Asymmetric Synthesis of *trans*-Benzoperhydroindan: Asymmetric Induction in Intramolecular Diels–Alder Reactions of *o*-Quinodimethanes

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Diastereofacial selection has been shown to occur in the asymmetric intramolecular Diels–Alder reactions of chiral *o*-quinodimethanes generated by thermal ring-opening of the chiral benzocyclobutenes (**1a,b,e,f**).

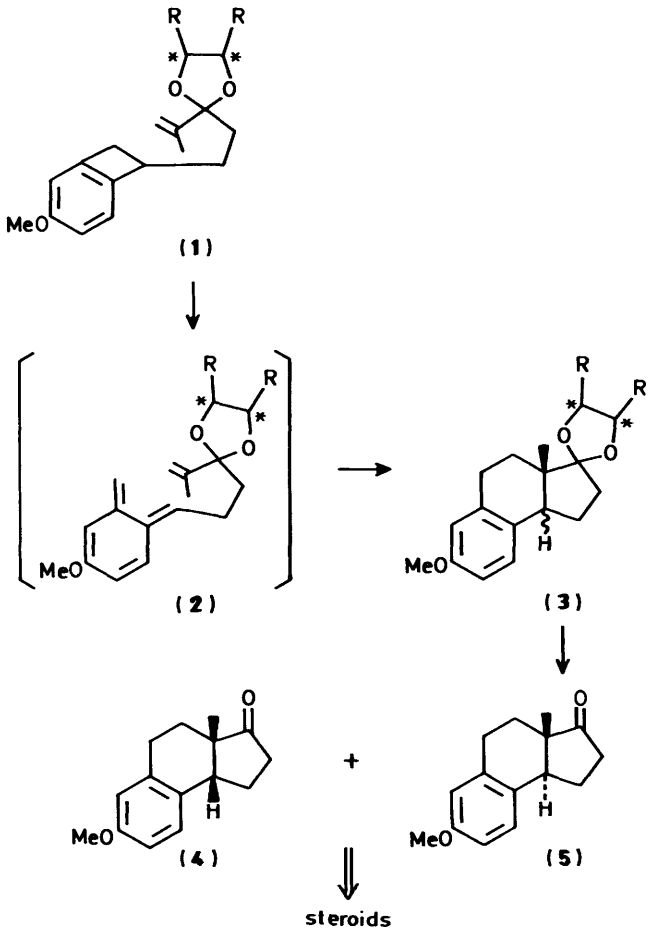
Although inter- and intra-molecular asymmetric induction in Diels–Alder reactions of dienes has been widely studied,[1] there have been fewer studies of asymmetric inductions in Diels–Alder reactions of *o*-quinodimethanes.[2] During our work[2b–d,3] directed towards the total synthesis of steroids *via* intramolecular Diels–Alder reactions, our attention has been focussed on the asymmetric synthesis of the des-AB-aromatic steroid *trans*-benzoperhydroindan, such a skeleton constituting an essential part of many physiologically important steroids and having potential as a synthon. We now report here an asymmetric synthesis of the *trans*-benzoperhydroindan (**5**) *via* an intramolecular Diels–Alder reaction of the chiral *o*-quinodimethane (**2**). The latter was generated by thermal ring-opening of the chiral benzocyclobutenes (**1a,b,e,f**) which have a C_2-symmetric acetal moiety as a chiral auxiliary.

The chiral substrates (**1a,b,e,f**) for the thermolysis were easily prepared from the enone (**6**)[3d] (see Scheme 2). Thus the acetal (**1a**) [*m/z* 302 (M^+)] was prepared in 97% yield by standard acetalisation [(−)-(2*R*,3*R*)butane-2,3-diol, camphorsulphonic acid, benzene] of the enone (**6**). The dimethoxy acetal (**7**)[3e] [*m/z* 276 (M^+)], obtained [$CH(OMe)_3$, camphorsulphonic acid, MeOH] from the enone (**6**) in 89% yield, was converted into the chiral acetals (**1b,c**) by the use of (−)-(2*S*,3*S*)-1,4-dimethoxybutane-2,3-diol,[4] or L-(+)-diethyl tartrate in 83 and 64% yields respectively. The dibenzyloxy acetal (**1e**) [*m/z* 514 (M^+)] was obtained in 78% overall yield by reduction [lithium aluminium hydride, THF] of the ester (**1c**), followed by benzylation [$PhCH_2Br$, NaH, DMF] of the alcohol (**1d**) [*m/z* 334 (M^+)]. Also the nine-membered acetal (**1f**) was prepared in 91% yield by silylation [1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, imidazole, dimethylaminopyridine, DMF] of the alcohol (**1d**).

Thermolysis of the chiral acetals (**1a,b,e,f**) was conducted in refluxing *o*-dichlorobenzene to afford the cyclised compound (**3**) as a stereoisomeric mixture, and this was then hydrolysed (10% HCl, MeOH) to give the ketones. The results are summarized in the Table.

As shown in the Table, the synthesis of the *trans*-benzoperhydroindan (**5**) was highly stereoselective, particularly so with (**1a**) and (**1f**) where the high-yield reaction proceeded in an almost exclusively stereoselective manner. The *trans*-benzoperhydroindan (**5**) was isolated by SiO_2 column chromatography, and the e.e. determined and compared with the literature value.[5] The selectivity and predominant formation of (+)-(**5**) for (**1b**), (**1e**), and (**1f**) and (−)-(**5**) for (**1a**) was well explained by proposing the transition states $\mathbf{T}_1$ and $\mathbf{T}_2$ which lead to (+)-(**5**) and (−)-(**5**) respectively. For (**1f**), the conformational rigidity of the nine-membered ring led to a lower yield of the (+)-*trans*-enantiomer (+)-(**5**).

Although the degree of asymmetric induction is not very high, this reaction has the following advantage. (i) The chiral substrate for this reaction can be obtained easily using C_2 symmetric diols; and (ii) chiral auxiliaries may be recycled. Thus, an asymmetric synthesis of *trans*-benzoperhydroindan, a potential intermediate in the synthesis of chiral steroids, was developed.



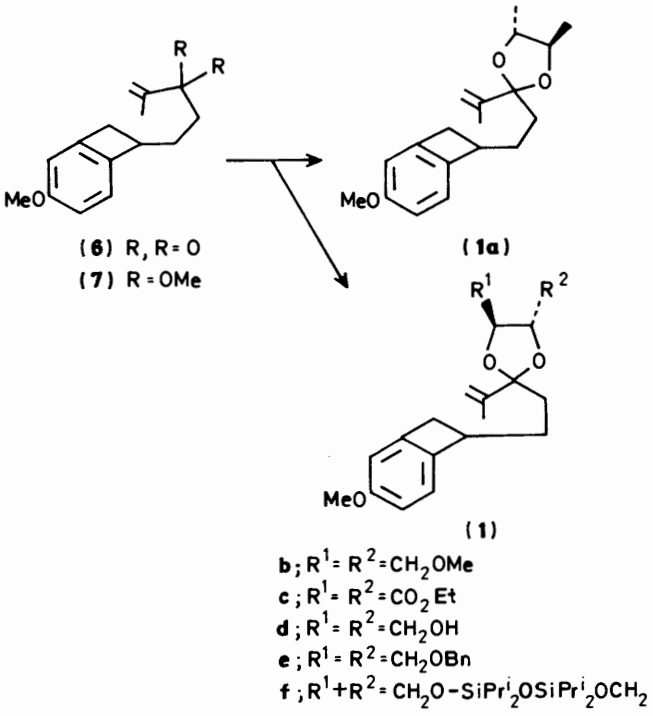
Scheme 1.

Experimental

General Methods.—I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer and n.m.r. spectra on a JEOL FX-90 spectrometer. Chemical shifts are reported as δ values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M-52G or a JEOL-DX-300 spectrometer. Optical rotations were measured with a JASCO-DIP-340 polarimeter. The phrase 'residue upon work-up' refers to the residue obtained when the organic layer

was separated, dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. All new compounds described in the Experimental Section were homogeneous on t.l.c.

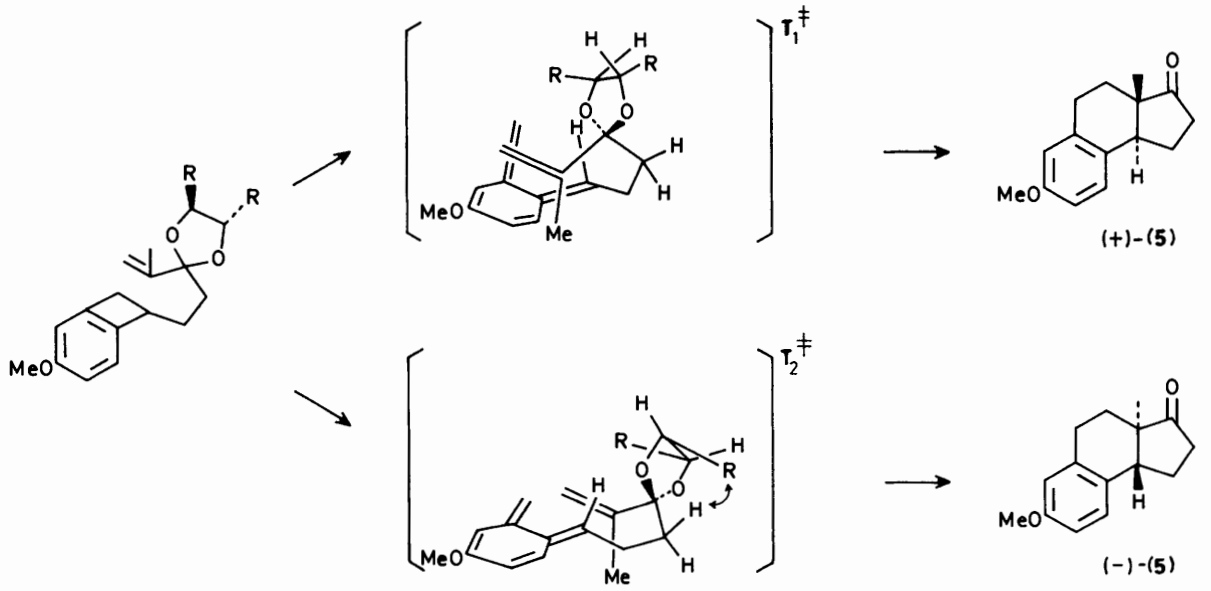
(4R,5R)-2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-*ethyl*]-2-*isopropenyl*-4,5-*dimethyl*-1,3-*dioxolane* (**1a**).—(2*R*,3*R*)-(−)-Butane-2,3-diol (24 mg, 0.26 mmol) and D-camphor-10-sulphonic acid (catalytic amount) were added to a solution of the enone (**6**) (40 mg, 0.17 mmol) in benzene (2 ml). The reaction mixture was refluxed in a flask fitted with a Dean-Stark trap for 11 h after which it was diluted with benzene (20 ml) and washed with saturated aqueous sodium hydrogen carbonate and saturated brine. The residue upon work-up was chromatographed on silica gel (1 g) with hexane–ethyl acetate (97:3, v/v) to yield the *acetal* (**1a**) (51 mg, 97%) as an oil (Found: C, 75.25; H, 8.75. $C_{19}H_{26}O_3$ requires C, 75.45; H, 8.65); $\delta_H(CDCl_3)$ 1.18 and 1.24 (each 3 H, each d, *J* 5.6 Hz, OCMe), 1.74 (3 H, s, =CMe), 3.74 (3 H, s, OMe), 4.84 and 5.14 (each 1 H, each d, *J* 1 Hz, $=CH_2$), and 6.64—6.98 (3 H, m, ArH); *m/z* 302 (M^+).



Scheme 2.

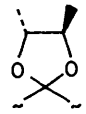
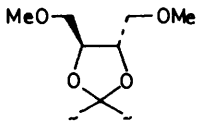
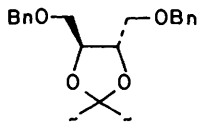
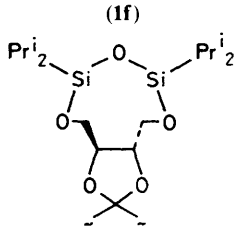
(4S,5S)-2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-*ethyl*]-2-*isopropenyl*-4,5-*bis*(*methoxymethyl*)-1,3-*dioxolane* (**1b**).—1,4-Dimethoxybutane-2,3-diol (249 mg, 1.66 mmol) and D-camphor-10-sulphonic acid (catalytic amount) were added to a stirred solution of the dimethoxy acetal (**7**) (305 mg, 1.10 mmol) in dichloromethane (10 ml) at room temperature. After being stirred for 4 h at the same temperature, the reaction mixture was diluted with water (20 ml) and extracted with dichloromethane, and the extract was washed with saturated aqueous sodium hydrogen carbonate and saturated brine. The residue upon work-up was chromatographed on silica gel (7 g) with hexane–ethyl acetate (94:6, v/v) to give the *methyl ester* (**1b**) (333 mg, 83%) as an oil (Found: C, 69.6; H, 8.45. $C_{21}H_{30}O_5$ requires C, 69.6; H, 8.35); $\delta_H(CDCl_3)$ 1.76 (3 H, s, =CMe), 3.37 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.80—3.96 (2 H, m, OCH), 4.88 and 5.16 (each 1 H, each d, *J* 1 Hz, $=CH_2$), and 6.65—7.00 (3 H, m, ArH); *m/z* 362 (M^+).

(4R,5R)-*Diethyl* 2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-1,3-*dioxolane*-4,5-*dicarboxylate* (**1c**).—L-(+)-Diethyl tartrate (2.18 g, 10.60 mmol), D-camphor-10-sulphonic acid (catalytic amount), and 3 Å molecular sieves (50 mg) were added to a solution of the dimethoxy acetal (**7**) (975 mg, 3.53 mmol) in toluene (33 ml). The reaction mixture was refluxed in a flask fitted with a Dean–Stark trap for 16 h after which it was diluted with toluene (30 ml), and the organic layer separated and washed with saturated aqueous sodium hydrogen carbonate and saturated brine. The residue upon work-up was chromatographed on silica gel (20 g) with hexane–ethyl acetate (9:1, v/v) to yield the *ethyl ester* (**1c**) (952 mg, 64%) as an oil (Found: C, 66.45; H, 7.35. $C_{23}H_{30}O_7$ requires C, 66.6; H, 7.25); $\nu_{max.}(CHCl_3)$ 1 740 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.27 and 1.30 (each 3 H, each t, *J* 7.2 Hz, CH_2Me),



Scheme 3.

Table. Thermolysis followed by acid hydrolysis of chiral acetal

	(1a)	(1b)	(1e)	(1f)
Chiral acetal				
(4) + (5) yield[a] from (1)	90%	95%	57%	82%
Ratio[b] (5):(4)	95:5	91:9	92:8	97:3
$[\alpha]_D^{25}$ of (5) in MeOH	−35.8° (*c* 0.58)	+11.8° (*c* 0.66)	+14.0° (*c* 0.96)	+28.6° (*c* 0.65)
E.e.[c]	36%	12%	14%	29%

[a] Purified and isolated by SiO_2 column chromatography. [b] Spectral data for (4) and (5) were identical with those of (±)-authentic sample[3a,e] except for the $[\alpha]_D^{25}$ value. [c] Determined in comparison with the value for the reported one: see ref. 5. $[\alpha]_D^{25}$ = +99° (*c* 1.1 in MeOH).

1.77 (3 H, s, =CMe), 3.77 (3 H, s, OMe), 4.23 and 4.29 (each 2 H, each q, *J* 7.2 Hz, CH_2Me), 4.66 and 4.85 (each 1 H, each d, *J* 6 Hz, 2 × $CHCO_2Et$), 4.90 and 5.20 (each 1 H, each d, *J* 1 Hz, $=CH_2$), and 6.62—7.05 (3 H, m, ArH); *m/z* 418 (M^+).

(4S,5S)-2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-*ethyl*]-4,5-*bis*(*hydroxymethyl*)-2-*isopropenyl*-1,3-*dioxolane* (**1d**).—A solution of the ethyl ester (**1c**) (111 mg, 0.27 mmol) in tetrahydrofuran (2 ml) was added to a stirred suspension of lithium aluminium hydride (10.2 mg, 0.27 mmol) in tetrahydrofuran (5 ml) at 0 °C and the mixture was stirred for 1 h. After being quenched with 10% aqueous sodium hydroxide (1 ml), the mixture was extracted with ether and the extract was washed with saturated brine. The residue upon work-up was chromatographed on silica gel (0.6 g) with hexane–ethyl acetate (85:15, v/v) to give the *alcohol* (**1d**) (74 mg, 83%) as an oil (Found: C, 68.1; H, 7.95. $C_{19}H_{26}O_5$ requires C, 68.25; H, 7.85); $\nu_{max.}(CHCl_3)$ 3 400 cm^{-1} (OH); $\delta_H(CDCl_3)$ 1.75 (3 H, s, =CMe), 3.73 (3 H, s, OMe), 3.88—4.04 (2 H, m, OCH), 4.90 and 5.13 (each 1 H, each d, *J* 1 Hz, $=CH_2$), and 6.64—7.06 (3 H, m, ArH); *m/z* 334 (M^+).

(4S,5S)-4,5-*Bis*(*benzyloxymethyl*)-2-[2-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2-*isopropenyl*-1,3-*dioxolane* (**1e**).—A solution of the alcohol (**1d**) (20 mg, 0.06 mmol) in anhydrous dimethylformamide (0.5 ml) was added to a suspension of sodium hydride (60% in oil; 7.2 mg, 0.18 mmol) in anhydrous dimethylformamide (1.0 ml) at 0 °C, and the mixture was stirred for 15 min at room temperature. Benzyl bromide (30 mg, 0.18 mmol) in anhydrous dimethylformamide (0.5 ml) was then added to it at 0 °C. After being stirred for 13 h at room temperature, the mixture was diluted with aqueous ammonium chloride (5 ml) and extracted with benzene. The extract was washed with saturated brine and the residue upon work-up was chromatographed on silica gel (1 g) with hexane–ethyl acetate (95:5, v/v) to afford the *benzyl ether* (**1e**) (29 mg, 94%) as an oil (Found: C, 77.3; H, 7.65. $C_{22}H_{38}O_5$ requires C, 77.0; H, 7.45); $\delta_H(CDCl_3)$ 1.79 (3 H, s, =CMe), 3.79 (3 H, s, OMe), 3.90—4.10 (2 H, m, OCH), 4.55 and 4.62 (each 2 H, each s, OCH_2Ph), 4.88 and 5.19 (each 1 H, each d, *J* 1 Hz, $=CH_2$), and 6.68—7.10 (3 H, m, ArH); *m/z* 514 (M^+).

2-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-6,6,8,8-*tetraisopropyl*-2-*isopropenyl*-3a,4,10,10a-*tetrahydro*-1,3-*dioxolo*[7,8-d][1,3,5,2,4]*trioxadisilonine* (**1f**).—1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (59 mg, 0.19 mmol), imidazole (13 mg, 0.19 mmol), and 4-dimethylaminopyridine (catalytic amount) were added at room temperature to a stirred solution of the alcohol (**1d**) (48 mg, 0.14 mmol) in dimethylformamide (2 ml). After being stirred for 17 h at the same temperature, the reaction mixture was diluted with water (20 ml) and extracted benzene, and the extract was washed with saturated aqueous ammonium chloride and saturated brine. The residue upon work-up was chromatographed on silica gel with hexane–ethyl acetate (95:5, v/v) to afford the *title compound* (**1f**) (75 mg, 91%) as an oil; $\delta_H(CDCl_3)$ 0.90—1.12 [24 H, m, 4 × $CH(Me)_2$], 1.77 (3 H, s, =CMe), 3.75 (3 H, s, OMe), 4.00—4.15 (2 H, m, OCH), 4.83 and 5.12 (each 1 H, each d, *J* 1 Hz, $=CH_2$), and 6.62—7.03 (3 H, m, ArH) [Found: M^+, 576.3307. $C_{31}H_{52}O_6Si_2$ requires *M*, 576.3302].

General Procedure for the Thermolysis of the Acetals (**1a,b,e,f**) *and Synthesis of* 7-*Methoxy*-3a-*methyl*-2,3,3a,4,5,9b-*hexahydro*-1H-*benz*[e]*inden*-3-*one* (**4**) *and* (**5**).—A solution of the acetal (0.19 mmol) in *o*-dichlorobenzene (10 ml) was heated at 180 °C for 4 h. After removal of the solvent, the residue was dissolved in acetone (8 ml) containing 10% aqueous hydrochloric acid (4 ml) and the solution stirred for 11 h at room temperature. The mixture was basified with sodium hydrogen carbonate and the solvent was evaporated. The residue was diluted with water (10 ml) and extracted with ether, and the extract was washed with saturated brine. The residue upon work-up was chromatographed on silica gel (2 g) with hexane–ethyl acetate (19:1, v/v) to give compounds (**4**) and (**5**); the yields and ratios of these are summarized in the Table. Spectral data for compounds (**4**) and (**5**) were identical with those of authentic samples[3a,e] except for the $[\alpha]_D^{25}$ value.

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