# A Rationally Designed Prototype of a Molecular Motor

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*Received March 24, 2000*

**Abstract:** A proof of principle of the first rationally designed, chemically powered, molecular-scale motor is described. The thermodynamic considerations leading to the choice of **6a** and **7a** as the initial prototypes are provided, and the synthesis of **6a** and **7a** and the separation of them from their atropisomers are detailed. The phosgene-powered unidirectional rotation of **6a** to its rotamer **6b** is demonstrated. It is further established that shortening the length of the tether (→**7a**) changes the rate-limiting step and accelerates the speed of rotation.

Motion is central—and essential—to life. Motors convert energy into coordinated movement. On the scale of daily living one relies on motors that use gasoline, electricity, and other commonplace forms of energy, and the mechanisms by which such devices operate are clearly understood. The development of motors of ever diminishing size has riveted the attention of inventors since the achievement of steam engines by Newcomen and Watt upward of two centuries ago. Nobel laureate physicist Richard Feynman once[1] posted a $1,000 prize for constructing an operating electric motor only $^1/_{64}$ in. cube (the award was collected within the year). More recently, microfabrication using photolithographic techniques has led to motors whose diameters are smaller than that of a human hair,[2] and an even tinier, laser-powered "Brownian ratchet" has been reported.[3−6] On the very small scale of biological machines—muscles, flagella, cilia, etc.—little[7] is known *at the atomic scale of resolution*,[8−10] of how these engines of motion achieve their controlled movement. This lack of atomic-level understanding persists despite numerous successful X-ray crystallographic,[11−13] and other studies,[14−18] that comprise what has been characterized[19] as the most extensive research effort in biophysics in the last forty years.

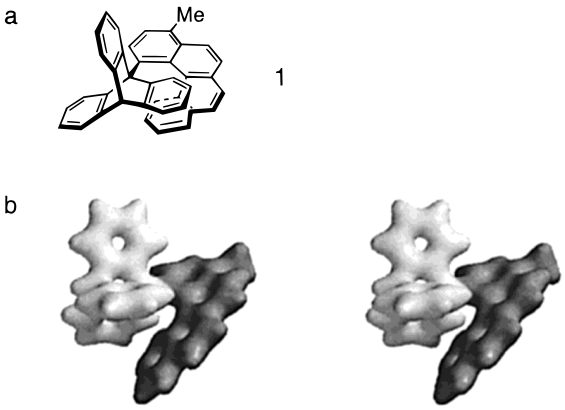


**Figure 1.** (a) Triptycyl[4]helicene **1**. (b) Stereoview of a calculated (AM1[26]) electron density surface map of the lowest energy conformation of **1**. The triptycene rotor is in lighter tones, the helicene stator in darker tones. The calculated barrier to rotation ($\Delta H^{\ddagger} = 22$ kcal/mol) around the triptycene/helicene bond in **1** is in good agreement with the experimentally determined value[23] ($\Delta G^{\ddagger} = 25$ kcal/mol).

We now describe in detail[20] a proof of principle of the first rationally designed, chemically powered,[21] molecular-scale motor. The prototype, with a molecular weight of <600, has been conceived and constructed de novo. It uses a fuel rich in chemical energy (phosgene) to channel background thermal energy into unidirectional rotary motion. The achievement of a molecular device that transforms chemical energy into unidirectional movement validates design principles that may also underlie the operation of biological motors, and provides atomic-level detail for one way of propelling such movement.

**The Concept.** Consider structure **1** (Figure 1a), reiterated as a stereoview in Figure 1b. Structure **1** consists of two main components, a three-bladed triptycene rotor (the lighter shaded unit in Figure 1b) and a [4]helicene stator (the darker colored component in Figure 1b). The triptycene and helicene are connected by a single bond (black wedge in **1**) that functions

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10.1021/ja001048f CCC: $19.00 
Published on Web 07/06/2000

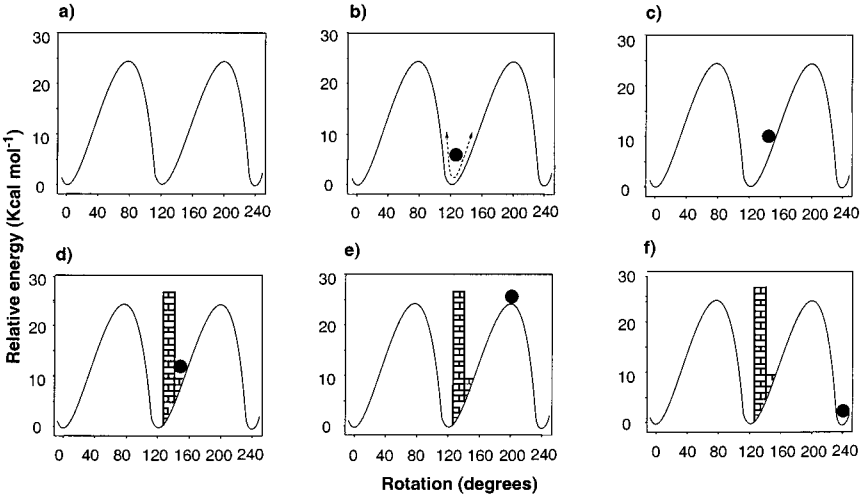


**Figure 2.** Schematic representation of the concepts underlying the design of the system. (a) Energy diagram representing 240° of rotation around the triptycene/helicene bond (black wedge in **1**), with a barrier of ~25 kcal/mol. (b) At any given time a single molecule (represented by the filled black circle) will usually exist in a low-energy conformation such as ~120° (=~0° and ~240° because of the 3-fold symmetry of the triptycene) around the triptycene/helicene bond. (c) Within a very brief time span, random thermal energy temporarily elevates all individual molecules to conformationally excited states (for example,[35] $t_{1/2}$ for thermally exciting molecules 10 kcal/mol above ground state at 25 °C is $2.3 \times 10^{-6}$ s). (d) Conformationally excited rotamers in **c** are trapped, and prevented from rotating back to a lower−energy conformation. **(**e) The trapped molecules are propelled by the random thermal energy to the top of the energy barrier (reversion to the position in **d**—but not **b**—is possible, but readily reversible). (f) Descent from the summit in **e** to the next energy minimum is easy and virtually irreversible (because the reverse reaction (**f**→**e**) has an energy requirement of +25 kcal/mol, which is effectively inaccessible ($t_{1/2}$ for achieving +25 kcal/mol is[35] 63.2 h at 25 °C).

as an axle. We have previously established,[22−25] that the barrier to rotation (25 kcal/mol) of the triptycene rotor around the triptycene/helicene bond in **1** is substantially higher than the barrier to rotation around typical carbon−carbon single bonds (~3−5 kcal/mol). In addition to being a stator, the helicene in **1** may be regarded as a stiff (but not entirely rigid) pawl that resists deformation and prevents easy rotation. Molecule **1** cannot be looked upon as a molecular ratchet, however, because when thermally stimulated rotation of the triptycene does occur, it occurs in clockwise and counterclockwise directions to an equal extent.[22,23] The helicene in **1** might best be pictured as a friction brake[27] that inhibits, but does not completely prevent, spontaneous rotation of the triptycene rotor (for reports of other molecular devices see, inter alia,[28−34]).

The essence of converting **1** into a molecular motor involves continuing the friction-braking action to prevent counterclockwise rotation, while using the chemical energy of phosgene to harvest ambient thermal energy, thereby selectively fostering clockwise rotation of the triptycene rotor. The unidirectional rotation derives ultimately from the asymmetric skew of the helicene. To us, the double acid chloride phosgene is reminiscent of another energy-rich molecule, ATP, which powers many biological motors.

The thermodynamics of the design are presented in detail in Figure 2. The basic strategy was to start with a molecule related to **1** whose rotational ground state is ~25 kcal/mol below the summit (see Figure 2b), but which could be trapped (schematically represented by a brick wall in Figure 2d; in actuality a tether is used) somewhat above that minimum by using a phosgene-powered chemical reaction. That trapping stations the trapped species in a new "base camp" energetically closer to the summit, and within easier (relative to Figure 2b) thermal reach of the mountaintop. Once the summit is achieved (Figure 2e), descent down the other side of the $E_{act}$ mountain then releases 25 kcal/mol of energy, which immediately diffuses through the system and thus is not directly available to drive the more energy-intensive reverse reaction (25 kcal/mol contrasted to the less demanding Figure 2, **d**→**e** forward process). Put another way, states **b** and **f** in Figure 2 are isoenergetic, and the rates of the **b**→**f** and **f**→**b** conversions will be identical; but by using the chemical energy of phosgene to trap **b** in the form of **c**, **c**→**f** is an exothermic transformation, and unidirectional rotation is driven by the negative $\Delta G$ for the **c**→**f** transformation.

To our mind, Buchwald's 1995 report[36] of the metal chelation-accelerated Bergman cyclization of the bisphoshino enediyne **2** to **3** provided ideal precedent in support of the "new base camp" strategy. In particular, conversion of **2** to its $PdCl_2$ complex **4** causes Bergman cyclization to occur ≥30 000 times faster than it does with **2** alone, which corresponds to reduction of the $E_{act}$ ($\Delta G$) by at least 6 kcal/mol. The reduction of the $E_{act}$ is achieved not by lowering the energy of the transition state but instead by raising the energy of the starting point. This ground-state destabilization happens because coordination of the two phosphines to the Pd (achieved by trapping a vibrationally

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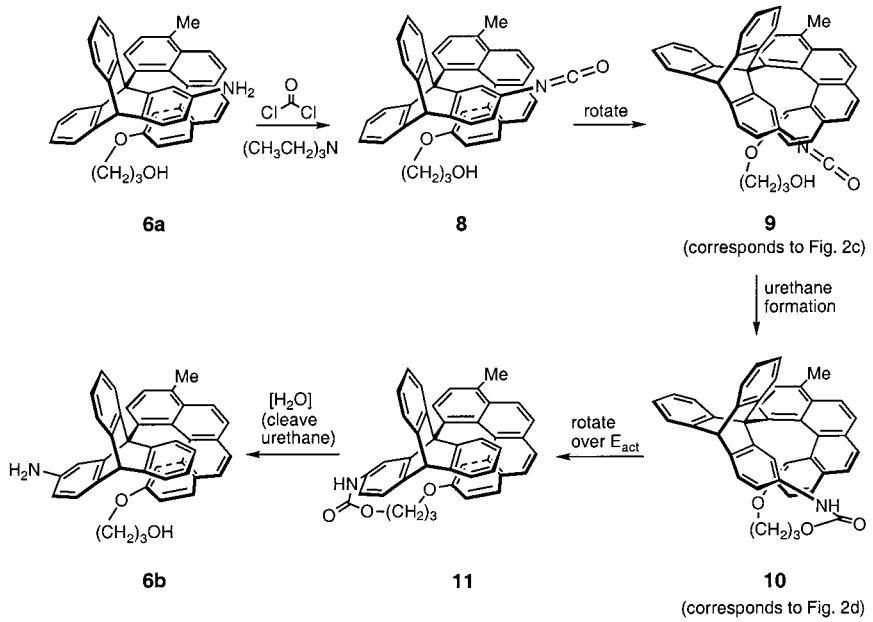
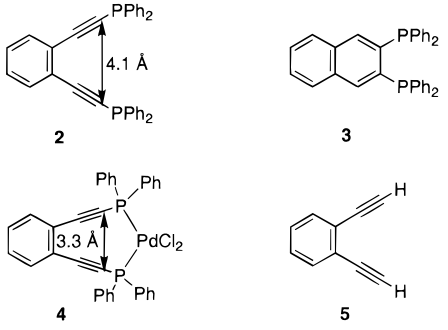
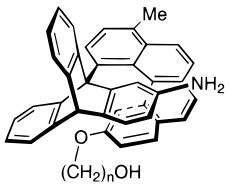



**Figure 3.** Sequence of events in the chemically powered rotation of **6a** to **6b**. See text for discussion. Although **6a** and **8** are not identical, to a first approximation they both conceptually correspond to Figure 2b. Compounds **9** and **10** correspond to Figure 2c and Figure 2d, respectively; compounds **11** and **6b** both correspond roughly to Figure 2f.

excited mode) forces the two terminal acetylenic carbons within 3.3 Å of each other (as opposed to 4.1 Å in the absence of Pd). Calculations[26] using **5** as the subject indicate that such a deformation destabilizes the ground-state enthalpy by 4.3 kcal/mol. In other words, the coordination of the phosphines to the Pd traps the enediyne part of the way up the energy of activation hill (just like the brick wall does in Figure 2d). The consequence is that the new $E_{act}$ barrier to Bergman cyclization is effectively lower. The system in **4** must still harness ambient thermal energy to surmount the $E_{act}$ hill, but the new base camp puts the summit within easier striking distance.

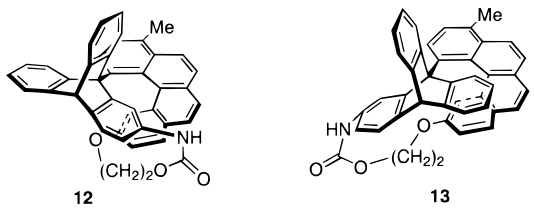



The molecules we chose as prototypes for a molecular rotary motor are **6** and **7**. Compounds **6** and **7** were chosen for several reasons. First, we wanted to use molecules as close in structure to **1** as possible, so that the knowledge acquired in the context of **1** could be most directly brought to bear. In particular, we hoped that by making no more changes than necessary, we would be able to maintain the close agreement between experiment and computer modeling found with **1** (the use of $\Delta H^{\ddagger}$ values to predict $\Delta G^{\ddagger}$ values is not rigorous, but we have found it quite useful; the calculated $\Delta H^{\ddagger}$ barrier to rotation in **1** is 22 kcal/mol; as noted above, the experimentally determined value for $\Delta G^{\ddagger}$ is 25 kcal/mol). Furthermore, we sought, by selecting **6** and **7** as targets, to make the synthetic component of the project no more difficult than necessary, by having it be as derivative of the synthesis of **1** as possible (the project still required several postdoc-years of effort). Compounds **6** and **7** differ from each other only by the length of the hydroxyalkoxy "tether" (vide infra).




**6**, n = 3 (as a mixture of atropisomers)
**7**, n = 2 (as a mixture of atropisomers)

Using **6** to illustrate, Figure 3 provides molecular detail for the concepts outlined in Figure 2. In essence, the proof of principle for the molecular motor starts with **6a**. Compound **6a** is one of three low-energy rotamers about the axle connecting the triptycene and helicene components (**6b** is a second low energy rotamer). Rotamer **6a** is to be activated by reaction with phosgene to give the isocyanate **8**. Isocyanate **8** is chemically "armed" to react with the OH group in the hydroxypropyl tether attached to the helicene, but in the rotational ground state **8**, the isocyanate and the OH group are too far apart to interact. However, at those instants when a clockwise rotation of the triptycene (not possible with a comparable counterclockwise rotation) brings the isocyanate and the OH group sufficiently close to react (see **9**), urethane formation (→**10**) can then result, irreversibly trapping the triptycene in a relatively high (compared to **8**; also see Figure 2d vs 2b) energy conformation around the triptycene/helicene axle. Ambient thermal energy will then drive the exoergic unidirectional rotation from **10** to **11**. Finally, **11** is cleaved to **6b**, thereby completing the chemically driven rotation of **6a** to **6b**.



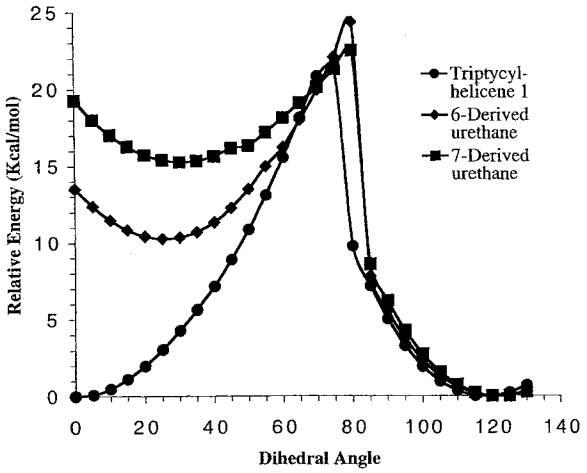


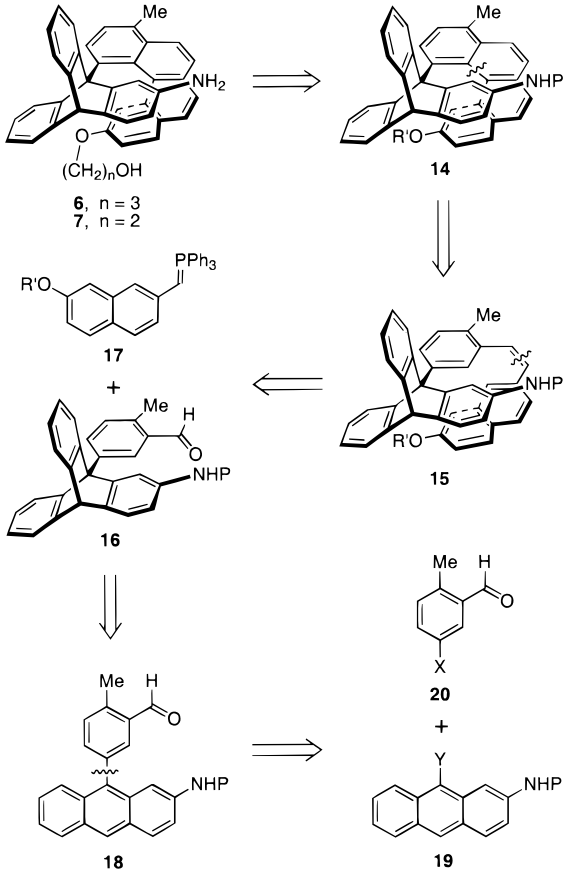

**Figure 4.** Calculated[26] (AM1) relative energies for rotation around the triptycene/helicene bond in **1** (●), the urethane derived from **6** (◆), and the urethane derived from **7** (■). See text for discussion.

As noted above, compounds **6** and **7** differ from each other only by the lengths of the hydroxyalkoxy "tether." In deciding on the appropriate length for the tether, it was necessary to balance two competing considerations. In the context of Figures 2 and 3, the higher on the $E_{act}$ hill (see Figure 2c and **9** in Figure 3) **9** is trapped (→**10**) the more facile (and exothermic) the rotation over the $E_{act}$ barrier of **10**→**11** will be. On the other hand, the higher in energy **9** is, the lower the population of the state, and the more energy-exacting the **9**→**10** conversion becomes. Calculations (AM1[26]) indicated that systems containing either a two- (**7**) or a three-carbon (**6**) tether were attractive candidates to engender unidirectional rotary motion. Figure 4 contains calculated energy diagrams for different conformations around the triptycene/helicene bond in **1**, **10** (the urethane derived from **6**), and **12** (the urethane derived from **7**). Since **1**, **10**, and **12** have inherently different heats of formation, the *y* axis in Figure 4 indicates relative, not absolute energies; the three systems have been arbitrarily normalized so that they have the same relative energy at $\theta = 120°$, and the dihedral angles (around the triptycene/helicene bond) are the same for **1**, **10** and **12**. The energy minima at $\theta = 25°$ and 30° for **10** and **12**, respectively, correspond to calculated lowest energy "prebarrier" conformations of **10** and **12** (the $\theta = 120°$ minima correspond to lowest-energy postbarrier conformations of **11** and **13**). As one would expect from examination of models, the prebarrier energy minimum for **12,** which has the shorter tether, is relatively higher than that for **10**. In the event (vide infra), systems **6** and **7** both succeeded, but with **6** the rate-limiting step is the **10**→**11** conversion, while with **7** it is the equivalent of the **9**→**10** conversion.

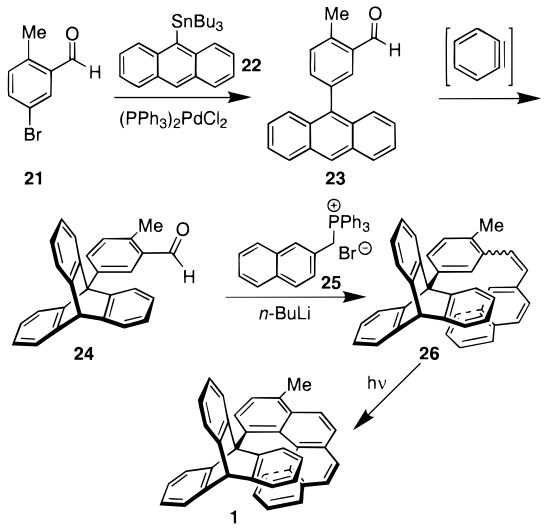
Given the foregoing as the design, attention turned to the synthesis of **6** and **7**.

**General Synthetic Strategy for Preparing 6 and 7.** A retrosynthetic analysis of **6** and **7** is summarized in Scheme 1; it is based heavily on our earlier route to **1**,[22,23] which is outlined in Scheme 2. The key precursor to **6** and **7** is **14**, which contains the basic triptycyl[4]helicene skeleton but lacks the fully elaborated functionality of **6** and **7**. In analogy to Scheme 2, we anticipated that **14** would be available from the photocyclization of stilbene **15**.[37] Stilbene **15** would be prepared by a Wittig reaction between the triptycylbenzaldehyde **16** and the naphthalene ylide **17**. Regioselective Diels−Alder addition of

**Scheme 1**




**Scheme 2**




benzyne across the central ring of the anthracene in aldehyde **18** was envisioned to afford the key triptycylbenzaldehyde unit **16**. Anthracenylbenzaldehyde **18** would be realized from cross-coupling of the benzaldehyde (**20**) and amidoanthracene (**19**) fragments employing either a Stille[38] or a Suzuki[39] coupling protocol.

## Results and Discussion

**Synthesis of Key Triptycene Intermediate 32**. The synthesis of **32**, a specific form of **16**, commenced with the acetylation

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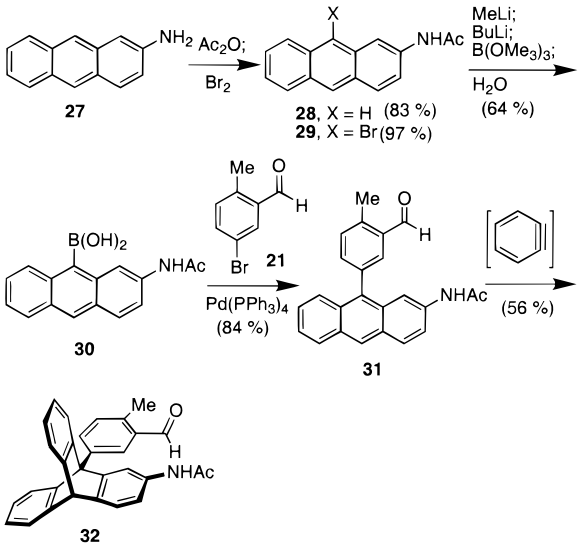
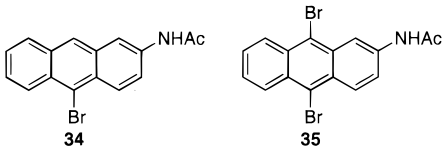
**Scheme 3**

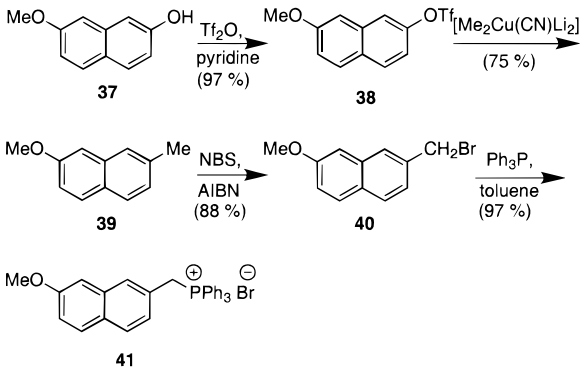



of the commercially available 2-aminoanthracene to furnish the corresponding amide **28** in good yield (Scheme 3).[40] The latter was then treated with molecular bromine to furnish bromide **29** in excellent yield.[41,42] That **29** rather than the regioisomer **34** would be produced was anticipated by application of the usual analysis of directing effects of substituents in electrophilic aromatic substitution. The prediction was confirmed by a NOE experiment that supported the connectivity in **29** but not **34**.




Treatment of **29** first with $CH_3Li$ (to remove the acidic NH − $CH_3Li$ is poor[43] at halogen/metal exchange) followed by *n*-BuLi and then trapping the resulting carbanion with $B(OCH_3)_3$ gave boronic acid **30** in good yield after an aqueous workup. Palladium-catalyzed coupling of **30** with readily available[44] 5-bromo-2-methylbenzaldehyde (**21**) employing a Suzuki[39] coupling protocol[45] provided anthracenylbenzaldehyde **31**. Diels−Alder addition of benzyne, which was generated in situ from anthranilic acid, to the anthracenylbenzaldehyde **31** afforded triptycene **32** in 56% yield.[46,47]

**Scheme 4**




**Synthesis of the Basic Triptycyl Helicene Framework**. With the triptycylbenzaldehyde **32** in hand, attention turned to construction of the helicene. To that end, phosphonium salt **41** was prepared from the commercially available 7-methoxy-2-naphthol (**37**) by the reaction sequence shown in Scheme 4. Naphthol **37** was treated with triflic anhydride in the presence of pyridine at 0 °C and then room temperature to give triflate **38** in excellent yield.[48] Triflate **38** was coupled[49] with a higher-order mixed methylcuprate, which was obtained from $CH_3Li$ and CuCN, to provide 7-methoxy-2-methylnaphthalene (**39**) in good yield. Benzylic bromination of **39** was accomplished with NBS in the presence of AIBN to provide the corresponding 2-(bromomethyl)-7-methoxynaphthalene (**40**). Bromination worked best when conducted under dilute conditions and with slow, portionwise addition of NBS.[50] Treating the benzylic bromide with triphenylphosphine in refluxing toluene provided phosphonium bromide **41** in excellent yield.[51]

A Wittig reaction between the ylide derived from **41** and aldehyde **32** led to the formation of stilbene **42**, as a 1:4 mixture of *Z*/*E* isomers ($^1$H NMR) in good yield, setting the stage for the stilbene photocyclization (Scheme 5).

In the synthesis of **1** (Scheme 2), the construction of the [4]-helicene unit by a stilbene photocyclization was achieved without difficulty. For **42**, as in the case of **26**, electronic effects were expected to favor the formation of the benzo[*c*]phenanthrene ring system (**43**) rather than the benz[*a*]anthracene **45**. In the synthesis of **1** we had used the methyl derivative **26** rather than the unsubstituted **46** because it was likely that with **46**, predominant formation of the undesired regioisomer **47** (by bond formation between the asterisked carbons in **46**) instead of the desired **1** would occur because of the steric bulk of the triptycene.[37] Inclusion[52] of the methyl group prevented the formation of a **47**-type product. We expected the methyl group

(39) (a) Fu, J. M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665−1668. (b) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519. (c) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405−1408. (d) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208. (e) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997−6000. (f) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093−5096. (g) Miller, R. B.; Dugar, S. *Organometallics* **1984**, *3*, 1261−1263. (h) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237−5243. (i) Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679−6682.

(40) Fedorov, B. P. *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* **1951**, 582−92 (*Chem. Abstr.* **1952**, *46*, 8077).

(41) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024−8034.

(42) If the reaction temperature exceeds 5 °C (or if more than 1 equiv of molecular bromine is used), the dibromide **35** is formed in significant amount.

(43) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080.

(44) Goodman, J. P.; St. Pyrek, J. *J. Heterocycl. Chem.* **1993**, *30*, 1645−1651. This procedure does not describe the separation of **21** from its regioisomers.

(45) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguimer, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292−296.

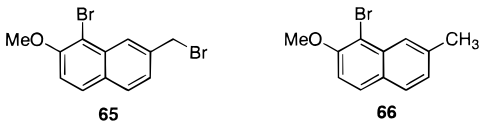
(46) The benzyne was generated from anthranilic acid with isoamyl nitrite and catalytic trichloroacetic acid (see Experimental Section).[47]

(47) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. Vol. V, pp 54−59.

(48) Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. v. R.; Effenberger, F.; Kurtz, W.; Tang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099−4103.

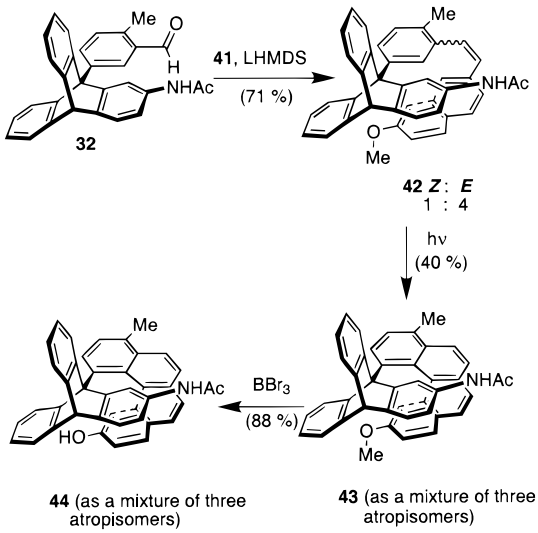
(49) McMurry, J. E.; Mohanraj, S. *Tetrahedron Lett.* **1983**, *24*, 2723−2726.

(50) (a) Wamser, C. C.; Scott, L. T. *J. Chem. Educ.* **1985**, *62*, 650−652. (b) Other reaction conditions resulted in varying amounts of undesired brominated products including molecules tentatively characterized as **65** and **66** (see Supporting Information).

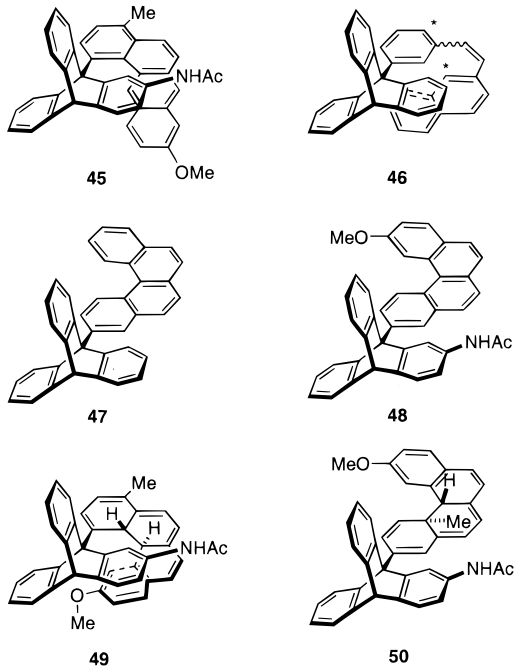



(51) Geerts, J. P.; Martin, R. H. *Bull. Soc. Chim. Belg.* **1960**, *60*, 563−569.

**Scheme 5**



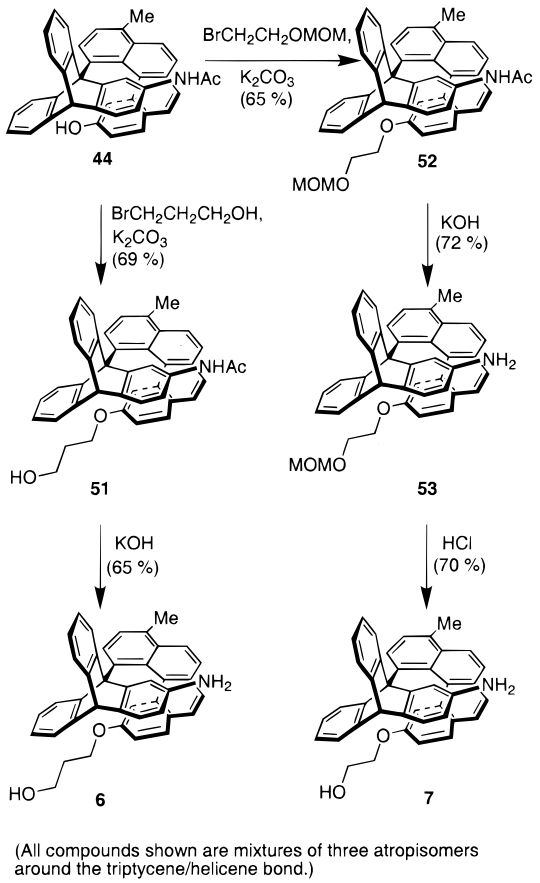

would serve the same purpose in the present instance, but when the same photocyclization conditions used for **26** were applied to **42**, the desired **43** was produced in less than 5% yield, and **48** was obtained as the major product. Extensive studies were required before this seeming impasse was overcome.




Compounds **43** and **48** presumably[37] arise from intermediates **49** and **50**, respectively, both of which are in equilibrium with stilbene **42**. The oxidation of **49** to **43** is accomplished by hydrogen atom abstraction by iodine atoms that are photochemically generated from $I_2$. The mechanism by which **48** is formed from **50** is not entirely clear, but a demethylation step is required, which means that different mechanisms operate in the **49** → **43** and **50** → **48** reactions. To foster the **42** → **43** transformation, the amount of iodine was increased by a factor

(52) One of the advantages of designing one's own synthetic target, rather than undertaking the synthesis of a natural product, is that an otherwise extraneous methyl group can always be added to block a side reaction. The disadvantage of designing the target is that, unlike natural products synthesis, it creates a situation of double jeopardy: not only does the synthesis have to succeed, but so must the design; otherwise there is little to show for the effort.

**Scheme 6**




of 6 relative to the earlier **26** → **1** conversion. Even more important to improving the yield of **43**, however, was to carefully control the internal temperature of the reaction by using external cooling (with a −20 °C cooling bath) in addition to the normal internal cold water cooling jacket. Evidently the processes leading to **43** and **48** have different sensitivities to reaction temperature, with a lower reaction temperature favoring the desired product at the expense of the undesired one. As a consequence of all these efforts, the yield of **43** was raised from <5% to approximately 40% (a substantial amount of **48** is still formed). The final reaction conditions involved irradiation of a benzene solution of **42** containing 6 equivalents of $I_2$ and excess propylene oxide (HI scavenger) with a medium pressure (450 W) mercury lamp through a Pyrex filter for 60 h followed, after workup, by chromatographic purification to provide **43** as a mixture of three rotamers.

At thermal equilibrium in $CHCl_3$, one of the atropisomers of **43** is the major component of the atropisomeric mixture. That atropisomer is the one easiest to separate from **48** by chromatography. Consequently, it was beneficial to allow a solution of the crude photolysis mixture in chloroform to stand in order to allow it to convert to primarily (70%, $^1$H NMR) the atropisomer most easily separated from **48**. Cleavage of the methyl ether with $BBr_3$ then produced phenol **44** in high yield.[53]

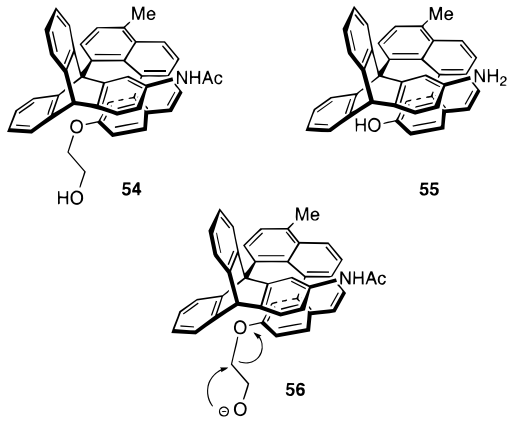
**Completion of the Synthesis of 6 and 7**. The reaction sequences that were applied to **44** for the synthesis of **6** and **7** are illustrated in Scheme 6. The three carbon tether was attached to the helicene unit by reacting the phenol **44** with 3-bromo-1-propanol and $K_2CO_3$ in refluxing acetone to provide the ether

(53) Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444−4446.

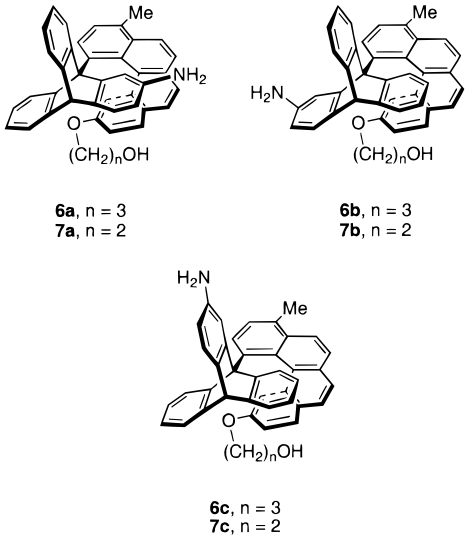
**51**.[54] The deprotection of the acetamide was effected with KOH in refluxing *n*-butanol/ethylene glycol[55] to afford the amino alcohol **6** as a mixture of three atropisomers.

Attempts to prepare the two-carbon tether analogue **7** by a similar sequence failed. Reaction of **44** with bromoethanol and $K_2CO_3$ in acetone afforded **54** cleanly, but attempts to hydrolyze the amide in **54** gave **55**, presumably because the phenoxide functioned as a leaving group in the fragmentation summarized in **56**. That fragmentation was suppressed by installation of the tether with the OH group protected as a MOM ether (so that a **56**-type alkoxide could not form during the amide hydrolysis) using 2-bromoethoxymethyl methyl ether[56] and $K_2CO_3$ in refluxing acetone.

The acetyl functionality in the resulting **52** was then removed with KOH in refluxing *n*-butanol/ethylene glycol to give **53**.[55] Finally, the MOM ether was cleaved with 12 N HCl in $CH_2Cl_2$/EtOH at room temperature to afford the amino alcohol **7**.[57]




**Atropisomer Separation and Conformation Elucidation.** Separation of the three atropisomers of compound **6** was attempted by column chromatography, using both silica and basic alumina; resolution, however, was poor and decomposition products were noted. Separations attempted with 1000 $\mu$m thick




preparative thin layer plates (silica, 20 × 20 cm) gave similarly unsatisfactory results. However, the use of 250 $\mu$m thick plates (silica, 20 × 20 cm) gave excellent resolution affording the clean separation of all three rotamers, with undetectable decomposition. It is necessary to take special efforts so that individual rotamers, once separated, do not thermally reequilibrate during the isolation process. To that end, the atropisomers were extracted from the silica gel using ice-cold solvent, and the extracts were evaporated at or below room temperature in vacuo by the use of a rotary evaporator fitted with a dry ice condenser.

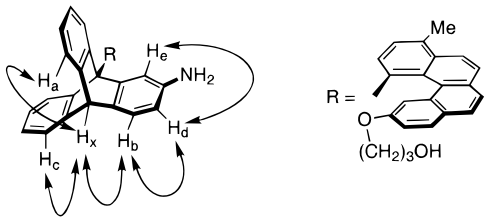



**Figure 5.** Summary of NOE and decoupling experiments on atropisomers.

The conformations of each atropisomer were initially tentatively assigned by use of 1- and 2-D low temperature $^1$H NMR. However, final structure proof for each atropisomer was determined by reaction with phosgene and triethylamine. The details of these reactions are described later in this paper.

Determination of atropisomer conformation was initiated by observing NOE interactions between the bridgehead ($H_x$) and aromatic triptycyl protons in each atropisomer. Only three NOE interactions of this type are possible and they involve the protons designated $H_a$, $H_b$, and $H_c$ in Figure 5.

Once determined, the resonances of these protons provided a starting point for a series of 1-D, NOE and decoupling experiments. The results of these experiments gave the chemical shifts and coupling relationships of all eleven triptycyl aromatic protons. Analysis of the spectra of each atropisomer showed two protons without adjacent protons (one ortho to the sole amino group in the triptycene unit and another adjacent to the alkoxy substituent of the helicene unit). The shielding or deshielding of these protons (particularly the triptycene lone proton by the helicene unit or, perhaps, vice versa) was expected to be indicative of a distinct conformation. The sole proton ortho to the amino group in the triptycene system was chosen to detect these magnetic effects. The elucidation of the conformation of **6a** serves to illustrate this point. One of three triptycene protons having an NOE with the triptycene bridgehead proton displayed a chemical shift at 6.68 ppm (d, $J = 7.5$ Hz) ($H_b$ in Figure 5). A 1-D decoupling experiment showed this proton to be directly coupled with a triptycyl proton at 5.78 ppm (dd, $J = 7.5$, 2.1 Hz) ($H_d$ in Figure 5). In turn, proton $H_d$ was shown by a 1-D decoupling experiment to be finely coupled with a triptycyl proton at 5.48 ppm (d, $J = 2.1$ Hz) ($H_e$ in Figure 5). Taken together, these results established that the proton at 5.48 ppm was adjacent to the sole amino functionality present in the molecule and indicated it to be significantly shielded by the adjacent helicene.[58] Similar analyses were applied to the remaining two atropisomers.

**Demonstration of Unidirectional Rotation.** At the outset of the study of the reaction of atropisomer **6a** with phosgene,

(54) Tsotinis, A.; Calogeropoulou, T.; Koufaki, M.; Souli, C.; Balzarini, J.; De Clercq, E.; Makriyannis, A. *J. Med. Chem.* **1996**, *39*, 3418−3422.

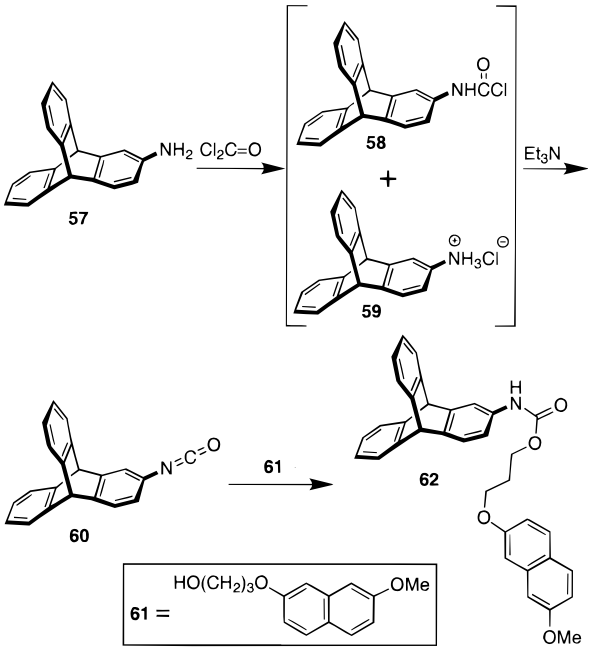
(55) Tietze, L. F.; Eicher, T. H. *Reactions and Syntheses in an Organic-Chemical Practical Course*; Thieme Verlag: Stuttgart, 1981; p 83 and references therein.

(56) Tamao, K.; Nakagawa, Y. *Org. Synth.* **1995**, *73*, 94−109.

(57) Inouye, M.; Fujimoto, K.; Furusyo, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 1452−1458.

(58) An example of this type of shielding can be seen not only in the atropisomers themselves, but also by comparing the $^1$H NMR spectrum of the unwanted photocyclization byproduct **48** with any of the three atropisomers of **6**. The spectra of atropisomers **6a**, **6b**, and **6c** all show peaks for triptycene protons upfield of 6.0 ppm. In contrast, the $^1$H NMR spectrum of **48** shows no peaks for aromatic protons, triptycene or otherwise, upfield of 7.00 ppm.

**Scheme 7**




the choice of whether to form a carbamate from the corresponding carbamoyl chloride or an isocyanate was considered. Semiempirical calculations at the PM3 level carried out on the appropriate derivatives of structure **6a** indicated that formation of the corresponding carbamate (plus HCl) from the carbamoyl chloride would be an endothermic process ($\Delta H = +7$ kcal/mol).[59] However, the formation of the carbamate from the corresponding isocyanate would be exothermic ($\Delta H = -7$ kcal/mol). Accordingly, carbamate formation via isocyanate was chosen. The procedure for the formation of isocyanates from amines was adapted from a protocol reported by Soulier et al.[60] In model studies with triptycene amine **57** it was found that use of five equivalents of triethylamine allowed for complete and rapid formation of isocyanate **60** without accumulation of **58** and/or **59** (Scheme 7). The excess base also aided in the formation of carbamate **62** in these studies.

When atropisomer **6b** was treated with 1 equivalent of phosgene (20% solution in toluene), followed by the addition of triethylamine (5 equiv) the rapid formation of carbamate **11** was seen (Scheme 8) but, importantly, **11** did not convert to **10**.

The reaction of atropisomer **6a**[61] under the same conditions resulted, ultimately, in the formation of carbamate **11**; however, the generation of **11** was preceded by formation of a compound now known to be **10** with a triptycyl bridgehead proton at 5.10 ppm, which converted to carbamate **11** over a period of 6.4 h (see Figure 6).

To determine if the compound responsible for the peak at $\delta$ 5.10 was isocyanate **8** (see Figure 3) or "pre-barrier" carbamate **10**, infrared monitoring using ReactIR technology was carried

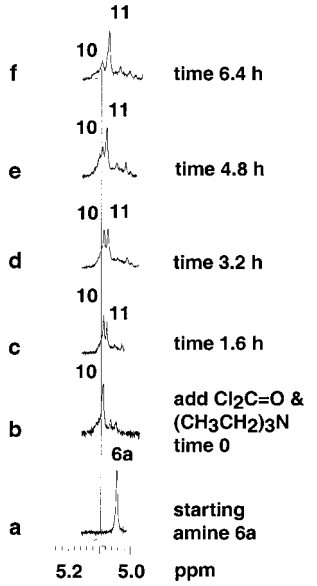
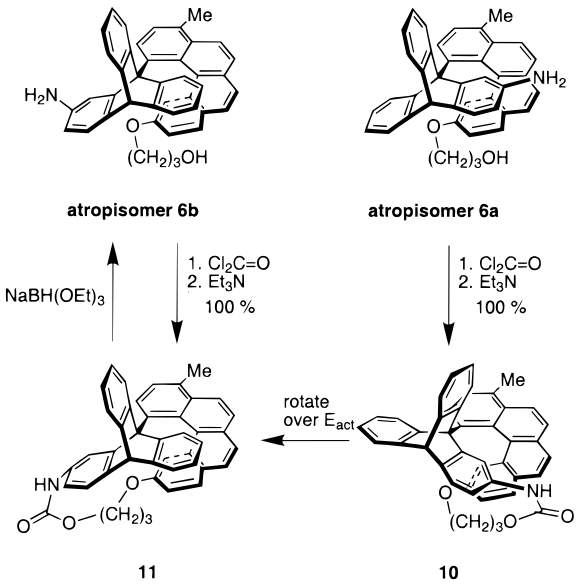



**Figure 6.** Spectroscopic evidence that phosgene fuels the unidirectional rotation of **6a**. Partial $^1$H NMR spectra (monitoring the bridgehead proton) indicate the sequence of events as a function of time. Numbers next to peaks in the spectra refer to structures in Figure 3 and Scheme 8. (a) **6a** in $CDCl_3$; (b) $t_0$; add $Cl_2C{=}O$ and $Et_3N$; **6a** is rapidly converted to intramolecular urethane **10** via isocyanate **8**; the isocyanates **8** and **9** convert to **10** too rapidly to be seen in the spectra. (c) After 1.6 h at ambient temperature (~22 °C) ~30% of **10** has rotated "over the hump" (Figure 2, **d**→**f**) to **11**. (d, e, f) Over further time, rotation of **10** to **11** continues, with unidirectional conversion of **10** to **11** > 80% complete in ~6 h. Urethane **11** was isolated and shown to be identical to material prepared directly from amine rotamer **6b** by reaction with $Cl_2C{=}O$/$Et_3N$. Control experiments established that **11** does not convert to **10**; i.e., that the conversion of **10**→**11** is unidirectional.

**Scheme 8**




out.[62] Due to a paucity of starting material, a ReactIR cell requiring a reaction volume ≤ 0.1 mL was constructed to make infrared monitoring on the 1−3 mg scale possible.[63] Model reactions using triptycene amine **57**, alcohol **61**, phosgene and triethylamine in anhydrous chloroform (stabilized by amylenes, not ethanol) provided a useful infrared reaction profile for

(59) If one includes in the calculation the $\Delta H$ (−8 kcal/mol) for the reaction $Et_3N + HCl \rightarrow Et_3NH^+ Cl^-$, the overall reaction is slightly exothermic ($\Delta H = -1$ kcal/mol)

(60) Soulier, J.; Yang, D.; Bremont, B.; Croci, T.; Guzzi, U.; Langlois, M. *J. Med. Chem.* **1997**, *40*, 1755−1761.

(61) Although we discuss the results in terms of a single enantiomer of **6a**, strictly speaking, the experiment was actually conducted on racemic material. Since enantiomers in an achiral environment give identical NMR spectra, carrying out the measurement on a single enantiomer would not have increased the information generated by the experiment and, therefore, would not have warranted the investment of effort required to develop a resolution of **6a**.

(62) ASI Applied Systems, Millersville, MD 21109, USA. For a bibliography of applications see: www.asirxn.com.

(63) The details of this cell will be published elsewhere.

isocyanate formation and reaction (see Scheme 7). A characteristic strong isocyanate peak indicating the formation of compound **60** could be seen at 2270 $cm^{-1}$ upon the addition of phosgene followed by triethylamine to a solution of amine **57**. Similarly, carbonyl absorption at 1735 $cm^{-1}$ corresponding to the formation of carbamate **62** could be seen when alcohol **61** was added into preformed isocyanate **60**. When the reaction of atropisomer **6a** with phosgene and triethylamine was monitored by infrared spectroscopy, no isocyanate absorption was seen. However, as expected, when atropisomer **6c** was studied under the same conditions, a clear absorption for an isocyanate functionality was observed. Thus it was concluded that in the reaction of atropisomer **6a** with phosgene and triethylamine, isocyanate **8** had only transient existence because of its virtually instantaneous conversion to carbamate **10** (Figure 3 and Scheme 8) which then rotated unidirectionally to **11** over time. Last, carbamate **11**, isolated from the reaction of atropisomer **6a** with phosgene and triethylamine, was cleaved at 0 °C with sodium borohydride in ethanol to give atropisomer **6b**.

The phosgene-promoted conversion of **6a** to **6b** constitutes the proof of principle of the first rationally designed, chemically powered molecular motor.

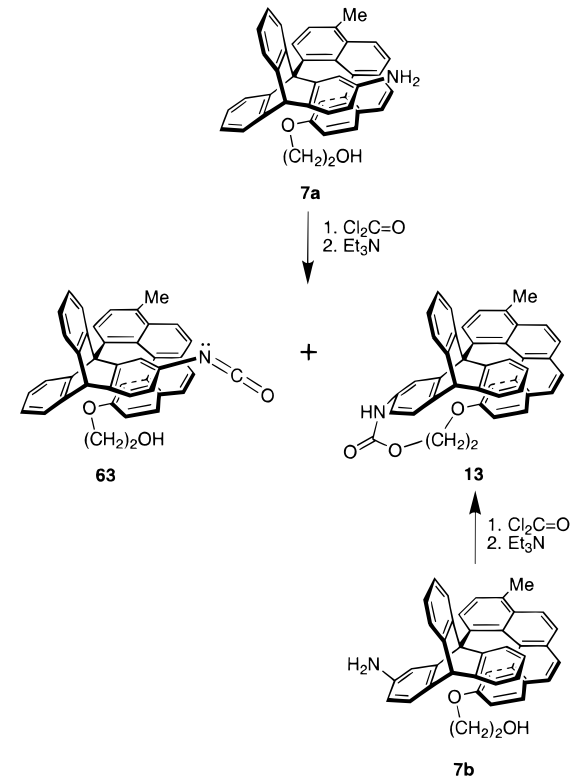
The use of $NaBH_4$ in ethanol is not the standard method for cleavage of a carbamate. The conversion of **11** to **6b** is, however, subject to severe experimental constraints, because it must be accomplished at a sufficiently low temperature that **6b**, once formed, is conformationally stable and does not equilibrate (or partly equilibrate) to a mixture of atropisomers **6a**, **6b** and **6c** under the reaction conditions [at room temperature in $CDCl_3$, pure **6b** rotates to a mixture of **6a** and **6c** (and **6b**) at comparable rates; an equilibrium mixture (∼2:1:2)[64] of **6a**, **6b**, and **6c** is reached in ∼12 h]. Intrusion of such an equilibration during the course of the reaction would have prevented us from demonstrating that the overall process was the unidirectional rotation of **6a** to **6b**. Neither acid- nor base-catalyzed hydrolysis of **11** could be accomplished under conditions where **6b** did not then equilibrate to a mixture of **6a**, **6b** and **6c** (urethanes are normally[65] hydrolyzed at 100 °C).

**A Faster Version.** Significant as we believe the achievement of unidirectional rotation of **6a** to **6b** to be, examination of Figure 4 nonetheless indicates that the half-life for rotation is long, being on the order of 3 h. As a first step in refining the design, and as a check that our understanding of the system is correct, we sought to modify **6a** in order to accelerate the speed of rotation. Consideration of Figure 2 suggests that if the molecule could be trapped higher on the $E_{act}$ hill, then conversion of Figure 2d to Figure 2e (and thence to Figure 2f) would occur faster and the rate of rotation would increase. That prediction is borne out.

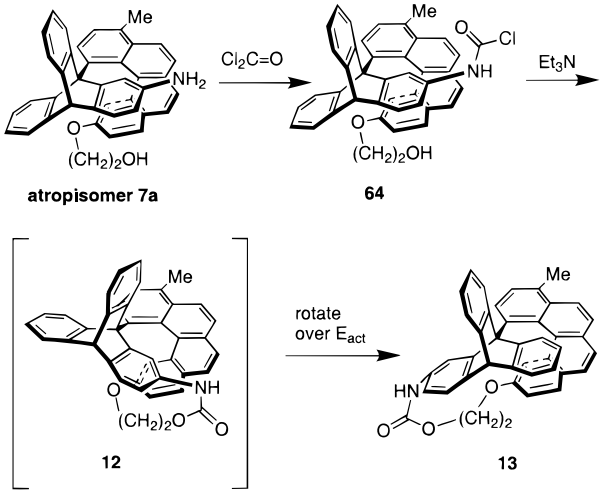
Common sense (and molecular modeling) suggest that the simplest way to modify **6a** so that **10** (Figure 3) is in a higher energy conformation around the triptycene/helicene bond is to use a shorter tether. As noted earlier, we had initially attempted to prepare **7a**, but encountered synthetic difficulties that led us to shift to **6a**. We now returned to the synthesis of **7a** and, as described above, overcame the synthetic obstacles and eventually secured **7a**. Compound **7a** was separated from its atropisomers **7b** and **7c** and the structures of all three atropisomers were established in the same fashion as with **6a**−**c**.

Reaction of **7a** with phosgene and triethylamine initially led to unexpected results (Scheme 9): the rapid formation of a mixture of "after-the-barrier" carbamate **13** and prebarrier isocyanate **63** in a 1:3 ratio. Furthermore, monitoring of the reaction by $^1H$ NMR indicated the mixture was stable, with no detectable conversion of isocyanate **63** into carbamate **13** over a period of several hours. (In contrast, when after-the-barrier amine rotamer **7b** was treated with 1 equiv of phosgene followed by 10 equiv of triethylamine, the instantaneous and virtually quantitative formation of carbamate **13** was seen).

**Scheme 9**




**Scheme 10**




In sharp contrast to the earlier experiments with atropisomer **6a**, it appeared that the formation of the analogue of "prebarrier" carbamate **10**, carbamate **12** (Scheme 10), did occur, but that **12** rotated so rapidly to give carbamate **13** that the presence of **12** could not be detected by NMR. As noted in the previous paragraph, however, isocyanate **63** does not appear to convert into carbamate **13**. To account for the formation of the amount of carbamate **13** that did form, we hypothesized that it arose from the carbamoyl chloride (**64**) initially produced in

(64) The composition (contrast Experimental Section regarding preparation of **6**) is somewhat solvent-dependent.

(65) For a leading reference, see: Adams, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 567−602.

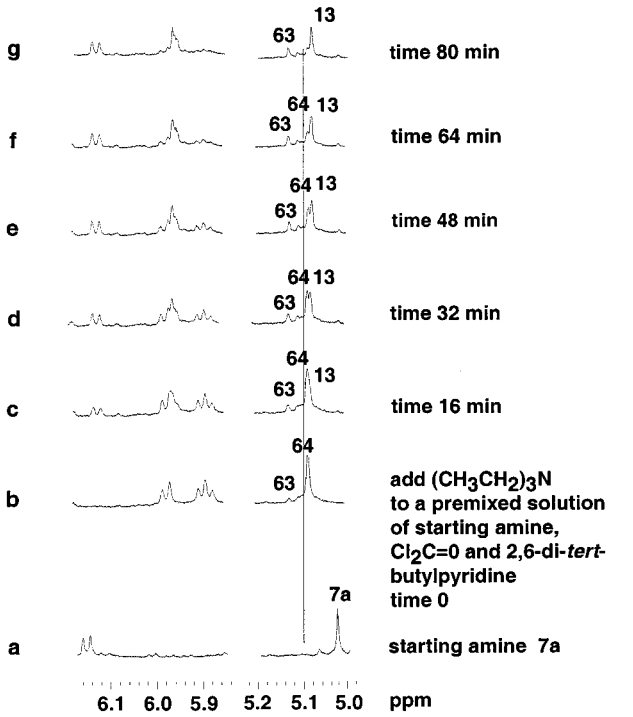



**Figure 7.** Partial $^1$H NMR spectra (monitoring the bridgehead proton) indicating the conversion of **7a** to **13**.

the reaction between **7a** and phosgene, and that **64** was more reactive toward cyclic urethane formation (Scheme 10) than the corresponding isocyanate **63**.

On the surface that explanation is thermodynamically counterintuitive because elementary bond energy calculations indicate the $\Delta H$ for intermolecular carbamate formation is several kcal/mol more exothermic when alcohols react with isocyanates than with carbamoyl chlorides.

The formation of **12**, whether from isocyanate **63** or carbamoyl chloride **64** is, however, an intramolecular reaction. We concluded that geometric constraints in **63** prevent its cyclization to **12**. To test this hypothesis, the synthesis of carbamoyl chloride **64** was carried out under conditions where the base-induced conversion of carbamoyl chloride **64** to isocyanate **63** was suppressed. Studies established that substitution of 2,6-di-*tert*-butylpyridine for triethylamine as the HCl scavenger in the reaction of **7a** with phosgene led to the near exclusive formation of carbamoyl chloride **64** instead of isocyanate **63**. On its own, carbamoyl **64** exhibited no significant tendency to cyclize to **12** (or **13**) and, instead converted to isocyanate **63** over 5 h. Cyclization of **64** to **12** could, however, be promoted by addition of triethylamine.

Accordingly, a mixture of amine **7a** and 2,6-di-*tert*-butylpyridine was allowed to react with phosgene followed by the addition of 5 equivalents of triethylamine. This reaction was monitored by $^1$H NMR and the conversion of carbamoyl chloride **64** almost exclusively to after-the-barrier carbamate **13** was seen over a period of 80 min (see Figure 7). Furthermore, treatment of **7a** and 2,6-di-*tert*-butylpyridine with phosgene and 15 equivalents of triethylamine gave identical results but required only fifteen minutes for reactions and rotation to be completed. Last, **7b** was allowed to react with phosgene and triethylamine and cleanly gave the expected carbamate **13**.

While the details (carbamoyl chloride rather than isocyanate) are different, the important conclusion from the study of **7a** (Figure 7) instead of **6a** (Figure 6) is that, as predicted, the use of a shorter tether not only accelerates the speed of rotation, but also changes the rate-limiting step from rotation over the barrier to formation of the initial carbamate.

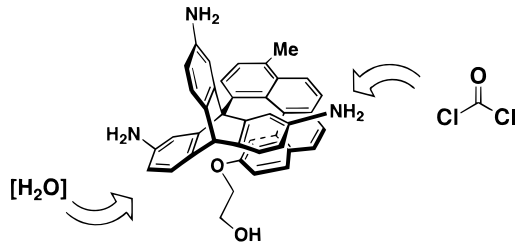



**Figure 8.** Schematic for a continually rotating molecular motor involving selective (and repeated) delivery of $Cl_2C{=}O$ to the amino group in the "firing" position and cleavage of the urethane only after each 120° of rotation has occurred.

## Conclusions

The unidirectional rotation of **6a** and **7a** constitute proof of principle of the first rationally designed chemically powered molecular motor. Much optimization remains to be done before a molecular system that rotates continuously and rivals the speed of its biological and mechanical counterparts is in hand. The next step, however, is now clear: To achieve repeated rotation by modifying **6a**/**7a** so that each blade of the triptycene is ready to be selectively armed at the appropriate time, and to include in the system (e.g., by attachment to the helicene) units with the appropriate spatial positioning that can capture and deliver $Cl_2C{=}O$, and cleave a urethane, as represented in Figure 8. Efforts in that direction are now in progress. Meanwhile, the concepts underlying the present work should be of general application to the understanding of biological and other motors.

## Experimental Section[66]

***N*-2-Anthracenylacetamide (28).** To a stirred suspension of commercially available 2-aminoanthracene (25 g; 0.13 mol) in anhydrous benzene (350 mL) was added neat acetic anhydride (40 mL; 0.42 mol) in one portion and the resulting heterogeneous mixture was heated at reflux for 12 h. The reaction was allowed to cool to room temperature and filtered to furnish a tan solid, which was washed several times with hexanes. The solid was air-dried and placed in a round-bottomed flask equipped with a $P_2O_5$ drying tube for further drying in a heated oil bath (110−120 °C) under house vacuum, affording 25 g (83%) of the title compound as a tan solid: mp 236−238 °C (lit.[40] mp 238−239 °C); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.20 (s, 1H), 8.50 (br s, 1H), 8.48 (s, 1H), 8.43 (s, 1H), 8.02 (apparent d, $J$ = 9.2 Hz, 3H), 7.54 (dd, $J$ = 9.2, 2.4 Hz, 1H), 7.50−7.43 (m, 2H), 2.15 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 168.7, 136.3, 131.7, 130.3, 128.8, 128.5, 128.1, 127.7, 125.8, 125.6, 124.92, 124.88, 121.0, 117.8, 113.6, 24.2.

***N*-(9-Bromo-2-anthracenyl)acetamide (29).** To a magnetically stirred cold (0 °C) suspension of acetamidoanthracene **28** (25 g; 0.11 mol) in anhydrous $CH_2Cl_2$ (500 mL) was added dropwise, via an addition funnel equipped with a $CaSO_4$ (anhyd) drying tube over a two day period, a solution of bromine (5.5 mL; 0.11 mol) in anhydrous $CH_2Cl_2$ (200 mL) (addition of $Br_2$ was stopped overnight; the reaction solution was recooled to 0 °C before $Br_2$ addition was resumed). The reaction was monitored by TLC (silica; $R_f$ of **28** = 0.34; $R_f$ of **29** = 0.41 EtOAc/hexanes; 3:2) and the addition of the bromine solution was stopped upon the disappearance of the starting amide. The resulting green heterogeneous mixture was allowed to warm to room temperature and filtered to furnish a green solid, which was washed several times with hexanes. The solid was then washed, successively, with water, saturated aqueous sodium bicarbonate and water until the filtrate was neutral to pH paper. The solid was air-dried overnight and placed in a round-bottomed flask, which was equipped with a $P_2O_5$ drying tube and heated in an oil bath (110−120 °C) for further drying under house

(66) For general experimental procedures see the Supporting Information.

vacuum. The title bromide was obtained in a yield of 33 g (97%) as a green solid. An analytically pure sample was obtained from ethanol as a bright yellow crystalline solid: mp 209−210 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.41 (s, 1H), 8.92 (s, 1H), 8.62 (s, 1H), 8.35 (d, $J$ = 8.4 Hz, 1H), 8.12 (d, $J$ = 2.0, Hz, 1H), 8.10 (d, $J$ = 3.6 Hz, 1H), 7.71−7.66 (m, 2H), 7.54 (t, $J$ = 7.6 Hz, 1H), 2.16 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 169.0, 138.5, 130.8, 130.7, 130.2, 129.7, 128.9, 128.0, 127.2, 126.4, 125.2, 121.1, 119.6, 117.8, 112.4, 24.3. Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46; Br, 25.43. Found: C, 60.94; H, 3.86; N, 4.42; Br, 25.24.

**2-(Acetylamino)-9-anthracenylboronic Acid (30).** To a cold (−78 °C) solution of bromoanthracene **29** (5.0 g; 0.016 mol) in anhydrous THF (80 mL) was added dropwise over 10 min a 1.4 M solution of methyllithium in ether (11.4 mL; 0.016 mol). The resulting reaction mixture was stirred at −78 °C for 0.5 h followed by the dropwise addition, over 5 min, of a 2.5 M solution of *n*-butyllithium in hexanes (6.4 mL; 0.016 mol) and the reaction mixture was stirred at −78 °C for 15 min. Subsequently, freshly distilled (from sodium metal) neat anhydrous trimethyl borate (6.9 mL; 0.080 mol) was added dropwise over 15−20 min and the resulting reaction mixture was stirred at −78 °C for an additional 2 h. The reaction was then quenched at −78 °C with 50 mL of water and to the two-phase mixture were added EtOAc (50 mL) and brine solution (50 mL). The phases were shaken and separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The organic phase and extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated to furnish a solid residue. The residue was taken up in EtOAc (∼50 mL), warmed on a steam bath and the hot solution was filtered; the filtrate was allowed to cool to room temperature. To the clear ethyl acetate filtrate was added additional EtOAc (100 mL) followed by hexanes (∼200 mL), until a cloudy solution resulted, and precipitation began to occur. The heterogeneous mixture was set aside at room temperature for 0.5−1 h and filtered to furnish a solid. A second (and sometimes a third) crop was obtained by evaporating the filtrate in vacuo, dissolving the residue at room temperature in ∼200 mL EtOAc, adding hexanes until precipitation began and allowing the mixture to stand about 10 minutes before collecting the precipitate. A total of 2.8 g (64%) of the title compound was afforded as a tan solid, which was not purified further because it is unstable to chromatography, heat or being in solution for extended periods: mp 239−240 °C dec; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.20 (s, 1H), 8.71 (s, 2H), 8.42 (s, 1H), 8.34 (s, 1H), 8.02 (d, $J$ = 8.0 Hz, 1H), 8.00 (d, $J$ = 9.2 Hz, 1H), 7.93 (d, $J$ = 8.4 Hz, 1H), 7.73 (dd, $J$ = 9.2, 2.0 Hz, 1H), 7.49−7.40 (m, 2H), 2.11 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 168.6, 136.0, 133.3, 133.1, 130.0, 128.9, 128.8, 128.5, 128.1, 125.7, 125.0, 124.5, 120.6, 117.9, 115.2, 24.2. Anal. Calcd for $C_{16}H_{14}BNO_3$: C, 68.85; H, 5.06; N, 5.02. Found: C, 69.14; H, 5.31; N, 4.84.

**5-Bromo-2-methylbenzaldehyde (21).**[44] To a stirred, cold (0 °C) suspension of anhydrous aluminum chloride (53.4 g; 0.40 mol) in anhydrous $CH_2Cl_2$ (150 mL) was added over 30 min via syringe neat 2-tolualdehyde (28 g; 0.23 mol). To the resulting stirred mixture was added at 0 °C dropwise, over a 6 h period, a solution of bromine (11.8 mL; 0.23 mol) in anhydrous $CH_2Cl_2$ (150 mL). The reaction was allowed to warm to room temperature, stirred for an additional 5 h, and poured over 500 g of crushed ice. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The original $CH_2Cl_2$ layer and the extracts were combined, washed successively with 2 M HCl (aqueous), saturated $NaHCO_3$ (aqueous), and brine solution, dried over anhydrous sodium sulfate, and concentrated to furnish a yellow oil. The oil was dissolved in hexanes (50 mL) and cooled in a −25 °C freezer to provide a yellow solid, which was collected by vacuum filtration. The solid was dissolved in hexanes (∼100 mL), warmed on a steam bath with decolorizing charcoal, filtered and cooled (−25 °C) to afford, after filtration, 13.6 g (30%) of the title compound as a colorless crystalline solid: mp 42−44 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.23 (s, 1H), 7.93 (d, $J$ = 2.4 Hz, 1H), 7.60 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.16 (d, $J$ = 8.4 Hz, 1H), 2.63 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 191.3, 139.5, 136.6 135.7, 134.3, 133.7, 120.3, 19.1. Anal. Calcd for $C_8H_7BrO$: C, 48.27; H, 3.54; Br, 40.14. Found: C, 47.96; H, 3.49; Br, 40.28.

**5-[2-(Acetylamino)anthracen-9-yl]-2-methylbenzaldehyde (31).** A mixture of boronic acid **30** (5.3 g; 0.019 mol) and aldehyde **21** (3.8 g; 0.019 mol) in a 500 mL three-neck, round-bottomed flask, were evacuated under house vacuum for 1 to 2 h and placed under an argon atmosphere. Separately, a flask containing a stock solution of 2.0 M $Na_2CO_3$ and a second flask containing anhydrous ethanol were evacuated under house vacuum for 1−2 h; the vacuum was released by admission of air. To the flask containing the boronic acid and the aldehyde were successively added anhydrous toluene (310 mL), 12.4 mL (0.025 mol) of the 2.0 M $Na_2CO_3$ solution, and anhydrous ethanol (6.2 mL; 0.11 mol) and the resulting heterogeneous mixture was deoxygenated by bubbling argon through it for 3.5 h. Tetrakis-(triphenylphosphine)palladium(0) (1.6 g; 7 mol %; Strem Chemicals, Inc.) was added to the heterogeneous mixture, which was heated at reflux for 12 h under argon with magnetic stirring. The reaction was allowed to cool to room temperature and then quenched with water (50 mL). To the bi-phasic mixture were added ethyl acetate (50 mL), additional water (50 mL) and brine solution (50 mL). The phases were shaken and separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The organic phase and extracts were combined, dried over sodium sulfate, and concentrated to furnish a brown oil. The residue was taken up in a minimum amount (∼100 mL) of chloroform (stabilized with 0.5% ethanol) followed by the addition of hexanes, until a cloudy solution resulted (∼30 mL), and the mixture was placed in a freezer (−26 °C) for 12 h. While still cold, the heterogeneous mixture was filtered (the solid was discarded) and the filtrate was concentrated to a residue. The residue was then dissolved in $CH_2Cl_2$ and flash chromatographed on a 5 × 30 cm silica gel column eluting with a solvent gradient (hexanes to 50% EtOAc/hexanes) to afford 5.6 g (84%) of the title compound as a golden fluffy solid: mp 134−136 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.27 (s, 1H), 8.44 (s, 1H), 8.02 (d, $J$ = 8.8 Hz, 1H), 7.99 (d, $J$ = 9.2 Hz, 1H), 7.83 (s, 1H), 7.70 (d, $J$ = 9.6 Hz, 1H), 7.65 (s, 1H), 7.54−7.33 (m, 6H), 2.77 (s, 3H), 2.11 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 193.0, 169.1, 139.9, 137.0, 136.6, 135.7, 135.0, 134.3, 132.2, 130.8, 130.7, 130.5, 129.5, 129.0, 128.6, 127.0, 126.1, 126.0, 124.9, 120.8, 114.0, 24.5, 19.6 (signals for two carbon atoms appear to be coincident). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.28; H, 5.40; N, 3.83.

**5-[2-(Acetylamino)-9,10[1′,2′]-benzenoanthracen-9(10*H*)-yl]-2-methylbenzaldehyde (32)**. Preparation of benzenediazonium carboxylate:[47] To a cold (0 °C) solution of anthranilic acid (27 g; 0.20 mol) in anhydrous THF (130 mL) was added all at once neat isoamyl nitrite (46 mL; 0.34 mol) followed by a catalytic amount (∼200−300 mg) of trichloroacetic acid. After 5 min, the cold bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred at that temperature for an additional hour. The solid was collected by gravity filtration and washed with anhydrous THF until (∼200 mL) a colorless filtrate resulted. The solid was then washed with anhydrous dioxane (∼200 mL) to displace THF (the dioxane wash was discarded). A hole was made in the filter paper and the solid diazonium salt was washed with 100−150 mL of anhydrous dioxane from the filter paper into a dry flask. [**CAUTION: Care must be exercised in not allowing the diazonium salt to come to dryness due to its highly explosive nature when dry**].

To a refluxing solution of aldehyde **31** (5.0 g; 0.014 mol) in anhydrous dioxane (140 mL) was added, over a period of 2−3 h, all of the freshly prepared diazonium salt (above) as the above slurry in dioxane. After the addition, the reaction mixture was heated at reflux for an additional 1 h and allowed to cool to room temperature. The reaction mixture was quenched with water (50 mL) and brine (50 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a viscous black residue. The residue was dissolved in a minimum (∼50 mL) of $CH_2Cl_2$; the solution was applied to the top of a 35 cm × 5.5 cm silica gel column which was then eluted with a solvent gradient (hexanes to 50% EtOAc/hexanes) to afford, after evaporation of the solvent, 3.4 g (56%) of the title compound as a brown fluffy solid. An analytically pure sample was obtained as yellow crystals, mp 184−186 °C after recrystallization from acetone/hexanes; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.38 (s, 1H), 8.60 (d, $J$ = 2.0 Hz,

1H), 8.22 (dd, $J$ = 8.0, 2.0 Hz, 1H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.44 (apparent d, $J$ = 7.6 Hz, 3H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.21 (bs, 1H), 7.17 (dd, $J$ = 8.0, 2.0 Hz, 1H), 7.13 (apparent d, $J$ = 7.6 Hz, 2H), 7.03 (apparent t, $J$ = 7.2, 6.8 Hz, 2H), 6.95 (apparent t, $J$ = 7.6, Hz, 2H), 5.41 (s, 1H), 2.82 (s, 3H), 2.05 (s, 3H); $^{13}$C NMR ($CDCl_3$, 126 MHz) $\delta$ 193.0, 168.8, 146.4, 146.3, 146.0, 142.6, 139.5, 136.6, 135.0, 134.7, 134.3, 134.0, 132.0, 125.3, 124.6, 124.0, 123.7, 123.5, 116.9, 116.4, 59.5, 54.3, 23.9, 19.0. HRMS (CI) calcd for $C_{30}H_{23}NO_2$ 429.1729, found 429.1740.

**7-Methoxy-2-naphthyl Trifluoromethanesulfonate (38).** To a cold (0 °C) solution of 7-methoxy-2-naphthol (5.0 g; 0.029 mol) in anhydrous $CH_2Cl_2$ (50 mL) were added neat anhydrous pyridine (14 mL; 0.17 mol) and trifluoromethanesulfonic anhydride (5.3 mL; 0.032 mol). The resulting reaction mixture was stirred in the cold bath for an additional 0.5 h and then at room temperature overnight. The reaction was quenched with water (25 mL) and extracted with EtOAc (5 × 50 mL). The organic extracts were combined, washed sequentially with water, 10% HCl (aqueous) and water, dried over anhydrous sodium sulfate, and concentrated to afford 8.5 g (97%) of the title compound as a yellow oil, which was used without further purification: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.82 (d, $J$ = 12.0 Hz, 1H), 7.76 (d, $J$ = 12.4 Hz, 1H), 7.64 (d, $J$ = 2.8 Hz, 1H), 7.25−7.21 (m, 2H), 7.14 (d, $J$ = 3.6 Hz, 1H) 3.93 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 159.5, 148.4, 135.6, 130.9, 130.0, 128.5, 119.5 (q, $J$ = 1280 Hz), 120.9, 118.6, 117.6, 106.4, 56.0.

**7-Methoxy-2-methylnaphthalene (39).** A cold (−78 °C) suspension of CuCN (dried under house and then high vacuum in a $P_2O_5$-equipped round-bottomed flask immersed in an oil bath at >100 °C; 5.0 g; 0.056 mol) in anhydrous THF (40 mL) was treated with a solution of 1.4 M methyllithium in ether (76 mL; 0.11 mol) and the resulting homogeneous solution was allowed to warm to −20 °C. The reaction mixture was kept at −20 °C for 10 min, recooled to −78 °C, and a solution of **38** (5.0 g; 0.016 mol) in anhydrous THF (80 mL) was introduced dropwise via a syringe over 30 min. Subsequently, the reaction was allowed to warm to −25 °C, placed in a freezer (−25 °C) for 2 days, and carefully quenched at that temperature by the dropwise (**CAUTION:** foaming) addition of 80 mL of saturated $NH_4Cl$ (aq). The mixture was then extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to furnish a dark yellow solid. The solid was chromatographed on a silica gel column (30 cm × 4 cm), eluting with 5% EtOAc/hexanes, to afford 2.1 g (75%) of the title compound as a colorless crystalline solid: mp 87−88 °C (lit.[67] mp 87.5−88.5 °C); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.68 (apparent t, $J$ = 9.2 Hz 2H), 7.52 (s, 1H), 7.16 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.09−7.06 (m, 2H), 3.91 (s, 3H), 2.49 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 157.9, 136.2, 135.0, 129.3, 127.6, 127.3, 126.1, 126.0, 117.9, 105.5, 55.4, 21.9. HRMS (CI) calcd for $C_{12}H_{12}O$ 173.0966, found 173.0962.

**2-(Bromomethyl)-7-methoxynaphthalene (40).** 7-Methoxy-2-methylnaphthalene (**39**, 500 mg; 2.9 mmol), 2,2′-azobisisobutyronitrile (AIBN, 9 mg; 2 mol %) and $CCl_4$ (120 mL) were introduced into a 250 mL two-neck, round-bottomed flask, which was fitted with a reflux condenser and an $N_2$ inlet. The mixture was heated at reflux, and *N*-bromosuccinimide (NBS, 517 mg; 2.9 mmol) was added in ∼10 mg portions over a 5 h period and the resulting reaction mixture was refluxed for an additional 2 h. The reaction was allowed to cool to room temperature, filtered and the yellow filtrate was concentrated to provide a yellow solid. The solid was recrystallized from hexanes to afford 640 mg (88%) of the title compound as a colorless crystalline solid: mp 107−108 °C (lit.[68] mp 108 °C); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.69−7.71 (m, 3H), 7.35 (dd, $J$ = 8.4, 1.6 Hz, 1H), 7.15 (dd, $J$ = 8.8, 2.4 Hz, 1H), 7.10 (d, $J$ = 2.7 Hz, 1H), 4.64 (s, 2H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 158.3, 135.8, 134.6, 129.4, 128.7, 128.6, 127.0, 124.7, 119.6, 106.1, 55.5, 34.4.

**[(7-Methoxy-2-naphthyl)methyl]triphenylphosphonium Bromide (41).** To a solution of bromide **40** (450 mg; 1.79 mmol) in anhydrous toluene (15 mL) was added triphenylphosphine (517 mg; 1.97 mmol) and the reaction mixture was heated at reflux for 20 h. The resulting suspension was allowed to cool to room temperature, and the solid was filtered off and washed with hexanes to provide 890 mg (97%) of the title compound as a colorless powder: mp 274−276 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.80−7.72 (m, 8H), 7.65−7.56 (m, 9H), 7.42 (d, $J$ = 11.2 Hz, 1H), 7.09−7.05 (m, 1H) 6.89 (d, $J$ = 3.2 Hz, 1H), 6.87−6.83 (m, 1H), 5.42 (s, 1H), 5.38 (s, 1H), 3.84 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 157.8, 134.9, 134.8, 134.24, 134.15 130.1, 130.0, 129.9, 128.84, 128.80, 128.0, 127.93, 127.89, 127.86, 125.92, 125.88, 124.8 124.7, 119.4, 118.0, 117.1, 105.6, 55.3, 31.0, 30.5. Anal. Calcd for $C_{30}H_{26}BrOP$: C, 70.18; H, 5.10. Found: C, 69.83; H, 5.06.

**2-(Acetylamino)-9,10-dihydro-9-[4-methyl-3-[2-(7-methoxy-2-naphthalenyl)ethenyl]phenyl]-9,10[1′,2′]-benzenoanthracene (42).** A cold (−78 °C) suspension of phosphonium salt **41** (3.4 g; 6.7 mmol) in anhydrous THF (200 mL) was treated with a 1.0 M solution of lithium bis(trimethylsilyl)amide (LHMDS) in THF (6.7 mL; 6.7 mmol). After 10 min, the cold bath was removed, and the reaction mixture was allowed to warm to room temperature. Subsequently, the reaction was cooled to −78 °C, followed by the dropwise addition over 20 min of a solution of aldehyde **32** (2.60 g; 6.05 mmol) in anhydrous THF (40 mL). The resulting mixture was kept stirring at −78 °C for an additional 2.5 h and then at room temperature overnight. The reaction was quenched with water (∼50 mL) and extracted with ethyl acetate (5 × 100 mL). The combined organic extracts were washed with brine solution until (∼5 × 30 mL) the aqueous layer became neutral to pH paper, dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a solid. The solid was chromatographed on silica gel (30 cm × 4 cm), eluting with EtOAc : hexanes : $CH_2Cl_2$ (2:1:1), to afford 2.5 g (71%) of a 1:4 mixture of the *Z* and *E* isomers of the title compound as a tan solid. The isomers can be separated by column chromatography (silica gel, EtOAc : hexanes : $CH_2Cl_2$; 1:2:1) for analyses and characterizations. ***Z*-Stilbene 42**: mp 128−130 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.90−7.86 (m, 2H), 7.64−7.53 (m, 4H), 7.29−7.23 (m, 4H), 7.09−7.01 (m, 4H), 6.92−6.74 (m, 6H), 6.62 (s, 1H), 6.35 (apparent t, $J$ = 7.2 Hz, 2H), 5.26 (s, 1H), 3.85 (s, 3H), 2.54 (s, 3H), 1.89 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 168.2, 158.1, 147.6, 146.5, 143.2, 137.8, 135.6, 135.5, 134.9, 134.3, 133.7, 132.2, 131.3, 131.0, 130.7, 130.4, 129.3, 128.0, 127.7, 127.6, 125.1, 124.8, 124.6, 124.5, 123.9, 123.7, 123.4, 119.0, 117.2, 116.9, 106.1, 60.0, 55.5, 54.6, 24.4, 19.9. HRMS (EI) calcd for $C_{42}H_{33}NO_2$ 583.2511, found 583.2505. ***E*-Stilbene 42**: mp 233−234 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.42 (d, $J$ = 2.4 Hz, 1H), 7.93 (dd, $J$ = 10.8, 2.4 Hz, 1H), 7.78−7.70 (m, 3H), 7.66−7.59 (m, 2H), 7.50 (d, $J$ = 8.0 Hz, 1H), 7.44−7.42 (m, 3H), 7.38 (d, $J$ = 8.0 Hz, 1H), 7.32 (m, 2H), 7.29−7.25 (m, 2H), 7.12−7.09 (m, 2H), 7.05−6.96 (m, 5H), 5.41 (s, 1H), 3.92(s, 3H), 3.65 (s, 3H), 2.09 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 168.3, 158.0, 147.5, 146.7, 143.1, 136.5, 135.6, 134.90, 134.86, 134.6, 133.8, 130.8, 130.6, 129.2, 128.6, 128.4, 128.1, 126.6, 125.8, 125.3, 124.7, 123.9, 123.6, 121.5, 118.6, 117.5, 116.8, 106.1, 60.2, 55.3, 54.6, 24.3, 19.7. Anal. Calcd for $C_{42}H_{33}NO_2$: C, 86.42; H, 5.70; N, 2.40. Found: C, 86.04; H, 5.75; N, 2.24.

**Photocyclization of Stilbene 42 to 2-(Acetylamino)-9,10-dihydro-9-(11-methoxy-4-methylbenzo[*c*]phenanthren-1-yl)-9,10[1′,2′]-benzenoanthracene (43). General Considerations.** The photoreactor, similar to Ace Glass catalog no. 7840, was a cylindrical glass vessel with a quartz immersion well, connected through a standard taper 60/40 ground glass joint. The immersion well was a double-walled quartz tube cooled by water containing an Hanovia 450-W medium-pressure quartz Hg vapor lamp (Ace Glass, Inc. catalog no. 7825-34) and a Pyrex filter. The molarity of the solutions with respect to the starting stilbene was kept in the $10^{-3}$ M range. Propylene oxide was used[69] to scavenge HI. The photoirradiation was monitored by $^1$H NMR (aliquots were taken via the angle joint and washed with 15% $Na_2S_2O_3$ (aqueous); the organic phase was dried over sodium sulfate, the solvent was evaporated, and the residue was dissolved in $CDCl_3$).

**Specific Procedure.** To the photochemical vessel containing a magnetically stirred solution of stilbene **42** (700 mg; 1.2 mmol) as a mixture of *E*/*Z* isomers in benzene (850 mL) were added iodine (1.8 g; 7.2 mmol) and propylene oxide (29.4 mL; 0.42 mol). The resulting

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solution was deoxygenated by bubbling argon through it for 2 h, using a long syringe needle reaching to the bottom of the reaction vessel, after which time the reaction was kept under a static argon atmosphere. The reaction was initially cooled to +10 °C (internal temperature) in a −20 °C dry ice/acetone bath, whose low temperature was maintained throughout the photolysis at approximately −20 °C with a Cryocool probe (Neslab; CC-100) once the dry ice had evaporated. The lamp was turned on; once the lamp is turned on, the internal reaction temperature increases. The reaction temperature was monitored *internally*, and *carefully* maintained at 24−28 °C (higher internal temperatures are seriously deleterious). An elapsed time of 60 h of irradiation was required for the completion of the reaction (for fire safety reasons the photolysis was not allowed to run unattended overnight, so the lamp and cooling were turned off overnight; in the morning, argon was bubbled through the reaction solution for 1 h and the reaction solution was recooled to +10 °C (internal temperature) in the −20 °C dry ice/acetone/Cryocool bath) before resuming the irradiation. When the $^1$H NMR assay indicated that the consumption of stilbene was essentially complete, the resulting mixture was washed three times with a total volume of 200 mL of 15% aqueous $Na_2S_2O_3$ and the aqueous wash was extracted with ethyl acetate (3 × 50 mL). The combined benzene and ethyl acetate layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated to furnish a dark brown residue. The residue was dissolved in chloroform (20 mL) containing 0.5% ethanol as stabilizer, kept at room-temperature overnight and then at −20 °C for 10 h; it was then quickly flash chromatographed on a 30 cm × 4 cm silica gel column (eluting with 15% ethyl acetate/hexanes to 40% ethyl acetate/hexanes) to afford 280 mg (40%) of the title compound as a yellow solid. The ratio of the atropisomers is solvent and temperature dependent. This procedure increases the amount of the atropisomer that is easiest to separate from **48** (the demethylated compound). Once separation of **43** from **48** was achieved, no effort was made to prevent reequilibration of the rotamers of **43**. The yellow solid is a mixture of the three possible atropisomers, which were not separated at this point, but immediately used for the next reaction sequence. The $^1$H NMR spectrum of the mixture of rotamers is too complex to list. It is provided in the Supporting Information.

**2-(Acetylamino)-9,10-dihydro-9-(11-hydroxy-4-methylbenzo[*c*]-phenanthren-1-yl)-9,10[1′,2′]-benzenoanthracene (44).** A cold (−78 °C) solution of methoxyhelicene atropisomers **43** (250 mg; 0.43 mmol) in anhydrous $CH_2Cl_2$ (11 mL) was treated with a 1.0 M solution of boron tribromide ($BBr_3$, 0.65 mL; 0.65 mmol; Aldrich) in $CH_2Cl_2$. The resulting mixture was stirred at −78 °C for 3 h, allowed to warm to room temperature, and stirred for an additional 2 h. The reaction mixture was poured onto 20 g of crushed ice, and the phases were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL); the organic layer and extracts were combined, washed with water (3 × 15 mL), dried over anhydrous sodium sulfate, and concentrated to furnish a yellow-green solid. The solid (preadsorbed on 10 g of silica gel) was flash chromatographed on silica gel (30 cm × 4 cm), eluting with a solvent gradient (25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to afford a total of 214 mg (88%) of the three atropisomers. The mixture was ordinarily used to prepare **51** or **52**, but one of the atropisomers could be isolated free of the others by the above separation. Consequently, the above separation provided 184 mg of one (mp 244 °C, dec) of the three atropisomers and 30 mg of a mixture of the other two isomers contaminated with the isolated isomer. Spectra of the single, pure atropisomer are: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.39 (s, 1H), 8.16 (d, $J$ = 8.8 Hz, 1H), 7.83 (d, $J$ = 8.8 Hz, 1H), 7.72−7.58 (m, 6H), 7.49 (s, 1H), 7.37 (s, 1H), 7.24 (s, 1H), 7.07−7.03 (m, 2H), 6.90 (d $J$ = 7.2 Hz, 1H), 6.64 (td, $J$ = 7.2, 1.2 Hz, 1H), 6.57 (td, $J$ = 7.6, 1.6 Hz, 1H), 6.49 (dd, $J$ = 8.4, 2.4 Hz, 1H), 6.42 (td, $J$ = 7.2, 1.6 Hz, 1H), 6.36 (d, $J$ = 7.6 Hz, 1H), 5.90−5.83 (m, 2H), 5.13 (s, 1H), 2.99 (s, 3H), 2.13 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 172.5, 155.5, 152.4, 150.3, 148.6, 145.3, 143.44, 143.41, 137.1, 135.6, 134.9, 134.6, 132.5, 131.1, 130.3, 130.1, 130.0, 128.5, 128.0, 127.3, 127.0, 126.5, 125.8, 124.8, 124.6, 124.3, 124.2, 124.1, 124.0, 123.4, 123.3, 123.2, 123.0, 122.7, 117.3, 111.7, 66.1, 55.8, 30.3, 23.7, 20.8. HRMS (EI) calcd for $C_{41}H_{29}NO_2$ 567.2198, found 567.2183.

**3-{[12-(2-[Acetylamino]-9,10[1′,2′]-benzenoanthracen-9(10*H*)-yl)-9-methylbenzo[*c*]phenanthren-2-yl]oxy}-1-propanol (51).** To a solution of phenol **44** (161 mg; 0.28 mmol; mixture of atropisomers) in anhydrous acetone (5 mL) were added potassium carbonate that had been heated in a crucible over a Meeker burner (100 mg; 0.72 mmol) and 3-bromo-1-propanol (0.39 mL; 4.3 mmol). The resulting mixture was heated at reflux for 12 h, diluted with ethyl acetate (50 mL) and washed with water (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL); the organic layer and extracts were combined, dried over sodium sulfate and concentrated to furnish a yellow glassy solid. The solid was chromatographed on silica gel and eluted with a solvent gradient (30% EtOAc/hexanes to 50% EtOAc/hexanes) to afford 123 mg (69%) of the title compound as a yellow crystalline solid consisting of all three possible atropisomers. The mixture of isomers was immediately used for the next reaction without further separation. The $^1$H NMR spectrum of the mixture of rotamers is too complex to list. It is provided in the Supporting Information.

**3-{[12-(2-Amino-9,10[1′,2′]-benzenoanthracen-9(10*H*)-yl)-9-methylbenzo[*c*]phenanthren-2-yl]oxy}-1-propanol (6).** To a solution of amide **51** (187 mg; 0.299 mmol) in *n*-butanol (2 mL) were added KOH pellets (667 mg; ∼10 mmol of KOH) and ethylene glycol (6 mL). The mixture was deoxygenated by bubbling argon through for 30 min (failure to deoxygenate results in substantial decomposition of **6**) and heated at reflux for 10 h. Subsequently, the reaction mixture was allowed to cool to room temperature, at which time a slight precipitate appeared. Deionized water (2 mL) was added to the heterogeneous mixture, which resulted in the formation of a flocculent precipitate. The solid was collected by vacuum filtration, dissolved in benzene (10 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to yield 150 mg of the title compound as a mixture of the three atropisomers in an approximate ratio of 1.5:1:2.5 (**atropisomer 6a : atropisomer 6b : atropisomer 6c**). The isomers were separated by semipreparative layer chromatography in 10 mg portions on 20 cm × 20 cm, 250 $\mu$m thick plates (Analtech, catalog no. 40011), using EtOAc as the developing solvent, to ultimately afford a combined weight of 110 mg (65%) of the respective pure atropisomers. The individual bands containing the respective atropisomers were scraped off and in each case the silica gel was rapidly extracted with 100 mL of ice-cold (to avoid rotamer reequilibration) chloroform (containing 0.5% ethanol as stabilizer). The chloroform was evaporated, in the absence of any heat source, using a rotary evaporator operating at aspirator vacuum equipped with a dry ice condenser. Pertinent spectral data are as follows: **Atropisomer 6a** ($R_f$ = 0.36): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.34 (d, $J$ = 6.3 Hz, 1H), 8.22 (d, $J$ = 8.7 Hz, 1H), 7.98 (s, 1H), 7.82 (t, $J$ = 8.4 Hz, 2H), 7.76−7.71 (m, 3H), 7.65 (d, $J$ = 8.1 Hz, 1H), 7.51 (apparent d, $J$ = 8.4 Hz, 1H), 7.33−7.26 (m, 3H), 7.01 (dd, $J$ = 7.8, 1.5 Hz, 1H), 6.68 (d, $J$ = 7.5 Hz, 1H), 6.69−6.60 (m, 1H), 6.52 (t, $J$ = 6.3 Hz, 1H), 6.15 (d, $J$ = 7.5 Hz, 1H), 5.78 (dd, $J$ = 7.5, 2.1 Hz, 1H), 5.48 (d, $J$ = 2.1 Hz, 1H), 5.03 (s, 1H), 3.65−3.41 (m, 4H), 3.44−3.35 (m, 2H), 3.01 (s, 3H), 2.01 (bs, 1H), 1.81−1.75 (m, 2H); **Atropisomer 6b** ($R_f$ = 0.42): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.45 (d, $J$ = 7.3 Hz, 1H), 8.22 (d, $J$ = 8.3 Hz, 1H), 7.92−7.85 (m, 2H), 7.85−7.71 (m, 3H), 7.65 (d, $J$ = 7.8 Hz, 1H), 7.54 (d, $J$ = 6.3 Hz, 1H), 7.43−7.32 (m, 4H), 6.84 (d, $J$ = 6.3 Hz, 1H), 6.81(d, $J$ = 7.8 Hz, 1H), 6.62 (dd, $J$ = 8.3, 2.0 Hz, 1H), 6.45 (t, $J$ = 7.3 Hz, 1H), 5.91 (d, $J$ = 8.0 Hz, 1H), 5.84 (t, $J$ = 1.9 Hz, 1H), 5.73 (d, $J$ = 2.0 Hz, 1H), 4.98 (s, 1H), 3.62−3.55 (m, 4H), 3.46−3.35 (m, 2H), 3.06 (s, 3H), 2.01 (bs, 1H), 2.01 (bs, 1H), 1.85−1.75 (m, 2H); **Atropisomer 6c** ($R_f$ = 0.27): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.20 (d, $J$ = 8.8 Hz, 1H), 7.93 (d, $J$ = 2.0 Hz 1H), 7.86−7.80 (m, 3H), 7.70 (apparent d, $J$ = 7.2 Hz, 3H), 7.36 (d, $J$ = 8.2 Hz, 1H), 7.35 (s, 1H), 7.00 (d, $J$ = 6.0 Hz, 1H), 6.88 (d, $J$ = 7.6 Hz, 1H), 6.73 (d, $J$ = 6.0 Hz, 1H), 6.62−6.60 (m, 2H), 6.53 (t, $J$ = 7.6 Hz, 1H), 6.38 (t, $J$ = 7.6 Hz, 1H), 6.30 (d, $J$ = 7.2 Hz, 1H), 5.94 (d, $J$ = 8.0 Hz, 1H), 5.81 (t, $J$ = 8.0 Hz, 1H), 5.02 (s, 1H), 3.70−3.60 (m, 4H), 3.50−3.40 (m, 2H), 2.99 (s, 3H), 2.02 (bs, 1H), 1.60−1.50 (m, 2H): HRMS (CI) calcd for $C_{42}H_{34}NO_2$ $[M + H]^+$ 584.2590, found 584.2570.

**2-(Acetylamino)-9,10-dihydro-9-[11-[2-(methoxymethoxy)ethoxy]-4-methylbenzo[*c*]phenanthren-1-yl]-9,10[1′,2′]-benzenoanthracene (52).** The phenol **44** (190 mg; 0.33 mmol) was added, as a mixture of the three atropisomers, to a suspension of potassium carbonate ($K_2CO_3$, 20 mg; 0.14 mmol), which had been activated by heating in a crucible over a Meeker burner, in anhydrous acetone (10 mL). To the

mixture was added 2-bromoethoxymethyl methyl ether[56] (1.0 mL; 6 mmol) and the reaction was stirred for 3 h at room temperature followed by addition of additional 2-bromoethoxymethoxy methyl ether (1.0 mL; 6 mmol). The resulting mixture was heated at reflux for 18 h, allowed to cool to room temperature, filtered, and the filtrate was concentrated to give a brown oil. The oil was heated in an oil bath (40 °C) in vacuo (0.5 Torr) to remove excess 2-bromoethoxymethyl methyl ether. The resulting oily residue was chromatographed on silica gel pretreated with triethylamine (2 mL), eluting with hexanes: EtOAc (1:3) to afford 141 mg (65%) of the title compound, comprising the three atropisomers, as a yellow solid: HRMS (EI) calcd for $C_{45}H_{37}NO_4$ 655.2723, found 655.2690. The $^1$H NMR spectrum of the mixture of rotamers is too complex to list. It is provided in the Supporting Information.

**2-Amino-9,10-dihydro-9-[11-[2-(methoxymethoxy)ethoxy]-4-methylbenzo[*c*]phenanthren-1-yl]-9,10[1′,2′]-benzenoanthracene (53).** A mixture of the three atropisomers of **52** (61 mg; 0.093 mmol) was suspended under argon in a mixture of ethylene glycol (6 mL) and *n*-butanol (2 mL), which was previously deoxygenated by bubbling argon through it. To this mixture was added potassium hydroxide pellets (105 mg; ∼1.6 mmol), and the mixture was heated at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and a slight precipitate resulted. Upon the addition of deionized water (2 mL) to the mixture, a flocculent precipitate was formed. The solid was collected by filtration, dissolved in benzene (10 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to afford 41 mg (72%) of the title compound, containing the three atropisomers, as a fluffy yellow solid. The solid was carried on to the next reaction without further purification. HRMS (EI) calcd for $C_{43}H_{35}NO_3$ 613.2617, found 613.2586. The $^1$H NMR spectrum of the mixture of rotamers is too complex to list. It is provided in the Supporting Information.

**2-{[12-(2-Amino-9,10[1′,2′]-benzenoanthracen-9(10*H*)-yl)-9-methylbenzo[*c*]phenanthren-2-yl]oxy}-1-ethanol (7).** The crude mixture from immediately above, consisting of the three atropisomers of **53** (41 mg; 0.068 mmol), was dissolved in a mixture of $CH_2Cl_2$ (5 mL) and ethanol (1 mL). The resulting mixture was deoxygenated by bubbling a steady stream of argon through the mixture for 30 min. Concentrated hydrochloric acid (10 $\mu$L) was added to the mixture and the reaction was stirred at room temperature under argon for 20 h. The reaction was then quenched with a saturated aqueous solution of $K_2CO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$ and evaporated to give 29 mg of crude **7** as a mixture of the three atropisomers in an approximate ratio of 3:2:5 (**atropisomer 7a** : **atropisomer 7b** : **atropisomer 7c**). Separation of the atropisomeric mixture was achieved as with **6**, using semipreparative plate chromatography on 20 cm × 20 cm, 250 $\mu$m thick plates (Analtech, catalog no. 40011), with 10 mg of the mixture per plate and developing the individual plates with ethyl acetate. The resulting bands containing the respective atropisomers were scraped off and in each case the silica gel was rapidly extracted with 100 mL of ice-cold chloroform (containing 0.5% ethanol as stabilizer). The chloroform was evaporated, in the absence of any heat source, using a rotary evaporator operating at aspirator vacuum equipped with a dry ice condenser. The three atropisomers were isolated to give a combined yield of 27 mg (70%). Pertinent spectral data are as follows: **Atropisomer 7a** ($R_f$ = 0.3): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.39 (d, $J$ = 7.3 Hz, 1H), 8.23 (d, $J$ = 8.5 Hz, 1H), 8.07 (s, 1H), 7.83 (apparent t, $J$ = 8.3 Hz, 2H), 7.76−7.72 (m, 3H), 7.63 (d, $J$ = 8.0 Hz, 1H), 7.53 (d, $J$ = 8.8 Hz, 1H), 7.32−7.21 (m, 3H), 7.01 (d, $J$ = 7.5 Hz, 1H), 6.69 (t, $J$ = 7.8 Hz, 1H), 6.64 (t, $J$ = 7.5 Hz, 1H), 6.52 (t, $J$ = 7.8 Hz, 1H), 6.14 (d, $J$ = 7.8 Hz, 1H), 5.76 (d, $J$ = 7.8, 1H), 5.51 (d, $J$ = 2.0 Hz, 1H), 5.05 (s, 1H), 3.65−3.55 (m, 4H), 3.44−3.35 (m, 2H), 2.98 (s, 3H), 2.01 (bs, 1H); **Atropisomer 7b** ($R_f$ = 0.7): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.40 (d, $J$ = 7.3 Hz, 1H), 8.22 (d, $J$ = 8.3 Hz, 1H), 7.92 (d, $J$ = 2.2 Hz, 1H), 7.85−7.76 (m, 2H), 7.75−7.65 (m, 3H), 7.54−7.51 (m, 1H), 7.43−7.32 (m, 3H), 6.84 (d, $J$ = 6.3 Hz, 1H), 6.81(d, $J$ = 7.8 Hz, 1H), 6.62 (dd, $J$ = 8.3, 2.0 Hz, 1H), 6.40 (t, $J$ = 7.3 Hz, 1H), 5.96 (d, $J$ = 8.0 Hz, 1H), 5.93 (dd, $J$ = 7.5, 2.0 Hz, 1H), 5.82 (t, $J$ = 7.5 Hz, 1H), 5.62 (d, $J$ = 2.0 Hz, 1H), 4.98 (s, 1H), 3.62−3.55 (m, 4H), 3.46−3.35 (m, 2H), 2.98 (s, 3H), 2.00 (bs, 1 H); **Atropisomer 7c** ($R_f$ = 0.25): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.18 (d, $J$ = 8.4 Hz, 1H), 8.04 (d, $J$ = 2.2 Hz, 1H), 7.88 (s, 1H), 7.83 (m, 2H), 7.71−7.67 (m, 3H), 7.38 (d, $J$ = 8.8 Hz, 1H), 7.35 (d, $J$ = 8.1 Hz, 1H), 7.01 (d, $J$ = 5.9 Hz, 1H), 6.89 (d, $J$ = 5.9 Hz, 1H), 6.74 (dd, $J$ = 8.1, 2.2 Hz, 1H), 6.64−6.58 (m, 2H), 6.54 (t, $J$ = 6.2 Hz, 1H), 6.40 (t, $J$ = 7.3 Hz, 1H), 6.25 (d, $J$ = 7.3 Hz, 1H), 6.00 (d, $J$ = 8.1 Hz, 1H), 5.84 (t, $J$ = 7.7 Hz, 1H), 5.03 (s, 1H), 3.76−3.70 (m, 2H), 3.58−3.50 (m, 2H), 3.48−3.41 (m, 2H), 2.98 (s, 3H), 2.01 (s, 1H). HRMS (EI) calcd for $C_{41}H_{31}NO_2$ (as a mixture of atropisomers) 569.2355, found 569.2345.

**Reaction of 6a with Phosgene: Demonstration of Unidirectional Rotation.** Because of the constraints (see above) associated with the isolation of single atropisomers, to ensure that any impurities (e.g., solvent residues) adventitiously introduced during separation and/or isolation did not mislead in the calculation of the quantity of phosgene to use, a calibration study was routinely carried out. The following procedure is illustrative.

Compound **6a** (nominally 5.0 mg) was dissolved in $CDCl_3$ (0.8 mL) and added to an oven-dried (200 °C) NMR tube. To this solution was added triethylamine (5 equiv based on 5.0 mg of **6a**). A $^1$H NMR spectrum was taken of the solution. The integration of the 6 methylene protons of triethylamine and the 3 methyl protons of the **6a** were compared and the amount of **6a** actually in the NMR tube based on the integrations was determined to be 3.6 mg. The solution was then evaporated.

Rotamer **6a** (calibrated, 3.6 mg, 0.006 mmol) was dissolved in $CDCl_3$ (0.8 mL) and added to an oven-dried (200 °C) NMR tube. To this solution was rapidly added, via a microsyringe, phosgene [1 equiv, 20% solution in toluene (Fluka), 3.0 $\mu$L]. After 5 min, triethylamine (8.6 $\mu$L, 10 equiv) was added and the reaction was then monitored by $^1$H NMR (see Figure 6). At the end of the reaction (∼10 h), the solution was poured into water (20 mL) and extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$ and evaporated to give 4.2 mg of a crude brown solid. The solid was dissolved in $CH_2Cl_2$ (1 mL) and applied to a 20 cm × 20 cm, 250 $\mu$m thick semipreparative thin-layer chromatography plate. The plate was developed with a 9:1 hexanes/ethyl acetate mixture. The major band ($R_f$ = 0.6) was removed and extracted with $CHCl_3$, to give 2.8 mg of carbamate **11**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.45 (d, $J$ = 7.3 Hz, 1H), 7.92−7.85 (m, 2H). 7.85−7.71 (m, 3H), 7.65 (d, $J$ = 7.8 Hz, 1H), 7.54 (d, $J$ = 6.3 Hz, 1H), 7.43−7.32 (m, 4H), 6.84 (d, $J$ = 6.3, 1H), 6.81 (d, $J$ = 7.8 Hz, 1H), 6.62 (dd, $J$ = 8.3, 2.0 Hz, 1H), 6.45 (t, $J$ = 7.3 Hz, 1H), 5.91 (d, $J$ = 8.0 Hz, 1H), 5.84 (t, $J$ = 1.9 Hz, 1H), 5.73 (d, $J$ = 2.0 Hz, 1H), 4.98 (s, 1H), 3.62−3.55 (m, 4H), 3.46−3.35 (m, 2H), 3.01 (s, 3H), 1.81−1.75 (m, 2H). HRMS (EI) calcd for $C_{43}H_{31}NO_3$ 609.2304, found 609.2277.

**Reaction of 6b with Phosgene to Give Carbamate 11.** Rotamer **6b** (8.6 mg, 0.015 mmol) was dissolved in $CDCl_3$ (0.25 mL) and added to an oven-dried (200 °C) NMR tube at room temperature. Phosgene [1 equiv, 20% solution in toluene (Fluka), 0.015 mmol, 7.2 $\mu$L] was next added and the mixture was shaken. After a period of 15 min, triethylamine (9 equiv, 20 $\mu$L, 0.14 mmol, distilled and stored over KOH) was added in one portion. The reaction was then immediately assayed by $^1$H NMR, which indicated that formation of carbamate **11** was complete. The crude mixture was evaporated, dissolved in $CH_2Cl_2$ and applied to a 20 cm × 20 cm, 250 $\mu$m thick silica semipreparative thin-layer chromatography plate, which was developed with 9:1 hexanes/ethyl acetate. A yield of 8.4 mg (92%) of carbamate **11** was obtained, which was identical to the carbamate obtained in the preceding reaction.

**Cleavage of Carbamate 11 to 6b**: The carbamate (5.6 mg) was dissolved with stirring in ethanol (5 mL) at 0 °C. To this solution was added excess $NaBH_4$ (1.0 g) over an 8-h period while maintaining the solution at 0 °C. The mixture was added to water and then neutralized using a 10% HCl solution. The solution was then extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and evaporated at aspirator vacuum at room temperature using a rotary evaporator fitted with a dry ice condenser. The resultant residue (5.2 mg) was dissolved in $CHCl_3$ (1 mL) and applied to a 20 cm × 20 cm, 250 $\mu$m thick semipreparative thin-layer chromatography plate. The plate was developed with a 9:1 hexanes/ethyl acetate solution. A major band ($R_f$ = 0.6) was removed and extracted with $CHCl_3$, to give 4.2 mg of the starting carbamate **11**. A second band ($R_f$ = 0.3) was

removed and gave 0.6 mg of solid rotamer **6b** which matched spectroscopically in every way with previously synthesized **6b**.

**Reaction of 7a with Phosgene: Accelerated Rotation.** Rotamer **7a** (4.3 mg, 0.0075 mmol) was dissolved in $CDCl_3$ (0.8 mL) and added to an oven dried (200 °C) NMR tube. To this solution was added 2,6-di-*tert*-butylpyridine (2 equiv, 2.9 $\mu$L, 0.015 mmol). Phosgene [1 equiv, 20% solution in toluene (Fluka), 0.0075 mmol, 3.7 $\mu$L] was next rapidly added. After a period of 5 min, triethylamine (5 equiv, 5.3 $\mu$L, 0.038 mmol, distilled and stored over KOH) was rapidly added. The reaction was then monitored by $^1$H NMR (Figure 7). After 80 min, the reaction had come to completion; the reaction mixture was quenched with an aqueous saturated $K_2CO_3$ solution (10 mL) and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried and evaporated, and the crude reaction product was purified by chromatography on a 250 $\mu$m × 20 cm × 20 cm semipreparative thin layer plate, eluting with 1:9 ethyl acetate/$CH_2Cl_2$. Pure carbamate **13** was isolated as an off-white solid (3.5 mg, 81%). $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$. 8.2 (s, 1H), 8.17 (d, $J$ = 8.8 Hz, 1H), 7.81 (d, $J$ = 8.8 Hz, 1H), 7.76 (s, 1H), 7.72−7.68 (m, 3H), 7.47 (apparent d, $J$ = 8.3 Hz, 1H), 7.37 (d, $J$ = 8.8 Hz, 1H), 7.20 (s, 1H), 7.05 (s, 1H), 7.02 (d, $J$ = 5.9 Hz, 1H), 6.91 (d $J$ = 6.4 Hz, 1H), 6.63 (t, $J$ = 7.3 Hz, 1H), 6.57−6.52 (m, 2H), 6.44−6.41 (m, 1H), 6.37 (s, 1H), 6.08 (d, $J$ = 7.8 Hz, 1H), 5.91 (apparent t, $J$ = 3.4 Hz, 2H), 5.08 (s, 1H), 4.65−4.61 (m, Hz, 1H), 3.99 (td, $J$ = 12, 2.6 Hz, 1H), 3.61 (d, $J$ = 10 Hz, 1H), 3.46 (dt, $J$ = 11, 2.7 Hz, 1H), 2.99 (s, 3H).

**Reaction of 7b with Phosgene to Give Carbamate 13.** Rotamer **7b** (3.8 mg, 0.0067 mmol) was dissolved in $CDCl_3$ (0.8 mL) and added to an oven-dried (200 °C) NMR tube. Phosgene [1.1 equiv, 20% solution in toluene (Fluka), 0.0071 mmol, 3.5 $\mu$L] was next added, and the mixture was shaken to give a light yellow solution, which later turned to a yellow solution. After a period of 10 min, triethylamine (10 equiv, 9.3 $\mu$L, 0.067 mmol, distilled and stored over KOH) was rapidly added. The reaction was then examined by $^1$H NMR, which indicated that conversion of **7b** to carbamate **13** was already complete. The crude mixture was evaporated, dissolved in $CH_2Cl_2$ and applied to a 20 cm × 20 cm, 250 $\mu$m thick semipreparative silica thin-layer chromatography plate, which was developed with 1:9 ethyl acetate/$CH_2Cl_2$. A yield of 3.9 mg (97%) of carbamate **13** was obtained, which was identical to the carbamate obtained in the preceding reaction.

**Acknowledgment.** The National Institutes of Health is gratefully acknowledged for support of this work (Grant Number GM56262). We are deeply indebted to Drs. Sally and Frank Mallory[37] for their help in reducing to practice the photocyclization of **42** to **43**. We also thank Mr. Jeffrey T. Sieglen and Dr. Bing Wang for assistance in the preparation of starting materials.

**Supporting Information Available:** General experimental procedures, details of preparations/characterizations of ancillary compounds (**35**, **48**, **57**, **61**, **65**, **66**), and $^1$H NMR spectra of atropisomer mixtures **43, 51, 52,** and **53** (too complex to list) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001048F