Carbohydrate Research, 138 (1985) C5–C9
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Total synthesis of α-cyclodextrin*

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(Received November 1st, 1984; accepted for publication January 3rd, 1985)

Cyclodextrins are well known as products of the degradation of starch by an amylase of *Bacillus macerans*[2]. The ability of cyclodextrins to form inclusion complexes by the insertion of a variety of organic molecules into their hydrophobic cavities has led to many efforts to develop efficient enzyme models from them mainly through chemical modifications of their hydroxyl functions[3]. However, no approach to the total synthesis of cyclodextrins has been described. We report here a total synthesis of α-cyclodextrin (**1**) *via* the intramolecular cyclization of a properly protected glucohexaose derivative (**3**).

Treatment of maltose octaacetate **4** with tributyltin allyloxide in the presence of tin(IV) chloride[4] in $ClCH_2CH_2Cl$ afforded a 73% yield of allyl glycoside **5**. This was converted into the isopropylidene derivative **6**, $[\alpha]_D$ +28.4° (*c* 0.16)*** in 62% overall yield by successive treatment with NaOMe–MeOH, then $(MeO)_2CMe_2$–TsOH in *N,N*-dimethylformamide (DMF). Benzylation of **6** with benzyl bromide and NaH in DMF gave an 83% yield of **7**, $[\alpha]_D$ +19.8° (*c* 0.535), which was solvolyzed in 1:1 AcOH–MeOH for 1 h at 80° to afford a 70% yield of **8** (from EtOAc–*i*-Pr_2O), m.p. 100.5–101.5°, $[\alpha]_D$ +23.6° (*c* 0.29); δ_C**** ($CDCl_3$) 69.0 (C-6a) and 62.3 (C-6b). The selective benzylation of **8** was performed by the stannylation method[5] [$(Bu_3Sn)_2O$, then BnBr–Bu_4NBr] to give a 95% yield of **9**, $[\alpha]_D$ +21.6° (*c* 0.46); δ_C ($CDCl_3$) 69.4 (C-6a) and 70.0 (C-6b). Acetylation of **9** gave **10**, $[\alpha]_D$ +28.0° (*c* 0.56), and deallylation of **10** with $PdCl_2$ and AcONa in aqueous AcOH[6] afforded a 93% yield of **11**, $[\alpha]_D$ +36.0° (*c* 0.67). The conversion of hemiacetal **11** into β-fluoride **13** was achieved in two steps in 80% yield *via* α-chloride **12**, $[\alpha]_D$ +81.9° (*c* 0.11), δ_H**** ($CDCl_3$) 6.06 (d, $^3J_{HH}$ 3.73 Hz, H-1a) and 5.57 (d, $^3J_{HH}$ 3.29 Hz, H-1b). The reagents used were (i) $SOCl_2$–DMF in $ClCH_2CH_2Cl$[7], and (ii) AgF in CH_3CN[8]. The fluoride **13** had $[\alpha]_D$ +45.4° (*c* 0.175); δ_H ($CDCl_3$) 5.38 (q, $^2J_{HF}$ 54.1 Hz, $^3J_{HH}$ 6.0 Hz, H-1a) and 5.54 (d, $^3J_{HH}$ 3.7 Hz, H-1b); δ_C ($CDCl_3$) 109.6 ($^1J_{CF}$ 217 Hz, $^1J_{CH}$ 172 Hz, C-1a) and 97.0 ($^1J_{CH}$ 173 Hz, C-1b)[9]; δ_F**** ($CDCl_3$) 133.7 ($^2J_{HF}$ 53.7 Hz, $^3J_{HF}$ 10.4 Hz)[10].

*Glucan Synthesis, Part V. For Part IV, see ref. 1.

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***Values of $[\alpha]_D$ were measured for $CHCl_3$ solutions at 25°, unless noted otherwise. Compounds with $[\alpha]_D$ recorded gave satisfactory elemental analyses.

****Values of δ_H and δ_C are expressed in p.p.m. downfield from tetramethylsilane. The letters a, b,. . . .f are used to designate the glucose residue (see Scheme 2) in which a cited H or C atom is located. Values of δ_F, expressed in p.p.m. upfield from trichlorofluoromethane, were measured against an internal standard of hexafluorobenzene (163.0 p.p.m.).

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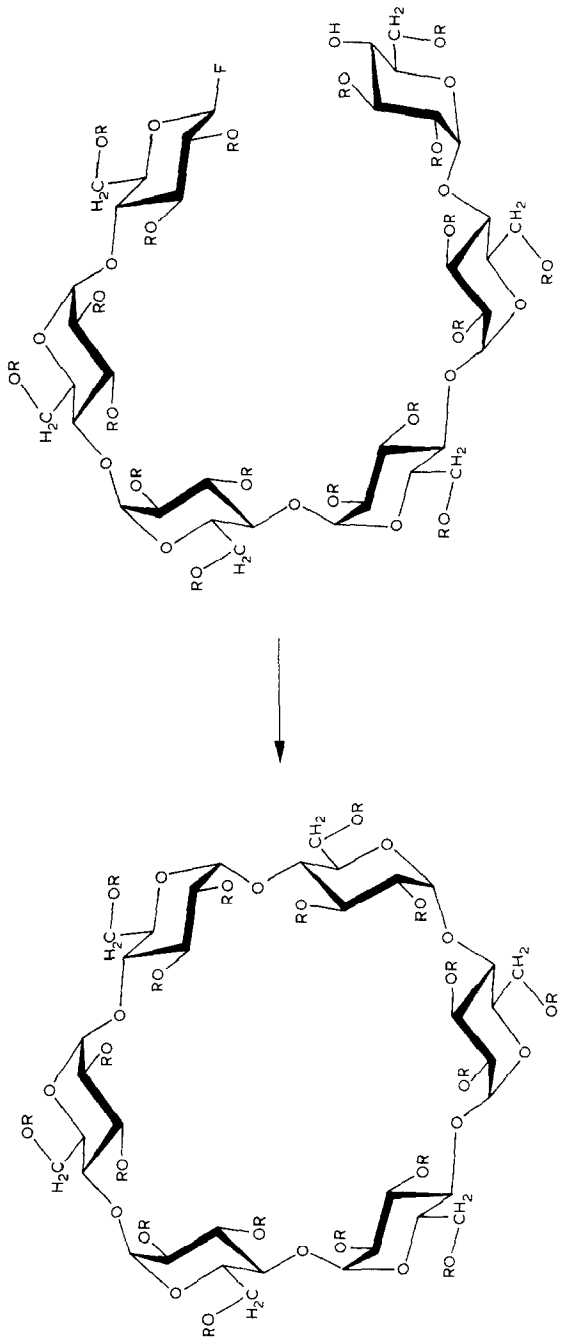
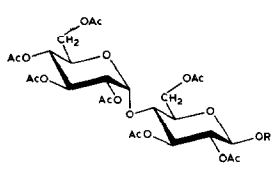


3 R = Bn

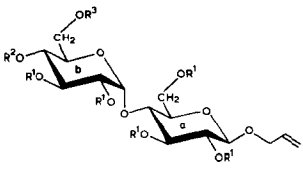
1 R = H

2 R = Bn

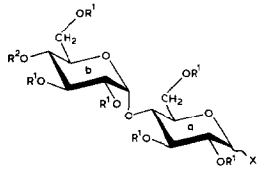
Scheme 1



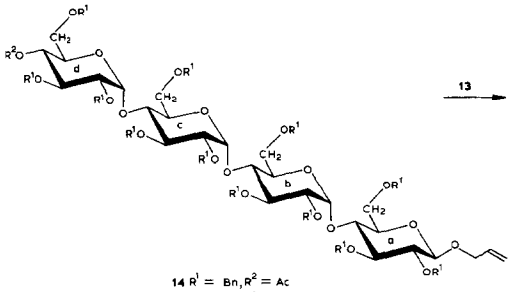
4 R = Ac
5 R = CH_2—CH=CH_2



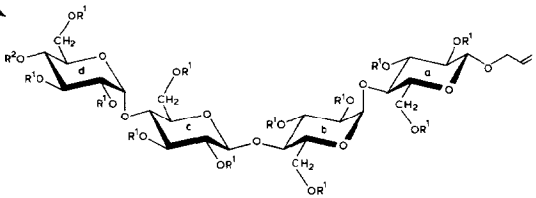
6 R^1 = H, R^2, R^3 = CMe_2
7 R^1 = Bn, R^2, R^3 = CMe_2
8 R^1 = Bn, R^2 = R^3 = H
9 R^1 = R^3 = Bn, R^2 = H
10 R^1 = R^3 = Bn, R^2 = Ac



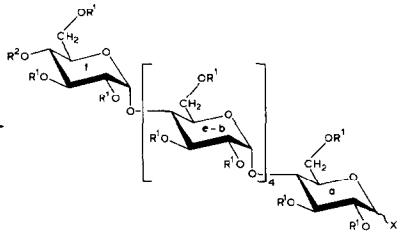
11 R^1 = Bn, R^2 = Ac, X = OH
12 R^1 = Bn, R^2 = Ac, X = Cl (α)
13 R^1 = Bn, R^2 = Ac, X = F (β)



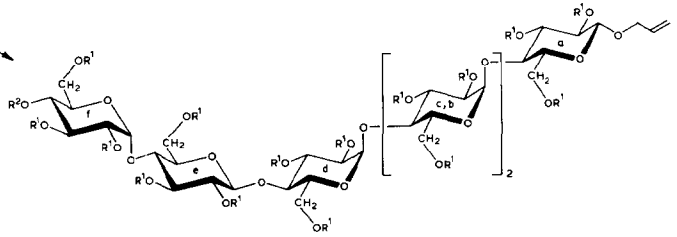
14 R^1 = Bn, R^2 = Ac
15 R^1 = Bn, R^2 = H



16 R^1 = Bn, R^2 = Ac



17 R^1 = Bn, R^2 = Ac, X = OCH_2CH=CH_2 (β)
18 R^1 = Bn, R^2 = H, X = OCH_2CH=CH_2 (β)
19 R^1 = Bn, R^2 = $COCH_2Cl$, X = OCH_2CH=CH_2 (β)
20 R^1 = Bn, R^2 = $COCH_2Cl$, X = OH (α, β)
21 R^1 = Bn, R^2 = $COCH_2Cl$, X = Cl (α)
22 R^1 = Bn, R^2 = $COCH_2Cl$, X = F (β)
3 R^1 = Bn, R^2 = H, X = F (β)



Scheme 2

23 R^1 = Bn, R^2 = Ac

Having both the glycosyl acceptor **9** and the glycosyl donor **13** prepared, we examined the coupling of these two intermediates. This was accomplished in the presence of $SnCl_2$, $AgOSO_2CF_3$, and powdered molecular sieves 4A in ether according to Mukaiyama *et al.*[11] to afford a 79% yield of a 1.8:1 mixture of the glucotetraose **14** and the β-anomer **16**, which were separated by flash chromatography on silica gel (elution with 20:1 toluene–EtOAc). Compound **14** had $[\alpha]_D$ +58.2° (*c* 0.152); δ_C ($CDCl_3$) 102.6 (C-1a), 96.3, 96.5, and 96.9 (C-1b, 1c, and 1d); for **16** the corresponding values were $[\alpha]_D$ +41.4° (*c* 0.236); δ_C ($CDCl_3$) 102.5 and 102.2 (C-1a and C-1c), and 96.9 (C-1b and 1d). Deacylation of **14** gave **15**, $[\alpha]_D$ +44.6° (*c* 0.26), and the subsequent glycosylation of **15** with the glycosyl donor **13** again afforded a 65% yield of coupling products, in this case a 2:1 mixture of the glucohexaoside **17** and the β-anomer **23**. Deacetylation of **17** with NaOMe in 1:1 MeOH–oxolane afforded alcohol **18** in 79% yield, $[\alpha]_D$ +64.7° (*c* 0.267); R_F 0.49 in 8:1 toluene–EtOAc; δ_C ($CDCl_3$) 102.6 (C-1a), 96.8, 96.6, and 96.3 (intensity ratio of 1:1:3, C-1b, 1c, 1d, 1e, and 1f). Acylation of **18** with monochloroacetic anhydride gave **19** (88%), $[\alpha]_D$ +69.4° (*c* 0.198); R_F 0.52 in 8:1 toluene–EtOAc, and deallylation[6] of **19** afforded the hemiacetal **20** (60%), $[\alpha]_D$ +73.8° (*c* 0.124); R_F 0.18 and 0.23 in 8:1 toluene–EtOAc. The conversion of **20** into β-fluoride **22** (73%) was achieved by the same two steps as the synthesis of **13** from **11**, namely by successive treatment with (i) $SOCl_2$ and DMF in $(CH_2Cl)_2$, and (ii) AgF in CH_3CN. Compound **22** had $[\alpha]_D$ +72.5° (*c* 0.131); R_F 0.57 in 8:1 toluene–EtOAc; δ_C ($CDCl_3$) 109.2 ($^1J_{CF}$ 217 Hz, C-1a), 96.7, 96.5, and 96.2 (intensity ratio of 2:1:2, C-1b, 1c, 1d, 1e, and 1f); δ_F ($CDCl_3$) 134.3 ($^2J_{HF}$ 53.7 Hz, $^3J_{HF}$ 10.4 Hz). Deacylation of **22** with NaOMe in 1:1 MeOH–oxolane for 2 h at 20° afforded the desired intermediate **3** in 95% yield, $[\alpha]_D$ +56.2° (*c* 0.211); R_F 0.37 in 8:1 toluene–EtOAc; δ_C ($CDCl_3$) 109.7 ($^1J_{CF}$ 217 Hz, C-1a).

Finally, slow addition of a solution of **3** in $ClCH_2CH_2Cl$ to the stirred mixture of $SnCl_2$, $AgOSO_2CF_3$, and powdered molecular sieves 4A in ether under argon afforded the intramolecular cyclization product **2** in 21% yield, $[\alpha]_D$ +49.6° (*c* 0.131); R_F 0.65 in 8:1 toluene–EtOAc. This product was completely identical, acorrding to its ^1H and ^{13}C-n.m.r. spectra, with the perbenzylated α-cyclodextrin obtainable from **1** by treatment with NaH and benzyl bromide. Debenzylation of **2** was achieved by catalytic hydrogen transfer[12] in the presence of 10% Pd-C in HCOOH–MeOH at 50° to give a quantitative yield of α-cyclodextrin **1**.

In conclusion, a regio- and stereo-controlled synthesis of α-cyclodextrin was achieved by use of the glycosyl fluoride **3** as the key intermediate for the intramolecular cyclization.

ACKNOWLEDGMENTS

We thank Dr. J. Uzawa and Ms. T. Chijimatsu for recording and measuring the n.m.r. spectra, and Dr. H. Homma and his staff for the elemental analyses. We also thank Emeritus Scientist Prof. M. Matsui for his kind encouragement, and Ms. A. Takahashi for her technical assistance.

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