Tetrahedron Letters,Vol.26,No.2,pp 215-218,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

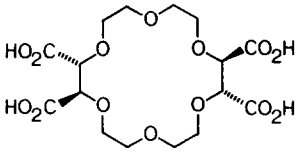
SYNTHESIS OF NOVEL MACROBICYCLIC POLYFUNCTIONAL CRYPTANDS

*Jean-Paul Behr, Cynthia J. Burrows, Richard Heng and Jean-Marie Lehn**

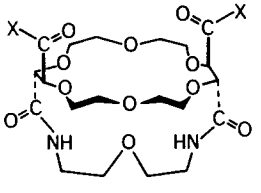
Institut Le Bel, Université Louis Pasteur, 4, rue Blaise Pascal, 67000 Strasbourg, France

Abstract : A pathway yielding both syn and anti-functionalized macrocycles derived from bis-tartaro-18-crown-6 (1) as well as a selective route to syn compounds have been developed and applied to the synthesis of new macrobicyclic polyether cryptands (2) and (3), which may also be obtained by direct bridging of the dianhydride (4).

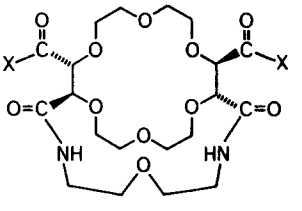
Macrocycles possessing functionalized side chains of defined stereochemistry have diverse applications in the design and synthesis of molecular receptors, catalysts and carriers[1]. The optically active 18-crown-6 (1), which incorporates two R,R-tartaric acid units[2], is particularly attractive both as a binding subunit and as a building block for the construction of macropolycyclic systems. The four carboxylates of (1) allow introduction of either four (via the tetraacid chloride)[2,3] or two (via the dianhydride (4))[4] side chains. Such derivatives form stable complexes with a variety of inorganic, organic and biological cations[3] through central anchoring into the macrocyclic cavity and lateral interaction with the side chains in quasi-axial orientation[3-5].



(1)



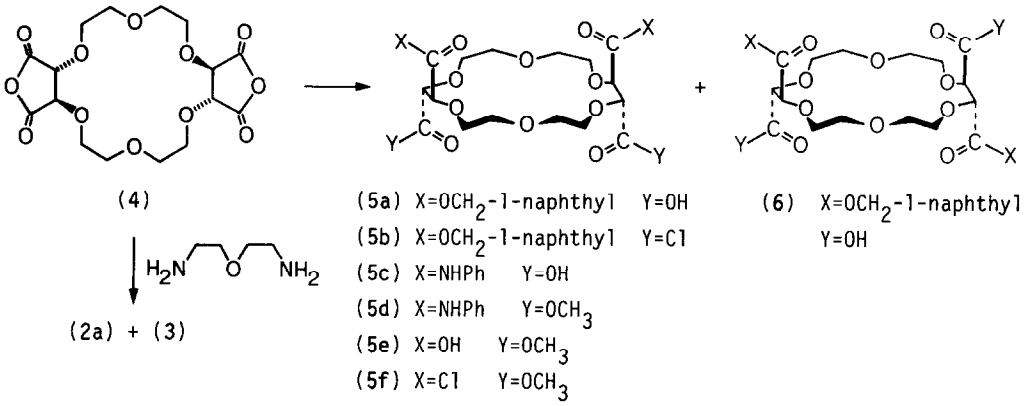
(2a) X=OH
(2b) X=OCH_2-1-naphthyl
(2c) X=OCH_3



(3) X=OH

In order to develop synthetic routes to macropolycyclic receptor molecules based on (1), we sought efficient methods giving access to key intermediates whose four sidechains were stereospecifically syn (or anti) doubly protected and doubly activated. Two such methods (**A** and **B**) were investigated : one leading to both the syn and anti diester-diacids (**5a**) and (**6**), as a mixture that was readily separable by column chromatography, and a second yielding selectively a syn isomer (**5e**). Either pathway could be employed for the synthesis

of the new polyfunctional macrobicyclic cryptands (**2a-c**), representing syn-bridged 18-crown-6 polyethers[6]. A third method (**C**) led directly to the syn compound (**2a**) together with its anti-bridged isomer (**3**).



(4)

(5a) X=OCH_2-1-naphthyl Y=OH
(5b) X=OCH_2-1-naphthyl Y=Cl
(5c) X=NHPh Y=OH
(5d) X=NHPh Y=OCH_3
(5e) X=OH Y=OCH_3
(5f) X=Cl Y=OCH_3

(6) X=OCH_2-1-naphthyl Y=OH

H_2N O NH_2

(2a) + (3)

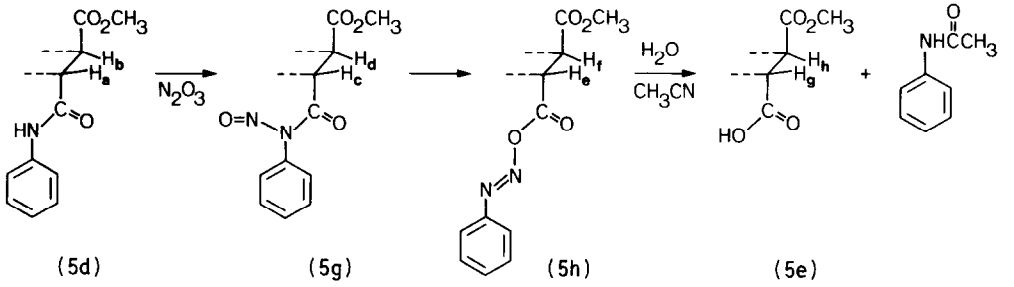
Method A. Treatment of the dianhydride (**4**) with two equivalents of a nucleophile generally leads to a mixture of syn and anti-substituted macrocycles[4]. In the present case, reaction of (**4**) with 1-naphthalenemethanol (2 equiv. pyridine in $CHCl_3$, 24 hrs at 25°C) gave a mixture of (**5a**) and (**6**) which were separated by flash column chromatography on silica ($CHCl_3$:MeOH:NH_4OH 70:16:1)[7]. The acid form of (**5a**) was regenerated by passage through a column of strong acid Dowex 50-X8 and was converted to the corresponding acid chloride (**5b**) by treatment with oxalyl chloride ($CHCl_3$, 12 hrs at 25°C).

Conversion to the macrobicycle (**2b**) was achieved under high dilution conditions in which $NH_2CH_2CH_2OCH_2CH_2NH_2$ plus 2 equiv. N-methylmorpholine and the diacid chloride (**5b**) as CH_2Cl_2 solutions were added slowly to CH_2Cl_2. Deprotection of the naphthalenemethyl esters (H_2, Pd/C, MeOH, 2hrs) afforded the dicarboxylic acid cryptand (**2a**) quantitatively[8].

Method B. We have previously reported exclusive syn-opening of the dianhydride (**4**) with aniline in the presence of triethyl amine to give nearly quantitative conversion to the syn-dianilide (**5c**)[4]. The carboxylate groups were protected as methyl esters ($SOCl_2$ in methanol, 0 to 20°, 12 hrs) affording (**5d**), whose anilide groups were subsequently hydrolyzed via the nitrosamide (**5g**).

The nitrosation procedure required carefully controlled conditions: N_2O_3 was bubbled into a solution of (**5d**) in anhydrous CH_3CN at 0° to give a persistent deep blue color, and the solution was left to warm gradually to room temperature. Following the reaction by ^1H-NMR of CD_3CN solutions indicated that formation of the nitrosoanilide (**5g**) was complete in 6-8 hours (H_a 4.37 d, H_b 4.42 d J = 3.0 Hz; H_c 5.81 d, H_d 4.83 d J = 2.0 Hz)[7b]. The subsequent slow rearrangement to the azoester (**5h**) (H_e 4.55 d, H_f 4.49 d J = 2.1 Hz)[7b] required an additional 8-15 hours[9,10]. Direct displacement of the benzenediazoate group by primary or secondary amine nucleophiles[11] was complicated by formation of nitrosamines from the HONO

present in solution and the sensitivity of (5h) to base, hence, the azoester was hydrolyzed to (5e) by one equivalent of H_2O after degassing the solution with a stream of N_2. The benzenediazonium hydroxide produced was trapped by solvent (CH_3CN) to give acetanilide.



(5d) (5g) (5h) (5e)

Removal of acetanilide by repeated extraction with isopropylether from 5% CH_3CN/H_2O gave compound (5e)[12] in an overall isolated yield of 90%. Compound (5e) was converted to the diacid chloride (5f) (PCl_5 in CH_2Cl_2)[13] from which the bicyclic cryptand (2c) was prepared by reaction with $H_2NCH_2CH_2OCH_2CH_2NH_2$ following a procedure analogous to that described above for (2a). Deprotection of the methyl esters with aqueous hydroxide was complicated by syn-anti interconversion (probably via cyclic imide formation), however, (2a) could be obtained by reaction with LiI in pyridine[14].

Method C. A direct reaction under high dilution conditions, in which CH_2Cl_2 solutions of $H_2NCH_2CH_2OCH_2CH_2NH_2$ plus 2 equiv. NEt_3 and of the dianhydride (4) were slowly added via two syringes to CH_2Cl_2, afforded a 1:1 mixture of the syn (2a) and anti (3)[15] bridged macrocycles; these were separated by HPLC (RP-C18, 7% MeOH/H_2O; 85% overall yield).

Conformational Features. The macrobicycles (2a) and (3) can exist in three forms : ii, oo or io depending on the orientation of the bridgehead C-H bonds in (i) or out (o) of the central cavity[6b,16]. The anti compound (3) can only be of the io type and apparently io ⇌ oi homeomorphic interconversion is slow on the NMR timescale, since four non-equivalent methine protons are observed. On the other hand, the syn isomer (2a) may be either ii, oo or a mixture of the two if interconversion is slow. NMR and HPLC studies indicate that a single syn compound is obtained by method C, which is identical to that derived from the syn reagent (5f), where the reacting functions may be expected to take up the quasi-axial orientation[5] shown in (5c); it forms strong complexes with ammonium cations; thus, the most likely form of the cryptand (2a) is the oo structure shown.

Cation complexation by (2a) and (3). Complexation of NH_4^+ and $HONH_3^+$ cations by the dianionic forms of (2a) and (3) was studied pH-metrically by determining the shift in pK_a of the bound cation, giving the following stability constants: (2a), log K_s = 3.2 (NH_4^+) 4.0 ($HONH_3^+$); (3) log K_s = 1.6 ($HONH_3^+$) (aqueous 0.1 M NMe_4Cl, 25°). The dianion of the oo syn cryptand (2a) binds cations much better than its io anti isomer (3), whose cavity is appreciably distorted. Although it is less charged, its complexes are as stable as those of the tetraanion of (1) (log K_s = 3.4 (NH_4^+), 4.9 ($HONH_3^+$)).

In summary, synthetic routes to tetrasubstituted 18-O_6 macrocycles have been investigated leading to syn and anti-difunctionalized derivatives[17] and to a new type of macrobicyclic polyfunctional cryptands, whose syn isomer (**2a**) has been shown to form strong cation complexes compared to its anti-bridged one (**3**). The key intermediates (**5b**), (**5f**) and (**6b**) as well as the macrobicycle (**2a**) are versatile building blocks providing access to new macropolycyclic receptor molecules with multiple binding sites. Studies along these lines are in progress.

Acknowledgements. The N.S.F.-C.N.R.S. Exchange of Scientists Program and the French Embassy are gratefully acknowledged for fellowships to C.J.B.

References and Notes

1. J.M. Lehn, Pure & Appl. Chem. **51**, 979 (1979).
2. J.P. Behr, J.M. Girodeau, R.C. Hayward, J.M. Lehn, J.P. Sauvage, Helv. Chim. Acta **63**, 2096 (1980).
3. J.P. Behr, J.M. Lehn, P. Vierling, Helv. Chim. Acta **65**, 1853 (1982).
4. J.P. Behr, J.M. Lehn, D. Moras, J.C. Thierry, J. Am. Chem. Soc. **103**, 701 (1981).
5. J.J. Daly, P. Schönholzer, J.P. Behr, J.M. Lehn, Helv. Chim. Acta **64**, 1444 (1981); J.P. Behr, J.M. Lehn, A.C. Dock, D. Moras, Nature **295**, 526 (1982); J.P. Behr, P. Dumas, D. Moras, J. Am. Chem. Soc. **104**, 4540 (1982).
6. Macrobicyclic polyethers of related type have been reported: a) A.C. Coxon, J.F. Stoddart, J. Chem. Soc., Perkin I **1977**, 767; D.G. Parsons, J. Chem. Soc. Perkin I **1978**, 451; Y. Nakatsuji, T. Mori, M. Okahara, J. Chem. Soc., Chem. Commun. **1984**, 1045; b) A.H. Haines, P. Karntiang, J. Chem. Soc., Perkin I **1979**, 2577.
7. a) Compound (**5a**) ^{1}H-NMR ($CDCl_3$): 2.8-3.9 (m, 16H, OCH_2); 4.22 (d, J=2.0 Hz, 2H, CH); 4.31 (d, J=2.0 Hz, 2H, CH); 5.50 and 5.91 (AB d, J=12 Hz, 4H, CH_2-naph); 7.4-8.1 (m, 14H, arom H). Compound (**6**) ^{1}H-NMR ($CDCl_3$): 2.8-4.0 (m, 16H, OCH_2); 4.18 (d, J=2.4 Hz, 2H, CH); 4.33 (d, J=2.4 Hz, 2H, CH); 5.58 and 5.89 (AB d, J=12 Hz, 4H, CH_2- naph); 7.4-8.1 (m, 14H, arom H); b) Chemical shifts are in ppm from TMS.
8. Compound (**2a**) ^{1}H-NMR (CD_3N): 3.0-3.8 (m, 24H, 20 OCH_2, 4 NCH_2); 4.18 (br s, 2H, CH); 4.30 (br s, 2H, CH); 7.49 (br s, 2H, NH)[7b].
9. For a general discussion, see: H. Zollinger "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds" Interscience Publishers, New York: 1961, p. 153.
10. A second treatment with N_2O_3 several hours after the first increases the yield and rate of reaction.
11. J. Garcia, J. Gonzales, R. Segura, F. Urpi, J. Vilarrasa, J. Org. Chem. **49**, 3322 (1984).
12. Compound (**5e**) ^{1}H-NMR ($CDCl_3$): 3.4-3.9 (m, 16H, 8 OCH_2); 3.81 (s, 6H, OCH_3); 4.38 (d, J=2 Hz, 2H, CH); 4.45 (d, J=2 Hz, 2H, CH)[7b].
13. Maintainance of the syn stereochemistry throughout was verified by treatment of the diacid chloride derivative with aniline, cleavage of the ester groups and comparison of the resulting product to syn and anti-dianilides whose X-ray structures and properties had been previously determined[4].
14. E. Taschner, B. Liberek, Roczniki Chimii **30**, 323 (1956); F. Elsinger, J. Schreiber, A. Eschenmoser, Helv. Chim. Acta **43**, 113 (1960).
15. Compound (**3**) ^{1}H-NMR (CD_3CN): 3.0-3.8 (m, 24H, 20 OCH_2, 4 NCH_2); 4.37 (d, J=2.0 Hz, 1H, CH); 4.50 (d, J=6.2 Hz, ^{1}H, CH); 4.53 (d, J=2.0 Hz, 1H, CH); 4.92 (d, J=6.2 Hz, 1H, CH). 7.01 (br m, 1H, NH); 7.30 (br m, 1H, NH)[7b].
16. C.H. Park, H.E. Simmons, J. Am. Chem. Soc. **94**, 7184 (1972).
17. For the synthesis of related anti-disubstituted macrocycles, see: T.M. Fyles, C.A. McGavin, D. Whitfield, J. Org. Chem. **49**, 753 (1984).

(Received in France 24 October 1984)