# Synthesis of Novel Chiral Macrocyclic Ligands bearing Methyl 4,6-*O*-Benzylidene-α-D-mannopyranoside

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*O*-Alkylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with t-butyl bromoacetate under phase-transfer conditions, followed by reduction and tosylation leads to an intermediate which was used in the formation of the two diaza-crown ethers (**3a**) and (**3b**) *via* condensation with 1,8-diamino-3,6-dioxaoctane in the presence of KF–$Al_2O_3$ and *N*,*N*-bisethoxycarbonyl-1,8-diamino-3,6-dioxaoctane in $Me_2SO$–NaH–KBr, respectively.

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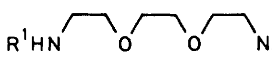
Chiral macrocyclic hosts have been of considerable interest for some time.[1] Incorporation of carbohydrate units into achiral macrocyclic rings afforded chiral hosts exhibiting complexing abilities with primary alkyl ammonium cations[2] and chiral recognition with racemic salts.[3] Replacement of two oxygen atoms by two tertiary amine functions leads to increased stabilities for the complexes with ammonium cations in comparison with all-oxygen-crown compounds[4] as a result of stronger hydrogen bond formation involving the nitrogen atoms in the host molecules. We now report a convenient synthesis of two chiral macrocyclic ligands containing both secondary and tertiary amine functions.

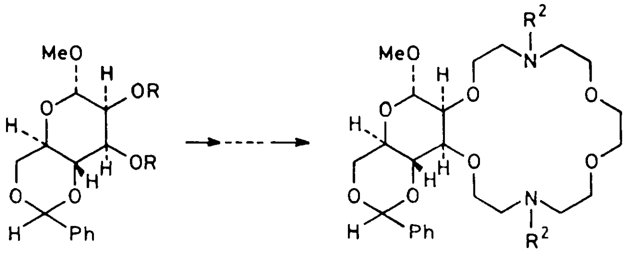
The heteromacrocyclic ligand (**3a**) was obtained as follows. *O*-Alkylation of (**1a**) with t-butyl bromoacetate under phase-transfer conditions[5] proceeded smoothly at room temperature (0.6 equiv. of $Bu^n_4N^+HSO_4^-$, $C_6H_6$–50% aqueous NaOH, 4



**(2)**

a; $R^1 = H$

b; $R^1 = CO_2Et$



(1)

a; R = H

b; R = $CH_2CO_2Bu^t$

c; R = $CH_2CH_2OH$

d; R = $CH_2CH_2OSO_2C_6H_4Me$-*p*

(3)

a; $R^2 = H$

b; $R^2 = CO_2Et$

c; $R^2 = Me$

equiv. of $BrCH_2CO_2Bu^t$, 0.5 h) to give (**1b**) (colourless oil) in 95% yield.† Reduction of (**1b**) with $LiAlH_4$ in boiling ether afforded 90% of (**1c**)[6] (viscous oil). Tosylation of (**1c**) (tosyl chloride, $Et_3N$, $CHCl_3$, 0 °C) provided (**1d**) in 85% yield, m.p. 127—128 °C. Condensation of the bistosylate (**1d**) (0.01 M) with the diamine (**2a**) (0.01 M) in the presence of KF on alumina[7] (2.5 equiv., 70 ml of tetrahydrofuran–acetonitrile, 1 : 1, reflux, 20 h) led to compound (**3a**) (oil) in 35% yield (after column chromatography on silica gel, 2% $Et_3N$ in MeOH): $^1H$ n.m.r. (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 7.47 (m, 5H, Ph), 5.72 (s, 1H, PhC*H*), 4.90 (s, 1H, MeOC*H*), 4.40—3.50 (m, 18H, 6 × $OCH_2$ and 6H from sugar unit), 3.47 (s, 3H, OMe), 2.87 (m, 8H, 4 × $NCH_2$), and 2.0 (br. 2 s, NH).

Condensation of the bistosylate (**1d**) with the bisurethane (**2b**) (dimethyl sulphoxide, NaH, KBr, room temperature, 48 h) gave 60% of (**3b**) (after column chromatography on silica gel, ethyl acetate) which was reduced with $LiAlH_4$ in boiling tetrahydrofuran for 2 h to give (**3c**) (colourless oil) in 90% yield: $^1H$ n.m.r. (100 MHz, $CDCl_3$, $Me_4Si$) $\delta$ 7.45 (m, 5H, Ph), 5.68 (s, 1H, PhC*H*), 4.80 (s, 1H, MeOC*H*), 4.40—3.50 (m, 18H, 6 × $OCH_2$ and 6H from sugar unit), 3.45 (s, 3H, OMe), 2.75 (m, 8H, 4 × $NCH_2$), and 2.40 and 2.32 (2 × s, 2 × NMe).

Beneficial features of these syntheses are the following: (i) the preparation of (**1c**) avoids ozonolysis of the 2,3-diallyl derivative of (**1a**);[6] (ii) the use of KF on alumina is the first example of its application to diaza-crown formation, and in addition it avoids high-dilution conditions. Finally, this approach provides a simple and convenient synthesis of novel chiral diaza-crown ethers of potential interest in host–guest chemistry.

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† Satisfactory analyses and spectral data were obtained for all new compounds.