Host–Guest Complexation. 10. Designed Chiral Recognition in Solution between Carboxyl-Containing Macrocyclic Polyethers and an α-Amino Acid[1,2]

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Abstract: Twelve racemic macrocyclic polyethers have been examined for their amenability to optical resolution through differential complexation with L-valine. The hosts were designed to test a model (structure **13**) for chiral recognition in complexation in solution based on complementary placement of binding sites and steric barriers in L-valine and hosts of the *S* configuration. The hosts contained one 1,1′-dinaphthyl chiral unit joined through oxygens in its 2,2′ positions to a polyethylene glycol chain to form macrocycles of the general structure, $\overline{D(OE)_nO}$, in which D is the dinaphthyl and E the CH_2CH_2 unit. In the model envisioned for the complex (**13**), the macrocycle of the host is the central hydrogen bonding site for the NH_3^+ group of valine. Two additional binding sites are provided by two identical side chains, $-CH_2OCH_2CO_2H$, attached at the 3,3′ positions of the 1,1′-dinaphthyl unit. The terminal carboxyl groups are separated by one being located on one side and the other being located on the opposite side of the macroring. One carboxyl group of the host was designed to hydrogen bond with the carboxyl of the valine guest, and the second in its anionic form to contact ion pair with the NH_3^+ group of the valine. In the envisioned diastereomeric complexes between 3,3′-$(HO_2CCH_2OCH_2)_2\overline{DO(EO)_5}$ (**1**) and valine (one of which is **13**), the two chiral elements are adjacent. In the complexes of the L-*S* or D-*R* configurations, the chiral elements are sterically complementary, but in those of the L-*R* or D-*S* configurations they are noncomplementary. This model was tested by distributing racemic **1** and L-valine between two layers composed of CD_3CO_2D–$CDCl_3$–D_2O in proportions that placed essentially all the valine and half the host in the D_2O-rich layer, and the other half of the host in the $CDCl_3$-rich layer. The L-valine complexed the *S* enantiomer of **1**, 2.9 times better than the *R* enantiomer of **1** in the D_2O-rich phase. Through liquid–liquid chromatography, racemic **1** in the mobile phase was resolved by L-valine in the stationary phase into its optically pure enantiomers. By distributing racemic valine and (*S*)-**1** between two layers composed of CD_3CO_2D–$CDCl_3$–D_2O of different proportions than before, essentially all the host remained in the $CDCl_3$-rich layer complexed with an equivalent of valine, and the remaining valine was in the D_2O-rich phase. The factor by which (*S*)-**1** preferred to complex L- over D-valine in the $CDCl_3$-rich phase was 1.5. To determine which structural components of **1** were necessary to its chiral recognition properties, 11 variants of **1** were tested. The requirements for highly structured molecular complexation in solution are discussed.

Biological chemistry includes a description of the state to which naturally occurring organic compounds have evolved. The survival capacity of these organic systems is critically dependent on structural recognition in complexation between organic entities in solution. Much of the direction of molecular traffic in, out of, and within the cell depends on complementary vs. noncomplementary structural relationships between organic entities. Since most biological compounds are asymmetric, chiral recognition is one of the cornerstones of structural recognition in complexation, and, therefore, one of the fundamental features of molecular evolution.

Studies of structural molecular complexes between organic compounds in solution not involving enzymes or genes have centered on the naturally occurring cyclodextrins as host compounds[3a–f] and on catalysis or inhibition of reaction rates through complexation.[3a–h] Most optical resolutions of racemates involve differences in formation rates or in energies of crystal lattices of diastereomers.[3m–o,s,t,z] Others involve solid–liquid[3n–r,v] or gas–liquid chromatography[3n–r,v] or dialysis.[3w] Distributions of the enantiomers of a racemate between water and optically active liquids[3u,x] gave a maximum optical purity of 2 ± 0.9%.[3u] A complete optical resolution by countercurrent extraction has appeared.[3y]

This series of papers describes the design and synthesis of organic host compounds that contain convergent binding sites arranged to contact divergent binding sites of selected guest compounds.[4] Binding sites thus far incorporated into hosts include ether oxygens,[4] thioethers,[4h] carboxyls,[4e,h,i] esters,[4e,h,i] alcohols,[4d,i] amides,[4i] tertiary amines,[4h,i] furan and tetrahydrofuran oxygens,[4b,g] pyridyl nitrogens,[4c,g] aromatic π bases,[4e] phenolic hydroxyls,[5a] methoxyl oxygens,[5a] and β-diketone groups.[5b,c] Hydrocarbon units that extend rigidly in three dimensions have been incorporated into host compounds to provide them with shape in the form of steric or chiral barriers. The diphenyl,[4g] dinaphthyl,[4g,h,i] ditetralyl,[4h] and [2.2]paracyclophanyl units[4f] have thus far been employed. Different individual binding forces holding host to guest that have been identified thus far include $ArN_2^+\cdots O(CH_2)_2$,[4a] $(NH_2)_2C{=}NH^+\cdots O(CH_2)_2$,[4a] $RNH_3^+\cdots N(\text{pyridyl})$,[4c] $RNH_3^+\cdots O(CH_2)_2$,[4a] $RNH_3^+\cdots \overline{O}_2C$,[4d] $RN^+\cdots O(CH_2)_2$,[4a] $RN^+\cdots \overline{O}_2CR$,[2b] $RN^+\cdots O{=}C(OCH_3)R$,[4d] $RN^+\cdots\pi\text{-Ar}$,[4d] $ROH\cdots O(CH_2)_2$,[4i] $ArOH\cdots O(CH_2)_2$,[5d] $RNH_3^+\cdots O(CH_3)Ar$,[5a] $M^+\cdots O(CH_2)_2$,[5a–c] $M^+\cdots \overline{O}_2C$,[4d,i] $M^+\cdots\pi\text{-Ar}$,[4d] $M^+\cdots O(CH_3)Ar$,[5a] and $M^+\cdots \overline{O}C{=}C$-.[5b,c]

Several criteria have been used for complex formation and for the structures of the complexes between organic hosts and guests. These include crystallization[4c,d,h,5d] and determination of the crystal structure of complexes,[6] ^1H NMR chemical shift comparisons between components and complexes,[4d,e,f,5e,h] lipophilization by complexing of polar guests by nonpolar hosts in nonpolar media,[2,4a–f,i,5d,e] and determination of association constants as a function of systematic structure changes in hosts and guests.[4a–e,5f]

One of the most appealing criteria for the structures of complexes in solution makes use of *thermodynamic chiral recognition.* Two enantiomers of a guest racemate are put in competition with one another for complexing one enantiomer of a host or, conversely, two enantiomers of a host racemate are put in competition with one another for complexing one enantiomer of a guest. The extent to which one diastereomer dominates over the other at equilibrium measures the *degree* of chiral recognition. The *direction* of the stereochemical bias in chiral recognition is given by the relative configurations of the host and guest in the more stable diastereomeric complex.[2b,5e,g,h] Comparisons between observation and expectation of the directions of the bias and the degrees of chiral recognition as a function of systematically changed structures of hosts and guests provides a practical means of identifying structural

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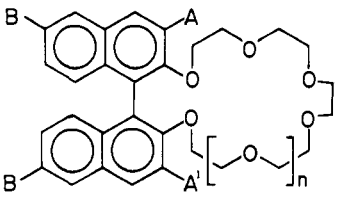
parameters responsible for stereochemical selection in complexation.[5g]

In our initial studies, the α-amino acids or their derivatives have been selected as guests for several reasons. (1) They are important enzyme substrates. (2) They possess highly polar binding sites that diverge from their chiral centers. (3) They provide a chiral series of structurally related available compounds whose absolute configurations, maximum rotations, and optical stabilities are known.

The host design was primarily based on the convergent placement of binding sites and chiral steric barriers in positions to complement their divergent counterparts in the α-amino acid guests. Possible host-guest structural relationships were visualized through examination of Corey-Pauling-Koltun (CPK) molecular models of potential complexes of the α-amino acids. Criteria applied to specific host selection were as follows. (1) The hosts had to contain binding sites for the NH_3^+ and CO_2H (or CO_2^-) groups of the α-amino acids. (2) Their chiral steric barriers had to be located in the envisioned complex close to the asymmetric center of the α-amino acid, and one complex in the molecular models had to appear more stable sterically than its diastereomeric alternative. (3) The hosts had to be amenable to systematic structural changes to establish the roles played in chiral recognition by the various molecular parts. (4) The hosts had to undergo a minimum amount of reorganization during complexation. (5) The parent hosts had to have C_2 axes so that the same complex was formed when the guest was complexed on either face of the macroring. (6) The host structures had to be as simple as possible. (7) The hosts had to possess a balance between hydrophilic and lipophilic properties that allowed them to be distributed between polar and nonpolar liquid phases. (8) The hosts had to be synthesizable on a scale large enough to produce workable quantities of compounds.

This paper describes the chiral recognition game played mainly in the "guest distinguishes between hosts" direction. Valine was selected as a standard guest because its isopropyl group has a moderately large steric requirement, because it possesses the desired hydrophilic-lipophilic balance, and because both enantiomers can be purchased.

The first section of the paper describes the model for the complexes on which the host selection was based. The second section deals with the test system used to measure the degree and direction of configurational bias in chiral recognition. The third section illustrates an application of chiral recognition in complexation to the total resolution of a racemic host. In the fourth section, the structural parts of the parent host required for chiral recognition are identified. The fifth section describes the results of a survey of other potential hosts.

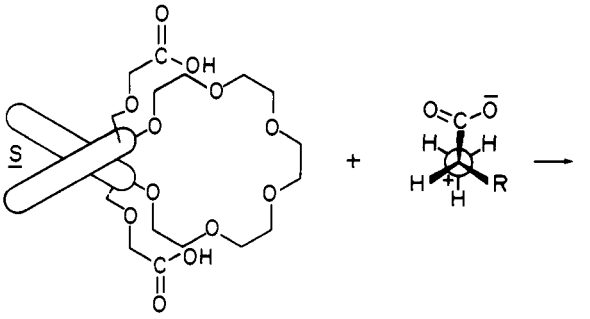


	n	A	A'	B
1	1	$CH_2OCH_2CO_2H$	$CH_2OCH_2CO_2H$	H
2	1	$CH_2OCH_2CO_2CH_3$	$CH_2OCH_2CO_2CH_3$	H
3	1	H	$CH_2OCH_2CO_2H$	H
4	1	CH_3	$CH_2OCH_2CO_2H$	H
5	1	H	H	$CH_2OCH_2CO_2H$
6	0	$CH_2OCH_2CO_2H$	$CH_2OCH_2CO_2H$	H
7	2	$CH_2OCH_2CO_2H$	$CH_2OCH_2CO_2H$	H
8	1	$CH_2SCH_2CO_2H$	$CH_2SCH_2CO_2H$	H
9	1	$CH_2SCH_2CH_2CO_2H$	$CH_2SCH_2CH_2CO_2H$	H
10	1	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	H
11	1	CH_2OH	CH_2OH	H
12	1	CH_2OH	$CH_2OCH_2CO_2H$	H

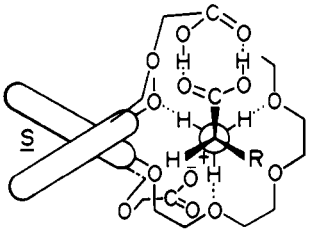
Results and Discussion

Model for Complexes on Which Host Selection Was Based. The hosts selected and synthesized for this study possess structures **1–12**. Their syntheses, maximum rotations, absolution configurations, and optical stabilities have been reported[4g,i] (compounds **3–5** were only prepared as racemates). These potential hosts all contain the chiral, optically stable 1,1′-dinaphthyl element attached at its 2,2′ positions through oxygens to a polyethylene glycol chain to form a macrocyclic ring. The cyclic ether oxygens are evenly spaced throughout the ring, which in their more stable gauche conformations[7] provide a hole on whose center the oxygen's electron pairs roughly converge. In CPK models, the two naphthalenes occupy planes roughly perpendicular to the best plane of the macroring, one protruding from one face tangent to the macroring, and the other from the other face tangent to the macroring. Substituents attached to the 3,3′ positions of the naphthalenes extend into the space on the two faces of the macroring, and are separated from one another by the macroring.

In CPK molecular models, parent host **1** of the *S* configuration appeared capable of complexing L-valine in a complementary way to give complex **13**. This structure is formed by



(S)-1 L-Amino acid



(S)(L)-13 complex

a proton transfer from the diacid host to the zwitterionic guest, and by hydrogen bonding and ion pairing of the resulting salt. In **13**, the six-oxygen macroring neatly hydrogen bonds the NH_3^+ group in a tripod arrangement, which places the axis of the C*-N bond parallel to the plane of the naphthalene ring and perpendicular to the best plane of the macroring. In this arrangement, the chiral center of valine, with its substituents, protrudes from one face of the macroring in close proximity to the naphthalene wall protruding from that face. Since (*S*)-**1** contains a C_2 axis, complexation from either face produces the same complex. The carboxylate ion formed by the proton transfer from host to guest acts as a counterion for the NH_3^+ group of the guest, and is centered below the central hole in contact with N^+. The arm carrying the carboxylate is of the right length and possesses low energy conformations which would permit the contact ion pair to form. The other arm of

Table I. Enantiomer Distribution Constant (EDC) Estimates in the $CDCl_3$-Rich Layer in the Partitioning of an Equivalent of Racemic Host (H) and Optically Pure L-Valine as Guest (G) and Their Complexes between Two Liquid Phases Composed from RCO_2D(H), $CDCl_3$, and D_2O

Run no.	Host Compd	Host Amt, mg[a]	Solvents, mL CD_3CO_2D	$CDCl_3$	D_2O	T, °C	Concn ratios at equilibrium[b] D_2O layer, [H]/[G]	$CDCl_3$ layer, [G]/[H]	Host in D_2O layer[c] %	Con-fign	Opt purity, %	CRF[d]	EDC[d]
1	**1**	66.4	0.60	0.30	0.20	24	0.5	<0.05	50	*S*	27	1.7	2.9
2	**1**	76.4	0.50	0.20	0.10	0	0.5	<0.10	45	*S*	8.5	1.18	1.4
3	**1**	70.4	0.55[e]	0.40	0.075	24	0.5	<0.10	50	*S*	16	1.38	1.9
4	**1**	76.4	0.40[e]	0.20	0.05	0	0.45	<0.10	52	*S*	27	1.7	2.9
5	**1**	76.4	0.35	1.00[f]	0.25	24	0.50	<0.10	50	*S*	8.3	1.25	1.6
6	**2**	98.0	0.60	0.20	0.15	24	0.55	0.20	64	*S*	3	1.06	1.1
7	**3**	76.0	0.65	0.20	0.19	24	0.40	<0.10	60		*g*	*g*	~1.0
8	**4**	80.0	0.60	0.24	0.21	24	0.50	0.26	42		*g*	*g*	~1.0
9	**5**	66.4	0.60	0.30	0.30	24	0.40	<0.10	39		*g*	*g*	~1.0
10	7	90.0	0.50	0.30	0.25	24	0.42	0.30	25	*S*	1.2	1.02	1.0
11	8	98.0	0.40[e]	0.30	0.14	24	0.50	0.30	38	*S*	12	1.27	1.7
12	**9**	80.0	0.60	0.24	0.22	24	0.55	0.31	64	*S*	4	1.08	1.1
13	**10**	72.0	0.60	0.20	0.28	24	0.60	<0.10	60	*S*	4	1.08	1.2
14	**11**	80.0	0.40	0.20	0.15	24	0.38	0.38	38	*S*	6.5	1.14	1.2
15	**12**	78.0	0.50	0.25	0.20	24	0.50	0.20	50	*S*	7	1.15	1.3

[a] Amount used in run. [b] Determined by ^1H NMR integrations. [c] Host was isolated and weighed and rotation taken. Percent is based on total isolated material from both layers = 100%. [d] Calculated from optical purity and eq 2. [e] HCO_2H used in place of CD_3CO_2D. [f] Benzene used in place of $CDCl_3$. [g] Rotation essentially zero at several wavelengths; optically pure materials rotation is unknown, but all structural relatives of **3**–**5** exhibit substantial rotations.

the host is of about the right length and possesses conformations amenable to placement of its carboxyl group in a position to hydrogen bond the carboxyl group of the protonated valine, and to thus restrict the rotation about the C*–N bond of the amino acid. This restriction fixes the positions of the H and R groups attached to C*. In the L-*S* diastereomer formulated (**13**), the H is directed much more toward the naphthalene wall than is the R group, which is directed away from the barrier. In the competing L-*R* diastereomer, the more bulky R group occupies the more hindered and the H the less hindered position.

Hosts **2** to **7** are structural modifications of **1** in which selected molecular parts of **1** are omitted, modified, or moved. A comparison of the chiral recognition exhibited by L-valine toward the enantiomers of **1** as compared with the enantiomers of **2** to **7** should identify those molecular parts responsible and necessary for the anticipated chiral recognition of the enantiomers of **1**. Hosts **8**–**12** are structured modifications of **1** which involve less drastic changes, being limited to the side chains attached to the 3,3′ positions of the dinaphthyl unit. These hosts were examined to see if shortening or lengthening the arms of the host would provide better or poorer chiral recognition than was observed for parent host **1**. It was hoped that the results would indicate roughly how useful CPK molecular model building of potential complexes is as a tool for designing complementary host-guest relationships.

Degree and Direction of Configurational Bias in Chiral Recognition. The degree of chiral recognition of a racemic host by optically pure L-valine was determined by distributing equivalent amounts of host and guest between two liquid phases composed of CD_3CO_2D (or HCO_2H), $CDCl_3$, and D_2O. The relative amounts of the three solvent components were adjusted to minimize the amounts of valine in the $CDCl_3$-rich layers, and to locate 36–64% of the host used in each layer at equilibrium. The relative amounts of host and guest in each layer were estimated (±5%) by ^1H NMR spectral integrations of appropriate bands. The ^1H NMR spectra of those layers containing substantial amounts of both hosts and guest gave chemical shifts of protons of both hosts and guest which indicated that complexation had occurred. The layers were separated, host was isolated from each layer, and its optical purity and sign of rotation determined. Table I records the results.

The direction of the configurational bias in chiral recognition in the D_2O-rich layer is given by the correlations of signs of rotation and absolute configurations of hosts[4i] and valine.[8] The degree of chiral recognition in the D_2O-rich phase where most of the complexation occurred was estimated as follows.

Equations 1 and 2 involve the following definitions: H_A is the more and H_B the less complexed (solubilized) host enantiomer in the D_2O-rich layer, leaving more H_B in the $CDCl_3$-rich layer; $[H_A]_{D_2O}$, $[H_A]_{CDCl_3}$, $[H_B]_{D_2O}$, and $[H_B]_{CDCl_3}$ are the concentrations at equilibrium of the enantiomeric hosts in the two phases; K_A and K_B are the distribution constants between the two phases of enantiomers A and B; CRF is the chiral recognition factor, in this case applicable to the D_2O-rich phase; EDC is the enantiomer distribution constant, in this case for the host between the two phases. Equations 1 and 2 relate these parameters.

$$K_A = [H_A]_{D_2O}/[H_A]_{CDCl_3} \quad K_B = [H_B]_{D_2O}/[H_B]_{CDCl_3}$$
$$\text{CRF} = [H_A]_{D_2O}/[H_B]_{D_2O} \quad (1)$$

$$\text{EDC} = K_A/K_B = \text{CRF} \cdot [H_B]_{CDCl_3}/[H_A]_{CDCl_3} \quad (2)$$

Under ideal conditions, no valine would be drawn into the $CDCl_3$-rich phase by complexation with host, and this lipophilic layer would be used only to store uncomplexed host. This condition was approached with hosts **1**, **3**, **5**, and **10**, and small deviations were observed with **2** and **12** (see [G]/[H] values in Table I). Serious deviations were found with the most lipophilic hosts, **4**, **7**, **8**, **9**, and **11**, where 0.26 to 0.38 of the host in the $CDCl_3$-rich phase was complexed with valine. Chiral recognition undoubtedly occurred to some extent in both layers when both partners of the complex were present, and probably with a configurational bias in the same direction in each phase (see below). To the extent that chiral recognition occurs in both layers in the same direction, the EDC values calculated with eq 2 would be lowered. Thus the EDC values of Table I are the most reliable measures of the potential complementary binding of host to guest when the $CDCl_3$-rich layers contain the least amounts of valine.

In a second type of experiment, optically pure host (*S*)-**1**[4i] and racemic valine (2.5 equiv) were distributed between the two phases formed from 1.0 mL of CD_3CO_2D, 1.5 mL of $CDCl_3$, and 0.5 mL of D_2O. At equilibrium at 24 °C the

aqueous phase contained ~1% total host (^{1}H NMR), and the $CDCl_3$-rich phase contained 99% host complexed with 1 mol equiv of valine, the remainder of the valine being in the D_2O-rich phase. The valine isolated from the organic phase was 12.5% optically pure in the L isomer, which gave a CRF_{CDCl_3} of 1.28 and an EDC of 1.5. Thus chiral recognition occurs with the same configurational bias in both the D_2O-rich and $CDCl_3$-rich media with host **1**.

Total Resolution of Host by Liquid–Liquid Chromatography. Not only did L-valine show the highest chiral recognition toward host **1** (two $CH_2OCH_2CO_2H$ arms) of those examined, but **1** drew the least amount of valine into the $CDCl_3$-rich layer (Table I, runs 1–5). Accordingly, L-valine was used to totally resolve racemic **1** by liquid–liquid chromatography. The stationary phase was composed of L-valine dissolved in a mixture of 4:1 (by volume) acetic acid saturated with benzene absorbed on diatomaceous earth. The mobile phase initially was composed of 1.0 g of racemic **1** dissolved in the same medium. The column was developed with benzene saturated with 4:1 (by volume) acetic acid–water. As anticipated, (*R*)-**1** eluted first, followed by (*S*)-**1** which had been complexed the more strongly. Appropriate fractions of each enantiomer that eluted from the column were combined to give (*R*)-**1** and (*S*)-**1** of ~90% optical purities. The former was rechromatographed on a D-valine chromatograph column to give 220 mg of optically pure (*R*)-**1**, $[\alpha]_{546}^{25}$ −76.5° (*c* 1.0, $CHCl_3$). The impure (*S*)-**1** was rechromatographed on an L-valine column to give optically pure (*S*)-**1**, $[\alpha]_{546}^{25}$ +76.5° (*c* 1.0, $CHCl_3$). A sample of (*S*)-**1** synthesized from starting materials of maximum rotation gave $[\alpha]_{546}^{25}$ +75.6° (*c* 1.0, $CHCl_3$).[4i] The initial fractions from each column contained valine eluted as complex. These fractions were discarded, accounting for much of the host used which was not obtained in an optically pure state. This experiment demonstrates that total resolution of hosts by guests can be accomplished by this multiplate technique, which is undoubtedly subject to considerable refinement.

Structural Parts of Host 1 That Are Required for Chiral Recognition. The results of runs 1–10 of Table I make it possible to identify what structural features of the hosts are required for complexation and for chiral recognition by L-valine. Host **1**, designed specifically so that its *S* enantiomer would have a complementary structural relationship with L-valine, provided the most satisfactory results. In runs 1–5, L-valine complexed (*S*)-**1** in the D_2O-rich layer better than (*R*)-**1** by factors that ranged from 2.9 to 1.4, depending on the temperature and solvent. Interestingly, the EDC values show opposite temperature dependencies when formic acid was substituted for CD_3CO_2D as a solvent component. Thus with CD_3CO_2D, the EDC dropped from 2.9 to 1.4 when the temperature was lowered from 24 to 0 °C, but, with HCO_2H, the EDC increased from 1.9 at 24 °C to 2.9 at 0 °C (runs 1–4). Host and guest must be hydrogen bonded to the solvent acids, and apparently the amount of solvent liberated upon complexation depends both on the configurational relationships and which solvent acid is employed. Substitution of the $CDCl_3$ of run 1 by benzene in run 5 dropped the EDC value from 2.9 to 1.6. Thus, even the character of the minor solvent component in the D_2O-rich phase plays a role in determining the relative free energies of the diastereomeric complexes. All of the runs made with the other hosts were conducted at 24 °C and with the CD_3CO_2D–$CDCl_3$–D_2O solvent combination except run 11, in which HCO_2H was substituted for CD_3CO_2D.

Host **1** contains two $CH_2OCH_2CO_2H$ arms attached at the 3,3′ positions, whereas, in **2**, the two arms are composed of $CH_2OCH_2CO_2CH_3$ groups. This change decreased the EDC from 2.9 of run 1 to ~1.1 in run 6. In host **3**, one of the $CH_2OCH_2CO_2H$ arms of **1** was omitted, and again chiral recognition essentially disappeared (run 7). In host **4**, one of the two $CH_2OCH_2CO_2H$ arms of **1** was replaced by a methyl group, and again chiral recognition disappeared (run 8). In host **5**, the two $CH_2OCH_2CO_2H$ arms of **1** were moved from their convergent 2,2′ positions to the divergent 6,6′ positions where they could not interact with complexed valine. As a result, chiral recognition completely disappeared (run 9). In host **6**, the macroring of **1** which contains six ether oxygens was decreased by one ethyleneoxy unit to a ring containing only five ether oxygens. As a result, host **6** failed to complex valine well enough to allow the host to be distributed in the D_2O-rich layer, and the EDC could not be determined. In host **7**, the macroring of **1** was expanded by one ethyleneoxy unit to give a macroring containing seven ether oxygens. As a result, although complexation occurred, essentially no chiral recognition was observed (run 10). This result suggests that the three alternate oxygens most remote from the chiral barrier of **7** (which are more basic than the aryloxy oxygens) are involved in the complex of **7** with valine. In CPK molecular models of valine and **7**, use of the remote oxygens places the chiral elements of host and guest distant enough from one another to not interact sterically.

These results show that the structural features of **1** necessary to chiral recognition in complexation by L-valine are as follows. (1) The macrocycle must contain six ether oxygens to bind the NH_3^+ group in a tripodal arrangement placing the chiral elements of host and guest close enough to one another to interact sterically. (2) Both carboxyl-terminated arms placed in the 3,3′ positions of the host are required, which shows both are involved in the binding and in the structuring of the complex. These necessary structural features make the L-*S* or D-*R* diastereomeric complexes more stable than the L-*R* or D-*S* complexes. This stability–configuration relationship is maintained in three media in which L-valine distinguishes between *S* and *R* host, and in a fourth medium in which *S* host distinguishes between D- and L-valine. Although the degree of chiral recognition differs with changes in medium and temperature, the stability–configuration relationship appears to be a property intrinsic to host–guest structure. Structure **13** for the more stable diastereomeric complex was arrived at by CPK molecular model examination in advance of experiment. It provides a qualitative explanation for the above results.

The EDC parameter of eq 2 is the ratio of two equilibrium constants (K_A/K_B) for the distribution of two enantiomers between two phases. Under ideal conditions, $K_A/K_B = (K_a)_A/(K_a)_B$, where $(K_a)_A$ is the association constant for host A with guest G to form complex $H_A{\cdot}G$, and $(K_a)_B$ is the association constant for host B with guest G in the D_2O-rich phase to form $H_B{\cdot}G$ (see eq 3 and 4). This relationship would apply to the D_2O-rich layer should the following conditions be fulfilled at equilibrium: (1) Guest was distributed solely in the D_2O-rich layer so that host–guest complexation could occur only in that layer. (2) The diastereomeric complexes formed in the D_2O-rich layer were both 1:1. (3) Essentially all of the host in the D_2O-rich layer was complexed. (4) The enantiomeric hosts distributed in the $CDCl_3$-rich layer were not associated, or, if associated, the free energies of association of configurationally like and unlike host were identical. Should these conditions be fulfilled, then the difference in free energies of the diastereomeric complexes in the D_2O-rich layer would be given by eq 5.

$$H_A + G \underset{CHCl_3}{\overset{(K_a)^A}{\rightleftharpoons}} H_A \cdot G \qquad (3)$$

$$H_B + G \underset{CHCl_3}{\overset{(K_a)_B}{\rightleftharpoons}} H_B \cdot G \qquad (4)$$

$$\Delta(\Delta G^\circ) = RT \ln \text{EDC} \qquad (5)$$

In runs 1–5, these conditions were not fulfilled but probably were approached. Application of eq 3 to the results of run 1 provides a difference in free energy between the diastereomeric

complexes of only 630 cal/mol, with the L-*S* diastereomer (**13**) being the more stable. The structure of the D-*S* diastereomer of **13** (the enantiomer of the L-*R* diastereomer) related to **13** is arrived at simply by exchanging in **13** the positions of the H and $(CH_3)_2CH$ groups attached to the chiral center of the valine part of the complex. In CPK molecular models, this diastereomer would appear to be less stable by a much greater amount than 630 cal/mol.

A plausible explanation is as follows. Complexation to form **13** involves a proton transfer from host to guest, which requires that their pK_as be properly related. The pK_a of protonated valine in water is ~2.3, and that of $CH_3OCH_2CO_2H$ (a model for **1**) is ~3.5.[9] Thus formation of **13** requires 0.7 kcal/mol of stabilizing free energy to be supplied by hydrogen bonding and ion pairing in the complex to provide for the "wrong way" proton transfer to form **13**. This stabilization energy is probably available in the sterically unhindered diastereomer **13**, but not in the competing diastereomer. Possibly L-valine, as a zwitterion, complexes (*R*)-**1** to form a much less structured complex than **13**, but one whose free energy is not far from that of **13** because the host to guest proton transfer was not required for its formation. If this explanation is correct, much higher EDC values would be observed if one of the arms of **1** was changed to a $CH_2PO_3H_2$ group.

Effect on Chiral Recognition of Varying the Character of the Arms of the Hosts. Runs 11–15 of Table I report the EDC values observed when small changes were made in the arms of host **1**. In **8**, two sulfur atoms replaced the two ether oxygens of the side chains of host **1**. Molecular models (CPK) of the dithia analogue of complex **13** are sterically similar to **13** itself. In run 11, an EDC value of 1.7 was obtained, in spite of the fact that, in the $CDCl_3$-rich layer, [G]/[H] = 0.30. Since formic acid had to be used in place of CD_3CO_2D to give even this good a distribution of components, the results of this run should be compared with that of run 2, in which host **1** and formic acids were used. Run 2 gave an EDC value of 1.4. Thus L-valine exhibits higher chiral recognition for the enantiomers of **8** than for those of **1** in the D_2O-rich layer. For **8** as for **1**, the L-*S*-diastereomeric complex is the more stable, as predicted by model examination. Host **8** was much better at lipophilizing valine than **1**, and the apparent EDC of 1.7 for host **8** probably represents the factor by which chiral recognition in the D_2O-rich layer dominated over that in the $CDCl_3$-rich layer.

Host **9** contains two $CH_2SCH_2CH_2CO_2H$ arms. In run 12 (with the usual CD_3CO_2D as one solvent component) **9** produced an EDC of only 1.1. However, [G]/[H] = 0.31 in the $CDCl_3$-rich layer, and L-valine may have competitively complexed *S* host in both layers. This result is inconclusive.

Host **10** contains two $CH_2CH_2CO_2H$ side chains in the 3,3′ positions. In run 13, **10** gave an EDC of only 1.2, in spite of the fact that little valine was drawn into the $CDCl_3$-rich layer. The shortness of the arms, the poor CH_2CH_2 conformations in the arms of the complex and the lower acidity of **10** compared with those of **1** all probably contribute to the virtual inability of L-valine to distinguish between the enantiomers of **10**.

Host **11** with two CH_2OH groups in its 3,3′ positions proved to draw as much L-valine into the $CDCl_3$-rich layer as L-valine drew **11** into the D_2O-rich layer. The apparent EDC of 1.2 only indicates that the extent of chiral recognition in the D_2O-rich layer was slightly higher than that in the $CDCl_3$-rich layer. Since **11** does not contain a carboxyl group, complexation of the zwitterionic form of L-valine must have occurred. The guest's carboxylate anion in the L-*S* complex is in a slightly better position to hydrogen bond the CH_2OH group of the host than in the L-*R* complex (CPK models).

Host **12** contains one $CH_2OCH_2CO_2H$ and one CH_2OH group substituted in its 3,3′ positions. In run 15 with **12** as racemic host, an EDC value of only 1.3 was observed, in spite of the fact that [G]/[H] = 0.20 in the $CDCl_3$-rich layer.

These results demonstrate that the highest chiral recognition obtained thus far involves hosts with two arms of either the $CH_2OCH_2CO_2H$ or $CH_2SCH_2CO_2H$ varieties. These arms probably provide the best pK_a relationships, the best chain lengths, and the best conformations for highly structured complexation. Interestingly, to the extent information is available, higher chiral recognition was observed in the more polar phase. Whenever chiral recognition in either phase was observed, the predicted L-*S*-diastereomeric complex was the more stable.

Examination of CPK molecular models in advance of experiment led to the design of a host of specialized structure **1** which exhibited the expected configurational bias in chiral recognition. This fact indicates that these models have potential predictive value. All the molecular parts initially envisioned as necessary to chiral recognition were found to be required. The results support structure **13** or a very similar structure as the main component in the mixture of complexes formed between L-valine and (*S*)-**1**. what the models do not do is to allow the structure of the less stable complex to be predicted. Thus any guess based on models as to free energy differences between diastereoisomeric complexes is tenuous. The degree of chiral recognition in complexation depends on the sum of a large number of small effects, some of which stabilize one diastereomer and some the other. What is observed is a net configurational bias which ultimately is attributable to lower steric repulsions between chiral elements in one diastereomer than in the other. The diastereomer with the less complementary steric relationships will make use of many small conformational adjustments to minimize its free energy, and undo the steric repulsions envisioned in the design of its structure. The fewer the number of adjustable conformational parameters available in host and guest, and the more negative the free energy of complexation for the more stable diastereomer, the greater the EDC values are likely to be.

The medium obviously plays a major role in determining EDC values, but probably not the direction of the chiral bias. The solvent has to be greatly reorganized during the complexation process. Large energies are exchanged when host and guest shed solvent to embrace one another. These exchange energies provide to the diastereomer with the less complementary steric relationships additional opportunities to minimize its free energy by adopting structures which involve the solvent in ways different from that of the diastereomer with the more complementary relationships. In other words, host-guest design is very complicated.

Experimental Section

General. All temperatures are Celsius. All ^1H NMR measurements were made on a Varian HA-100 spectrometer. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter in a 1-dm thermostated cell. Most of compounds **1–12** have been reported in paper 9 of this series both as racemates and as enantiomers of maximum rotation except **3–5**, whose racemates only were reported.[4i]

Distribution Experiments between Two Liquid Phases of Racemic Host and Optically Pure L-Valine. The procedure used for host compounds **1–12** is illustrated by run 1 (Table 1). Racemic **1**, 2,3,4,5-di-1,2-[3-(2,5-dioxa-4-oxopentyl)naphtho]-1,6,9,12,15,18-hexaoxocycloeicosa-2,4-diene (66.4 mg or 0.10 mmol) was dissolved in 0.60 mL of CD_3CO_2D in an NMR tube, and 1 mol equiv was added of L-valine (11.7 mg, 0.10 mmol) of rotation $[\alpha]^{25}_{546}$ +32.2° (*c* 2.5, 1 N HCl in H_2O).[8] The ^1H NMR spectrum of the resulting solution was substantially different from the spectrum of the individual components superimposed on one another. Specifically, the $ArCH_2O$ produced a singlet in uncomplexed **1**, but split into an AB quartet upon complexation, and the $ArOCH_2$ and $(CH_3)_2CH$ all underwent changes in their chemical shifts upon complexation. Deuteriochloroform (0.30 mL, ethanol-free) was added and then D_2O. The mixture was shaken at ~24 °C to give two phases. The amounts of D_2O and $CDCl_3$ were systematically varied until the host was distributed approximately equally in the two phases. The ^1H NMR spectral inte-

grations of several bands in each phase were used to determine what amounts of each solvent component gave this distribution. In run 1, 0.60 mL of CD_3CO_2D, 0.30 mL of $CDCl_3$, and 0.20 mL of D_2O were used. The amounts used in the other runs are recorded in Table I. At equilibrium, the D_2O-rich layer (~0.75 mL) contained ~95% valine and ~50% **1** used, whereas the $CDCl_3$-rich layer (~0.25 mL) contained ~5% valine and ~50% **1** used (^1H NMR integrations of both layers). Appropriate ^1H NMR comparisons[5h] indicated that **1** in the D_2O-rich layer and valine in the $CDCl_3$-rich layer were complexed, and that complexation-decomplexation was fast on the ^1H NMR time scale. The layers were separated (the meniscus being discarded) and evaporated under vacuum at 25 °C. The remaining residues were each dissolved in 10 mL of 0.1 M aqueous HCl. Each of the resulting solutions was extracted with two 10-mL portions of $CHCl_3$, and the appropriately combined $CHCl_3$ extracts were washed with 5 mL of 0.1 M HCl in water, dried with $MgSO_4$, and evaporated under vacuum at <30 °C. The residues were dried at 30 °C and 50 μ for 3 h as films to give samples of **1**·0.5H_2O. A 40-mg sample of optically pure (*S*)-**1**[4i] was submitted to the same procedure omitting the valine to give recovered (*S*)-**1**·0.5H_2O (32 mg), $[\alpha]^{25}_{546}$ −24.6° (*c* 1.0, THF). The residue isolated from the original D_2O-rich phase gave 26 mg of host (40%), $[\alpha]^{25}_{546}$ −6.7° (*c* 1.0, THF), 27% optically pure in (*S*)-**1**·0.5H_2O. The residue isolated from the original $CDCl_3$-rich phase was 26 mg (40%), $[\alpha]^{25}_{546}$ +6.7° (*c* 1.0, THF), of 27% optically pure (*R*)-**1**·0.5H_2O. Thus the ratio of [(*S*)-**1**/(*R*)-**1**] in the D_2O-rich phase was 63%/37% = 1.7 = CRF_{D_2O}, the ratio of [(*R*)-**1**/(*S*)-**1**] in the $CDCl_3$-rich phase was 63%/37% = 1.7, and the EDC = 1.7 × 1.7 = 2.9. The rotation of (*S*)-**1** obtained by synthesis from optically pure starting materials is $[\alpha]^{25}_{546}$ +75.6° (*c* 1.0, $CHCl_3$) and $[\alpha]^{25}_{546}$ −24.9° (*c* 1.0, THF). Since traces of water were difficult to remove from **1** (24 h, 30 °C, and <50 μ as a foam), and since the magnitudes of rotation of samples of **1** were sensitive to the amount of water when taken in $CHCl_3$ but not in THF, the rotations were taken in THF unless the samples were thoroughly dried as foams at 30 °C and >50 μ for 24 h.

Table I records for runs 1-12 the amounts and kinds of hosts, the amounts and kinds of solvents, the temperatures, the ratios of the concentrations of hosts and guest in the D_2O-rich and $CDCl_3$-rich layers at equilibrium, the percents of hosts initially used that were isolated from the D_2O-rich layers, and their configurations, percent optical purities, and CRF and EDC values. Rotations taken in $CHCl_3$ involved samples of foams dried at 30 °C and <50 μ for 24 h, and those taken in THF, at 30 °C and <50 μ for 3 h. Rotations of samples and drying procedures for the various hosts recovered from the partitioning experiments were always taken under the same conditions used for the optically pure reference samples. Care was taken not to optically fractionate the hosts in any way during their isolation. About 80-90% of the total host used was accounted for in isolated material.

Run 15 further exemplifies the method. The layers formed from 78 mg (0.128 mmol) of **12**, 0.50 mL of CD_3CO_2D, 0.25 mL of $CDCl_3$, 0.20 mL of D_2O, and 15 mg (0.128 mmol) of optically pure L-valine, after being shaken for 1 min at 24 °C, were separated, and the relative amounts of valine and **12** were estimated for the $CDCl_3$-rich layer by ^1H NMR spectral integrations as follows. The areas under the peaks are in arbitrary units: calculated for [G]/[H] = 0.20, 30 ($ArCH_2$), 15 ($ArCH_2OCH_2$), 155 (rest of aliphatic H's of host), 2 ($CH(CH_3)_2$), 9 ($CH(CH_3)_2$); found, 30 ($ArCH_2$), 15 ($ArCH_2OCH_2$), 152 (rest of aliphatic H's of host), 2 ($CH(CH_3)_2$), 12 ($CH(CH_3)_2$). The relative amounts of valine and **12** estimated in the D_2O-rich layer gave spectral integrations as follows: calculated for [H]/[G] = 0.50, 70 (ArH), 196 (host-aliphatic H's plus CHN), 14 ($CH(CH_3)_2$), 84 ($CH(CH_3)_2$); found, 70 (ArH), 195 (host-aliphatic H's plus CHN), 13 ($CH(CH_3)_2$), 90 ($CH(CH_3)_2$).

From the D_2O-rich layer after drying at 30 °C and >50 μ for 24 h was isolated 31 mg of **12**, $[\alpha]^{25}_{546}$ +5.0° (*c* 1.0, $CHCl_3$), which compares with $[\alpha]^{25}_{546}$ −80.4° (*c* 1.0, $CHCl_3$) for optically pure (*R*)-**12**;[4i] so the sample was 6% optically pure (*S*)-**12**, or 54% (*S*)-**12** and 46% (*R*)-**12**, and the CRF was 1.15. From the $CDCl_3$-rich layer was isolated 31 mg of **12**, $[\alpha]^{25}_{546}$ −5.2° (*c* 1.0, $CHCl_3$). This material was 6% optically pure (*R*)-**12**. The total amount of starting host accounted for was ~82%.

Distribution of Racemic Valine and Optically Pure (*S*)-1 between Two Liquid Phases. Optically pure (*S*)-**1**[4i] (0.400 g or 0.602 mmol) was dissolved in 1.0 mL of CD_3CO_2D containing 0.177 g (1.51 mmol) of racemic valine. Deuteriochloroform (1.5 mL) and D_2O (0.50 mL) were added and shaken in a centrifuge tube for 1 min at 24 °C. The layers were separated (the meniscus was discarded) to give ~2.3 mL of the $CDCl_3$-rich layer and ~0.7 mL of the D_2O-rich layer. The ^1H NMR spectra of each phase was then taken. Integrations of the various proton resonances indicated that the D_2O-rich phase contained only ~1% of the total host, and the $CDCl_3$-rich phase contained the remaining host plus 1 mol equiv (~40%) of the valine used. The $CDCl_3$-rich phase was evaporated to dryness at <30 °C (vacuum). The residue was dissolved in 10 mL of water, washed with five successive 10-mL portions of $CHCl_3$, and evaporated to dryness at <30 °C (vacuum), and the solid valine was dried at 24 °C at 50 μ for 24 h to give 37 mg of valine, $[\alpha]^{25}_{546}$ +4.0° (*c* 2.0, 1 N HCl), which is 12.5% optically pure L-valine (optically pure L-valine, $[\alpha]^{25}_{546}$ +32.2° (*c* 2, 1 N HCl)). Thus the $CDCl_3$-rich layer was 56% L-valine and 44% D-valine, and gives a CRF_{CDCl_3} = 1.27. The molar ratio in the D_2O-rich phase, D-valine/L-valine, which equals $[G_B]_{D_2O}/[G_A]_{D_2O}$, was estimated by difference (the total of each enantiomer not found in the $CDCl_3$-rich layer) to be 1.17. Thus $EDC_{CDCl_3} = CRF_{CDCl_3} \cdot ([G_B]_{D_2O}/[G_A]_{D_2O}) \sim 1.5$.

Total Resolution of Racemic Host 1 by Liquid-Liquid Chromatography. A solution of 6.0 g of optically pure L-valine (51.2 mmol) was dissolved in a mixture of 40 mL of acetic acid and 10 mL of water. This solution was saturated with benzene, and mixed with 60 g of Celite (Johns-Manville "Analytical Filter-Aid" grade). The resulting "dry" appearing solid was dry packed into a column. Extra Celite (5 g) was added at the top to give a 60-cm by 3-cm stationary liquid phase. Racemic **1** (1.0 g or 1.5 mmol) was dissolved in an 8 mL of acetic acid-2 mL of water solution. The resulting solution was saturated with benzene and added at the top of the column, which was then washed with benzene saturated with 4:1 (by volume) acetic acid-water.

Each 40-mL fraction of the column eluate was evaporated at <30 °C (vacuum) and dissolved in 3 mL of 0.1 M aqueous HCl. The water was extracted with three successive 3-mL portions of $CHCl_3$, and the combined organic extracts were washed with 3 mL of 0.1 M aqueous HCl. The organic phase was dried with $MgSO_4$, transferred to a tared flask, evaporated, and dried at 24 °C at 0.1 mm for 30 min as a foam. Each fraction was weighed and its rotation taken. The first nine fractions were virtually empty, fractions 10 and 11 contained a total of 19 mg of low rotating material which was discarded, and fractions 12-16 were combined to give 336 mg of material which gave $[\alpha]^{25}_{546}$ −69.2° (*c* 1, $CHCl_3$), which corresponds to ~90% optically pure (*R*)-**1**. Fractions 17-20 contained 161 mg of lower rotating material which was discarded. Fractions 21-34 were combined to give 363 mg of material which gave $[\alpha]^{25}_{546}$ +70.0 (*c* 1, $CHCl_3$), which corresponds to 90% optically pure (*S*)-**1**.

The 336 mg of 90% optically pure (*R*)-**1** was rechromatographed in the same way on a column identical to the first except that optically pure D-valine was used in the stationary phase. Fractions 6-10 contained 31 mg of optically impure material, whereas fractions 11-12, 13-14, 18-19, 20-23, and 24-25 gave rotations within experimental error of one another. Combined fractions 11-25 gave 220 mg (44% of theory) of optically pure (*R*)-**1**, $[\alpha]^{25}_{546}$ −76.5° (*c* 1, $CHCl_3$) after drying as a foam at 24 °C at <50 μ at 30 °C.

The 363 mg of 90% optically pure (*S*)-**1** was rechromatographed on a column identical with that initially used with optically pure L-valine in the stationary phase. Fractions 5-8 contained 22.5 mg of **1** which was optically impure, whereas 9-22 gave rotations within experimental error of one another. These were combined and dried as a foam at 30 °C and <50 μ for 24 h to give 270 mg (54% of theory) of (*S*)-**1**, $[\alpha]^{25}_{546}$ +76.5° (*c* 1, $CHCl_3$).

References and Notes

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Chemistry of 4,4-Dimethoxycyclohexa-2,5-dienone. Unusual Formation of Bridged Polycyclic Compounds

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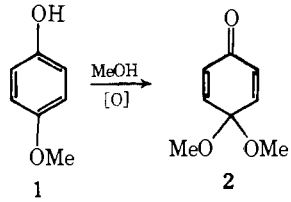
Abstract: Michael reactions of 4,4-dimethoxycyclohexa-2,5-dienone (**2**), readily available by electrochemical or chemical oxidation of *p*-methoxyphenol, were studied. Reaction of **2** with morpholine gave a mono-Michael adduct; methoxide gave a mixture of mono and bis adducts, and MeSH and PhSH gave only bis adducts. Reaction of **2** with Na_2S gave good yields of a novel polycyclic compound, decahydro-3,3,8,8-tetramethoxy-2,7-epithio-1,4-ethanonaphthalene-5,9-dione (**10**). Reaction of **10** with trimethyl orthoformate gave ketal **14** (decahydro-3,5,8,8,9,9-hexamethoxy-2,7-epithio-3,5-epoxy-1,4-ethanonaphthalene). Desulfurization and hydrolysis of **14** gave **16** (decahydro-1,4-ethanonaphthalene-2,5,8,10-tetraone), which is formally a Diels–Alder dimer of hydroquinone. Wolff–Kishner reduction of **16** gave the known hydrocarbon **17**, verifying the structures of **16** and **10**.

Introduction

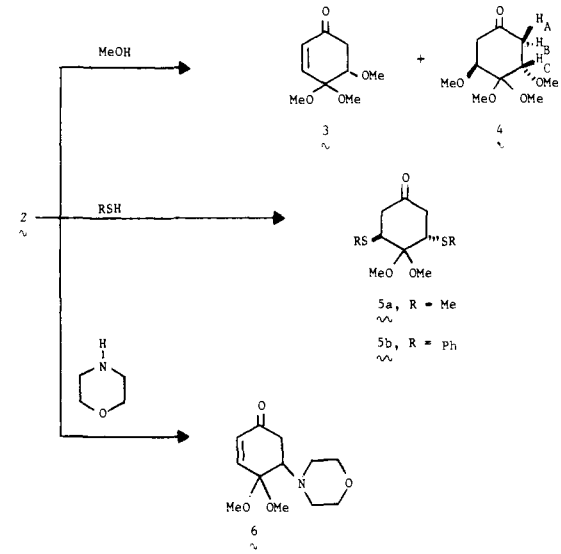
Several workers[1-3] have recently reported syntheses of 4,4-dimethoxycyclohexa-2,5-dienone (**2**), based on chemical



1 2

or electrochemical oxidation of *p*-methoxyphenol (**1**). Although this work has made **2** readily available, little work has focused on the chemistry of **2**.[4] We have prepared **2** by anodic oxidation of **1** in MeOH and have studied reactions of **2** with nucleophiles. The addition of LiOH to a methanolic solution of **2** caused spontaneous Michael addition of MeOH to give an equilibrium mixture of **2** (trace), **3** (83%), and **4** (17%) which was separable by gas chromatography (GC). The assignment of stereochemistry in **4** is based on the ^1H NMR spectrum which showed the -OMe absorptions of the ketal as equivalent. In addition, the absorptions of the ring protons (H_A, H_B, H_C) matched the computer-calculated spectrum (at both 60 and 100 MHz) for the trans isomer but not the cis isomer.

Scheme I



Attempts to produce pure **4** by refluxing the reaction mixture for 48 h failed to change the mixture.

Reaction of **2** with MeSH or PhSH gave only bis adducts

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