diagnostic absorptions: δ 1.1 (d, 3 H, CH_3) and 3.3 (m, $W_{1/2}$ = 18 Hz, 1 H, CHOH) for the anti,exo alcohol and δ 1.1 (d, 3 H, CH_3) and 4.2 (m, $W_{1/2}$ = 15 Hz, 1 H, CHOH) for the anti,endo isomer.

Aluminum Isopropoxide Equilibrations of 8-Methyl-2-bicyclo[5.1.0]octanols. A 0.2-g sample of 97% *anti,endo*- and 3% *anti,exo*-8-methyl-2-bicyclo[5.1.0]octanols, 0.5 g of freshly distilled $Al(OiPr)_3$, and 0.1 mL of anhydrous acetone were dissolved in 25 mL of dry isopropyl alcohol, separated into four Pyrex ampules, sealed, and heated at 100 °C. Periodically an ampule was opened, the contents were poured into 50 mL of ether, and the ether solution was washed successively with three 10-mL portions of saturated aqueous NH_4Cl and three 10-mL portions of saturated aqueous NaCl. After being dried over $MgSO_4$, the solution was concentrated by distillation and analyzed by using both NMR and GLC techniques. The composition of the equilibrating mixture gradually changed until after 57 h an equilibrium position of 15% anti,endo and 85% anti,exo was reached which remained unchanged on further heating for a total of 130 h.

In a similar manner, a sample initially composed of 50% *syn,endo*- and 50% *syn,exo*-8-methyl-2-bicyclo[5.1.0]octanols was converted completely to the syn,exo alcohol after 57 h. As little as 0.03% of the syn,endo isomer could have been detected in the mixture were it present.

Reaction of Cyclopenten-3-ol with Ethylidene Iodide Using Diethylzinc. A three-necked, round-bottomed, 100-mL flask was oven dried, purged with nitrogen, and introduced into a drybox. Degassed anhydrous ether (30 mL) was added to the flask, a magnetic stirring bar was inserted, and the necks were closed with rubber septums which were securely wired on. Then, 10 mL (0.098 mol) of diethylzinc, which had been earlier transferred into a single-necked, round-bottomed flask from a lecture bottle, was removed with a syringe and added into the ether in the reaction flask. The flask containing the diethylzinc in ether was removed from the drybox, and the contents were stirred under a slow stream of nitrogen while cooling in an ice bath. Cyclopenten-3-ol (4.2 g, 0.050 mol) was added dropwise with a syringe over a period of 30 min, taking care that no excessive foaming occurred. Ethylidene iodide (7.4 mL, 0.065 mol) was also added dropwise with similar caution. After the additions were completed, the mixture was allowed to stir in the ice bath for 30 min more and then at room temperature for 20 h. The reaction mixture was worked up by adding it dropwise into 100 mL of a cooled (ice–water bath), stirred solution of saturated aqueous NH_4Cl. At the end of the addition, the mixture was allowed to stand at room temperature with stirring for several hours. The solids formed were filtered on a Büchner funnel and washed with about 50 mL of ether. The combined ether solutions were washed with four 25-mL portions of saturated aqueous Na_2CO_3 and two 15-mL portions of saturated aqueous NaCl and dried over $MgSO_4$. The ether was removed and the resulting oil distilled through a short-path, semimicro apparatus to give 3.7 g of material, bp 60–95 °C (16 mm). Examination by NMR revealed that the distillate contained 45% by weight of unreacted cyclopenten-3-ol. Thus, the yield of 6-methyl-2-bicyclo[3.1.0]hexanols based on reacted cyclopenten-3-ol was 60%. Analysis on a 46-m Carbowax 20M glass capillary column revealed that the ratio of the isomeric bicyclohexanols in the mixture was 76% anti,endo and 24% syn,endo.

Reaction of Cyclohepten-3-ol with Ethylidene Iodide Using Diethylzinc. In a manner similar to that for the analogous reaction with cyclopenten-3-ol, the reaction of cyclohepten-3-ol[11] (7.2 g, 0.064 mol), ethylidene iodide[12] (9.6 mL, 0.098 mol), and diethylzinc (10 mL, 0.096 mol) in 30 mL of ether for 17 h at room temperature gave after the workup and distillation 6.7 g of material, bp 90–95 °C (12 mm). By NMR, this was found to contain 28% by weight of unreacted cyclohepten-3-ol. Thus, the yield of 8-methyl-2-bicyclo[5.1.0]octanols based on reacted cyclohepten-3-ol was 72%. Analysis on a 46-m Carbowax 20M glass capillary column showed that the isomeric composition of the methylbicyclooctanols was 49% anti,endo, 10% anti,exo, 20% syn,endo, and 21% syn,exo.

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Registry No. Cyclopenten-3-ol, 3212-60-0; cyclohexen-3-ol, 822-67-3; cyclohepten-3-ol, 4096-38-2; *anti*-6-methyl,*endo*-2-bicyclo[3.1.0]hexanol, 80865-50-5; *syn*-6-methyl,*endo*-2-bicyclo[3.1.0]hexanol, 80865-51-6; *anti*-7-methyl,*endo*-2-bicyclo[4.1.0]heptanol, 62862-03-7; *syn*-7-methyl,*endo*-2-bicyclo[4.1.0]heptanol, 62862-02-6; *anti*-8-methyl,*endo*-2-bicyclo[5.1.0]octanol, 81520-65-2; *anti*-8-methyl,*exo*-2-bicyclo[5.1.0]octanol, 62929-22-0; *syn*-8-methyl,*endo*-2-bicyclo[5.1.0]octanol, 81520-66-3; *syn*-8-methyl,*exo*-2-bicyclo[5.1.0]octanol, 62862-00-4; ethylidene iodide, 594-02-5; zinc, 7440-66-6; cuprous chloride, 7758-89-6; diethylzinc, 557-20-0; *anti*-8-methyl,2-bicyclo[5.1.0]octanone, 62929-23-1; *syn*-8-methyl,2-bicyclo[5.1.0]octanone, 62862-01-5; *endo*-2-bicyclo[5.1.0]octanol, 6202-97-7; *exo*-2-bicyclo[5.1.0]octanol, 6142-49-0.

Synthesis of Stereoisomeric Crown Ethers Composed of *cis*- and *trans*-2,5-Bis(hydroxymethyl)tetrahydrofuran Units and Their Selective Transport of Alkali Metal Cations through Liquid Membranes

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Optical resolution of *trans*-tetrahydrofuran-2,5-dicarboxylic acid (**13**) was carried out via the (+)-2-(1-aminoethyl)naphthalene salt, and conversion of the (+) enantiomer **13** into (+)-2,5-dimethyltetrahydrofuran (**17**) of known configuration established its 2*R*,5*R* configuration. Condensation of (+)- and (−)-*trans*-ditosylates **15** and *cis*-ditosylate **20** with pyrocatechol afforded (−)-D_2-*trans,trans*-**8**, (−)-C_1-*cis,trans*-**9**. *meso*-C_{2h}-*trans,trans*-**10**, and a mixture of *meso*-C_{2h}-**11** and meso-C_{2v}-cis,cis crown ethers **12**. Their selective transport of alkali metal cations is reported.

From the culture solutions of various *Streptomyces* strains there have been isolated quite a variety of antibiotics[1] which possess potent physiological activity by virtue of their ionophoric properties, e.g., the uncoupling

0022-3263/82/1947-2429$01.25/0

Chart I

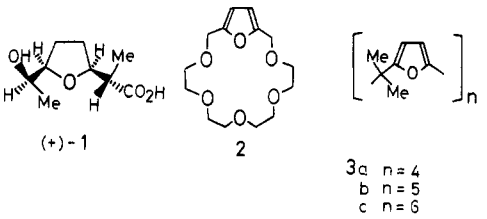
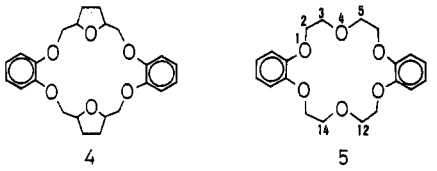


Chart II



oxidative phosphorylation in mitochondria. Most of these antibiotics have 2,5-disubstituted tetrahydrofuran units as a common structural feature; e.g., nigericin,[2] grisorixin,[3] monensin,[4] X-206,[5] X-537A,[6] dianemycin,[7] A-204A,[8] boromycin,[9] and the actin group.[10] Among these, the actin family exhibits an especially fascinating structural feature from the standpont of the stereochemistry of "enveloping"[11] in that they are composed of two pairs of enantiomeric 2,5-disubstituted tetrahydrofuran units and afford meso compounds with S_4 symmetry. Nonactin,[12,13] the simplest representative, is shown to be constructed from two units each of (+)- and (−)-nonactic acids (1) alternatively combined together to form a 28-membered macrocycle (Chart I).

X-ray crystallography of the potassium rhodanate complex of nonactin has confirmed that the complex assumes a conformation with approximate S_4 symmetry, enclosing the central potassium cation in the hydrophilic "hole" by cubic 8-coordination with four carbonyl and four tetrahydrofuran oxygen atoms. So far, two types of model crown ethers possessing a 2,5-disubstituted tetrahydrofuran moiety have been synthesized, both by catalytic hydrogenation of the furan precursors **2**[14] and **3**.[15] And

Chart III

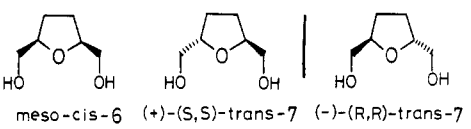


Chart IV

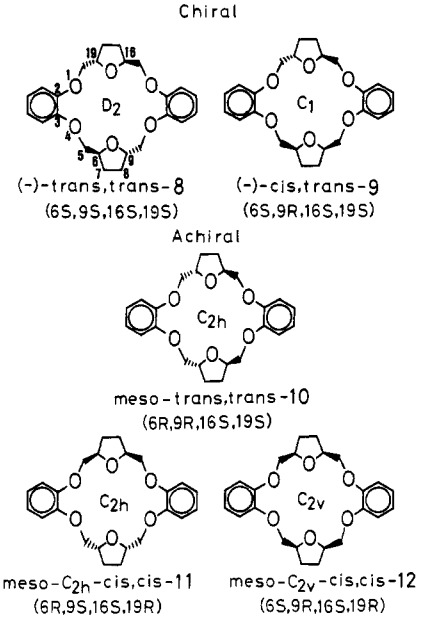
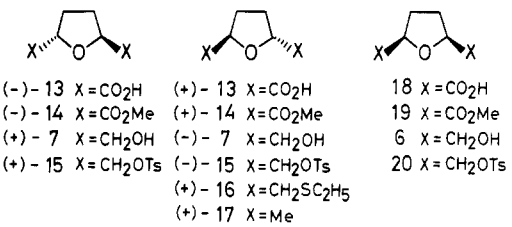


Chart V



for the crown ethers derived from **3a–c**, a study[15] has been made to examine the relationship between the size of the cavity in these ionophores and the ionic radii of the metal cations transported through the liquid membrane. Unfortunately, however, these reported 16-, 20-, and 24-membered crown ethers are apparently complex mixtures of various stereoisomers whose isolation by Al_2O_3 column chromatography was reported to be unsuccessfull. The stereochemistry of these compounds has been left to be elucidated except for the probable 2,5-cis configuration in the tetrahydrofuran moiety.

This situation coupled with our continuing interests on gyrochiral molecules prompted us to prepare all of the theoretically possible stereoisomers of the 18-membered crown ether **4** composed of two tetrahydrofuran moieties of well-defined stereochemistry and to compare their ionophoric characters with that of closely related dibenzo-18-crown-6 (**5**) whose 3–5 and 12–14 bridgings with ethylene groups eventually afford **4** (Chart II).

Our synthetic approach consisted of three stages: (a) preparation of *cis*-**6** and *trans*-2,5-bis(hydroxymethyl)-tetrahydrofuran (**7**) (Chart III), (b) determination of the

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(13) For a recent review on macrocyclic ionopohores, see: Masamune, S.; Bates, G. S.; Cprcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.
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Table I. $Eu(TFC)_3$ Enantiomer Differentiation in the NMR Spectral Data of (±)-, (−)-, and (+)-Dimethyl Tetrahydrofuran-2,5-dicarboxylates (14)[a]

ester	chemical shift		
	CH_2CH_2	CO_2CH_3	$CHCO_2CH_3$
(±)-14, (−)-14, (+)-14 without $Eu(TFC)_3$	1.9–2.4 (m)	3.68 (s)	4.58 (br s)[b]
(±)-14 with $Eu(TFC)_3$	2.5–3.2 (m)	3.86 (s), 3.90 (s)	5.62 (br s),[b] 6.12 (br s)[b]
(−)-14 with $Eu(TFC)_3$	2.5–3.0 (m)	3.84 (s)	5.73 (br s)[c]
(+)-14 with $Eu(TFC)_3$	2.7–3.2 (m)	3.94 (s)	6.00 (br s)[c]

[a] Chemical shifts are given parts per million (δ); the solvent was CCl_4. [b] Peak width at half-height = 0.11 ppm. [c] Peak width at half-height = 0.12 ppm.

absolute configurations of the gyrochiral trans isomers, and (c) ring closure of these tetrahydrofuran units with pyrocatechol to obtain the stereoisomers with various symmetries[16] as illustrated in Chart IV.

Results and Discussion

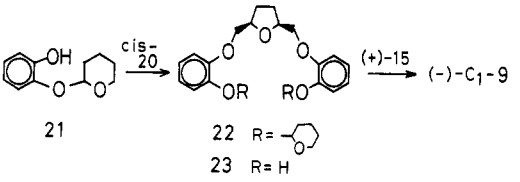
Optical Resolution and Absolute Configuration of *trans*-Tetrahydrofuran-2,5-dicarboxylic Acid (13, Chart V). By use of Lean's procedure,[17] a mixture of (±)-*trans*-**13** and *meso-cis*-tetrahydrofuran-2,5-dicarboxylic acids (**18**) was prepared, and the isomers were separated by fractional recrystallization from water. Several trials indicated that optical resolution of the *trans*-dicarboxylic acid **13** was best accomplished via the (+)-2-(1-aminoethyl)naphthalene salt whose fractional recrystallization from ethanol afforded a sparingly soluble salt ($[\alpha]_D$ −11.0°) and a soluble salt ($[\alpha]_D$ −5.4°). Decomposition of these salts separately followed by recrystallization of the isolated acids from diethyl ether yielded the (−)-dicarboxylic acid **13** (mp 64.5–65 °C; $[\alpha]_{405}$ −5.4°) and the (+) enantiomer **13**: mp 63–65 °C; $[\alpha]_{405}$ + 5.3°.[18]

The optical purity of the acid **13** was determined by means of the chiral shift reagent $Eu(TFC)_3$, and 0.1–0.2 molar equiv of the shift reagent was added to the CCl_4 solutions containing (±)-, (−)-, and (+)-dimethyl esters **14**.

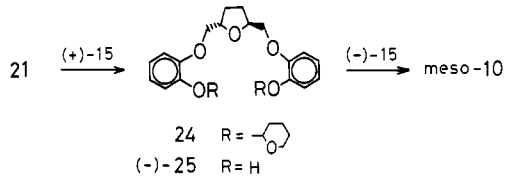
Table I summarizes the results which indicate the following: (a) the CO_2CH_3 and $CHCO_2CH_3$ signals of the racemic modification are clearly split into two peaks of equal intensity; (b) the peaks in lower magnetic fields correspond to the (+) enantiomer; (c) the absence of the signals due to their opposite enantiomers in the spectra of the (+)- and (−)-dimethyl esters **14** suggested their almost 100% optical purity, assigning $[\alpha]_{405}$ (abs) 5.3 ± 0.1° and $[\alpha]_{405}$ (abs) 4.0 ± 0.1° to **13** and **14**, respectively.

Turning to the absolute configuration of optically active dicarboxylic acid **13**, our strategy for its assignment was to convert **13** into *trans*-2,5-dimethyltetrahydrofuran (**17**), whose absolute configuration has been established by Mihailović and co-workers.[19] A routine sequence of conversions involving $LiAlH_4$ reduction and tosylation of the resulting (−)-diol **7** converted the (+)-dimethyl ester **14** (36% optical purity) into (−)-ditosylate **15** which was then reacted with sodium ethanethiolate to afford (+)-dithioether **16**. Finally, refluxing with Raney nickel in ethanol transformed the (+)-dithioether **16** into (+)-(2*S*,5*S*)-2,5-dimethyltetrahydrofuran (**17**); bp 93–95 C; $[\alpha]_D$ +7.3° (EtOH). This correlation assigned the absolute configurations shown in Chart V to various intermediates, and our knowledge of the optical purity of **14** enabled us to calculate $[\alpha]_D$ (abs) +20.3° for *trans*-2,5-dimethyltetrahydrofuran (**17**) which is close to Mihailovic's maximal $[\alpha]_D$ +22.95° value.

Scheme I



Scheme II



Synthesis of (−)-D_2-Trans,trans Crown Ether 8. Since its D_2 symmetry demands two *trans*-2,5-disubstituted tetrahydrofuran units of same chirality combining with two pyrocatechol to make up the 18-membered cavity, the synthesis of D_2-*trans,trans*-**8** appears the simplest among the five crown ethers shown in Chart IV.

By use of the same sequence of conversions described for the (+) enantiomer **13**, (−)-(2*S*,5*S*)-2,5-tetrahydrofurandicarboxylic acid (**13**; $[\alpha]_{405}$ −5.4° (100% optical purity)) was transformed into the (+)-(2*S*,5*S*)-ditosylate **15** ($[\alpha]_D$ +11.1°) whose condensation with pyrocatechol was carried out in tetrahydrdofuran solution which contained potassium *tert*-butoxide. Purification through Al_2O_3 column chromatography afforded a 24% yield of (−)-(6*S*,9*S*,16*S*,19*S*)-D_2-*trans,trans*-**8**: mp 207–208 °C; $[\alpha]_D$ −21.0°.

Synthesis of (−)-C_1-Cis,trans Crown Ether 9 (Scheme I). For the synthesis of the crown ether **9**, having two tetrahydrofuran units of different stereochemistry, it is imperative to introduce these units at different stages of ring closure, and the actual synthetic course is summarized in Scheme I.

cis-Ditosylate **20** (mp 128–129 °C) was prepared from the *cis*-dicarboxylic acid **18** by the same sequence of conversions described for the (+)-trans isomer **15**. Refluxing the tetrahydrofuran solution of **20** with slightly more than 2 mol of pyrocatechol monotetrahydropyranyl ether **21** and potassium *tert*-butoxide led to formation of **22** (91% yield; mp 55–56 °C) which was hydrolyzed with *p*-toluenesulfonic acid to **23**, mp 57.9–59.5 °C. Final condensation of **23** with the (+)-(2*S*,5*S*)-ditosylate **15** ($[\alpha]_D$ +11.1°) was carried out in tetrahydrofuran containing potassium *tert*-butoxide, and the (−)-(6*S*,9*R*,16*S*,19*S*) crown ether **9** isolated in a 37% yield crystallized on trituration in acetone to melt at 155–158 °C and had $[\alpha]_D$ −4.2°.

Synthesis of Meso-C_{2h}-trans,trans Crown Ether 10 (Scheme II). Since this meso crown ether **10** is composed of two *trans*-tetrahydrofuran units with opposite chirality,

(16) Unless stated differently, the symmetry of the crown ethers discussed in this paper refers to their highest available symmetry.

(17) Lean, B. *J. Chem. Soc.* **1900**, 103.

(18) In this paper, all structural formulas with (+) or (−) rotational specifications are illustrated in their absolute configurations.

(19) Mihailović, M. L.; Mamuzić, R. I.; Zigić-Mamuzić, L.; Bošnjak, J.; Cekovič, Z. *Tetrahedron* **1967**, *23*, 215. In the above paper, the absolute configuration of (+)-(2*S*,5*S*)-2,5-dimethyltetrahydrofuran (**17**) was depicted differently, but this has been corrected by Klyne: Klyne, W.; Buckingham, J. "Atlas of Stereochemistry"; Chapmann and Hall: London, 1978; Vol. 2, p 5.

Table II. NMR Spectral Data of the Stereoisomeric Crown Ethers 8–10 and a Mixture of 11 and 12[a]

crown ether	chemical shift			
	CH_2CH_2	OCH_2CH	$OCHCH_2$	aromatic protons
(−)-*D_2-trans,trans*-**8**	1.6–2.5 (m, 8 H)	3.9–4.2 (m, 8 H)	4.48 (br s, 4 H)	6.89 (s, 8 H)
(−)-*C_1-cis,trans*-**9**	1.7–2.4 (m, 8 H)	3.8–4.2 (m, 8 H)	4.30 (br s, 2 H), 4.59 (br s, 2 H)	6.86 (s, 4 H), 6.89 (s, 4 H)
meso-C_{2h}-trans,trans-**10**	1.6–2.1 (m, 4 H), 2.1–2.4 (m, 4 H)	4.0–4.1 (m, 8 H)	4.65 (br s, 4 H)	6.91 (s, 8 H)
mixture of *meso-C_{2h}-cis,cis*-**11** and *meso-C_{2v}-cis,cis*-**12**	1.6–2.3 (m, 8 H)	3.8–4.2 (m, 8 H)	4.30 (br s, 4 H)	6.84 (s, 8 H)

[a] Chemical shifts are given parts per million (δ); the solvent was $CDCl_3$.

it is imperative to introduce these enantiomeric *trans*-tetrahydrofuran units at a different stage of ring closure as described for the preparative of (−)-*C_1-cis,trans*-**9**.

Scheme II illustrates the sequence of conversions leading to *meso-C_{2h}-trans,trans*-**10** which involved the condensation of (+)-(2*S*,5*S*)-ditosylate **15** ($[\alpha]_D$ +11.1°) with pyrocatechol tetrahydropyranyl ether **21** as the first step. Al_2O_3 column chromatography of the product yielded a 93% yield of **24** whose hydrolysis with *p*-toluenesulfonic acid gave (−)-**25**: mp 88–90 °C; $[\alpha]_D$ −16.3°. Final ring closure of (−)-**25** with the enantiomeric (−)-(2*R*,5*R*)-ditosylate **15** ($[\alpha]_D$ −10.8°) completed the synthesis of the meso-C_{2h}-trans,trans crown ether **10** (mp 195–197 °C) which exhibited no optical activity as expected.

Synthesis of a Mixture of Meso-cis,cis Crown Ethers 11 and 12. Depending upon the modes of combination of diastereotopic surfaces in *meso-cis*-ditosylates **20**, condensation of two molecules of **20** and two molecules of pyrocatechol should yield two types of meso-cis,cis crown ethers, one with C_{2h} and the other with C_{2v} symmetry. By use of the procedure described for the preparation of *D_2-trans,trans*-**8**, condensation between *meso-cis*-ditosylate **20** and pyrocatechol was carried out to give a 15% yield of a glassy product (*m/e* 412 (M^+)). Apparently this material is a mixture of C_{2h}-**11** and C_{2v} isomer **12**; separation by column chromatography or TLC was unsuccessful.

^{1}H NMR Spectra of the Stereoisomeric Crown Ethers. Table II summarizes the 100-MHz ^{1}H NMR spectral data of (−)-*D_2-trans,trans*-**8**, (−)-*C_1-cis,trans*-**9**, *meso-C_{2h}-trans,trans*-**10**, and the mixture of *meso-C_{2h}*-**11** and *meso-C_{2v}-cis,cis*-**12**.

Among these isomers, *C_1-cis,trans*-**9** appears conspicuous in that it exhibits two kinds of O–CH and aryl proton signals, reflecting its unique asymmetric feature.

Kinetics of Selective Transport of Alkali Metal Cations. Measurement of the relative rate of transport of alkali metal cations through a $CHCl_3$ liquid membrane containing the crown ethers reported in this paper and dibenzo-18-crown-6 (**5**)[20] was carried out as described in the Experimental Section. Table III tabulates the initial rates obtained by extrapolation. A casual inspection of this table reveals several interesting features: (a) Although K^+ ion transport is most rapid in each case, these stereoisomeric crown ethers differ considerably in their transport ability. (b) *meso-C_{2h}-trans,trans*-**10** is conspicuous in its high transport rate for K^+ ion, which is higher than the flexible parent compound **5**.

This result seems to arise from its unique structure, having two chiral components with opposite chirality, reminiscent of the similar molecular aspect inherent to nonactin of S_4 symmetry. (c) The mixture of *meso-C_{2h}*-**11** and *meso-C_{2v}-cis,cis*-**12** shows almost no discrimination toward Na^+, K^+, and Cs^+.

Table III. Relative Rates of Transport of Alkali Metal Cations through a Bulk Organic Liquid Membrane (at 25 °C)

carrier (2.40 × 10^{-4} mol/L)[a]	cation (2.40 × 10^{-3} mol/L)[b]	10^{-8} (rate of transport), mol/h	rel rate
(−)-*D_2-trans,trans*-**8**	Li^+	0.147	1
	Na^+	2.30	15.6
	K^+	16.14	109.8
	Cs^+	7.08	48.2
(−)-*C_1-cis,trans*-**9**	Li^+	0.654	4.45
	Na^+	17.04	115.9
	K^+	27.5	189.2
	Cs^+	4.61	31.36
meso-C_{2h}-trans,trans-**10**	Li^+	0.409	2.78
	Na^+	10.3	70.07
	K^+	40.5	275.5
	Cs^+	2.65	18.03
mixture of *meso-C_{2h}-cis,cis*-**11** and *meso-C_{2v}-cis,cis*-**12**	Li^+	0.334	2.27
	Na^+	5.21	35.44
	K^+	9.00	61.22
	Cs^+	7.08	48.16
dibenzo-18-crown-6 (**5**)	Li^+	0.177	1.20
	Na^+	0.660	4.49
	K^+	32.1	218.4
	Cs^+	6.00	40.82

[a] Concentration of crown ether in $CHCl_3$ layer. [b] Concentration of metal picrate in water phase I.

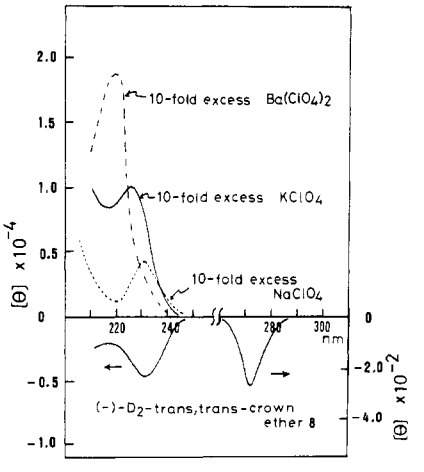


Figure 1. Complexing and CD spectral changes in (−)-*D_2*-trans,trans crown ether **8** (in methanol).

Complexing and CD Spectral Changes[21] in the Chiral Crown Ethers 8 and 9. We took advantage of

(20) Dibenzo-18-crown-6 purchased from Aldrich was used without purification.

(21) CD spectral changes in (8*S*,12*S*)-8,12-dimethylbenzo-15-crown-5 were utilized to measure the formation constants of complexes: Mack, M. P.; Hendrixon, R. R.; Palmer, R. A.; Ghirardelli, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7830.

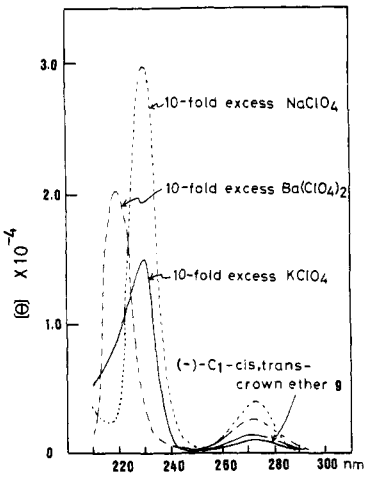


Figure 2. Complexing and CD spectral changes in (-)-C_1-cis,trans crown ether **9** (in methanol).

two *o*-xylene chromophores in the chiral crown ethers **8** and **9** to obtain information on their expected conformational changes during complex formation. As can be see from Figures 1 and 2, fairly large changes in their Cotton effects were observed in both cases, and (-)-D_2-*trans*,-*trans*-**8** even changes the sign of Cotton effect by complexing.

Although it is premature to draw any concrete image of their conformational change from these observations, it seems safe to suggest that (a) the large ellipticity increase on complexing reflects the fact that these crown ethers must assume somewhat more rigid conformations in the complexes than in their free states in solution and that (b) complexing with divalent Ba^{2+} would be quite different from that with alkali metal cations.

Experimental Section

Infrared spectral data were taken on a Hitachi 260-10 spectrophotometer, and ^1H NMR spectra were obtained from a JNM-MH-100. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter, and mass spectra were taken with a Hitachi RMS-4 spectrometer. Elemental analyses were determined on a Yanagimoto CHN-Corder, Type II. All melting and boiling points are uncorrected.

Optical Resolution of *trans*-Tetrahydrofuran-2,5-dicarboxylic Acid (13). A mixture of *trans*-tetrahydrofuran-2,5-dicarboxylic acid [**13**: mp 64.5–65 °C (lit.[17] mp 59–62 °C); 8.01 g, 0.0450 mol], (+)-2-(1-aminoethyl)naphthalene (15.4 g, 0.0900 mol), and ethanol (30 mL) was refluxed for 3 h. Allowing the mixture to stand overnight at room temperature resulted in a solid precipitate which was collected to yield a mixture of salts: 15.7 g; $[\alpha]^{20}_D$ +0.75° (*c* 0.621, EtOH). Fractional recrystallization of the salt from ethanol (six times) gave 7.63 g of the levorotatory salt, $[\alpha]^{20}_D$ -11.0° (*c* 0.560, EtOH). The collected filtrates were reserved for isolation of the enantiomer **13**.

A mixture of the levorotatory salt (7.00 g) and 10% aqueous KOH (20 mL) was stirred for 12 h at room temperature and extracted with ether to remove the resolving agent (4.5 g). After being acidified with diluted aqueous H_2SO_4, the mixture was extracted continuously for 7 days with ether. The ethereal extract was concentrated to give a solid, which was recrystallized from ether to yield (-)-**13**: 1.85 g; mp 64.5–65 °C; $[\alpha]^{21}_{405}$ -5.4° (*c* 0.895, MeOH).

Anal. Calcd for $C_6H_8O_5 \cdot H_2O$: C, 40.42; H 5.66. Found: C, 40.35; H, 5.56.

When the dextrorotatory salt [5.65 g, $[\alpha]^{21}_D$ +17.9° (*c* 0.550, EtOH)] from the collected filtrates was treated as described above for the diastereomeric salt, it gave (+)-**13**: 1.31 g; mp 63–64 °C; $[\alpha]^{21}_{405}$ +5.3° (*c* 1.02, MeOH).

Anal. Calcd for $C_6H_8O_5 \cdot H_2O$: C, 40.42; H, 5.66. Found: C, 40.70; H, 5.51.

(-)-(2*S*,5*S*)-*trans*-2,5-Bis(methoxycarbonyl)tetrahydrofuran (14). To a chilled suspension of (-)-**13**, $[\alpha]^{21}_{405}$ -5.4° (9.30 g, 0.0522 mol) in 100 mL of ether was added an excess ethereal solution of diazomethane prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, and the routine workup afforded 6.50 g (97% yield) of (-)-**14**: bp 94–95 °C (0.8 mm); $[\alpha]^{22}_{405}$ -4.1° (*c* 1.05, MeOH); IR (neat film) 1740, 940, 840, 785 cm^{-1}.

Anal. Calcd for $C_5H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.80; H, 6.42.

(+)-(2*R*,5*R*)-trans-2,5-Bis(methoxycarbonyl)tetrahydrofuran (14). By the same method described for the (-) enantiomer, the (+)-dicarboxylic acid **13** (2.33 g; $[\alpha]^{21}_{405}$ +5.3°) was esterified to provide 2.22 g (91% yield) of the (+)-dimethyl ester **14**: bp 132–135 °C (2 mm); $[\alpha]^{22}_{405}$ +4.0° (*c* 1.10, MeOH).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.10; H, 6.40.

(±)-*trans*-2,5-Bis(methoxycarbonyl)tetrahydrofuran (14). The same procedure described above converted the (±)-dicarboxylic acid **13** (1.86 g) into the (±)-dimethyl ester **14**: 1.80 g (95% yield); bp 133–135 °C (2 mm).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.90; H, 6.39.

***cis*-2,5-Bis(methoxycarbonyl)tetrahydrofuran (19).** The *cis*-dicarboxylic acid **18** [8.00 g; mp 125–126 °C (lit.[17] mp 124–125 °C)] was converted into the *cis*-dimethyl ester **19** [8.55 g (91% yield); bp 116–117 °C (3 mm)] in the same manner as described above: IR (neat film) 1740, 925, 800, 770 cm^{-1}; ^1H NMR (CCl_4) δ 2.10–2.25 (m, 4 H), 3.70 (s, 6 H), 4.40 (br s, 2 H).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.88; H, 6.49.

(+)-(2*S*,5*S*)-*trans*-2,5-Bis(hydroxymethyl)tetrahydrofuran (7). To a suspension of $LiAlH_4$ (3.10 g, 81.6 mmol) in dry ether (120 mL) was added dropwise a solution of the (-)-dimethyl ester **14** [$[\alpha]^{22}_{405}$ -4.1°; 6.00 g (31.9 mmol)] in dry ether (80 mL). After the mixture was refluxed for 12 h, diluted aqueous H_2SO_4 was carefully added to the mixture with ice cooling. A deposited solid was collected and boiled with $CHCl_3$ to extract organic substances. The $CHCl_3$ extract was combined with the ethereal extract and dried ($MgSO_4$). After the solution was concentrated, the residue was distilled to afford 3.45 g (82% yield) of (+)-**7**: bp 118–120 °C (5 mm); $[\alpha]^{22}_D$ +42.0° (*c* 1.11, $CHCl_3$); IR (neat film) 3350, 1050 cm^{-1}.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.35; H, 8.96.

(-)-(2*R*,5*R*)-*trans*-2,5-Bis(hydroxymethyl)tetrahydrofuran (7). The same procedure described above converted the (+)-dimethyl ester **14** (2.00 g; $[\alpha]^{22}_{405}$ +4.0°) into (-)-**7**: 1.11 g (79% yield); bp 120–122 °C (5 mm); $[\alpha]^{22}_D$ -41.5° (*c* 0.950, $CHCl_3$).

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.32; H, 8.90.

***cis*-2,5-Bis(hydroxymethyl)tetrahydrofuran (6).** The same $LiAlH_4$ reduction of the *cis*-dimethyl carboxylate **19** (4.50 g) gave *cis*-**6**: 2.53 g (80% yield); bp 134–137 °C (6 mm).

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.55; H, 8.91.

(+)-(2*S*,5*S*)-*trans*-2,5-Bis(tosylmethyl)tetrahydrofuran (15). To a chilled solution of the (+)-glycol **7** [$[\alpha]^{22}_D$ +42.0°; 4.17 g (31.6 mmol)] in pyridine (40 mL) was added *p*-toluenesulfonyl chloride (18.0 g, 94.2 mmol), and the mixture was stirred for 12 h at room temperature. The reaction mixture was poured into ice–water and made acidic with diluted aqueous HCl to deposit crystals which were collected, washed with water, and dried to afford a solid which was recrystallized from acetone–ether to give 13.5 g (97% yield) of the (+)-ditosylate **15**: mp 94–95 °C; $[\alpha]^{22}_D$ +11.1° (*c* 0.823, $CHCl_3$); IR (KBr) 1595, 1350, 1190, 1170, 970, 820 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}O_7S_2$: C, 54.53; H, 5.49; S, 14.56. Found: C, 54.46; H, 5.57; S, 14.50.

(-)-(2*R*,5*R*)-*trans*-2,5-Bis(tosylmethyl)tetrahydrofuran (15). By the same procedure described above, the (-)-glycol **7** (1.00 g; $[\alpha]^{22}_D$ -41.5°) was converted into the (-)-ditosylate **15** (3.10 g, 93% yield), which was recrystallized from acetone–ether: mp 85–87 °C; $[\alpha]^{28}_D$ -10.8° (*c* 1.19, $CHCl_3$).

Anal. Calcd for $C_{20}H_{24}O_7S_2$: C, 54.53; H, 5.49; S, 14.56. Found: C, 54.27; H, 5.32; S, 14.30.

***cis*-2,5-Bis(tosylmethyl)tetrahydrofuran (20).** The *cis*-ditosylate **20** (7.28 g, 95% yield) was prepared from the *cis*-glycol **18** (2.30 g). The ditosylate was purified by recrystallization from acetone–ether; mp 128–129 °C (lit.[22] mp 130.5 °C).

Anal. Calcd for $C_{20}H_{24}O_7S_2$: C, 54.53; H, 5.49; S, 14.56. Found: C, 54.47; H, 5.47; S, 14.40.

(+)-(2*R*,5*R*)-*trans*-2,5-Bis[(ethylthio)methyl]tetrahydrofuran (16). A solution of ethanethiol (1.90 g, 17.5 mmol) in absolute ethanol (10 mL) was added dropwise to a solution of sodium ethoxide in absolute ethanol [prepared from Na (440 mg, 19.1 mmol) and absolute ethanol (20 mL)], and the mixture was stirred for 1 h at room temperature. The (−)-ditosylate **15** [$[\alpha]^{22}_D$ −3.9° (optical purity 36%); 3.50 g (7.95 mmol)] was added, and the mixture was refluxed for 15 h. After being poured into water, the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residue was distilled to afford the (+)-dithioether **16**: 1.23 g (70% yield); bp 135–136 °C (6 mm); $[\alpha]^{22}_D$ +16.3° (*c* 0.700, $CHCl_3$).

Anal. Calcd for $C_{10}H_{20}OS_2$: C, 54.50; H, 9.15; S, 29.10. Found: C, 54.30; H, 9.05; S, 29.08.

(+)-(2*S*,5*S*)-*trans*-2,5-Dimethyltetrahydrofuran (17). A mixture of the (+)-dithioether **16** [$[\alpha]^{22}_D$ +16.3°; 1.10 g (5.00 mmol)], Raney nickel (10 g), and ethanol (40 mL) was refluxed for 15 h. After the Raney nickel was removed, the filtrate was diluted with water and extracted with pentane. The extract was washed with water, dried ($CaCl_2$), and concentrated. Distillation of the residue afforded 350 mg (64% yield) of (+)-**17**: bp 93–95 °C (760 mm); $[\alpha]^{21}_D$ +7.3° (*c* 0.252, EtOH). Calculation based on the optical purity (36%) of the starting material **16** affords $[\alpha]_D$ (abs) +20.3° for **17** [lit.[19] bp 92–94 °C (760 mm); $[\alpha]_D$ −22.95° (EtOH); racemic modificatin lit.[23] bp 92–93 °C (760 mm)].

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.66; H, 12.01.

(−)-(6*S*,9*S*,16*S*,19*S*)-2,3,12,13-Dibenzo-1,4,11,14-tetraoxa-6,9,16,19-dioxocycloeicosa-2,12-diene [(−)-Trans,trans Crown Ether 8]. To a solution of pyrocatechol (2.40 g, 21.8 mmol) in dry THF (250 mL) was added potassium *tert*-butoxide (4.90 g, 43.8 mmol), and the mixture was refluxed for 1 h in a N_2 atmosphere. To the boiling mixture was added a solution of the (+)-ditosylate **15** [$[\alpha]^{22}_D$ +11.1°; 8.00 g (18.2 mmol)] in dry THF (100 mL) dropwise over an 8-h period, and the reaction mixture was refluxed for an additional 48 h. After the reaction mixture was cooled, a precipitated solid was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with CH_2Cl_2. The extract was washed with 10% aqueous KOH and water, dried ($MgSO_4$), and concentrated to give an oily residue, which was chromatographed on neutral alumina. Fractions eluted with benzene–$CHCl_3$ (1/1 v/v) gave 2.10 g of an oily produce whose crystallization from acetone–hexane afforded (−)-**8**: 1.83 g (24% yield); mp 207–209 °C; $[\alpha]^{21}_D$ −21.0° (*c* 0.883, $CHCl_3$); IR (KBr) 3050, 1590, 1500, 1260, 745 cm^{-1}; mass spectrum, *m/e* 412 (M^+).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.67; H, 6.87.

(6*R*,9*S*,16*S*,19*R*)-2,3,12,13-Dibenzo-1,4,11,14-tetraoxa-6,9,16,19-dioxocycloeicosa-2,12-diene (Meso-C_{2h}-cis,cis Crown Ether 11) and (6*S*,9*R*,16*S*,19*R*)-2,3,12,13-Dibenzo-1,4,11,14-tetraoxa-6,9,16,19-dioxocycloeicosa-2,12-diene (Meso-C_{2v}-cis,cis Crown Ether 12). Condensation of the *cis*-ditosylate **20** (8.00 g, 18.2 mmol) with pyrocatechol (2.00 g, 18.2 mmol) was carried out by the same procedure described for the preparation of (−)-**8**. The crude products were chromatographed on neutral alumina, and fractions eluted with benzene–$CHCl_3$ (1/1 v/v) gave 1.14 g (15% yield) of a mixture of **11** and **12** as a glassy solid: IR (KBr) 3050, 1590, 1500, 1260, 745 cm^{-1}; mass spectrum, *m/e* 412 (M^+).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.60; H, 6.80.

***cis*-2,5-Bis[[2-[(2-tetrahydropyranyl)oxy]phenoxy]-methyl]tetrahydrofuran (22).** To a solution of pyrocatechol tetrahydropyranyl ether[24] (5.29 g, 27.2 mmol) in dry THF (110 mL) was added potassium *tert*-butoxide (3.06 g, 27.3 mmol), and then the mixture was refluxed for 2 h. After the mixture was cooled to room temperature, a solution of the *cis*-ditosylate **20** (5.00 g, 11.4 mmol) in dry THF (20 mL) was added to the mixture all at once. The mixture was refluxed for an additional 48 h in an N_2 atmosphere. After filtration of a deposited solid, the filtrate was concentrated to give an oily residue, which was poured into water and extracted with ether. The extract was washed with 5% aqueous NaOH and water and dried ($MgSO_4$). Removal of the solvent gave an oily product which was chromatographed on neutral alumina. Fractions eluted with hexane–benzene (1/1 v/v) afforded 4.99 g (91% yield) of **22**: mp 55–56 °C; IR (KBr) 3070, 2940, 1590, 1495, 1255 cm^{-1}.

Anal. Calcd for $C_{28}H_{36}O_7$: C, 69.40; H, 7.48. Found: C, 69.69; H, 7.37.

This material was used for the next reaction without further purification.

***cis*-2,5-Bis[(2-hydroxyphenoxy)methyl]tetrahydrofuran (23).** A mixture of the *cis*-bis(tetrahydroxypyranyl) derivative **22** (3.31 g, 6.82 mmol), *p*-toluenesulfonic acid (180 mg, 1.04 mmol), and absolute methanol (150 mL) was stirred for 15 h at room tempereature. Cooling of the reaction mixture deposited a solid which was collected on a filter paper, washed with water, and dried over $CaCl_2$ to afford 1.86 g (86% yield) of **23**: mp 57.5–59.5 °C; IR (KBr) 3230, 1590, 1500, 1265, 750 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_5 \cdot H_2O$: C, 64.66; H, 6.63. Found: C, 64.89; H, 6.65.

This material was used for the next reaction without further purification.

(−)-*trans*-2,5-Bis[(2-hydroxyphenoxy)methyl]tetrahydrofuran (25). Condensation of the (+)-*trans*-ditosylate **15** (8.00 g, $[\alpha]^{22}_D$ +11.1°) with pyrocatechol tetrahydropyranyl ether (8.82 g) was carried out by the same procedure as described above. The crude product was chromatographed on neutral alumina, and fractions eluted with hexane–benzene (1/1 v/v) afforded 8.15 g (93% yield) of the bis(tetrahydropyranyl) ether **24** as a colorless oil. By the same procedure as described above, **24** (7.63 g) was converted into (−)-**25**, which was purified by recrystallization from hexane to afford (−)-**25**: 3.13 g (63% yield); mp 88–90 °C; $[\alpha]^{28}_D$ −16.3° (*c* 0.812, $CHCl_3$); IR (KBr) 3350, 1590, 1495, 1265, 750 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.49; H, 6.37.

(−)-(6*S*,9*R*,16*S*,19*S*)-2,3,12,13-Dibenzo-1,4,11,14-tetraoxa-6,9,16,19-dioxocycloeicosa-2,12-diene [(−)-Cis,trans Crown Ether 9]. To a solution of **23** (2.22 g, 7.02 mmol) in dry THF (260 mL) was added potassium *tert*-butoxide (1.58 g, 14.1 mL), and the mixture was refluxed for 2 h. To the boiling mixture was added slowly a solution of the (+)-ditosylate **15** [$[\alpha]^{22}_D$ +11.1°; 2.48 g (5.64 mmol)] in dry THF (110 mL) over a 5-h period, and the mixture was gently refluxed for an additional 48 h in an N_2 atmosphere. After the mixture cooled, a deposited solid was filtered, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2, washed with 10% aqueous KOH and water, and dried ($MgSO_4$). After evaporation of the solvent, the residue was triturated with acetone to give 856 mg (37% yield) of **9**, which was recrystallized from benzene–hexane: mp 156–158 °C; $[\alpha]^{22}_D$ −4.2° (*c* 0.650, $CHCl_3$); IR (KBr) 3060, 1590, 1500, 1260, 745 cm^{-1}; mass spectrum, *m/e* 412 (M^+).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.60; H, 6.89.

(6*R*,9*R*,16*S*,19*S*)-2,3,12,13-Dibenzo-1,4,11,14-tetraoxa-6,9,16,19-dioxocycloeicosa-2,12-diene (Meso-trans,trans Crown Ether 10). Condensation of (−)-**25** (3.00 g; $[\alpha]^{28}_D$ −16.3°) with the (−)-ditosylate **15** (3.35 g; $[\alpha]^{28}_D$ −10.8°) was carried out by following the same procedure as described for the preparation of (−)-**9**. The crude product was triturated with acetone to afford **10** (1.70 g, 43% yield) which was recrystallized from benzene: mp 195–197 °C; $[\alpha]^{22}_D$ 0.00 ± 0.02° (*c* 1.50, $CHCl_3$); IR (KBr) 3070, 1590, 1500, 1260, 740 cm^{-1}; mass spectrum, *m/e* 412 (M^+).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.85; H, 7.06.

Kinetics of Transport. In a cylindrical glass vessel of 38-mm inner diameter was held a glass tube (24-mm inner diameter)

(22) Gagnaire, D.; Monzeglio, P. *Bull Soc. Chim. Fr.* **1965**, 474.
(23) Reynolds, D. D.; Kenyon, W. O *J. Am. Chem. Soc.* **1950**, *72*, 1953.
(24) Parham, W. E.; Anderson, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 4187.

which separated the two aqueous phases. The outer aqueous phase (I) contained specified concentrations of metal picrate in pure water (6 mL), and the inner aqueous phases (II) contained pure water (6 mL). The $CHCl_3$ layer (25 mL) lay below these aqueous phases and bridged them across the separation by way of the central glass tube. The organic layer contained the crown ethers as the carrier and was stirred at a constant speed (60 rpm) with a magnetic stirring bar (30-mm length) at 25 ± 1 °C. Transport of metal picrates was followed by monitoring the absorbance at 357 nm of the aqueous phase (II).

Acknowledgment. This research was partially supported by grant from the Ministry of Education, Japan (454153).

Registry No. 5, 14187-32-7; **6**, 2144-40-3; (+)-**7**, 81370-88-9; (−)-**7**, 81370-89-0; (−)-**8**, 81340-19-4; (−)-**9**, 81370-90-3; **10**, 81370-91-4; **11**, 81370-92-5; **12**, 81370-93-6; (±)-**13**, 81340-20-7; (+)-**13**, 81370-94-7; (+)-**13** (+)-2-(1-aminoethyl)naphthalene, 81370-95-8; (−)-**13**, 81370-96-9; (−)-**13** (+)-2-(1-aminoethyl)naphthalene, 81370-97-0; (±)-**14**, 81340-21-8; (+)-**14**, 81370-98-1; (−)-**14**, 81370-99-2; (+)-**15**, 81371-00-8; (−)-**15**, 81371-01-9; (+)-**16**, 81340-22-9; (+)-**17**, 81422-48-2; **18**, 2240-81-5; **19**, 1472-01-1; **20**, 1472-00-0; **21**, 21645-25-0; **22**, 81340-23-0; **23**, 81340-24-1; **24**, 81371-02-0; (−)-**25**, 81371-03-1; pyrocatechol, 120-80-9.

Synthetic Applications of 2-Cyano-1,2,3,6-tetrahydropyridines. Improved Synthesis of the Fundamental Tetracyclic Framework of Dasycarpidone[1]

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2-Cyano-1,2,3,6-tetrahydropyridines **2b–d**, with a functionalized C-4 substituent, were prepared from the corresponding pyridinium salts by sodium borohydride reduction in the presence of sodium cyanide. Reaction of these 2-cyanotetrahydropyridines with indolylmagnesium iodide afforded 3-(1,2,3,6-tetrahydro-2-pyridyl)indoles **3b–d**. Alternatively, **3c** and **3d** were prepared in excellent yield by condensation of 2-cyanotetrahydropyridines **2c** and **2d** with indole in acetic acid medium. Deethyldasycarpidone was obtained from **3b** in poor or moderate yields by three alternative procedures and from **3c** in a three-step sequence. The preparation of deethyldasycarpidone from 2-cyanotetrahydropyridine **2c** via the (tetrahydropyridyl)indole **3c** constitutes an improved synthesis of this tetracyclic ring system. Similarly, 20-deethyl-4-demethyldasycarpidone was obtained from (tetrahydropyridyl)indole **3d**.

The main synthetic applications of α-amino nitriles are based on their ability to form iminium salts by loss of cyanide ion.[2] Specifically, 2-cyano-1,2,3,6-tetrahydropyridines, easily accessible from the corresponding pyridinium salts,[3] are versatile synthetic intermediates since they constitute masked 2,5-dihydropyridinium salts[3-5] which are able to react with activated aromatic rings such as indole. This property has been applied to the preparation of hexahydroindolo- and hexahydrobenzo[*g*]indolo[2,3-*a*]quinolizines,[6] the alkaloids containing these nuclei deplancheine[7] and dihydrogambirtannine,[8] and 6*H*-pyrido[4,3-*b*]carbazole[9] systems such as ellipticine.[10] Similarly, Husson et al.[11] have shown that 2-cyano-1,2,5,6-tetrahydropyridines are potential 2,3-dihydropyridinium salts from which they synthesized 20-epiuleine[12] and the fundamental tetracyclic framework of the indole alkaloid ervitsine.[13] In addition, 2,5-dihydropyridinium salts resulting from 2-cyano-1,2,3,6-tetrahydropyridines can isomerize in acidic medium to 2,3-dihydropyridinium salts,[3,4] and this behavior has found application to the stereospecific synthesis of β-benzo-[4,14] and β-naphthomorphans.[15,16] On the other hand, 2-cyano-1,2,3,6-tetrahydropyridines, via the corresponding iminium salts, can undergo substitution of the cyano group by Grignard reagents[17] such as benzyl-,[16] thenyl-, or benzo[*b*]thienylmethylmagnesium halides,[19] which constitutes the key step of the most straightforward synthesis of 6,7-benzomorphans[18] and thienomorphans.[19,20]

In previous papers we described the reaction of 2-cyano-1,2,3,6-tetrahydropyridines with the indole Grignard reagent,[19] as well as with the indole lithium or potassium salts,[21] to give 3-(tetrahydro-2-pyridyl)indoles. These systems can be considered as precursors of the characteristic 3-(2-piperidyl)indole moiety[22] common to the most

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