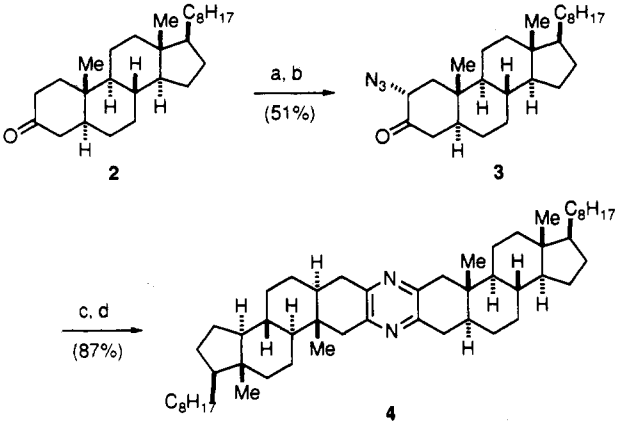
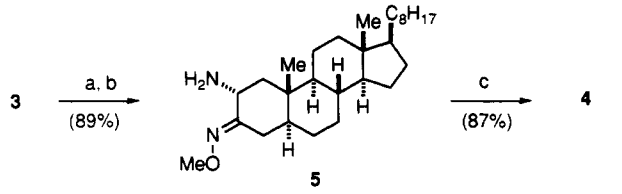
Scheme I[a]



[a] Key: (a) $C_5H_5NH^+Br_3^-$, AcOH; (b) NaN_3, *N*-methylpyrrolidone; (c) Ph_3P, H_2O, THF; (d) *p*-TsOH, ethanol.

Scheme II[a]



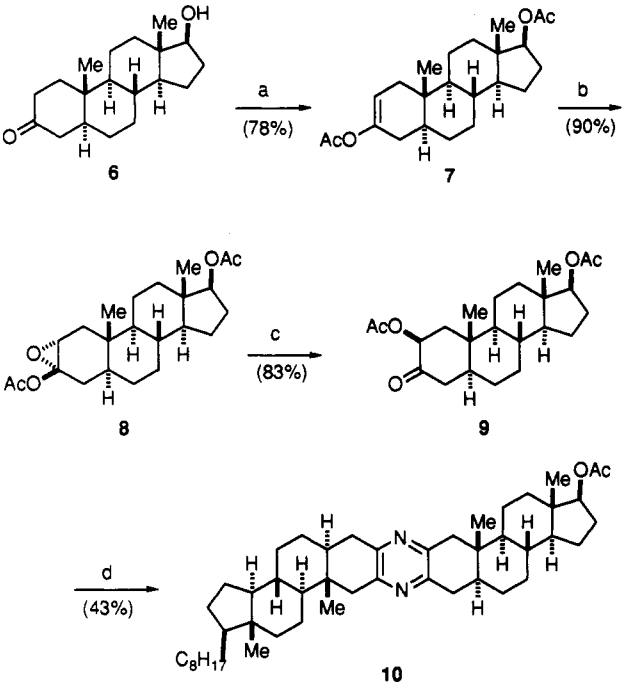
[a] Key: (a) $MeONH_3^+Cl^-$, pyridine; (b) Ph_3P, H_2O, THF; (c) toluene, 140 °C, 24 h.

pyrazines have been prepared from 2-oximino ketones in lower yield (35–54%).[5]

The symmetrical bis-cholestanyl pyrazine was also prepared as shown in Scheme II. Thus, treatment of azido ketone **3** with *O*-methylhydroxylamine provided the *O*-methyloxime, which was reduced with triphenylphosphine in aqueous THF to obtain the 2-amino-3-oxime derivative of cholestane **5**. This material was heated in toluene at 140 °C to obtain pyrazine **4** in about 77% overall yield from **3**.

For the preparation of unsymmetrical bis-steroidal pyrazines, the protocol illustrated in Scheme III was developed. Androstanone **6** was converted to the Δ^2 enol acetate **7**,[6] which was oxidized with dimethyldioxirane[7] to obtain epoxide **8** which crystallized as a single isomer. This material was rearranged to the 2β-acetoxy 3-ketone **9** by refluxing in toluene containing 10% pyridine. When a mixture of **9** and amino oxime **5** were heated in toluene at 90 °C for 24 h and then at 145 °C for a further 24 h, the unsymmetrical pyrazine **10** was formed in 43% yield.

Scheme III[a]



[a] Key: (a) Ac_2O, $HClO_4$, EtOAc; (b) dimethyldioxirane, acetone; (c) toluene, reflux; (d) compound **5**, toluene, 90 °C, 24 h; 145 °C, 24 h.

Control experiments show that amino oxime **5** reacts preferentially with the acetoxy ketone **9** at 90 °C to give a mixture of isolable, but inseparable, intermediates which subsequently form pyrazine **10** upon prolonged heating. The optimum temperature for pyrazine formation was found to be 145 °C. Initial heating at the lower temperature of 90 °C avoids the dimerization of amino oxime **5** which occurs at elevated temperatures (Scheme II).

Acknowledgment. This research was supported by a research grant from the United States Public Health Service (GM 46057) and by an SERC Postdoctoral Fellowship to S.C.S.

Supplementary Material Available: Experimental procedures and analytical data for all new compounds reported in this paper (3 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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A New Approach to the Synthesis of the CC-1065/Duocarmycin Pharmacophore

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Summary: The spirocyclic 1,2,7,7a-tetrahydrocycloprop-[1,2-*c*]indol-4-one subunit of CC-1065 and duocarmycin A, which comprises the common pharmacophore of the two antibiotics, has been efficiently synthesized in six steps from readily available starting materials. The key step of the synthesis utilizes a zirconocene-stabilized benzyne complex.

CC-1065 and duocarmycin A (Figure 1), potent antitumor antibiotics, have received much recent attention.[1]

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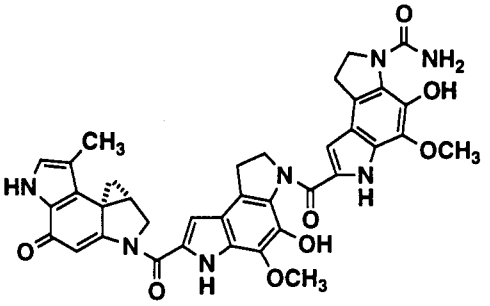


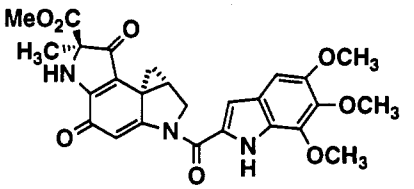


Figure 1.

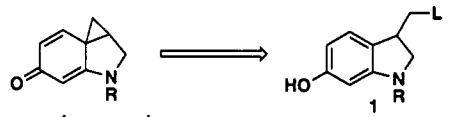
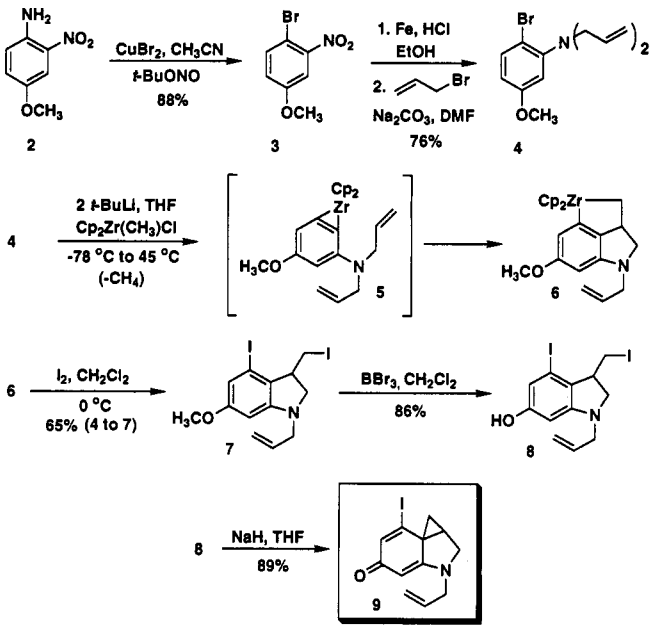


Figure 2.

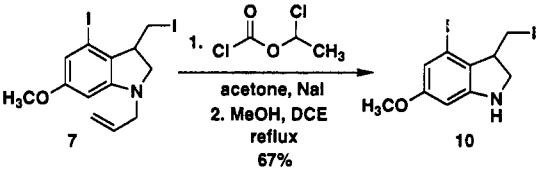
Boger and co-workers have shown that these and related compounds alkylate DNA via a similar mechanism and that CC-1065 and duocarmycin A contain a common pharmacophore.[2] The pharmacophore consists of a spirocyclic 1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one subunit (Figure 2).

The synthesis of this pharmacophore and related analogues has been the subject of several recent reports.[3] In 1981, Wierenga recognized that access to the "key structural type" 1 (Figure 2), a precursor to the pharmacophore, required a regioselective synthesis of 6-hydroxyindolines.[4] Closure of the indolines to the spirocycle could be accomplished using the Winstein cyclization.[5] In this paper, we report an efficient new approach for the synthesis of these compounds from readily available starting materials. The target 1 is constructed in six steps from commercially available material, utilizing a nascent zirconocene-stabilized benzyne complex in the key step of the synthesis.

Scheme I



Scheme II



Recently, we reported the synthesis of 3,4-disubstituted indoline and indole derivatives using the intramolecular insertion of an olefin into a zirconocene-stabilized benzyne complex.[6] We reasoned that we could utilize this methodology to construct analogs of the CC-1065/duocarmycin A pharmacophore. The requisite substrate was prepared as shown in Scheme I. Commercially available 4-methoxy-2-nitroaniline **2** was converted to aryl bromide **3** in 88% yield utilizing copper(II) bromide and *tert*-butyl nitrite.[7] Reduction of the nitro group with Fe/HCl[8] followed by diallylation of the resulting amine with allyl bromide in the presence of $NaHCO_3$ gave aniline **4** (76% yield from **3**). Treatment of a THF solution of **4** and zirconocene (methyl)chloride with 2 equiv of *t*-BuLi at −78 °C followed by warming to 45 °C gave zirconacycle **6** via

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the intermediate zirconocene complex **5**.[6] Zirconacycle **6**, which was observed by ^{1}H NMR, was treated with iodine to give diiodoindoline **7**. Compound **7** can thus be prepared from **4** in a "one-pot" procedure in an isolated yield of 65%. Treatment of **7** with BBr_3[9] afforded phenol **8** in 88% yield, which was used immediately after purification. Treatment of **8** with sodium hydride in THF[3] at 25 °C cleanly gave tetrahydrocycloprop[1,2-*c*]indol-4-one analog **9** in 89% yield as a brownish solid. Although the instability of **9** precluded its purification by chromatography (silica, alumina), it was reasonably pure after filtration of the reaction mixture to remove the sodium salts and removal of the solvent in vacuo (see supplementary material for spectroscopic data). Dienone **9** was found to be stable as a solid for approximately 1 h at room temperature. In solution, however, it proved to be much less stable, affording insoluble material after approximately 30 min in THF at room temperature.

In order to allow for the synthesis of a number of analogs of CC-1065, it is necessary to deprotect the nitrogen in **7**. We found most useful a modification of the method of Olofson,[10] who has demonstrated that tertiary amines can be selectively dealkylated using 1-chloroethyl chloroformate (ACE-Cl). Although aromatic amines have been deprotected using ACE-Cl,[11] the procedures usually require high temperatures and a large excess of the chloroformate. Under these conditions, **7** either decomposed or failed to react with ACE-Cl due to the low nucleophilicity of the nitrogen. We found that if the reaction between **7** and ACE-Cl is conducted in refluxing acetone using 2 equiv of the chloroformate and 3 equiv of sodium iodide (see Scheme II) dealkylation proceeds in good yield. The addition of sodium iodide presumably causes acyl halide exchange to occur to produce a more reactive iodoformate[12] which then reacts with the amine to produce the intermediate carbamate and allyl iodide. Cleavage of the intermediate carbamate was best effected in refluxing methanol with 1,2-dichloroethane as cosolvent. Using these conditions, **7** could be converted to **10** in an overall yield of 67%. It has been demonstrated by Boger and co-workers that indolines such as **10** as can be coupled with a variety of compounds such as phosphodiesterase dimer (PDE-1) to give functional CC-1065 analogs.[3]

The use of this methodology in the synthesis of more substituted pharmacophore analogs is currently being investigated.

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Supplementary Material Available: Experimental details for the preparation and spectroscopic characterization of compounds **2-10**, as well as ^{1}H and ^{13}C NMR spectra for compounds **4, 7, 8, 9, 10** and liquid chromatograms of compounds **8** and **10** (17 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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(14) **Note:** Compounds related to **7-10** have been shown to alkylate DNA, and thus they should be handled with caution.[3e]

Salt Effects on a Hydrophobically Accelerated Diels-Alder Reaction Follow the Hofmeister Series

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Summary: The rate of the Diels-Alder reaction between *N*-ethylmaleimide and anthracene-9-carbinol in aqueous sodium salt solutions follows a linear relationship with the size of the anion.

Since the first report of an accelerated Diels-Alder reaction in aqueous media by Rideout and Breslow,[1a] considerable effort has been devoted to determining the source of the rate acceleration.[1-9] It has been suggested that hydrophobic effects are the principal forces responsible for the rate enhancement. In order to reduce their solvent contact with water, organic solutes will tend to aggregate in aqueous solution, and this hydrophobic packing gives rise to the large rate acceleration.[1] Evidence supporting this explanation was found by exploiting the effects of different salts on the aqueous Diels-Alder reaction; since different salts attenuate the magnitude of the hydrophobic effect, such salts are a useful probe.[1b] Some salts, such as LiCl, are salting-out agents which make organics less soluble in water and in doing so enhance the hydrophobic effect. Other salts such as guanidinium chloride are salting-in agents and tend to make organics more soluble in aqueous solution, thus diminishing the hydrophobic effect. Consistent with these ideas are the observations

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