be isolated in sufficient quantities from this photolysis.

Compound **6** was independently synthesized by reduction of 130 mg (0.31 mmol) of **3** in ethanol with $NaBH_4$ (19 mg, 0.50 mmol) at room temperature to give 104 mg (80%) of **6** as a white solid (97% purity by GLC on column A at 270 °C). The product was purified by recrystallization from acetone/hexane to afford 71 mg of white crystals (mp 58-59 °C). Its spectroscopic data were identical with those of the photoproduct.

Preparative Photolysis of 3α-(Dimethylphenylsiloxy)androstan-17-one (3) in Acetonitrile without TEA. A degassed solution of **3** (61.5 mg, 14.5 mM) in acetonitrile (10 mL) was irradiated as described above at 33 °C for 40 min. Chromatography of the reaction mixture on silica gel with 10% EtOAc/hexane afforded the epimer, 3α-DPS-5α,13α-androstan-17-one (**7**) as a white solid (7.6 mg, 18%) and the aldehyde **8** (5.2 mg, 12%). Spectral data for 3α-DPS-5α,13α-androstan-17-one (**7**): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58-7.37 (m, 5 H, arom), 4.00 (m, 3β-H), 2.3-1.0 (m, 22 H), 0.97 (s, 18-CH_3), 0.57 (s, 19-CH_3), 0.34 (s, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 151.2 MHz) δ 222.74, 139.03, 133.39, 129.26, 127.64, 67.27 (3C-OSi), 51.48, 50.86, 50.17, 38.38, 37.78, 36.24, 36.03, 33.92, 32.94, 32.22, 32.06, 29.34, 28.39, 25.32, 22.24, 21.26, 11.07, -0.95, -1.00; IR (KBr) 1738 (C=O), 1374, 1249, 1163, 1122, 1078, 1048, 1014, 987, 961, 941, 921, 877, 865, 839, 818, 784, 744, 725 cm^{-1}; MS *m/e* EI 409 (M - CH_3, 57), 137 (100); high-resolution FAB MS (*m/e*) calcd (M + 1) 425.2866, found 425.2876.

Spectral data for 3α-DPS-13,17-seco-5α-androst-13-en-17-al (**8**): ^1H NMR ($CDCl_3$, 300 MHz) δ 9.76 (s, HC=O), 7.57-7.37 (m, 5 H, arom), 4.02 (m, 3β-H), 1.55 (s, 18-CH_3), 0.68 (s, 19-CH_3), 0.34 (s, $SiCH_3$), 0.33 (s, $SiCH_3$).

A mixture of **7**, **8**, and **9** obtained from the photolysis of **3** (10 mg) in isopropyl alcohol was subjected to GLC/MS: for **7**, MS *m/e* EI M^+ = 424; for **8**, M^+ = 424; and for 2-propyl 3α-DPS-13,17-seco-5α-androstan-17-oate (**9**), M^+ = 484.

Experiments with Cyclohexanone. Degassed solutions of **3** (15 mM) in iPrOH (1 mL) saturated by $NaHCO_3$ were irradiated in the Rayonet reactor by 8 254-nm lamps at room temperature for 6 min in the absence and presence of cyclohexanone (10.2-30.6 mM). The solutions were analyzed by GLC (column A at 270 °C) with an internal standard (3β-DPS-5α-androstan-17-one) to monitor **3**, while cyclohexanone and cyclohexanol were analyzed on the same column using a gradient temperature program starting from 50 °C.

Quenching by *cis*-1,3-Pentadiene. Compounds **1** and **3** (17 mM) were photolyzed in the presence and absence of *cis*-1,3-pentadiene (59 and 119 mM) in CH_3CN with 32.3 and 59.2 mM TEA for **1** and **3**, respectively. Irradiations were with the Nd:YAG laser. The formation of **4-7** was assayed by GLC on column A at 270 °C with 3β-DPS-5α-androstan-17-one as an internal standard. In a separate experiment, **1** (16.2 mM) and the diene (0-180 mM) were irradiated in CH_3CN with the 16 254-nm lamps in the Rayonet reactor for 65 min. The reactions were analyzed by GLC on column B (245 °C) using 3α-DPS-5α-androstan-17-one as an internal standard. The data were corrected for absorption by the diene at 254 nm (ϵ_{254} = 15 M^{-1} cm^{-1}).

Quantum Efficiency Determinations. For laser studies, a Vycor cuvette containing 2 mL of argon-degassed sample solution (ca. 15-17 mM) was placed in a sample holder. The solution was irradiated with either the 266- or 308-nm laser beam for 4-16 min (varying from sample to sample). The photolysate was analyzed by GLC on column A (at 270 °C) with 3β-DPS-5α-androstan-17β-ol (prepared by silylation of epiandrosterone with DPSCl as described for the preparation of **3**) as the internal standard. The quantum efficiencies for epimerization of **1** and **3** (both 15 mM) in CH_3CN were determined by photolysis in the Rayonet reactor equipped with 16 254-nm lamps for 60 and 10 min, respectively. The formation of **5** and **7** was quantitated by GLC on colum B at 250 °C with 3β-DPS-5α-androstan-17-one as an internal standard. Actinometry was performed using the *E*/*Z* isomerization of (*E*)-1-phenyl-2-butene, for which the quantum efficiency of isomerization has been determined to be 0.20.[61] The hexane solution of (*E*)-1-phenyl-2-butene was irradiated for 4 min, and the amount of *Z* isomer was determined by GLC on column A at 80 °C. The conversion to *Z* isomer was corrected for back reaction. The quantum efficiency studies in the presence of *cis*-1,3-pentadiene were determined in analogous fashion with the data for **1** and **3** plotted in Figures 1 and 2, respectively.

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Enantioselective Complexation of Organic Ammonium Ions by Simple Tetracyclic Podand Ionophores

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Abstract: A series of enantiomerically pure, C_2-symmetric tetracyclic podands are synthesized and studied. These host molecules have methyl substitution, which allows only a few low-energy conformations, and they form well-defined complexes with chiral ammonium salts. With derivatives of α-phenethylammonium hexafluorophosphate as guests, binding enantioselectivity ranges from ~0 to 60% ee. X-ray structures of several podand/chiral ammonium perchlorate complexes are described along with a conformational analysis of the podands and their complexes.

Large rings are among the most characteristic structural features of synthetic host molecules. This is not surprising given comparisons of the binding properties of notable receptors and their acyclic analogues. In the case of pentaglyme dimethyl ether (**1**) versus 18-crown-6 (**2**), macrocyclic **2** binds *tert*-butylammonium ion 10^4 times more tightly than does **1**.[1] The case of spherand **4** is even more dramatic, with the macrocyclic **4** binding lithium and sodium 10^{12} and 10^{10} times more effectively than does **3** (Figure 1).[2] As Cram has pointed out, the function of the macrocyclic linkage is to *preorganize* the ligand to favor its binding conformation, a conformation which may be disfavored both entropically and enthalpically in the corresponding acyclic receptor or *podand*.[3]

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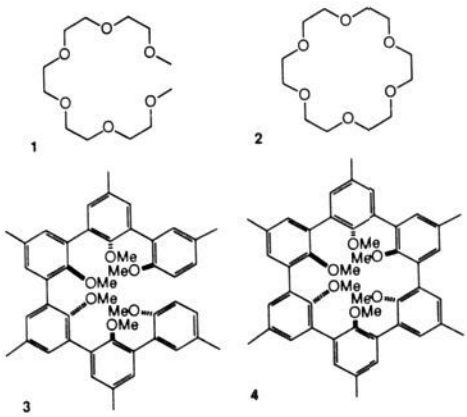

Figure 1.

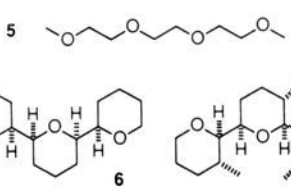

Figure 2.

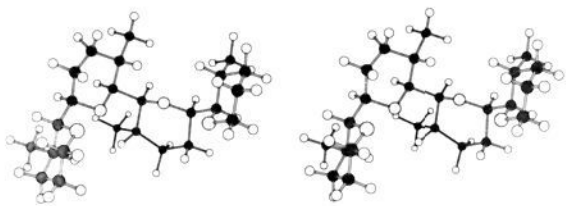

Figure 3.

Forming large rings is not, however, the only way to induce organic molecules to form preorganized binding sites. Such preorganization can also be achieved by forming normal rings and incorporating conformational locking mechanisms. Many of the naturally occurring ionophores (e.g., monensin) use such structural motifs to form conformationally restricted cation binding sites.[4] Thus, podands can also be preorganized into binding conformations and exhibit those special binding properties which are normally associated with macrocyclic structures.

In this paper, we describe the synthesis and properties of a series of tetracyclic podand ionophores (e.g., **7**) which are related to the triglyme dimethyl ether (**5**) (Figure 2). These podands, however, are much less conformationally heterogeneous than the corresponding acyclic glyme ethers. In comparison with **5** which has >750 distinct conformations within 3 kcal/mol of the global minimum energy conformation, **6** has only ~25.[5a] Flexibility can be reduced further by adding certain methyl substituents which form a kind of conformational lock. The locking mechanism operates by favoring certain conformations of the inter-ring bonds and gives **7** only one conformation capable of binding cations within the lowest 3 kcal/mol according to molecular mechanics.[5b]

The conformation of **7** which is calculated to be the most stable is shown in stereo in Figure 3. This particular stereoisomer was chosen to favor an ion-binding geometry in which the glyme-like backbone exists in a conformation qualitatively the same as that found in the X-ray structure of potassium 18-crown-6. This

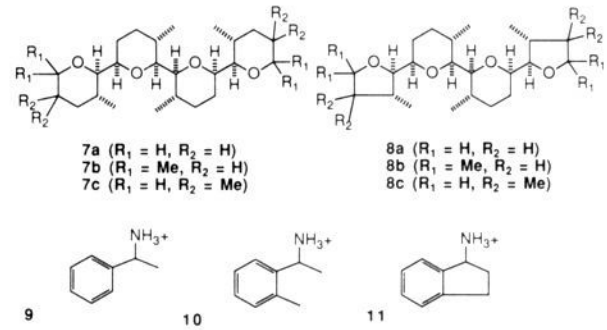

Figure 4.

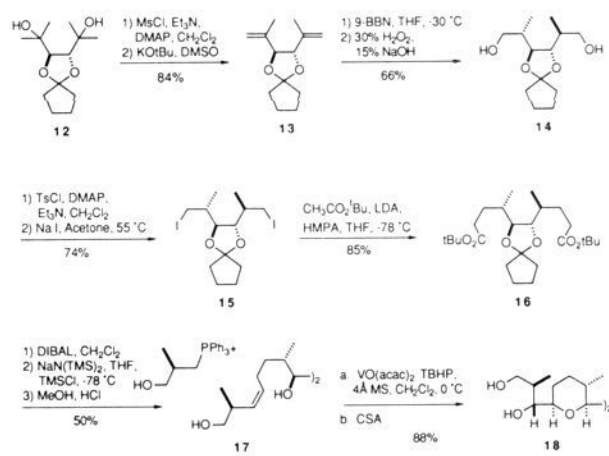

Figure 5. Synthesis of key intermediate **18**.

conformation is C_2-symmetric and has an open, cation-binding site within what appears to be a highly chiral environment. As such, it would be expected to bind guests such as chiral organic ammonium ions enantioselectively. The binding site of **7** is particularly interesting because it is structurally well-defined, a situation which is not common in chiral host–guest systems and which makes possible a detailed understanding of the mechanism of enantioselective molecular recognition.

In the paragraphs which follow, we describe syntheses of tetracyclic podands **7a–c** and **8a–c** and studies of their enantioselective complexation with ammonium ions **9–11**. Since the binding sites of tetrahydropyranoid (THP, **7**) and tetrahydrofuranoid (THF, **8**) podands were expected to distinguish chiral guests primarily on steric grounds, we chose ammonium ion guests with well-distinguished chiral substituent sizes (H, Me, (CH_2), Ph). Guests **10** and **11** serve as conformationally restricted analogues of **9** (Figure 4).

Experimental Studies

Synthesis. All podands described here are C_2-symmetric and are synthesized using a bidirectional strategy starting from the adduct of methyl Grignard and enantiomerically pure diethyl tartrate. All podands are prepared from a common intermediate (**18**) whose synthesis is summarized in Figure 5. While most of the steps are straightforward, several points are worthy of note. In a previous communication, for example, we described a single-step but low-yield sulfuryl chloride elimination of **12** to **13**.[5b] More recently, we discovered a more effective (84% yield) two-step procedure which proceeded via base-promoted elimination of an intermediate mesylate. Interestingly, a 7-membered cyclic sulfite was a major byproduct if DMAP was omitted in the mesylation step. Stereoselection in the synthesis followed from literature precedent.[6] Thus, the double hydroboration could be carried out with either 9-BBN or disiamylborane and gave **14** with selectivity of ~10:1. The following Wittig coupling was cis-selective to the

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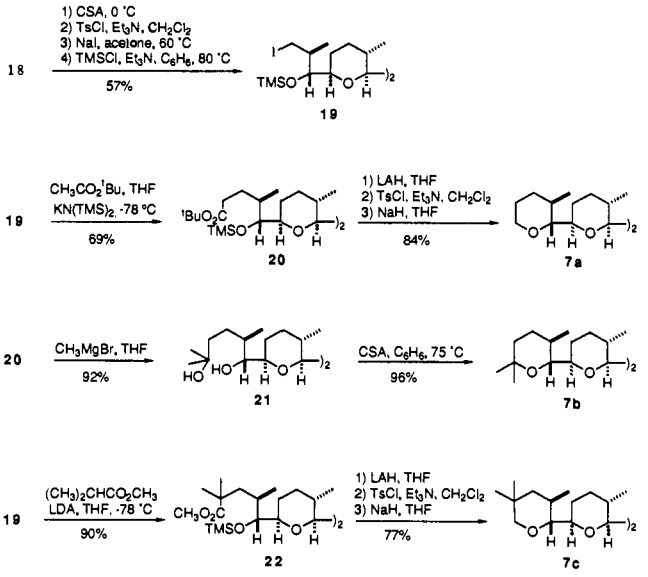

Figure 6. Syntheses of THP podands.

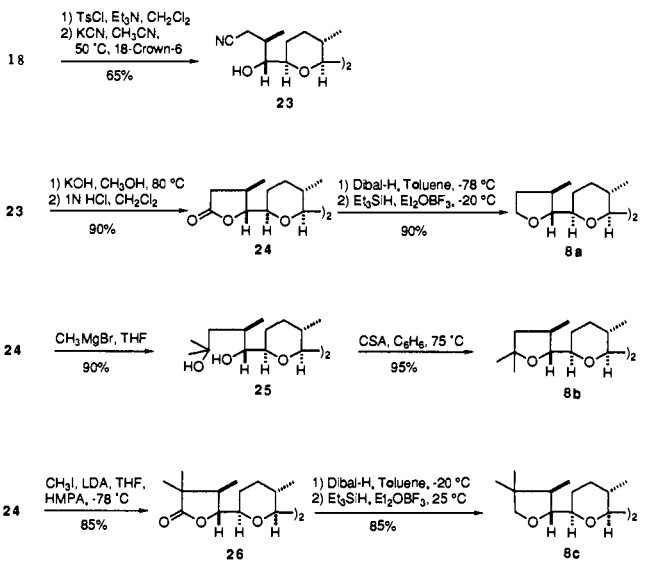

Figure 7. Syntheses of THF podands.

extent of 18:1.[7] If the phosphorane reagent hydroxyl was left unprotected by TMS, the *trans*-alkene became the major product. Next, the vanadium-catalyzed epoxidation[8] was directed by the well-defined conformational preference of the homoallylic hydroxyl to the α-face of the alkene. Finally, an acid-catalyzed epoxy alcohol cyclization closed the central two tetrahydropyran rings to provide **18** in good yield.

With **18** in hand, the desired podands were readily available. The THP podands **7** were all prepared as outlined in Figure 6 by ester enolate alkylations of the primary iodide **19**. The THF podands **8** were synthesized from the related tosylate via cyanide displacement and lactonization to **24** as shown in Figure 7. The precursors of the α-dimethyl podands **7b** and **8b** both cyclized in high yield under the influence of camphorsulfonic acid in benzene. The terminal THP rings of podands **7a** and **7c** were closed by a Williamson etherification, while the THF rings of **8a** and **8c** were prepared by BF_3-catalyzed silane reduction of the corresponding hemiacetals.

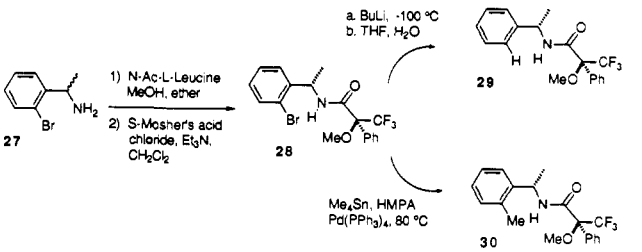

Figure 8.

While the amines corresponding to **9** and **11** have been resolved and their configurations assigned previously,[9] the *o*-methyl-α-phenethylamine **10** had to be prepared, resolved, and assigned. To this end, racemic **10** was prepared from *o*-methylacetophenone by lithium aluminum hydride reduction of its oxime. To establish the absolute configuration of its enantiomers, we partially resolved *o*-bromo-α-phenethylamine by recrystallization of *N*-Ac-L-leucine salt from methylene chloride/hexane.[10] After reaction of the amine with (*S*)-Mosher's acid chloride, we metalated the aryl bromide with *n*-butyllithium and protonated it at low temperature to give **29** (Figure 8). The major isomer of the α-phenethylamine derivative **29** had the *S* configuration as shown by comparison with authentic material. With the configuration of the *o*-bromo-α-phenethylamine moiety in **28** defined as *S*, we coupled the aryl bromide with tetramethyltin using tetrakis(triphenylphosphine)palladium to give **30**.[11] We found that the ^1H and ^{13}C NMR spectra of **30** were identical to those of the same Mosher amide of the enantiomer of **10**, which bound more tightly to our podands.

Binding Experiments. The relative association energies of the podands **7** and **8** for enantiomeric ammonium ions **9**–**11** were measured by an extraction method.[12a] Thus a 0.5–1 M solution of the ammonium chloride in 0.6–1.2 M $LiPF_6$ in D_2O was shaken with an equal volume of $CDCl_3$ containing the podand (0.01–0.05 M). Through appropriate control experiments, we established that these salts of **9**–**11** did not partition measurably into $CDCl_3$ in the absence of podand. We also found that, unlike the more hydrophilic glyme ethers, our podands were not extracted into the aqueous salt solutions. Consequently, the enantioselectivity of the binding process could be determined directly by measuring the enantiomeric excess (% ee) of the podand-extracted ammonium salt.

In many cases, this determination was made by direct inspection of the ^1H NMR data, because the host functioned as an effective chiral shift reagent for the extracted ammonium salt guests. Thus the diastereomeric podand complexes of the *R* and *S* ammonium ions were often distinct by NMR spectroscopy, and enantioselection could be measured directly by integration of resolved equivalent protons of the enantiomeric guests. Typically, resolved guest protons included both the chiral center CH and the ortho hydrogens of the aromatic ring. Another method for enantiomeric excess determination involved making Mosher amides of the podand-extracted ammonium salts. Thus the $CDCl_3$ phase containing the complexes was separated and treated with Mosher's acid chloride and triethylamine to give pairs of diastereomeric Mosher amides. These diastereomeric Mosher amides were always distinct by ^1H or ^{19}F NMR spectroscopy, and absolute configuration assignments could be made by comparison with authentic materials (see above). The Mosher amide method was used whenever there was poor resolution of equivalent protons in enantiomeric guests and was also used to confirm the results of the direct NMR measurements. In cases where both methods could

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Table I. Enantioselective Binding Results for Six Podand Hosts and Three Ammonium Ion Guests

	7a	**7b**	**7c**	**8a**	**8b**	**8c**
9	80% Bound 40% ee (S)	<5% Bound	20% Bound 10% ee (S)	52% Bound 12% ee (S)	31% Bound 18% ee (S)	40% Bound 6% ee (S)
10	95% Bound 53% ee (S)	<5% Bound	<5% Bound	52% Bound 60 % ee (S)	45% Bound 49% ee (S)	40% Bound 50% ee (S)
11	>95% Bound 20% ee (S)	5% Bound	77% Bound 5% ee (S)	93% Bound 40% ee (R)	47% Bound 55 % ee (R)	60% Bound 56 % ee (R)

be used, the enantiomeric excesses we measured were the same within 5%.

For a given guest, the percentage of podand which is bound to ammonium ion provides a measure of the ionophoric character of a podand and is also directly determined by NMR analysis. Because our ammonium ions do not partition measurably from D_2O to $CDCl_3$ in the absence of podand, the ratio of ^1H NMR integrations of a proton from ammonium ion to podand defines the ratio of bound to total podand.

The enantioselective binding results are summarized in Table I. Several trends are apparent. Primary among these trends is that our L-tartrate-derived podands selectively bound the *S* enantiomer of ammonium ions **9** and **10** in all cases where enantioselectivity could be measured. The indanylammonium ion **11** behaved differently. With the THF podands **8**, the *R* enantiomer of guest **11** was bound preferentially. With the THP podand **7a**, the enantioselectivity change was less marked for **11** relative to **9** and **10**, but it too was shifted toward the *R* isomer.

Another trend may be seen by examining the "% bound" data in the table. These entries give the proportion of total podand which is bound to the extracted ammonium ion guests and reflect the relative binding energy of different podands for a given guest. While all of the THF podands exhibit effective binding to ammonium ions **9–11** in our extraction experiments, the binding of ammonium ions to the THP podands is much more sensitive to substitution. Thus podand **7b** shows very little extraction of ions **9–11**, while **7a** extracts these ions into $CDCl_3$ more effectively than does any of the other podands. Podand **7c** is intermediate in its ion-binding strength. With a sterically less demanding ammonium ion, efficient extraction by **7b** and **7c** could be restored: benzylammonium hexafluorophosphate was extracted into chloroform by **7b** and **7c** to the extent of 35% and 95%, respectively.

The difference between the THF and THP podands likely results from the conformationally more rigid and sterically more enclosed nature of the latter's ion-binding site. Thus, the more flexible THF podands have more opportunities to adjust their structures to accommodate methyl substituents and still form relatively unstrained complexes. One such opportunity for conformational change that is present in **8** but not **7** is particularly striking and will be described in following sections.

The effect of podand methylation on enantioselectivity seems to mirror its effect on binding strength as described in the preceding paragraphs. Thus with the THP podands, β-dimethylation (**7c**) not only reduces binding energy relative to **7a** but also diminishes enantioselectivity where it could be measured. With the THF podands, neither α- nor β-dimethylation had much of an effect on either binding energy or enantioselectivity. Indeed, the most remarkable property of the THF podands (**8a–c**) is the similarity of their binding to the three ammonium ions we studied.

In addition to examining how enantioselectivity varied with host and guest structure, we briefly investigated how it was affected by the choice of counterion and solvent. Studies by Cram and co-workers[12] previously noted that some salts (e.g., bromide) of α-amino acid esters gave significantly lower enantioselectivity than others (e.g., hexafluorophosphate) in binding to certain chiral chrown ether hosts. *In contrast, we found no such dependence* in the two podand systems which we examined (**7a**/**9** and **8a**/**11**).

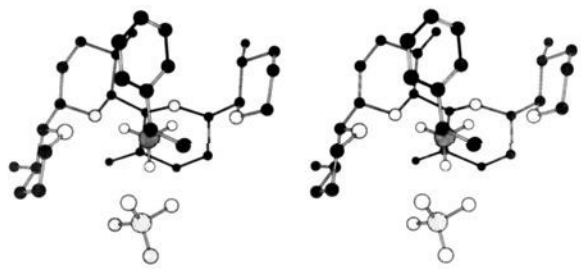

Figure 9. X-ray structure of **7a**/(*S*)-**9** perchlorate.

Thus, we observed essentially the same enantioselection (±5%) with ammonium salts derived from HBr, $HClO_4$, HCl + LiBr, HCl + $LiClO_4$, and HCl + $LiPF_6$. The nature of the solvent, however, did exert a significant effect on enantioselectivity. With **8a**/**11**·PF_6, enantioselectivity (ee) for the *R* guest varied from 22 to 40 to 47% when the solvent was changed from CD_2Cl_2 to $CDCl_3$ to C_6D_6. Collectively, these results make it clear that any quantitative model of molecular recognition will need to incorporate the entire system, including the solvent and associated counterions.

Structures of Complexes. When a mixture of **7a** and the perchlorate salt of **9** were allowed to stand, large crystals of the complex (mp = 77–81 °C) formed. X-ray crystallography gave the structure shown in Figure 9 in stereo.[13a] Ammonium hydrogen positions were calculated using 1.0-Å NH bond lengths and assuming a tetrahedral nitrogen with a staggered arrangement relative to the attached sp^3 carbon. It can be seen that two of the ammonium hydrogens form hydrogen bonds to the podand while the third is directed toward the perchlorate counterion. In the structure shown, the left-most three THP oxygens are 3.2, 2.9, and 2.9 Å from the ammonium nitrogen, while the right-most THP oxygen is 3.4 Å from nitrogen. The ammonium hydrogens appear to be bound primarily to the central two THP ring oxygens with O–H distances of 2.0 and 2.2 Å. The two terminal THP oxygens also appear to be involved in binding, with O–H distances of ~2.5 Å each. Thus the left-most three THP rings in the X-ray structure shown are the most tightly bound to the ammonium ion guest. This distortion away from a more symmetrical complex corresponds to a leftward translation of the guest within the binding site. Such a translation may minimize steric interactions between the podand and the ammonium α-methyl group. The guest phenyl group lies across the face of one of the THP rings at a separation (C–C distance ~3.9 Å) appropriate for van der Waals association. This geometry also directs an aromatic ortho hydrogen toward the right-most THP ring oxygen. The corresponding (C)H–O distance of ~2.6 Å likely provides a weak but favorable electrostatic interaction and may further stabilize the aromatic ring in the orientation shown. Significant aromatic (C)H···O hydrogen bonds have been suggested previously to lie in the range of 2.2–2.4 Å.[14]

(13) Crystal structure determined by the following: (a) Arnold L. Rheingold at the University of Delaware. (b) John Dewan at New York University.

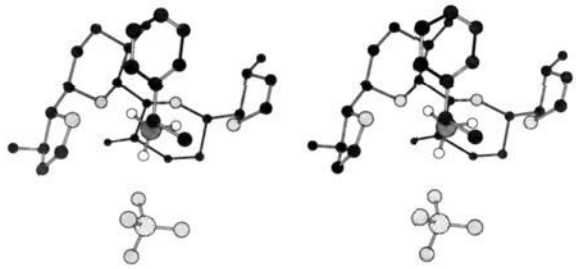

Figure 10. X-ray structure of **8a**/(*S*)-**9** perchlorate.

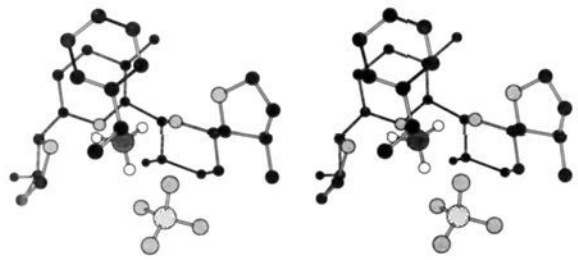

Figure 11. X-ray structure of **8a**/(*R*)-**9** perchlorate.

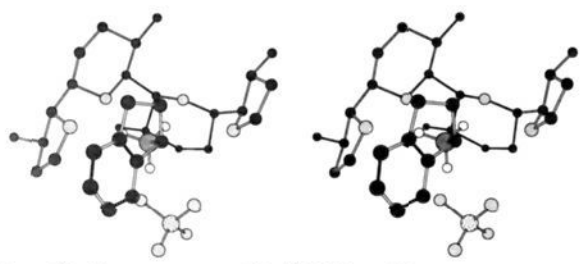

Figure 12. X-ray structure of **8a**/(*S*)-**11** perchlorate.

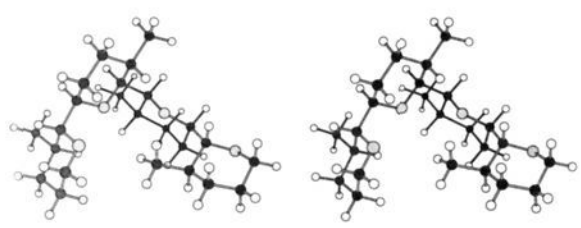

Figure 13.

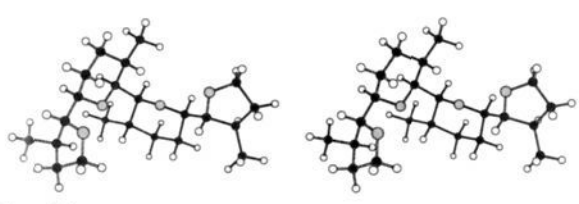

Figure 14.

Related X-ray structures of the complexes of the THF podand **8a** are shown below.[13b] Comparison of the **8a**/(*S*)-**9** structure (Figure 10) with the previous **7a**/(*S*)-**9** X-ray structure shows that the two structures are closely related. These are complexes of the more stable diastereomeric host–guest pair and they appear to place the chiral substituent methyl in the less sterically demanding site. The corresponding structure of **8a** with (*R*)-**9** (Figure 11) shows the analogous methyl pointed toward the left THF ring, which is presumably the more hindered site. Interestingly, the right THF ring is reoriented and incorporates a normally high-energy *syn*-pentane interaction (see discussion below). The less stable **8a**/(*S*)-**11** complex (Figure 12) differs from the other three structures in that the phenyl group lies in the plane of the ammonium ion binding site.

All of the X-ray structures obtained incorporate two strong hydrogen bonds between ammonium hydrogens and podand oxygens, with the remaining hydrogen bond from ammonium to perchlorate. As in the **7a**/(*S*)-**9** structure, the four oxygens of THF podand **8a** do not appear to contribute equally to the hydrogen-bonding network which holds the complexes together. In each case, some ether oxygens have significantly shorter distances to the calculated ammonium hydrogen positions than others. For the **8a** complexes with (*S*)-**9**, (*R*)-**9**, and (*S*)-**11**, the four (left to right in the figures) O–H(N) distances are 2.5/1.9/2.2/2.4 Å, 1.9/2.3/2.0/3.2 Å, and 2.1/2.3/2.0/2.7 Å, respectively. Thus, the most tightly bound oxygens seem to vary in the different structures. In all structures, the ammonium nitrogen lies within a few tenths of an angstrom of the best plane through the podand oxygens. These structural features suggest a cation-binding site which is slightly larger than a primary ammonium ion. The complexes of **8a** with (*S*)- and (*R*)-**9** both exhibit the same type of aryl H/ether O proximity described above with (C)H–O distances of 2.6 and 2.5 Å, respectively.

Discussion and Conclusion

The podand ionophores described here are of interest because they are conformationally well-defined. With the THP podands **7** for example, there is only a single low-energy conformation which is capable of binding an ion by more than two oxygens. This conformation is shown in the X-ray structure and ligates the ammonium ion by all four of the podand's oxygens. This conformation of the THP podand is characterized by low-energy conformations of the substructures as judged by MacroModel MM2[15] calculations. Thus chairlike 6-membered rings with equatorial substituents are favored by ~3 kcal/mol over the next most stable conformation (a diaxially substituted chair). The remaining conformational degrees of freedom are the inter-ring bonds. The methyl substituents disfavor those rotamers of inter-ring bonds having syn (+gauche,–gauche) pentane-like CH_3/CH_2 interactions by 4.9 kcal/mol. The other two rotamers are closer in energy, but the higher energy one (+1.0 kcal/mol) is destabilized by a syn CH_3/O interaction. It also appears sterically incapable of cation binding; the terminal THP ring methyl substituent not only destabilizes an undesired conformer but also fills the binding site, as shown in the stereopair diagram in Figure 13. The sole remaining rotomer is the one found in the X-ray structure of the complex.

Prior to the X-ray determination of the **7a** complex of (*S*)-α-phenethylammonium (**9**) perchlorate, we carried out Monte Carlo conformational searches of the corresponding diastereomeric cationic complexes. These searches were conducted as we described previously for single molecules using the MacroModel AMBER force field;[15] however, the search here involved both torsion angle variations and translational/rotational movements of the ammonium ion within the binding site of the podand. These random movements involved torsion angle rotations up to ±180° and α-phenethylammonium ion rigid body rotations up to ±180° and translations up to ±1 Å. Torsion angle rotations were carried out around the α-phenethylammonium nitrogen. The lowest energy conformation of the (*S*)-**9** complex with **7a** found by the search is essentially the same as that found in the crystal structure of **7a**/(*S*)-**9**·ClO_4. When the perchlorate was eliminated from the X-ray structure and the resulting cationic complex minimized, the result was identical with the global minimum from the conformational search. The conformational search with **7a**/(*R*)-**9** gave as the global minimum a structure analogous to the (*S*)-**9** complex but with the guest chiral H and Me substituents switched. In this regard, they resemble the crystal structures of the (*R*)-

(14) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panuto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415. Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5603.

(15) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. The MacroModel implementation of MM2 uses the same parameters and equations from MM2(87) except for the electrostatic treatment which is based on atomic partial charges. The MacroModel implementation of AMBER is identical with the authentic field in all respects.

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

and (*S*)-**9** complexes with the THF podand.

In comparison with the THP podand **7a**, the THF podand **8a** is more flexible. While the lowest conformation found by Monte Carlo conformational search closely resembled **7a**, there were approximately a dozen conformers from 1 to 3 kcal/mol above the global minimum. Surprisingly, some of these conformers incorporated the unfavorable *syn*-pentane CH_3/CH_2 interaction, which served as an effective conformational lock in the THP podands **7** (e.g., see Figure 14).

Molecular mechanics showed that such syn-pentanoid conformations were only destabilized by ~1 kcal/mol in the 5-membered ring system of **8a**. Acyclic *syn*-pentanes normally relax to give −60, +90° torsion angles as a way of avoiding high-energy nonbonded contacts. There is usually a significant energetic price for the relaxation to a 90° torsion angle. In the case of **8a**, however, the 90° torsion nicely maps into a low-energy torsion angle for adjacent trans substituents on a 5-membered ring. Thus much of the strain associated with the 90° torsion is already built into **8a**. Another property of 5-membered rings which favors the unusual *syn*-pentane-like conformations is their relatively large exocyclic bond angles. In the X-ray structures in the figures, this expansion can be seen in the exocyclic ring angles to methyl, which average 113° with the THP podands and 115° with the THF podands.

In the *complexes* of the THF podands, conformations having *syn*-pentane substructures may even be the lowest energy forms. Molecular mechanics conformational searching on the perchlorate **8a**/(*S*)-**9** complex finds the X-ray conformation to be ~1 kcal/mol *less* stable than an analogous structure having the right-most ring of the THF podand rotated to form a *syn*-pentane-containing conformation. This unusual stabilization follows from a favorable electrostatic interaction between the reoriented THF dipole and the perchlorate anion. After the molecular mechanics analysis of the **8a**/**9** complexes was completed and syn-pentanoid conformations of **8a** were predicted to be low in energy, the X-ray structure of **8a**/(*R*)-**9** was solved and found to contain just such a low-energy substructure.

As the above paragraphs indicate, structures generalized from idealized (e.g., diamond lattice) models may not constitute effective conformational locks when 5-membered rings are involved. Because conformational energies may vary with structure in subtle ways, we suggest that any new conformational locking mechanism be subjected to a thorough conformational analysis with a well-parametrized force field before it is built into a real molecule.

While most of the podands described here showed energetic preferences between the enantiomeric ammonium ions studied, the extent of selectivity ranged only as high as 0.8 kcal/mol. One possible reason for the only moderate enantioselectivity is that our podands and/or their complexes are not conformationally homogeneous. The THF podands in particular seem to exist in several distinct low-energy conformations having well-defined binding sites. If all such conformers had the same preferences for binding to a given set of guests, then mixtures of host conformers would be expected to display poor selectivity among those guests. Podand flexibility may also explain why the enantioselectivities of the methylated THF podands **8b** and **8c** differ so little from that of **8a**. With several conformations available plus facile pseudorotation of the 5-membered rings, the flexible THF podands are better able to adopt their structures as necessary to achieve favorable binding geometries in spite of changes in substitution.

In contrast, the THP podands appear to be conformationally homogeneous. So why are these conformationally restricted THP podands not more enantioselective? We believe that there are two answers. First, though the THP podands may be homogeneous, their complexes likely consist of several different configurations or binding modes in which the ammonium ion guest binds to the podand in different orientations. These distinct binding modes differ primarily in their $N-C_\alpha$ torsion angle. The X-ray structures of the THF podands with the α-phenethylammonium (**9**) and the indanylammonium (**11**) ion guests show two such orientations. In the former complex, the guest aromatic ring lies perpendicular to the plane defined by the podand oxygens, while in the latter it lies in the plane. Second, for a given binding mode (e.g., phenyl in plane) complexes of enantiomeric guests may be similar in energy due to residual flexibility of the complex. One relevant and available degree of freedom leading to poor enantioselection is rotation around the phenyl centroid/ammonium nitrogen axis.

Molecular mechanics calculations on the alternative binding orientations and on the various substituent positions suggest that all are within 1.5 kcal/mol of one another. Thus, even with our conformationally homogeneous THP podands, we find low enantioselectivity as a result of multiple binding modes and only moderate intrinsic enantioselectivity for each mode.

In conclusion, our THP podands themselves may be conformationally homogeneous, but their complexes appear to be structurally heterogeneous. Consequently, the enantioselectivity we observe with this series of podands is only moderate. To improve enantioselectivity, it will be necessary to endow our receptors with a mechanism which allows them to distinguish more effectively between alternative binding modes. Such work is underway at this time.[17]

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise indicated, on a Varian VX400 400-MHz and a Varian VX300 300-MHz spectrometer, respectively. Chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.27 ppm for ^1H, 77.0 ppm for ^{13}C) as an internal reference. Infrared spectra were obtained as neat liquids or in a KBR pellet. High-resolution mass spectral (HRMS) data were obtained with a JEOL JMS-DX 303HX spectrometer. Melting points are uncorrected. Flash chromatography was carried out on 40–63 μm silica gel as described previously.[16] Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were distilled under nitrogen just prior to use from sodium/benzophenone and calcium hydride, respectively. All numbered compounds were of >90% purity as judged by 400-MHz ^1H NMR, ^{13}C NMR, and thin-layer chromatography.

(*o*-Methylphenethyl)ammonium Hydrochloride (10). A dry flask equipped with a reflux condenser was charged with *o*-methylacetophenone (2.9 g, 21.6 mmol), potassium bicarbonate (9.0 g, 90 mmol), hydroxylamine hydrochloride (5.94 g, 85 mmol), and CH_3OH (90 mL). The mixture was heated at reflux for 1 h and cooled. Ether (100 mL) was added, and the solid which formed was removed by filtration. After evaporation of the methanol/ether solvent mixture, fresh ether was added and the ethereal solution was washed once with 1 N HCl, saturated aqueous $NaHCO_3$, and brine solution. Drying over anhydrous $MgSO_4$ and removal of solvent afforded a mixture of *o*-methylacetophenone oximes (2.76 g, 85%).

A dry flask equipped with a reflux condenser charged with $LiAlH_4$ (2.7 g, 71 mmol) and THF (150 mL) was heated to reflux under nitrogen. *o*-Methylacetophenone oxime (2.76 g, 18.3 mmol) in THF (20 mL) was added dropwise via cannula. The mixture was cooled to 20 °C after 1 h, and $Na_2SO_4 \cdot 10H_2O$ was added cautiously. A white solid formed and was removed by filtration after 30 min. Anhydrous HCl in CH_3OH (5 mL of acetyl chloride was added carefully to 20 mL of CH_3OH) was added to the filtrant. Removal of solvent afforded **10** (2.89 g, 91% from the oxime) as a white solid, which was recrystallized from CH_3OH and ether (mp = 168 °C): ^1H NMR 1.64 (d, 3 H, J = 6.8 Hz), 2.38 (s, 3 H), 4.67 (m, 1 H), 7.16–7.24 (m, 3 H), 7.63 (m, 1 H), 8.74 (br s, 3 H); ^{13}C NMR 20.66, 21.70, 48.99, 126.74, 128.38, 129.93, 132.26, 136.41, 137.49; IR (KBr) 2900, 1600, 1530, 1460, 1400, 2500 cm^{-1}; HRMS mass calcd for $C_9H_{14}N$ 135.1048, found 135.1037.

Di-*tert*-butyl Alcohol 12. A dry flask equipped with a reflux condenser and Dean–Stark trap was charged with (+)-diethyl-L-tartrate (51.5 mL, 250 mmol), cyclopentanone (25.2 g, 300 mmol), toluenesulfonic acid monohydrate (500 mg, 2.6 mmol), and 250 mL of benzene and was heated at reflux for 10 h. The cooled reaction mixture was neutralized with K_2CO_3 (3 g, 30 mmol) and filtered through a pad of silica gel (100 g). The solvent was removed, and the residue was transferred to an addition funnel equipped flask containing anhydrous THF (600 mL). After cooling the solution to 0 °C under nitrogen, CH_3MgBr (3.0 M in diethyl ether; 400 mL, 1200 mmol) was added dropwise with stirring. The reaction mixture was warmed to 25 °C and stirred for 4 h before recooling to 0 °C. Saturated NH_4Cl solution was then added cautiously, and the aqueous layer was extracted three times with ether. The organic layers were combined, washed with brine, and dried (Na_2SO_4). Removal of solvent and recrystallization from CH_2Cl_2 afforded **12** (49.2 g, 80%)

(17) This work was supported by NIH Grant HL25634.

as a white crystalline solid (mp = 156 °C): ^{1}H NMR 1.27 (s, 6 H), 1.31 (s, 6 H), 1.62–1.84 (m, 8 H), 2.55 (br s, 2 H), 3.77 (s, 2 H); ^{13}C NMR 23.94, 24.70, 29.26, 38.43, 71.28, 83.41, 119.0; IR (CCl_4) 3290, 3000, 2950, 1378, 1178, 1333, 1111 cm^{-1}; HRMS exact mass calculated for $C_{13}H_{24}O_4$ 244.1675, found 244.1649.

Diene 13. Methanesulfonyl chloride (25 mL, 322 mmol) was added dropwise to a stirred mixture of **12** (25 g, 102 mmol), Et_3N (76 mL, 612 mmol), 4-(dimethylamino)pyridine (25 g, 205 mmol), and CH_2Cl_2 (600 mL) at 0 °C. The resulting mixture was stirred for 20 min. The solvent was then removed, and DMSO (600 mL) and potassium *tert*-butoxide (40 g, 356 mmol) were added. After the reaction was stirred for 16 h, water (600 mL) was added and the mixture was extracted three times with hexanes. Evaporation followed by flash chromatography (2–30% ether in petroleum ether) afforded diene **13** (12.5 g, 59%) in a monodehydrated byproduct (7.15 g, 31%) as colorless oils. The byproduct was resubmitted to the same dehydration conditions, yielding more **13** (5.5 g, total 84%): ^{1}H NMR 1.79 (s, 6 H), 1.60–1.90 (m, 8 H), 4.14 (s, 2 H), 4.97 (s, 2 H), 5.05 (s, 2 H); ^{13}C NMR 18.83, 24.76, 38.69, 84.35, 115.72, 120.30, 142.83; IR (neat) 2972, 1729, 1652, 1452, 1435, 1374, 1331, 1303, 1193, 1109, 1040, 984, 903 cm^{-1}; HRMS exact mass calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1441.

Diol 14. An oven-dried flask was charged with **13** (3.4 g, 16.3 mmol) and anhydrous THF (20 mL) and then cooled to −20 °C under argon. 9-BBN (0.5 M in THF, 100 mL, 50 mmol) was added dropwise via syringe with stirring, and the reaction mixture was warmed to 25 °C and stirred for 3 h. After recooling to −20 °C, NaOH solution (15% w/v H_2O, 50 mL) and H_2O_2 solution (30%, 50 mL) were added slowly, and the mixture was stirred for 8 h. The aqueous mixture was extracted three times with ether, and the combined organic layers were washed with brine and dried ($MgSO_4$). Column chromatography (30–60% ether in pentane) afforded **14** (2.62 g, 66%) as a viscous oil: ^{1}H NMR 0.94 (d, 6 H, J = 6.4 Hz), 1.5–2.0 (m, 10 H), 2.7 (br s, 2 H), 3.63 (m, 4 H), 3.81 (m, 2 H); ^{13}C NMR 14.31, 23.41, 37.71, 38.37, 65.88, 83.67, 119.51; IR (neat) 3361, 2962, 1451, 1333, 1205, 1080, 1030 cm^{-1}; HRMS exact mass calcd for $C_{13}H_{24}O_4$ 244.1675, found 244.1659.

Diiodide 15. A dry flask was charged with **14** (9.2 g, 38 mmol), Et_3N (12.7 mL, 91 mmol), toluenesulfonyl chloride (15.8 g, 83 mmol), and 4-(dimethylamino)pyridine (500 mg, 4.1 mmol) in CH_2Cl_2 (150 mL). After stirring for 72 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 and washed with water and then brine. Filtration through a pad of silica (50 g) and removal of solvent afforded a yellow oil. The oil was dissolved in acetone (150 mL) containing NaI (13.5 g, 90 mmol), and the mixture was heated at reflux for 3 h. The mixture was then cooled, acetone was removed at reduced pressure, and water was added. After three extractions with ether, the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (3–7% ether in pentane) afforded **15** (13.0 g, 74%) as a colorless oil: ^{1}H NMR 1.00 (d, 6 H, J = 6.8 Hz), 1.5–1.9 (m, 10 H), 3.29 (dd, 2 H, J = 5.68, 9.6 Hz), 3.418 (dd, 2 H, J = 2.91, 9.6 Hz), 3.69 (d, 2 H, J = 8.2 Hz); ^{13}C NMR 13.67, 18.00, 23.62, 38.29, 38.61, 82.65, 119.67; IR (neat) 2933, 1641, 1460, 1337, 1174, 1109 cm^{-1}; HRMS exact mass calcd for $C_{13}H_{22}I_2O_2$ 463.9709, found 463.9723.

Diester 16. *n*BuLi (2.0 M in pentane, 31.5 mL, 63 mmol) was added dropwise to a flame-dried, argon-filled flask containing diisopropylamine (9.81 mL, 70 mmol) and anhydrous THF (90 mL) at −78 °C. After the mixture was stirred for 5 min at −78 °C, *tert*-butyl acetate (9.43 mL, 70 mmol) was added dropwise via syringe. Dry HMPA (30 mL) was added after 5 min followed by addition of **15** (6.5 g, 14 mmol) in 5 mL of THF. After the solution was stirred for 30 min at −78 °C, saturated aqueous NH_4Cl was added to the reaction mixture. Upon warming to 25 °C, the aqueous layer was extracted three times with ether. The organic extracts were washed three times with 1 M HCl and once with brine. Removal of solvent followed by flash chromatography (6–12% ether in pentane) afforded **16** (5.12 g, 83%) as a colorless oil: ^{1}H NMR 0.89 (d, 6 H, J = 6.4 Hz), 1.43 (s, 18 H), 1.5–1.7 (m, 12 H), 1.92 (m, 2 H), 2.1–2.4 (m, 4 H), 3.60 (d, 2 H, J = 8 Hz); ^{13}C NMR 17.52, 24.81, 28.75, 29.46, 34.50, 37.35, 39.24, 81.36, 84.98, 119.92, 174.51; IR (neat) 2976, 1735, 1465, 1376, 1105, 865 cm^{-1}; HRMS exact mass calcd for $C_{25}H_{44}O_6$ 440.3138, found 440.3134.

Diene Tetrol 17. Diisobutylaluminum hydride (1 M in CH_2Cl_2, 7.5 mL, 7.5 mmol) was added dropwise over 20 min with stirring to a flame-dried flask under argon containing **16** (1.1 g, 2.5 mmol) and CH_2Cl_2 (30 mL) at −78 °C. After the solution was stirred for an additional 10 min at −78 °C, CH_3OH (1.5 mL) was added dropwise, and the reaction mixture was poured into a saturated Rochelle salt solution (40 mL) and stirred for 1 h until the organic layer became clear. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). Removal of solvent and flash chromatography (35–50% ether in pentane) afforded the crude dialdehyde as a colorless oil.

Sodium bis(trimethylsilyl)amide (1.0 M in THF, 30 mL, 30 mmol) was added dropwise to a flame-dried flask containing [(*R*)-(+)-3-hydroxy-2-methylpropyl]triphenylphosphonium bromide (Aldrich) (6.44 g, 15.5 mmol) and THF (90 mL) at 0 °C. The resulting orange suspension was warmed to 25 °C, stirred for 2 h, and then cooled to 0 °C. Chlorotrimethylsilane (1.90 mL, 15.5 mmol) was added dropwise, and the mixture was stirred for 30 min at 25 °C and cooled to −78 °C. The above dialdehyde in 5 mL of THF was added via cannula, and the reaction mixture was warmed slowly to 25 °C and stirred for 5 h. Ether (50 mL) and saturated NH_4Cl were added, and the aqueous layer was extracted three times with ether. The combined organic layers were washed once with 1 M HCl and once with saturated brine solution and then dried over anhydrous $MgSO_4$. Removal of solvent and flash chromatography (50–70% ether in pentane) afforded the cyclopentylidene-protected diene, to which was added CH_3OH (30 mL) and 1 M HCl (15 mL). After this mixture was stirred for 3 days, $NaHCO_3$ was added to neutralize the solution, CH_3OH was removed, and the aqueous portion was extracted three times with $CHCl_3$. The organic layers were combined and dried over anhydrous Na_2SO_4. Removal of solvent and flash chromatography (50–70% ethyl acetate in pentane) afforded **17** (425 mg, 50%) as a pale white solid (mp = 81 °C): ^{1}H NMR 0.91 (d, 6 H, J = 6.4 Hz), 0.93 (d, 6 H, J = 6.4 Hz), 1.28 (m, 2 H), 1.6–1.8 (m, 4 H), 2.0 (m, 4 H), 2.24 (m, 4 H), 2.50 (br s, 2 H), 2.72 (m, 2 H), 3.3–3.4 (m, 4 H), 3.51 (m, 2 H), 5.24 (t, 2 H, J = 8.0 Hz), 5.53 (dt, 2 H, J = 5.0, 8.0 Hz); ^{13}C NMR 16.05, 17.02, 24.79, 32.55, 34.80, 35.18, 67.70, 74.99, 132.11, 132.50; IR (KBr) 3352, 2923, 1453, 1036 cm^{-1}; HRMS exact mass calcd for $C_{20}H_{38}O_4$ 342.2770, found 342.2751.

Bis-tetrahydropyran 18. *tert*-Butyl hydroperoxide (5.5 M in isooctane, 9.0 mL, 49.5 mmol) was added dropwise with stirring to **17** (1.13 g, 3.3 mmol), $VO(acac)_2$ (45 mg, 0.17 mmol), and CH_2Cl_2 (12 mL) at 0 °C. After it was allowed to stand for 12 h, the reaction mixture was evaported at reduced pressure, and the residue was purified by flash chromatography (2–15% CH_3OH in CH_2Cl_2). Camphorsulfonic acid (3 mg) was added to three combined chromatography fractions representing diepoxide, monoepoxide/monotetrahydropyran, and bis-tetrahydropyran (silica gel TLC, 10% MeOH/EtOAc; R_f = 0.45, 0.30, 0.20, respectively). The solvent was removed after 1 h, and filtration through a pad of silica gel afforded **18** (1.05 g, 85%) as a pale white solid: ^{1}H NMR 0.70 (d, 6 H, J = 6.8 Hz), 0.82 (d, 6 H, J = 6.8 Hz), 0.99 (m, 2 H), 1.35 (m, 2 H), 1.75 (m, 2 H), 1.92 (m, 2 H), 2.01 (m, 2 H), 2.15 (m, 2 H), 2.82 (d, 2 H, J = 9.2 Hz), 3.16 (dt, 2 H, J = 11.5, 2.2 Hz), 3.30 (dd, 2 H, J = 8.5, 2.2 Hz), 3.76 (dd, 2 H, J = 7.2, 10.8 Hz), 3.85 (dd, 2 H, J = 4.1, 10.8 Hz); ^{13}C NMR 15.210, 18.544, 29.075, 31.743, 34.247, 38.847, 69.148, 79.698, 80.263, 83.470; IR (KBr) 3360, 2915, 1657, 1456, 1082 cm^{-1}; HRMS exact mass calcd for $C_{20}H_{38}O_6$ 374.2668, found 374.2665.

Diiodide 19. A dry flask under argon was charged with **18** (878 mg, 2.3 mmol), Et_3N (0.98 mL, 7.0 mmol), toluenesulfonyl chloride (991 mg, 5.2 mmol), and CH_2Cl_2 (30 mL). After 3 days at 25 °C, saturated NH_4Cl solution was added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. Removal of solvent afforded a yellow oil, to which acetone (10 mL) and NaI (1.5 g, 10 mmol) were added. The flask was fitted with a condenser, and the mixture was heated at reflux for 2.5 h. The solvent was then removed, water (15 mL) was added, and the solution was extracted three times with ether. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed, and flash chromatography (40–60% ether in pentane) afforded a colorless oil. A dry flask was charged with the oily product, Et_3N (1.7 mL, 12 mmol), chlorotrimethylsilane (1.3 mL, 10 mmol), and benzene (20 mL). The mixture was heated at reflux for 2 h, cooled to 25 °C, and filtered through Celite with ether. The solvent was removed, and flash chromatography (4–7% ether in pentane) afforded **19** (1.07 g, 63%) as a colorless oil: ^{1}H NMR 0.15 (s, 18 H), 0.77 (d, 6 H, J = 6.4 Hz), 0.97 (d, 6 H, J = 6.4 Hz), 1.15 (m, 2 H), 1.41 (m, 2 H), 1.51 (m, 2 H), 1.72 (m, 2 H), 1.86 (dt, 2 H, J = 3.2, 10.0 Hz), 2.96 (d, 2 H, J = 9.2 Hz), 3.22 (dt, 2 H, J = 2.5, 11.5 Hz), 3.27 (dd, 2 H, J = 6.5, 9.4 Hz), 3.35 (dd, 2 H, J = 3.1, 7.1 Hz), 3.398 (dd, 2 H, J = 3.1, 9.5 Hz); ^{13}C NMR 1.06, 17.44, 18.39, 27.50, 29.92, 33.00, 36.88, 78.66, 79.54, 82.50; IR (neat) 2953, 1250, 1123, 1086 cm^{-1}; HRMS exact mass calcd for $C_{26}H_{52}I_2O_4Si_2$ 738.1494, found 738.1436.

Diester 20. *tert*-Butyl acetate (0.61 mL, 4.5 mmol) was added dropwise with stirring to a flame-dried, argon-filled flask containing potassium bis(trimethylsilyl)amide (838 mg, 4.2 mmol) and THF (10 mL) at −78 °C. After the solution was stirred for 20 min at −78 °C, **19** (582 mg, 0.79 mmol) was added via cannula. The reaction mixture was stirred for 10 min and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (8–12% ether in pentane) gave **20** (390 mg, 69%) as a colorless oil: ^{1}H NMR 0.35 (s, 18 H), 0.91 (d, 6 H, J = 6.4 Hz), 0.99 (d, 6 H,

J = 6.4 Hz), 1.0–1.2 (m, 2 H), 1.30 (m, 2 H), 1.47 (s, 18 H), 1.4–1.48 (m, 4 H), 1.59 (m, 2 H), 1.73 (m, 2 H), 1.80 (m, 2 H), 2.02 (m, 2 H), 2.18 (ddd, 2 H, J = 7.1, 8.8, 15.3 Hz), 2.32 (ddd, 2 H, J = 5.7, 9.4, 15.3 Hz), 3.02 (m, 2 H), 3.33 (q, 2 H, J = 1.8, 5.1 Hz), 3.44 (t, 2 H, J = 5.1 Hz); ^{13}C NMR 2.51, 18.14, 19.24, 27.39, 28.73, 29.48, 31.66, 34.67, 34.93, 80.67, 81.63, 81.86, 84.22, 174.05; IR (film) 2929, 1730, 1458, 1366, 1250, 1154, 882, 840 cm^{-1}; HRMS exact mass calcd for $C_{24}H_{38}O_6$ (lactone) 422.2682, found 422.2668.

THP Podand 7a. A THF solution of $LiAlH_4$ (1.0 M, 2 mL, 2 mmol) was added dropwise with stirring under argon to diester **20** (232 mg, 0.32 mmol) in THF (9 mL). Excess $Na_2SO_4 \cdot 10H_2O$ was added cautiously after 30 min. The white solid which formed was filtered from the reaction mixture and washed with EtOAc. Removal of the solvent afforded a waxy white solid, to which was added CH_2Cl_2 (20 mL), Et_3N (0.03 mL, 0.2 mmol), and toluenesulfonyl chloride (29 mg, 0.15 mmol). After the mixture was stirred for 2 days at room temperature, saturated aqueous NH_4Cl was added. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed to afford a yellow oil.

The above yellow oil in THF (0.5 mL) was added dropwise with stirring to a flame-dried flask under argon containing NaH (37 mg, 1.5 mmol) and THF (3 mL) at 0 °C. After stirring for 1 h, water was cautiously added. The aqueous mixture was extracted three times with ether. The combined organic layers were washed with brine solution and dried over $MgSO_4$. Removal of solvent followed by flash chromatography (50% ether in pentane) afforded **7a** (107 mg, 84%) as a colorless oil: ^{1}H NMR (C_6D_6) 0.79 (d, 6 H, J = 6.4 Hz), 0.81 (d, 6 H, J = 6.4 Hz), 0.92 (dq, 2 H, J = 4, 11 Hz), 1.06 (dq, 2 H, J = 2, 11 Hz), 1.15 (m, 2 H), 1.26 (m, 2 H), 1.60 (m, 2 H), 1.75 (m, 4 H), 2.0–2.3 (m, 6 H), 2.63 (dd, 2 H, J = 2, 10 Hz), 2.89 (d, 2 H, J = 9.2 Hz), 3.10 (ddd, 2 H, J = 2, 11, 11 Hz), 3.28 (ddd, 2 H, J = 2, 2, 11 Hz), 4.05 (dd, 2 H, J = 2, 11 Hz); ^{13}C NMR 18.44, 19.02, 27.67, 28.62, 31.14, 32.18, 34.20, 34.48, 70.03, 77.66, 83.79, 86.75; IR (film) 3604, 3560, 2919, 2847, 2729, 1616, 1458, 1442, 1100 cm^{-1}; HRMS calcd mass for $C_{24}H_{42}O_4$ 394.3083, found 394.3092.

Diester 22. *n*BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) was added dropwise with stirring to a flame-dried flask under argon containing diisopropylamine (0.30 mL, 2.2 mmol) and THF (3.0 mL) at −78 °C. After the mixture was stirred for 5 min at −78 °C, methyl isobutyrate (0.252 mL, 2.2 mL) was added dropwise via syringe. After 5 min, dry HMPA (1.0 mL) was added followed by cannula addition of **19** (100 mg, 0.134 mmol). After additional stirring for 15 min, aqueous NH_4Cl was added to the reaction mixture. Upon warming to 25 °C, the aqueous layer was extracted three times with ether. The combined organic layers were washed with 1 M HCl and brine and dried ($MgSO_4$). Removal of solvent followed by flash chromatography (40–50% ether in pentane) afforded **22** (69.5 mg, 96%) as a colorless oil: ^{1}H NMR 0.80 (d, 6 H, J = 6.4 Hz), 0.98 (s, 18 H), 0.99 (d, 6 H, J = 6.8 Hz), 1.18 (m, 2 H), 1.25 (s, 6 H), 1.28 (s, 6 H), 1.46 (br s, 2 H), 1.54–1.60 (m, 6 H), 1.80–1.86 (m, 6 H), 2.35 (m, 2 H), 3.02 (d, 2 H, J = 9.2 Hz), 3.41 (dt, 2 H, J = 2.1, 11.2 Hz), 3.84 (dd, 2 H, J = 2.1, 10.4 Hz), 3.49 (s, 6 H); ^{13}C NMR 3.72, 18.49, 18.70, 26.84, 27.64, 28.74, 29.00, 31.69, 34.06, 45.12, 83.83, 83.87, 89.09, 178.53; IR (neat) 2959, 2927, 2851, 2364, 2344, 1734, 1458, 1387, 1142, 1105 cm^{-1}; HRMS exact mass calcd for $C_{30}H_{54}O_8$ 478.3294, found 478.3296.

β-Dimethyl THP Podand 7c. Diester **22** (69 mg, 0.126 mmol) in THF (0.5 mL) was added at 25 °C via cannula to an argon-filled flask fitted with a reflux condenser containing $LiAlH_4$ (80 mg, 2.1 mmol) in THF (3.5 mL). The mixture was heated at reflux for 2 h and then cooled to 25 °C. $Na_2SO_4 \cdot 10H_2O$ was added cautiously. After the mixture was stirred for 30 min, the solid which formed was filtered and washed with THF. Removal of solvent followed by flash chromatography (0–10% CH_3OH in ethyl acetate) afforded a diol (62 mg, 99%) as a wax: ^{1}H NMR 0.83 (d, 6 H, J = 6.4 Hz), 0.83 (s, 6 H), 0.91 (d, 6 H, J = 6.4 Hz), 0.92 (s, 6 H), 1.25 (m, 4 H), 1.50 (m, 2 H), 1.78 (m, 8 H), 1.90 (dq, 2 H, J = 3.2, 12.4 Hz), 2.4 (br s, 4 H), 3.10 (d, 4 H, J = 11.2 Hz), 3.178 (d, 2 H, J = 11.2 Hz), 3.37 (dt, 2 H, J = 2.0, 11.2 Hz), 3.47 (dd, 2 H, J = 10.8, 2.0 Hz); ^{13}C NMR 18.35, 21.42, 24.86, 27.88, 29.58, 31.79, 32.31, 34.10, 43.04, 71.23, 78.88, 80.76, 83.39; IR (neat) 3357, 2926, 2850, 1460, 1110 cm^{-1}; HRMS exact mass calcd for $C_{28}H_{54}O_6$ 486.3920, found 486.3890.

The above diol (62 mg, 0.126 mmol), Et_3N (0.07 mL, 0.5 mmol), toluenesulfonyl chloride (65 mg, 0.34 mmol), and 4-(dimethylamino)-pyridine (2 mg, 0.016 mmol) in CH_2Cl_2 (5 mL) were mixed. After the mixture was stirred at room temperature for 4 days, saturated aqueous NH_4Cl solution was added. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). The solvent was removed at reduced pressure to yield a yellow oily ditosylate.

The crude ditosylate in THF (0.5 mL) was added with stirring to a flame-dried flask under argon containing NaH (50 mg, 2.08 mmol) in THF (3 mL) at 0 °C. The mixture was warmed to 25 °C and stirred for 2 h. Saturated aqueous NH_4Cl was then added, and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent and flash chromatography (30–40% ether in pentane) afforded **7c** (43 mg, 77%) as a colorless oil: ^{1}H NMR 0.79 (d, 6 H, J = 6.4 Hz), 0.81 (d, 6 H, J = 6.4 Hz), 0.96 (dd, 2 H, J = 1.6, 12.8 Hz), 1.06 (s, 12 H), 1.18–1.36 (m, 4 H), 1.50 (ddd, 2 H, J = 3.6, 3.8, 12.0 Hz), 1.90 (m, 6 H), 2.05 (m, 2 H), 2.63 (d, 2 H, J = 1.6, 10.0 Hz), 3.02 (d, 2 H, J = 11.2 Hz), 3.03 (d, 2 H, J = 9.2 Hz), 3.47 (dt, 2 H, J = 1.6, 11.2 Hz), 3.53 (dd, 2 H, J = 2.6, 10.8 Hz); ^{13}C NMR 17.0, 17.9, 24.2, 25.9, 27.1, 27.5, 29.7, 31.0, 33.2, 46.9, 76.8, 78.3, 82.9, 85.7; IR (neat) 3753, 2926, 2364, 1460, 1098 cm^{-1}; HRMS calcd mass for $C_{28}H_{50}O_4$ 450.3709, found 450.3730.

Tetrol 21. CH_3MgBr (3.0 M in THF, 0.5 mL, 1.5 mmol) was added via syringe to a dry flask under argon containing the crude diester **20** (50 mg, 0.069 mmol) and THF (5.0 mL). After 3 h, saturated aqueous NH_4Cl was added to the reaction mixture, and the aqueous phase was extracted three times with ether. The combined organic layers were washed with 1 M HCl and saturated brine solution and dried over $MgSO_4$. The solvent was removed, and flash chromatography (5–10% CH_3OH in ethyl acetate) afforded **21** (27 mg, 94%) as a colorless oil: ^{1}H NMR 0.82 (d, 6 H, J = 6.4 Hz), 0.94 (d, 6 H, J = 6.4 Hz), 1.22 (s, 12 H), 1.37 (m, 2 H), 1.47–1.80 (m, 16 H), 2.0 (br s, 4 H), 3.09 (d, 2 H, J = 9.2 Hz), 3.27 (dd, 2 H, J = 4.8, 4.8 Hz), 3.35 (dm, 2 H, J = 9.0, 4.8 Hz); ^{13}C NMR 17.77, 18.34, 25.03, 27.31, 29.40, 30.40, 30.78, 31.70, 33.98, 36.80, 42.41, 79.50, 79.78, 83.36; IR (neat) 3357, 2926, 1377, 1109 cm^{-1}; HRMS calcd mass for $C_{28}H_{54}O_6$ 486.3920, found 486.3898.

α-Dimethyl THP Podand 7b. A dry flask equipped with a condenser was charged with **21** (15 mg, 0.032 mmol), benzene (1.0 mL), and camphorsulfonic acid (~1 mg) and heated to reflux for 3 h. The solvent was removed after cooling the mixture, and flash chromatography (20–30% ether in pentane) of the residue afforded **7b** (13.8 mg, 96%) as a colorless oil: ^{1}H NMR 0.76 (d, 6 H, J = 6.8 Hz), 0.81 (d, 6 H, J = 6.4 Hz), 1.10 (s, 6 H), 1.14 (m, 2 H), 1.21 (m, 2 H), 1.26 (s, 6 H), 1.34 (m, 4 H), 1.60 (m, 4 H), 1.80 (m, 4 H), 1.98 (m, 4 H), 2.95 (d, 2 H, J = 9.2 Hz), 2.99 (dd, 2 H, J = 1.6, 10.8 Hz), 3.34 (dd, 2 H, J = 1.6, 11.6 Hz); ^{13}C NMR 17.15, 17.49, 21.79, 24.80, 27.09, 29.47, 29.83, 30.39, 30.84, 33.24, 36.03, 71.79, 78.09, 82.64; IR (neat) 3752, 2925, 2364, 1459, 1378, 1231, 1112, 1017 cm^{-1}; HRMS calcd mass for $C_{28}H_{50}O_4$ 450.3709, found 450.3704.

Dicyanide 23. A dry flask under argon was charged with **7** (1.79 g, 4.7 mmol), Et_3N (2.0 mL, 14.3 mmol), toluenesulfonyl chloride (2.03 g, 10.6 mmol), and CH_2Cl_2 (60 mL). After the mixture was stirred for 3 days at 25 °C, saturated NH_4Cl solution was added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. Removal of solvent afforded a yellow oil, to which acetonitrile (100 mL), KCN (1.33 g, 20.4 mmol), and 18-crown-6 (7.11 g, 20.4 mmol) were added. The flask was heated at 50 °C for 2 days and then cooled to 25 °C. The solvent was removed at reduced pressure, and flash chromatography (50–75% ether in petroleum ether) gave **23** (1.2 g, 65%) as a colorless oil: ^{1}H NMR 0.83 (d, 6 H, J = 6.6 Hz), 1.12 (d, 6 H, J = 6.8 Hz), 1.21–1.32 (m, 2 H), 1.490–1.550 (m, 2 H), 1.65–1.81 (m, 4 H), 1.92 (ddd, 2 H, J = 13.1, 6.7, 3.9 Hz), 1.93–2.05 (b, 2 H), 2.050–2.140 (m, 2 H), 2.44 (dd, 2 H, J = 16.8, 7.9 Hz), 2.64 (dd, 2 H, J = 16.8, 4.3 Hz), 3.12 (d, 2 H, J = 9.4 Hz), 3.19 (dd, 2 H, J = 7.9, 3.0 Hz), 3.39 (dt, 2 H, J = 8.9, 2.5 Hz); ^{13}C NMR 16.50, 16.95, 20.91, 27.85, 30.31, 32.32, 33.50, 77.21, 77.28, 81.96, 119.42; IR (neat) 3394, 2927, 2853, 2246, 1736, 1648, 1459, 1423, 1382, 1351, 1319, 1231, 1113, 1069, 1036, 1008 cm^{-1}; HRMS exact mass calcd for $C_{22}H_{37}O_4N_2$ (M + H) 393.2753, found 393.2758.

Dilactone 24. A flask was charged with **23** (1.06 g, 2.7 mmol), KOH (12.07 g, 216 mmol), H_2O (40 mL), and MeOH (100 mL). The flask was heated at 80 °C overnight under a reflux condenser and then cooled to 25 °C. The mixture was acidified by adding a mixture of 1 N HCl (250 mL) and CH_2Cl_2 (250 mL). The two-phase system was stirred at 25 °C for 12 h. The organic layer was then separated, and the aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined, washed with saturated $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed, and flash chromatography (35–65% ether in petroleum ether) afforded **24** (0.957 g, 90%) as a colorless oil, which crystallized upon standing (mp = 145–147 °C): ^{1}H NMR 0.81 (d, 6 H, J = 6.6 Hz), 1.05 (d, 6 H, J = 4.2 Hz), 1.52–1.64 (m, 6 H), 1.73–1.83 (m, 2 H), 1.88 (ddd, 2 H, J = 12.2, 7.0, 3.8 Hz), 2.11 (dd, 2 H, J = 17.4, 6.7 Hz), 2.51–2.58 (m, 2 H), 2.77 (dd, 2 H, J = 17.4, 8.9 Hz), 3.04 (d, 2 H, J = 9.3 Hz), 3.38 (dt, 2 H, J = 10.6, 3.5 Hz), 4.03 (dd, 2 H, J = 5.4, 3.7 Hz); ^{13}C NMR 17.05, 19.39, 26.69, 30.34, 31.25, 32.43, 36.94, 78.32, 82.75, 87.95, 176.85; IR (neat) 2929, 2850, 1777, 1458, 1379,

1349, 1216, 1172, 1107, 1071, 1032, 1009 cm^{-1}; HRMS exact mass calcd for $C_{22}H_{35}O_6$ (M + H) 395.2433, found 395.2450.

THF Podand 8a. Diisobutylaluminum hydride (1.0 M in hexanes) was added portionwise to a solution of **24** (60 mg, 0.152 mmol) in toluene (10 mL) at −78 °C until TLC indicated the disappearance of **24**. The mixture was then poured into acetic acid (4 mL) and ice (15 g) with rapid stirring. $CHCl_3$ (30 mL) was added, and the two-phase system was stirred vigorously for 10 min. Additional $CHCl_3$ (30 mL) was added, and the stirring was continued for 1 h. The organic layer was separated, washed twice with saturated $NaHCO_3$ and brine, and finally dried over anhydrous $MgSO_4$. Removal of solvent afforded the lactol as a thick, colorless oil. The lactol was placed in a dry flask containing triethylsilane (80 mg, 0.73 mmol) in CH_2Cl_2, chilled to −78 °C under nitrogen. Boron trifluoride etherate (0.065 mL, 0.53 mmol) was added dropwise, and the mixture was allowed to stand at −20 °C for 12 h, at which point TLC indicated that all starting material had been consumed. The reaction mixture was quenched by the addition of cold, saturated $NaHCO_3$. The solution was warmed to 25 °C and extracted with ether (three times). The combined ethereal extracts were washed with brine and dried ($MgSO_4$). The solvent was removed at reduced pressure, and flash chromatography (20–60% ether in petroleum ether) afforded **8a** (50 mg, 90%) as a colorless, thick oil: ^{1}H NMR 0.80 (d, 2 H, J = 6.4 Hz), 1.04 (d, 2 H, J = 6.7 Hz), 1.18 (m, 2 H), 1.46–1.52 (m, 4 H), 1.65 (m, 2 H), 1.83–2.02 (m, 4 H), 2.06–2.11 (m, 2 H), 2.28 (m, 2 H), 1.67 (d, 2 H, J = 9.1 Hz), 3.23 (dt, 2 H, J = 11.6, 2.8 Hz), 3.33 (dd, 2 H, J = 7.3, 3.1 Hz), 3.290–3.87 (m, 4 H); ^{13}C NMR 17.01; 18.06, 27.88, 30.31, 33.08, 34.22, 35.01, 67.65, 78.48, 82.74, 87.58; IR (neat) 2952, 2927, 2869, 2848, 1456, 1376, 1322, 1230, 11556, 1124, 1096, 1072, 1048, 1024, 1006 cm^{-1}; HRMS exact mass calcd for $C_{22}H_{38}O_4$ 366.2770, found 366.2784.

Di-*tert*-butyl Alcohol 25. CH_3MgBr (3.0 M in ether, 2 mL, 6 mmol) was added with stirring to a dry, argon-filled flask containing **24** (100 mg, 0.254 mmol) in THF (5.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and allowed to stand overnight. Additional CH_3MgBr (3.0 M in ether, 2 mL, 6 mmol) was added at 0 °C with stirring, and the mixture was again allowed to stand overnight at room temperature. The reaction was finally quenched by careful addition of saturated aqueous NH_4Cl, and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine and then dried ($MgSO_4$). The solvent was removed at reduced pressure, and flash chromatography (50–100% ethyl acetate in hexanes) afforded **25** (80 mg, 87% yield, plus 18 mg of unreacted starting material **24**) as a colorless oil: ^{1}H NMR 0.83 (d, 6 H, J = 6.5 Hz), 0.93 (d, 6 H, J = 6.9 Hz), 1.20–26 (m, 2 H), 1.23 (s, 6 H), 1.25 (s, 6 H), 1.39 (dd, 2 H, J = 14.6, 4.0 Hz), 1.45–1.48 (m, 2 H), 1.76–1.91 (m, 8 H), 2.03 (m, 2 H), 3.09 (d, 2 H, J = 9.3 Hz), 3.10 (b, 2 H), 3.39 (dt, 2 H, J = 11.2, 2.0 Hz), 3.68 (b, 4 H); ^{13}C NMR 17.33, 20.30, 27.74, 28.84, 30.40, 31.19, 31.87, 32.78, 48.39, 70.27, 78.35, 78.98, 81.79; IR (neat) 3650, 3320, 2967, 2926, 2870, 2852, 1638, 1459, 1439, 1377, 1316, 1229, 1163, 1106, 1066, 1008 cm^{-1}; HRMS calcd mass for $C_{26}H_{51}O_6$ (M + H) 459.3686, found 459.3703.

α-Dimethyl THF Podand 8b. A dry flask was filled with **25** (15 mg, 0.033 mmol), benzene (1.0 mL), and camphorsulfonic acid (1 mg) and was heated at reflux for 3 h. The solvent was removed after cooling, and flash chromatography (20–30% ether in petroleum ether) of the residue afforded **8b** (13 mg, 95%) as a colorless oil: ^{1}H NMR 0.79 (d, 6 H, J = 6.4 Hz), 1.02 (d, 6 H, J = 6.6 Hz), 1.19 (s, 6 H), 1.27 (s, 6 H), 1.41 (t, 2 H, J = 11.5 Hz), 1.50 (m, 4 H), 1.71 (b, 2 H), 1.81–1.89 (m, 4 H), 1.93 (dd, 2 H, J = 12.1, 7.4 Hz), 2.37–2.48 (m, 2 H), 2.98 (d, J = 8.8 Hz), 3.26 (dt, 2 H, J = 10.3, 3.1 Hz), 3.49 (dd, J = 8.8, 3.2 Hz); ^{13}C NMR 16.98, 17.43, 27.22, 28.93, 29.49, 30.55, 33.11, 33.98, 48.18, 77.81, 79.96, 82.70, 87.12; IR (neat) 2965, 2927, 2848, 1456, 1377, 1364, 1143, 1111, 1091, 1070, 1010 cm^{-1}; HRMS calcd mass for $C_{26}H_{46}O_4$ 422.3396, found 422.3409.

Dimethyl Dilactone 26. *n*BuLi (1.6 M in hexane, 10 mL, 16 mmol) was slowly added to a flame-dried, argon-filled flask containing diisopropylamine (2.17 mL, 15.5 mmol) in THF (15 mL) at −78 °C. After the mixture was stirred for 40 min, **24** (100 mg, 0.254 mmol) in THF (15 mL) was added slowly down the cold wall of the flask via syringe. The mixture was stirred at −78 °C for 10 min. Dry HMPA (2.6 mL) was then added followed by syringe addition of MeI (0.95 mL, 15.3 mmol, filtered through basic aluminum prior to use). After stirring for 2 h at −78 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl. Upon warming to 25 °C, the aqueous layer was extracted three times with ether. The combined extracts were washed with water and brine. Drying ($MgSO_4$) and removal of solvent followed by flash chromatography (25–60% ether in petroleum ether) afforded **26** (97 mg, 85%) as a colorless oil: ^{1}H NMR 0.81 (d, 6 H, J = 6.5 Hz), 0.99 (d, 6 H, J = 6.9 Hz), 1.07 (s, 6 H), 1.21 (s, 6 H), 1.53–1.65 (m, 6 H), 1.80–1.91 (m, 4 H), 2.26 (m, 2 H), 3.03 (d, 2 H, J = 9.0 Hz), 3.38 (dt, 2 H, J = 7.3, 3.9 Hz), 3.98 (dd, 2 H, J = 10.2, 4.1 Hz); ^{13}C NMR 10.75, 16.91, 18.81, 23.27, 27.08, 30.18, 32.66, 40.58, 42.88, 77.20, 82.66, 84.27, 182.00; IR (neat) 2966, 2929, 2851, 1771, 1458, 1222, 1123, 1071, 1032, 1002 cm^{-1}; HRMS exact mass calculated for $C_{26}H_{42}O_6$ 450.2981, found 450.2969.

β-Dimethyl THF Podand 8c. Diisobutylaluminum hydride (1.0 M in hexanes) was added portionwise to a solution of **26** (100 mg, 0.222 mmol) in toluene (10 mL) at −20 °C and then stirred until TLC indicated the disappearance of starting material. The mixture was then poured into a slurry of ice (22 g) and acetic acid (6 mL) with rapid stirring. $CHCl_3$ (45 mL) was added, and the two-phase system was stirred vigorously for 10 min. Additional $CHCl_3$ (90 mL) was added, and the stirring was continued for 1 h. The organic layer was isolated, washed with aqueous $NaHCO_3$ (twice) and brine, and then dried over $MgSO_4$. Removal of solvent afforded the crude dilactol, which was placed in a dry flask containing triethylsilane (495 mg, 4.26 mmol) in CH_2Cl_2 at −78 °C under nitrogen. Boron trifluoride etherate (0.25 mL, 20.33 mmol) was then added dropwise, and the mixture was allowed to warm slowly to room temperature. After 3 h, the reaction was quenched at −20 °C by addition of saturated aqueous $NaHCO_3$. The solution was warmed to 25 °C and extracted with ether (3 times). The extracts were washed with brine and dried ($MgSO_4$). Solvent removal and flash chromatography (14–17% ethyl acetate in hexanes) afforded **8c** (80 mg, 85%) as a colorless oil: ^{1}H NMR 0.80 (d, 6 H, J = 6.3 Hz), 0.86 (d, 6 H, J = 7.0 Hz), 0.90 (s, 6 H), 0.96 (s, 6 H), 1.15–1.23 (m, 2 H), 1.43–1.49 (m, 2 H), 1.60 (m, 2 H), 1.82–1.94 (m, 6 H), 2.99 (d, 2 H, J = 9.0 Hz), 3.19 (dt, 2 H, J = 12.4, 2.8 Hz), 3.48–3.53 (m, 6 H); ^{13}C NMR 11.08, 17.05, 20.60, 23.69, 27.72, 30.36, 33.17, 41.26, 43.17, 78.79, 80.62, 82.82, 86.76; IR (neat) 2954, 2926, 2870, 2848, 1462, 1376, 1102, 1072, 1040 cm^{-1}; HRMS exact mass calcd for $C_{26}H_{46}O_4$ 422.3395, found 422.3375.

Determination of Enantioselective Binding. Binding experiments were executed by extracting an aqueous solution of a racemic guest alkylammonium chloride (0.3–1.2 M) and $LiPF_6$ (0.6–1.2 M) with a $CDCl_3$ solution (0.02–0.05 M) of the podand host molecule. The concentration of guest ammonium salt was made as large as possible so long as no guest was extracted into the organic phase in the absence of podand host. ^{1}H NMR analysis of the organic phase generally allowed for direct determination of enantioselectivity of binding because the host acts as a chiral shift reagent for extracted (bound) guest molecules (enantiomeric guests have diastereomeric complexes).

Extracted guests were also derivatized as Mosher amides as follows. The organic phase was treated with excess Et_3N and a large excess of Mosher's acid chloride (MTPACl). The Mosher's amide was then crudely purified by flash chromatography, and diastereomeric excess was determined by ^{1}H NMR and ^{19}F NMR spectroscopy. This procedure served as a confirmation of the direct ^{1}H NMR determination. In both procedures, absolute configurations were established by comparison with authentic materials.

Crystallization of Podand/Aluminum Perchlorate Complexes. All crystalline complexes whose X-ray structures were reported in the text were obtained as follows. The guest-free amine was treated with perchloric acid in methanol, and the corresponding perchlorate salt recrystallized. Podand (0.02 mmol) and the above perchlorate (0.02 mmol) were then dissovled in a minimum volume of *n*-butanol. After addition of ~0.5 mL of *n*-octane and mixing, the solvents were removed in vacuo to give a thick oil. After standing at room temperature for 1–3 days, the oil crystallized. The solid was collected and dissolved in a minimum volume of *n*-butanol at 70 °C. The solution was sealed in a small vial and allowed to stand at room temperature for 1–3 days, during which time the crystals used in the X-ray analyses formed.

Resolution of *o*-Bromo-α-phenethylamine (27) and MTPA Amide 28. *N*-Acetyl-L-leucine (2.16 g, 12.5 mmol) was added to a solution of *o*-bromo-α-phenethylamine (5.0 g, 25.1 mmol) in CH_2Cl_2 (150 mL). A white solid formed and was dissolved by gentle heating. Hexane (50 mL) was added, and the flask was sealed and allowed to stand overnight. After 12 h, a fine crystalline solid formed and was collected by filtration. The product was recrystallized as above to yield 1.8 g (39% yield) of the partially resolved leucine salt of **27**.

The crystalline salt (19 mg, 0.051 mmol) was suspended in Et_2O and washed twice with 0.5 N aqueous NaOH. The ether phase was dried ($MgSO_4$), and the solvent was removed at reduced pressure. The oily residue (**27**) was dissolved in CH_2Cl_2 (2.0 mL) and treated with diisopropylethylamine (44 μL, 0.255 mmol) and (*S*)-methoxy(trifluoromethyl)phenylacetyl chloride (65 mg, 0.046 mmol). After 2 h, the reaction mixture was washed with saturated aqueous NH_4Cl and the organic phase removed. The aqueous phase was extracted twice with additional CH_2Cl_2, and the organic phases were combined. After drying (Na_2SO_4) and solvent removal, the oily product (**28**, 20 mg, 95%) was isolated by flash chromatography on silica gel (10% ether in pentane).

NMR analysis revealed a 3:1 mixture of diastereomeric products: ^{1}H NMR major diastereomer 1.51 (d, 3 H, J = 6.8 Hz), 3.44 (q, 3 H, J = 1.6 Hz), 5.42 (m, 1 H), 7.1-7.6 (m, 10 H), minor diastereomer 1.54 (d, 3 H, J = 6.8 Hz), 3.47 (q, 3 H, J = 1.6 Hz), 5.39 (m, 1 H), 7.1-7.6 (m, 10 H); ^{13}C NMR 20.72, 49.29, 55.11, 123.02, 127.02, 172.16, 127.64, 127.78, 128.42, 128.55, 128.98, 129.46, 133.48, 141.11, 121.90, 125.85; IR (neat) 3329, 2926, 1686, 1508, 1450, 1269, 1165, 1106, 1025, 755 cm^{-1}; HRMS exact mass calcd for $C_{18}H_{17}NO_2BrF_3$ 415.0399, found 415.0346.

MTPA Amide of α-Phenethylamine 29. n-BuLi (1.0 mL of a 1.6 M solution in hexane) was added to a flame-dried flask at -100 °C containing the above aryl bromide **28** (20 mg, 0.048 mmol) in anhydrous THF (4 mL). After the mixture was stirred for 30 min, water was added with vigorous stirring. After this solution was stirred to room temperature, ether (5 mL) was added, and the resulting solution was washed with saturated aqueous NH_4Cl. After drying ($MgSO_4$), solvent removal gave the product as a colorless oil. ^{1}H NMR showed a 3:1 mixture of diastereoisomers, from which the major component was identical to the corresponding MTPA amide of authentic (S)-α-phenethylamine.

MTPA Amide of o-Methyl-α-phenethylamine 30. Partially resolved aryl bromide **28** was dissolved in dry HMPA (1.0 mL) under argon. $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) and tetramethyltin (79.2 mg, 0.44 mmol) were added, and the mixture was heated at 70 °C for 38 h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl. After extraction three times with Et_2O and drying ($MgSO_4$), the solvent was removed at reduced pressure, and the residue was rechromatographed on silica gel (8-12% ether in pentane). The product (**30**) was a 3:1 mixture of diastereoisomers (^{1}H NMR spectroscopy) whose components were identical to the corresponding MTPA amides of racemic o-methyl-α-phenethylamine: ^{1}H NMR major diastereomer 1.53 (d, 3 H, J = 6.9 Hz), 2.34 (s, 3 H), 3.43 (q, 3 H, J = 1.5 Hz), 5.33 (dq, 1 H, J = 1.5, 6.9 Hz), 6.96 (m, 1 H), 7.1-7.6 (m, 9 H), minor diastereomer 1.50 (d, 3 H, J = 6.9 Hz), 2.40 (s, 3 H), 3.36 (q, 3 H, J = 1.5 Hz), 5.36 (dq, 1 H, J = 1.5, 6.9 Hz), 6.96 (m, 1 H), 7.1-7.6 (m, 9 H); ^{13}C NMR 18.99, 20.64, 20.96, 45.54, 45.61, 121.72, 126.25, 126.30, 127.45, 127.55, 127.67, 128.45, 128.60, 129.42, 130.76, 130.85, 136.00, 140.60; IR (neat) 3415, 3335, 2965, 1686, 1502, 1452, 1266, 1167, 1100, 988, 758, 715 cm^{-1}; HRMS exact mass calcd for $C_{19}H_{20}NO_2F_3$ 351.1446, found 351.1460.

Supplementary Material Available: Crystallographic unit cell parameters and atomic coordinates for the four crystal structures described in the text (5 pages). Ordering information is given on any current masthead page.

Disulfide Bond Formation Using the Silyl Chloride-Sulfoxide System for the Synthesis of a Cystine Peptide

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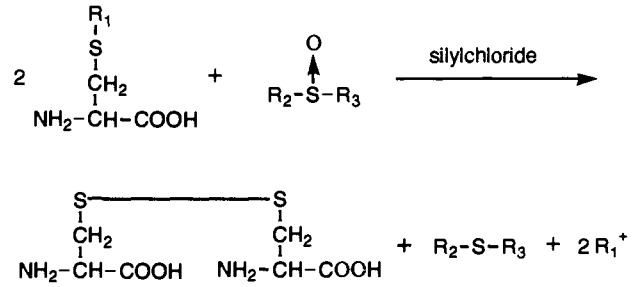
Abstract: An efficient method for disulfide bond formation in peptides by the silyl chloride-sulfoxide system is described. Methyltrichlorosilane in trifluoroacetic acid, in the presence of diphenyl sulfoxide, is found to cleave various S-protecting groups of cysteine to form cystine directly within 10-30 min. No side reactions were observed with nucleophilic amino acids such as Met, His, or Tyr, except for Trp, under the reaction conditions of the silyl chloride-sulfoxide treatment. A chlorination of the indole moiety of unprotected Trp, rather than sulfur-sulfur bond formation, is a dominant reaction when the peptide containing unprotected Trp is treated with the chlorosilane-sulfoxide. However, the disulfide bond can be formed efficiently with no modification at the indole ring by treatment of the peptide having a formyl-protected Trp residue with the silyl chloride-sulfoxide system. The formyl group is removed by a brief treatment at basic pH without affecting the disulfide bond formed by the silyl chloride-sulfoxide treatment. This new disulfide bond forming reaction in trifluoroacetic acid is successfully applied to the syntheses of oxytocin, human brain natriuretic peptide, and somatostatin without any solubility problem.

Introduction

For the synthesis of a cystine-containing peptide such as calcitonin, insulin, or a variety of growth factors, a disulfide bond forming reaction is a key step in both solution- and solid-phase syntheses. In general, air oxidation or iodine oxidation has been employed for this reaction. However, several problems associated with the formation of a disulfide bond using these conventional methods have been overlooked.[1]

Air oxidation is one of the mildest methods to construct a disulfide bond but usually requires a long reaction time (several hours to several days).[2] The reaction also requires a high dilution of reduced peptide to prevent the formation of different conformers or polymers.[3] In addition, hydrophobic or basic peptides tend to aggregate and precipitate out of the solution in spite of these mild reaction conditions since the reaction has to be conducted in aqueous medium at slightly basic pH.[4] In contrast, the disulfide bond can be formed within a relatively short time (several minutes to several hours) by iodine oxidation of the peptide having S-Acm[5] or Trt cysteine.[6] The reaction can be performed in both aqueous and organic medium at acidic pH. However, the iodine oxidation needs particularly controlled conditions since several nucleophilic amino acids such as Met, Tyr, His, and Trp are susceptible to

Scheme I



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