Synthetic Chiral Macrocyclic Crown Ligands: A Short Review

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Introduction.

An important characteristic of synthetic macrocyclic multidentate ligands (crown compounds) is that they complex with a wide variety of metal, ammonium and diazonium cations. Another important feature of cation complexation by macrocycles is the selectivity often shown towards one cation in a closely related series of cations. For example, 18-crown-6 forms a much more stable complex in either water or methanol solvent with K^+ than with any of the other alkali metal cations (1). Many biological functions also involve cation complexation. Hemin, chlorophyll, vitamin B-12 and many other molecules are metal containing complexes that are vital to the systems they serve. In nature, enzymes exhibit the property of selectivity to a remarkable degree. Enzymatic reactions are catalyzed so selectively that the reaction occurs the same way every time.

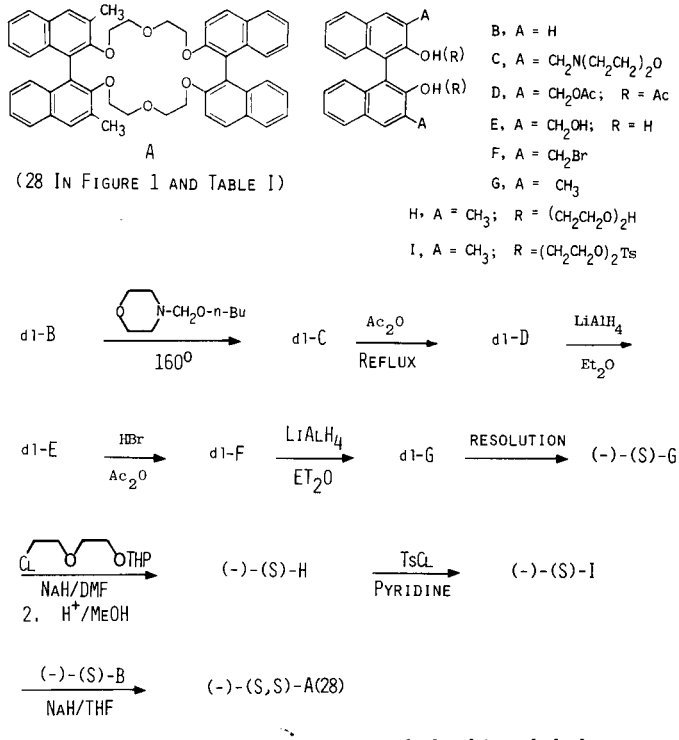
Almost as soon as the synthetic macrocyclic compounds became known through the work of Pederson (2), chemists realized that asymmetric derivatives of these molecules could serve as models for the study of chiral recognition in enzymatic and other reactions. Since that time, the design and synthesis of chiral molecules to effect specific chemical changes has been accomplished by several investigators (3-7).

Natural macrocyclic polysugars (known as the cyclodextrins) exhibit chiral recognition and behave as model enzymes (8-10). The first synthetic chiral macrocyclic compounds were reported in 1972 by Wudl and Gaeta (11) and since then a host of different chiral macrocycles have been synthesized. Cram and his coworkers first began reporting their excellent work on chiral binaphthyl macrocyclic compounds in 1973 (12) and shortly thereafter Lehn, Stoddart and others reported their work on chiral crown synthesis (4-7). This short review summarizes the synthetic work on chiral macrocyclic ligands to the end of 1980, gives a listing of these compounds and briefly reports on their uses.

Chiral Macrocyclic Ligands with Binaphthyl Subcyclic Units.

Rotation about the carbon-carbon single bond of 2,2'-dihydroxy-1,1'-binaphthyl is restricted enough so that this compound can be resolved into its *R* and *S* isomers.

SCHEME I



Cram and his coworkers have used the binaphthyl compounds to make a large number of chiral macrocyclic polyether ligands. In general these chiral binaphthyl crowns were prepared by reacting one to three equivalents of optically pure 2,2'-dihydroxy-1,1'-binaphthyl (or a derivative thereof) with the necessary oligoethyleneglycol ditosylate in tetrahydrofuran/potassium *t*-butoxide or potassium hydroxide (3,12-17).

Preparation of (*S,S*)-2,3,4,5-di-1,2-(3-methylnaphtho)-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene (Compound **28**, see Scheme I) (3).

Racemic 2,2'-dihydroxy-1,1'-binaphthyl (**B** in Scheme I) was stirred at 160° for 5 days in the presence of 4-(butoxymethyl)morpholine to form the 3,3'-bis(*N*-morpholinomethyl) derivative (**C**). This compound was in turn dissolved in acetic anhydride and refluxed for 8 days to form

Table I
Chiral Macrocyclic Compounds Derived from the Binaphthyl Unit (a)

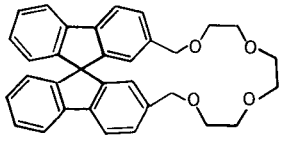
Crown	Substituents	[α]	*R/S*	Mp (Bp) °C	% Yield	References
1	n = 0; R = R′ = H	+546	*S*	216-217	23	13
2	n = 1; R = R′ = H	+77	*S*	231-232	5	12,13
3	n = 2; R = R′ = H	−127	*S*	gum	65	13
4	n = 3; R = R′ = H	−63	*S*	gum	52	13
5	n = 4; R = R′ = H	−70.5	*S*	oil	64	13,18
6	n = 3; R = R′ = CH_2OH	−56.1	*S*	glass	6	14
7	n = 4; R = R′ = CH_2OH	−34.0	*S*	glass	55	14
8	n = 5; R = R′ = CH_2OH	−16.4	*R*	glass	57	14
9	n = 3; R = R′ = $CH_2OCH_2CO_2CH_3$	−95.7	*S*	glass	51	14
10	n = 4; R = R′ = $CH_2OCH_2CO_2CH_3$	−25.7	*S*	glass	44	14
11	n = 5; R = R′ = $CH_2OCH_2CO_2CH_3$	−19.5	*R*	glass	54	14
12	n = 3; R = R′ = $CH_2OCH_2CO_2H$	−107.4	*S*	glass	65	14
13	n = 4; R = R′ = $CH_2OCH_2CO_2H$	−24.4	*S*	glass	90	14
14	n = 5; R = R′ = $CH_2OCH_2CO_2H$	−15.0	*R*	glass	50	14
15	n = 4; R = $CH_2OCH_2CO_2H$, R′ = CH_2OH	+24.2	*R*	glass	82	14
16	n = 4; R = R′ = CH_2Cl	−9.5	*S*	glass	81	14
17	n = 4; R = R′ = $CH_2SCH_2CO_2H$	+12.0	*S*	glass	72	14
18	n = 4; R = R′ = $CH_2SCH_2CH_2CO_2H$	−33.6	*S*	glass	58	14
19	n = 4; R = R′ = $CH_2CH_2CO_2H$	−94	*S*	glass	85	14
20	n = 4; R = R′ = CH_2SH	+11	*S*	glass		19
21	n = 4; R = R′ = CH_2SH	−11	*R*	glass		19
22	R = R′ = H	−221 (solvate)	*S,S*	123-126	31	18,20
23	R = R′ = H	+221 (solvate)	*R,R*	123-126		18,20
24	R = R′ = H	meso		283-284	2	18
25	R = CH_2OH, R′ = H	+170	*R,R*	oil	28	20
26	R = CH_2Cl, R′ = H	+122	*R,R*	glass	76	3,20
27	R = CH_3, R′ = H	+152	*R,R*	foam	32	3,20
28	R = CH_3, R′ = H	−152	*S,S*	foam	64	3
29	R = CH_3, R′ = H	+44.2	*S,R*	foam	16	3
30	R = $CH(CH_3)_2$, R′ = H	+71	*R,R*	foam	75	3
31	R = $C(CH_3)_2OH$, R′ = H	+73	*R,R*	foam	28	3
32	R = $CH_2OCH_2CO_2CH_3$, R′ = H	+116	*R,R*	glass	77	3
33	R = $CH_2OCH_2CO_2H$, R′ = H	+110	*R,R*	glass	76	3
34	R = CH_3, R′ = CH_3	+135	*R,R*	glass	28	3
35	R = CH_3, R′ = CH_3	−134	*S,S*	glass	28	3
36	R″ = R = B = Br, R′ = H	+124	*R,R*	189-191	91	3,21
37	R″ = R = B = CH_3CO, R′ = H	−87	*S,S*	264-265	89	3
38	R″ = R = B = $CH_2CO_2CH_3$, R′ = H		*S,S*	174-175	98	3
39	R″ = R = B = $CH{=}CH_2$, R′ = H	−52	*S,S*	glass	47	3
40	R″ = R = B = $SO_3(Ba)_{1/2}$, R′ = H	−180	*S,S*	>360	50	3
41	R″ = R = B = $C(CH_3)_3$, R′ = H	−122	*S,S*	289-291	45	3
42	R″ = R = B = $Si(CH_3)_2$-O-silica gel, R′ = H		*R,R*			21
43	R″ = R = Br, R′ = CH_3, B = H	+172	*R,R*	135-143	69	22
44	R″ = R = CH_2CH_2OH, R′ = CH_3, B = H		*R,R*	glass	6	22
45	R″ = CH_2CH_2OH, R′ = CH_3, B = H	+164	*R,R*	glass	60	3
46	R″ = $CH_2CH_2OCH_2$-polystyrene, R′ = CH_3, R = B = H		*R,R*			22
47		−223	*S,S*	foam	60	13
48		−175	*S,S,S*	glass	40	13
49		−141	*S,S,R*	247-249	58	13
50	R = Br	+16	*R,R*	foam	68	3
51	R = H	+99	*R,R*	211-212	90	3
52	R = CH_3	+93	*R,R*	foam	70	3
53	R = CH_3	−39.4	*S,S*	foam	42	3

Table I Continued

Crown	Substituents	[α]	*R/S*	Mp (Bp) °C	% Yield	References
54	R = R′ = H	−55	*S,S*	235-236	98	3
55	R = R′ = H	+53	*R,R*	234-235	92	3
56	R = R′ = CH_3	+22.2	*R,R*	foam	88	3
57	R = R′ = Br	+98.1	*S,S*	foam	96	3
58	R = CH_3, R′ = H	+35.4	*R,R*	foam	70	3
59	R = H	−106	*S,S*		85	3
60	R = Br	+47.6	*S,S*	foam	94	3
61	X = CH_2OCH_2, Y = $(CH_2)_3$	−193	*S,S*	foam	41	13
62	X = CH_2OCH_2, Y = 	−214.9	*S,S*	foam	13	13
63	X = CH_2OCH_2, Y = 	−241.9	*S,S*	foam	43	13
64	X = CH_2OCH_2, Y = 	−218	*S,S*	glass	26	13
65	X = $CH_2CH_2CH_2$, Y = 	−240	*S,S*	foam	29	13
66	X =  , Y = 	−269	*S,S*	foam	43	13
67	X =  , Y = 	−250	*S,S*	295-298	31	13
68	X = O	−92	*S*	190-192	60	23
69	X = H_2	−151	*S*	oil	90	23
70	X = O	−42	*S*	glass	50	23
71	X = H_2	−68	*S*	oil	90	23
72		+68.2	*S*		7	24
73		−46.0	*R*		6	24

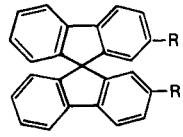
(a) Structures are shown in Figure 1.

SCHEME II



A

(76 IN FIGURE 2 AND TABLE II)

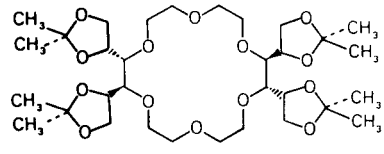


B. R = Ac
C. R = COOH
D. R = CH_2OH
E. R = CH_2Br

dl-B $\xrightarrow[\text{DIOXANE}]{\text{NaOH / } Br_2}$ dl-C $\xrightarrow{\text{REDUCTION}}$ dl-D $\xrightarrow{\text{RESOLUTION}}$

(-)-(S)-D $\xrightarrow[\text{AcOH}]{\text{HBr}}$ (-)-(S)-E $\xrightarrow[\text{K-T-OBu/}C_6H_6]{\text{HO(CH}_2\text{CH}_2\text{O)}_3\text{CH}_2\text{CH}_2\text{OH}}$ (-)-(S)-A (76)

SCHEME III



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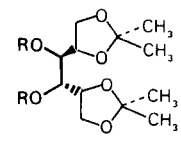
(88 IN FIGURE 3 AND TABLE III)



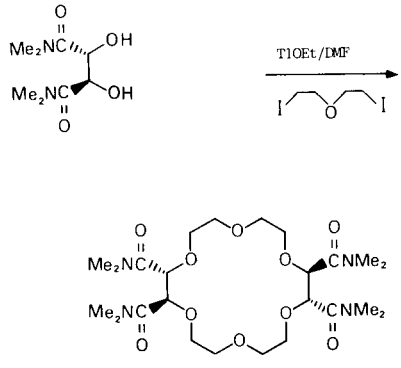
B. R = H
C. R = $CH_2CH{=}CH_2$
D. R = CH_2CH_2OH
E. R = CH_2CH_2OTs

D-MANNITOL $\xrightarrow[ZnCl_2]{(CH_3)_2CO}$ D-B $\xrightarrow[C_6H_5CH_3]{KOH/CH_2{=}CHCH_2Br}$ D-C

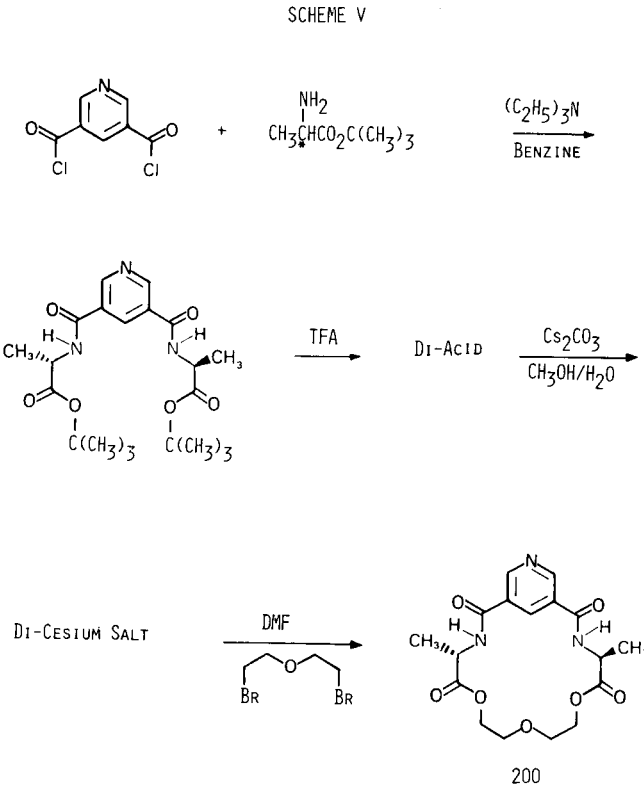
D-D $\xrightarrow[\text{2. } NaBH_4]{\text{1. } O_3\ -78^oC}$ D-E $\xrightarrow[\text{PYRIDINE}]{TsCl}$ D-D $\xrightarrow[\text{DMSO/NaH}]{\text{D-D}}$ D-A (88)

3,3'-diacetoxymethyl-2,2'-diacetoxy-1,1'-binaphthyl (**D**). The 3,3'-bis(hydroxymethyl) derivative (**E**) was prepared by reducing the acetoxy compound with lithium aluminium hydride in ether. Reaction with dry hydrogen bromide gas in glacial acetic acid gave 3,3'-bis(bromomethyl)-2,2'-dihydroxy-1,1'-binaphthyl (**F**) which was in turn reduced with lithium aluminium hydride to give the 3,3'-dimethyl derivative (**G**). Optical resolution of **G** was effected by recrystallizing the salt formed from a phosphate ester of **G** and cinchonine to give the (+)-(*R*) diol. The mother liquors from the above recrystallizations were hydrolyzed and reacted with strychnine to get pure (-)-(*S*) diol **G** ($[\alpha]_{578}^{25}$ -36.9°, c = 1.0, chloroform). Pure (-)-(*S*) diol G was then reacted with (2-chloroethoxy)ethyl-2-tetrahydropyranyl ether in the presence of DMF and sodium hydride to obtain the 2,2'-bis(5-hydroxy-3-oxa-1-pentyloxy) derivative (**H**). After hydrolysis, the tosyl derivative of this compound (**I**) was prepared and reacted with pure (-)-(*S*) binaphthol in sodium hydride and THF to give macrocycle **28** ($[\alpha]_{578}^{25}$ -152°, c = 1.0, chloroform) (Scheme 1).

SCHEME IV



SCHEME V



200

More than seventy chiral macrocyclic ligands based on the binaphthyl moiety have been prepared using procedures similar to those shown above. These compounds are shown in Figure 1 and are listed in Table I along with some of their physical properties. There are hundreds of nonchiral compounds containing the binaphthyl moiety to be found in the references.

The chiral macrocyclic ligands with the binaphthyl unit have been used in chiral recognition studies. The complex of racemic α-phenylethylammonium hexafluorophosphate with (*S,S*)-**22** was examined by proton nmr spectroscopy and found to contain 62% of the (+)-α-phenylethyl-

Table II

Chiral Macrocyclic Compounds with Restricted Movement (a)

Crown		*R/S*	[α]	Mp (Bp) °C	% Yield	References
74	n = −1	*S*	−318	gum		44
75	n = 0	*S*		171-172		44
76	n = 1	*R*	−78.5	149-151		44
77	n = 1	*S*	+80			44
78	n = 2	*R*	−71.8	125-126		44
79	n = 2	*S*	+71.2	125-126		44
80	n = 3	*R*	−58.1	143-144		44
81	n = 3	*S*	+59.5	144-145		44
82	n = 1	*S,S*	+50	324-326		44
83	n = 2	*S,S*	+137	gum		44
84	n = 3	*S,S*	+29	226-228		44
85	n = 1		+1.06		18	46,47
86	n = 2		−1.0		21	46,47

(a) Structures are shown in Figure 2.

Table III
Chiral Macrocyclic Ligands Containing Carbohydrate Units (a)

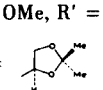
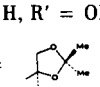
Crown	Substituents	[α]	Mp (Bp) °C	% Yield	References
87	R = 		oil	13	4
88	R = 	+7.6		14	4
89	R = 	−6.9	60-66		52
90	R = 	+24.6	69-71	90	4
91	R = 	+48.4		95	4
92	R = 	+4.7		56	4
93	R = 		oil	10	4
94		+35.8	(120-122) 0.03 mm	19	53
95	R = OMe, R′ = H, R″ = H	+102.9	115		54
96	R = OMe, R′ = H, R″ = 	+90.0		29	54
97	R″ = R = H, R′ = OMe	+30.2	141-143	20	55
98	R = H, R′ = OMe, R″ = 	+26.5			55
99	R = OMe, R′ = H, R″ = H, n = 1	+77	134	13	56
100	R = OMe, R′ = H, R″ = H, n = 0	+57	98	10	56
101	R = OMe, R′ = H, R″ = H, n = 1	+37.6	52-56		54
102	R = OMe, R′ = H, n = 1, R″ = 	+69.4	44-46	40	54
103	R = R″ = H, R′ = OMe, n = 1	−47.0	78-80		55
104	R = H, R′ = OMe, n = 1 R″ = 	−98.4			55
105	R = H	+30.6			57

Table III continued

Crown	Substituents	[α]	Mp (Bp) °C	% Yield	References
106	R = 	+24.6			57
107		+60.1			57
108		−107.6	192-193	15	58
109		−55.4	(207) 0.01 mm	34	58
110	R =  , R′ = CO_2Et	−11.9		33	59
111	R =  , R′ = Me	+38.8	106-108	86	59
112	R = 	−22	147-149	7.5	59
113	R = 	−1.6	50-54	4	60
114		+50.2	229-230		51,61
115		+164	238-240		61
116		+36.6	233-234		51,61
117		+180	167-167.5		61
118		+31	oil		56
119	R = H (b)	+115	132-134		51
120	R = $COCH_3$ (b)	+94	161.4		51
121	n = 1	+14.1	129-130	68	50
122	n = 2	+32.7	105-107	70	50
123		+41.2	gum	70	50
124		+84.4	gum	72	50
125	n = 1	+53.8	gum	65	50
126	n = 2	+93.4	gum	75	50

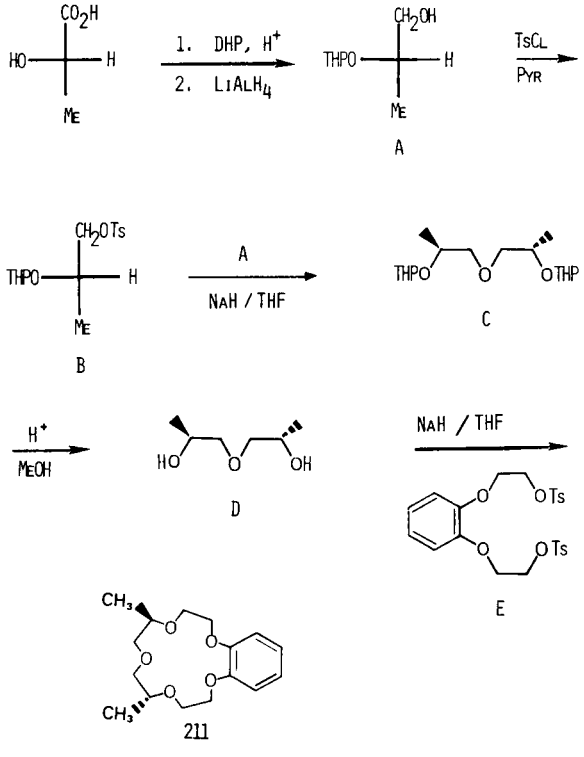
(a) Structures are shown in Figure 3. (b) The tetrahydropyran ring on the right of the structure **119-120** could be turned over.

ammonium salt and 38% of the (-)-isomer (18). Using an extraction process, Cram and coworkers showed that the complex of (*S,S*)-**28** with the methyl phenylglycinate salt gave an enantiomer distribution constant (EDC) (20) of 12 compared with only 3 for (*S,S*)-**22** (25). By varying structural parameters, an EDC as high as 18 has been obtained using this simple extraction technique. Very high EDC values (up to 52) were observed in a mixed deuterioacetonitrile-deuteriochloroform solvent system (26). Many different solvent systems, macrocyclic ligands, and amino acid salts have been evaluated by this method (27-30). The reverse concept has also been employed wherein racemic macrocyclic compound mixtures were totally resolved by the use of liquid-liquid chromatography and optically pure L-valine (31,32). Silica gel or polystyrene resins bound with optically active macrocyclic ligands with binaphthyl subcyclic units have been used to resolve amino acid and aminoester salts. The polystyrene bound hosts proved to

be the most effective resolving agents with separation ratios as high as 26 being observed (21,22,33-35). Cram and coworkers have also employed the use of liquid membranes (water/chloroform/water) to effect good enantiomer separation of racemic amino acid salts. Enantiomeric compounds with optical purities of 70 to 90% were obtained through the operation of a liquid membrane system (36,37).

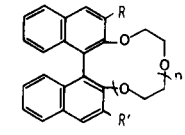
Model enzyme catalysis reactions have been studied using the macrocyclic binaphthyl compounds (19,38). Transacylation reactions (thiolysis) between chiral hosts (thiols) and enantiomeric α-amino ester salts were carried out. Reaction rates between macrocyclic thiols and *p*-nitrophenyl aminoacid esters were compared with reaction rates obtained using open chain thiol analogs. Rate enhancements of up to 1700 times were found with macrocyclic ligands containing thiol groups versus open chain thiols. Chiral recognition factors of up to 8 were observed in these reactions where the (*S*) isomer of the macrocyclic thiol host hydrolyzed *p*-nitrophenyl L-phenylalanine faster than the (*R*) isomer did (19,38).

SCHEME VI



Asymmetric synthesis with chiral host-guest molecules have led to chiral products of up to 80% optical purity using these macrocycles as host molecules. Reactions studied were Michael addition, Gabriel synthesis and the alkylation of carbanions (39). Several excellent reviews

FIGURE 1: CHIRAL MACROCYCLIC COMPOUNDS CONTAINING THE BINAPHTHYL UNIT



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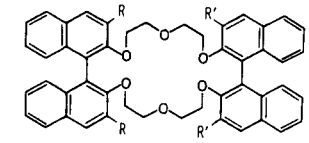
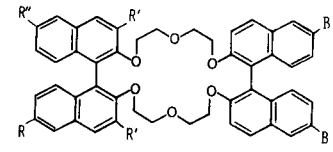


22-35



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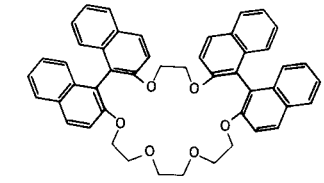

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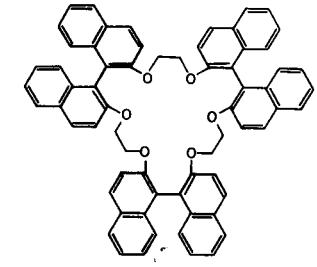

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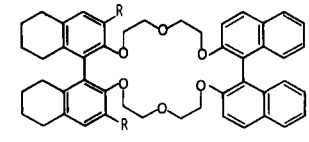

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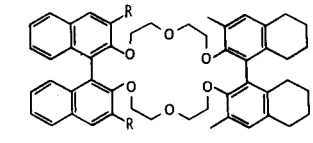

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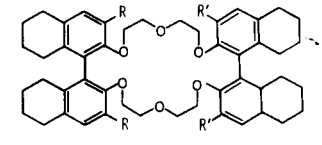

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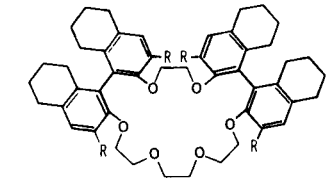

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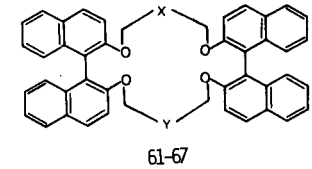

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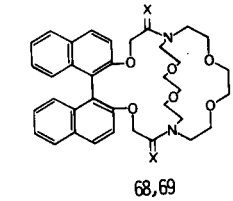

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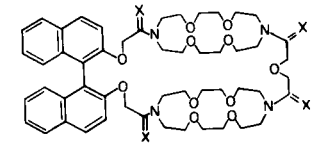

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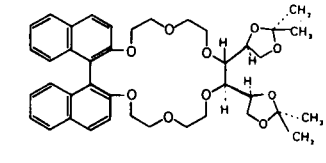


72,73

Table IV
Chiral Macrocyclic Compounds Derived from Tartaric Acid (a)

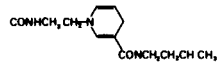
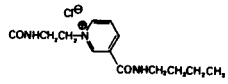
Crown	Substituents	[α]	Mp (Bp) °C	% Yield	References
127	$CONMe_2$				68
128	$CH_2O\text{-}CH_2Ph$	+19.3	40	3	4
129	$CONMe_2$	+84	65	12	68
130	CO_2H	+24	60-70	95	68
131	CO_2Me	+49	oil	85	68
132	CH_2OH		oil		70
133	CH_2SH	−10.8			71
134	CH_2OTs				71
135	CH_2OCH_2Ph	+5.0	oil	26	70
136	CH_2OCOCH_3	−9.6		61	70
137	CH_2SCOPh				71
138	$CH_2OCH_2CH_2OCH_2Ph$				71
139	$CH_2OCH_2CH_2OH$				71
140	$CH_2OCH_2CH_2OTs$				71
141	$CH_2OCH_2CH_2SCOPh$				71
142	$CH_2OCH_2CH_2SH$	+2.5			71
143	$CH_2CH_2CH_2OCH_2Ph$				71
144	$CH_2CH_2CH_2OH$				71
145	$CH_2CH_2CH_2OTs$				71
146	$CH_2OCH_2CH_2SCOPh$				71
147	$CH_2OCH_2CH_2SH$	−26.9			71
148	CH_2OH		oil	65	4,68
149	CO_2H	+67	213	>95	68
150	CH_2CN	+19	136-137	75	68
151	CH_2CO_2H	−23	197-201	95	68
152	CH_2OTs	−9	122-123	45	68
153	$COCl$		180	95	68
154	CH_2NMe_2	−31.2	oil	80	68,72
155	$CONMe_2$	+108	186	19	68
		+108.4	181-182		73
156	$CONMe_2$	−108.3	181-182		73
157	$CONHMe$	+66	255	20	68
158	$CON(n\text{-}Bu)_2$	+49	81	95	68
159	CH_2OCH_2Ph	+5	oil	11	4
160	CH_2OAc	−20.5	81	89	4
161	CH_2OCPh_3			73	4
162	$CO_2^-NMe_4^+$				74
163	$CONHCH_2CO_2Me$		188		75
164	$CONHCH_2CO_2^-NMe_4^+$				75
165	$CONHCH_2CH_2NH_2$		174-177	95	76
166	$CONH(CH_2)_2NHCO_2CH_2Ph$		214-215	70	76
167	L-$CONHCH(CO_2Me)CH_2SH$	+41	204-205	66	5
168	L-$CONHCH(CO_2Me)CH_2SCH_2Ph$	−44.5	139-140	87	5
169	(*S*)-$CONHCH(CO_2Me)CH_2Ph$	+7.4	195-196		77
170	$CONHCH_2CH_2$-(3-indole)		223	65	76
171	$CONHCH_2CH_2$-(4-imidazole)				75
172	CONH(1-pyrene)	+11.3	248	57	73
173	CONH(1-pyrene)	−11.2	245	65	73
174	L-$CONHCH(CO_2Me)CH_2$(3-indole)	+8.2	135-138	65	73
175	D-$CONHCH(CO_2Me)CH_2$(3-indole)	−8.3	135-138	77	73
176	LD-$CONHCH(CO_2Me)CH_2$(3-indole)	+3.0	145-150	70	73
177	DL-$CONHCH(CO_2Me)CH_2$(3-indole)	−3.0	145-150	70	73
178	L-$CONHCH(CO_2)CH_2$(3-indole)NMe_4^+				75
179					76
180					76

Table IV continued

Crown	Substituents	[α]	Mp (Bp) °C	% Yield	References
181	R = CH_2OCH_2Ph, X = O	+4.3	oil	23	70
182	R = CH_2OCH_2Ph, X = H_2	+17	oil	90	70
183	R = $CONMe_2$	+107	224	15	67,68
184	X = O		153-154	~100	68
185	X = NMe	+147	12	~100	68
186	R = $CONMe_2$			13	68
187	R = COOH	+40	glass		74
188	R = $CONMe_2$	+110	oil		74

(a) Structures are shown in Figure 4.

Table V

Chiral Macrocyclic Ligands Derived from Amino Acids (a)

Crown	Substituents			[α]	Mp (Bp) °C	% Yield	References
	R^1	R^2	n				
189	CH_3	CO_2CH_3	1	+4.2	164-165		82
190	CH_3	CO_2Me	2	+3.6	121-122		82
191	$PhCH_2$	CO_2Me	1	−52.6	144-145		82
192	CH_2Ph	CO_2Me	2	−52.4	127-128		82
193	C_6H_5	CH_3	1	−34.2	157-159		82
194	n = 1			+14.4	173	10	84
195	n = 1			meso	243-244	8	84
196	n = 2			+17.35	257-259	18	84
197	n = 2			meso	247-208	15	84
198	n = 3			−47.55	207-209	20	84
199	n = 3			meso	185	18	84
200	R = CH_3			−94.0	259-262	22	6
201	R = $CH(CH_3)_2$			−126.8	251-254	32	6
202	R = $CH(CH_3)_2$			−159.6	dec	80	6
203	R = $CH(CH_3)_2$			−133.9	140.5-142.4	98	6
204					98-99		11
205					94-95	40	11
206				−26.3	oil	70	83

(a) Structures are shown in Figure 5.

have been written by Cram concerning his work on host-guest chemistry with the binaphthyl macrocyclic compounds (40-42).

Lehn and coworkers have incorporated the chiral binaphthyl system into their bi- and tricyclic cryptands. The resulting chiral cryptands have been used in selective complexation and transport studies. Racemic potassium mandelate was enriched 10% in the (-) isomer using a chloroform/water membrane system (23,43). Stoddart and his coworkers have prepared a number of macrocyclic compounds containing both chiral binaphthyl and chiral carbohydrate moieties. One of their compounds exhibited chiral recognition for α-phenylethylamine·HPF_6 with an *R*:*S* ratio of 63:37 (24).

Other Chiral Macrocyclic Ligands with Optical Activity through Restricted Movement.

Other restricted systems besides binaphthyl have been used to impart chirality to marcocyclic systems. Prelog and his coworkers have synthesized a number of chiral macrocyclic ligands from 9,9′-spirobifluorene derivatives.

Synthesis of (-)-(*S*)-2,2′-(2,5,8,11-tetraoxadodecano)-9,9′-spirobifluorene (Compound **76**, see Scheme II) (44).

(±)-2,2′-Diacetyl-9,9′-spirobifluorene (**B** in Scheme II) (45) was reacted with bromine and sodium hydroxide to form the 2,2′-dicarboxy derivative (**C**) which was then reduced with sodium dihydro-bis(2-methoxyethoxy)-aluminate to form 9,9′-spirobifluorene-2,2′-dimethanol (**D**). The dimethanol compound was then esterified with (-)-camphanecarboxylic acid to effect isomeric separation. After hydrolysis, (-)-(*S*)-9,9′-spirobifluorene-2,2′-dimethanol [(-)-(*S*)-**D**] was reacted with hydrogen bromide in acetic acid to form dibromo compound **E**. The dibromide was added to a mixture of triethyleneglycol and potassium-*t*-butoxide in benzene to give the final macrocyclic compound (**76**), mp 149-151°, $[\alpha]_D^{25}$ -78.5°, c = 1, chloroform.

The chiral macrocyclic ligands containing the 9,9′-spiro-

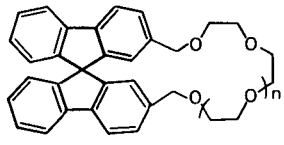
bifluorene subcyclic unit are shown in Figure 2 and are listed in Table II. Chiral macrobicyclic ligands based on D-glycerol prepared by Haines and coworkers (46-47) are also given in Figure 2 and Table II.

The spiro macrocyclic ligands complexed α-phenylethylammonium salts better than they did the alkaline metal cations and a small degree of enantiomer selectivity was observed (44). The enantiomer selectivity of these compounds was evalutated by electrochemical methods. Enantiomer selectivity was not great with ratios of only 1.2 to 1. A number of circular dichroism measurements were also made with these macrocyclic compounds (7,48). Haines and coworkers have synthesized a number of interesting macrocyclic ligands that exhibit chirality due to restricted out,in-in,out isomerism (46,47).

Chiral Macrocyclic Ligands Containing Carbohydrate Units.

Some carbohydrate compounds are ideal as chiral starting materials for macrocyclic compounds. They contain an abundance of ethyleneoxy subunits, a high degree of functionality and most important, are an inexpensive source of optical activity. Stoddart and his coworkers as well as others have synthesized a large number of macrocyclic ligands incorporating carbohydrate molecules.

FIGURE 2: CHIRAL MACROCYCLIC COMPOUNDS WITH RESTRICTED MOVEMENT



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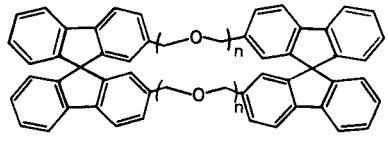

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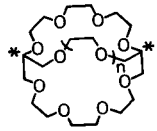

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Since the carbohydrates contain several chiral centers, only those with C-2 symmetry can be used if more than one carbohydrate unit is to be incorporated into the ring. D-Mannitol, D-glucose, D-galactose, D-altrose and L-iditol have all been used. In general, all the functional groups of the carbohydrate except the hydroxyl groups on the center two carbons are blocked. The macrocyclic compound is then prepared in the usual manner.

Synthesis of DD-1,2:1′,2′:5,6:5′,6′-tetra-*O*-isopropylidene-3,3′:4,4′-bis-*O*-oxydiethylenedi-D-mannitol (Compound **88**, see Scheme III) (4,49).

D-Mannitol was reacted with acetone and zinc chloride to give the blocked 1,2:5,6-di-*O*-isopropylidene derivative (**B** in Scheme III). Compound **B** was then heated overnight in toluene in the presence of potassium hydroxide and allyl bromide to give the 3,4-di-*O*-allyl derivative (**C**). Treatment with ozone followed by a sodium borohydride reduction gave the "half-crown" diol (**D**). Reaction of the diol **D** with the bis-tosylate ester (Compound **E**), prepared from diol **D**, in DMSO/sodium hydride gave the final macrocyclic compound (**88**) as a liquid, $[\alpha]_D$ + 7.6°, c = 0.59, chloroform (Scheme III).

Some innovative synthetic methods have been employed in the preparation of macrocyclic ligands containing carbohydrate units. DeCesare and Gross have improved the yields of the carbohydrate crowns by employing a two phase synthesis system (50). Szejtli and his coworkers have used the addition of a hydroxy function across a vinyl ether to effect ring closure (51).

More than forty chiral macrocyclic ligands containing carbohydrate units have been prepared. Figure 3 shows these compounds and Table III gives the relevant physical properties and references.

Chiral macrocyclic ligands derived from carbohydrate precursors have not shown a great degree of enantiomer selectivity. Enantiomeric differentiation ratios of 62:38 for α-phenylethylamine·HPF_6 salt have been achieved using chiral compound **88** (4,52,62). Stoddart and his coworkers have studied the complexation of alkylammonium salts with their chiral carbohydrate macrocyclic ligands using a temperature dependent proton nmr technique. When the macrocycle has diastereotopic faces, the low temperature proton nmr technique has proven to be a good tool in observing diastereoisomeric α and β complexes (α-complex on one face, β complex on the other). At temperatures of -60° or lower, the complexation-solvation-recomplexation is slow on the nmr time scale. At those temperatures, isomer ratios (α:β) of as high as 97:3 were observed (55,57-59,60,61,63). Several reviews by Stoddart on his work have been published (64-66).

Chiral Macrocyclic Ligands Derived from Tartaric Acid.

Tartaric acid has proven to be an excellent starting material for the preparation of chiral macrocyclic ligands. It is readily available in both the (*d*) and (*l*) isomers and contains a high degree of functionality. Macrocycles containing tartarate chirality are prepared by much the same

Table VI
Chiral Macrocyclic Compounds Derived from Other Chiral Acids (a)

Crown	Substituents			[α]	Mp (Bp) °C	% Yield	References
	R	R′	R″				
207					oil		86
208							86
209					(114-116) at 0.025 torr		87
210					(118-124) at 0.025 torr		87
211					42-43		85
212					63-64		86
213					oil		86
214					(110-115) at 0.025 torr		86
215				+41.65	(110-120) at 0.025 torr	31	86,88
216					(120-125) at 0.5 torr		86
217				+20.5	(130-132) at 0.4 torr	24	88
218				+20.74	(124-130) at 0.5 torr	25	88
219				+22.21	(138-142) at 0.7 torr	27	88
220							89
221							89
222							89
223					50-52		86
224					99-99.8		86
225							89
226					44-46		86
227				meso	109-110	6.5	90
228				meso	137	5.6	90
229				meso	136-137	3	90
230				meso	92	1.9	90
231				meso	160	8.4	90
232				meso	199-200	6.7	90
233							89
234					oil		86
235					94.5-95		86
236				meso	oil	67	91
237	CH_3	H	H	−13.6 (*S,S*)	94	48.5	92
238	CH_3	H	H	+13.2 (*R,R*)	91-92	23.6	92
239	CH_3	H	H	meso	102-103	38.1	92
240	CH_3	H	OMe	−6.9 (*S,S*)	98-99	17.3	92
241	CH_3	H	Cl	−4.0 (*R,R*)	oil	75.8	92
242	H	C_6H_5	H	−91 (*R,R*)	127-128	44	93
243	H	C_6H_5	H	+87 (*S,S*)	126-128	51	93
244	H	C_6H_5	H	meso	100-102	49	93
245	H	C_6H_5	OMe	+80.9 (*S,S*)	140-142	28	93
246	CH_3	H		+46.5 (*S,S*)	(170/1 mm)	22.2	92
247	CH_3	H		−46.1 (*R,R*)	oil	17.3	92
248	CH_3	H		meso	oil		92
249	H	C_6H_5		+90.7 (*S,S*)	76-87	42.7	93
250	CH_3	H		−27.3 (*S,S*)	80	23.5	92
251	CH_3	H			oil		92
252	CH_3	H		meso	oil		92
253	H	C_6H_5		+90.4 (*S,S*)	130-132	25.8	93
254	CH_3	H		+57.8 (*S,S*)	58	22.7	92

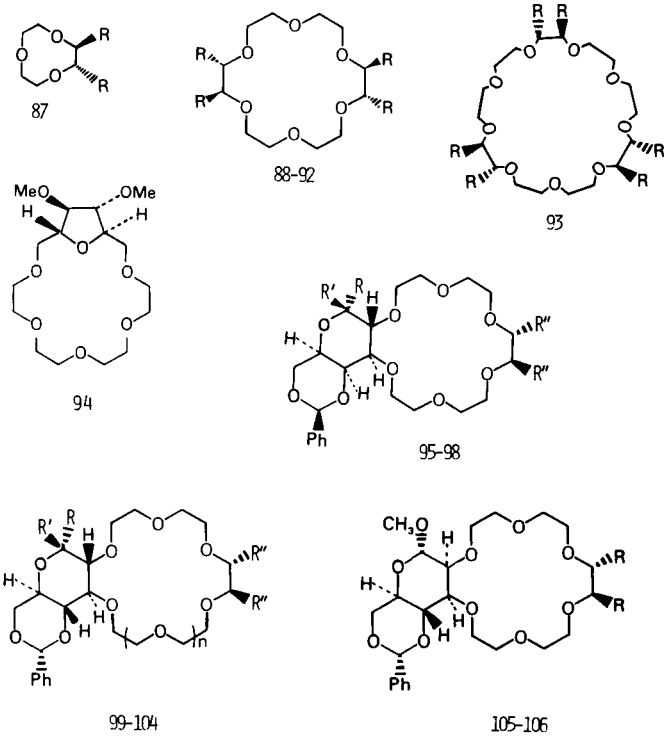
(a) Structures are shown in Figure 6.

Table VII
Chiral Macrocyclic Ligands Derived from Miscellaneous Sources (a)

Crown	Substituents		[α]	Mp (Bp) °C	% Yield	References
255	R = CPh_3	n = 1	−18.3	oil	59	47
256	R = CPh_3	n = 2	−18.1	oil	40	47
257	R = H	n = 1	+12.9	oil	74	47
258	R = H	n = 2	+19.2	oil	63	47
259	R = OCH_2Ph					95
260	R = OH					95
261	R = SCOPh					95
262	R = SH		+47.7			95
263	R = OCH_2Ph					95
264	R = OH					95
265	R = SCOPh					95
266	R = SH		−14.1			95
267	n = 0		+36.5	oil	42	94
268	n = 1		+25.1	oil	37	94
269			+39.2	77-80	31	94

(a) Structures are shown in Figure 7.

FIGURE 3: CHIRAL MACROCYCLIC LIGANDS CONTAINING CARBOHYDRATE UNITS



general procedure as those crowns containing carbohydrate units.

Synthesis of (2*R*,3*R*,11*R*,12*R*)-(+)-*N*,*N*,*N*',*N*',*N*'',*N*'',*N*''',*N*'''-octamethyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3,11,12-tetracarboxamide (Compound **155**, Scheme IV) (67,68).

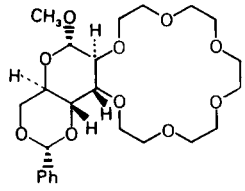
The bis(*N*,*N*-dimethylamide) of L(+)-tartaric acid (69) was reacted with thallium ethoxide in DMF in the presence of bis(2-iodoethyl)ether. The reaction was heated at 90° for 90 minutes, cooled, treated with water and then evaporated under vacuum. The residue was filtered over alumina and then recrystallized from acetone/heptane to give macrocycle **155**, mp 186°, $[\alpha]_D^{25} = +108°$, c = 1.5, chloroform (Scheme IV).

A considerable number of chiral macrocyclic ligands have been derived from tartaric acid. The structures and physical properties of these compounds are given in Figure 4 and Table IV, respectively.

The primary interest in the macrocyclic ligands synthesized from tartaric acid has been in their use as molecular catalysts for model enzyme studies (6,74-76,78). Lehn and Sirlin have compared the rates of thiolysis by compound **167** of a number of primary ammonium salts, specifically the *p*-nitrophenyl esters of some amino acids and di- and tripeptides (5). They observed that the salts of either the L-amino acids or peptides were selectively thiolyzed. There were definite structural effects as shown by the fact that the thiolysis of the *p*-nitrophenyl ester of the glycine-glycine salt was 15,000 times faster than that of the salt of L-proline-glycine (5). Behr and Lehn studied the nicotinamide-tryptophane charge-transfer interactions using these tartaric acid derived crown compounds (78). Matsui and Koga have shown that the length and make up of the thiol bearing side chain on the macrocycle have a marked effect on the rate of thiolysis (71). Experiments involving rate enhancement of pyridinium to dihydropyridine hydrogen transfer (76), membrane electrode enantiomer selectivity (71), asymmetric reductions (72,81) and chiral recognition elucidated by photophysical techniques (73) have also been carried out using tartaric acid based macrocycles. Reviews have been written by Lehn concerning work on chiral macrocyclic ligands derived from tartaric acid (79,80).

Chiral Macrocyclic Ligands Derived from Amino Acids.

FIGURE 3 (CONT.)



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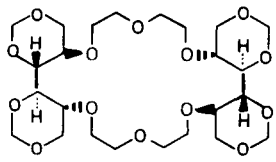

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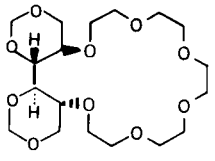

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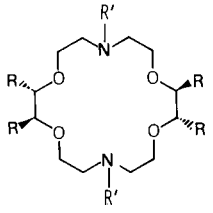

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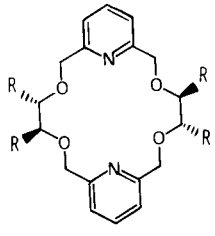

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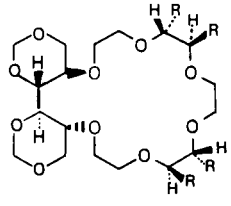

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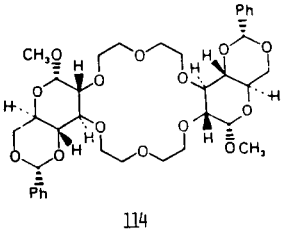

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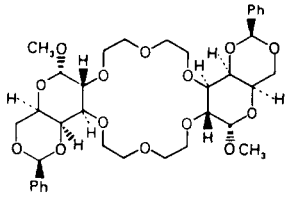

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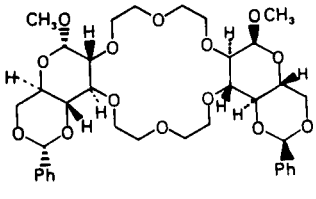

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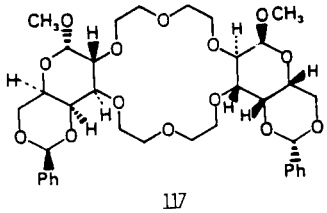

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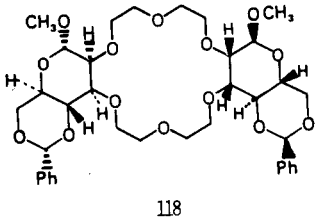

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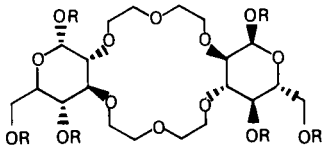
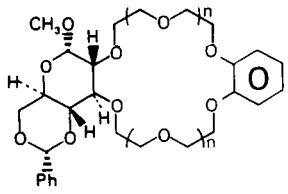


119,120

FIGURE 3 (CONT.)



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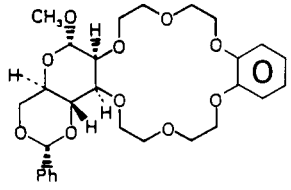

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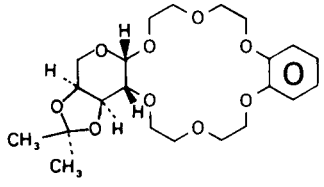

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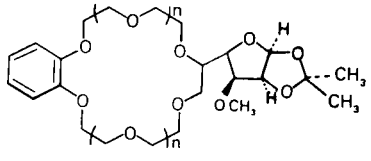


125,126

A number of optically active macrocyclic ligands have been prepared using amino acids as the source of chirality. L-Alanine (6,82), L-aspartic anhydride (83), L-phenylalanine (82), D-α-phenylethylamine (82), L-proline (11), L-valine (6) and α-phenylglycine (84) have all been used to make a wide variety of compounds.

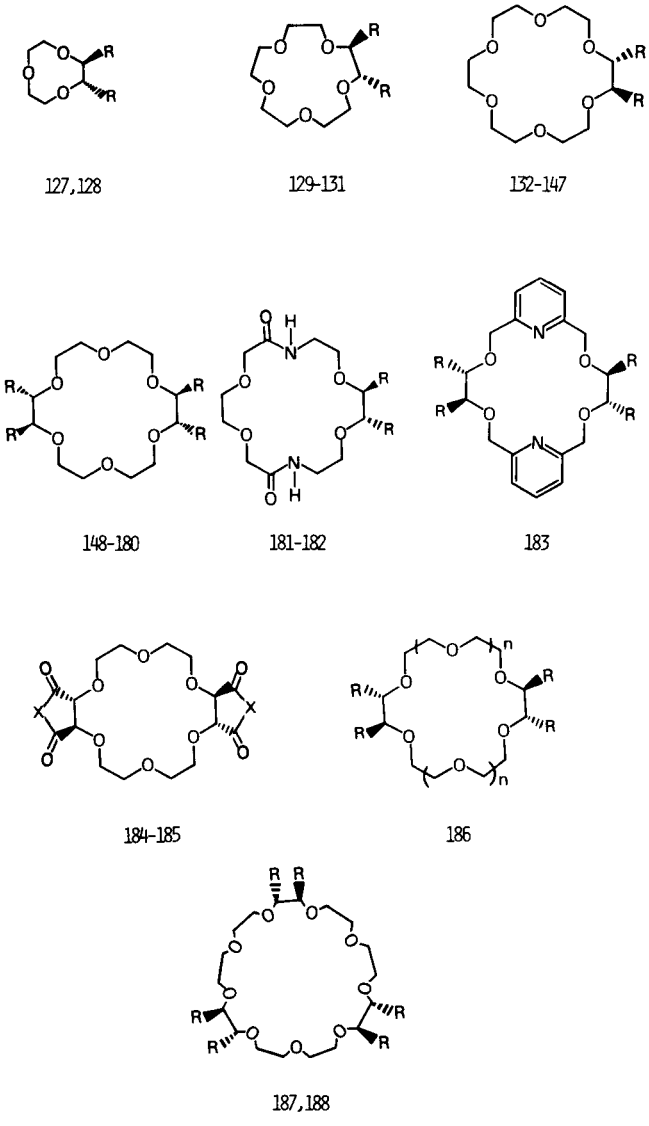
Preparation of 4,14-dimethyl-6,9,12-trioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetraone (Compound **200**, Scheme V) (6).

3,5-Pyridinedicarbonyl chloride and the *t*-butylester of L-alanine were reacted together in benzene and triethylamine (see Scheme V). The optically active diamide thus formed was then treated with trifluoroacetic acid to remove the *t*-butyl groups. Ring closure was effected by the addition of bis(2-bromoethyl)ether to the cesium salt of the diacid in DMF. The optically active macrocyclic ligand thus formed gave a rotation of -94°, c = 0.95, DMF (Scheme V). Macrocycle **200** was methylated and reduced to form the dihydropyridine derivative **203** (6).

Figure 5 shows the structures of the macrocyclic ligands derived from the amino acids and Table V lists their physical properties.

Most chiral crowns derived from amino acids have not

FIGURE 4: CHIRAL MACROCYCLIC COMPOUNDS DERIVED FROM TARTARIC ACID



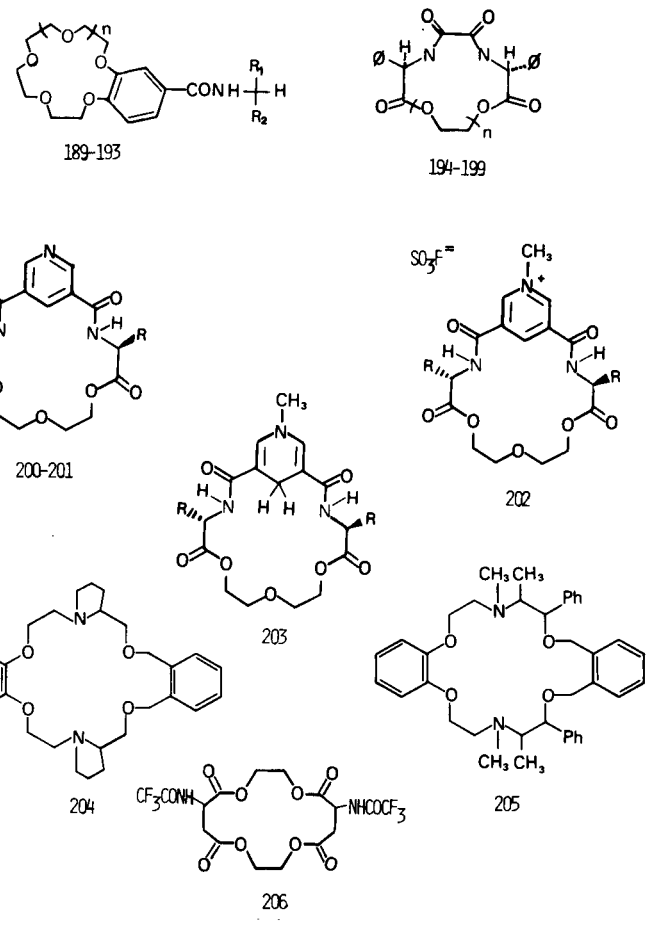
127,128 129-131 132-147

148-180 181-182 183

184-185 186

187,188

FIGURE 5: CHIRAL MACROCYCLIC COMPOUNDS DERIVED FROM AMINO ACIDS



189-193 194-199

200-201 202

203

204 205

206

as yet been evaluated for their ability to effect chiral recognition or act as catalysts. Kellogg used the above synthesized dihydropyridine crowns to effect asymmetric reductions of a number of aromatic ketones. Optical yields as high as 86% have been achieved using these macrocycles (6). Some circular dichroism work has also been done on certain amino acid based macrocyclic ligands (82).

Macrocyclic Ligands Derived from Other Chiral Acids.

Optically active macrocyclic ligands have been prepared from several other chiral acids such as L-lactic acid, D-and L-mandelic acids and di-α,α′-dimethylglutaric acid. Optically active propylene oxide which can be prepared from lactic acid has also been used.

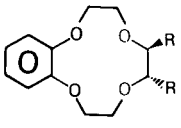
Synthesis of (8*S*,12*S*)-8,12-dimethyl-5,6,8,9,11,12,14,15-octahydro[*b*]benzo-1,4,7,10,13-pentaoxacyclopentadecin (Compound **211**, Scheme VI) (85).

L-(+) Lactic acid was reacted with dihydropyran in the presence of acid to form the blocked acid derivative which was then reduced to the blocked propane diol (**A**, Scheme VI). Compound **A** was then treated with tosyl chloride in pyridine to form the tosyl ester (**B**). The blocked tosyl derivative **B** was then reacted with **A** in DMF and sodium hydride. The chiral blocked dipropylene glycol (**C**) thus formed was deblocked in acidified methanol. Ring closure was achieved by treating glycol **D** with the ditosylate ester of 1,2-bis(2-hydroxyethoxy)benzene (**E**) in the presence of THF and sodium hydride (Scheme VI). Complete physical properties for compound **211** were not reported (85).

Figure 6 shows the structures of macrocyclic ligands derived from a variety of chiral acids and Table VI lists their phyiscal properties.

The above synthesized compound (**211**) was used in circular dichroism studies (85). Bradshaw and his coworkers have used optically active macrocyclic ligands derived

FIGURE 6: CHIRAL MACROCYCLIC COMPOUNDS DERIVED FROM OTHER CHIRAL ACIDS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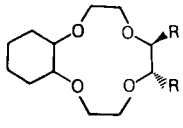
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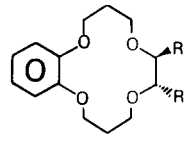
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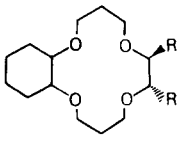
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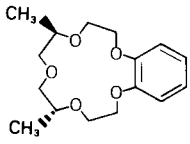
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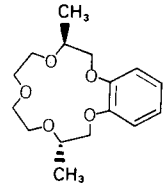
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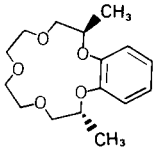
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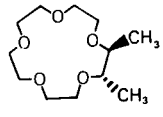
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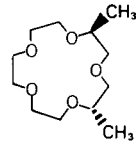
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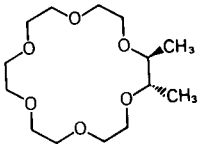
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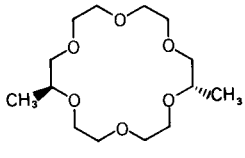
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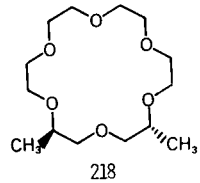
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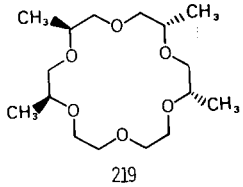
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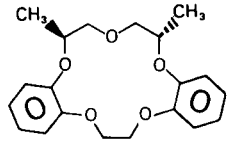
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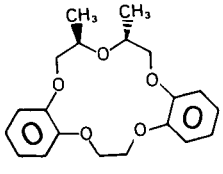
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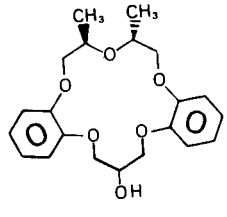
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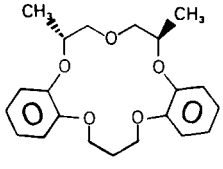
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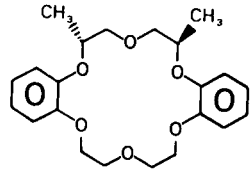
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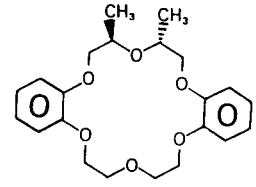
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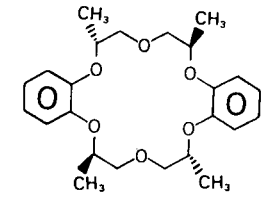
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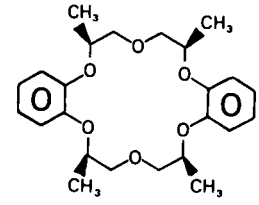
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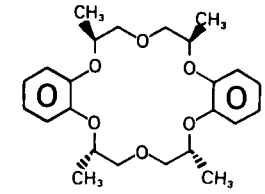
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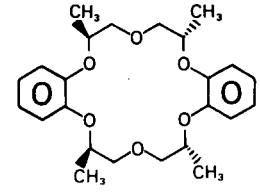
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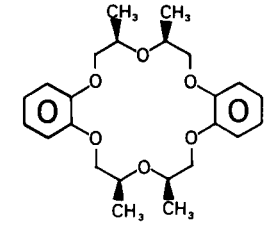
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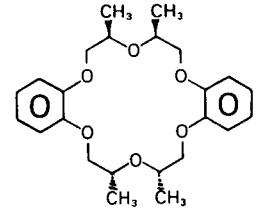
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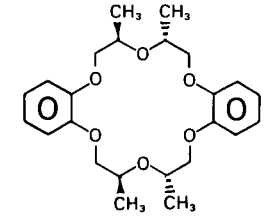
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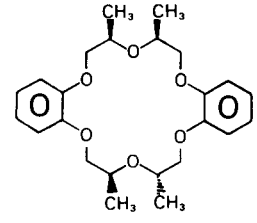
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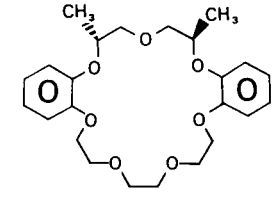
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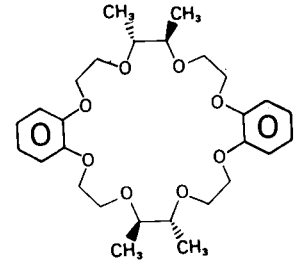
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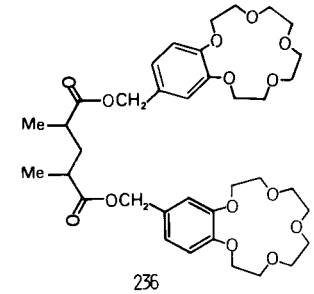
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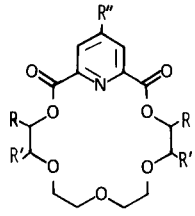
FIGURE 6 (CONT.)



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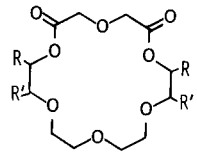

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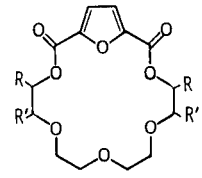

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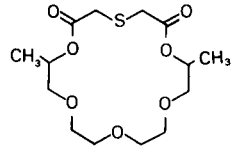

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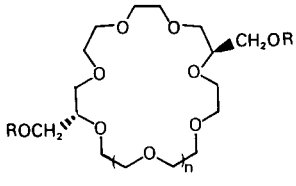
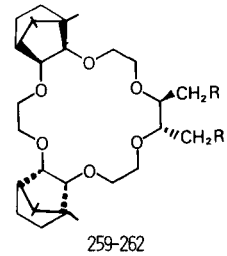
FIGURE 7: CHIRAL MACROCYCLIC LIGANDS DERIVED FROM MISCELLANEOUS SOURCES



255-258



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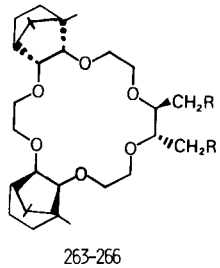

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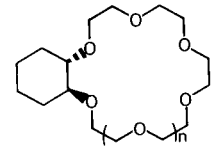

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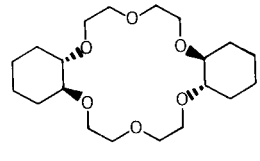

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from lactic and mandelic acids in low temperature proton nmr studies (92,93).

Chiral Macrocyclic Ligands Derived from Miscellaneous Sources.

A number of other interesting chiral materials have been used to prepare optically active macrocycles. (+) 1,2-Cyclohexanediol (94), (+)- and (-)-camphane-2,3-diol (95) have been used to prepare chiral macrocyclic ligands. The macrocycles synthesized from camphanediol were used in thiolysis reactions and showed a significant rate increase for the thiolysis of *p*-nitrophenyl amino ester salts (95). Figure 7 shows these chiral ligands and Table VII lists their physical properties.

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