Enantioconvergent Route to α-Cuparenone from Dicyclopentadiene

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A formal enantioconvergent route to α-cuparenone from dicyclopentadiene has been devised by employing lipase catalysed kinetic hydrolysis as the key step.

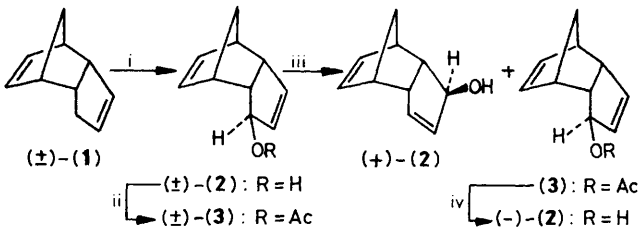
The bicyclic sesquiterpene, α-cuparenone (**11**) and its congeners present an interesting synthetic challenge owing to the steric congestion about the cyclopentane ring.[1] We report here an efficient enantioconvergent construction of α-cuparenone[2] (**11**), obtained in both enantiomeric forms in nature,[3] from dicyclopentadiene (**1**) by employing lipase catalysed kinetic hydrolysis[4] as the key step.

Stirring racemic 1-acetoxydicyclopentadiene (**3**), readily accessible in a large quantity from dicyclopentadiene (**1**) in two steps *via* the alcohol[5] (**2**), with lipase† [20% w/w of (**3**)] in a phosphate buffer (0.1 M) containing acetone (10 : 1 v/v) at room temperature for five days gave a mixture (*ca.* 1 : 2) of the alcohol (**2**) and the unchanged acetate (**3**) which were readily separated by silica gel column chromatography. The alcoholic product was further purified by repeated recrystallization (×3) from n-hexane to give the homochiral (+)-alcohol‡ [(+)-(**2**)], m.p. 72—72.5 °C, $[\alpha]_D^{25}$ +99.1° (*c* 0.98, $CHCl_3$), in 30% yield from the starting racemic acetate [(±)-(**3**)]. The unchanged product was saponified and the resulting alcohol

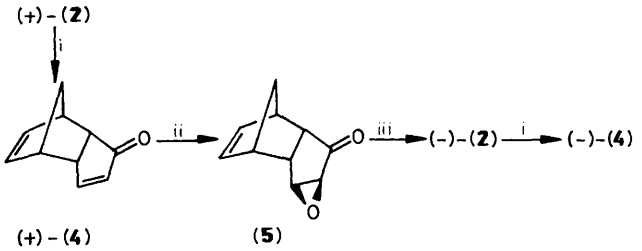
† *Candida cylindracea* (Lipase My), purchased from Meito Sangyo Co., Japan, was used without purification.

‡ Satisfactory spectral (i.r., ^{1}H-n.m.r., m.s.) and analytical (combustion and/or high resolution mass spectral) data were obtained for all new isolable compounds.

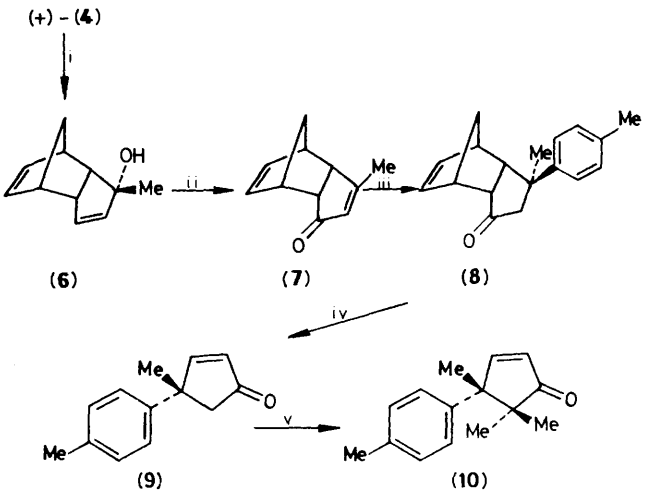
was recrystallized repeatedly (×5) from n-hexane to give the homochiral (−)-alcohol [(−)-(**2**)], m.p. 72—72.5 °C, $[\alpha]_D^{25}$ −98.5° (*c* 0.95, $CHCl_3$), in 22% overall yield from the starting acetate [(±)-(**3**)] (Scheme 1).



Scheme 1. *Reagents and conditions*: i, SeO_2, 1,4-dioxane, H_2O; reflux, 2 h; ii, acetyl chloride (1.5 equiv.), pyridine (1.2 equiv.), benzene, 0 °C to room temp., 1 h; iii, lipase [20% w/w of (**3**)], 0.1 M phosphate buffer/acetone (10 : 1 v/v), room temp., 5 days; iv, KOH (1.5 equiv.), 1,4-dioxane, H_2O, room temp., 12 h.



Scheme 2. *Reagents and conditions*: i, pyridinium chlorochromate (1.5 equiv.), CH_2Cl_2, room temp., 12 h; ii, 30% H_2O_2 (3.0 equiv.), 0.5 M NaOH (0.3 equiv.), MeOH, 0 °C room temp., 30 min; iii, $NH_2NH_2H_2O$ (10 equiv.), acetic acid (1.0 equiv.), EtOH, room temp., 30 min.



Scheme 3. *Reagents and conditions*: i, MeLi (1.2 equiv.), THF, −70 °C, 15 min; ii, pyridinium chlorochromate (2.0 equiv.), CH_2Cl_2, 0 °C to room temp., 4 h; iii, *p*-bromotoluene (5.0 equiv.), Mg (5.0 equiv.), CuI (5.2 equiv.), $BF_3{\cdot}Et_2O$ (1.5 equiv.), Et_2O, −20 °C room temp., 1 h; iv, *o*-dichlorobenzene, reflux, 5 h; v, NaH (3.0 equiv.), MeI (2.5 equiv.), 0 °C to room temp., 12 h; vi, 10% Pd–C (cat), H_2, MeOH, room temp., 1 h.

Oxidation of the (+)-alcohol [(+)-(**2**)] by pyridinium chlorochromate (PCC) furnished the known (+)-enone[6] [(+)-(**4**)], m.p. 59—60 °C, $[\alpha]_D^{25}$ +158.8° (*c* 1.01, MeOH) [lit. m.p. 59—59.5 °C;[5] $[\alpha]_D^{23}$ +141.6° (MeOH)[6]], in 90% yield. Treatment of the resulting enone (**4**) with alkaline hydrogen peroxide afforded the epoxide (**5**) in 90% yield as a single isomer. Exposure of (**5**) to hydrazine hydrate in ethanol at room temperature in the presence of acetic acid,[7] gave the (−)-alcohol [(−)-(**2**)], $[\alpha]_D^{25}$ −100.5° (*c* 0.90, $CHCl_3$), in 70% yield, which afforded the (−)-enone [(−)-(**4**)], m.p. 59—60 °C, $[\alpha]_D^{25}$ −152.0° (*c* 0.45, MeOH), in 87% yield on oxidation with PCC (Scheme 2).

Having established formal interconversion between both enantiomers of the alcohol (**2**) and the enone (**4**), we then carried out transformation of the (+)-enone (**4**) into (+)-α-cuparenone (**11**). Treatment of (+)-(**4**) with methyl-lithium gave the enol (**6**) in 65% yield as a single epimer which on oxidation[8] with PCC furnished the enone (**7**) in 63% yield. Reaction of (**7**) with excess *p*-tolylmagnesium bromide (5.0 equiv.) in the presence of copper(I) iodide (5.2 equiv.) and boron trifluoride–ether (1.5 equiv.)[9] allowed selective 1,4-addition to give the ketone (**8**) in 63% yield as a single epimer. Refluxing the ketone (**8**) in *o*-dichlorobenzene induced smooth retro-Diels–Alder reaction to give the known enone[2c,2e] (**9**), $[\alpha]_D^{22}$ − 139.15° (*c* 0.95, EtOH) {lit.[2e] $[\alpha]_D^{26}$ + 139° (*c* 1.18, EtOH)}, in 61% yield, which previously has been converted into (+)-α-cuparenone (**11**) in two steps.[2c,10] Compound (**9**) afforded (+)-α-cuparenone (**11**), m.p. 51—53 °C, $[\alpha]_D^{22}$ +173.1° (*c* 0.64, $CHCl_3$) {lit.[3a] m.p. 52—53 °C, $[\alpha]_D^{30}$ +177° ($CHCl_3$)}, in 60% overall yield by sequential methylation and catalytic reduction.

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