A Novel Approach to Optically Active *trans*-Benzoperhydroindan (2,3,3a,3b,4,5-Hexahydro-1*H*-benz[*e*]indene)

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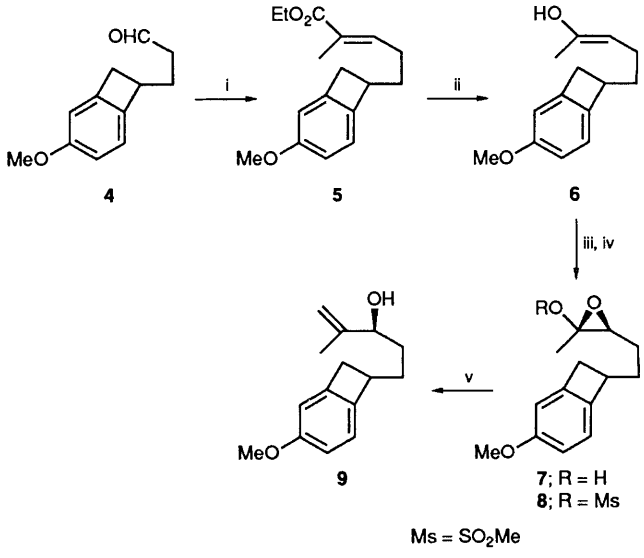
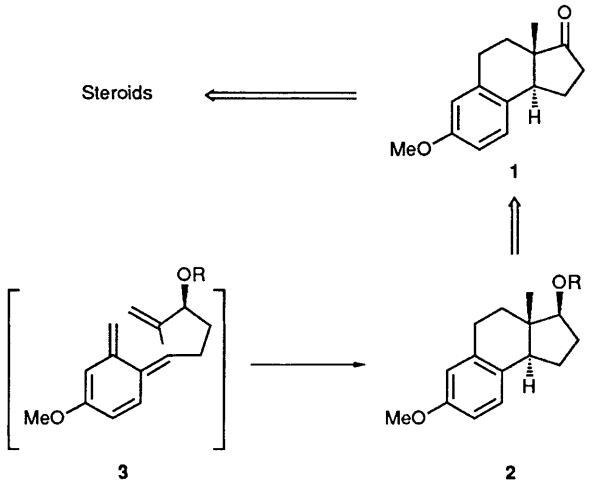
Optically active *trans*-benzoperhydroindan **1** and its enantiomer have been synthesised by thermolysis of the optically active alkenic benzocyclobutene **10** as a key process.

The des-*A*,*B*-aromatic steroid, *trans*-benzoperhydroindan, has emerged as a cornerstone for the synthesis of a variety of steroids;[1] the 17-oxo compound **1** (steroid numbering) has growing importance as a potential synthon for physiologically important steroids.[2] During our work[3] directed towards the asymmetric synthesis of des-*A*,*B*-aromatic 17-keto steroid, we have developed a novel approach which relies on the stereoselective [4 + 2] cycloaddition reaction of alkenic *o*-quinodimethane **3** to give the *C*,*D* *trans*-fused des-*A*,*B*-aromatic steroid **2** and herein we describe the results.

The synthesis of the optically active benzocyclobutenes **10a–e**, substrates for generating **3**, was straightforward (Scheme 2).† The benzocyclobutenyl aldehyde **4**,[4] easily obtainable in large quantities from 1-cyano-4-methoxybenzocyclobutene,[5] was subjected to the Wittig reaction to give the unsaturated ester **5** selectively (96%), which on reduction with diisobutylaluminium hydride (DIBAL) afforded the alcohol **6** (85%). Asymmetric epoxidation of the allyl alcohol **6** was effected by following the Sharpless procedure to give the chiral epoxy alcohol **7** (96%) with a high degree (88% e.e.) of enantiomeric excess.‡ Mesylation of **7**, followed by reductive epoxide ring opening of **8** afforded the isopropenyl alcohol **9** (100% overall from **7**). Standard derivatisation procedure for **9** furnished the substrates; **10a**: [triisopropylsilyl trifluoromethanesulphonate (TIPSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min]; **10b**: [*tert*-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h]; **10c**: [*tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole, 4-*N*,*N*-dimethylaminopyridine (DMAP), dimethylformamide (DMF), room temp., 2 days]; **10d**: [benzyloxymethyl chloride (BOMCl), Pr^i_2NEt, DMAP, CH_2Cl_2, room temp., 18 h]; **10e**: [dihydropyran (DHP), *p*-TsOH (Ts = $MeC_6H_4SO_2$), CH_2Cl_2, room temp., 1 h].

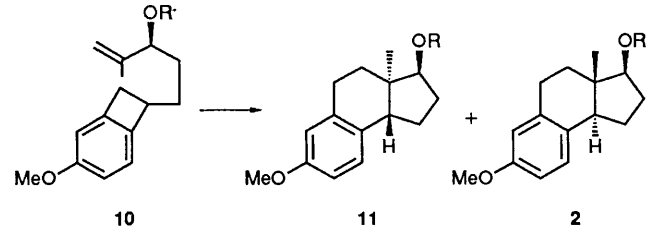


Scheme 2 *Reagents and conditions*: $Ph_3P{=}CMeCO_2Et$, benzene, room temp., 2 h; ii, DIBAL, THF, −33 °C, 1 h; iii, Bu^tOOH, $Ti(OPr^i)_4$, (+)-L-diisopropyl tartrate, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 3 h; iv, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; v, Zn, NaI, DMF, 100 °C, 30 min (THF = tetrahydrofuran)



Scheme 1

Table 1[a]



Entry	Substrate	Product ratio[b] **2**:**11**	Isolated yield[c] (%)
1	**10a**: R = $(Pr^i)_3Si$	2:1	81
2	**10b**: R = Bu^tMe_2Si	2.3:1	100
3	**10c**: R = Ph_2Bu^tSi	1.5:1	94
4	**10d**: R = $PhCH_2OCH_2$	1:1.3	89
5	**10e**: R = THP[d]	1.2:1	72

[a] All reactions were run under argon in boiling *o*-dichlorobenzene for 3 h. [b] The isomer (**2** and **11**) ratio was determined by ^{1}H NMR integration of angular methyl signals [δ 0.56 for **2** (R–H) and δ 0.63 for **11** (R = H)] of the corresponding alcohols which were derived as follows: for entries 1–3, initial products were desilylated (Bu_4NF, THF, room temp., 2 h) and for entries 4 and 5, initial products were treated with 10% HCl. [c] All yields are based on purified products by passing through a short column (SiO_2). [d] THP = tetrahydropyran-2-yl.

† All new substances exhibited spectroscopic data [IR, ^{1}H NMR (500 MHz) and mass spectrometry] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data.

‡ The enantiomeric excess of the epoxy alcohol **7** was determined by comparing the ^{1}H NMR (500 MHz) of the methoxy(trifluoromethyl)phenylacetyl (MTPA) esters derived [MTPA acid, DCC, DMAP, CH_2Cl_2, room temp., 12 h] from **7** and the corresponding racemic epoxy alcohol which was prepared by epoxidation [Bu^tO_2H, $VO(acac)_2$ (acac = pentane-2,4-dianoto), CH_2Cl_2, 0 °C, 30 min] of **6**.

Thermolyses of these substrates **10a–e** afforded the *trans*-fused des-*A*,*B*-aromatic steroids **2** and **11** selectively in high yields (*Table* 1). The isomers **11** (R = H) and **2** (R = H) were easily separated on silica gel column chromatography and were oxidized [pyridinium chlorochromate (PCC), room temp., CH_2Cl_2, 2 h] to give the ketone **1** {$[\alpha]_D^{20}$ + 108°, lit.,[6] $[\alpha]_D^{25}$ + 99°} (57%) and its enantiomer {$[\alpha]_D^{20}$ − 109°} (74%) respectively. These results show that either chiral *trans*-benzoperhydroindan **1** or its enantiomer could be synthesised selectively by using a chiral catalyst with an asymmetric epoxidation step.

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