Synthesis of Configurationally Chiral Cryptands and Cryptates from Carbohydrate Precursors

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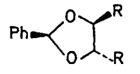
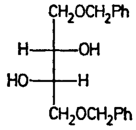
Summary Optically pure configurationally chiral 18-crown-6 and 9-crown-3 cryptands have been synthesised from L-tartaric acid and D-mannitol and some of the 18-crown-6 derivatives have been shown to form cryptates with metal and primary alkylammonium cations.

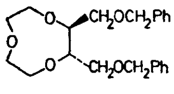
THE ability[1] of macrocyclic polyethers of the 18-crown-6 type to complex with primary alkylammonium salts has led to the development of so-called host-guest chemistry[2] by Cram *et al.*[3] Carbohydrates and their derivatives are not only rich in substituted bismethylenedioxy units for incorporation into the 18-crown-6 constitution but they also provide a relatively inexpensive source of chirality for synthesising hosts with potential for exhibiting chiral recognition towards enantiomeric guests. This prospect has now been realised by utilising L-tartaric acid and D-mannitol separately in two independent synthetic schemes to prepare chiral 18-crown-6 cryptands.[4]‡



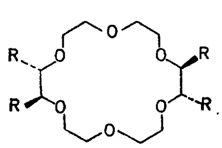
L-(1) R = CO_2Et
L-(2) R = CH_2OH
L-(3) R = CH_2OCH_2Ph



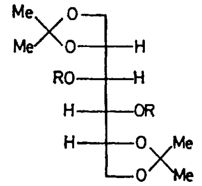
L-(4)



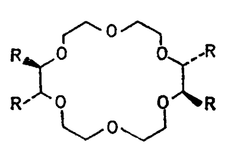
L-(5)



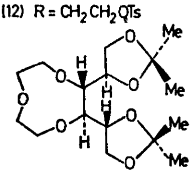
LL-(6) R = CH_2OCH_2Ph
LL-(7) R = CH_2OH
LL-(8) R = CH_2OAc
LL-(9) R = CH_2OCPh_3



D-(10) R = $CH_2CH{=}CH_2$
D-(11) R = CH_2CH_2OH
D-(12) R = CH_2CH_2OTs

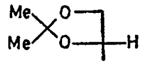


DD-(8) R = CH_2OAc

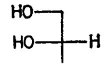


D-(14)

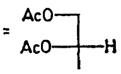
DD-(13) R =



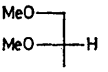
DD-(15) R =



DD-(16) R =



DD-(17) R =



Diethyl L-tartrate was converted (35%) into its *O*-benzylidene derivative L-(**1**),[5] m.p. 45 °C, $[\alpha]_D$ − 33·8° (*c* 1·5, $CHCl_3$), which was reduced to the diol L-(**2**), m.p. 68—69 °C, $[\alpha]_D$ − 11·4° (*c* 2·1, MeOH), with $LiAlH_4$ in Et_2O (92% yield). Benzylation of L-(**2**) afforded (96%) the dibenzyl ether L-(**3**) as an oil which was subjected to acid-catalysed hydrolysis (Zeo-Karb 325 resin, H^+ form) in H_2O–Me_2CO (reflux) to give the dibenzyl ether L-(**4**), m.p. 60—61 °C, $[\alpha]_D$ − 5·5° (*c* 5·0, $CHCl_3$), of threitol in 15% yield. Reaction of L-(**4**) with NaH and $(TsOCH_2CH_2)_2O$[6] in Me_2SO at 40 °C for 60 h afforded the dibenzyl ether L-(**5**) (4%), $[\alpha]_D$ + 19·3° (*c* 5·8, $CHCl_3$), and the tetrabenzyl ether LL-(**6**), (12%), $[\alpha]_D$ + 5·8° (*c* 3·5, $CHCl_3$), as oils after chromatography (Et_2O) on silica. Hydrogenolysis (10% Pd–C) of LL-(**6**) gave (75%) the tetraol LL-(**7**) which was characterised as the tetra-acetate LL-(**8**), m.p. 69—74 °C, $[\alpha]_D$ − 20·5° (*c* 5·0, $CHCl_3$), ^1H n.m.r. spectrum ($CDCl_3$): τ 5·50—6·00 (8H, m, 4 × $AcOCH_2$), 6·06—6·48 (20H, m, CH and CH_2 protons), and 7·94 (12H, s, 4 × Me). Conversion of the tetraol LL-(**7**) into the tetratrityl ether LL-(**9**), $[\alpha]_D$ − 3·9° (*c* 0·86, $CHCl_3$), was also carried out in order to increase the steric bulk of the substituent groupings attached to the four chiral centres in the 18-crown-6 cryptand.

In order to associate bulky substituents more intimately with the 18-crown-6 constitution, and at the same time double the number of chiral centres, a synthetic scheme emanating from D-mannitol was devised and implemented. 1,2:5,6-Di-*O*-isopropylidene-D-mannitol[7] was converted (91%) into its diallyl ether D-(**10**), $[\alpha]_D$ + 8·9° (*c* 1·42, $CHCl_3$), which was then subjected to ozonolysis followed by reduction ($NaBH_4$) to give the diol D-(**11**), m.p. 73—74°C, $[\alpha]_D$ + 15·1° (*c* 0·96, $CHCl_3$), in 14% yield after chromatography (EtOAc) on silica. Conversion (26%) of D-(**11**) into the ditosylate D-(**12**), m.p. 91—92 °C, $[\alpha]_D$ + 12·1° (*c* 0·7, $CHCl_3$), was followed by the reaction of equimolar proportions of D-(**11**) and D-(**12**) with NaH in Me_2SO at 50 °C for 40 h to afford the tetra-*O*-isopropylidene derivative DD-(**13**), $[\alpha]_D$ + 7·6° (*c* 0·59, $CHCl_3$), as an oil (14%) after chromatography (Et_2O) on alumina. Subsequently, DD-(**13**) (14%) was isolated together with the di-*O*-isopropylidene derivative D-(**14**) (6%), $[\alpha]_D$ + 5·1° (*c* 0·98, $CHCl_3$), as an oil after chromatography (Et_2O) on alumina of the products resulting from reaction between 1,2:5,6-di-*O*-isopropylidene-D-mannitol,[7] $(TsOCH_2CH_2)_2O$,[6] and NaH in Me_2SO at 50 °C for 4 h. Acid-catalysed hydrolysis (Zeo-Karb 325 resin, H^+ form) of DD-(**13**) in H_2O–Me_2CO (reflux) gave quantitatively the octaol DD-(**15**), m.p. 58–60 °C, which was characterised as its octa-acetate DD-(**16**), $[\alpha]_D$ + 48·4° (*c* 0·57, $CHCl_3$), ^1H n.m.r. spectrum ($CDCl_3$): τ 4·64—4·86 (4H, m, 4 × AcOC*H*), 5·28—5·82 (8H, AB portion of an ABX system, J_{AB} 12·5, J_{AX} 3·0, J_{BX} 6·5 Hz, 4 × $AcOCH_2$), 6·12—6·54 (20H, m, other CH and CH_2 protons), and 7·92 and 7·94 (2 × 12H, 2 × s, 8 × Me), and its octamethyl ether DD-(**17**), $[\alpha]_D$ + 4·7° (*c* 1·1, $CHCl_3$). Treatment of the octaol DD-(**15**) with $NaIO_4$ (6 mol) in H_2O at 22 °C for 48 h followed by reduction ($NaBH_4$) and acetylation afforded DD-(**8**), $[\alpha]_D$ + 20·2° (*c* 5·0, $CHCl_3$), and thus provided enantiomerically-related DD and LL cryptands of the tetra-acetate (**8**) from D-mannitol and L-tartaric acid, respectively.

The cryptands L-(**5**), LL-(**6**), LL-(**8**), DD-(**8**), LL-(**9**), DD-(**13**), DD-(**14**), DD-(**16**), and DD-(**17**) all dissolved alkali metal and primary alkylammonium salts in organic solvents. The formation of cryptates (*ca.* 1:1) with t-butylammonium thiocyanate in $CDCl_3$ was accompanied by significant changes in the ^1H n.m.r. spectra of the cryptands. A quantitative assessment of complexing power was obtained by measuring stability constants defined as equilibrium constants (*K* in $l\,mol^{-1}$) for the equilibrium:

$$M^+X^- + \text{Cryptand} \overset{K}{\rightleftharpoons} \text{Cryptate}^+\,X^-.$$

Stability constants were measured potentiometrically[8] in MeOH with an ion-selective electrode in the case of alkali metal chlorides and by an ^1H n.m.r. spectroscopic method[9] in $CDCl_3$ in the case of primary alkylammonium thiocyanates. Stability constants for LL-(**6**) ($Bu^tNH_3^+$, 2·0 × 10^4), LL-(**9**) ($Bu^tNH_3^+$, <1·0 × 10^4), and DD-(**13**) (Na^+, 3·9 × 10^3; K^+, 3·0 × 10^4; Rb^+, 4·6 × 10^4; $Bu^tNH_3^+$, <30; $PhCH_2NH_3^+$, 1·5 × 10^6) indicate that these 18-crown-6

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‡ Professor J.-M. Lehn has suggested the use of the term 'cryptand' to describe all types of cavity-containing ligands. The recommended usage of the term 'cryptate' is discussed in ref. 11.

cryptands form strong cationic complexes. The dramatic decrease in the stabilities of the t-butylammonium thiocyanate complexes as the steric bulk of the substituent groups of the hosts is increased is not unexpected. Inspection of CPK space-filling models indicates that the steric interaction between the t-butyl group of the guest and the substituent groups of the host becomes quite important in DD-(**13**) assuming a three-point binding model[10] involving hydrogen bonding of the hydrogens on NH_4^+ to alternate oxygens in the 18-crown-6 cycle. By contrast, the models show that the benzylammonium cation is accommodated comfortably by the host and so it is not surprising that benzylammonium thiocyanate forms a strong complex with DD-(**13**).

This investigation demonstrates the ability of configurationally chiral cryptands to form cryptates[11]‡ with metal and primary alkylammonium cations.

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