

Synthesis of (S, S)-1, 5-bis(4-alkyl-5-hydroxy-2-oxo-3-azapentyl)-1, 5-diazacyclooctane

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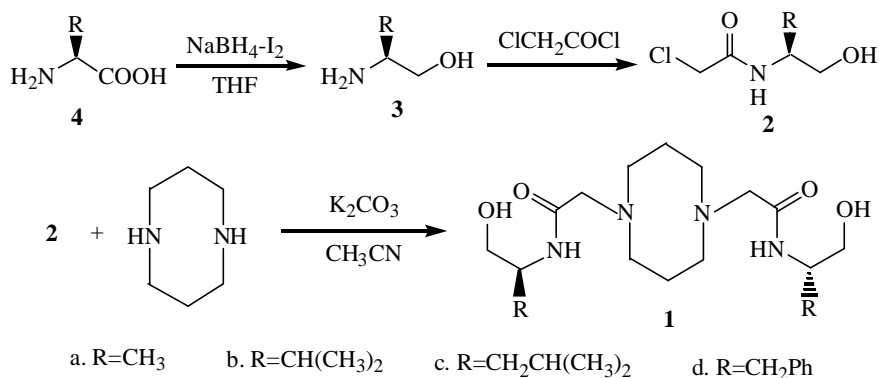
Abstract: Synthesis of a series of chiral aza crown ethers ((S,S)-1, 5-bis (4-alkyl-5-hydroxy-2-oxo-3-azapentyl)-1, 5-diazacyclooctane) are described.

Keywords: Chiral aza crown ether, 1,5-diazacyclooctane, synthesis.

Crown ether derivatives have been extensively developed to provide enhanced structural recognition of substrate alkyl-ammonium cations. In particular a number of investigations of complexation of chiral alkylammonium salts by chiral crown ethers have been reported. The enantioselectivity has been applied in the chromatographic resolution of amino acid perchlorates. In general the crown ethers used in these studies have been based upon derivatives of 2, 2' -dihydroxy-1, 1' -binaphthyl¹ or derivatives of suitable optically active natural products² such as tartaric acid and carbohydrate derivatives. Because the aza crown ethers³ and their polycyclic derivatives⁴ could form strongly bound and well defined complexes with primary alkylammonium salts, a number of aza crown ether analogues in which the chirality is derived from an α -amino acid have been reported⁵. But the chiral aza crown ethers, in which 1, 5-diazacyclooctane is connected with chiral side chains, have not been reported. In this paper, we designed and synthesized a series of new chiral aza crown ethers [**1a-d** (S, S)-1, 5-bis (4-alkyl-5-hydroxy-2-oxo-3-azapentyl)-1, 5-diazacyclooctane]. Based on the special structures of the 1, 5-diazacyclooctane, we anticipated that these chiral aza crown ethers show high enantiomer recognition factors for the salts of chiral alkylammonium salts.

The overall procedure is shown in **Scheme 1**. Treatment of L-amino acids **4a-d** with sodium borohydride-iodine in THF afford the corresponding chiral amino-alcohol **3a-d**⁶. The N-chloroacetamido alcohols **2a-d** were prepared by the reaction of the corresponding amino alcohol with chloroacetyl chloride⁷. Thus the title compounds **1a-d** were obtained by alkylating of 1,5-diazacyclooctane with each of these side chains **2a-d** in the present of anhydrous K₂CO₃. The structure of compounds **1a-d** were confirmed by elemental analysis, IR and ¹H NMR spectra⁸.

Scheme 1



References and notes

- D. J. Cram, J. M. Cram, *Acc. Chem. Res.*, **1978**, *11*, 8; S. C. Peacock, D. M. Walba, F. C. A. Gaeta, R. C. Helgeson, D. J. Cram, *J. Am. Chem. Soc.*, **1980**, *102*, 2043.
- W. Hain, R. Lehnert, H. Rottele, G. Schrodet, *Tetrahedron Lett.*, **1978**, 625; J. P. Behr, J. M. Lehn, D. Moras, J. C. Thierry, *J. Am. Chem. Soc.*, **1981**, *103*, 701.
- M. R. Johnson, I. O. Sutherland, R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 357.
- M. R. Johnson, I. O. Sutherland, R. F. Newton, *J. Chem. Soc., Chem. Commun.*, **1979**, 309.
- F. Gaeta, F. Wudl, *J. Chem. Soc., Chem. Commun.*, **1972**, 107; B. Bosnic-Kasnar, D. Kolbah, M. Zinic, *Tetrahedron Lett.*, **1980**, *21*, 1365.
- M. J. McKennon, A. I. Meyers, *J. Org. Chem.*, **1993**, *58*, 3568.
- D. J. Chadwich, I. A. Cliff, I. O. Sutherland, R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1707.
- 1a**: colorless oil, yield 82%. $[\alpha]_D^{10}$ -50.2 (c 3.21, CHCl₃). C₁₆H₃₂N₄O₄ (Calcd: C, 55.79; H, 9.36; N, 16.27; Found: C, 55.62; H, 9.47; N, 16.32). IR (neat)v: 3341, 1651, 1525, 1455, 1043 cm⁻¹. ¹H NMR (CDCl₃, δ ppm): 1.20 (d, 6H, J=6.8Hz, -CH₃), 1.78 (m, 6H, -CH₂ + -OH), 2.77 (m, 8H, N-CH₂), 3.22 (m, 4H, -CH₂), 3.53, 3.72 (m, 4H, O-CH₂), 4.08 (m, 2H, N-CH), 7.45 (br, 2H, -NH). **1b**: colorless oil, yield 76%. $[\alpha]_D^{10}$ -34.9 (c 1.52, CHCl₃). C₂₀H₄₀N₄O₄ (Calcd: C, 59.97; H, 10.07; N, 13.99; Found: C, 60.12; H, 9.87; N, 13.82). IR (neat) v: 3345, 1655, 1527 cm⁻¹. ¹H NMR (D₂O, δ ppm): 0.77, 0.81 (dd, 12H, J=20.6, 6.7Hz, -CH₃), 1.72 (m, 6H, -CH₂+ -CH), 1.54 (m, 4H, -CH₂), 2.72 (m, 8H, N-CH₂), 3.23 (s, 4H, -CH₂), 3.51, 3.57 (m, 6H, O-CH₂+N-CH). **1c**: colorless oil, yield 78%. $[\alpha]_D^{10}$ -45.9 (c 3.79, CHCl₃). C₂₂H₄₄N₄O₄ (Calcd: C, 61.65; H, 10.35; N, 13.07; Found: C, 61.85; H, 10.13; N, 12.98). IR (neat) v: 3336, 1654, 1524 cm⁻¹. ¹H NMR (CDCl₃, δ ppm): 0.93 (t, 12H, J=3.0Hz, -CH₃), 1.41 (m, 4H, C-CH₂), 1.61 (m, 2H, -CH), 1.78 (m, 4H, -CH₂), 2.78 (m, 8H, N-CH₂), 3.22 (m, 4H, N-CH₂), 3.55, 3.70 (m, 4H, O-CH₂), 4.05 (m, 2H, N-CH), 7.36 (br, 2H, CONH). **1d**: colorless oil, yield 83%. $[\alpha]_D^{10}$ -25.9 (c 4.04, CHCl₃). C₂₈H₄₀N₄O₄ (Calcd: C, 67.71; H, 8.12; N, 11.28; Found: C, 67.48; H, 8.22; N, 11.40). IR (neat) v: 3341, 1651, 1525, 1455, 1043 cm⁻¹. ¹H NMR (CDCl₃, δ ppm): 1.53 (m, 4H, -CH₂), 1.82 (br, 2H, -OH), 2.53 (m, 8H, N-CH₂), 2.90 (m, 4H, Ar-CH₂), 3.11 (m, 4H, -CH₂), 3.63, 3.71 (m, 4H, O-CH₂), 4.18 (m, 2H, N-CH), 7.20-7.30 (m, 10H, Ar), 7.48 (br, 2H, -NH).

Received 14 February, 2001