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An enantiodivergent route to α-cuparenone utilizing chiral cyclopentenol having a latent *meso* structure

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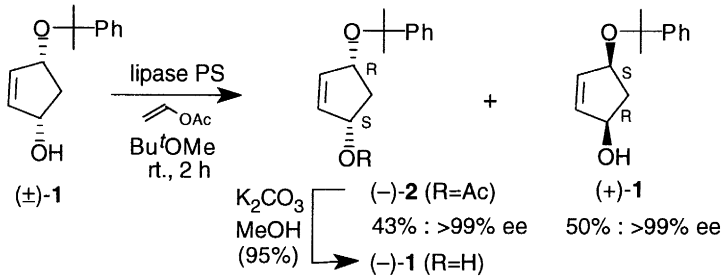
Abstract

An efficient enantiodivergent route to α-cuparenone, a sesquiterpene isolated in both enantiomeric forms, has been developed utilizing a chiral cyclopentanoid starting material having a latent *meso* structure.

Keywords: cyclopentanones; enantiocontrol; diastereoselection; hydroxylation; terpenes and terpenoids.

Recently, we obtained[1] enantiopure (*cis*-1,4)-4-cumyloxy-2-cyclopenten-1-ol **1** in both enantiomeric forms in excellent yields via resolution of the racemic alcohol (±)-**1** under lipase-mediated kinetic transesterification conditions (Scheme 1). Since the alcohol **1** has a latent *meso* structure, both of the enantiomers may be utilized as a common chiral precursor capable of carrying out either enantiodivergent or enantioconvergent synthesis if its hydroxy and cumyloxy functionalities can be chemically discriminated. We wish to report here an enantiodivergent route to α-cuparenone[2,3] **18**, a sesquiterpene occurring in both enantiomeric forms in nature,[4] where the single enantiomer (−)-**1** plays a double role.



Scheme 1.

The enantiopure alcohol (−)-**1** was first transformed into the *tert*-butyldimethylsilyl (TBS) ether (−)-**3**, $[\alpha]_D^{31}$ −47.01 (*c* 1.00, $CHCl_3$). Catalytic dihydroxylation[5] of (−)-**3** occurred diastereoselectively

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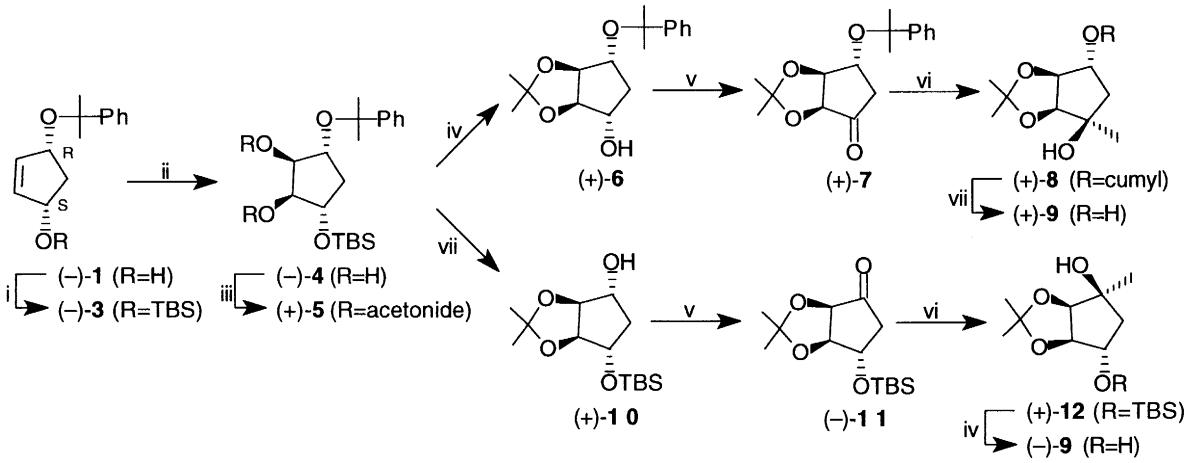
from the opposite side of the 1,4-substituents to give the single diol (−)-**4**, mp 48–49°C, $[\alpha]_D^{30}$ −10.25 (*c* 0.75, $CHCl_3$), which was converted into the acetonide (+)-**5**, $[\alpha]_D^{30}$ +20.76 (*c* 0.95, $CHCl_3$), under standard conditions.

Desilylation of (+)-**5** with tetrabutylammonium fluoride (TBAF) gave the cyclopentanol (+)-**6**, mp 110–111°C, $[\alpha]_D^{29}$ +19.75 (*c* 0.75, $CHCl_3$). Although (+)-**6** suffered considerable decomposition under standard oxidation conditions, it produced the ketone (+)-**7**, mp 98–99°C, $[\alpha]_D^{29}$ +144.15 (*c* 0.92, $CHCl_3$), excellently, under Dess–Martin conditions.[6] Despite its double β-oxyketone structure, the (+)-**7** obtained was found to be quite stable under ordinary conditions. Reaction of (+)-**7** with methyllithium in the presence of cerium(III) chloride[7] occurred diastereoselectively from the convex face to give the tertiary alcohol (+)-**8**, $[\alpha]_D^{31}$ +36.67 (*c* 0.92, $CHCl_3$), as the single product. Removal of the cumyl group of (+)-**8** under hydrogenolysis conditions proceeded without difficulty to afford the cyclopentanediol (+)-**9**, mp 88–89°C, $[\alpha]_D^{32}$ +11.74 (*c* 0.95, $CHCl_3$). Overall yield of (+)-**9** from (−)-**1** was 55% in seven steps.

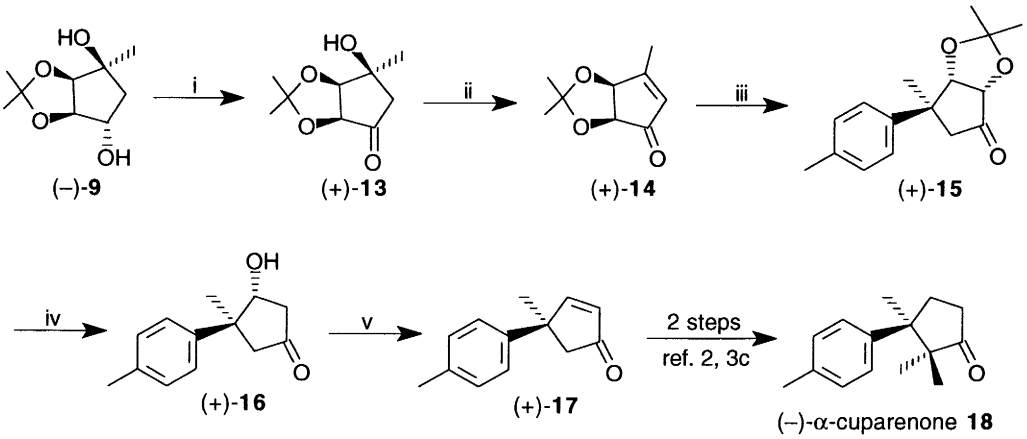
On the other hand, (+)-**5** was first subjected to hydrogenolysis to give the siloxy-alcohol (+)-**10**, $[\alpha]_D^{25}$ +5.52 (*c* 1.02, $CHCl_3$). Dess–Martin conditions allowed facile oxidation of (+)-**10** to give the ketone (−)-**11**, $[\alpha]_D^{28}$ −136.59 (*c* 1.22, $CHCl_3$), without initiation of β-elimination. Reaction of (−)-**11** with methyllithium in the presence of cerium(III) chloride as above gave, diastereoselectively, the tertiary alcohol (+)-**12**, $[\alpha]_D^{29}$ +0.65 (*c* 1.30, $CHCl_3$), which, on desilylation by TBAF, afforded the enantiomeric diol (−)-**9**, mp 88–89°C, $[\alpha]_D^{28}$ −11.16 (*c* 1.01, $CHCl_3$). Overall yield of (−)-**9** from (−)-**1** was 61% in seven steps. It was noted that the 1,2-addition occurred stereoselectively from the opposite side of the 2,3-acetonide functionality in both (+)-**7** and (−)-**11** irrespective of the presence of a bulky substituent on the convex face, respectively (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) TBSCl, imidazole, DMF (95%); (ii) OsO_4 (cat.), NMO, 50% aq. THF (90%); (iii) 2,2-dimethoxypropane, PPTS (cat.), CH_2Cl_2 (99%); (iv) TBAF, THF (93% for **6** and 88% for (−)-**9**); (v) Dess–Martin oxidation (96% for **7** and 97% for **11**); (vi) MeLi, $CeCl_3$, THF, −78°C (86% for **8** and 88% for **12**); (vii) H_2, 10% Pd–C, $CHCl_3$ (cat.), AcOEt (85% for (+)-**9** and 96% for **10**)

Having accomplished the enantiodivergent transformation of (−)-**1** into both enantiomeric diols (+)- and (−)-**9**, synthesis of α-cuparenone (−)-**18** was next examined using one of the enantiomers, (−)-**9**, to establish an enantiodivergent synthesis in the formal sense. Thus, oxidation of (−)-**9** with pyridinium chlorochromate (PCC) in dichloromethane proceeded neatly to give the β-hydroxyketone (+)-**13**, mp 72°C, $[\alpha]_D^{28}$ +189.61 (*c* 1.19, $CHCl_3$), without initiation of β-elimination. The generation of the tertiary β-hydroxyketone (+)-**13** in a stable form was synthetically of interest as it allows further modification at

this stage if such is considered desirable. Facile dehydration occurred to give the enone (+)-**14**, $[\alpha]_D^{25}$ +20.71 (*c* 1.03, $CHCl_3$), when (+)-**13** was warmed in acetic acid at 40°C. Treatment of (+)-**14** with a Grignard reagent in the presence of copper(I) bromide and trimethylsilyl chloride[8] allowed convex-face selective 1,4-addition to yield the single cyclopentanone (+)-**15**, $[\alpha]_D^{28}$ +178.14 (*c* 1.08, $CHCl_3$), carrying a benzylic quaternary stereogenic center. Conversion of (+)-**15** into the known enone (+)-**17**, serving as the key intermediate of (−)-α-cuparenone **18**, was carried out efficiently in a sequential two-step reaction involving the reductive cleavage of the α-oxyketone functionality using aluminum amalgam.[9] Thus, treatment of (+)-**15** with aluminum amalgam in ethanol allowed facile α-cleavage to give the β-hydroxyketone (+)-**16**, $[\alpha]_D^{28}$ +40.48 (*c* 1.35, $CHCl_3$), excellently, as a stable product. This was stirred with diluted hydrochloric acid in dioxane at 40°C to initiate β-elimination to give rise to the target enone (+)-**17**, $[\alpha]_D^{29}$ +141.70 (*c* 1.04, EtOH) [lit.[2]: $[\alpha]_D^{22}$ −139.15 (*c* 0.95, EtOH) for the enantiomer], from which (−)-α-cuparenone **18** has been obtained in three steps.[2,3c] Overall yield of (+)-**17** from (−)-**9** was 54% in five steps (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) PCC, CH_2Cl_2 (90%); (ii) AcOH, 40°C (93%); (iii) 4-MeC_6H_4MgBr, $CuBr{\cdot}SMe_2$, HMPA, TMSCl, THF, −78°C, then TBAF, THF (87%); (iv) Al–Hg, EtOH (91%); (v) 10% HCl:dioxane (1:1), 40°C (81%)

In summary, we have devised an enantiodivergent route to α-cuparenone on the basis of the latent *meso* structure of the chiral starting material. The present procedure also constitutes an enantioconvergent route to both (+)- and (−)-cuparenones in the formal sense as the enantiomeric starting material could give the same enantiomeric pair, enantiodivergently. Although only the synthesis of α-cuparenone was shown in this report, a series of the polyoxygenated bicyclic cyclopentanoids involved in the synthesis may be widely utilized as versatile chiral building blocks owing to their biased structures which make diastereocontrol very easy.

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