CHEMISTRY LETTERS, pp. 283-284, 1989.

Synthesis of (+)-3,4,8,9,13,14,18,19,23,24,28,29-Dodecaethoxy-1,6,11,16,21,26-hexaazacyclotriacontane. The First D_6-Symmetry Organic Molecule with Known Absolute Configuration

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The high-symmetry chiral macrocyclic polyamides and polyamines were synthesized by using (+)-tartaric acid as a chiral source. The title compound, one of the amines, is the first D_6-symmetry organic molecule with known absolute configuration.

Among chiral organic compounds with dihedral symmetry (D_n, $n \geq 2$), a various kinds of D_2-symmetry molecules have been prepared in optically active modifications.[1)] Since the first synthesis of the optically active D_3-symmetry compound was reported by Farina,[2)] several organic compounds belonging to this point group were synthesized[1)] and a few macrocyclic compounds with D_4 symmetry were also prepared in optically active forms.[3)] But, as far as we know, there is no report described for the preparation of an organic molecule with higher dihedral symmetry than D_4 symmetry. We here report the syntheses of high-symmetry chiral[1)] macrocyclic polyamides and polyamines with known absolute configuration in enantiomerically pure forms, and the 30-membered hexa-amine 1 is the first organic compound with D_6 symmetry.

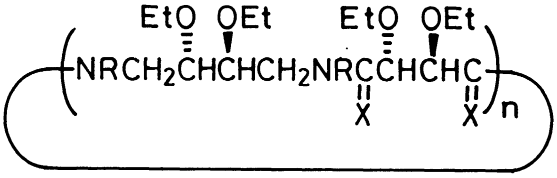
Reduction of (+)-10, bp 120-122 °C (6 mmHg (1 mmHg=133.322 Pa)); $[\alpha]_D^{29}$ +73.4° (acetone), prepared from (+)-tartaric acid, with $LiAlH_4$ afforded (+)-13, bp 95 °C (0.8 mmHg); $[\alpha]_D^{30}$ +43,6° (acetone), which was transformed to 14. Reaction of 14 with potassium phthalate in N,N-dimethylformamide (DMF) at 100 °C followed by treatment with hydrazine hydrate in ethanol under reflux[4)] gave (-)-15, bp 104-106 °C (7 mmHg); $[\alpha]_D^{20}$ -39.2° ($CHCl_3$), in 33% overall yield based upon 10. By treatment of 10 with NH_3 in methanol followed by $LiAlH_4$ reduction, the amine 15 was also prepared in a yield of 24% for two steps. Treatment of (+)-11, mp 125-126.5 °C; $[\alpha]_D^{25}$ +67.1° (H_2O), with thionyl chloride and a small amount of DMF at 80 °C gave 12, bp 90-93 °C (7 mmHg). High dilution condensation of 12 with (-)-15 in benzene and triethylamine at room temperature gave the mixture of macrocyclic polyamides, which was chromatographed on alumina to afford the tetra-amide 5[5)] (12% yield), mp 188-190 °C (recrystallized from ether); $[\alpha]_D^{22}$ +21.6° ($CHCl_3$), and the glassy hexa-amide 4 (19%), $[\alpha]_D^{22}$ +69.1° ($CHCl_3$). The structures of these amides 4 and 5 were confirmed on the basis of their mass and ^1H NMR spectra as well as elemental analyses. In this reaction, the formation of a small amount of the diamide 6 was detected, but it could not be isolated.

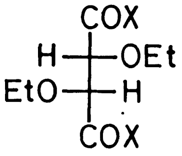
Reaction of (+)-4 with diborane in tetrahydrofuran (THF) under reflux followed by acid hydrolysis and basification[6)] afforded the free hexa-amine 1 (75%), $[\alpha]_D^{20}$

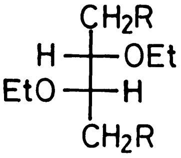
+80.1° (MeOH), as a colorless oil, which was treated with p-toluenesulfonyl chloride in ether and aqueous NaOH solution to afford 7 (glassy solid, 60%), $[\alpha]_D^{20}$ -77.8° ($CHCl_3$). Analogously, the free tetra-amine 2 (oil, 88%), $[\alpha]_D^{20}$ -17.7° (MeOH), and 8 (glassy solid, 40%), $[\alpha]_D^{25}$ -16.7° ($CHCl_3$), were prepared from (+)-5.

In contrast with the condensation of the amine with the acyl chloride, Atkins' procedure$^{7)}$ gave the 10-membered tosylamide 9 and the 20-membered tosylamide 8, and in this case, the 30-membered compound 7 did not obtained. Treatment of 15 with p-toluenesulfonyl chloride in ether and aqueous NaOH solution gave (-)-16 (86%), mp 110-112 $^{\circ}$C (recrystallized from EtOH); $[\alpha]_D^{29}$ -5.88° ($CHCl_3$), which was treated with sodium ethoxide in ethanol to give the disodium salt as a white solid. Reaction of 14 with the disodium salt in DMF at 95-100 $^{\circ}$C afforded the mixture of tosylamides, which was chromatographed on alumina to give 9 (20%), mp 180-181 $^{\circ}$C (from ether); $[\alpha]_D^{25}$ +70.7° ($CHCl_3$), and 8 (12%). Reaction of 14 with 16 and NaH in DMF at 95-100 $^{\circ}$C followed by chromatography also provided 8 (11%) and 9 (19%). The detosylation of 8 and 9 were performed by treatment with $LiAlH_4$ in THF under reflux to give 2 (55%) and 3 (oil, 51%), $[\alpha]_D^{24}$ +39.2° (EtOH), respectivery.

Highest attainable symmetry of the 30-membered hexa-amine 1, having one C_6 axis and six C_2 axes (dihedral axes) perpendicular to it, is D_6 and the compound is the first organic molecule with this symmetry. The 20-membered tetra-amine 2 and the 10-membered diamine 3 belong to the D_4 and D_2 point group, respectivery.







1 n = 3 R = H X = H_2
2 n = 2 R = H X = H_2
3 n = 1 R = H X = H_2
4 n = 3 R = H X = O
5 n = 2 R = H X = O

6 n = 1 R = H X = O
7 n = 3 R = Ts X = H_2
8 n = 2 R = Ts X = H_2
9 n = 1 R = Ts X = H_2

10 X = OMe
11 X = OH
12 X = Cl

13 R = OH
14 R = OTs
15 R = NH_2
16 R = NHTs

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(Received November 2, 1988)