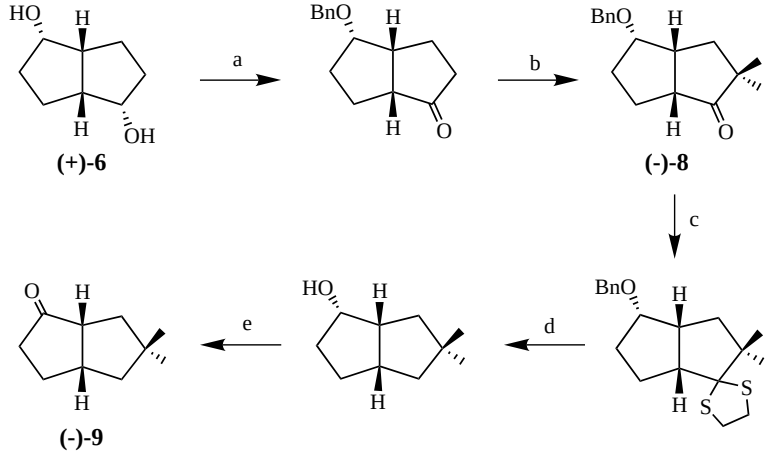

(+)-Sulcatine **G 1** (+)-Kelsoene **2** Poduran **3** (-)-Sulcatine **G 4**

* Corresponding author.



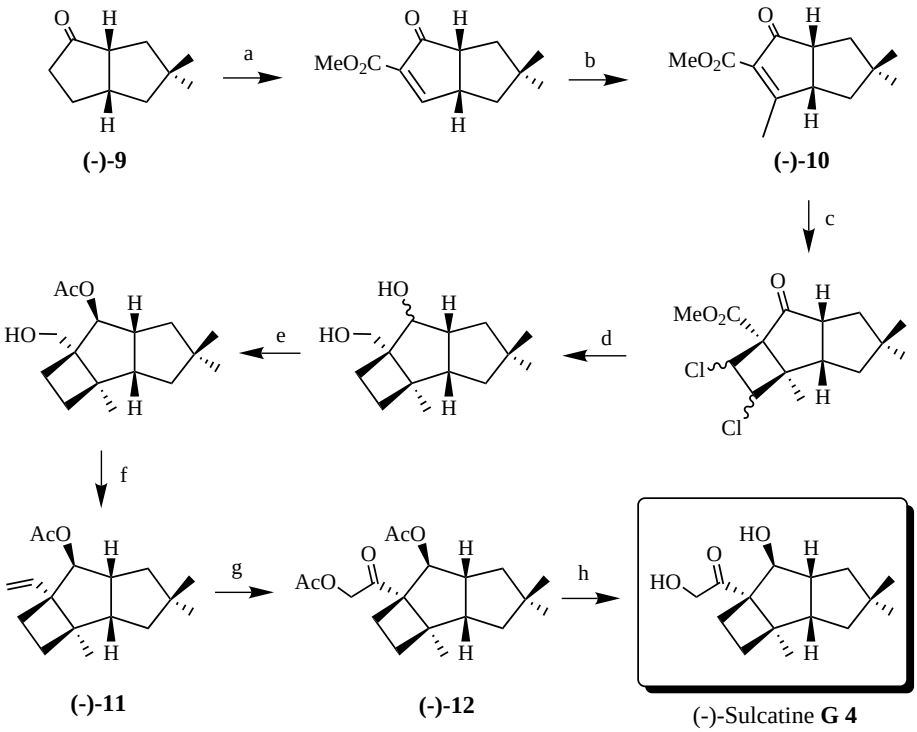

**5** (±)-**6** (1*R*,2*S*,5*R*,6*S*)-(+)-**6** >98%ee (1*S*,2*R*,5*S*,6*R*)-(+)-**7** >99%ee

**Scheme 1.** *Reagents and conditions*: (a) i. $PdCl_2$, $Pb(OAc)_4$, AcOH, rt, 72 h, 70%; ii. KOH, MeOH, rt, 3 h, 95%; (b) vinyl acetate, Amano lipase PS-30, $^t$BuOMe, rt, 6 days, 82%.




**(+)-6** **(-)-8** **(-)-9**

**Scheme 2.** *Reagents and conditions*: (a) i. NaH, BnBr, $Bu_4N^+I^-$, THF, rt, 12 h, 87%; ii. PCC, DCM, rt, 94%; (b) KO$^t$Bu, $^t$BuOH, MeI, 0°C–rt, 8 h, 91%; (c) i. $(CH_2SH)_2$, PTSA, benzene, 96%; (d) Raney-Ni, EtOH, reflux, 6 h, 92%; (e) PCC, DCM, rt, 3 h, 90%.




**(-)-9** **(-)-10** **(-)-11** **(-)-12** (-)-Sulcatine **G 4**

**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% $H_2O_2$, DCM, 0°C, 15 min, 82% (two steps); (b) i. MeMgI, CuI, $Et_2O$, −10°C, 2 h, 96%; ii. NaH, PhSeCl, THF, 0°C, 15 min; iii. 30% $H_2O_2$, DCM, 0°C, 15 min, 50%, (two steps); (c) *trans*-1,2-dichloroethylene, $C_6H_{12}$, *hv*, Pyrex, rt, 6 h, 95%; (d) i. DIBAL-H, DCM, rt, 3 h, ii. sodium naphthalenide, DME, rt, 1 h; iii. $H_2$, $PtO_2$, EtOAc, 1 h, 60% (three steps); (e) i. $^t$BDMS-Cl, imidazole, DMAP, DCM, 8 h, rt, 92%; ii. $Ac_2O$, DMAP, DCM, rt, 20 h, 100%; iii. 2N $H_2SO_4$, MeOH–$H_2O$ (4:1), rt, 2 h, 90%; (f) i. PCC, DCM, rt, 2 h, 91%; ii. $MePPh_3I$, KO$^t$Bu, THF, 0°C, 10 min, 92%; (g) i. $OsO_4$, NMMO, $Me_2CO$–$H_2O$ (4:1), rt, 2 h, 86%; ii. $Ac_2O$, DMAP, DCM, 0°C, 30 min, 100%; iii. PCC, DCM, rt, 6 h, 77%; (h) i. $Sc(OTf)_3$, MeOH–$H_2O$ (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 previously[5] furnished (−)-sulcatine G **4**, $[\alpha]_D$ −40 (*c* 0.25, $CHCl_3$), 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, $CHCl_3$).[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

We thank JNCASR for the financial support. One of us (K.S.) thanks UGC for the award of a research fellowship.

## References

1. Arnone, A.; Nasini, G.; Vajna de Pava, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2723.
2. (a) Konig, G.; Wright, A. D. *J. Org. Chem.* **1997**, *62*, 3837; (b) Nabeta, K.; Yamamoto, K.; Hashimoto, M.; Koshino, H.; Funatsuki, K.; Katoh, K. *Chem. Commun.* **1998**, 1485; (c) Hashimoto, T.; Ikeda, H.; Takaoka, S.; Tanaka, M.; Asakawa, Y. *Phytochemistry* **1999**, *52*, 501; (d) Warmers, U.; Wihstutz, K.; Bulow, N.; Fricke, C.; Konig, W. A. *Phytochemistry* **1998**, *49*, 1723; (e) Warmers, U.; Konig, W. A. *Phytochemistry* **1999**, *52*, 1519.
3. Schulz, S.; Messer, C.; Dettner, K. *Tetrahedron Lett.* **1997**, *38*, 2077.
4. (a) Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **1999**, *40*, 4877; (b) Mehta, G.; Sreenivas, K. *Synlett* **1999**, 555; (c) Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **2001**, *42*, 2855; (d) Piers, E.; Orellana, A. *Synthesis* **2001**, 2138; (e) Fietz-Razavian, S.; Schulz, S.; Dix, I.; Jones, P. G. *Chem. Commun.* **2001**, 2154.
5. Mehta, G.; Sreenivas, K. *Chem. Commun.* **2001**, 1892.
6. (a) Henry, P. M.; Davies, M.; Ferguson, G.; Philips, S.; Restivo, R. *Chem. Commun.* **1974**, 112; (b) Mehta, G.; Rao, K. V. *Ind. J. Chem.* **1991**, *30B*, 457.
7. All new compounds reported here were duly characterized on the basis of spectroscopic (IR, $^1H$ and $^{13}C$ NMR) and analytical data and their specific rotations were determined.
8. Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron Lett.* **1987**, *28*, 4547. For a recent review on the synthesis of polyquinane natural products, see: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.