Synthesis of enantiopure *cis*-decalins from microbially-derived *cis*-1,2-dihydrocatechols

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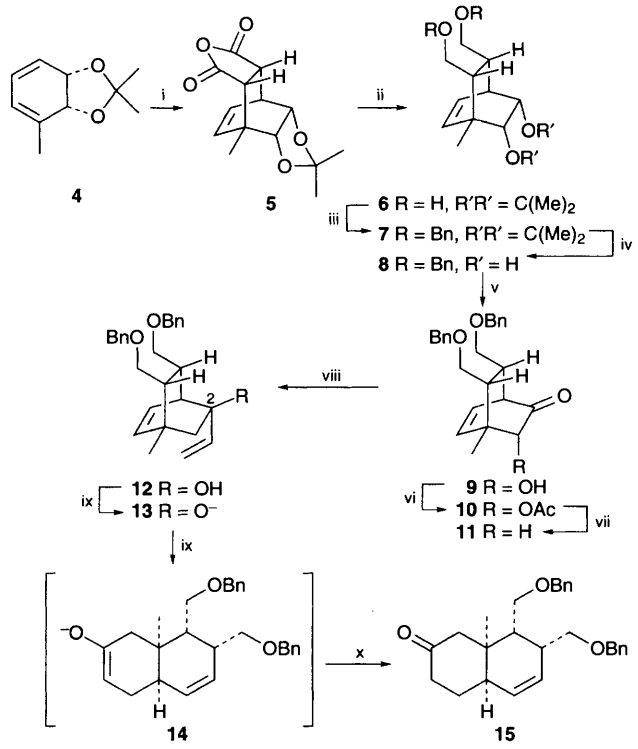
The microbially-derived *cis*-1,2-dihydrocatechol 3 is converted, *via* reaction sequences involving Diels–Alder cycloaddition and anionic oxy-Cope rearrangement steps, into the enantiopure *cis*-decalins 15 and 26; using simple modifications of this chemistry the pseudo-enantiomer 22 of decalin 15 is also prepared from diol 3.

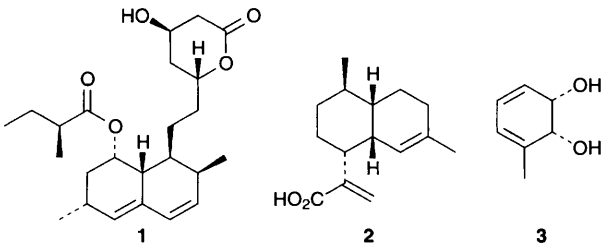
The decalin moiety is a structural subunit common to many natural products[1] including, for example, mevinolin **1**, a medicinally significant agent for reducing cholesterol in blood plasma,[2] and artemisinic acid **2**, a precursor to the important anti-malarial agent artemisinin (Qinghaosu).[3] Numerous methods for the synthesis of decalins have been developed with the Robinson annulation,[4] Diels–Alder cycloaddition,[5] Heck-type cyclisation,[6] double-Michael[7] and tandem Michael–Claisen[8] condensation procedures being especially notable. The anionic oxy-Cope rearrangement of 2-vinylbicyclo[2.2.2]oct-5-en-2-ols provides a further approach[9] but is limited by the paucity of monochiral bicyclo[2.2.2]octenyl systems which would allow for the synthesis of enantiopure decalins. The capacity of microbially-derived and monochiral *cis*-1,2-dihydrocatechols[10] such as **3**† to engage, as the 4π-component, in diastereofacially selective Diels–Alder cycloaddition reactions with the resultant formation of bicyclo[2.2.2]octenes[10c,11] has prompted us to investigate the possibility of elaborating these adducts into decalins. Preliminary results of such a study are reported herein.

Diels–Alder cycloaddition (Scheme 1) of maleic anhydride with the acetonide **4**, readily prepared[12] from diol **3**, afforded adduct **5**‡ (68%) {mp = 104–105 °C (sealed tube); $[\alpha]_D$ = +15 (*c* 1.0, 15 °C)§}. Lithium aluminium hydride reduction of anhydride **5** gave the expected diol **6** (88%) {mp = 155–156 °C; $[\alpha]_D$ = +24 (*c* 1.0, 14 °C)} which was subsequently protected as its bis-benzyl ether **7** (99%) {$[\alpha]_D$ = +32 (*c* 1.6, 15 °C)}. Hydrolysis of the acetonide unit within compound **7** gave diol **8** (100%) {$[\alpha]_D$ = +44 (*c* 1.1, 14 °C)} which was oxidised, in a regioselective fashion, to the acyloin **9** (97%) {$[\alpha]_D$ = −40 (*c* 1.0, 14 °C)} using the sterically demanding oxoammonium salt derived from 4-acetamido-TEMPO (4-AcNH-TEMPO) and toluene-*p*-sulfonic acid (*p*-TsOH).[13] Deoxygenation of the derived acetate **10** (92%) {$[\alpha]_D$ = −19 (*c* 1.1, 13 °C)} was achieved with freshly prepared samarium diiodide in THF–acetic acid.[14] The resulting ketone **11** (88%) {$[\alpha]_D$ = −129 (*c* 1.6, 15 °C)} was then reacted with vinylmagnesium bromide to give a mixture of alcohol **12** (61%) {$[\alpha]_D$ = +7 (*c* 1.0, 14 °C)} and its C-2 epimer (20%) {$[\alpha]_D$ = +4 (*c* 0.8, 14 °C)} which could be separated from one another chromatographically. Compound **12** was then treated with potassium hydride and 18-crown-6 (18-C-6) to give anion **13** which underwent smooth rearrangement to enolate **14**. Subsequent protonation of this latter species then afforded decalin **15** (80% from **12**) {$[\alpha]_D$ = +80 (*c* 0.6, 14 °C)}.

A complementary approach to decalins is shown in Scheme 2. Thus, diol **8** was selectively converted into the *tert*-butyldimethylsilyl ether **16** (68%) {$[\alpha]_D$ = +39 (*c* 0.9, 18 °C)} Swern oxidation[15] of which gave ketone **17**. Desilylation of the latter compound with *tetra*-butylammonium fluoride (TBAF) gave acyloin **18** (90% from **16**) {$[\alpha]_D$ = +126 (*c* 1.4, 17 °C)} which was deoxygenated *via* the corresponding acetate **19**. The resulting ketone **20** (86% from **18**) {$[\alpha]_D$ = +224 (*c* 0.9, 14 °C)} was then reacted with vinylmagnesium bromide to give an inseparable 1 : 1 mixture of alcohol **21** and its C-2 epimer (85% combined yield). Subjection of these compounds to



Scheme 1 *Reagents and conditions*: i, maleic anhydride, CH_2Cl_2, 0–18 °C, 24 h; ii, $LiAlH_4$, THF, 66 °C, 3 h; iii, BnBr, NaH, Bu_4NI, DMF, 0–18 °C, 18 h; iv, AcOH, H_2O, 80 °C, 16 h; v, 4-AcNH-TEMPO, *p*-TsOH, CH_2Cl_2, 18 °C, 3 h; vi, Ac_2O, pyridine, CH_2Cl_2, 18 °C, 18 h; vii, SmI_2, AcOH, THF, 18 °C, 20 min; viii, $H_2C{=}C(H)MgBr$, THF, 0 °C, 3 h; ix, KH, 18-C-6, THF, 60 °C, 2 h; x, aqueous workup. Bn = benzyl.



standard anionic oxy-Cope rearrangement conditions gave decalin **22** (55%) {$[\alpha]_D$ = −48 (*c* 0.7, 18 °C)}.¶ Compound **22** is a pseudo-enantiomer of decalin **15**.

Modification of the synthetic sequences described above enabled preparation of a more functionalised decalin derivative (Scheme 3). Thus, subjection of compound **9** to a Mitsunobu reaction using *p*-nitrobenzoic acid as nucleophile[16] afforded the labile ester **23** (60%) {$[\alpha]_D$ = −1.7 (*c* 0.8, 20 °C)}. In contrast to the previous cases (Schemes 1 and 2), addition of vinylmagnesium bromide to the ketone carbonyl in compound **23** proceeded with excellent diastereoselectivity and in the desired sense. Vinylation was accompanied by ester cleavage and the resultant diol **24** was then selectively converted into monobenzyl ether **25** (50% from **23**) {$[\alpha]_D$ = +51 (*c* 1.1, 15 °C)} under standard conditions. Upon treatment with potassium hydride and 18-C-6, compound **25** underwent rearrangement to decalin **26** (60%) {$[\alpha]_D$ = +155 (*c* 0.4, 20 °C)}.

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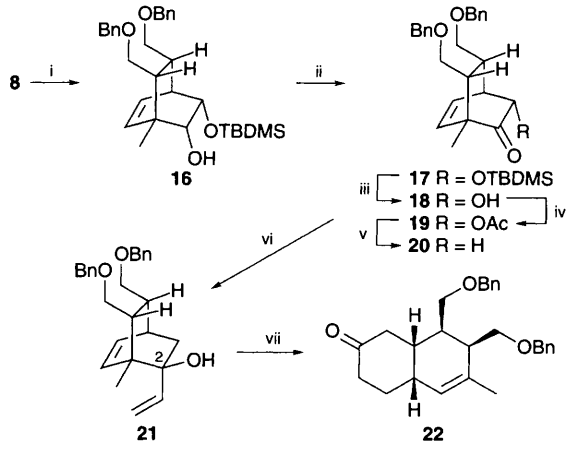
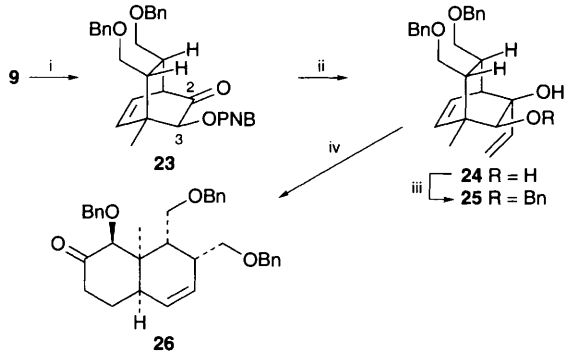


Scheme 2 *Reagents and conditions*: i, TBDMSCl, imidazole, DMF, 18 °C, 24 h; ii, Me_2SO, TFAA, CH_2Cl_2, −60 °C, 1 h; iii, TBAF, THF, CH_2Cl_2, 18 °C, 18 h; iv, Ac_2O, pyridine, CH_2Cl_2, 18 °C, 18 h; v, SmI_2, AcOH, THF, 18 °C, 20 min; vi, H_2C=C(H)MgBr, THF, 0 °C, 3 h; vii, KH, 18-C-6, THF, 60 °C, 2 h then aqueous workup. TBDMSCl = *tert*-butyldimethylsilyl chloride; TFAA = trifluoroacetic anhydride.



Scheme 3 *Reagents and conditions*: i, PPh_3, DEAD, *p*-$O_2NC_6H_4CO_2H$, 0–18 °C, 0.5 h; ii, H_2C=C(H)MgBr, THF, 0 °C, 3 h; iii, BnBr, NaH, DMF, 0–18 °C, 2 h; iv, KH, 18-C-6, THF, 60 °C, 2 h then aqueous workup. PNB = *p*-nitrobenzoate; DEAD = diethyl azodicarboxylate.

Footnotes

† Around 20 such *cis*-1,2-dihydrocatechols are now available commercially from the following sources: Genencor International Inc., South San Francisco, CA; ICI Fine Chemicals, Manchester, U.K.; Enzymatix, Cambridge, U.K.; Janssen Chimica, Geel, Belgium.

‡ All new compounds had spectroscopic data [IR, UV, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

§ All optical rotations were determined using chloroform as solvent.

¶ 2-*epi*-**21**, which is incapable of undergoing Cope rearrangement, could not be isolated from the reaction mixture and, at present, the fate of this compound is unknown.

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