Tetrahedron Vol 40, No. 15, pp. 2971 to 2973, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd.

SYNTHESIS OF NOVEL CHIRAL [2.2.1] CRYPTANDS INCORPORATING SUGARS†

M. PIETRASZKIEWICZ*, P. SAŁAŃSKI and J. JURCZAK
Institute of Physical Chemistry and Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

Abstract—Chiral N, N'-dimethyl diaza-crown ethers bearing functionalized α-D-gluco-, α-D-galacto-, and α-D-mannopyranoside residues are transformed into the corresponding [2.2.1] cryptands with bis(2-iodoethyl) ether under high-pressure conditions and subsequent demethylation. Alternatively, α-D-manno-diaza-18-crown-6 reacts with diglycolic acid dichloride under high-dilution conditions to form bisamide which is reduced to the corresponding chiral [2.2.1] cryptand.

A great number of chiral macrocyclic receptors have been synthesized[1] since Wudl and Gaeta reported the first example of the synthesis of chiral macrocyclic ligands.[2] Chiral macrocyclic ligands form diastereomeric complexes with optically active primary ammonium cations, and this important phenomenon has been applied in separation of enantiomers.[3] Interpretation of chiral recognition is relatively easy as far as ligands with C_n or D_n symmetry are concerned. However, when receptors of C_1 symmetry are taken into account, averaged chiral recognition with enantiomeric ammonium cations can be observed and its interpretation is not clear. To avoid these difficulties our attempts focused on design of the molecular receptors such that only one side of the macrocyclic framework is accessible for inclusion of guest molecule. In the preceding paper[4] we reported the synthesis of a chiral diaza-crown ethers bearing derivatized α-D-glucose, α-D-galactose and α-D-mannose which could serve as synthons for desired receptors via quaternization-demethylation method.[5] Now we report full experimental data concerning the synthesis of chiral [2.2.1] cryptands.

RESULTS AND DISCUSSION

Examination of the spatial models of α-D-galacto- and α-D-manno diaza-crown ethers **1b** and **1c**, respectively, revealed that introduction of an additional bridge leading to cryptand [2.2.1] framework should proceed from less hindered side whereas for the α-D-glucose derivative **1a** both sides of the macrocyclic ring are almost equally accessible.

We have examined two alternative routes leading to the same cryptands of the type **3**. Route I consists on the reaction of the α-D-gluco-, α-D-galacto-, and α-D-manno N, N'-dimethyl diaza-crown ethers **1a**, **b**, **c**, respectively, with bis(2-iodoethyl) ether under high-pressure conditions[5] (8 kbar at ambient temperature). High pressure quaternization reaction proceeded very cleanly to give white solid quaternary salt in quantitative yield. Demethylation reaction was followed by triphenylphosphine in boiling dimethylformamide[6] resulting desired title compounds in excellent yield.

Route II consists on the reaction of α-D-manno diaza-crown ether **4**[7] with diglycolic acid dichloride[8] in toluene under high dilution conditions[5] to give bisamide **5** as a single product. Reduction of **5** with lithium aluminium hydride led to the cryptand **3c** in rather poor yield, thus the α-D-gluco- and α-D-galacto diaza-crown ethers of the type **4** were not applied in this way.

Although the high-dilution technique has been broadly applied in the syntheses of various cryptands and crown ethers, it is limited to compounds possessing no reducible groups. As demonstrated in route II, bisamide **5** is formed in good yield (65%). However, this way suffers from serious drawback due to reduction step since diborane cannot be used (cleavage of benzylidene protecting group, acidic work up) and reduction with lithium aluminium hydride gives poor results.

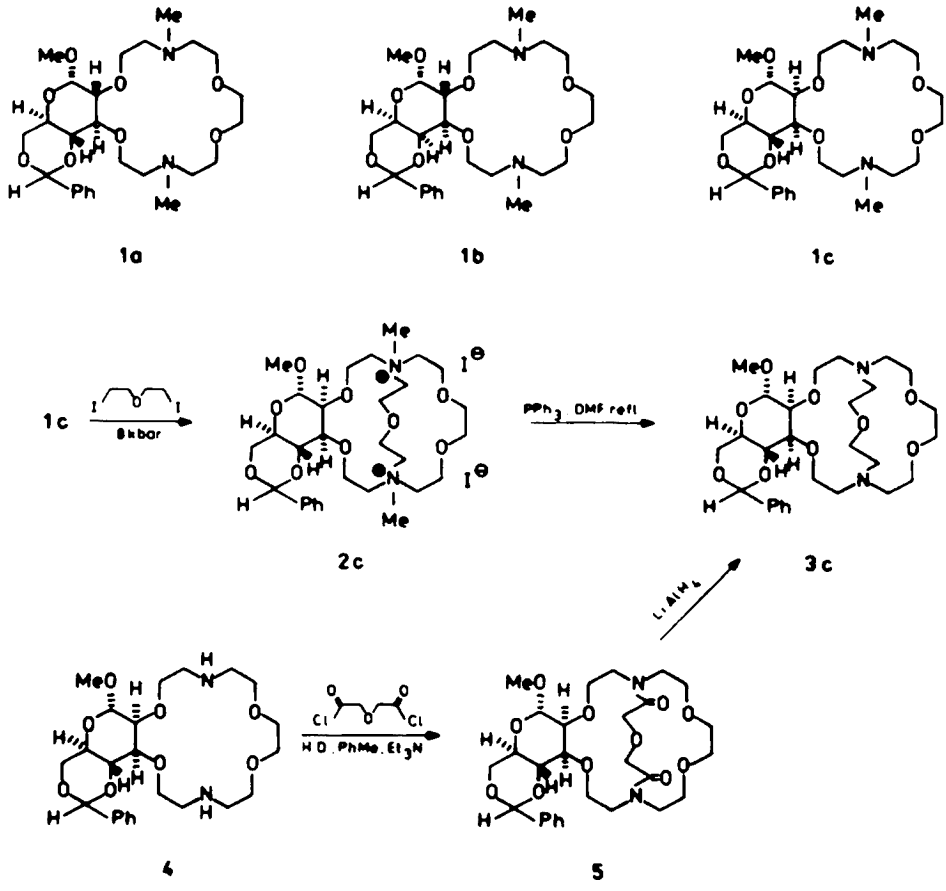
Quaternization-demethylation procedure has been reported by Newkome,[9] but the quaternization reaction was carried out under thermal conditions in *ca.* 40% yield. It is well known that the Menshutkin reaction is strongly accelerated by pressure,[10] thus we obtained the quaternary salts of the type **2** in quantitative yield. It is noteworthy that quaternary salts precipitated under high-pressure conditions which considerably simplified the work-up. Hence, we replaced powerful demethylation agents like "superhydride" or "Selectride ®" by triphenylphosphine.

Following this, the scope of the method presented herein is greatly extended. Thus, more elaborated cryptands possessing more sensitive groups may be synthesized in this way.

EXPERIMENTAL

^{1}H NMR spectra were recorded with Jeol JNM-4H-100 and Bruker SY 200 WH spectrometers for $CDCl_3$ solutions (δ scale, TMS as internal standard). Mass spectra were obtained with a LKB 2091 spectrometer at 15 eV. All the solvents were of analytical grade. Toluene was distilled over calcium hydride and triethylamine with phthalic anhydride and then over calcium hydride. High-pressure experiments were carried out in the piston-cylinder type apparatus described earlier.[11]

†Preliminary communication, see Ref. 5.



Starting materials. Compounds **1a**, **1b**, **1c** and **4** were prepared according to ref. 4. Bis(2-iodoethyl) ether was synthesized by the method of ref. 12. Diglycolic acid dichloride was obtained according to ref. 8.

Quaternization reaction under high pressure: general procedure. **1a–c** (0.102 g, 0.2 mmol) and bis(2-iodoethyl) ether (0.0652 g, 0.2 mmol) were dissolved in dry acetone (5 ml) and placed into a Teflon tube which after sealing with screwed cap was placed in a high-pressure apparatus and compressed to 8 kbar at 25° for 20 h. After completion of the reaction, white solid which precipitated during the reaction course and the mother-liquor were added to hexane (20 ml) and the precipitate was filtered off. Yields of quaternary salts **2a–c** in all cases were quantitative. **2a**: (found: C, 42.77; H, 5.81; N, 3.42. $C_{30}H_{50}O_9N_2I_2$ requires: C, 43.07; H, 6.02; N, 3.35%). **2b**: (found: C, 42.81; H, 6.11; N, 3.41%). **2c**: (found: C, 42.65; H, 5.87: N, 3.11%).

Demethylation with triphenylphosphine: general procedure. **2a–c**(0.0836 g, 0.1 mmol) and triphenylphosphine (0.0524 g., 0.2 mmol) were refluxed in dimethylformamide (0.4 ml) and monitored by TLC (alumina MN "Polygram ALOXN/UV$_{254}$", 2% methanol in methylene chloride v/v) until Ph_3P disappeared. After evaporation under diminished pressure, the residue was chromatographed on alumina (neutral II activity, 5% methanol in methylene chloride v/v). All the products **3a–c** were oils. **3a**: 82% yield (found: C, 60.91; H, 8.05; N, 4.42. $C_{28}H_{44}O_9N_2$ requires: C, 60.85; H, 8.02; N, 5.07%); MS, *m/z* (%): 553 (M^+, 1.2), 510 (31), 438 (27), 232 (25), 172 (100), 158 (27), 126 (32), 115 (51), 102 (25); ^{1}H NMR, 100 MHz, δ: 7.50 (5H, m, Ph), 5.67 (1H, s, PhCH), 4.92 (1H, d, MeOCH), 4.45–3.42 (22H, m), 3.55 (3H, s, OCH_3), 3.15–2.55 (12H, m, NCH_2). **3b**: 79% yield (found: C, 60.39; H, 7.67; N, 4.55%); MS, *m/z* (%): 553 (M^+, 1.3), 510 (19), 438 (25), 232 (29), 172 (100), 158 (17), 126 (39), 115 (37), 102 (22); ^{1}H NMR, 100 MHz, δ: 7.56 (5H, m, Ph), 5.62 (1H, s, PhCH), 5.02 (1H, d, MeOCH), 4.50–3.40 (22H, m), 3.52 (3H, s, OCH_3), 2.92–2.60 (12H, m, NCH_2). **3c**: 87% yield (found: C, 60.45; H, 7.87; N, 4.62%); MS, *m/z* (%): 553 (M^+, 1.8), 510 (28), 438 (22), 232 (34), 172 (100), 158 (22), 126 (46), 115 (49), 102 (18); ^{1}H NMR, 200 MHz, δ: 7.42 (5H, m, Ph), 5.59 (1H, s, PhCH), 4.79 (1H, s, MeOCH), 4.28–3.38 (22H, m), 3.39 (3H, s, OCH_3), 2.82–2.66 (12H, m, NCH_2).

Formation of the [2.2.1] *cryptand framework* (**4**) *by a high dilution procedure*. **4**(0.202 g, 0.42 mmol) and diglycollic acid dichloride (0.0734 g, 0.42 mmol) were dissolved separately in toluene (20 ml each) and added dropwise simulteneously to vigorously stirred toluene (500 ml) containing triethylamine (3 ml) during 3 h under argon, with the aid of syringe pump. After filtration, toluene was evaporated, the residue dissolved in chloroform (50 ml) containing triethylamine (0.5 ml) and shaked with water (10 ml). Removal of the solvent yielded the crude product which was purified on alumina (Merck 90, 70–230 mesh, II–III activity, 2% methanol in methylene chloride v/v). Yield of **5** (semi-solid) 65% (found: C, 57.43; H, 6.31; N, 4.45. $C_{28}H_{40}O_{11}N_2$ requires: C, 57.92; H, 6.94; N, 4.82%); MS, *m/z* (%): 581 (M^+, 1), 479 (22), 352 (23), 262 (92), 142 (66), 114 (26), 100 (100); ^{1}H NMR, 200 MHz, δ: 7.49–7.32 (5H, m, Ph), 5.59 (1H, s, PhCH), 4.79 (1H, d, MeOCH), 4.29–3.68 (30 H, m), 3.65 (3H, s, OCH_3).

Reduction of bisamide **5**. Bisamide **5** (0.1403 g, 0.24 mmol) was stirred under argon with lithium aluminium hydride (0.092 g, 2.4 mmol) in tetrahydrofuran (15 ml) for 5 days at

ambient temperature. After dilution with THF (100 ml) the excess of $LiAlH_4$ was destroyed by 10% aqueous LiOH. Filtration, washing with water, and evaporation of solvent gave the residue which was chromatographed on alumina (Merck 90, 70–230 mesh, II–III activ., 2% methanol in methylene chloride v/v) Yield of **3c**–15%. The product was identical with the **3c** obtained in high-pressure experiment.

Acknowledgements—High-dilution experiments were performed in the laboratory of Physical Organic Chemistry, Université Louis Pasteur (Strasbourg, France) led by Prof. J. -M. Lehn to whom we express our gratitude. This work was also supported financially by Grant 03.10 from Polish Academy of Sciences.

REFERENCES

[1]S. T. Jolley, J. S. Bradshaw and R. M. Izaat, *J. Heterocycl. Chem.* **19**, 3 (1982).
[2]F. Wudl and F. Gaeta, *J. Chem. Soc.* Chem. Commun. 107 (1972).
[3]R. C. Hegelson, K. Koga, J. M. Timko and D. J. Cram, *J. Am. Chem. Soc.* **95**, 3021 (1972).
[4]M. Pietraszkiewicz and J. Jurczak, *Tetrahedron*, **40** 2967 (1984).
[5]M. Pietraszkiewicz, P. Sałański and J. Jurczak, *J. Chem. Soc.* Chem. Commun. 1184 (1983).
[6]Tse-Lok Ho, *Synth. Commun.* **3**, 99 (1973).
[7]M. Pietraszkiewicz and J. Jurczak, *J. Chem. Soc.* Chem. Commun. 132 (1983).
[8]R. Anschütz and F. Biernaux, *Liebigs Ann. Chem.* **273**, 64 (1890).
[9]G. R. Newkome, V. K. Majestic and F. R. Fronczek, *Tetrahedron Letters* 3039 (1981).
[10]T. Asano and W. J. LeNoble, *Chem. Rev.* **78**, 407 (1978).
[11]J. Jurczak, *Bull. Chem. Soc. Jpn.* **52**, 3438 (1979).
[12]S. Kulstad and L. A. Malmsten, *Acta Chem. Scand.* **33**, 469 (1979).