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SYNTHESIS OF (+)-(3S,6S,10S,13S,17S,20S,24S,27S)-1,8,15,22-TETRAAZA-3,6;10,13;17,20;24,27-TETRAEPOXYCYCLOOCTACOSANE. AN ENANTIOMERICALLY PURE TETRAAZACROWN ETHER WITH D_4 SYMMETRY AND OF KNOWN ABSOLUTE CONFIGURATION

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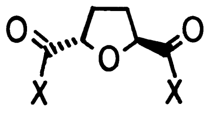
The title azacrown ether, which was synthesized using (+)-(2S,5S)-trans-2,5-bis(aminomethyl)tetrahydrofuran and (+)-(2S,5S)-trans-2,5-bis(hydroxymethyl)tetrahydrofuran as the C_2 building blocks, is the first optically active organic molecule of D_4 symmetry with known absolute configuration.

A macromonocycle which contains four secondary amino functions and belongs to the D_4 point group is an interesting compound which may be used for constructing high symmetry chiral macropolycyclic cryptands.1) However, as far as we know,2) no enantiomerically pure organic molecule with D_4 symmetry has been reported. In this communication, we wish to report the synthesis of an optically active tetraazacrown ether 14 with D_4 symmetry and of known absolute configuration.

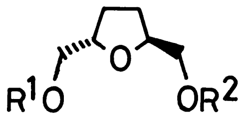
(+)-(2S,5S)-trans-2,5-Bis(hydroxymethyl)tetrahydrofuran (4)3) and (+)-(2S,5S)-trans-2,5-bis(aminomethyl)tetrahydrofuran (7) were C_2 building blocks which were used for constructing D_4-tetraazacrown ether 14. Treatment of (-)-(2S,5S)-trans-tetrahydrofuran-2,5-dicarboxylic acid (1)3) with thionyl chloride afforded the acid chloride 2 which was reacted with aqueous ammonia with ice cooling to afford the (-)-amide 3,4) mp 158 °C $[\alpha]_D^{27}$ -29.9° (MeOH), in 95% overall yield from 1. Reduction of (-)-3 with $LiAlH_4$ in THF at reflux gave a 55% yield of the (+)-amine 7, bp 75-76 °C (4 mm) $[\alpha]_D^{21}$ +22.4° (MeOH). The (+)-amine 7 was also prepared via the N-alkylphthalimide 9 as follows. The (+)-ditosylate 6,3) prepared from (+)-4, was treated with potassium phthalimide in dimethylformamide (DMF) at 100 °C to give the (+)-N-alkylphthalimide 9, mp 200-202 °C $[\alpha]_D^{20}$ +103° ($CHCl_3$). Hydrolysis5) of (+)-9 furnished (+)-7 in 35% overall yield from 6. After (+)-7 was tosylated with tosyl chloride in 10% aqueous NaOH solution, the N,N-ditosylate 8, mp 121 °C, was treated with sodium ethoxide in ethanol to give the disodium salt 10. The condensation5) of 10 with (+)-5, prepared from (+)-4, in DMF at 95 °C afforded 11. Tosylation of 11 with tosyl chloride in pyridine followed by alumina chromatography ($CHCl_3$ eluent) gave the tosylate 12, $[\alpha]_D^{22}$ +23.2° ($CHCl_3$), as a glass in 23% overall yield from 8. The cyclization was achieved by the condensation5) of (+)-12 with 10 in DMF at 95 °C for 3 h and alumina chromatography (benzene eluent) of the product furnished a 13% yield of the tetraazacrown ether 13, $[\alpha]_D^{23}$ +43.0° ($CHCl_3$), as a glass. In the enantiomer differential transport,6) the macrocycle 13 transported preferentially the S enantiomer of the guest, methyl (±)-phenylglycinate hydrochloride, in 15%

enantiomer excess. The tosyl groups of 13 were removed by reduction with $LiAlH_4$ in THF at reflux and the crude product was chromatographed on alumina ($MeOH-CHCl_3$ eluent) to furnish a 88% yield of the azacrown ether 14, $[\alpha]_D^{20}$ +11.1° ($CHCl_3$), as a colorless oil.

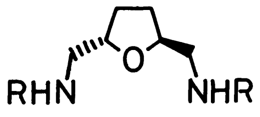
The azacrown ether ring of the macromonocycle 14 is a 24 membered ring with alternating O and N sites and the highest attainable symmetry of 14 is D_4, a molecule with D_4 symmetry is rarely found among organic compounds. Since the azacrown ether 14 contains four free secondary amino functions, it may serve as a key molecule for constructing high symmetry chiral macropolycyclic cryptands.



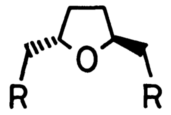
1 X = OH
2 X = Cl
3 X = NH_2



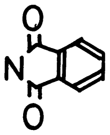
4 $R^1 = R^2 = H$
5 $R^1 = H$ $R^2 = Ts$
6 $R^1 = R^2 = Ts$

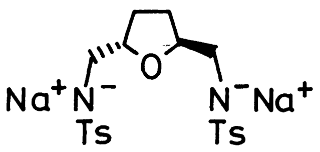


7 R = H
8 R = Ts

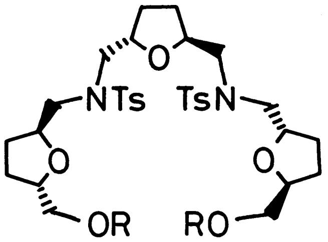


9 R =

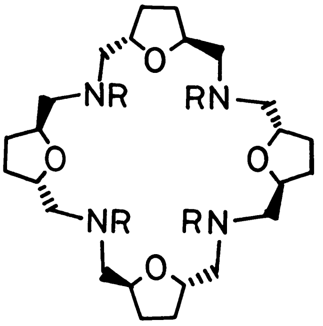




10



11 R = H
12 R = Ts



13 R = Ts
14 R = H

References

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2) M. Farina, C. Morandi, Tetrahedron, 30, 1819 (1974); M. Nakazaki, Topics in Stereochemistry, 15, 199 (1984).

3) M. Nakazaki, K. Naemura, M. Makimura, A. Matsuda, T. Kawano, and Y. Ohta, J. Org. Chem., 47, 2429 (1982).

4) All new compounds gave satisfactory elemental analysis and spectral data (^1H NMR and IR). ^1H NMR spectral data for the selected compounds are as follows, 12: δ 1.4-2.2 (m, 12H, CH_2CH_2), 2.42 (s, 12H, CH_3), 3.1-3.4 (m, 8H, NCH_2), 3.8-4.3 (m, 10H, OCH_2 and OCH), 7.1-7.4 (m, 8H, aromatic), 7.66 (d, J=8 Hz, 4H, aromatic), 7.77 (d, J=8 Hz, 4H, aromatic); 13: δ 1.3-2.1 (m, 16H, CH_2CH_2), 2.38 (s, 12H, CH_3), 3.0-3.3 (m, 16H, NCH_2), 3.8-4.3 (m, 8H, OCH), 7.26 (d, J=8 Hz aromatic), 7.64 (d, J=8 Hz, aromatic); 14: δ 1.3-2.2 (m, 16H, CH_2CH_2), 3.0-3.4 (m, 16H, NCH_2), 3.8-4.3 (m, 8H, OCH), 4.2 (br s, 4H, NH).

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