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CHIRAL AMINOACID CONTAINING MACROCYCLES

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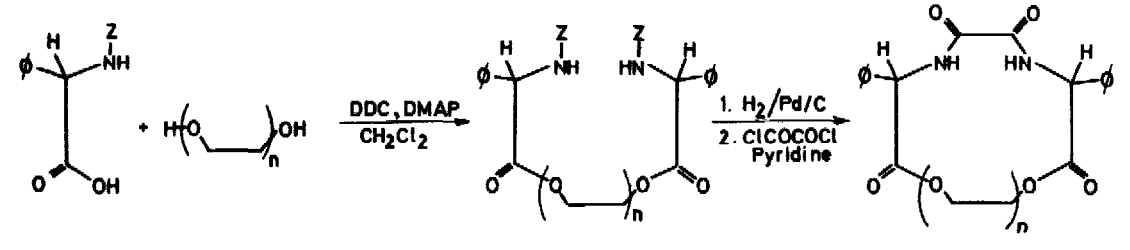
Abstract: Optically active macrocycles (R, R)-8-10 and diastereomeric mixtures of (±)-8-10 and meso-(R, S)-8-10 were prepared containing two (R)- or (S)- α-phenylglycine units as sources of chirality.

Chiral macrocyclic ethers and their analogues are of particular interest as enzyme models[1]. A number of chiral crown ethers have been synthesised with carbohydrate[2,3], tartaric acid[4], D- Ψ -ephedrine[5], cyclohexane-1,2-diol[6], binaphthol[7], and spirobifluorene[8] units as sources of chirality incorporated in a polyethyleneglycolic macrocycle. On the other hand some naturally occuring chiral macrocyclic antibiotics e.g. valinomycin and depsipeptide antibiotics[9] having aminoacid residues as sources of chirality exhibit high selectivity toward different metal ions, associated with their biological activity. However, chiral "crown like" compounds with aminoacid residues incorporated in a polyethyleneglycolic ring were not known until recently[10].

We report here the syntheses of amide-ester and amide-ester-ether type chiral macrocycles 8-10 as optically active (R, R)-8-10 compounds and diastereomeric mixtures of racemates (±)-8-10 and meso-(R, S)-8-10 isomers.



(R)-1	n = 1 2	n=1 (R,R) 5; (±) and (R,S)-5	n=1 (R,R) 8; (±) and (R,S)-8
(±)-1	n = 2 3	n=2 (R,R) 6; " -6	n=2 (R,R) 9; " -9
	n = 3 4	n=3 (R,R) 7; " -7	n=3 (R,R) 10; " -10

Z = -COOCH$_2$-φ

Diastereomeric mixtures of (±) and (R, S)-5-7 as well as optically active (R, R)-5-7 diesters have been prepared in high yields by the room temperature DCC condensations of diols 2-4 with two moles of N-carbobenzoxy protected racemic (±)- or (R)-(-)-α-phenylglycine 1. As a catalyst we used 4-dimethylaminopyridine (DMAP), which was recently proved to be very effective in DCC esterifications[11].

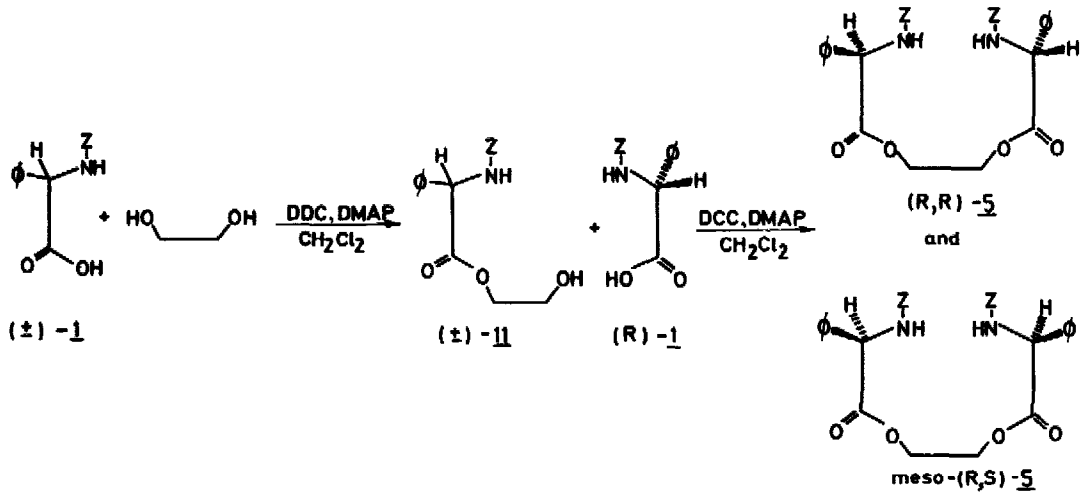
TABLE 1

Spectroscopic data, melting points, optical rotations and yields of diesters 5-7

Compound[a]	^{1}H-nmr[b], δ, ppm	IR[c], cm^{-1}	m.p. °C	[d] $[\alpha]_D^{20}$	Yield %
(R, R)-5	4, 16 broad 2H; 5,03 s 2H; 5,23 d 1H (J=8Hz); 5,85 d 1H (J=8Hz); 7,33 s 10H.	3390, 1680, 1725 1525	154-6	-82,7	92
(±)-5 and (R.S)-5			117-20	-	84
(R, R)-6	3,38 m 2H; 4,12 m 2H; 5,02 s 2H; 5,30 d 1H (J=8Hz); 5,93 d 1H (J=8Hz); 7,30 s 10H.	3320, 1680, 1730 1530	95-6	-79,01	84
(±)-6 and (R, S)-6			45	-	86
(R, R)-7	3,32 s 2H; 3,46 m 2H; 4,18 m 2H; 5,03 s 1H; 5,33 d 1H (J=8Hz); 5,96 d 1H (J=8Hz); 7,26 s 10H.	3360, 1695, 1740 1540	55	-69,35	70
(±)-7 and (R, S)-7			oil	-	70

a) C,H,N analysis within 0,3%. b) 100 MHz nmr, TMS as internal standard.
c) KBr. d) c=1,0 in $CHCl_3$.

We were not able to detect components of diastereomeric mixtures (±)-5-7 and meso-(R,S)-5-7 by t.l.c. analysis, nor by ^{1}H-nmr 100 MHz or ^{13}C-nmr although some differences are noticeable in IR-spectra. Indirect proof that meso-(R,S)-5-7 isomers were also formed in a considerable extent was achieved by the synthesis of diastereomeric mixture (R,R)-5 and meso-(R,S)-5 which gave identical ^{1}H-nmr spectra with (R,R)-5 and a mixture of (±)-5 and (R,S)-5 but exhibited an $[\alpha]_D^{20}$ of -33,5° (c=1,0 $CHCl_3$).



Hydrogenolytic removal of N-protection groups from diesters (R,R)-5 and a mixture of (±)-5 and (R,S)-5 using palladium on charcoal as a catalyst gave diamines which were cyclised in the next step with oxalyl chloride. Reaction was carried out in high-dilution conditions (0,008 M solutions, 50°C, 4 days) in dry benzene by simultaneous addition of reactants during 15 hours. Tenfold molar excess of pyridine was used to bind HCl formed in the reaction. Macrocycles 8-10 were isolated by column chromatography on silica using ethyl acetate/hexane 1:1 as eluent.

TABLE 2

Spectroscopic data, melting points, optical rotations and yields of macrocycles (R,R)-8-10 and diastereomeric mixtures (±)-8-10 and meso-(R, S)-8-10

Compound[a]	^{1}H-nmr[b], δ, ppm	IR[c], cm^{-1}	m.p. °C	[d] $[\alpha]_D^{20}$	Yield %
(R, R)-8	4,23 m 2H; 5,63 d (J=9,77 Hz) 1H; 7,42 s 10H; 7,67 d 1H (J=9,77 Hz).	3340, 1745 1660, 1500	173	+14,4	10
(±)-8 and (R, S)-8			243-4	-	8
(R, R)-9	3,67 m 2H; 4,05 m 1H; 4,55 m 1H; 5,60 d 1H (J=8,3 Hz); 7,42 s 10H; 7,93 d 2H (J=8,3 Hz).	3420, 3380 1745, 1680 1510	257-9	+17,35	18
(±)-9 and (R, S)-9			247-8	-	15
(R, R)-10	3,57 m 4H; 4,40 m 2H; 5,60 d 1H (J=7,33 Hz); 7,42 s 10H; 7,93 d 1H (J=7,33 Hz).	3320, 1745 1670, 1510	207-9	-47,55	20
(±)-10 and (R, S)-10			185	-	18

a) Satisfactory C, H, N analysis and molecular weight (MS) obtained. b) 100 MHz nmr, TMS as internal standard. c) KBr. d) c=1,0 in $CHCl_3$.

We believe that our (R,R)-8-10 macrocycles are optically pure because (R,R)-10 showed negligible differences in optical rotations after three recrystallizations from ethyl acetate/hexane and acetone/hexane mixtures.

Complexation and ionophoric ability studies of macrocycles 8-10 are in progress.

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