Chiral Crown Ethers derived from (+)-(1*S*, 2*S*)-*trans*-Cyclohexane-1,2-diol

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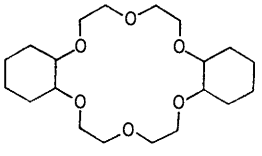
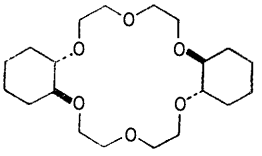
Preparations are described of (+)-*trans,anti,trans*-dicyclohexyl-18-crown-6 (2). (+)-*trans*-cyclohexyl-15-crown-5 (5). and (+)-*trans*-cyclohexyl-18-crown-6 (6) from (+)-*trans*-cyclohexane-1,2-diol. Each of the crown ethers was converted into a typical cryptate.

SINCE the discovery by Pedersen [1] of the ability of macrocyclic polyethers to form complexes with metal cations, there has been considerable interest in the synthesis and chemistry of monocyclic crown ethers and macrobicyclic polyethers.[2] A more recent development has been the design of chiral cryptands with two general aims in mind: (i) the resolution of racemic modifications *via* diastereoisomeric complexes (' chiral recognition '), and (ii) stereoselective catalysis of reactions which lead to enantiomeric products (chiral catalysis). Two styles of architecture can be recognised amongst existing chiral cryptands: those based on optically active binaphthyls,[3] and those derived from naturally occurring polyols or tartaric acids.[4]

Amongst Pedersen's original crown ethers was dicyclohexyl-18-crown-6 (1), obtained by hydrogenation of dibenzo-18-crown-6 [1,5] and now known to be a mixture of the *cis,syn,cis*- and *cis,anti,cis*-isomers.[6] Because of its greater lipophilicity compared with the simple 18-crown-6, compound (1) has found favour as a phase transfer catalyst.[7] Some time ago it occurred to us that if an efficient route to dicyclohexyl-18-crown-6 from *trans*-cyclohexane-1,2-diol could be devised, then resolution at an appropriate stage would allow preparation of the chiral crown (2) (one enantiomer shown).



(1)



(2)

Ingeneous stereocontrolled syntheses of *trans,syn,trans*- and (±)-*trans,anti,trans*-dicyclohexyl-18-crown-6 have been achieved by Stoddart and Wheatley,[8] but their approach was unsuitable for optically active cyclohexane-1,2-diol because of the low overall yield.

Exploratory experiments with (±)-*trans*-cyclohexane-1,2-diol showed that direct cyclisation with 2,2'-oxybis(ethyl tosylate) patterned on Dale and Kristianson's synthesis of 18-crown-6 [9] was unsatisfactory because of low yields.[10] Attention was thus turned to an indirect

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[2] For reviews see C. J. Pedersen, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16; J. M. Lehn, *Structure and Bonding*, 1973, **16**, 1; D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803; G. W. Gokel and H. D. Durst, *Synthesis*, 1976, 168.

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[4] J.-M. Girondeau, J.-M. Lehn, and J.-P. Sauvage, *Angew. Chem. Internat. Edn.*, 1975, **14**, 764; W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1975, 833.

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[6] N. K. Dalley, D. E. Smith, R. M. Izatt, and J. J. Christensen, *J.C.S. Chem. Comm.*, 1972, 90; D. E. Fenton, M. Mercer, and M. R. Truter, *Biochem. Biophys. Res. Comm.*, 1972, **48**, 10; M. Mercer and M. R. Truter, *J.C.S. Dalton*, 1973, 2215.

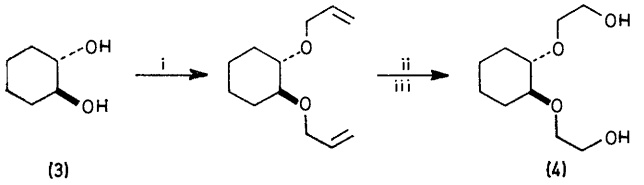
[7] D. Landini, F. Montanari, and F. M. Pirisi, *J.C.S. Chem. Comm.*, 1974, 879.

[8] J. F. Stoddart and C. M. Wheatley, *J.C.S. Chem. Comm.*, 1974, 390.

[9] J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, 1972, **26**, 1471.

[10] P. A. Wilkinson, Part II Thesis, Oxford, 1973.

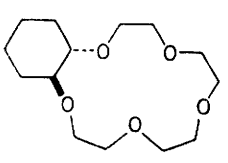
approach *via* the ' half-crown ' diol (4) involving final cyclisation with an equimolar mixture of (4) and its ditosylate analogous to Greene's synthesis of 18-crown-6.[11] The route finally adopted is that shown in the Scheme. The sluggish reactivity of the cyclohexanediol towards *O*-alkylation was circumvented by use of the reactive allyl bromide, and the desired functionality was then generated by ozonolysis and reductive work-up with sodium borohydride. The diol (4) underwent cyclisation with its ditosylate on treatment with potassium t-butoxide in benzene to give the *trans,syn,trans*-isomer of dicyclohexyl-18-crown-6. The marked tendency for pairing of (+)- with (−)- in the cyclisation to give the *meso*-form of the crown ether emphasises the need, from the point of view of the chiral crown ether synthesis, for precursors of relatively high optical purity. Resolution at the crown ether stage is not a viable possibility, at least for the dicyclohexyl system.



SCHEME Reagents: i, NaH–$Me_2N{\cdot}CHO$–$CH_2{:}CH{\cdot}CH_2Br$; ii, O_3–MeOH at −70 °C; iii, $NaBH_4$ at 0 °C

The resolution of (±)-*trans*-cyclohexane-1,2-diol *via* the monomenthyloxyacetate has been reported by Wilson and Read,[12] but in our hands the procedure was wasteful in materials. A more satisfactory, if slow resolution was achieved by crystallisation of the diastereoisomeric strychnine salts of the hemisulphate diester from *trans*-cyclohexane-1,2-diol.*,[13] This method gave (+)-(1*S*,2*S*)-diol [absolute configuration as in (3) [15]] which was converted into the ' half-crown ' (4) in 76% yield by the above procedure. Tosylation followed by cyclisation as before gave (+)-*trans,anti,trans*-dicyclohexyl-18-crown-6 (2), $[\alpha]_D$ +39.2°.

The availability of the optically active diol (4) allowed two other chiral crown ethers to be prepared. These were (+)-cyclohexyl-15-crown-5 (5), $[\alpha]_D$ +36.5°, from cyclisation with 2,2′-oxybis(ethyl tosylate), and (+)-cyclohexyl-18-crown-6 (6), $[\alpha]_D$ +25.1°, from 2,2′-ethylenedioxybis(ethyl tosylate).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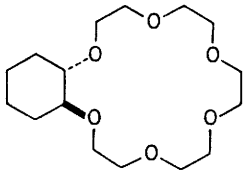
(6)

The following typical crystalline cryptates of the three chiral crown ethers were prepared by standard procedures.[1] These are listed along with the molecular rotation for each (in EtOH), and in parentheses is quoted the molecular rotation for the free crown ether: [(5), NaCNS], +157° (+99°); [(6), NH_4CNS], +158° (+77.5°); [(2), KI], +311° (+146°). The marked difference in molecular rotation between the free and the complex ligand presumably reflects a significant conformational change on complexation. In the case of the ammonium thiocyanate complex of cyclohexyl-18-crown-6 (6), mutarotation was also observed. Further work is needed to clarify this phenomenon.

EXPERIMENTAL

trans-1,2-*Bis(allyloxy)cyclohexane*.— *trans*-Cyclohexane-1,2-diol [16] (25 g, 0.22 mol) and allyl bromide (80 ml, 0.93 mol) in dry dimethylformamide (500 ml) were stirred at 0 °C, and sodium hydride (24 g, 1 mol) was added in small portions. Vigorous effervescence occurred. The mixture was then stirred for 3 h, and heated on a steam-bath for 1 h. Water was added to the cooled mixture and the product was isolated by extraction with ether. Distillation from a large flask (foaming) gave the *diallyl ether* as a pale yellow oil (36 g, 85%), b.p. 110—116° at 15 mmHg (Found: C, 73.4; H, 10.2. $C_{12}H_{20}O_2$ requires C, 73.45; H, 10.25%), τ (CCl_4) 3.9—4.4 (2 H, m, $-CH=$), 4.6—5.1 (4 H, m, $=CH_2$), 5.95 (4 H, m, $O{\cdot}CH_2$), 6.85 (2 H, m, $CH{\cdot}O$), and 8—9 (8 H, m, ring CH_2).

trans-2,2′-(1,2-*Cyclohexylidene)dioxydiethanol* (4).—*trans*-1,2-Bis(allyloxy)cyclohexane (27.4 g) in methanol (300 ml) was cooled in a methanol–solid CO_2 bath. The reaction vessel was connected to an ozoniser working at an efficiency of *ca.* 6.4%, and a stream of ozonised oxygen was passed through for 15 h at 19 l h^{-1}. The excess of ozone, indicated by the blue colour, was then removed by flushing with dry nitrogen (2 h). After warming to 0 °C, sodium borohydride (16 g) was added, the mixture was stirred for 1 h, and hydrochloric acid (2M; 120 ml) was added. Methanol and water were removed in a rotary evaporator and the residue was triturated with chloroform. Inorganic solids were filtered off, the solution was evaporated, and the residue was distilled to give the *diol* (4) (20.1 g, 65%), b.p. 111° at 0.15 mmHg (Found: C, 58.4; H, 9.7. $C_{10}H_{20}O_4$ requires C, 58.8; H, 9.85%), τ (CCl_4) 6.13 (2 H, s, OH), 6.41 (8 H, m, $O{\cdot}CH_2$), 6.85 (2 H, m, $=CH{-}O$), and 8—9 (8 H, m, ring CH_2).

trans-2,2′-(1,2-*Cyclohexylidene)dioxybis(ethyl toluene*-p-*sulphonate*).—Toluene-*p*-sulphonyl chloride (12 g, 0.063 mol) was dissoved in pyridine (50 ml) at 0 °C and the diol (4) (5 g, 0.025 mol) was added. After stirring the solution for 3 h, water (5 ml) was added and after a further 15 min the mixture was poured into water. Ether (250 ml) and sulphuric acid were added until the aqueous phase was acidic, and the product was isolated with ether. Evaporation of the dried ether solution gave the *bistoluene*-p-*sulphonate* as a viscous oil (11.7 g, 94%) (Found: C, 56.0; H, 6.35; S, 12.3. $C_{24}H_{32}S_2O_8$ requires C, 56.25; H, 6.25; S, 12.5%), τ (CCl_4)

* An improved method for making the hemisulphate salt might result from use of the procedure of Cantrall *et al.*[14]

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[15] Th. Posternak, D. Reymond, and H. Friedli, *Helv. Chim. Acta*, 1955, **38**, 205.
[16] A. Roebuck and H. Adkins, *Org. Synth.*, Coll. Vol. 3, 1955, p. 217.

2.52 (8 H, q, aryl H), 6.25 (8 H, O·CH_2), 7.01 (2 H, m, =CH–O), 7.6 (6 H, s, Me), and 8—9 (8 H, m, ring CH_2).

trans,syn,trans-*Dicyclohexyl*-18-*crown*-6.—The diol (4) (1.02 g) and its ditosylate (2.56 g) were dissolved in dry benzene (100 ml), and potassium t-butoxide (1.86 g) was added. After heating under reflux for 2 h the solution was filtered to remove potassium tosylate, and the benzene was removed. The residue was dissolved in ether and chromatographed in ether on a column of silica gel. Early fractions, shown by t.l.c. to contain starting materials, were discarded; evaporation of later fractions gave a solid (1.68 g) which was recrystallised from ether–light petroleum (b.p. 30—40 °C) to yield *trans,syn,trans*-dicyclohexyl-18-crown-6, m.p. 118—119° (lit.,[8] 120—121°), n.m.r. spectrum identical with that of authentic material.*

(+)-trans,anti,trans-*Dicyclohexyl*-18-*crown*-6.— *trans*-Cyclohexane-1,2-diol was resolved by the method of Derx [13] *via* the diastereoisomeric strychnine salts of the hemisulphate diester. Crude diol (2.5 g) from the less soluble strychnine salt (27.5 g) was crystallised from benzene and had m.p. 108—109° (lit.,[17] 108—109°), $[\alpha]_D^{20}$ + 36.3° (*c* 1 in H_2O). On the basis of the highest rotation reported, $[\alpha]_D^{18}$ −46.5° for the (−)-enantiomer,[12] this material contains 80% enantiomeric excess of the (*S,S*)-enantiomer.

The (+)-diol (2.4 g) was converted into the diallyl ether (3.14 g, 80%) and the latter in turn into the ' half-crown' diol (4) (3.0 g, 90%) as for the racemic material. A portion of the optically active diol (1.02 g) was converted into the ditosylate (2.0 g, 78%) as before.

To a solution of this ditosylate (2.0 g) and the (+)-diol (4) (0.79 g) in dry benzene (50 ml) was added potassium t-butoxide (0.92 g) with stirring at 20 °C under N_2. After heating under reflux for 3 h and filtration, the benzene was removed. Chromatography on alumina and elution with dichloromethane gave (+)-*trans,anti,trans*-dicyclohexyl-18-crown-6 as a crystalline solid (0.45 g, 31%), m.p. 71—74°, raised to 77—80° on crystallisation from ether–light petroleum (lit.,[8] 77—80° for racemic modification) (Found: C, 64.65; H, 9.6. Calc. for $C_{20}H_{36}O_6$ C, 64.5; H, 9.75%), $[\alpha]_D^{20}$ +39.2° † (*c* 1 in EtOH), τ ($CDCl_3$) 5.9—6.5 (16 H, m, O·CH_2), 6.84 (4 H, m, O·CH), and 8.03, 8.33, and 8.82 (4 H, 4 H, and 8 H respectively, m, ring CH_2).

The *potassium iodide derivative* prepared by the general method of Pedersen [1] had m.p. 120—170° (Found: C, 43.2; H, 7.2. $C_{20}H_{36}KIO_6$ requires C, 44.6; H, 6.75%), $[\alpha]_D^{22}$ +57.80 (*c* 1 in EtOH), τ ($CDCl_3$) 6.1—6.35 (16 H, m, O·CH_2), 6.36—6.65 (4 H, m, O·CH), and 7.87, 8.28, and 8.80 (4 H, 4 H, and 8 H, respectively, m, ring CH_2).

(+)-trans-*Cyclohexyl*-15-*crown*-5 (2,5,8,11,14-*Pentaoxabicyclo*[13.4.0]*nonadecane*).—2,2′-Oxybis(ethyl tosylate) [18] (2.08 g) was added to a stirred solution of the (+)-diol (4) (1.02 g) and sodium t-butoxide (0.96 g) in dry benzene (50 ml) under nitrogen at 20 °C. After heating under reflux for 4 h, filtration, and evaporation the product was chromatographed on alumina. Elution with dichloromethane gave (+)-trans-*cyclohexyl*-15-*crown*-5 as an oil (0.5 g, 42%) (Found: C, 60.8; H, 9.55. $C_{14}H_{26}O_5$ requires C, 61.3; H, 9.55%), $[\alpha]_D^{22}$ +36.5° (*c* 1 in EtOH), τ ($CDCl_3$) 5.8—6.5 (16 H, m, O·CH_2), 6.8 (2 H, m, O·CH), and 8.02, 8.32, and 8.80 (2 H, 2 H, and 4 H, respectively, m, ring CH_2).

The *sodium thiocyanate derivative*, prepared by Pedersen's procedure,[1] was a crystalline solid, m.p. 90—107° (Found: N, 4.55. $C_{15}H_{26}NNaO_5S$ requires N, 3.95%), $[\alpha]_D^{22}$ +44.6° (*c* 0.9 in EtOH), $\nu_{max.}$ (Nujol) 2 060 cm^{-1} (CNS), τ ($CDCl_3$) 6.15—6.7 (18 H, m, O·CH_2 and O·CH), and 7.82, 8.23, and 8.72 (2 H, 2 H, and 4 H, respectively, m, ring CH_2).

(+)-trans-*Cyclohexyl*-18-*crown*-6 (2,5,8,11,14,17-*Hexaoxabicyclo*[16.4.0]*docosane*).—2,2′-Ethylenedioxybis(ethyl tosylate) [19] (1.06 g) and the (+)-diol (4) (0.46 g) were treated with potassium t-butoxide (0.51 g) in dry benzene (50 ml) as before. (+)-trans-*Cyclohexyl*-18-*crown*-6 was obtained after chromatography on alumina (elution with dichloromethane) as an oil (0.27 g, 37%) (Found: C, 60.15; H, 9.35. $C_{16}H_{30}O_6$ requires C, 60.35; H, 9.5%), $[\alpha]_D^{22}$ +25.1° (*c* 1 in EtOH), τ ($CDCl_3$) 6.05—6.45 (20 H, m, O·CH_2), 6.8 (2 H, m, O·CH), and 8.0, 8.32, and 8.8 (2 H, 2 H, and 4 H respectively, m, ring CH_2).

The crystalline *ammonium thiocyanate complex* had m.p. 119—140° (Found: N, 6.3. $C_{17}H_{34}N_2O_6S$ requires N, 7.1%), $\nu_{max.}$ (Nujol) 2 050 cm^{-1} (CNS), τ ($CDCl_3$) 2.3—3.8br (4 H, NH_4), 6.0—6.8 (22 H, m, O·CH_2 and O·CH), and 7.75, 8.28, and 8.82 (2 H, 2 H, and 4 H respectively, m, ring CH_2), $[\alpha]_D^{22}$ +57.5° soon after making up solution, diminishing to +40.2° after 1 h (*c* 1 in EtOH).

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† We consider that this value corresponds to significantly greater than 80% enantiomeric excess (the value estimated for the starting cyclohexanediol), owing to the marked propensity of racemic materials to give *trans,syn,trans*-crown ether.

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