Molecular Receptors. Synthesis of Macrocyclic Polyethers with Intra-annular Functional Groups using Dibutylstannylene Derivatives of Vicinal Diols

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Symmetrical and unsymmetrical macrocyclic polyethers containing the 1,3-xylyl sub-unit and intra-annular functional groups have been synthesised from 2,6-bis(bromomethyl)anisole and dibutylstannylene derivatives of ethylene glycol, a chiral glycol derived from (+)-tartaric acid, and *trans*-cyclohexane-1,2-diol.

The realisation that ion binding characteristics of macrocyclic polyethers can be varied by attaching additional binding sites in the form of functional groups to the periphery of the macrocycle has been an important feature of recent developments with synthetic molecular receptors.[1] The emphasis has been on chemically inert receptors and few systems have evolved in which the reversible reception of a guest species is associated with a reversible chemical change in a strategically placed functional group in the receptor.[2] In one such recent case we showed how synergism between a macrocyclic polyether and an intra-annular phenolic group can be exploited to bind ammonia and some alkylamines as their ammonium and alkylammonium phenoxides.[3] The construction of large, more complex receptors with more than one intra-annular functional group and additional options such as chirality or unusual symmetry features poses problems of synthesis for which we now propose a partial solution. The design of such systems, which require convergence of binding sites and functional groups, should facilitate the development of catalytically active receptors capable of imitating enzymes.

The Williamson ether synthesis forms the basis of most routes to macrocyclic polyethers and although it can be used conveniently in a one-pot procedure, yields are frequently low owing to the difficulty of directing the reaction to provide cyclic products in preference to acyclic polymers.† Moreover, in the absence of a specific template effect mixtures of cyclic oligomers are often obtained. In earlier work, for example, we found that 2,6-bis(bromomethyl)anisole (**1**) and ethylene glycol in tetrahydrofuran (THF) with sodium hydride gave the dimeric macrocycle (**2**) (<20%) contaminated with higher oligomers.[4] Similar difficulties were encountered when the much less accessible chiral glycol (−)-(**3**)[5] was condensed with

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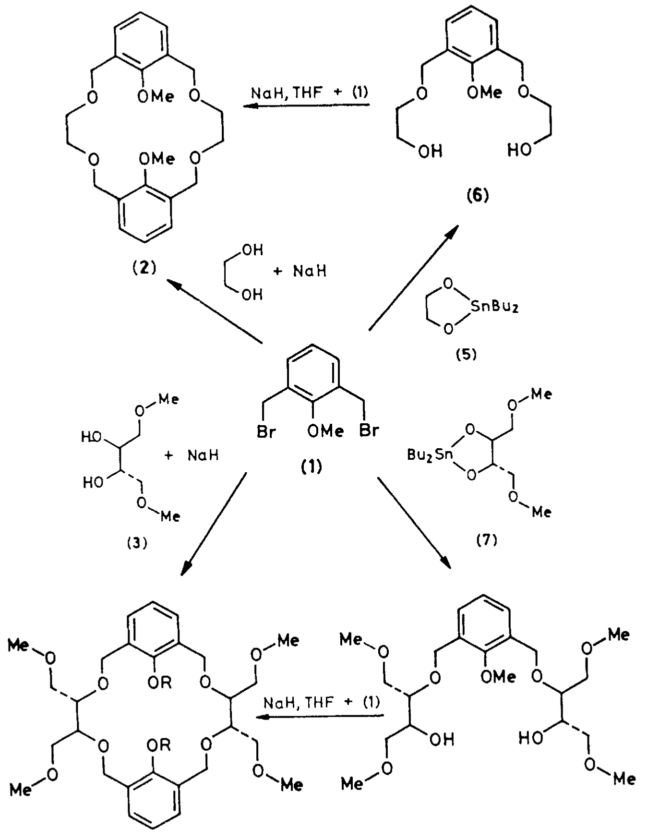
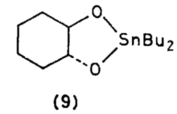
† Several multistep routes to a variety of synthetic crown ethers are summarised in reference 1.



(4) R = Me
(16) R = H

(8)



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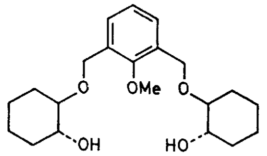

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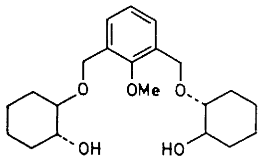

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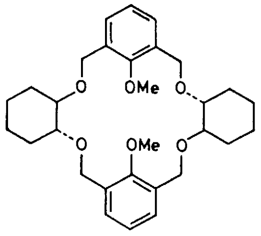

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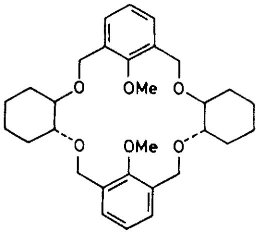

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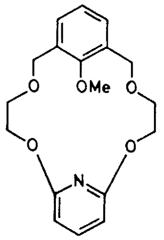
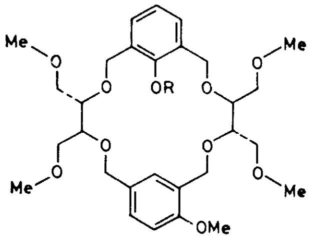


(14)



(15) R = Me
(17) R = H

the same dibromide, the cyclic products in this case consisting of the dimer (**4**) (22%), a tetramer (12%), and probably higher oligomers, which were difficult to separate. A more crucial disadvantage of the one-pot Williamson method is the fact that only symmetrical macrocycles can be produced in this way, thereby limiting the scope for introducing more than one kind of intra-annular functional group.

Some of these difficulties can be circumvented by the use of dibutylstannylene derivatives of glycols[6,7] and a two-step procedure. Dibutylstannylation activates one hydroxy-group of a glycol towards electrophilic attack after which the second hydroxy-group can be released by hydrolysis.[7] Thus treatment of the dibromide (**1**) with the dibutylstannylene derivative of ethylene glycol (**5**) (1 : 2 molar ratio) in hot dimethylformamide (DMF) followed by an aqueous work-up furnished the diol (**6**)‡ in excellent yield. When this diol, without purification, was exposed to sodium hydride followed by the dibromide (**1**) in THF, the dimeric macrocycle (**2**), m.p. 153—154 °C, was isolated in 60% yield with little or no contamination by higher oligomers. The chiral glycol (−)-(**3**)[5] and (±)-*trans*-cyclohexane-1,2-diol were also incorporated efficiently into 1,3-xylyl-based macrocycles using the same stepwise approach. Treatment of (**3**) with dibutyltin oxide in hot benzene gave the dibutylstannylene derivative (**7**) (>95%) as a low melting solid. Reaction of (**7**) with the dibromide (**1**) (2:1 molar ratio) in hot DMF produced the diol (**8**) (87%) as an oil after an aqueous work-up. In a similar fashion the dibromide (**1**) and the known dibutylstannylene derivative (**9**)[8] of (±)-*trans*-cyclohexane-1,2-diol produced a mixture of the diols (**10**) and (**11**) in *ca.* 40% yield. Exposure of the diol (**8**) to sodium hydride followed by the dibromide (**1**) in THF produced the crystalline macrocycle (**4**), m.p. 101—102 °C, in 50% yield. Cyclisation of the diol mixture (**10**) and (**11**) using the same reagents produced the mixed cyclohexyl-1,3-xylyl macrocycles (**12**) and (**13**) (40%) as a crystalline solid, m.p. 202—204 °C.

The success of this stepwise synthesis makes it now possible to incorporate polyether units into macrocycles using two or more different structural subunits and at the same time vary the number and/or nature of intra-annular functional groups. For example, treatment of the diol (**6**) with sodium hydride followed by 2,6-dichloropyridine in hot xylene produced the crystalline macrocycle (**14**) (*ca.* 10%) m.p. 70—71 °C, possessing both an intra-annular methoxy substituent and an intra-annular basic nitrogen atom. Alternatively, macrocycles can be formed with intra-annular and extra-annular substituents, an illustrative example being the reaction of the diol (**8**) with sodium hydride and 2,4-bis(bromomethyl)anisole which produced the macrocycle (**15**) in 40% yield.

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‡ All new compounds have ^{1}H n.m.r., ^{13}C n.m.r., and ^{1}H-decoupled ^{13}C n.m.r. spectra in full accord with the assigned structures.

The intra-annular methoxy groups in these macrocyles are readily converted into phenolic hydroxy groups. Thus treatment of (**4**) with anhydrous lithium iodide[3,9] in hot pyridine gave the bis-phenol (**16**) as an oil. A similar reaction with the macrocycle (**15**) showed that it is possible to differentiate between the two methoxy groups: the intra-annular substituent was smoothly cleaved by lithium iodide in pyridine, leaving the extra-annular substituent intact, and the product isolated was the phenolic macrocycle (**17**).[10]

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References

1 For comprehensive surveys of synthetic crown ethers and related macrocycles see C. J. Pedersen, *Aldrichimica Acta*, 1971, **4**, 1; 'Synthetic Multidentate Macrocyclic Compounds,' eds. R. M. Izatt and J. J. Christensen, Academic Press, New York, 1978; J. S. Bradshaw and P. E. Stott, *Tetrahedron*, 1980, **36**, 461; 'Progress in Macrocyclic Chemistry,' Vol. 1, eds. R. M. Izatt and J. J. Christensen, Wiley, New York; G. W. Gokel and H. D. Durst, *Synthesis*, 1976, 168; J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 95.

2 For recent studies of intramolecular interactions between functional groups and cyclic polyether receptors see M. N. Newcomb and D. J. Cram, *J. Am. Chem. Soc.*, 1975, **97**, 1258; K. E. Koenig, R. C. Helgeson, and D. J. Cram, *ibid.*, 1976, **98**, 4018; T. Matsui and K. Koga, *Tetrahedron Lett.*, 1978, 1115; G. W. Gokel, D. M. Dishong, and C. J. Diamond, *J. Chem. Soc., Chem. Commun.*, 1980, 1053; J. P. Behr, J. M. Girodeau, R. C. Hayward, J. M. Lehn, and P. J. Sauvage, *Helv. Chim. Acta.*, 1980, **63**, 2096; W. H. Rastetter and D. P. Phillion, *J. Org. Chem.*, 1981, **46**, 3204; F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 149.

3 M. A. McKervey and D. L. Mulholland, *J. Chem. Soc., Chem. Commun.*, 1977, 438.

4 D. L. Mulholland, Ph.D. Thesis, National University of Ireland, 1978.

5 Prepared from (+)-tartaric acid by the method of D. Seebach, H. O. Kalinowski, B. Bastani, G. Grass, H. Daum, H. Dorr, N. P. Dupreez, V. Ehrig, W. Langer, C. Nussler, Hoc-An Oei, and H. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301.

6 The use of dibutylstannylene derivatives as templates in the synthesis of macrocyclic polyamides and lactones has been described by A. Shanzer and N. Mayer, *J. Chem. Soc., Chem. Commun.*, 1980, 176; A. Shanzer and E. Berman, *ibid.*, p. 259.

7 For a recent survey of the structure and use in synthesis of dibutylstannylene derivatives of glycols see S. David and A. Thiettry, *Tetrahedron Lett.*, 1981, 2647 and 2885.

8 W. J. Considine, *J. Organomet. Chem.*, 1966, **5**, 263. Dibutylstannylene derivatives (**5**) and (**7**) are represented here as symmetrical monomers for convenience only. In fact (**5**) is known to be a dimer with non-equivalent O–Sn bonds, see reference 7 for details.

9 For the use of lithium iodide in the demethylation of anisole see I. T. Harrison, *Chem. Commun.*, 1969, 616.

10 For the recent use of the allyl group as a protecting group for phenols in crown ether synthesis see M. van der Leij, H. J. Oosterink, R. H. Hall, and D. N. Reinhoudt, *Tetrahedron*, 1981, **37**, 3661.