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AN EFFICIENT PROCEDURE FOR THE SYNTHESIS AND ISOLATION OF (+)-(2*R*,3*R*,11*R*,12*R*)- AND (-)-(2*S*,3*S*,11*S*,12*S*)-TETRAPHENYL-18-CROWN-6

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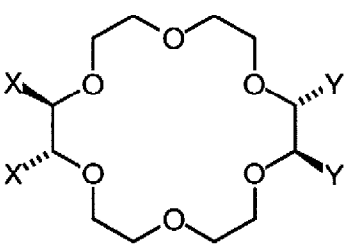
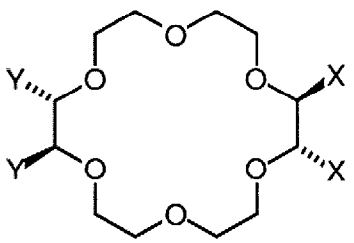
Summary: *The enantiomers of the chiral 2,3-diphenyl- and 2,3,11,12-tetraphenyl-1,4,7,10,13,16-hexaoxacyclo-octadecanes have been prepared in single step reactions from the readily-available chiral precursors, (*RR*)- and (*SS*)-hydrobenzoins, followed by bulk isolations of the pure 18-crown-6 derivatives via their 1:1 crystalline complexes with potassium nitrate (for the diphenyl derivative) or calcium nitrate (for the tetraphenyl derivative), obtained directly from the worked-up crude reaction mixtures: X-ray crystal structures characterise the uncomplexed (*RRRR*)-tetraphenyl-18-crown-6 and the 1:1 complex formed between its (*SSSS*)-enantiomer and calcium nitrate.*

During the last fifteen years, chiral crown ethers[1] have been employed extensively in molecular recognition processes designed for the enantiomeric differentiation of racemic substrates and as a basis for the creation of enzyme mimics and analogues.[2] Both enantiomers, *i.e.* (***RRRR***)-**TP18C6** and (***SSSS***)-**TP18C6**, of 2,3,11,12-tetraphenyl-1,4,7,10,13,16-hexaoxacyclo-octadecane[3-6] have been employed successfully as chiral auxiliaries (1) *in stoichiometric amounts* to form ammonia-borane adducts[7] capable[8,9] of effecting the enantioselective reductions of prochiral aromatic ketones [PhCOR where R = Me, Et, Pr^i, Bu^t] to the corresponding (*S*) and (*R*) aromatic secondary alcohols with enantiomeric excesses of up to 90% and (2) *in catalytic amounts* to provide potassium cyanide complexes[10] capable[9,11] of promoting the asymmetric phase transfer formation, with benzaldehyde as substrate and benzoyl chloride as trapping agent, of the optically-active benzoylated cyanohydrins in up to 40% enantiomeric excess. The stereospecific synthesis[3,8] of (***RRRR***)-**TP18C6** and (***SSSS***)-**TP18C6** by base-promoted reactions of (*RR*)- and (*SS*)-hydrobenzoin respectively with diethyleneglycol bistosylate gives the **TP18C6** derivatives in chemical yields which rarely exceed 25%, following difficult and painstaking purification by silica gel chromatography.



(***RRRR***)-**TP18C6**
(***RRRR***)-**TA18C6**
(***RR***)-**DP18C6**

X = Y = C_6H_5
X = Y = p-$MeOC_6H_4$
X = C_6H_5 & Y = H



(***SSSS***)-**TP18C6**
(***SSSS***)-**TA18C6**
(***SS***)-**DP18C6**

Moreover, until last year, resolved samples of (*RR*)- and (*SS*)-hydrobenzoin were relatively hard to accumulate in any useful quantities, following classical procedures such as (1) spontaneous resolution of enantiomers by entrainment[12] or (2) fractional crystallisation of diastereoisomeric derivatives, *e.g.* bismenthoxyacetates.[3] This situation was transformed dramatically with the announcement[13] from the Sharpless group at MIT of a highly efficient catalytic asymmetric *cis*-dihydroxylation procedure[14] whereby the pure enantiomers of hydrobenzoin can be obtained[15] reliably and efficiently on a 100 g scale from the inexpensive prochiral precursor, *trans*-stilbene. Thus, it is now possible[15] to synthesise (***RRRR***)-**TP18C6** and (***SSSS***)-**TP18C6** stereospecifically from (*RR*)- and (*SS*)-hydrobenzoins, provided an efficient regime for isolating enantiomeric **TP18C6** derivatives can be found. Here, we report on a procedure[16] by which (***RRRR***)-**TP18C6** and (***SSSS***)-**TP18C6** can be crystallised directly from their crude reaction mixtures using calcium nitrate[17] as the complexing agent. Subsequent decomplexation can be achieved by partitioning the complexes between chloroform and water to afford the pure **TP18C6** enantiomers in up to 42% yield. The *uncomplexed* (*RRRR*)-enantiomer and the *calcium nitrate complex* of the (*SSSS*)-enantiomer have both been characterised[18] by X-ray crystallography: we take the opportunity to compare their solid state structures with those of the most closely-related 18C6 derivatives[5,6,19] and their complexes.[5,8,9,17]

In contrast with the 1:1 adduct formed[8,9] between (***RRRR***)-**TP18C6** and ammonia-borane, where one pair of vicinal phenyl groups is axial whilst the other pair is equatorial, in the 1:1 complex of calcium nitrate with (***SSSS***)-**TP18C6**, all four phenyl substituents are pseudo-equatorial (Figs. 1 and 2). The structure of (***SSSS***)-**TP18C6**.$Ca(NO_3)_2$ differs strikingly from that of the analogous $Ca(NO_3)_2$ complex[17] of (2*R*,3*R*,11*R*,12*R*)-2,3,11,12-tetramethyl-18-crown-6, where all four methyl groups are pseudo-axial. The all-equatorial orientation of the phenyl substituents in (***SSSS***)-**TP18C6**.$Ca(NO_3)_2$ allows ion-pairing of the axially-disposed nitrate ligands to the 10-coordinate calcium ion.[20]

In common with (***SSSS***)-**TP18C6**.$Ca(NO_3)_2$ and (***RRRR***)-**TA18C6**,[19] both crystallographically independent molecules of uncomplexed (***RRRR***)-**TP18C6** have their four phenyl groups arranged equatorially. Although one (Fig. 3a) of these two molecules has — like (***RRRR***)-**TA18C6**[19] — molecular C_2 symmetry, the other (Fig. 3b) does not. Interestingly, the C_2 symmetric (***RRRR***)-**TP18C6** possesses two almost eclipsed —OCH_2CH_2O— units, a feature not observed previously in any of the diastereoisomeric 2,3,11,12-tetraphenyl- or 2,3,11,12-tetra-anisyl-18-crown-6 derivatives.[5,8,9,19]

Since the procedure reported here for synthesising and isolating (***RRRR***)-**TP18C6** and (***SSSS***)-**TP18C6** *avoids the use of chromatography*, it is convenient to operate it on a gram scale. *The method*, which has also been employed successfully[21] by us[22] to obtain pure samples of (***RR***)-**DP18C6** and (***SS***)-**DP18C6**, *via* their 1:1 complexes (*cf.* ref. 17) with KNO_3, *is probably quite a general one.*

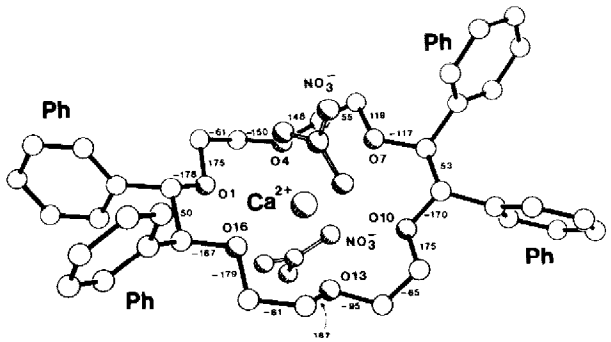
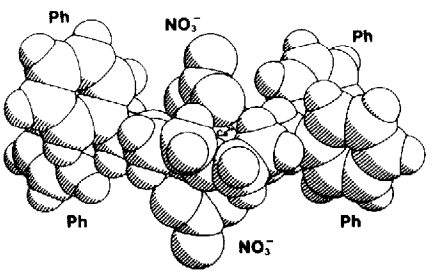


Fig. 1. Ball-and-stick representation of the major occupancy conformation of (***SSSS***)-**TP18C6**.$Ca(NO_3)_2$ with torsional angles shown on the macrocyclic ring

Fig. 2. Space filling representation of (***SSSS***)-**TP18C6**.$Ca(NO_3)_2$



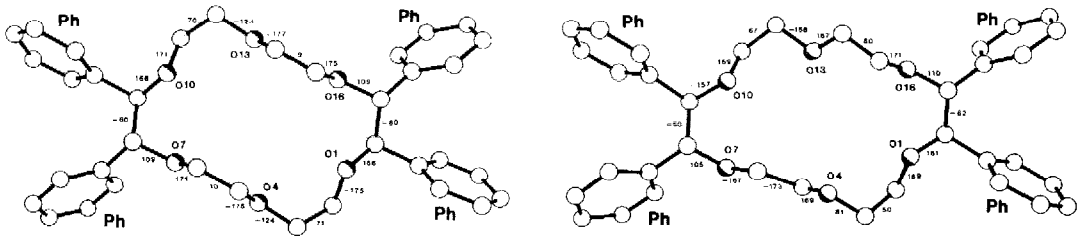


Fig. 3. Ball-and-stick representation of the two crystallographically independent conformations [(a) and (b)] of (***RRRR***)-**TP18C6** in the crystal. Torsional angles are shown on the macrocyclic rings.

References and Footnotes

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15. We are grateful to *Professor K. Barry Sharpless* for providing us with details of the method prior to its publication. It provided samples of (RR)- and (SS)-hydrobenzoins with optical purities of 99%.
16. The crude reaction product (2.45 g), obtained after a conventional work up of a reaction (90°C for 3 days) of (*SS*)-hydrobenzoin (1.0 g, 4.7 mmol) with diethyleneglycol bistosylate (1.90 g, 9.5 mmol) in dry dioxane (150 ml) containing NaH (250 mg) and K_2CO_3 (65 mg), was dissolved in dry $CHCl_3$ (25 ml), and excess (5.65 g) of dry $Ca(NO_3)_2$ — prepared by grinding the tetrahydrate into a fine white powder and drying (100°C) it under reduced pressure (0.05 mm Hg) for 6 h — was added portionwise during 30 min with stirring under N_2. [If less $Ca(NO_3)_2$ is used, then the yield of the complex decreases.] The suspension was stirred at 45°C for 48h, before being cooled and filtered to remove excess of $Ca(NO_3)_2$. The filtrate was concentrated to afford a yellow paste (2.45 g) which solidified on addition of Et_2O (20 ml). After dissolving the solid product in $CHCl_3$ (8 ml), dry DME (6 ml) was added, whereupon the solution became cloudy. Addition of no more than 0.5 ml of $CHCl_3$ removed the cloudiness and the solution was cooled to 0°C. [The volumes employed of both the solvent and the precipitant are critical. If the solution is too concentrated, impurities will contaminate the 1:1 complex. Conversely, if the solution is too dilute, then a low yield of the 1:1 complex will be obtained.] Seed crystals (15 mg) of pure

(***SSSS***)-**TP18C6**.$Ca(NO_3)_2$ were introduced and the solution was allowed to stand at -30°C under Ar for 18 h. [Again, the amount of seed crystals employed is important. If the amount used is too much, crystallisation will occur too quickly and the resulting 1:1 complex will be impure. If less than 10 mg of seed crystals is used, they tend to dissolve in the solution — even at low temperatures — before crystallisation of the 1:1 complex occurs.] The crystalline precipitate (1.57 g) of the 1:1 complex was filtered off, washed with cold hexane (5 ml) and dried under vacuum. [A few single crystals of (***SSSS***)-**TP18C6**.$Ca(NO_3)_2.0.75CH_2Cl_2$, m.p. > 300°C, suitable for *X*-ray crystallography, were grown by slow evaporation of a solution (1 ml) of the 1:1 complex (10 mg) in CH_2Cl_2:DME (3:1, v/v).] The 1:1 complex was redissolved in $CHCl_3$ (10 ml) and the solution was extracted with H_2O (15 ml). The $CHCl_3$ solution was separated, dried, and concentrated to give crystalline (***SSSS***)-**TP18C6** (1.11 g, 42%), m.p. 112°C (lit.[3] m.p. 113-114°C), $[\alpha]_D$ -8.2° (*c*, 0.9 in $CHCl_3$), δ_H ($CDCl_3$) 3.62-3.94 (16H, m, 8 x CH_2), 4.55 (4H, s, 4 x CH), and 6.89-7.25 (20H, m, 4 x C_6H_5). A similar procedure was used to prepare (***RRRR***)-**TP18C6**, m.p. 113 °C (lit.[3] m.p. 113-114°C), $[\alpha]_D$ +7.9° (*c*, 0.9 in $CHCl_3$) in 36% yield from (*RR*)-hydrobenzoin. Recrystallisation of (***RRRR***)-**TP18C6** from CH_2Cl_2-n-pentane afforded single crystals suitable for X-ray structural analyses.

17. The purification of (2*R*,3*R*,11*R*,12*R*)-tetramethyl-1,4,7,10,13,16-hexaoxacyclo-octadecane has been achieved by forming a crystalline complex with calcium nitrate. See R.B. Dyer, D.H. Metcalf, R.G. Ghirardelli, R.A. Palmer, and E.M. Holt, *J. Am. Chem. Soc.*, 1986, **108**, 3621.
18. Crystal data: For (***SSSS***)-**TP18C6**.$Ca(NO_3)_2.0.75CH_2Cl_2$: tetragonal, a = 11.898(8), c = 56.412(33) Å, V = 7986 Å^3, space group $P4_32_12$, Z = 8, ρ = 1.32 g cm^{-3}, μCu-*K*α = 28 cm^{-1}, 4322 independent observed reflections [$|F_o| \geq 3\sigma(|F_o|)$, $\theta \leq 58°$]. For (***RRRR***)-**TP18C6**.CH_2Cl_2: monoclinic, a = 8.835(2), b = 23.419(5), c = 16.939(6) Å, β = 96.51(2)°, V = 3482 Å^3, space group $P2_1$, Z = 4 (2 crystallographically independent molecules), ρ = 1.25 g cm^{-3}, μCu-Kα = 20 cm^{-1}, 3807 independent observed reflections [$|F_o| \geq 3\sigma(|F_o|)$, $2\theta \leq 116°$]. Data for both structures were measured on a Nicolet R3m diffractometer using the ω-scan routine with graphite-monochromated Cu-*K*α radiation. Both structures were solved by direct methods and refined anisotropically to give for (***SSSS***)-**TP18C6**.$Ca(NO_3)_2.0.75CH_2Cl_2$, R = 0.072, R_w = 0.080 (there being two alternative sites observed for (C11) with occupancies of 40 and 60%), and for (***RRRR***)-**TP18C6**.CH_2Cl_2, R = 0.068, R_w = 0.068. Further details of the crystal structure investigations can be obtained from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.
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20. Coordination [Ca...O] distances are in the range 2.44-2.64 Å apart from those involving O(1) and O(10), which are 2.73 and 2.80 Å, respectively.
21. The crude reaction product (1.7 g), isolated after reaction (reflux for 16 h) of (*RR*)-hydrobenzoin (0.8 g, 3.7 mmol) with pentaethyleneglycol bistosylate (1.9 g, 3.7 mmol) in dry dioxane (205 ml) containing NaH (0.18 g, 7.5 mmol), was dissolved in $CHCl_3$ (18 ml) and dry powdered KNO_3 (2 g) was added portionwise and the mixture was stirred vigorously under N_2 for 18 h. After filtering off the excess of KNO_3, the $CHCl_3$ solution was concentrated to afford a solid residue (1.8 g), which was redissolved in $CHCl_3$ (5 ml) by gentle warming before dry DME (6 ml) was added. The precipitate which formed was redissolved by the addition of a minimum (1-2 ml) of $CHCl_3$ and the solution was cooled to 0°C before seed crystals (5-10 mg) of (***RR***)-**DP18C6**.KNO_3 were introduced. After 16 h under Ar at -30°C, the crystalline product (0.74 g), m.p. 162-165°C, was collected following filtration and washing with n-hexane. The 1:1 complex (***RR***)-**DP18C6**.KNO_3 was redissolved in $CHCl_3$ (5 ml) and the KNO_3 removed by repeated aqueous extraction. Concentration of the $CHCl_3$ solution afforded pure (***RR***)-**DP18C6** (0.56 g, 36%), m.p. 81-83°C, $[\alpha]_D$ +20.9° (*c*, 1.55 in $CHCl_3$), δ_H ($CDCl_3$) 3.42-3.90 (20 H, m, 10 x CH_2), 4.55 (2 H, s, 2 x CH), and 6.98-7.25 (10 H, m, 2 x C_6H_5). A similar procedure was used to prepare (***SS***)-**DP18C6**, m.p. 82-84°C, $[\alpha]_D$ -21.3° (*c*, 1.21 in $CHCl_3$) in 27% yield from (*SS*)-hydrobenzoin.
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