Highly Enantioselective Elimination of *meso*-Compounds

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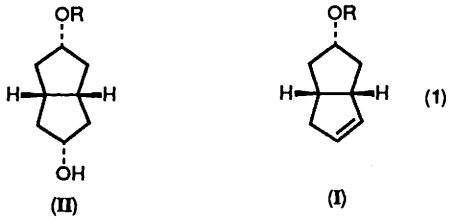
Useful chiral synthons for the synthesis of natural products, consisting of derivatives of the fixed five-membered ring system bicyclo[3.3.0]oct-2-ene, were obtained in high optical purity (87–99% e.e.) by asymmetric elimination of the corresponding achiral (*meso*) trifluoromethanesulphonates with chiral *N,N*-dimethyl-1-phenylethylamine. However, asymmetric elimination of the chiral (+)-camphor-10-sulphonates with an achiral base resulted in low optical purity. In this enantioselective asymmetric elimination, the concave side of bicyclic ring system seems to play an important role. Asymmetric elimination of the monotriflate of *cis*-cyclohexane-1,4-diol resulted in a product with unsatisfactory optical purity.

There are a number of biologically active natural products containing five-membered rings, such a prostaglandins and prostacyclin. As part of our research into the synthesis of these compounds, we have undertaken the synthesis of optically active bicyclo[3.3.0]oct-2-ene derivatives (**I**) by asymmetric elimination [equation (1)]. Compounds (**I**) seem to be useful



chiral synthons for the synthesis of natural products such as brefeldin A,[1] as well as carbacyclin (carbocyclic analogue of prostacyclin), because (±)-(**I**) has already been converted into the carbocyclic analogue;[2] in addition, the fission of the double bond seems to provide the required functional groups for the synthesis of brefeldin A.

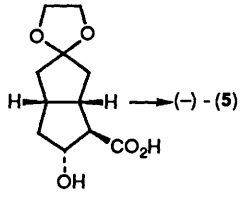
In asymmetric elimination of monocyclic *meso*-compounds with the OH function in the plane of symmetry, highly enantioselective elimination is rarely observed. Goldberg and Sahli[3] succeeded in their synthesis of 4-methylcyclohexene with 70% optical yield by pyrolysis of optically active 4-methylcyclohexyl *p*-tolyl sulphoxide. Cope elimination of the optically active *N*-oxide was examined by Berti and Bellucci,[4] but it resulted in the formation of 4-methylcyclohexene with only 30% enantiomeric excess (e.e.). In the bicyclo[3.3.0]octane ring system, Gais and co-workers[5] succeeded in asymmetric elimination of an optically active β-hydroxy sulphoximide to an alkenyl sulphoximide with 98% diastereoisomer excess (d.e.). However, this method seems to be tedious for the preparation of the substrate, and the product is not very advantageous from the synthetic viewpoint.

We now describe[6] a synthesis of synthetically important chiral bicyclo[3.3.0]octenes based on asymmetric elimination. In the synthesis of the optically active compounds (**I**), the ideal procedure is considered to be the asymmetric elimination of the alcohol function in the *meso*-compound (**II**). There are two methods for this elimination. One is asymmetric elimination by treatment with achiral bases after conversion of the alcohol function in substrates (**II**) into a chiral leaving group such as the optically active camphorsulphonic ester. The other is asymmetric elimination by chiral bases after conversion of the alcohol function in substrates (**II**) into an achiral leaving group such as triflate.

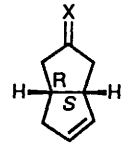
Asymmetric Elimination by Achiral Bases.—Compounds (**II**) have a characteristic structure with both a concave and a convex side. This interesting structure suggests that there are remarkable differences in the facility of reagent approach or elimination of leaving group between the two sides of the molecule. In other words, the concave side in substrates (**II**) seems to fix the conformation for the *endo*, bulky leaving group (camphorsulphonate). In the case of (+)-camphor-10-sulphonate as leaving group, the asymmetric elimination using Bu^{t}OK was examined, and the results shown in Table 1 were obtained.

Although this asymmetric elimination resulted in unsatisfactory optical yields,† it is noteworthy that addition of 18-crown-6 (entries 4 and 7) or Al $(CH_2COCH_2COCH_3)_3$ (or $LiCH_2COCH_2COCH_3$)‡ (entries 5 and 8) afforded the product with the reversed optical rotation (+)-(**6**), in contrast to the case with Bu^{t}OK. This may be rationalized as follows. Two conformers (**IIIA**) or (**IIIB**) of the substrate are presumed. Examination of

† It was difficult to determine the optical purity of the products by the usual methods such as the α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester method or by ^{13}C NMR spectroscopy, because the two diastereoisomers could not be observed as separated peaks. Consequently, we were forced to determine the optical purities by comparison with the specific rotations of the authentic compounds, which could be prepared from the optically active hydroxy acid[7] *via* dehydrative decarboxylation by treatment with DMF-DMF dimethyl acetal (see Experimental section).



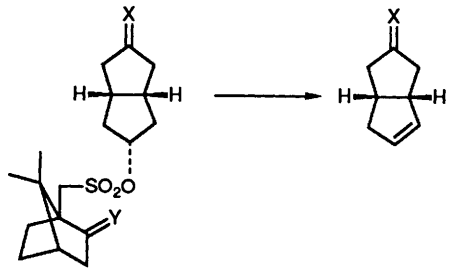
$[\alpha]^{25}_D$ +23.4°
(*c* 7.1, $CHCl_3$)



X	$[\alpha]_D^{25}(CHCl_3)$
(–)-(7) O	–160.5° (*c* 0.74)
(–)-(5) OCH_2CH_2O	–59.2° (*c* 1.65)
(–)-(8) ---OH, —H	–75.4° (*c* 1.00)
(–)-(6) ----OMEM, —H	–50.9° (*c* 2.75)

‡ $Al(acac)_3$ or Li(acac).

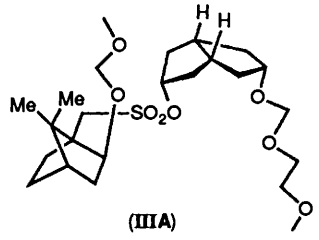
Table 1. Elimination of camphorsulphonates (1)–(4).[a,b]



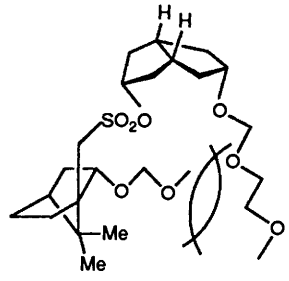
(1) X = OCH_2CH_2O, Y = O — (−)-(5)
(2) X = OCH_2CH_2O, Y = —OMEM, ···· H — (−)-(5)
(3) X = ····OMEM, — H, Y = —OMEM, ···· H — (−)-(6)
(4) X = ····OMEM, — H, Y = — OCH_2OMe, ···· H — (−)-(6)

Entry	Substrate	Base (3 mol equiv.)	Temp. (°C)	e.e (%)	$([\alpha]_D)^f$	Product
1	(1)	Bu^{t}OK	−50	10	(−5.9°)	(−)-(5)
2	(2)	Bu^{t}OK	−50	12	(−7.1°)	(−)-(5)
3	(4)	Bu^{t}OK	r.t.	13	(−6.6°)	(−)-(6)
4	(4)	Bu^{t}OK + *c*	−80	12	(+6.1°)	(+)-(6)
5	(4)	*d*	−50	31	(+15.8°)	(+)-(6)
6	(3)	Bu^{t}OK	r.t.	12	(−6.1°)	(−)-(6)
7	(3)	Bu^{t}OK + *c*	−50	12	(+6.1°)	(+)-(6)
8	(3)	*e*	−50	21	(+10.7°)	(+)-(6)

[a] Chemical yield 11–54%. [b] Solvent tetrahydrofuran (THF) except for entry 2 [dimethyl formamide (DMF)]. [c] 18-Crown-6. [d] $Al(acac)_3$. [e] Li(acac). [f] Measured in $CHCl_3$ (25 °C).



(IIIA)



(IIIB)

stereomodels suggests that conformer (**IIIA**) is the more favourable conformation than is (**IIIB**), in which there is a steric repulsion between the dimethyl and methoxyethoxymethoxy (MEM) substituents. Therefore, elimination seems to proceed in conformer (**IIIA**). It is likely that K^+ ion in Bu^{t}OK chelates between SO_2 and the ether oxygen on the hindered side, and causes abstraction of hydrogen H^a as shown in structure (**IVA**) to afford (−)-(**6**). On the other hand, bulky 18-crown-6 forms a clathrate compound of K^+ at the less hindred side, as shown in structure (**IVB**). This allows the abstraction of hydrogen H^b to afford (+)-(**6**), in contrast to the case of Bu^{t}OK. Similarly, $Al(acac)_3$ or Li(acac) approaches from the less hindered side to abstract hydrogen H^b, affording product (+)-(**6**). Next, our attention was directed to asymmetric elimination by chiral bases.

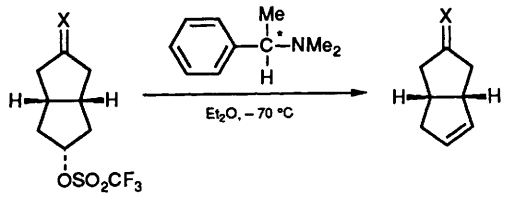
Asymmetric Elimination by Chiral Bases.—Triflate ion[8] is considered to be readily eliminated by amine bases. On the assumption that chiral amines will be able to discriminate between the two *trans*-protons on each side of the *endo*-triflate leaving group, this elimination is considered to proceed in an asymmetric manner.

Triflates with various protecting groups were subjected to asymmetric elimination by chiral amines [quinine, quinidine, (−)-nicotine, (−)-ephedrine, (+)- and (−)-*N*,*N*-dimethyl-1-phenylethylamine]. Among the tested elimination reactions (Table 2), (−)- and (+)-*N*,*N*-dimethyl-1-phenylethylamine afforded the products, in 70–99% yield, with much higher optical purities than in the case of asymmetric elimination of a chiral leaving group by achiral bases. In particular, entry 7 gave the best result (93% e.e). Taking into account the optical purity *

* Attempts to determine the optical purities of chiral *N*,*N*-dimethyl-1-phenylethylamine employed for asymmetric elimination by using chiral shift reagents resulted in failure. The authentic chiral dimethylamine could be prepared from (*S*)-(−)-1-phenylethylamine (R. F. Borch and A. I. Hassid, *J. Org. Chem.*, 1972, **37**, 1673), which is commercially available, and could be confirmed to be 100% e.e by analysis using the chiral shift reagent tris-[(+)-3-(trifluoromethylhydroxymethylene)-camphorato]europium [$Eu(tfc)_3$]. Thus, based on the reliable specific rotation ($[\alpha]_D^{25}$ −45.1°), (*S*)-(−)- and (*R*)-(+)-*N*,*N*-dimethyl-1-phenylethylamine employed for asymmetric elimination were determined to be 95 and 93% e.e, respectively.

Employed chiral amine	$[\alpha]_D^{25}$ (MeOH)	e.e (%)
(*S*) (−)	−42.7° (*c* 1.25)	95.0
(*R*) (+)	+41.9° (*c* 1.35)	93.0

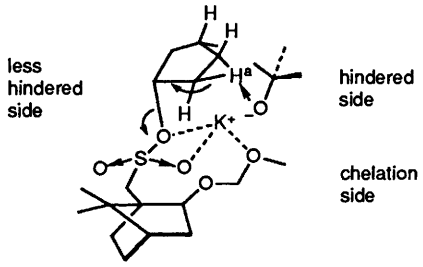
Table 2. Elimination of triflates (9)–(12).



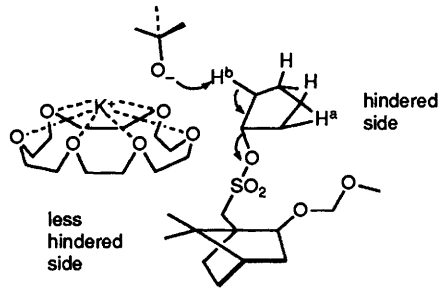
(9) X = OCH_2CH_2O (−)-(5)
(10) X = O (−)-(7)
(11) X = ---- OMEM, — H (−)-(6)
(12) X = $OCH_2CH_2CH_2O$ (−)-(13)

Entry	Substrate	Base	e.e. (%)	$[\alpha]_D^{25}(CHCl_3)$	Product
1	(10)	(*R*)(+)	41(44)	+65.8°	(+)-(7)
2	(10)	(*S*)(−)	49(52)	−78.6°	(−)-(7)
3	(9)	(*R*)(+)	81(87)	+48.0°	(+)-(5)
4	(9)	(*S*)(−)	89(94)	−52.0°	(−)-(5)
5	(12)	(*R*)(+)	85(89)	+136.4°	(+)-(13)
6	(12)	(*S*)(−)	86(91)	−138.0°	(−)-(13)
7	(11)	(*R*)(+)	93(99)	+47.3°	(+)-(6)
8	(11)	(*S*)(−)	84(88)	−42.8°	(−)-(6)

Number in parentheses: revised values on the basis of the optical purity of the employed chiral amine. Optical purity of compound (13) was estimated after conversion into the ketone (7). Chemical yield > 70%.



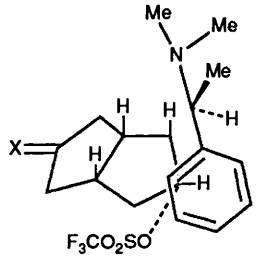
(IVA)



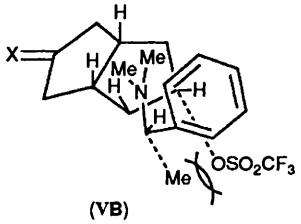
(IVB)

of (+)-*N*,*N*-dimethyl-1-phenylethylamine, this asymmetric elimination is considered to proceed stereospecifically (99% e.e). The decrease of optical purity in entry 8 in comparison with entry 7 may be caused by a slight rise * in temperature (−70 °C) during the dropwise addition of the chiral amine. The low enantioselectivity of entries 1 and 2 may be attributed to a remarkable reduction of the steric hindrance on the concave side, which may permit a non-selective approach of the chiral amine.

The following asymmetric elimination mechanism is tentatively proposed. Stereochemical repulsion between the triflate and the protecting group in the concave side seems to facilitate the elimination of the *endo*-triflate. When the triflate is about to leave, the chiral base may approach from the convex side to compensate the resulting carbocation by the participation of the π-orbitals in the benzene ring and concomitantly to remove the *trans* hydrogen by the dimethylamino group as shown in structure (**VA**). On the other hand, approach of amine as shown in structure (**VB**) may be unfavourable, because of stereochemical repulsion between the C–Me and the triflate.



(VA)



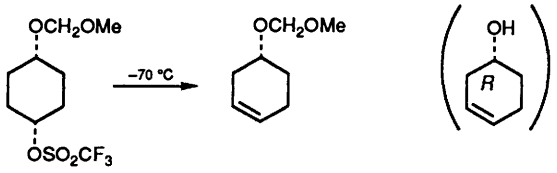
(VB)

Success in the asymmetric elimination of the bicyclo-[3.3.0]octane ring system prompted us to apply this method to *cis*-cyclohexane-1,4-diol derivatives.[9] The optical purity of the cyclohex-3-enol derivative product was determined by examination of the 270 MHz ^1H NMR spectrum after conversion into the MTPA ester, and the absolute configuration was established by comparison with a standard sample of (*S*)-(**15**).† Asymmetric elimination of substrate (**14**) with (*S*)-(−)-

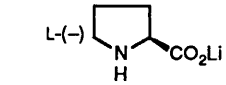
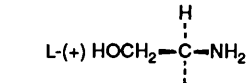
* In this asymmetric elimination, the reaction temperature seems to play an important role, because the elimination reaction in entry 3 (at −50 °C) afforded compound (+)-(**11**) with low optical purity (55% e.e).

† (*S*)-(−)-cyclohex-3-enol was prepared from the known compound (see H. Suemune, M. Hizuka, T. Kamashita, and K. Sakai, *Chem. Pharm. Bull.*, 1989, **37**, 1379); the absolute stereochemistry was determined according to conventional methods.

Table 3. Elimination of triflate (**14**).



(**14**) (**15**)

Entry	Base (10 mol equiv.)	Solvent	Product Abs. config.	Product ee(%)
1	D-(+)-CSA•Ca salt [a] (mol equiv.)	MeOH	*R*	10
2	L-(−) 	MeOH	*S*	19
	L-(+) 			
3		Et_2O	*R*	22

[a] CSA = Camphor-10-sulphonic acid.

N,N-dimethyl-1-phenylethylamine afforded only a 5% e.e of cyclohex-3-enol. Among the tested chiral bases, (+)-camphorsulphonic acid Ca salt, L-proline Li salt, and L-(+)-valinol afforded the product with optical purity as shown in Table 3. The low optical purity in the monocyclic ring system products suggests strongly that the concave side in the bicyclo[3.3.0]loactane ring system plays an important role in asymmetric elimination.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-PS-100 or a JNM-GM-270 spectrometer. Mass spectra were taken on a JEOL JMS-D-300 spectrometer. Specific rotations were measured on a JASCO DIP-4 polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70–230 mesh) was used. TLC was performed on silica gel F_{254} plates (Merck). All organic solvent extracts were washed with brine and dried on anhydrous sodium sulphate.

General Procedure for Asymmetric Elimination of (+)-Camphorsulphonates (*Table* 1).—(*i*) A solution of a base (0.9 mmol) in THF (5 ml) was added dropwise to a stirred solution of a(+)-camphorsulphonate (0.3 mmol) in THF (10 ml) under N_2. After being stirred for 48 h, the reaction mixture was diluted with ether (100 ml). The organic layer was washed and dried, then concentrated under reduced pressure to leave an oily residue, which was subjected to column chromatography on silica gel.

(ii) Bu^{t}OK (0.9 mmol) was added dropwise to a stirred mixture of a(+)-camphorsulphonate (0.3 mmol) and 18-crown-6 (1.8 mmol) in THF (10 ml) under N_2; the mixture was stirred for 45 h, and then was subjected to a similar work-up as in (i).

General Procedure for Asymmetric Elimination of Triflates with Chiral Amines (*Table* 2).—A solution of optically active *N,N*-dimethyl-1-phenylethylamine (3 mmol) in diethyl ether (5 ml) cooled to −70 °C was added dropwise to a stirred solution of the triflate (0.3 mmol) in diethyl ether (10 ml) at −70 °C under N_2. The mixture was stirred for 4–6 h, then diluted with diethyl ether (100 ml), and the organic layer was successively washed with 1% aqueous HCl and brine, then dried. Removal of the solvent under reduced pressure afforded an oily residue, which was subjected to column chromatography on silica gel.

General Procedure for Asymmetric Elimination of Triflate (**14**) *with Chiral Bases* (*Table* 3).—Asymmetric elimination was carried out in a similar manner to that described for the bicyclic ring system. The employed amine bases were as shown in Table 3, as well as (+)-*N,N*-dimethyl-1-phenylethylamine.

Synthesis of Substrates.—Substrates were prepared from bicyclo(3.3.0)octane-3,7-dione by conventional methods.

3α-[(+)-Camphorsulphonyloxy]-7,7-ethylenedioxy-1β,5β-bicyclo[3.3.0]*octane* (**1**). *Needles* m.p. 69–71 °C (from hexane–AcOEt) (Found: C, 60.3; H, 7.7. $C_{20}H_{30}O_6S$ requires C, 60.28; H, 7.59%); $[\alpha]_D^{25}$ +28.8° (*c* 1.3 in $CHCl_3$); ν_{max} (Nujol) 1 740, 1 360, 1 170, 1 120, and 1 090 cm^{-1}; δ_H ($CDCl_3$) 0.88 and 1.12 (3 H, each, s, Me × 2), 2.97 and 3.60 (1 H each, d, *J* 15 Hz, CH_2SO_2), 3.88 (4 H, s, OCH_2CH_2O), and 5.01 (1 H, m, $CHOSO_2$); *m/z* 398 (M^+, 2), 166 (100), 138 (11), and 122 (4%).

7,7-Ethylenedioxy-3α-{(1R,2S,4S)-2-[(2-methoxyethoxy)-methoxy]bornane-10-sulphonyloxy}-1β,5β-bicyclo[3.3.0]*octane* (**2**). Oil; $[\alpha]_D^{25}$ − 2.83° (*c* 0.92 in $CHCl_3$); ν_{max} (film) 1 355, 1 335, 1 170, and 1 045 cm^{-1}; δ_H ($CDCl_3$) 0.84 and 1.00 (3 H each, s, Me × 2), 2.88 and 3.65 (1 H each, d, *J* 15 Hz, CH_2SO_2), 3.38 (3 H, s, OMe), 3.46–3.84 (4 H, m, OCH_2CH_2O), 3.89 (4 H, s, OCH_2CH_2O), 4.77 (2 H, s, OCH_2O), and 4.94 (1 H, m, $CHOSO_2$); *m/z:* 488 (M^+, 14), 473 (6), 457 (22), and 399 (100%).

3α-(2-Methoxyethoxy)methoxy-7α-{(1R,2S,4S)-2-[(2-methoxyethoxy)methoxy]bornane-10-sulphonyloxy}-1β,5β-bicyclo[3.3.0]*octane* (**3**). Oil; $[\alpha]_D^{25}$ − 3.88° (*c* 1.39 in $CHCl_3$); ν_{max} (film) 2 940, 2 880, 1 450, 1 360, 1 165, and 1 040 cm^{-1}; δ_H ($CDCl_3$) 0.85 and 1.00 (3 H each, s, Me), 3.38 (6 H, s, OMe × 2), 2.87 and 3.63 (1 H each, d, *J* 14 Hz, CH_2SO_2), 3.52–3.72 (8 H, m, OCH_2CH_2O × 2), 3.92 and 4.10 (1 H each, m, C*H*OMEM × 2), 4.71 and 4.76 (2 H each, s, OCH_2O × 2), and 4.94 (1 H, m, $CHOSO_2$); *m/z* 428 (1), 383 (1), 339 (6), and 216 (100%).

3α-(2-Methoxyethoxy)methoxy-7α-[(1R,2S,4S)-2-methoxy-methoxyborane-10-sulphonyloxy]-1β,5β-bicyclo[3.3.0]*octane* (**4**). Oil; $[\alpha]_D^{25}$ − 0.82° (*c* 1.22 in $CHCl_3$); ν_{max} (film) 2 930, 2 880, 1 450, 1 355, and 1 155 cm^{-1}; δ_H ($CDCl_3$) 0.83 and 1.02 (3 H each, s, Me × 2), 2.87 and 3.62 (1 H each, d, *J* 14 Hz, CH_2SO_2), 3.36 and 3.38 (3 H each, s, OMe × 2), 3.50–3.64 (4 H, m, OCH_2CH_2O), 3.82 (1 H, m, C*H*OMOM), 4.08 (1 H, m, C*H*OMEM), 4.66 and 4.68 (2 H each, s, OCH_2O × 2), and 4.93 (1 H, m, $CHOSO_2$); *m/z* 490 (M^+, 88), and 459 (100), 445 (95), and 339 (62%).

3,3-Ethylenedioxy-7α-trifluoromethylsulphonyloxy-1β,5β-bicyclo[3.3.0]*octane* (**9**). The product was subjected to asymmetric elimination without chromatographic purification. δ_H ($CDCl_3$) 1.43–2.47 (10 H, m), 3.83 (4 H, s, OCH_2CH_2O), and 5.43–5.63 (1 H, m, CHOTf).

3α-Trifluoromethylsulphonyloxy-1β,5β-bicyclo[3.3.0]*octan-7-one* (**10**). Oil; δ_H ($CDCl_3$) 1.43–2.69 (10 H, m) and 5.42–5.62 (1 H, m, CHOTf).

3α-[(2-Methoxyethoxy)methoxy]-7α-trifluoromethylsulphonyloxy-1β,5β-bicyclo[3.3.0]*octane* (**11**). Oil; δ_H ($CDCl_3$) 1.25–2.53 (10 H, m), 3.39 (3 H, s, OMe), 3.47–3.72 (4 H, m, OCH_2CH_2O), 4.08–4.27 (1 H, m, C*H*OMEM), 4.72 (2 H, s, OCH_2O), and 5.43–5.64 (1 H, m, CHOTf).

3,3-(Propane-1,3-diyldioxy)-3α-trifluoromethylsulphonyloxy-1β,5β-bicyclo[3.3.0]*octane* (**12**). Oil; δ_H ($CDCl_3$) 1.45–2.53 (12 H, m), 3.82–3.97 (4 H, m, OCH_2CCH_2O), and 5.41–5.62 (1 H, m, CHOTf).

cis-1-Methoxymethoxy-4-trifluoromethylsulphonyloxycyclohexane (**14**). Oil; prepared from *cis*-cyclohexane-1,4-diol; δ_H ($CDCl_3$) 1.26–2.18 (8 H, m), 3.38 (3 H, s, OMe), 3.76–3.90 (1 H,

m, C*H*OMOM), 4.72 (2 H, s, OCH_2O), and 5.59–5.65 (1 H, m, CHOTf).

Standard Samples.—(S)-*Cyclohex-3-enol* (**15**). Oil; $[\alpha]_D^{25}$ −5.13° (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3 350, 1 645, 1 440, 1 360, and 1 035 cm^{-1}; δ_H ($CDCl_3$) 1.56–2.42 (6 H, m), 1.58 (1 H, br, OH), 3.92–4.01 [1 H, m, C*H*(OH)], and 5.56–5.70 (2 H, m, CH=CH).

(1R,5S)-*Bicyclo*[3.3.0]*oct-6-en-3-one* (−)-(**7**). A mixture of (−)-(**5**) (84 mg) and 5% aqueous HCl (1 ml) in EtOH (5 ml) was stirred for 1 h at room temperature, and diluted with AcOEt. The AcOEt extract was washed successively with 5% aq. $NaHCO_3$ and brine, then dried. Removal of the solvent under reduced pressure afforded an oily residue, which was purified by column chromatography on silica gel (1 g). The fraction eluted with 10% diethyl ether in hexane afforded the ketone (−)-(**7**) (41 mg, 66%) as an oil, ν_{max} (film) 1 740, 1 635, and 1 110 cm^{-1}; δ_H ($CDCl_3$) 1.76–3.16 (7 H, m), 3.41 (1 H, m, CH), and 5.70 (2 H, m, CH=CH); *m/z* 122 (M^+, 100), 80 (88), and 66 (9%).

(1S,5R)-7,7-*Ethylenedioxybicyclo*[3.3.0]*oct-2-ene* (−)-(**5**). DMF dimethyl acetal (1.38 g, 11.6 mmol) was added to a solution of the optically active hydroxy acid[7] (440 mg, 1.93 mmol) in $CHCl_3$ (10 ml). After being stirred for 15 h at room temperature, the mixture was evaporated under reduced pressure to leave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% diethyl ether in hexane afforded compound (−)-(**5**) (99 mg, 31%) as an oil, ν_{max} (film) 1 615, 1 110, and 1 080 cm^{-1}; δ_H ($CDCl_3$) 1.40–2.38 (5 H, m), 2.70 (2 H, m, 4-H_2), 3.20 (1 H, m, 1-H), 3.68 (4 H, s, OCH_2CH_2O), and 5.60 (2 H, m, CH=CH); *m/z* 166 (M^+, 61), 138 (14), 122 (13), and 86 (100%).

(1R,3S,5S)-*Bicyclo*[3.3.0]*oct-6-en-3-ol* (−)-(**8**). $NaBH_4$ (13 mg, 0.34 mmol) was added to a solution of ketone (−)-(**7**) (41 mg, 0.34 mmol) in EtOH (2 ml) at 0 °C. After 10 min, brine was added, the mixture was extracted with diethyl ether, and the extract was dried. The solvent was removed under reduced pressure to afford an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% diethyl ether in hexane gave the alcohol (−)-(**8**) (24 mg, 58%) as an oil, ν_{max} (film) 3 325, 1 610, and 1 080 cm^{-1}; δ_H ($CDCl_3$) 1.28–2.44 (6 H, m), 2.71 (2 H, m, 8-H_2), 3.18 (1 H, m, 5-H), 4.19 (1 H, m, CHO), and 5.60 (2 H, m, CH=CH); *m/z* 124 (M^+, 7), 106 (84), and 91 (100%).

(1S,5R,7S)-7-[(2-*Methoxyethoxy*)*methoxy*]*bicyclo*[3.3.0]*oct-2-ene* (−)-(**6**). Mixture of compound (−)-(**8**) (20.5 mg, 0.17 mmol), MEMCl (74 mg, 0.60 mmol), and *N,N*-di-isopropylethylamine (307 mg, 2.38 mmol) in CH_2Cl_2 (0.5 ml) was stirred for 4 h at room temperature, diluted with brine, extracted with CH_2Cl_2, and the extract was dried. Removal of the solvent under reduced pressure afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 2% diethyl ether in hexane gave compound (−)-(**6**) (32 mg, 91%) as an oil, ν_{max} (film) 1 645, 1 445, 1 160, 1 110, and 1 050 cm^{-1}; δ_H ($CDCl_3$) 1.21–1.68 (8 H, m), 3.48–3.73 (4 H, m, OCH_2CH_2O), 3.40 (3 H, s, OMe), 4.02 (1 H, m, C*H*OMEM), 4.70 (2 H, s, OCH_2O), and 5.60 (2 H, m, CH=CH); *m/z* 212 (M^+, 3), 167 (8), 137 (4), and 106 (100%).

References

1 C. Le. Drian and A. E. Greene, *J. Am. Chem. Soc.*, 1982, **104**, 5473.
2 M. Demuth and K. Schaffner, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 820.
3 S. I. Goldberg and M. S. Sahli, *J. Org. Chem.*, 1967, **32**, 2059.
4 G. Berti and G. Bellucci, *Tetrahedron Lett.*, 1964, 3853.
5 I. Erdelmeier, H. J. Gais, and H. J. Linder, *Agnew. Chem., Int. Ed. Engl.*, 1986, **25**, 935; S. Sakane, J. Fujisawa, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 6154; J. M. Wilson and D. J. Cram, *J. Org. Chem.*, 1984, **49**, 4930.
6 Preliminary report; H. Kashihara, H. Suemune, T. Kawahara, and K. Sakai, *Tetrahedron Lett.*, 1987, **28**, 6489.
7 K. Kojima, S. Amemiya, K. Koyama, and K. Sakai, *Chem. Pharm. Bull.*, 1985, **33**, 2688.
8 P. T. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, 1982, 85.
9 R. C. Olberg, H. Pines, and V. N. Ipatieff, *J. Am. Chem. Soc.*, 1944, **66**, 1096.

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