Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3629-3632, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0609-2

Synthesis of Novel Chiral Macrocycles: Crown Ethers Derived from D-Glucose

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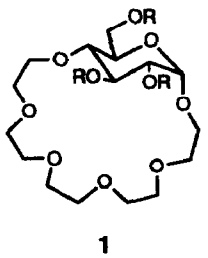
Abstract: Two new macrocycles (1 and 2) incorporating a crown ether and a glucose unit have been synthesized efficiently in six steps from α-allyl glucopyranoside.Preliminary complexation studies with alkali metal and ammonium ions are described.

Modification of crown ethers by incorporating chiral units was first introduced by Cram[2] and subsequently developed by many others.[3,4] The ability of such systems to discriminate between enantiomers of guest alkylammonium salts as well as their catalytic activity have attracted considerable attention as potential enzyme mimics[5]. A particularly interesting group of chiral crown ethers were those developed from carbohydrate units originally introduced by Stoddart[3] and more recently by Penades and co-workers[6].Carbohydrate derivatives are ideally suited for developing novel chiral compounds due to their rich array of bis methylenedioxy units and the ease with which these hydroxl groups can be introduced into the crown ether periphery using standard protocols in carbohydrate chemistry.

We now report here the synthesis of two novel derivatives **1** and **2** derived from D-glucose.Unlike previously reported compounds,**1** and **2** belong to a novel class of chiral crown ethers in which a glucose unit is introduced through 1,4-hydroxyl groups. Apart from conferring a novel topology to the macrocycle, the additional hydroxyl groups at 2,3 and 6 positions are placed closer to the crown ether cavity and offer great potential for introducing additional binding or catalytic sites.



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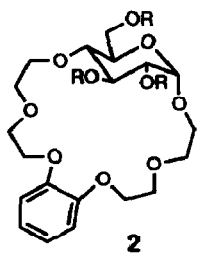
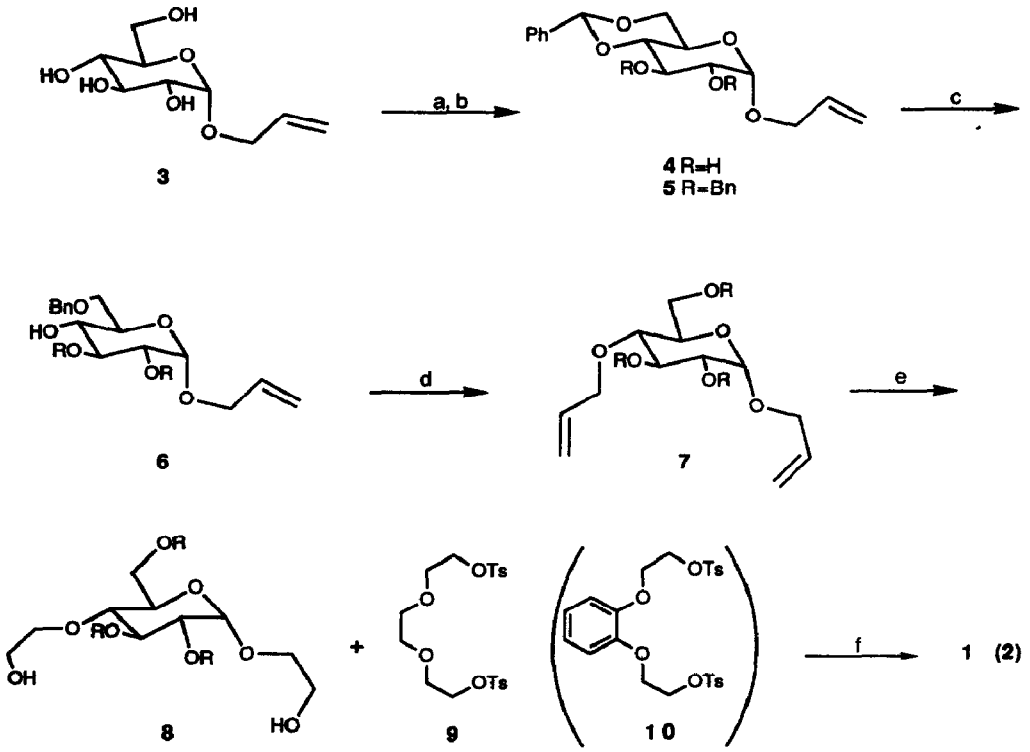


2

Synthesis of **1** and **2** were achieved efficiently as outlined in the Scheme. The benzylidene derivative **4** was conveniently prepared from α-allyl -D-glucopyranoside by treatment with benzaldehyde in DMF using dimethyl sulphate -DMF adduct as the catalyst[7](colourless crystalline needles,mp.118°C,70%).Benzylation by NaH-benzyl chloride in refluxing THF furnished the dibenzyl derivative **5** as a crystalline solid in excellent yield (91%, mp.86°C).The benzylidene acetal was reductively opened using HCl-$NaCNBH_3$ in ether-THF[8] at room temperature[9] to obtain allyl 2,3,6 tri-O-benzyl-α-D-glucopyranoside **6** as a glassy solid in 80% yield.The structure of the product was clearly established by ^1H and ^{13}C spectral data[10]. Treatment of **6** with NaH-allyl bromide in refluxing THF afforded the 1,4 diallyl derivative **7** in 98% yield.Ozonolysis of the diallyl derivative **7** in methanol at -78° C followed by reductive workup ($NaBH_4$, -78° C→RT) furnished the diol **8** in 79% yield.



a) C_6H_5-CHO, DMF-$(CH_3)_2$ SO_4, RT, 18h; b) $C_6H_5CH_2Cl$, NaH, THF, 70°C, 20-24h; c) $NaCNBH_3$-HCl (ether), THF, RT, 10 min.; d) allyl bromide, NaH, THF, 70 °C,5h; e) O_3, MeOH, -78°C, $NaBH_4$; f) NaH, **9**/**10** ,THF, 70°C, 24h.

Coupling the diol **8** with triethylene glycol ditosylate **9** using NaH in refluxing THF[11] (24h) afforded macrocycle **1** in34% yield after purification by column chromatography (silica, hexane-ethyl acetate), as a glassy solid. In a similar fashion, coupling of the diol **8** with the ditosylate **10** furnished the macrocycle **2** in 29% yield. The structures of both **1** and **2** were confirmed by NMR, mass spectra and microanalysis[12,13].

The binding abilities of chiral macrocycles **1** and **2** were evaluated by extraction of lithium, sodium, potassium, cesium, and ammonium picrates. The association constants (K_a) in chloroform at 27° C were measured by Cram's picrate method.[14] The K_a values were much lower than those of simple crown derivatives[15]. However these values are of the same order of magnitude as reported in the literature for monosaccharide derived crown ethers[6]. Macrocycle **1** showed relatively good binding towards potassium and ammonium ions.

Table 1. Association constants in $CDCl_3$ at 27° C

Host	Li^+	Na^+	K^+	Cs^+	NH_4^+
1	2,700	3,600	30,000	5,400	49,500
2	4,000	3,000	13,000	3,000	9,000

We are currently investigating the binding properties of **1** and **2** with particular regard to enantioselective complexation with ammonium ions.We are also extending the synthetic approach to bis dextro crown derivatives.

Acknowledgement: We thank CSIR, New Delhi for the financial support of this work.

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9. When carried out at 0°C, the reaction proceeded very slowly. However, at slightly elevated temperature(25°C) smooth conversion occured to yield **6** in very good yield[8].
10. ^{1}H (400 MHz) and ^{13}C (100 MHz) spectrum of **6** in $CDCl_3$: ^{1}H δ,3.45-3.80(bm, 7H), 4.05(m, 1H), 4.2 (m, 1H), 4.4-5.1(bm, 7H), 5.35(m, 2H), 5.95(m, 1H),and 7.3(m, 15H); ^{13}C δ, 68.5, 69.5, 70.0, 70.5, 73.0, 74.0, 75.5, 80.0, 81.5, 96.0, 119.5, 128.5, 134.0, 138.0, 139.0; IR (neat): 620, 750, 1460, 1500, 1600, 900, 3040,and 3400cm^{-1} . $[\alpha]_D^{25}$: 24.811 (c, 1.38 ; $CHCl_3$). Anal. calcd. for $C_{30}H_{34}O_6$: C,73.42; H, 6.98. Found: C, 72.95; H, 6.89.
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12. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectrum of **1** in $CDCl_3$: ^{1}H δ ,3.6 (bs, 27H), 4.6(m, 3H),4.9 (m, 3H), 7.25(m, 15H); ^{13}C δ , 67.5, 68.4, 69.8, 70.8, 71.1, 71.6, 73.3, 77.8, 79.6, 82.0, 97.2, 128.7, 129.8, 138.4,and 139.0. IR(neat): 610, 700, 740, 1100, 1370, 1460, 1610, , 2900, and, 3040cm^{-1}.$[\alpha]_D^{26}$ 12.003 (c, 0.96; $CHCl_3$); MS: M/z 653.4 (MH^+). Anal.calcd.for $C_{37}H_{48}O_{10}$: C, 68.08; H, 7.4 Found: C, 68.46, H, 7.4.
13. ^{1}H (300 MHz) and ^{13}C (75 MHz)spectrum of **2**in $CDCl_3$: δ ,3.45-4.25(bm, 23H), 4.34(d, 1H) 4.75(m, 5H), 6.9(s, 4H), 7.25(m, 15H); ^{13}C δ , 68.7, 69.0, 69.6, 70.6, 71.2, 75.8, 77.7, 80.1, 96.3, 115.3, 121.9, 127.8, 128.5,129.6,132.7,and145.6. IR(neat): 600, 700, 740,1260, 1370, 1460, 1500, 1600, 2900, and 3040cm^{-1}. $[\alpha]_D^{26}$ 29.407 (c, 1.5; $CHCl_3$); MS: M/z 701.4 (MH^+). Anal. calcd.for.$C_{41}H_{48}O_{10}$: C, 70.26; H, 6.90. Found: C, 70.46; H, 6.85.
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(*Received in UK* 10 *January* 1994; *revised* 21 *March* 1994; *accepted* 24 *March* 1994)