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TETRAHEDRON: *ASYMMETRY*

A new stereocontrolled route to (+)-curcuphenol, a phenolic sesquiterpene from the marine sponge *Didiscus flavus*

Tsutomu Sugahara and Kunio Ogasawara *

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

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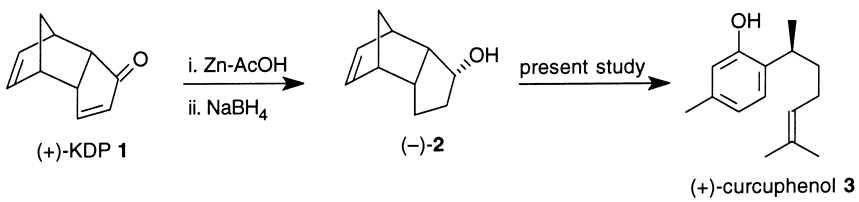
Abstract

Using a synthetic equivalent of chiral 2-cyclopentenol, (+)-curcuphenol, a cytotoxic bisabolane type sesquiterpene isolated from the marine sponge *Didiscus flavus*, has been synthesized through a concurrent retro-Diels–Alder reaction and Claisen rearrangement reaction.

Enantiomerically pure ketodicyclopentadiene **1**, accessible in both enantiomeric forms, is used in the construction of a variety of natural products as a synthetic equivalent of chiral cyclopentadienone.[1,2] It has also been used as a synthetic equivalent of chiral 2-cyclopentenol after chemo- and stereoselective reduction[3] to chiral *endo*-alcohol[4] **2**. We report here an alternative utilization of **2** as an equivalent of chiral 2-cyclopentenol tolerated under the Mitsunobu reaction conditions. Although the Mitsunobu reaction[5] is one of the best methods for the preparation of aryl ethers from phenols and alcohols with inversion of the latter's configuration, a considerable racemization is sometimes observed when chiral allylic alcohols are used as substrates.[6,7] We describe here a new synthesis of a cytotoxic bisabolane sesquiterpene (+)-curcuphenol **3**, isolated from the marine sponge *Didiscus flavus*,[8–11] starting with the Mitsunobu reaction of the allyl alcohol equivalent (−)-**2** which proceeded without any racemization (Scheme 1).



Scheme 1.

Thus, the reaction of (−)-**2**, mp 96°C, $[\alpha]_D^{28}$ −13.1 (*c* 0.5, $CHCl_3$) (prepared from enantiomerically pure (+)-KDP **1**: >99% ee by HPLC [12]), with two equivalents each of 3-methylphenol, diisopropyl

* Corresponding author. Fax: +81-22-217-6845; e-mail: konol@mail.cc.tohoku.ac.jp

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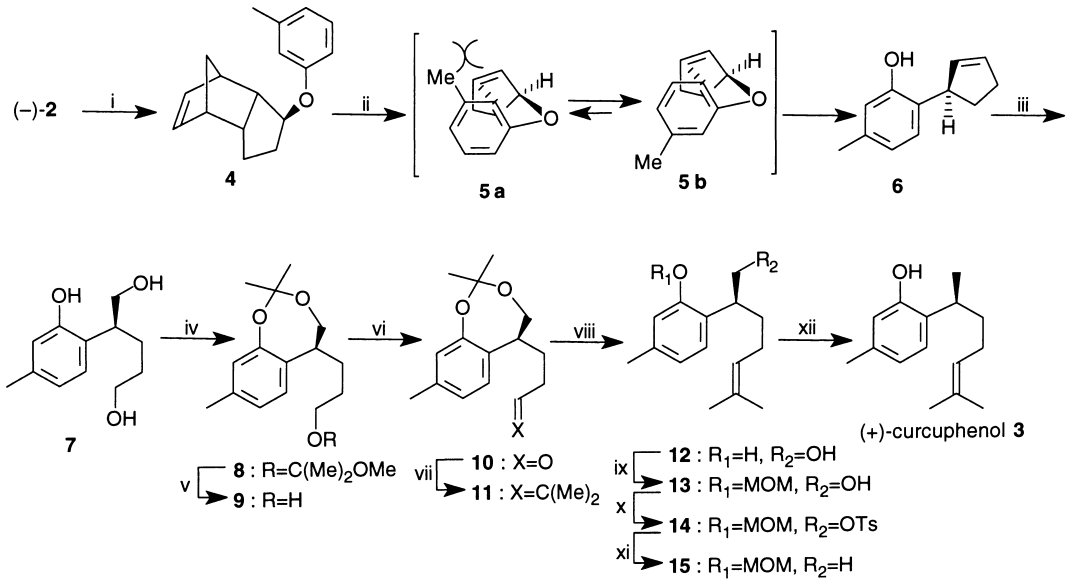
azodicarboxylate (DIPAD) and triphenylphosphine (TPP) in THF at room temperature furnished the *exo*-aryl ether **4**, $[\alpha]_D^{28}$ +44.7 (*c* 1.2, $CHCl_3$), in 77% yield after 24 h (Scheme 2). The reaction was found to proceed without losing the original chiral integrity of (−)-**2** as confirmed by HPLC analysis using a chiral column[12] (>99% ee).



Scheme 2. *Reagents and conditions*: (i) 3-MeC_6H_4OH (2 equiv.), DIPAD (2 equiv.), TPP (2 equiv.), THF, room temp., 24 h (77%); (ii) diphenyl ether, reflux, 50 min (51%; 68% based on consumed **4**); (iii) O_3, MeOH, −78°C, then $NaBH_4$, −78°C to 0°C (88%); (iv) $Me_2C(OMe)_2$, PPTS (cat.), CH_2Cl_2, room temp., then benzene, ~70°C; (v) SiO_2, CH_2Cl_2, room temp. (~6 h) (76% from **7**); (vi) SO_3–pyridine, DMSO, Et_3N, room temp., 40 min; (vii) $iPrP^+Ph_3I^-$, BuLi, THF, 0°C, 45 min (78% from **9**); (viii) 1 N HCl:THF (1:2), room temp., 45 min (94%); (ix) NaOH (2 equiv.), $(C_8H_{17})_3N^+MeCl^-$(0.1 equiv.), $MeOCH_2Cl$ (4 equiv.), room temp., 1 h (47%; 66% based on consumed **12**); (x) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, room temp., 24 h; (xi) $NaBH_4$, DMSO, 70°C, 1.5 h (90% from **13**); (xii) conc. HCl (cat.), MeOH:THF (1:4), room temp., 24 h (88%)

Upon thermolysis in boiling diphenyl ether (~280°C) for 50 min, the 3-arylcyclopentene **6**, $[\alpha]_D^{29}$ +105.5 (*c* 1.1, $CHCl_3$), was obtained in 51% yield in one step as the single product with some recovery of the starting material (~20%) by concurrent retro-Diels–Alder reaction and Claisen rearrangement.[13] Prolonged heating did not increase the amount of **6** significantly though the starting material disappeared. Since 3-methylphenol was detected from the reaction mixture, a competitive elimination reaction of the allyl ether **4** was presumed to occur under the thermolysis conditions. Regioselective generation of the single 2,5-disubstituted phenol **6** may be reasoned by preferential intervention of the less hindered **5b** of two possible transition states (**5a** and **5b**) having orbitally favored chair-like conformations[14] in the Claisen rearrangement. Disappointingly, the enantiomeric excess of the product **6** was found to be 88% ee indicating about 6% loss of the original chiral integrity during the thermolysis conditions which may be due to a competitive [1,3]-sigmatropic rearrangement[15] in the Claisen rearrangement.

In order to confirm the absolute configuration as well as to utilize the rearrangement product, the cyclopentene **6** thus obtained was transformed into (+)-curcuphenol[8] **3** whose absolute configuration had already been established.[11] On sequential single-flask ozonolysis and sodium borohydride reduction, **6** afforded the triol **7**, $[\alpha]_D^{29}$ +19.3 (*c* 1.6, MeOH), in 88% yield. To discriminate the three hydroxy functionalities in the molecule, **7** was reacted with 2,2-dimethoxypropane in the presence of PPTS[16] to afford the diacetonide **8**, which on brief exposure to silica gel suspended in dichloromethane allowed specific deacetalization to give selectively the primary alcohol **9**, $[\alpha]_D^{29}$ −18.4 (*c* 1.4, $CHCl_3$), in

satisfactory overall yield. Oxidation[17] of **9** followed by the Wittig reaction of the resulting aldehyde **10** gave the isopropylidene product **11**, $[\alpha]_D^{29}$ +4.8 (*c* 0.7, $CHCl_3$), which, on acid-hydrolysis, afforded the diol **12**, $[\alpha]_D^{27}$ +32.6 (*c* 1.0, $CHCl_3$). The overall yield of **12** from **7** was 55%. The phenolic hydroxy functionality of **12** was selectively protected by treating with methoxymethyl chloride in the presence of a phase transfer catalyst[18] to give the aryl ether **13** in 47% yield with some recovery of the starting material (~20%), although the yield of **13** was less than satisfactory. While the phenolic hydroxy functionality was blocked, the primary hydroxy functionality was removed by its tosylation followed by borohydride reduction[19] of the resulting tosylate **14** to give the penultimate intermediate **15**, $[\alpha]_D^{27}$ +7.9 (*c* 0.1, $CHCl_3$), bearing a secondary methyl functionality, in 90% yield. Finally, **15** was acid-hydrolyzed to give (+)-curcuphenol **3**, $[\alpha]_D^{27}$ +26.0 (*c* 0.3, $CHCl_3$), ($[\alpha]_D$ +24.6±2 for the natural product;[8] $[\alpha]_D^{29}$ +29.5 (*c* 0.2, $CHCl_3$) for the enantiomerically pure sample after purification by preparative HPLC using a chiral column[12]), in 88% yield. Enantiomeric excess of the product was determined to be 90% ee by HPLC[12] using a chiral column which corresponded to that of the thermolysis product **6**.

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