Chiral Molecular Tweezers†

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ABSTRACT

In this Account, a summary of our work on the synthesis and chemistry of chiral molecular tweezers and certain related species is presented. The framework around which the structures to be discussed were built was Kagan's ether, a short history of which will be given. Chiral molecular tweezers of various sizes were constructed and shown to exhibit binding to various π acids. An analysis of chiral recognition was performed using variable temperature chiral high-performance liquid chromatography. It was shown that the chiral discrimination was essentially enthalpic in nature. Other forays into the chemistry of Kagan's ether analogues have also been made through the synthesis of a chiral catalyst and a chiral molecular square.

Introduction

Molecular Tweezers. The term molecular tweezer was coined by Whitlock to describe a simple molecular receptor characterized by two flat, generally aromatic pincers, separated by some kind of tether, a tether that is more or less rigid.[1] In their original publication, Whitlock and Chen described molecular tweezers represented by **1**, in which two caffeine molecules were separated by a diyne spacer (Figure 1). Molecular tweezers of this type were described as possessing two of the three features needed to enhance the binding of an aromatic guest molecule. These are (1) the presence of a spacer that prevents self-association, (2) a spacer that establishes a distance between the pincers of the tweezer of about 7 Å (plane to plane or centroid to centroid), ideal for the inclusion of a single aromatic guest, and (3) a spacer that holds the pincers rigidly in a syn conformation. The diyne tether of **1** did not meet this latter criterion, but the definition and criteria established by Whitlock clearly set the stage for further developments.

Zimmerman and co-workers exploited these principles to design new molecular tweezers that made use of a spacer that enforced a syn conformation of the complexing pincers (referred to as chromophores) of the tweezer.[2] Two representative examples are depicted as **2** and **3** (Figure 2). Such tweezers still exhibit conformational mobility. The pincers can potentially rotate about the bonds that connect them to the spacer, and they do, even

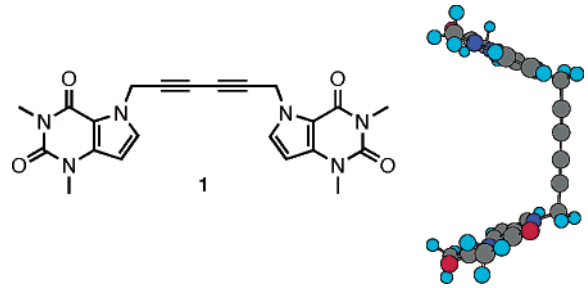

FIGURE 1. A molecular tweezer prepared by the Whitlock group.

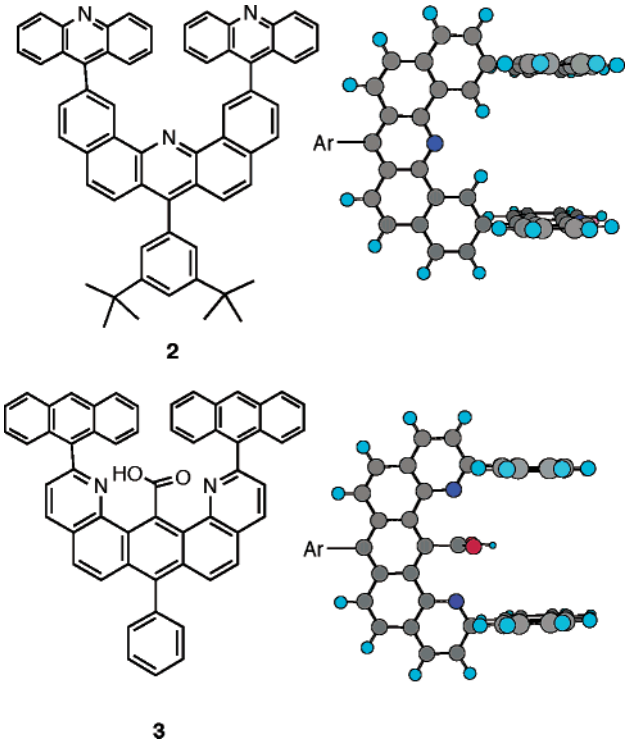

FIGURE 2. Examples of rigid molecular tweezers prepared by the Zimmerman group.

when the pincers are substituted with sterically bulky groups. This potential problem actually contains within it a solution to a different problem. As the pincers rotate, the distance between them changes, shrinking by a relatively large amount. Such rotation changes the cavity size into which a guest might fit, allowing some optimization to take place during the binding process. Another interesting feature of these tweezers is the functional group imbedded deep within the cavity of each tweezer. This has especially important implications for **3**, which has been used to bind adenine with very high affinity.

Another class of molecular tweezers pioneered by Klärner and co-workers is represented by compounds **4** (Figure 3) and **5**. Compound **5** has been referred to as a molecular clip, but it is worth noting that although the concepts of molecular tweezers and molecular clips are sometimes considered separately, there seems to be relatively little to distinguish the two groups. It should also be pointed out that the concept of molecular tweezer as

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† This paper is dedicated to the memory of Mildred Brudd.

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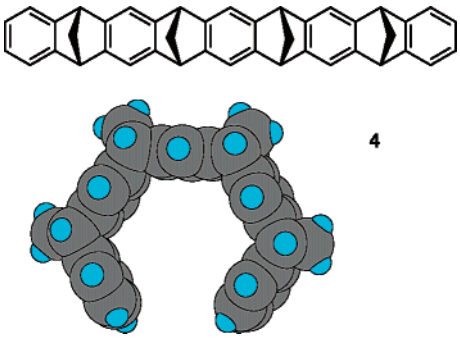
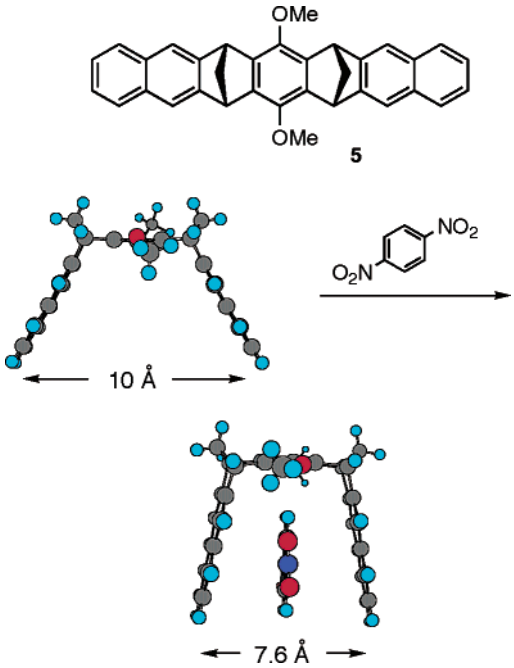
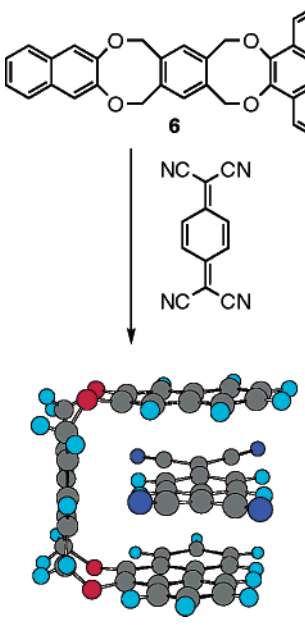


FIGURE 3. A molecular tweezer prepared by the Klärner group.

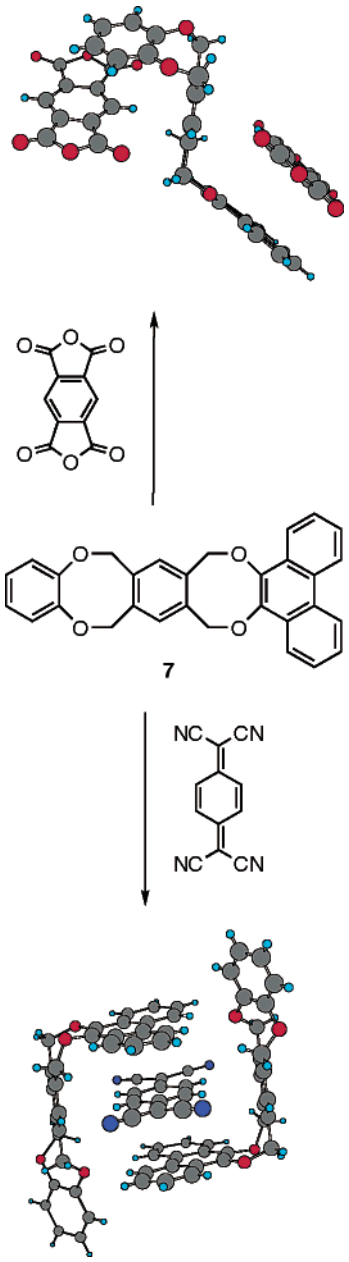
Scheme 1. Illustration of the Tweezer-like Motion of 5 upon Guest Binding



Scheme 2. A Flexible Molecule Tweezer Prepared by the Fukazawa Group Is Capable of Adopting a Conformation to Achieve Guest Binding

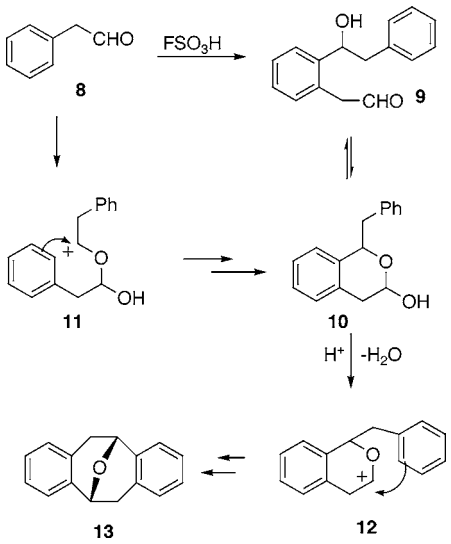


Scheme 3. A Flexible Molecular Tweezer Prepared by the Fukazawa Group That Does Not Bind Guests



defined by Whitlock is slightly modified in **4**. Thus, although the pincers of the tweezer **4** are held apart by the rigid spacer, they are not parallel and are expected to form complexes with guests that are more encapsulated by the host than by a less curved molecular tweezer. Indeed, **4** is not far removed from being a macrocycle. On the other hand, a species such as **5** is more in accord with the definition of the molecular tweezer presented above. In fact, it really does behave like a tweezer. It even closes on guests in a tweezer-like fashion as shown in Scheme 1. The distance between the tweezer's pincers is around 10 Å before guest complexation, as measured between the endmost, equivalent carbon atoms at each end of the structure (X-ray). Reaction with 1,4-dinitrobenzene produces a host–guest complex in which this distance has been reduced to 7.6 Å.[3] Other examples of

Scheme 4. Synthesis of Kagan's Ether and Proposed Mechanism of Formation



this behavior have been documented. Details of this elegant work have been recently summarized.[4]

A different class of molecular tweezers has been introduced by Fukazawa and co-workers.[5] These are represented by **6** and **7**. Rather than possessing a rigid spacer between the pincers, these systems are rather flexible, but sufficiently so that adopting a conformation necessary for guest binding is not so energetically demanding as to preclude binding. Interestingly, tweezer **6** can form 1:1 complexes with guests in the solid state and in solution in which the pincers do clamp down on the guest (Scheme 2). In contrast, tweezer **7** formed 1:2 and 2:1 host−guest complexes in the solid state, the phenylene pincer apparently not being large enough to favorably interact with a guest (Scheme 3).

Many other types of molecular tweezers are known, but details of their chemistry are beyond the scope of this review. Suffice it to say that any molecular cleft in which convergent functional groups are separated by a spacer to create a cavity for guest binding might be and has been called a molecular tweezer. Thus, various molecular clefts,[6] clips,[7] and jaws[8] might all be considered molecular tweezers. Furthermore, compounds that possess some kind of hinge and can open and close in a tweezer-like fashion have been referred to as molecular tweezers.[9]

Kagan's Ether. Our work is based on the scaffold known as Kagan's ether, and it is instructive to present some details on the history of this compound. Kagan and co-workers reported the formation of **13** in 14% yield upon treatment of phenylacetaldehyde with fluorosulfonic acid in carbon tetrachloride.[10] Two possible mechanisms for the formation of **13** have been proposed (Scheme 4). One begins with ortho alkylation of one molecule of phenylacetaldehyde (**8**) by another to form **9**, followed by lactol formation, oxocarbenium ion formation, and ring closure (**9** → **10** → **12** → **13**). The other begins with attack of one aldehyde functionality on another to form **11**. Intramolecular alkylation then proceeds to give **10**, which goes to product as previously described. Jung and co-workers

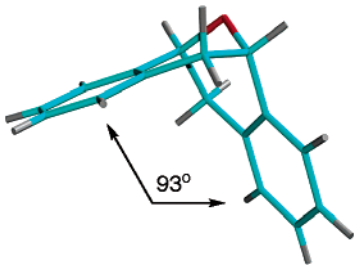


FIGURE 4. Crystal structure of Kagan's ether.

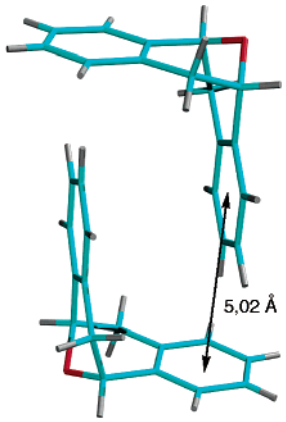
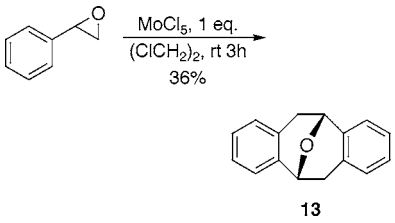


FIGURE 5. Crystal structure of Kagan's ether showing "dimerization" in the solid state.

described the preparation of **13** soon after Kagan's initial report, trimethylsilyl iodide (TMSI) being the reagent used to induce bicyclic ether formation.[11] Functionalized analogues of Kagan's ether have been prepared.[12] Other approaches to Kagan's ether have been attempted. For example, although low yields of **13** were obtained by treating styrene oxide with FSO_3H,[12] a recent patent reports that the reaction of styrene oxide with $MoCl_5$ in 1,2-dichloroethane affords **13** in 36% yield (eq 1).[13]



(1)

What attracted our attention to **13** was its shape and chirality. The crystal structure of **13** shows that the molecule is bent with a 93° angle between the two phenylene rings (Figure 4).[14] We reasoned that by allowing two molecules of **13** to share a phenylene ring, we might be able to produce compounds that behaved as molecular tweezers and were chiral as well.

Interestingly, **13** packs in the crystal as a dimer joined by edge−face interactions between the two monomers, one phenylene ring in each serving as a hydrogen bond donor and another as an acceptor (Figure 5). The centroid to centroid distance between the two interacting aromatic rings is 5.02 Å, giving a H-to-centroid distance of 2.66 Å. The centroid−H−centroid angle is 1.3°. These might be described as typical values for this edge−face interaction.

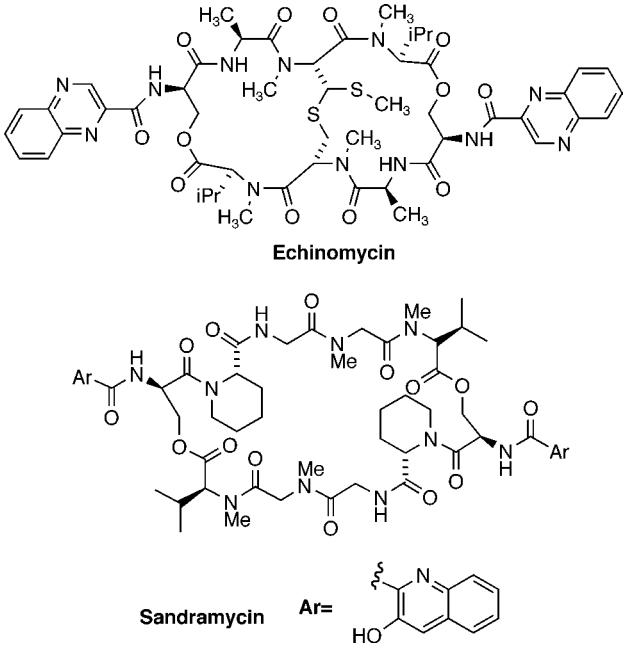


FIGURE 6. Examples of naturally occurring chiral molecular tweezers.

Edge−face interactions are generally recognized as weak but important factors in the interaction between aromatic systems.[15] As observed in Kagan's ether itself, such interactions turned out to be quite important in the host−guest chemistry of the molecular tweezers built from this scaffold. Because of the twist in the molecule, there is very little stacking between the phenylene rings.

Chiral Molecular Tweezers. There is in fact not much known about chiral molecular tweezers. The quinoxaline and quinoline antitumor antibiotics, such as echinomycin and sandramycin (Figure 6), are representative of a family of compounds that possess rigid, cyclic depsipeptide or peptide backbones to which are appended heterocyclic rings that serve as pincers as the compounds bind DNA.[16] It was compounds of this type that served as a motivation for one of our studies involving synthetic molecular tweezers.

Synthetic chiral molecular tweezers are rare. Maitra and co-workers have reported the synthesis of such tweezers using a bile acid as a scaffold. An example (**14**) is shown in Figure 7.[17] These bind electron-deficient aromatic species with reasonable affinities.

In work somewhat related to our own, Pardo and co-workers prepared the chiral molecular tweezer **15** (Figure 8), using Tröger's base as a scaffold around which the tweezer was built.[18] The crystal structure shows that two molecules interact with each other in the solid state. A displaced edge−face interaction is evident; the hydrogen of the nitrated ring of one tweezer is positioned directly over a single carbon atom of the methylated ring of the other tweezer. The centroid to centroid distance between the rings is 5.5 Å. Interestingly, the distance between the endo methylene hydrogens of **15** and the oxygens of the "guest" nitro group is between 2.47 and 2.57 Å, a rather close contact.

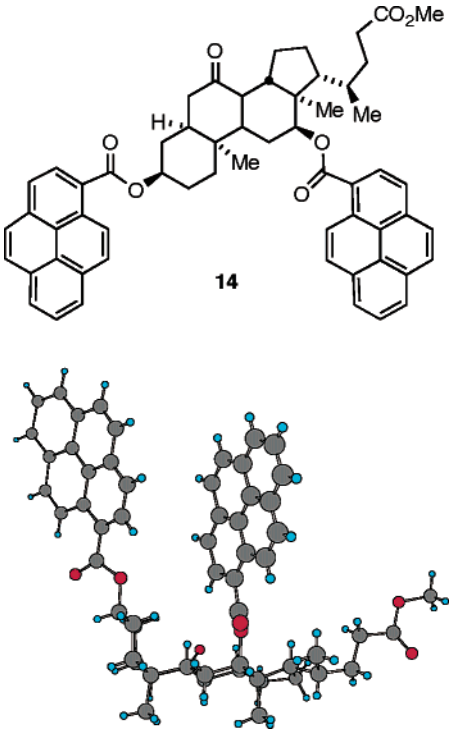


FIGURE 7. A chiral molecular tweezer prepared by the Maitra group.

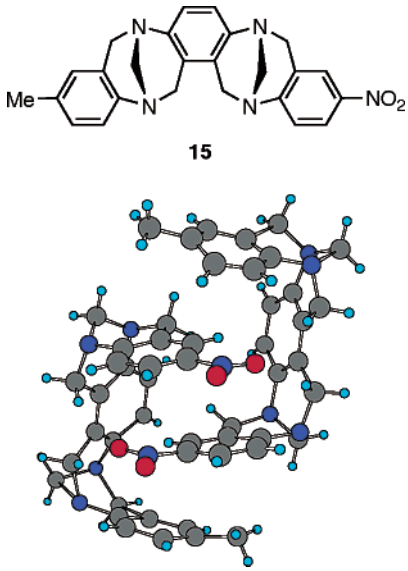


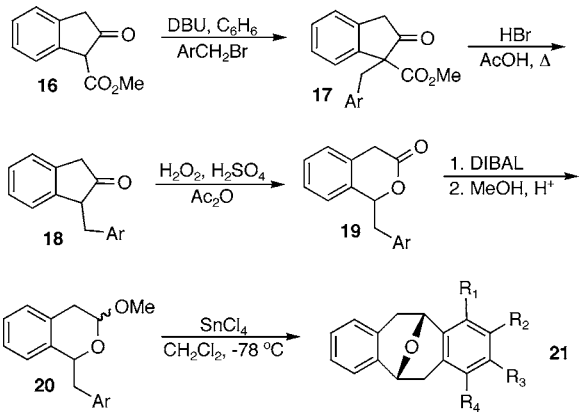
FIGURE 8. A chiral molecular tweezer prepared by the Pardo group.

Synthesis of Kagan's Ether Analogues

Our first endeavor in this area was to establish a synthetic route to molecular tweezers. We anticipated the need for a stepwise approach and thus developed a route to Kagan's ether analogues.

Our approach began with 1-carbomethoxy-2-indanone (**16**), a readily available compound (Scheme 5).[19] Deprotonation with the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and alkylation with a benzyl halide afforded **17**. Decarboxylation was accomplished by heating in acetic acid in the presence of concentrated HBr to give **18**. A Baeyer−Villiger oxidation that made use of 90% H_2O_2

Scheme 5. Synthetic Route for the Preparation of Unsymmetrical Analogues of Kagan's Ether



served to produce lactone **19**. Reduction with DIBAL and acetal formation afforded **20**. These compounds could be treated with $SnCl_4$ in dichloromethane at low temperature to afford **13** and various analogues **21**, generally in good to excellent yields. The reaction did not work, however, when even a slightly deactivating bromo substituent was on the aryl ring. This has implications for the synthesis of molecular tweezers using this chemistry, but they are not serious.

A Simple Chiral Molecular Tweezer: Clathrate Formation

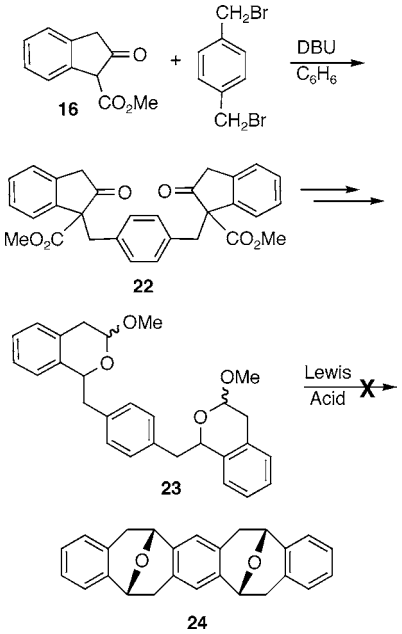
The methodology that we developed was applied to an "outside-in" approach to the synthesis of a chiral molecular tweezer. Ketoester **16** was alkylated with 1,4-bis-(bromomethyl)benzene and converted uneventfully over several steps to **23**. However, all attempts to convert **23** to molecular tweezer **24** were unsuccessful, only small amounts of the desired product being formed (Scheme 6).

In light of this problem, we decided to pursue an "inside-out" approach to **24**. Thus, the bis-acetal **25** was prepared over several steps from 1,4-dibromo-2,5-dimethylbenzene. Halogen−metal exchange and quenching with phenylacetaldehyde afforded the *d*,*l* and meso isomers of **26** in 35% yield each. Treatment with tosic acid followed by ring closure with $SnCl_4$ afforded **24** and **27** in 57% and 75% yields, respectively (Scheme 7).[20]

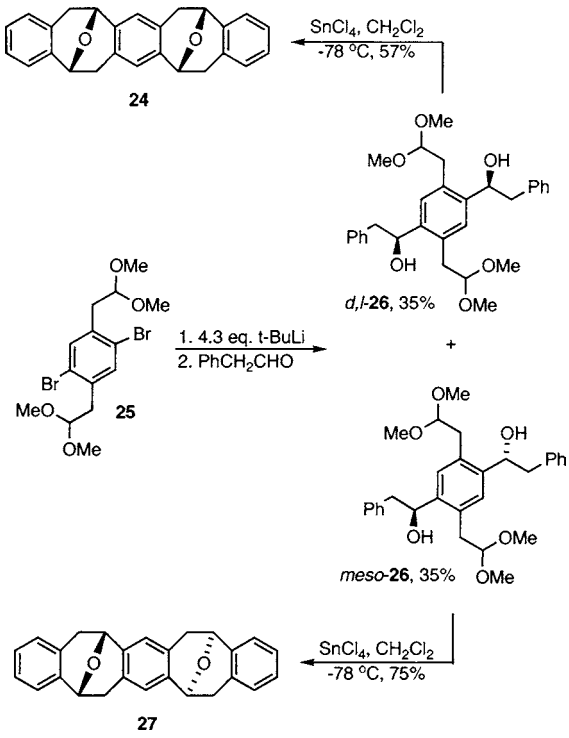
It is interesting to note that the separation of the isomers of **26** was quite easy, due to large differences in their polarity. This difference in polarity arises from a difference in relative configurations between the molecules and preferred conformations that result from the minimization of benzylic strain.[21] Thus, *meso*-**26** possesses a conformation that places one hydroxy group on each side of the plane defined by the central phenylene ring. However, in *d*,*l*-**26** both hydroxy groups are on the same face of this plane, giving the molecule one relatively very polar face, which facilitates absorption to silica gel (Figure 9).

We attempted to bind π acids to the cleft within **24**, but had no success. NMR studies showed little to no

Scheme 6. Unsuccessful Initial Route to Molecular Tweezer 24



Scheme 7. Successful Route to the Molecular Tweezer 24 and Its Diastereomer 27



interactions between **24** and a variety of π acids. In the solid state, however, racemic **24** crystallized from ethyl acetate to form a structure in which two tweezer molecules faced each other, though somewhat offset. Measurements associated with this structural motif are shown in Figure 10. The arrangement created a cavity between the tweezers with dimensions large enough to include a solvent molecule (10.7 Å × 7.3 Å). Offset stacks of these empty spaces created infinite channels in the crystal structure. The inclusion complex with ethyl acetate was fairly stable, surviving at 0.1 Torr at room temperature for

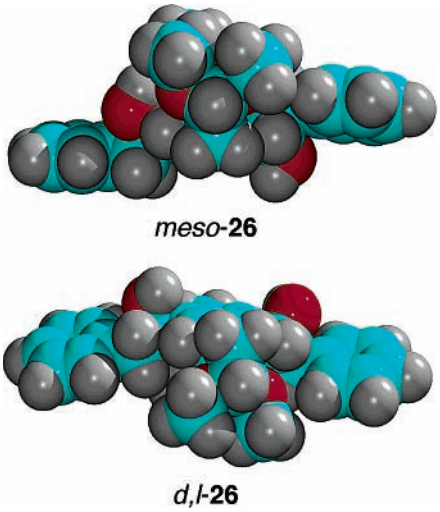


FIGURE 9. Minimized conformations of the diastereomers of **26** illustrating the origins of their polarity differences.

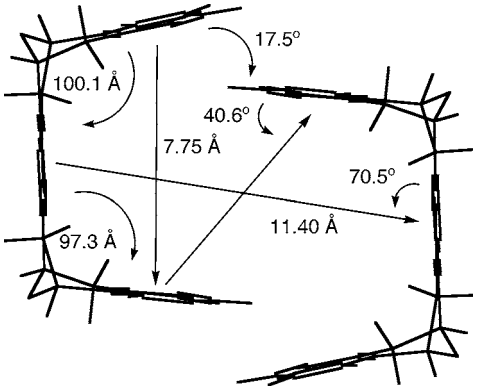


FIGURE 10. Crystal structure of the clathrate of **24** and ethyl acetate showing distance and angle relationships between two face-to-face, but offset, molecular tweezers.

12 h without change. The ratio of **24** to ethyl acetate appeared to be 2:1 according to the crystal data, but NMR suggested a 2.7:1 ratio, probably due to the inclusion of other volatiles or loss of solvent molecules near crystal edges.

The ethyl acetate between the tweezers was disordered at room temperature, but a better idea of its location within the cavity was gleaned from a lower temperature (163 K) crystal study. A structure is shown in Figure 11. The shape of the ethyl acetate within the cavity resembled an (*E*) alkene, and we hypothesized that **24** might be useful in separating mixtures of small disubstituted alkenes. All attempts to realize this failed.

Other small esters appeared to form clathrates with **24**, but these were not characterized. However, an attempt was made to take advantage of the oxygen bridges in **24** and the phenomenon of halogen bonding[22] in the hope of creating a crystal structure with two kinds of channels, one formed by solvent inclusion as discussed above and the other formed by a cavity created through halogen bonding between oxygen atoms of adjacent tweezers.

In the event, crystal growth from a solution of **24** and iodine in ethyl acetate afforded crystals that indeed contained both iodine and **24** but no solvent molecules

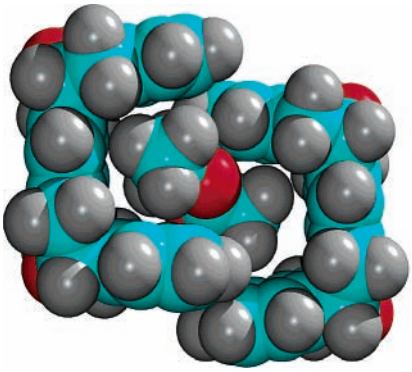


FIGURE 11. Crystal structure of the clathrate between **24** and ethyl acetate.

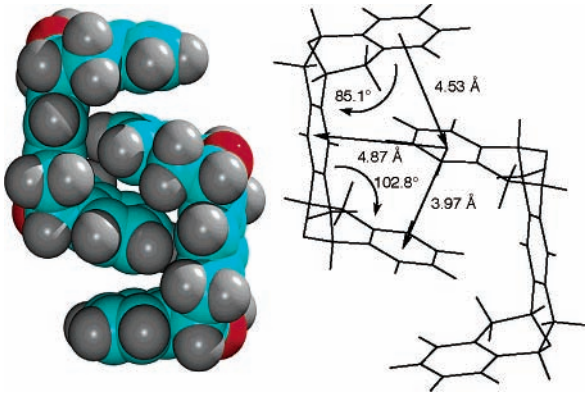


FIGURE 12. Portion of the crystal structure of **24**/I_2 inclusion complex.

and no channels or spaces into which a guest might locate.[23] In this structure, the tweezers collapsed into each other forming a "yin–yang" structure as shown in Figure 12. An edge–face interaction and an offset stacking arrangement are evident in this structure. The centroid–centroid distance in this "dimer" was 4.87 Å, corresponding to a H–centroid distance of 2.67 Å. These and other measurements are shown in Figure 12. The iodine was nestled in a cavity created by two opposing molecules of **24**, surrounded by four other dimer units of **24**, sealing off the cavity. A structure is shown in Figure 13. The oxygen–iodine distance was 2.82 Å, and the iodine–iodine bond distance was 2.70 Å. This latter value is slightly longer than the I–I bond in iodine (2.66 Å), as expected when electron donation occurs to the antibonding orbital of the iodine molecule. The I–O distance is much shorter than the sum of the van der Waals radii of both elements (3.63 Å) and larger than the sum of the covalent radii (1.99 Å). These results are rather typical.[24]

Compound **27** was characterized by crystallography.[25] The packing of this compound involves edge–face interactions as shown in Figure 14. No further studies on this compound were conducted.

We also prepared a functionalized version of **24**, namely, the bis-phenol **30**.[26] This compound was a solid but not crystalline and did not appear to form clathrates or interact with π acids. Interestingly, we were able to show in the synthesis of **30** that a sufficiently nucleophilic arene can undergo cyclization with protic acids (Scheme

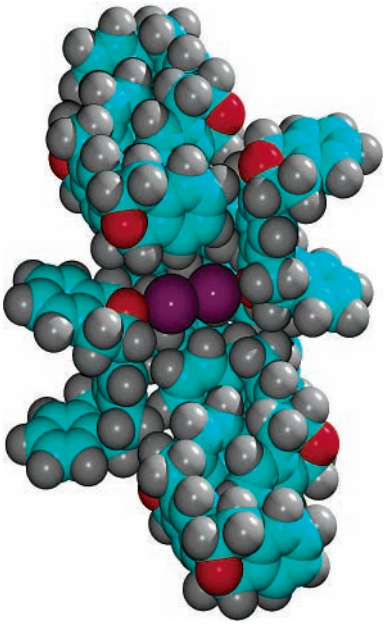


FIGURE 13. Portion of the crystal structure of **24**/I_2 inclusion complex showing I_2 in halogen bonding with oxygens of molecules of **24**.

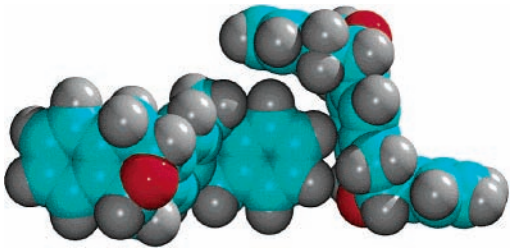
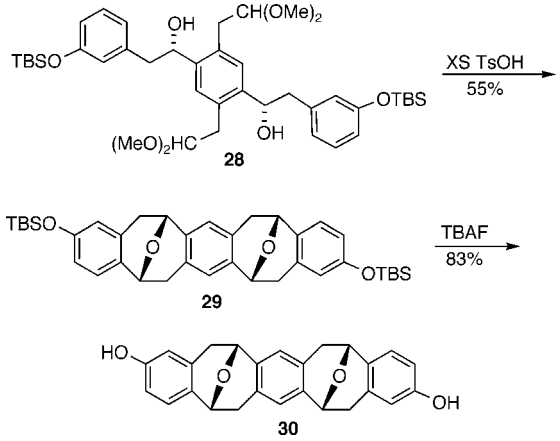


FIGURE 14. Crystal structure of **27**.

Scheme 8. Synthesis of Functionalized Tweezer 30



8). Thus, treatment of **28** with excess tosic acid in CH_2Cl_2 at room temperature afforded **29** in 55% yield, an improvement in terms of both yield and step count with respect to the procedure using $SnCl_4$. Desilylation with fluoride then gave **30**.

Deeper Tweezers I: Naphthalene Pincers

Upon finding that **24** could not effectively bind π acids, we set out to prepare a tweezer that had larger pincers and would thus possess a deeper cleft or pocket into which a guest might fit. We had three choices with respect to a target possessing naphthalene pincers. These are shown in Figure 15. As can be seen, the "overlap" between these pincers is best for **31** and **32** and worst for **33**. We chose **32** as our target and successfully prepared the compound in the same fashion as for **24**.[27]

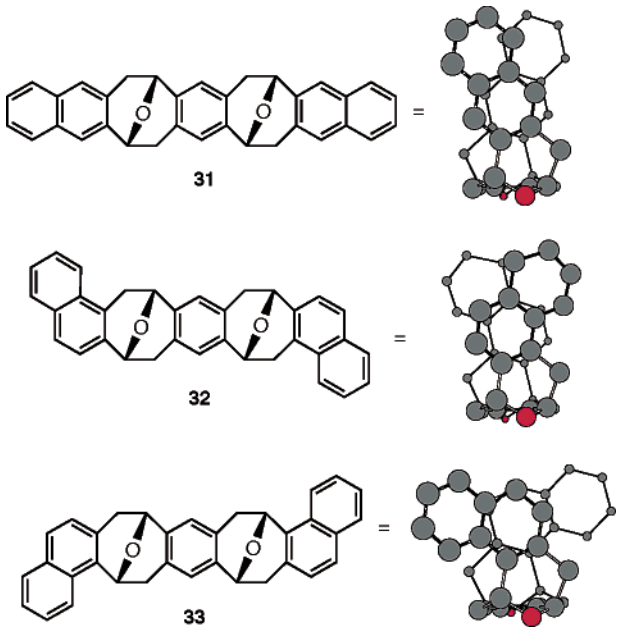


FIGURE 15. Possible chiral molecular tweezers with naphthalene pincers.

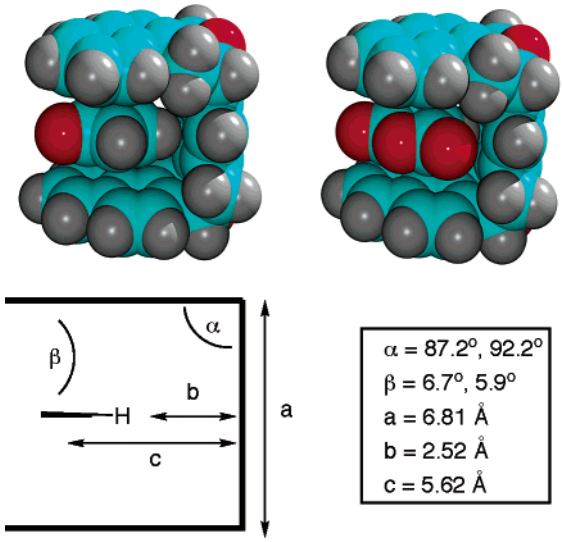


FIGURE 16. Crystal structure of maleic anhydride/**32** complex.

In contrast to **24**, **32** formed solid-state inclusion complexes with π acidic systems. For example, when **32** and maleic anhydride were dissolved in $CHCl_3$ and the solvent was allowed to evaporate slowly, crystals of a host–guest complex were formed. Two views of the complex are shown in Figure 16, along with a diagram indicating various distances and angles. The distance between the naphthalene groups of tweezer **32** is 6.81 Å. These rings are also nearly perpendicular to the central

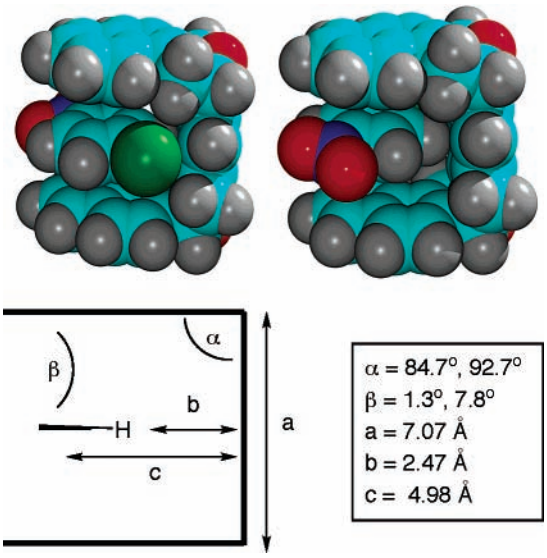


FIGURE 17. Crystal structure of 4-chloronitrobenzene/**32** complex.

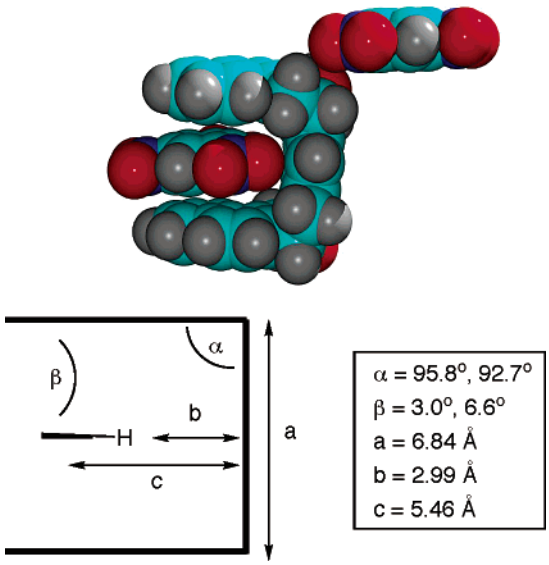


FIGURE 18. Crystal structure of 2TNB/**32** complex.

phenylene ring of **32**. Finally, they are very nearly parallel to the plane defined by the guest.

As might be expected, an edge−face interaction exists between the maleic anhydride and the host with a calculated H−centroid distance of 2.52 Å. Stacking interactions are also apparent in the complex. Although other factors may be important in the solid state, these two features are common to all of the inclusion complexes of **32** that we have studied and to other related molecular tweezers.

The host−guest complex arising from the binding of 4-chloronitrobenzene showed these common features. Views of the complex and relevant measurements are given in Figure 17. Interestingly, the complex is formed regioselectively in the solid state. In principle, hydrogens ortho to either the nitro group or the chloro group could interact with the phenylene ring of **32**. Only those ortho to the chlorine do so. Although this might be a result of packing forces, it is possible that the length of the carbon−chlorine bond (1.74 Å) allows a closer approach of the electropositive ortho hydrogen to the phenylene ring of **32** than would be possible for those ortho to the nitro group, leading to a stronger stabilizing interaction.

The complex between **32** and 1,3,5-trinitrobenzene (TNB) showed features similar to the others. Structural details are given in Figure 18. Two features of this structure are of particular interest. First, the calculated distance of the hydrogen of the guest oriented toward the phenylene ring of **32** is 2.99 Å, much larger than that observed in the complexes of **32** with the other two guests. Presumably, this is due to unfavorable interactions of the nitro groups of the guest with the hydrogens on the phenylene ring of the tweezer, which preclude a closer approach. Second, the crystals obtained in this experiment were formed in a 2:1 stoichiometry of TNB/**32**. One of the TNB molecules is within the host. The other is located outside. It apparently forms a hydrogen bond to the oxygen of one host and stacks on top of another host. This means two host−guest units are joined via this TNB molecule.

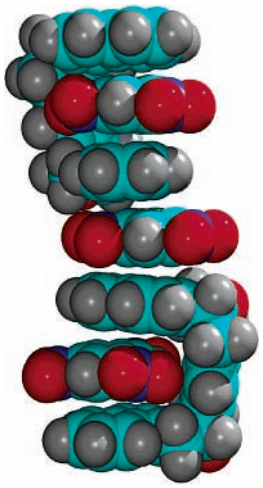


FIGURE 19. Crystal structure of 2TNB/**32** complex showing a portion of infinite π stacks.

Further, the extra TNB molecule results in a packing arrangement in which infinite π stacks are created in the crystal structure (Figure 19). This differs from the other host−guest complexes, which pack in a herringbone fashion, complexes in one layer interacting with complexes in the next layer via edge−face interactions.

Solution phase binding studies with **32** and TNB were conducted using NMR titration experiments. In chloroform at room temperature, the data indicated a binding constant in the range of 45−120 M^{-1}.

Deeper Tweezers II: Dibenzofuran (DBF) Pincers.

A tweezer with a pocket deeper than **32** is **34**, which we synthesized.[28] A crystal structure of the TNB complex of this host is shown in Figure 20, along with relevant measurements. There is nothing too surprising about the complex, except that the calculated distance from the hydrogen on the TNB to the centroid of the phenylene ring (*b*, Figure 20) of **34** is 3.22 Å, substantially larger than

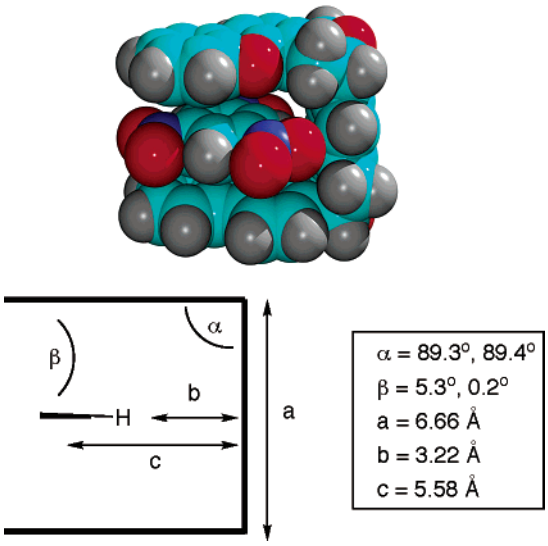
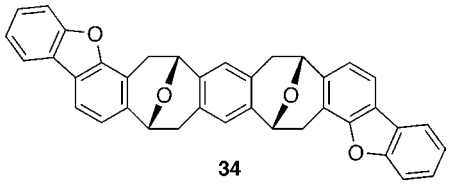


FIGURE 20. Crystal structure of TNB/**34** complex.



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the corresponding distance in the **32**/TNB complex. One rationalization for this is that the greater surface area provided by the DBF pincers in **34** simply gives the TNB room to move, minimizing untoward steric interactions. It also then suggests that the edge−face interaction may not be that stabilizing, an idea that has been supported in a number of studies.[15]

Solution studies of **34** with TNB in chloroform solution gave a binding constant of 2000 M^{-1}. This is as expected on the basis of the greater surface area within the cavity of the tweezer.

Recognition of a Chiral Guest by a Chiral Molecular Tweezer.

We pursued chiral recognition by **34** using chiral chromatography. A chiral π acidic stationary phase, a (3*R*,4*S*) Whelk-O 1 column, was used in the study. The structure of the chiral selector of this column is shown in Figure 21. Because of its resemblance to TNB, it was anticipated to be a good guest for **34**.

We initially investigated the effect of solvent on enantioselectivity. The results are summarized in Table 1, which presents retention factors (k_1) for the least strongly bound enantiomer and separation factors (α), which correspond to enantioselectivity. For mixtures of alcohols in CH_2Cl_2, enantioselectivity decreased with decreasing size of the alcohol (entries 1−3). Ethyl acetate gave the worst enantioselectivity (entry 4). Also in Table 1 are k_1 and α values for **13** and **24** using 20% 2-propanol (IPA) in CH_2Cl_2 as an eluent. Both numbers increase as a function of surface area of the host. The final entries of Table 1 further illustrate the dependence of solvation on enantiomer recognition. The implication is that although

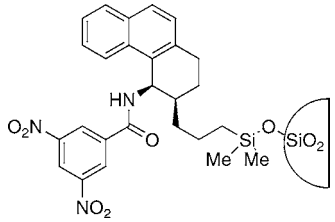


FIGURE 21. Chiral selector on the WhelkO 1 HPLC column.

Table 1. Chromatographic Data for Molecular Tweezers on a (3*S*,4*R*)-Whelk-O 1 Column

entry	solvent	tweezer	α	k_1
1	20% IPA/CH_2Cl_2	**34**	1.75	0.92
2	20% EtOH/CH_2Cl_2	**34**	1.65	0.85
3	20% MeOH/CH_2Cl_2	**34**	1.57	0.89
4	EtOAc	**34**	1.36	1.60
5	20% IPA/CH_2Cl_2	**13**	1.21	0.096
6	20% IPA/CH_2Cl_2	**24**	1.40	0.12
7	20% IPA/hexane	**24**	1.25	12.22
8	CH_2Cl_2	**24**	1.40	0.67

Table 2. Results from Variable Temperature HPLC Analysis of Dibenzofuran and 34 on a (3*S*, 4*R*)-Whelk-O 1 Column Using 10% IPA in CH_2Cl_2 as Eluent

entry	compound	ΔH (kcal/mol)	ΔS (cal/(mol K))
1	dibenzofuran	−1.76	−9.9
2	all *R* **34**	−1.40	−5.2
3	all *S* **34**	−1.89	−5.5

solvation of hosts and guests by an achiral solvent should not be different for individual hosts and guests, the complexes are diastereomeric and could be stabilized to different extents by solvation.

The extent to which enantiomer discrimination could be achieved was examined using a variable temperature HPLC study. With 10% IPA in CH_2Cl_2 as eluent, **34** was chromatographed on the (3*R*,4*S*) Whelk-O 1 column between 0 and 70 °C. A van't Hoff analysis was performed, and the results are summarized in Table 2, along with data for dibenzofuran. It was interesting to see that the enthalpy change for dibenzofuran was about the same for both enantiomers of the tweezer, although the tweezer has two pincers with which to bind a guest. However, the entropy lost to dibenzofuran was about twice that for either tweezer. In the end, the discrimination between the enantiomers was found to be enthalpic in nature, the more strongly bound enantiomer binding better by 0.5 kcal/mol.

We proposed that the more strongly bound enantiomer of **34** would have the all *S* configuration. In collaboration with the Fleischauer group, we subsequently determined the absolute configurations of the enantiomer via preparative chromatographic separation, determination of the CD spectrum for each and comparison of these data to calculated spectra.[29] In fact, the more retained isomer of **34** on the (3*R*,4*S*) Whelk-O 1 column was the all *S* enantiomer.

An Expanded Tweezer.

In the hope of building tweezers that could function as DNA bis-intercalators, we decided to pursue the synthesis

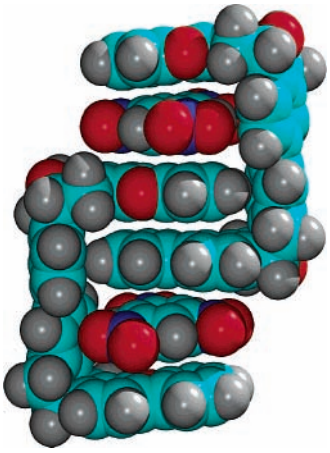
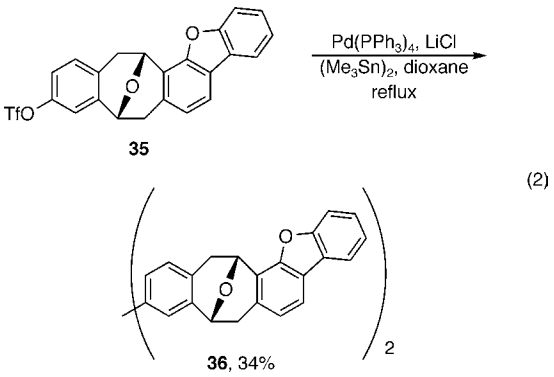


FIGURE 22. Crystal structure of TNB/**36** complex.

of an expanded tweezer. The site exclusion principle implies that DNA bis-intercalators should be built such that the distance between the pincers is around 10.5 Å, sufficient to bind two base pairs.[30] Nature has constructed many bis-intercalators in accord with this principle (cf. Figure 6). We thus set out to begin a study aimed at discovering whether expanded molecular tweezers could be made and whether they would bind guests. To that end, we chose to synthesize and explore the molecular tweezer **36**.[31]

The synthesis of **36** was largely in accord with reactions already discussed. Key to its preparation was a self-coupling of the triflate **35**. Treatment of this compound with hexamethyl ditin in the presence of palladium afforded the tweezer **36**, in addition to a methylated side product (eq 2). This reaction was performed on the



(2)

racemic triflate, yet only the chiral, but racemic, tweezer was isolated, suggesting an interesting stereoselectivity in the coupling step.

The inclusion complex of **36** with TNB was grown from a chloroform–methylene chloride–nitrobenzene solution. A structure is shown in Figure 22, along with relevant measurements. Despite the degree of freedom afforded by the biaryl linker, the tweezer has its pincers oriented in the same direction. The space between the pincers is appropriate for the inclusion of two aromatic guests (10.4 Å). Stacking and edge–face interactions were predictably in place. Packing of these units does not give rise to infinite π stacks, but instead each assembled unit of two

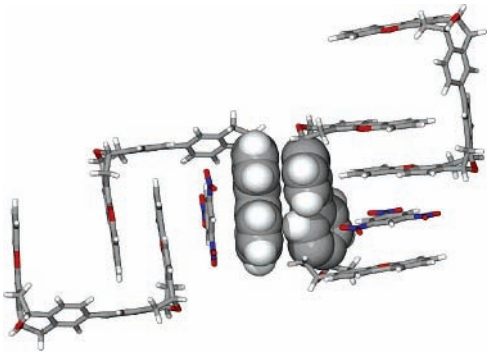
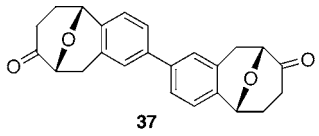


FIGURE 23. Crystal structure of TNB/**36** complex showing packing interactions in the crystal.

tweezers and two guests packs in a bottom to side fashion such that a dibenzofuran of one host–guest group interacts with the biphenyl unit of another group via both stacking and an edge–face interaction (Figure 23).

Of course, **36** would not be suitable for applications with nucleic acids, due to its lack of water solubility. Furthermore, it would be appropriate to synthesize a series of molecular tweezers in a high-throughput fashion. To that end, a scaffold such as **37** would be useful because



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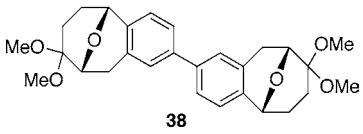

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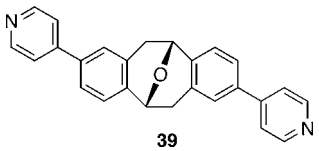
it could be used to prepare a number of tweezers via various annulation reactions such as the Fisher indole synthesis and the Friedländer quinoline synthesis. We have recently prepared **38** and are working toward these goals.

Other Structures Derived from Kagan's Ether

Kagan's ether is a chiral structure the application of which is not limited to the synthesis of molecular tweezers. We recently incorporated it into a chiral salen complex, though without much success.[32] We also used it to prepare a chiral molecular square, using ligand **39** to assemble around a metal center.[33] This work is still in its infancy.



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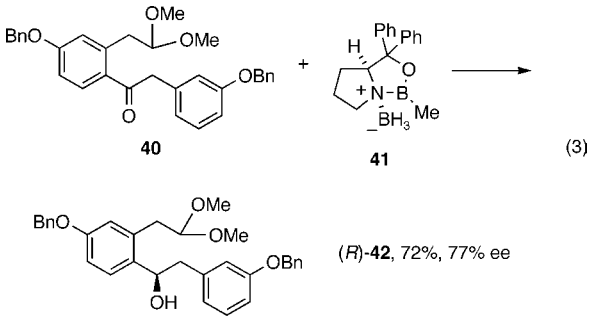
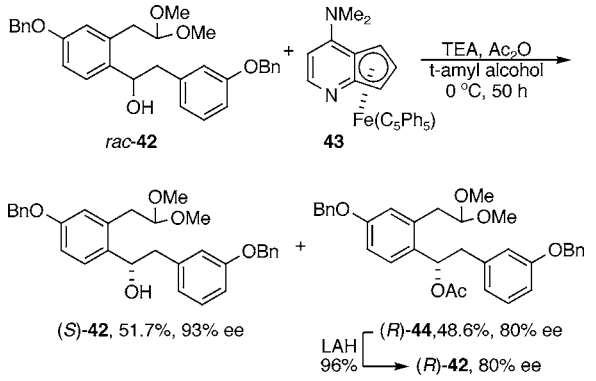
It is worth mentioning some chemistry associated with this research that is relevant to the synthesis of chiral molecular tweezers. In our approach to **39**, we reduced ketone **40** with oxazaborolidine **41** and obtained the alcohol (*R*)-**42** in 77% ee (eq 3). Enantiomeric purity was achieved via recrystallization of a later intermediate. We



also showed that racemic alcohol **42** could be kinetically resolved using Fu's catalyst **43**, affording **42** in high ee (Scheme 9). The selectivity factor for this reaction was 30. Both these processes and no doubt others bode well for the high-yield synthesis Kagan's ether derivatives, including molecular tweezers, which are both chiral and nonracemic.

Scheme 9. Asymmetric Reactions of Relevance to Chiral Molecular Tweezer Synthesis



Conclusion

The development of synthetic chiral molecular tweezers is still in an early stage. They are interesting receptors themselves and have and will contribute to other adventures in supramolecular chemistry. They represent building blocks upon which large supramolecular, chiral, and functional assemblies can be created. We are excited by these possibilities and other research avenues, including asymmetric charge-transfer catalysis and the development and exploration of chiral charge-transfer polymers, which may have useful electronic or optical properties. Supramolecular chemistry still has molecular chemistry as its foundation, and continued work in areas such as chiral molecular tweezers will reap benefits both at the molecular and supramolecular levels.

I offer my thanks to all of the co-workers who helped shape this program. Our research in this area was made possible by grants from the Elsa U. Pardee Foundation and the University of Missouri Research Board, to whom I am extremely grateful. Thanks to Professor Yoshimasa Fukazawa for supplying crystal data for the inclusion complex between ***7*** *and pyromellitic dianhydride. Many thanks to Dr. Charles Barnes, a great colleague and crystallographer. My gratitude goes out to Mr. Joseph Szekely for his help in producing some of the graphics seen in the Account.*

References

(1) Chen, C.-W.; Whitlock, H. W., Jr. Molecular tweezers: a simple model of bifunctional intercalation. *J. Am. Chem. Soc.* **1978**, *100*, 4921−4922.

(2) Zimmerman, S. C. Rigid molecular tweezers as hosts for the complexation of neutral guests. *Top. Curr. Chem.* **1993**, *165*, 71−102.

(3) Klärner, T.-G.; Panitzjy, J.; Bläser, D.; Boese, R. Synthesis and supramolecular structures of molecular clips. *Tetrahedron* **2001**, *57*, 3673−3687.

(4) Klärner, F.-G.; Kahlert, B. Molecular tweezers and clips as synthetic receptors. Molecular recognition and dynamics in receptor−substrate complexes. *Acc. Chem. Res.* **2003**, *36*, 919−932.

(5) Kurebayashi, H.; Haino, T.; Usui, S.; Fukazawa, Y. Structure of supramolecular complex of flexible molecular tweezers and planar guest in solution. *Tetrahedron* **2001**, *57*, 8667−8674.

(6) For some examples and references, see: (a) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Butler, D. N.; Mahadevan, I. B.; Russell, R. A. Building BLOCK strategies for the synthesis of molecular clefts with inside functionality. *Org. Lett.* **1999**, *1*, 199−202. (b) Banwell, M. G.; Gable, R. W.; Greenwood, R. J.; Lambert, J. N.; Mackay, M. F.; Walter, J. M. Ring-fused gem-dibromocyclopropanes as precursors to "tunable" molecular clefts possessing convergent functional groups. *Synlett* **1997**, 953−955. (c) Shimizu, K. D.; Dewey, T. M.; Rebek, J., Jr. Convergent functional groups. 15. Synthetic and structural studies of large and rigid molecular clefts. *J. Am. Chem. Soc.* **1994**, *116*, 5145−5149.

(7) For examples and references, see: (a) Reek, J. N. H.; Elemans, J. A. A. W.; de Gelder, R.; Beurskens, P. T.; Rowan, A. E.; Nolte, R. J. M. Self-association and self-assembly of molecular clips in solution and in the solid state. *Tetrahedron* **2002**, *59*, 175−185. (b) Wu, A.; Chakraborty, A.; Fettinger, J. C.; Flowers, R. A., II; Isaacs, L. Molecular clips that undergo heterochiral aggregation and self-sorting. *Angew. Chem., Int. Ed.* **2002**, *41*, 4028−4031.

(8) Sun, D.; Than, F. S.; Reed, C. A.; Chaker, L.; Poyd, P. D. W. Supramolecular fullerene-porphyrin chemistry. Fullerene complexation by metalated "jaws porphyrin" hosts. *J. Am. Chem. Soc.* **2002**, *124*, 6604−6612.

(9) Yurke, B.; Turberfield, A. J.; Jills, A. P., Jr.; Simmel, F. C.; Neumann, J. L. A DNA-fuelled molecular machine made of DNA. *Nature* **2000**, *406*, 605−608.

(10) Kagan, J.; Chen. S.-y.; Agdeppa, D. A., Jr.; Watson, W. H.; Zabel, V. The synthesis of 1,2,5,6,-dibenzo-9-oxa-[3.3.1]-bicyclonona-2,6-diene, a novel reaction of phenylacetaldehyde in fluorosulfonic acid. *Tetrahedron Lett.* **1978**, *19*, 4469−4470. The yield for **13** was originally reported to be 50%, but this was later found to be irreproducible. See ref 12.

(11) (a) Jung, M. E.; Mossman, A. B.; Lyster, M. A. Direct synthesis of dibenzocyclooctadienes via double ortho Friedel−Crafts alkylation by the use of aldehyde-trimethylsilyl iodide adducts. *J. Org. Chem.* **1978**, *43*, 3698−3701. (b) Jung, M. E.; Miller, S. J. Total synthesis of isopavine and intermediates for the preparation of substituted amitriptyline analogues: facile routes to substituted dibenzocyclooctatrienes and dibenzocycloheptatrienes. *J. Am. Chem. Soc.* **1981**, *103*, 1984−1992.

(12) Kagan, J.; Agdeppa, D. A., Jr.; Chang, A. I.; Chen, S.-A.; Harmata, M. A.; Melnick, B.; Patel, G.; Poorker, C.; Singh, S. P. Reactions of phenylacetaldehydes in fluorosulfuric acid. *J. Org. Chem.* **1981**, *46*, 2916−2920.

(13) Takahashi, T. Production method of dibenzo cyclo chemical compound. Jpn. Kokai Tokkyo Koho 2003261571, 2003.

(14) Zabel, V.; Watson, W. H.; Kagan, J.; Agdeppa, D. A., Jr.; Chen, S.-A. 2,3,6,7-Dibenzo-9-oxa-[3.3.1]-bicyclonona-2,6-diene, $C_{16}H_{14}O$. *Cryst. Struct. Commun.* **1978**, *7*, 727−732.

(15) Jennings, W. B.; Farrell, B. M.; Malone, J. F. Attractive intramolecular edge-to-face aromatic interactions in flexible organic molecules. *Acc. Chem.* Res. **2001**, *34*, 885−894.

(16) Waring, M. J. Echinomycin and related quinoxaline antibiotics. In *Molecular Aspects of Anticancer Drug−DNA Interactions*; Neidle, S., Waring, M. J., Eds.; CRC: Boca Raton, FL, 1993; Vol. 1, Chapter 7.

(17) (a) Potluri, V. K.; Maitra, U. Bile acid-derived molecular tweezers: study of solvent effects in binding, and determination of thermodynamic parameters by an extraction-based protocol. *J. Org. Chem.* **2000**, *65*, 7764−7769. (b) D'Souza, L. J.; Maitra, U. Design, synthesis, and evaluation of bile acid-based molecular tweezers. *J. Org. Chem.* **1996**, *61*, 9494−9502.

(18) (a) Mas, T.; Pardo, C.; Salort, F.; Elguero, J.; Torres, M. R. A new entry to bis-Tröger's bases. *Eur. J. Org. Chem.* **2004**, 1097−1104. (b) Carree, F.; Pardo, C.; Galy, J.-P.; Boyer, G.; Robin, M.; Elguero, J. A shorter synthesis of symmetrical 2,11-dimethyl-bis-Tröger's bases. A new molecular tweezer. *ARKIVOC* **2004**, 86−93. (c) Mas,

T.; Pardo, C.; Elguero, J. New molecular tweezers with a bis-Troeger's base skeleton. [Erratum for Vol. 66, 2001]. *J. Org. Chem.* **2001**, *66*, 4104. (d) Pardo, C.; Sesmilo, E.; Gutierrez-Puebla, E.; Monge, A.; Elguero, J.; Fruchier, A. New chiral molecular tweezers with a bis-Troeger's base skeleton. *J. Org. Chem.* **2001**, *66*, 1607−1611.

(19) Harmata, M.; Murray, T. Molecular clefts. 1. Synthetic methodology for the preparation of analogues of Kagan's ether. *J. Org. Chem.* **1989**, *54*, 3761−3763.

(20) Harmata, M.; Barnes, C. L. Molecular clefts. 2. An analogue of Kagan's ether as a molecular cleft: synthesis and clathrate formation with ethyl acetate. *Tetrahedron Lett.* **1990**, *31*, 1825−1828.

(21) Hoffmann, R. W. Allylic 1,3-strain as a controlling factor in stereoselective transformations. *Chem. Rev.* **1989**, *89*, 1841−1860.

(22) Metrangolo, P.; Resnati, G. Halogen bonding: a paradigm in supramolecular chemistry. *Chem.—Eur. J.* **2001**, *7*, 2511−2519.

(23) Harmata, M.; Barnes, C. L. Unpublished results from this laboratory.

(24) Ouvrara, C.; Le Questel, J.-Y.; Berthelot, M.; Laurence, C. Halogen-bond geometry: a crystallographic database investigation of dihalogen complexes. *Acta Crystallogr.* **2003**, *B59*, 512−526.

(25) Harmata, M.; Barnes, C. L. 5α,8β,14α,17α-5,6,8,9,14,15,17,178-Octahydro-5,17:8,14-diepoxy-dibenzo[*e,e'*]benzo[1.2-*a*:4.5-*a'*]dicyclooctene. *Acta Crystallogr.* **1993**, *C49*, 115−116.

(26) Harmata, M.; Tyagarajan, S. Synthesis of a functionalized chiral molecular tweezer. In *Molecular Recognition and Inclusion*; Proceedings of the Ninth International Symposium on Molecular Recognition and Inclusion, Lyon, France, September 7−12, 1996; Coleman, A. W., Ed.; Kluwer: Dordrecht, The Netherlands, 1998; pp 353−356.

(27) Harmata, M.; Kahraman, M.; Tyagarajan, S.; Barnes, C. L. Welch, C. J. Molecular clefts derived from Kagan's ether. Synthesis and solid-state inclusion complexes of a chiral molecular tweezer. In *Molecular Recognition and Inclusion*; Proceedings of the Ninth International Symposium on Molecular Recognition and Inclusion, Lyon, France, September 7−12, 1996; Coleman, A. W., Ed.; Kluwer: Dordrecht, The Netherlands, 1998; pp 109−116.

(28) Harmata, M.; Barnes, C. L. Molecular Clefts. 3. The crystal structure of a chiral molecular tweezer and its guest. *J. Am. Chem. Soc.* **1990**, *112*, 5655−5657.

(29) Fleischhauer, J.; Harmata, M.; Kahraman, M.; Koslowski, A.; Welch, C. J. The determination of the absolute configuration of a chiral molecular tweezer using CD spectroscopy. *Tetrahedron Lett.* **1997**, *38*, 8655−8658.

(30) For leading references, see: Williams, L. D.; Egli, M.; Gao, Z.; Rich, A. DNA intercalation: helix unwinding and neighbor-exclusion. In *Structure & Function, Vol. 1 Nucleic Acids*, Proceedings of the Seventh Conversation in Biomolecular Stereodynamics, Albany, New York, June 1991; Sarma, R. H., Sarma, M. H., Eds.; Adenine Press: Schenectady, NY, 1992; pp 107−125.

(31) Harmata, M.; Barnes, C. L.; Karra, S. R.; Elahmad, S. Molecular clefts. 4. An approach to structural analogues of echinomycin: synthesis of a new class of synthetic molecular tweezers. *J. Am. Chem. Soc.* **1994**, *116*, 8392−8393.

(32) Harmata, M.; Wu, Y.; Kahraman, M.; Welch, C. J. The preparation of chiral salicylaldehydes based on Kagan's ether. *Synth. Commun.* **2001**, *31*, 3345−3359.

(33) Harmata, M.; Kahraman, M. Synthesis of a chiral molecular square with two organic corners. *Tetrahedron Lett.* **1999**, *40*, 4133−4136.

AR030164V