products indicative of initial oxidation at the tertiary amine group.[10] As shown in Scheme I, the array of products can be accounted for by initial formation of intermediates A, B, and C. The solvent medium appears to have a major effect on partitioning between the intermediates. Intermediates B and C are expected to be formed from an aminium radical cation.[11] We propose that formation of the aminium radical cation can also lead to C16–C21 fragmentation and formation of intermediate A. The possible role of an aminium radical cation in oxidative fragmentation of catharanthine by Fe(III) has been suggested recently.[12]

At the present time the pathways giving rise to the secondary oxidation products **9** and **10** are unclear. Also, we have not yet assigned stereochemistry at C16 for **2**, **3**, **7**, and **8**. This stereochemical assignment could provide information about the conformational stability of intermediates A and D. *The salient result is that under certain conditions C16–C21 fragmentation occurs upon oxidation of catharanthine by DDQ, generating an intermediate that can be trapped by nucleophiles.* The cyclopropanes **7**, **8**, and **10** also represent a novel variation on the *iboga* alkaloid skeleton. We are continuing to explore the mechanistic and synthetic implications of these observations.

Acknowledgment. This research was supported by NIH Grant GM-41105.

Supplementary Material Available: Experimental description of the isolation of compounds **2–10** and characterization data including NMR, MS, and IR (53 pages). Ordering information is given on any current masthead page.

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Synthesis of the Angular Anthraquinone Subunit of Dynemicin A

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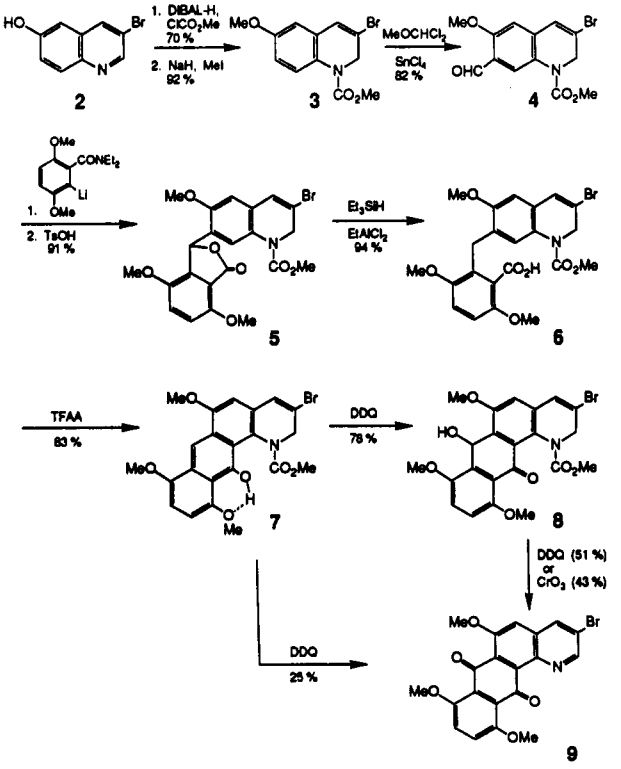
Summary: A concise synthesis of the L-shaped anthraquinone subunit of dynemicin A is reported.

The antibacterial and anticancer agent dynemicin A (**1**, Figure 1) has been the subject of recent synthetic and biochemical investigations owing to its unique molecular structure and remarkable properties.[1,2] Recently, we reported a facile access to systems related to **1** via a transannular Diels–Alder pathway.[2a] Further advances toward the synthesis of the natural product and analogous DNA cleaving agents require general methods to construct angular anthraquinone systems[3] annulated to nitrogen heterocycles. In addition, independent assay of the DNA binding properties of molecules containing such subunits may prove fruitful. We now report a concise synthetic pathway to these molecules that should be applicable to enediyne containing systems (Scheme I).

Reduction–acylation of the known 3-bromo-6-hydroxyquinoline (**2**)[4] proceeded cleanly, using modified Reissert conditions (70% yield).[5] Subsequent methylation of the phenol gave a 1,2-dihydroquinoline (**3**) (92% yield), which was expected to be a substrate for a direct anthraquinone annulation. Unfortunately, Friedel–Crafts reactions of **3** and 2,5-dimethoxyphthalic anhydride, which were examined with a variety of Lewis acids and reaction conditions, proved unrewarding.[6] However, formylation of **3** ($MeOCHCl_2$, $SnCl_4$, CH_2Cl_2, 0 °C → rt)[7] provided aldehyde **4** as the predominant isomer (**4**: positional isomer at C5 ~6:1) in 82% yield.[8] Addition of the lithio derivative of *N*,*N*-diethyl-3,6-dimethoxybenzamide[9] to **3** provided a mixture of alcohol and lactone products that was readily converted to lactone **5** after brief treatment with TsOH in toluene at reflux temperature (91% overall yield). A more convergent route to **5** employed a Friedel–Crafts alkylation reaction of **3** with 3-bromo-4,7-dimethoxy-

Scheme I



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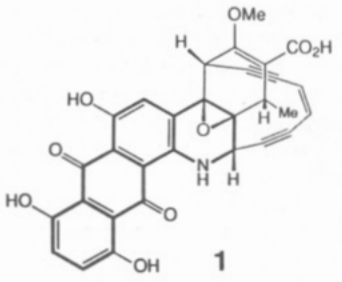

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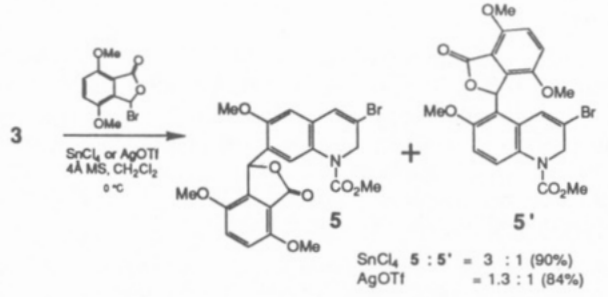
Figure 1. Structure of dynemicin A.

Scheme II



phthalide (Scheme II).[10] The reaction was promoted with $SnCl_4$ in CH_2Cl_2 at 0 °C and gave an inseparable mixture of **5** and **5'** (3:1) in 90% yield. A similar reaction using silver triflate activation[11] proceeded to form an isomeric mixture with little regioselectivity (1.3:1).

Reduction of lactone **5** under standard conditions (Zn, Zn–Cu couple, or Et_3SiH/TFA, rt) gave no reaction. However, treatment of **5** with $Et_3SiH/EtAlCl_2$ (−78 → 0 °C, CH_2Cl_2) resulted in the formation of carboxylic acid **6** in 94% yield. Intramolecular Friedel–Crafts cyclization of **6** proceeded smoothly with TFAA in CH_2Cl_2 at rt to provide the air-sensitive anthracenol **7**,[12] which was rapidly oxidized to the surprisingly stable ketol **8** with DDQ in THF at 0 °C (78% yield). Ketol **8** could also be obtained directly from **7** by an oxidation with DDQ (benzene, reflux) in 25% yield. The structure of this unusual keto tautomer of a hydroquinone was verified by X-ray crystallography (Figure 2A).[13] The asymmetric unit consisted of an unusual packing of three independent molecules of **8** and two solvent molecules of CH_2Cl_2. Each of the molecules displayed the geometric features seen in the anthraquinone subunit of triacetyl dynemicin A,[1b] including a bowed ring system and bent carbonyls. While triacetyl dynemicin A showed bowing of approximately 15°, the three independent molecules of **8** in the crystal structure show values of 16.9°, 26.2°, and 34.0° for the dihedral angle between the right- and left-hand aromatic rings of the ketol. In addition, the carbonyl is seen to strongly deviate from sp^2 geometry, with an average deviation of 29.7° from the plane of the middle semiquinone ring. The absence of a hydroquinone tautomer in either the solution or the solid state may be in part due to the high steric hindrance that would result between the carbamoyl group and a flat hydroquinone ring system.

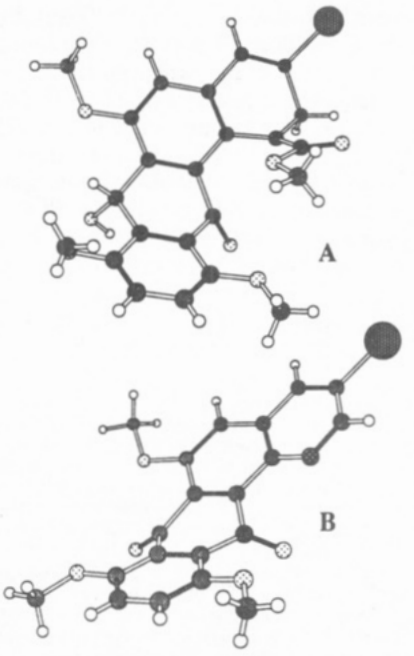


Figure 2. Chem 3D models of **8** and **9** based on X-ray coordinates.

Further attempts to oxidize the OH site of **8** with a variety of oxidizing reagents such as DDQ, CrO_3, PCC, PDC, CAN, $AgNO_3$, NBS, and TFAA/DMSO did not give

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(13) Ketol **8** was crystallized from CH_2Cl_2/isooctane as clear, yellow rectangular cubes. A single crystal (~0.3 × 0.2 × 0.15 mm) was analyzed by X-ray diffraction at −30 °C using Cu K_α radiation (λ = 1.541 78 Å) and found to have the following refined unit cell parameters: a = 14.660 (3) Å, b = 15.127 (3) Å, c = 17.230 (3) Å, α = 70.450 (9)°, β = 75.97 (2)°, and γ = 88.96 (2)°; 9521 unique reflections were collected with $0° \le 2\theta \le 115°$, of which 6724 (70.6%) were judged observed ($|F_o| \ge 4.0\sigma(|F_o|)$). Analysis of calculated E statistics indicated the data set to be centrosymmetric and the space group $P\bar{1}$ (Z = 6), a choice that was verified by successful structure solution and refinement. The structure was solved by using direct methods and the SHELX-86 package of programs, revealing an unusual asymmetric unit, which contained three independent molecules of **8** and two moderately well-ordered molecules of CH_2Cl_2. Refinement of the 99 atom model against the data using blocked full-matrix least squares converged at a standard crystallographic discrepany index of 0.0668 and a weighted residual of 0.0682.

the desired anthraquinone derivative containing a 1,2-dihydroquinone moiety. However, compound 8 can be fully oxidized to the orange anthraquinone 9 by using either DDQ (benzene, reflux) or CrO_3 (AcOH/acetone, rt). A crystal structure of anthraquinone 9 (Figure 2B) showed clearly a bowed angular anthraquinone system similar to that observed in the crystal structure of triacetyl dynemicin A.[1b,14] The amount of ring bowing in this instance is similar to that seen in 8: 22.7° between the right- and left-hand aromatic rings of the anthraquinone. The average deviation of the carbonyls from the plane of the middle ring in 9 is 30.4°, which is similar to that observed in 8. Such an orientation of the carbonyls is likely derived from steric interactions of the carbonyls with *peri*-substituted groups. The difficulty in the selective oxidation of 8 may also be rationalized by the severe buttressing effects in a dihydroquinoline–anthraquinone structure. The prior removal of the carbamoyl group from 8 (structure 2A) may be necessary to achieve complete oxidation to an anthraquinone moiety.

In summary, the applicability of methods for linear anthraquinone synthesis[9,12] to the construction of the angular anthraquinone subunit of dynemicin A has been demonstrated. The DNA binding behavior of novel angular anthraquinone–quinoline systems such as 9 and the application of this chemistry to enediyne-containing molecules will be the subject of future reports from these laboratories.

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Supplementary Material Available: Complete spectral data for compounds 3–9 and crystallographic data for compound 8 and 9 (including experimental details, atomic coordinates and thermal parameters, bond distances and angles, and torsional angles) (28 pages). Ordering information is given on any current masthead page.

(14) Anthraquinone 9 was crystallized from $CHCl_3$/isooctane as clear, orange triangular plates. An appropriately sized (~0.40 × 0.25 × 0.15 mm) single crystal was mounted with epoxy in a cold N_2 (g) stream (-30 °C) and analyzed by X-ray diffraction. Preliminary rotation and axial photos indicated only triclinic symmetry, while least-squares refinement of 20 centered diffraction maxima with $20° \leq 2\theta \leq 45°$ gave refined unit cell parameters: a = 7.236 (2) Å, b = 13.293 (3) Å, c = 13.868 (0) Å, α = 62.87 (2)°, β = 87.48 (2)°, and γ = 87.99 (2)°; 3234 unique reflections were collected with $0° \leq 2\theta \leq 115°$, of which 2874 (88.9%) were judged observed ($|F_o| \leq 4.0\sigma(|F_o|)$). Examination of the complete data set showed the space group to be $P\bar{1}$ (Z = 2), a choice that was verified by successful structure solution and refinement. The structure was solved by using direct methods and the SHELX-86 package of programs. The asymmetric unit was shown to consist of a 1:1 ratio of 9 and chloroform. Refinement utilized full-matrix least squares and converged to a standard residual of 0.0793. Large, unaccounted-for electron density peaks were observed in the final difference maps at ~1 Å from the bromine and are thought to be experimentally observed lone pairs.

Solvent and Substituent Effects on the Reaction of Phenylchlorocarbene with Pyridine

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Summary: The absolute rate of reaction of phenylchlorocarbene with pyridine is not a function of solvent polarity but does respond to placement of polar substituents para to the carbene center.

We recently reported that carbenes react very rapidly with pyridine to form ylides whose long lifetimes and intense absorptions in the visible region of the electromagnetic spectrum make them ideal probes of carbene dynamics in laser flash photolysis (LFP) studies.[1] The technique has rapidly found use in the study of arylhalo-,[2] alkylhalo-,[3] alkylalkoxy-,[4] and dialkylcarbenes.[5] A probe method is used to determine rate constants for a carbene reaction with substrates when neither the carbene nor the substrate is capable of generating a useful signal. A probe that is insensitive to solvents and substituent effects is particularly useful because it allows study of the substrate of interest rather than the probe itself. For this reason we felt it necessary to systematically study the effect of solvent polarity and substituent on the absolute rate of ylide formation with a representative carbene.

Table I. The Effect of Solvent upon the Absolute Rate Constant for Reaction of Phenylchlorocarbene with Pyridine at 293 K

solvent	ϵ[9]	k (M^{-1} s^{-1})
hexane	1.89	(7.56 ± 0.93) × 10^8
toluene	2.38	(3.74 ± 0.38) × 10^8
ethyl acetate	6.02	(2.94 ● 0.36) × 10^8
α,α,α-trifluorotoluene	9.18	(4.20 ± 0.32) × 10^8
o-dichlorobenzene	9.93	(5.37 ± 0.64) × 10^8
2-butanone	18.5	(4.73 ● 1.06) × 10^8
propionitrile	27	(3.58 ± 0.35) × 10^8
acetonitrile	36.2	(3.94 ± 0.40) × 10^8
sulfolane	44	(2.90 ± 0.30) × 10^8

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