Molecular Clefts. 4. An Approach to Structural Analogues of Echinomycin: Synthesis of a New Class of Synthetic Molecular Tweezers†

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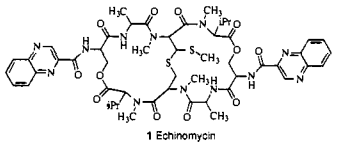
Echinomycin (**1**) is an antitumor antibiotic isolated from *Streptomyces echinatus*.[1,2] It exhibits activity against Gram-positive bacteria and has been shown to possess antimycoplasma and antiviral in addition to antitumor activity.[3] Evidence suggests

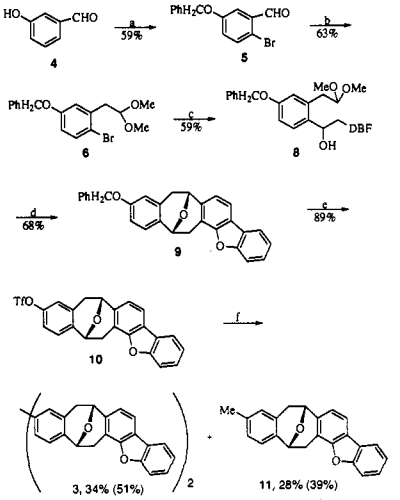


1 Echinomycin

that the mechanism of action of echinomycin and related antibiotics resides in their ability to inhibit DNA directed RNA synthesis.[4] The activity and unique mode of action of echinomycin has been sufficiently interesting to inspire clinical trials of the drug as an antitumor agent.[3,5] The molecular basis of this activity appears to be due to the ability of quinoxaline antibiotics to act as DNA bis-intercalators. Structurally, the octadepsipeptide backbone of these systems serves as a rigid spacer to keep the quinoxaline rings approximately 10 Å apart. This leaves sufficient space for these molecular tweezers to "pinch" two base pairs as they bind to the DNA double helix. X-ray data have been collected which provide solid evidence for this type of interaction.[6] Presumably, Nature has selected this binding motif in accord with the site exclusion principle, an empirical conclusion based on the observation that bis-intercalation generally does not occur on both sides of a single base pair.[7]

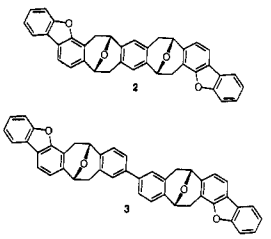
The synthesis of echinomycin has been reported, as has the synthesis of analogues which are the result of changes made to the octadepsipeptide backbone or the intercalating quinoxaline rings.[8] We are interested in synthesizing structures which bear a structural or topographical similarity to echinomycin but which are otherwise quite different. Our work on chiral molecular tweezers based on Kagan's ether led to the synthesis of

Scheme 1[a]



[a] (a) (1) Br_2, $CHCl_3$, 25 °C; (2) NaH, THF/DMF (5:1), 0 °C, $PhCH_2Br$. (b) (1) $Ph_3P{=}CHOMe$, THF, 25 °C; (2) MeOH, $(MeO)_3CH$, H_2SO_4, reflux. (c) (1) *n*-BuLi, THF, −78 °C; (2) dibenzofuran-(DBF)acetaldehyde (**7**). (d) (1) catalyst TsOH, CH_2Cl_2; (2) $SnCl_4$, CH_2Cl_2, −78 °C. (e) (1) H_2/Pd–C, MeOH–EtOAc (1:2); (2) Tf_2O, collidine, CH_2Cl_2, 0 °C. (f) $Pd(PPh_3)_4$, $(Me_3Sn)_2$, LiCl, dioxane, reflux.

2.[9,10] While this compound has potential as a DNA intercalator,



the space between the dibenzofuran rings is only about 7 Å. Bis-intercalation would require a violation of the site exclusion principle. We required a molecular tweezer which possessed C_2 symmetry but was larger. These and other design considerations led to compound **3** as an initial target.

The biaryl spacer in **3** may be problematic in that it adds a degree of freedom to the molecule not conducive to the bis-intercalation event. Conversely, such a linkage should greatly facilitate the synthesis of compounds of this class. Furthermore, consideration of rotational minima about the biaryl linkage suggests that at any one time at least 25% of the molecules should possess a conformation in which both intercalating chromophores are syn and disposed appropriately for bis-intercalation.[11]

The synthesis of **3** is shown in Scheme 1. Bromination of *m*-hydroxybenzaldehyde followed by protection gave aldehyde **5** in good yield.[12] Wittig homologation and subsequent acetal formation led to the acetal **6**. Halogen–metal exchange and reaction of the resulting organolithium with **7** gave **8** in fair yield. This hydroxyacetal was converted to the key building block **9** in 68% overall yield via what has become standard chemistry in our group.[9] Deprotection and triflate ester formation proceeded smoothly to afford **10**.[13] Interestingly, several attempts at coupling

† Dedicated to the memory of Professor Elmer O. Schlemper (1939–1994).

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(11) The dihedral angle of biphenyl is 0° in the solid state, about 45° in the gas phase, and has been assigned varying values in between these extremes in solution. For data and leading references, see: (a) Tsuzuki, S.; Tanabe, K. *J. Phys. Chem.* **1991**, *95*, 139. (b) Jaime, C.; Font, J. *J. Org. Chem.* **1990**, *55*, 2637.

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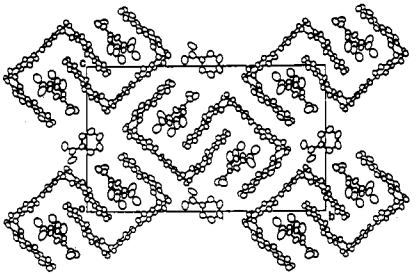

Figure 1. Packing diagram for 3-TNB-NB inclusion complex; projection down the *a* axis.

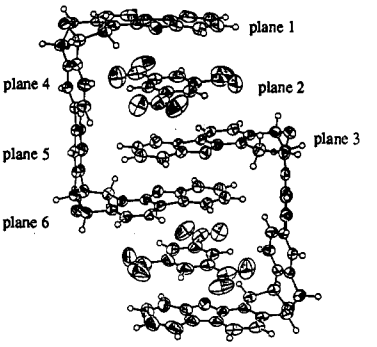

Figure 2. ORTEP plot for the 3-TNB complex. Thermal ellipsoids are drawn at the 50% probability level.

Table 1. Distances (Å) and Angles (in Parentheses) between Least-Squares Planes in 3-TNB Complex as Defined in Figure 2

plane	2	3	4	5	6
1	3.4 (4.6)	6.8 (4.9)	(94.2)	(94.4)	10.4 (4.9)
2		3.3 (5.4)	5.3[a] (91.2)	(93.6)	6.9(5.4)
3			(89.7)	4.8[b] (89.6)	3.5(0)
4				(31.4)	(89.7)
5					(89.6)

[a] Centroid of TNB to plane 4. [b] Centroid of distal ring of dibenzofuran to plane 5.

10 with itself using the standard Stille protocol were not very successful.[14] In the best case run to date, the yield of 3 was 34%, and the yield of methylation product 11 28%. These yields become 51% and 39%, respectively, if recovered starting material is considered. Two different sources of hexamethylditin were used, and several different sets of reaction conditions were examined. It is probable that methyl transfer occurred from an aryltrimethyltin compound.[15] Finally, 3 can exist as a *meso* or a *d,l* isomer. Thus far we have only been able to isolate the *d,l* isomer. Resolution of this compound into two approximately equal intensity peaks on a chiral HPLC column (Chiracel OJ, 1.5 mL/min, hexane/ethyl acetate linear gradient from 0–50% ethyl acetate over 25 min) established the compound as chiral. High-resolution mass spectral analysis gave a mass of 622.2115, suggesting the molecular formula $C_{44}H_{30}O_4$. Finally, ^1H and ^{13}C NMR data strongly suggested the structure of 3 as indicated.[16] In light of the excellent mass balance obtained in the coupling reaction, excellent stereoselectivity is apparent. The mechanistic basis of this stereoselectivity, however, remains unclear.[17]

The structure of 3 was indisputably confirmed by X-ray analysis. While 3 itself was amorphous, slow evaporation of a solution of chloroform/methylene chloride-containing 3, trinitrobenzene (TNB), and nitrobenzene (NB) resulted in the formation of an inclusion complex which gave crystals suitable for X-ray diffraction analysis.[18] A packing diagram is shown in Figure 1. Within the cleft of tweezer 3 is a dibenzofuran from a different tweezer as well as a TNB molecule. An ORTEP plot of this structure is shown in Figure 2. This nicely illustrates the ability of 3, like echinomycin, to simultaneously "pinch" two π systems. Donor–acceptor stacking interactions are clearly evident, as are edge–face interactions between the biaryl spacer and the guests, both serving to stabilize the complex.[9,19,20] Distances between the least-squares planes defined in Figure 2 are presented in Table 1. The stacked planes are essentially parallel and packed within the expected van der Waals distance. They are within a few degrees of being perpendicular to the planes defined by the biphenyl spacer unit. The hydrogen of the TNB (plane 2) is calculated to be 2.9 Å from the centroid of the closest phenyl ring of the spacer unit (i.e., plane 4). Two of the hydrogens of the dibenzofuran (plane 3) come into proximity to plane 5 and are 3.0 and 2.6 Å from the centroid of that phenyl ring. All of these distances fall with the range for favorable edge–face interactions.[19,21] Finally, and as expected, the biphenyl unit has a dihedral angle of 31.4°, comparable to the minima found in biphenyl itself.[11] These data further confirm the importance of aromatic interactions in the stabilization and, consequently, design of host–guest and supramolecular systems.[9,21]

In summary, we have prepared the molecular tweezer 3 by a stereoselective biaryl coupling procedure. The space between the chromophores in 3 (10.4 Å) is sufficient to accommodate two π systems. Mechanistic studies of the biaryl coupling reaction, the synthesis of water-soluble congeners of 3, and the study of this and other classes of molecular tweezers for the preparation of new materials will be reported in due course.

Acknowledgment. This work was supported by a grant from the Elsa U. Pardee Foundation, to whom we are grateful. We thank the National Science Foundation for partial support of the NMR (PCM-8115599) and MS (PCM-88117116) facilities at the University of Missouri—Columbia and for partial funding for the purchase of a 500 MHz spectrometer (CHE-89-08304) and an X-ray diffractometer (CHE-90-11804).

Supplementary Material Available: Figures showing the structure and atom labeling of 3-TNB; tables of positional parameters, thermal parameters, interatomic distances, interatomic angles, dihedral angles, and least-squares planes for 3-TNB (15 pages); listing of observed and calculated structure factors for 3-TNB (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(16) Data for 3: ^1H NMR (500 MHz, $CDCl_3$) δ 7,82 (d, 2H, J = 7.5), 7.70 (d, 2H, J = 7.9 Hz), 7.49 (d, 2H, J = 8.2 Hz), 7.36 (t, 2H, J = 8.1 Hz), 7.28–7.25 (m, 2H), 7.22 (d, 2H, J = 8.1 Hz), 7.14 (d, 2H, J = 8.1 Hz), 7.06–7.05 (m, 4H), 5.45 (d, 4H, J = 5.9 Hz), 3.65 (dd, 2H, J = 6.2, 16.5 Hz), 3.61 (dd, 2H, J = 6.4, 16.6 Hz), 3.20 (d, 2H, J = 16.3 Hz), 2.85 (d, 2H, J = 16.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 154.2, 139.6, 136.9, 136.6, 131.7, 127.6, 126.7, 125.6, 124.9, 124.4, 122.6, 122.2, 120.4, 119.8, 118.0, 116.4, 111.5, 69.5, 68.7, 36.2, 30.7.
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