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SYNTHESES OF MACROCYCLES FROM L-AMINO ACID

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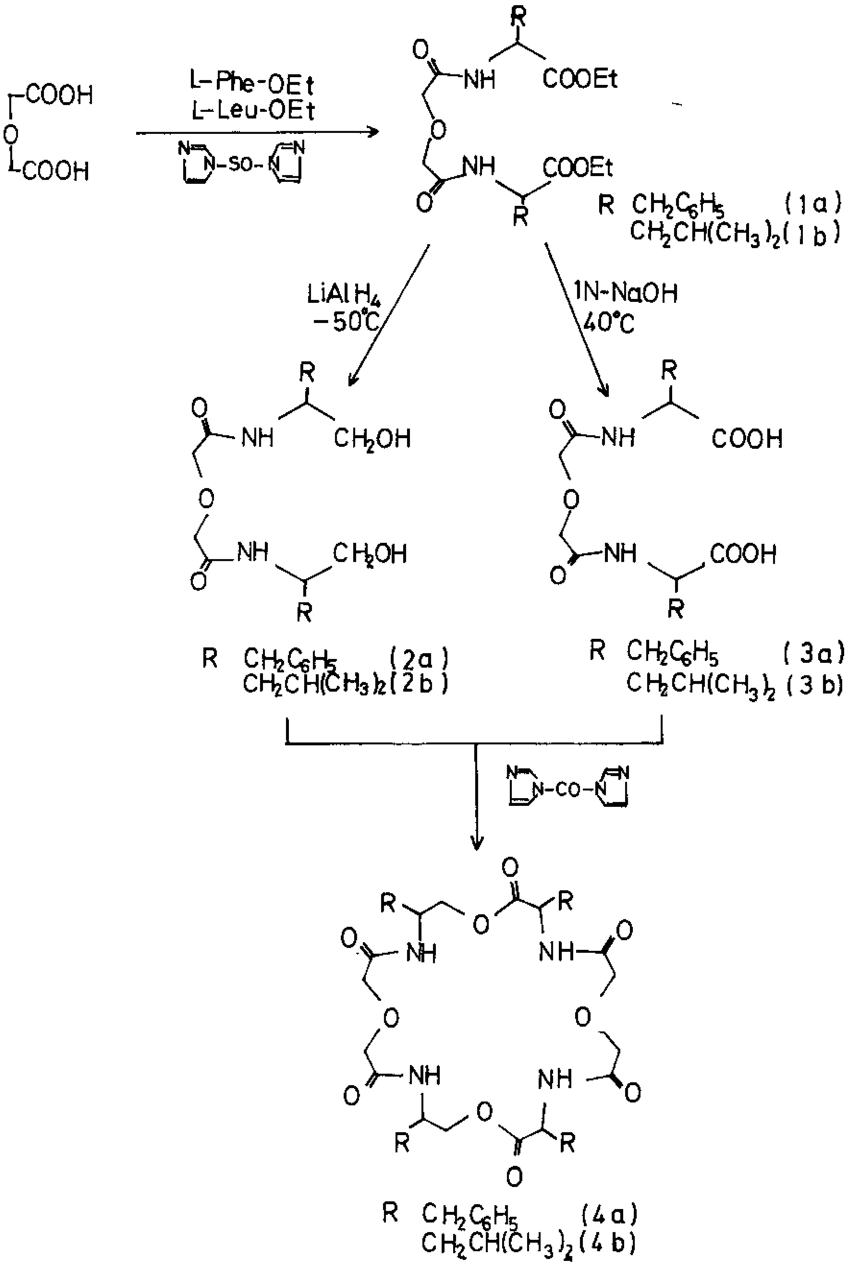
Abstract - Syntheses of 24-membered macrocycles were achieved by using L-phenylalanine and L-leucine as constituents.

A number of chiral crown and azacrown ethers have been synthesized by utilizing carbohydrates[1], tartaric acid[1,2], D-ψ-ephedrine[1], and adrenaline[7] as the chiral natural source. Also, some macrocyclic compounds which have a 12-, 15-, or 18-membered ring have been prepared from α-amino acid to introduce chirality into their rings or the side chains[1-6]. These chiral macrocycles can form complexes with primary ammonium salts and exhibit chiral recognition in the process. One of them can be used as a stereoselective catalyst. We report here the preparation of macrocyclic compounds, one of which contains two L-phenylalanine moieties and the others two L-leucine moieties.

Condensation of diglycolic acid with the ethyl ester of L-phenylalanine or L-leucine in anhydrous tetrahydrofuran using N,N'-thionyldiimidazole[8-9] under stirring for 7 h at ambient temperature gave ethyl diester (1a)(70.0% yield, mp 129.5-130.5°C) or (1b)(68.7% yield, mp 63.5°C), respectively. The yield of this reaction was low when dicyclohexylcarbodiimide was used instead of N,N'-thionyldiimidazole as a condensing agent. Reduction of each ethyl diester (1a) and (1b) was carried out using $LiAlH_4$ in anhydrous tetrahydrofuran for 3 h at -50°C to afford the diol (2a) (80.7% yield, mp 128.0-130.0°C) and (2b)(oily substance, a portion of which was converted into the diacetate, mp 52.5-53.5°C, for confirmation by analysis). Reduction of dicarboxylic acid (3a) with diborane to (2a) did not yield a good result. On the other hand, the ethyl diesters (1a) and (1b) were hydrolyzed with a slight excess of 1 N NaOH in methanol with stirring for 7 h at 40°C, giving the dicarboxylic acids (3a)(97.9% yield, mp 151.5-152.5°C) and (3b)(81.4% yield, mp 129.0°C). Attempt to convert benzyl diester, whith was prepared from diglycolic acid and L-phenylalanine benzyl ester, into dicarboxylic acid (3a) by hydrogenolysis gave less satisfactory result. The macrocyclic compounds (4a) and (4b) were obtained by condensation of (2a) with (3a) or (2b) with (3b). To the dicarboxylic acid (3a) in anhydrous tetrahydrofuran, an equivalent of N,N'-carbonyldiimidazole was added gradually under ice-cooling and stirring. After a few minutes, the


COOH
O
COOH
L-Phe-OEt
L-Leu-OEt
N-SO-N
COOEt
NH
R
R CH2C6H5 (1a)
CH2CH(CH3)2 (1b)
LiAlH4
−50°C
1N-NaOH
40°C
CH2OH
COOH
R CH2C6H5 (2a)
CH2CH(CH3)2 (2b)
R CH2C6H5 (3a)
CH2CH(CH3)2 (3b)
N-CO-N
R CH2C6H5 (4a)
CH2CH(CH3)2 (4b)

diol (2a) in anhydrous tetrahydrofuran was added to the reaction mixture, and stirring was continued for 14 h at 0°C. Next, the mixture was treated in the usual way to afford macrocyclic compound (4a)(8.78% yield, mp 173.0-174.5°C). The macrocycle (4b) was obtained from the dicarboxylic acid (2b) and the diol (3b) in a similar manner and purified by column chromatography on silica gel using ethyl acetate as eluent (24.3% yield, mp 65.5-67.5°C). The proposed structures for these compounds (1a,b, 2a, 2b-diacetate, 3a,b, 4a,b,) were supported by their MS and IR spectra and elemental analyses.

We are planning to examine the formation of complexes of these macrocyclic compounds with alkali or alkaline earth metal ions and ammonium ion and their transport of amino acid salts through an organic liquid membrane.

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