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 muelleriana2d and Tritomaria quinquedentata2e 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). 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. 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-

* Corresponding author.
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, 'BuOMe, 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'Bu, 'BuOH, MeI, 0°C–rt, 8 h, 91%; (c) i. (CH₃SH)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. MeMgl, 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. BDMS-Cl, imidazole, DMAP, DCM, 8 h, rt, 92%; ii. Ac₂O, DMAP, DCM, rt, 20 h, 100%; iii. 2N H₂SO₄, MeOH–H₂O (4:1), rt, 2 h, 90%; (f) i. PCC, DCM, rt, 2 h, 91%; ii. MePPh₃I, KO'Bu, THF, 0°C, 10 min, 92%; (g) i. OsO₄, NMMO, Me₃CO–H₂O (4:1), rt, 2 h, 85%; ii. Ac₂O, DMAP, DCM, 0°C, 30 min, 100%; iii. PCC, DCM, rt, 6 h, 77%; (h) i. Sc(O Tf)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. Finally, acetate hydrolysis as reported previously4 furnished ($-$)-sulcatine G 4, $[\alpha]_D -40 \ (c \ 0.25, \text{CHCl}_3)$, which was spectroscopically identical with the natural product but had opposite specific rotation to that reported for the naturally occurring sulcatine G 1 $[\alpha]_D +44.5 \ (c \ 0.15, \text{CHCl}_3)$. 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

7. All new compounds reported here were duly characterized on the basis of spectroscopic (IR, 1H and 13C NMR) and analytical data and their specific rotations were determined.