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## Synthesis of Configurationally Chiral Cryptands and Cryptates from Carbohydrate Precursors

By W. David Curtis, Dale A. Laidler, J. Fraser Stoddart,\* and Graham H. Jones†

(Department of Chemistry, The University, Sheffield S3 7HF, and

†Corporate Laboratory, Imperial Chemical Industries Ltd., P.O. Box No. 11, The Heath, Runcorn, Cheshire WA7 4QE)

Summary Optically pure configurationally chiral 18crown-6 and 9-crown-3 cryptands have been synthesised from L-tartaric acid and D-mannitol and some of the 18crown-6 derivatives have been shown to form cryptates with metal and primary alkylammonium cations. to the development of so-called host-guest chemistry<sup>2</sup> by Cram *et al.*<sup>3</sup> 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-

THE ability<sup>1</sup> of macrocyclic polyethers of the 18-crown-6 type to complex with primary alkylammonium salts has led

mannitol separately in two independent synthetic schemes to prepare chiral 18-crown-6 cryptands.<sup>4</sup><sup>+</sup>



Diethyl L-tartrate was converted (35%) into its O-benzylidene derivative L-(1),<sup>5</sup> m.p. 45 °C,  $[\alpha]_D - 33.8^\circ$  (c 1.5, CHCl<sub>3</sub>), which was reduced to the diol L-(2), m.p. 68-69 °C,  $[\alpha]_D - 11.4^\circ$  (c 2.1, MeOH), with LiAlH<sub>4</sub> in Et<sub>2</sub>O (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 H2O-Me2CO (reflux) to give the dibenzyl ether L-(4), m.p. 60-61 °C,  $[\alpha]_{D} - 5.5^{\circ}$  (c 5.0, CHCl<sub>3</sub>), of threitol in 15% yield. Reaction of L-(4) with NaH and (TsOCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O<sup>6</sup> in Me<sub>2</sub>SO at 40 °C for 60 h afforded the dibenzyl ether L-(5) (4%),  $[\alpha]_{D} + 19.3^{\circ}$  (c 5.8, CHCl<sub>3</sub>), and the tetrabenzyl ether LL-(6), (12%),  $[\alpha]_D + 5.8^{\circ}$  (c 3.5, CHCl<sub>3</sub>), as oils after chromatography (Et<sub>2</sub>O) 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,  $[\alpha]_{D} - 20.5^{\circ}$  (c 5.0, CHCl<sub>3</sub>), <sup>1</sup>H n.m.r. spectrum (CDCl<sub>3</sub>):  $\tau$  5.50-6.00 (8H, m, 4 × AcOCH<sub>2</sub>), 6.06-6.48 (20H, m, CH and CH<sub>2</sub> protons), and 7.94 (12H, s,  $4 \times Me$ ). Conversion of the tetraol LL-(7) into the tetratrityl ether LL-(9),  $[\alpha]_D - 3.9^\circ$  (c 0.86, CHCl<sub>3</sub>), 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<sup>7</sup> was converted (91%) into its diallyl ether D-(10),  $[\alpha]_D + 8.9^\circ$  (c 1.42, CHCl<sub>3</sub>), which was then subjected to ozonolysis followed by reduction (NaBH<sub>4</sub>) to give the diol D-(11), m.p. 73-74°C,  $[\alpha]_{D}$  + 15.1° (c 0.96, CHCl<sub>3</sub>), in 14% yield after chromatography (EtOAc) on silica. Conversion (26%) of D-(11) into the ditosylate D-(12), m.p. 91--92 °C,  $[\alpha]_D + 12 \cdot 1^\circ$  (c 0.7, CHCl<sub>3</sub>), was followed by the reaction of equimolar proportions of D-(11) and D-(12) with NaH in Me<sub>2</sub>SO at 50 °C for 40 h to afford the tetra-O-isopropylidene derivative DD-(13),  $[\alpha]_{D} + 7.6^{\circ}$  (c 0.59, CHCl<sub>3</sub>), as an oil (14%) after chromatography (Et<sub>2</sub>O) on alumina. Subsequently, DD-(13) (14%) was isolated together with the di-O-isopropylidene derivative D-(14) (6%),  $[\alpha]_{D} + 5.1^{\circ}$  (c 0.98, CHCl<sub>3</sub>), as an oil after chromatography (Et<sub>2</sub>O) on alumina of the products resulting from reaction between 1,2:5,6-di-Oisopropylidene-D-mannitol,7 (TsOCH2CH2)2O,6 and NaH in Me<sub>2</sub>SO at 50 °C for 4 h. Acid-catalysed hydrolysis (Zeo-Karb 325 resin, H<sup>+</sup> torm) of DD-(13) in H<sub>2</sub>O-Me<sub>2</sub>CO (reflux) gave quantitatively the octaol DD-(15), m.p. 58-60 °C, which was characterised as its octa-acetate DD-(16),  $[\alpha]_{D} + 48.4^{\circ}$ (c 0.57, CHCl<sub>3</sub>), <sup>1</sup>H n.m.r. spectrum (CDCl<sub>3</sub>): τ 4.64-4.86 (4H, m, 4  $\times$  AcOCH), 5.28–5.82 (8H, AB portion of an ABX system,  $J_{AB}$  12.5,  $J_{AX}$  3.0,  $J_{BX}$  6.5 Hz,  $4 \times AcOCH_2$ ),  $6\cdot 12$ — $6\cdot 54$  (20H, m, other CH and CH<sub>2</sub> protons), and  $7\cdot 92$ and 7.94 (2  $\times$  12H, 2  $\times$  s, 8  $\times$  Me), and its octamethyl ether DD-(17),  $[\alpha]_{D}$  + 4.7° (c 1.1, CHCl<sub>3</sub>). Treatment of the octaol DD-(15) with NaIO<sub>4</sub> (6 mol) in H<sub>2</sub>O at 22 °C for 48 h followed by reduction (NaBH<sub>4</sub>) and acetylation afforded DD-(8),  $[\alpha]_{\rm D}$  + 20.2° (c 5.0, CHCl<sub>3</sub>), and thus provided enantiomerically-related DD and LL cryptands of the tetraacetate (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<sub>3</sub> was accompanied by significant changes in the <sup>1</sup>H 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  $1 \text{ mol}^{-1}$ ) for the equilibrium:

$$\begin{array}{c} K\\ M^+X^- + \text{Cryptand} \rightleftharpoons \text{Cryptate}^+ X^-. \end{array}$$

Stability constants were measured potentiometrically<sup>8</sup> in MeOH with an ion-selective electrode in the case of alkali metal chlorides and by an <sup>1</sup>H n.m.r. spectroscopic method<sup>9</sup> in CDCl<sub>3</sub> in the case of primary alkylammonium thiocyanates. Stability constants for LL-(6) (Bu<sup>t</sup>NH<sub>3</sub><sup>+</sup>,  $2\cdot 0 \times 10^4$ ), LL-(9) (Bu<sup>t</sup>NH<sub>3</sub><sup>+</sup>,  $<1\cdot 0 \times 10^4$ ), and DD-(13) (Na<sup>+</sup>,  $3\cdot 9 \times 10^3$ ; K<sup>+</sup>,  $3\cdot 0 \times 10^4$ ; Rb<sup>+</sup>,  $4\cdot 6 \times 10^4$ ; Bu<sup>t</sup>NH<sub>3</sub><sup>+</sup>, <30; PhCH<sub>2</sub>NH<sub>3</sub><sup>+</sup>,  $1\cdot 5 \times 10^6$ ) indicate that these 18-crown-6

<sup>&</sup>lt;sup>‡</sup> 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 thiocvanate 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<sup>10</sup> 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<sup>11</sup><sup>‡</sup> with metal and primary alkylammonium cations.

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