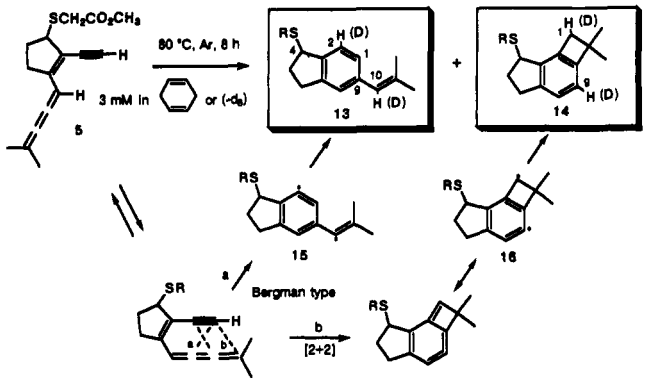
Scheme IV



ydration according to Wender's procedure[8] yielded *E* olefin **4** exclusively (61%)[12] as an air-sensitive pale yellow oil.[7]

Although the reaction of **4** with methyl thioglycolate in chloroform in the presence of triethylamine at room temperature under an argon atmosphere did not proceed, in DMSO it quickly gave **12**, a formal S_N2 product, surprisingly. In acetonitrile, however, the desired vinylogous S_N2' product **5** as a colorless liquid, was isolated in 46% yield together with a 15% yield of **12** after 2 h (Scheme III), while the yield of **12** increased when the reaction was prolonged.[13] The enyne[3]cumulene **5** exhibiting characteristic downfield resonances (^{13}C NMR) of the inner carbons (C9, δ 160.2; C10, δ 151.8)[14] is air-sensitive but seems to be rather stable at room temperature ($t_{1/2} \approx 2$ days in $CDCl_3$ with air) compared with tetramethyl[3]cumulene.[15,9c]

Thermolysis of **5** in deoxygenated 1,4-cyclohexadiene (0.003 M) at 80 °C showed its first-order decay ($k = 1.8 \times 10^{-4}$ s^{-1}, $t_{1/2} = 1.1$ h)[16] and yielded styrene derivative **13** (19%) and benzocyclobutane derivative **14** (21%), presumably through Bergman-type cyclization[2] leading to diradical intermediate **15** (path a) and through [2 + 2] cycloaddition[17] leading to diradical **16** (path b), respectively, in addition to polymeric materials (Scheme IV). These putative radical intermediates were supported by deuterium incorporation at the relevant positions. In 1,4-cyclohexadiene-d_8 (96.6% deuterium contents at allylic positions)[18] deuterium was incorporated at C2 and at C10 of **13** (16% yield) to the extent of 90% and 91%, respectively, and at C1 (>85%) and at C9 (92%) of **14** (16% yield).[16,19] When benzene was used as cosolvent with 1,4-cyclohexadiene (10:1, 80 °C),[16] **13** was poduced in much less yield (4%), while the yield of **14** did not change virtually (18%). This may reflect the longer lived σ,π-diradical intermediate **16** effected by both benzylic resonance[5a] and steric hindrance due to the *gem*-dimethyl group. Furthermore, **5** appears to be thermally less reactive than related acyclic enynallenes such as (*Z*)-3,5,6-octatrien-1-yne ($k = 3.2 \times 10^{-3}$ s^{-1}, at −78 °C).[5a,20]

In conclusion, we have demonstrated that the noncyclic cross-conjugated diene–diyne system **4** can undergo the thiol-triggered vinylogous propargylic rearrangement[9] (vinylogous S_N2' reaction) in the presence of amine leading to enyne[3]cumulene **5** that constitutes a simulation experiment on the proposed mechanism of thiol-triggered aromatization of neocarzinostatin chromophore **1**,[1] and disclosed that **5** is capable of not only Bergman-type cyclization[2] but also [2 + 2] cycloaddition reaction to produce a benzocyclobutane derivative.

Acknowledgment. This work was made possible through funds provided by the Ministry of Education, Science and Culture, Japanese Government [Grant-in-Aid for Scientific Research on Priority Areas No. 01649503 (Multiplex Organic Systems)] and by the Mitsubishi Foundation as well as the CIBA-GEIGY, the Shorai, and the TERUMO Life Science Foundations.

Supplementary Material Available: Spectral data (^1H NMR, ^{13}C NMR, IR, UV, and HRMS and/or MS) for new compounds **4**, **5**, **7–14** (7 pages). Ordering information is given on any current masthead page.

(12) Determined by NOE experiment between 1-H and 8-H; no NOE between 6-Hs and 8-H.

(13) Isolated **5** rearranged rapidly to **12** in DMSO at room temperature in the presence of methyl thioglycolate and triethylamine.

(14) Representative spectral data of **5**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (dddd, 1 H, J = 3.9, 4.0, 8.8, 13.8 Hz, H^{5a}), 2.00 (s, 3 H, H^{12}), 2.00 (s, 3 H, H^{12}), 2.43 (dddd, 1 H, J = 7.2, 8.1, 9.0, 13.8 Hz, H^{5b}), 2.54 (br ddd, 1 H, J = 4.0, 7.2, 17.5 Hz, H^{6a}), 2.69 (br ddd, 1 H, J = 8.1, 8.8, 17.5 Hz, H^{6b}), 3.31 (d, 1 H, J = 15.1 Hz, SCH_2), 3.42 (br s, 1 H, H^1), 3.49 (d, 1 H, J = 15.1 Hz, SCH_2), 3.74 (s, 3 H, OCH_3), 4.15 (br d, 1 H, J = 9.0 Hz, H^4), 6.34 (br s, 1 H, H^8); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.46 (CH_3, C^{12}), 25.32 (CH_3, C^{12}), 31.00 (CH_2, C^5), 31.67 (CH_2, C^6), 32.49 (CH_2, SCH_2), 52.31 (CH_3, OCH_3), 53.86 (CH, C^4), 79.22 (C, C^2), 85.28 (CH, C^1), 98.30 (CH, C^8), 119.78 (C, C^3), 121.01 (C, C^{11}), 151.11 (C, C^7), 151.82 (C, C^{10}), 160.20 (C, C^9), 170.98 (C, CO_2); IR (film) ν 3292, 2954, 2932, 2852, 2100, 2050, 1738, 1620, 1549, 1437, 1350, 1282, 1207, 1129, 1011, 756 cm^{-1}; UV (cyclohexane) λ_{max} (log ϵ) 334 (4.51), 303 (sh 4.22), 231 nm (3.61); EIMS (70 eV) m/z 274 [33.4%, M$^+$], 201 [8.53%, M$^+$ − ($CH_2CO_2CH_3$)], 167 [bp, M$^+$ − ($SCH_2CO_2CH_3$)]; HRMS (EI, 70 eV) calcd for $C_{16}H_{18}O_2S$ 274.1027, found 274.1029.

(15) Skattebøl, L. *Tetrahedron* **1965**, *21*, 1357.

(16) Monitored by HPLC, the first-order disappearence was also observed in other degassed solvents at 80 °C: 1,4-cyclohexadiene-d_8, $k = 1.7 \times 10^{-4}$ s^{-1}; benzene–1,4-cyclohexadiene (10:1), $k = 1.9 \times 10^{-4}$ s^{-1}; and tetrahydrofuran, $k = 5.4 \times 10^{-5}$ s^{-1} (at 65 °C).

(17) (a) Intermolecular [2 + 2] cycloaddition of [5]cumulene with hexafluoro-2-butyne was reported, see: Hartzler, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 4527. (b) For [2 + 2] cycloadditions of allenes and alkynes, see: Pasto, D. J.; Kong, W. *J. Org. Chem.* **1988**, *53*, 4807; **1989**, *54*, 3215 and references therein.

(18) Prepared by the reduction of benzene-d_6 (99.6%) with Na (2.5 equiv) in HMPA in the presence of CH_3CH_2OD (2.0 equiv) and CH_3CO_2D (3.0 equiv) at room temperature in 36% yield (99.9% isomeric purity by GC) after fractional distillation (cf. Whitesides, G. M.; Ehmann, W. J. *J. Am. Chem. Soc.* **1969**, *91*, 3800; *J. Org. Chem.* **1970**, *35*, 3565).

(19) Extent of deuterium incorporation was determined by 400-MHz ^1H NMR.

(20) At this moment, however, it has not been concluded that enyne-[3]cumulenes are generally more stable than the corresponding enyne-allenes, because the substitution patterns and the bond angles of central double bond are not identical between **5** and (*Z*)-3,5,6-octatrien-1-yne.[5a]

Oxidative Fragmentation of Catharanthine by Dichlorodicyanoquinone

Richard J. Sundberg,* Phyllis J. Hunt, Patrice Desos, and Kumar G. Gadamasetti

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received July 31, 1990

Summary: Oxidation of catharanthine by DDQ leads to formation of products resulting from fragmentation of the C16–C21 bond as well as C3 and C5 dehydrogenation. Among the products are compounds containing a cyclopropane ring formed by bonding between C14 and C16. Cyclopropane ring formation can be also be observed from the intermediate generated by Potier–Polonovski fragmentation of catharanthine *N*-oxide.

0022-3263/91/1956-1689$02.50/0

The oxidative fragmentation of the *iboga* alkaloid catharanthine (1) at C16–C21 is a crucial step in both the chemical synthesis and biosynthesis of the dimeric *vinca* alkaloids of the vinblastine type.[1] We have been searching for new ways of effecting fragmentation based on the premise that C16–C21 cleavage might be initiated by one-electron oxidation to an aminium radical.[2] We now report the oxidative fragmentation of 1 by dichlorodicyanoquinone (DDQ).

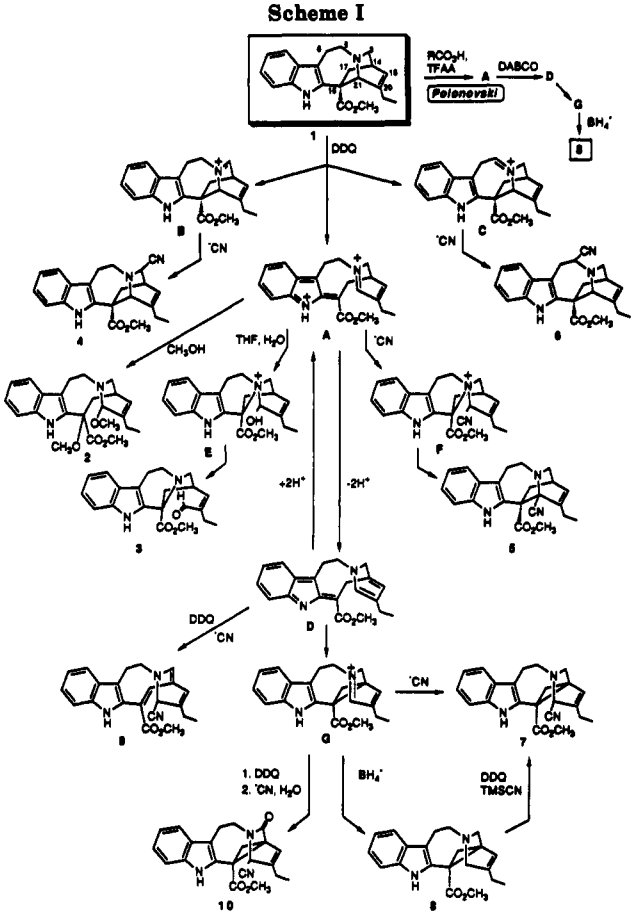
Addition of DDQ (1.5 equiv) to a solution of 1 in methanol at −5 to 0 °C gives a red solution which fades to yellow over 20 min. The major product (30–35% isolated yield) under these conditions is 2 (Scheme I). The structure was assigned on the basis of the ^1H and ^{13}C NMR data given in Tables I and II. The assignments were confirmed by the corresponding heteronuclear 2D spectrum. The formation of 2 is presumed to occur through the fragmented intermediate A or a species in equilibrium with A.[3]

When oxidation is carried out in THF containing 20% water a related product 3 is obtained in 30% yield. This product can arise by addition of a molecule of water to A followed by N4–C16 closure and ring opening of the intermediate E to generate the aldehyde 3. Under these conditions 3-cyanocatharanthine 4 is also isolated in ~ 10% yield. The formation of 4 indicates that there is competing formation of the iminium ion intermediate B. The source of the cyanide ion must be DDQ.[4] The crucial spectroscopic features supporting structure 3 is the aldehydic C21 proton at 9.95 ppm and the correlated carbonyl ^{13}C at 190.7 ppm. The other assignments of the proton spectrum given in Table I were confirmed by decoupling experiments.

When the oxidation is carried out in the nonnucleophilic solvents THF or benzene, the product mixture is rather complex (vide infra). However the material balance is improved by carrying out the oxidation in the presence of trimethylsilyl cyanide (TMSCN, 3 equiv) and $LiClO_4$ (catalytic, 15 mol %). The TMSCN evidently traps the initial oxidation products and minimizes subsequent oxidation. In benzene the major product is 21-cyanocatharanthine 5, which is isolated in 68% yield along with a small amount (3%) of 3-cyanocatharanthine 4. In THF the products are 4 (18%), 5 (16%), and 5-cyanocatharanthine 6 (10%).

Compounds 4, 5, and 6 were identified on the basis of ^1H and ^{13}C NMR data given in Tables I and II. Compounds 4 and 6 are new, but 5 was previously isolated and characterized by Mangeney and co-workers as a product of Polonovski–Potier fragmentation of catharanthine *N*-oxide by trifluoroacetic anhydride followed by exposure to methanolic KCN.[5] A mechanism of the type suggested by Mangeney et al. can account for the formation of 5 from a *C16–C21 fragmented intermediate*. Intermediate F could be formed by cyanide addition at C21 followed by N4–C16 closure. Conversion of F to 5 can occur by a Stevens rearrangement.[6] Thus C16–C21 fragmentation

Scheme I



is the dominant pathway in benzene, whereas in THF, C16–C21 fragmentation is competitive with C3 and C5 dehydrogenation.

In the absence of a nucleophilic solvent component, other products are formed by further transformation of the initial intermediates. When oxidation is carried out in benzene (25 °C) for 30 min, followed by addition of KCN (5 equiv) and 18-crown-6, the major product is 21-cyanocatharanthine, 5 (25–30% yield). A minor product is the previously unreported cyclopropane 7 (7% yield). Small amounts of 9 were also isolated.[7] The structure of 7 is based on the ^1H and ^{13}C data in Tables I and II and a heteronuclear 2D spectrum which coroborates those assignments. Particularly significant is the upfield position and small geminal coupling constant (J = 4.5 Hz) of the C17 (cyclopropyl) methylene group.

The formation of 7 could take place through intermediate D, formed by deprotonation of the dihydropyridinium ion A. The dihydropyridine D would possess a nucleophilic site at C14 which could add to C16 to form the iminium intermediate G. This mechanism is supported by the finding that treatment of the intermediate generated by Potier–Polonovski fragmentation[1] of catharanthine *N*-oxide (trifluoroacetic anhyride, −78 → 0 °C) with the base DABCO and then sodium borohydride at 0 °C results in formation of the cyclopropane 8 in 40% yield. Com-

(1) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. Potier, P. *J. Nat. Prod.* **1980**, *43*, 72. Kutney, J. P. *Nat. Prod. Rep.* **1990**, *7*, 85.

(2) See for example: Haugen, C. M.; Whitten, D. G. *J. Am. Chem. Soc.* **1989**, *111*, 7281. Ci, X. and Whitten, D. G. *J. Am. Chem. Soc.* **1989**, *111*, 3459 and preceeding papers.

(3) For example, A might exist as an adduct with 2,3-dichloro-5,6-dicyanohydroquinone.

(4) While the reactivity of DDQ towards tertiary amines has not been investigated, analogy with chloranil indicates cyanide release by nucleophilic substitution could occur, cf. ref 9a.

(5) Mangeney, P.; Langlois, N.; Leroy, C.; Riche, C.; Langlois, Y. *J. Org. Chem.* **1982**, *47*, 4261.

(6) Stevens, T. S. *Prog. Org. Chem.* **1968**, *7*, 48. Lepley, A. R.; Giumanini, A. C. *Mechanisms of Molecular Migration, Vol. 3*; Thygarajan, B. S., Ed.; Wiley Interscience: New York, 1971; pp 297–440. Pine, S. H. *Org. React.* **1970**, *18*, 403.

(7) As shown by the data in Tables I and II, only the C5 and C6 methylene groups occur in the upfield region of the spectrum. One of the C6 protons occurs at extraordinarily high field. The ultraviolet spectrum shows absorption maxima at 272, 306, 338, and 408 nm. The spectroscopic data do not entirely exclude an isomeric dihydropyridine structure in which the cyano substituent is at C3 having C14–C15 and C20–C21 double bonds.

Table I. Proton NMR Data

	3	5, 6	14	15	17	21	CO_2CH_3	CH_2CH_3	other
1	2.8 m (2)	2.9 m, 3.3 m (2), 3.6 m	2.9 m	5.93 dm	1.8 dd, 2.7 dm	4.18 s	3.75 (3)	1.07 t (3)	-
					J_{gem} = 14			2.10 m, 2.35 m	
								J_{gem} = 18	
2	3.0 m[a], 3.2 m[a]	3.3 m (2), 3.0 m, 2.6 m	3.05 m	5.51 d	2.22 dd, 2.5[a] m	4.76 s	3.78 s (3)	1.0 t (3)	3.22 s[b] (16-OMe)
	J_{gem} = 9			J = 9	J_{gem} = 13			2.04 q (2)	3.24 s[b] (21-OMe)
3	3.08 dd, 3.26 t	3.3 m (2), 3.0 m, 2.6 m	3.65 m	6.52	2.67 dd, 2.35	9.95 s	3.79 s (3)	1.00 t (3)	
	J_{gem} = 11			J = 10	J_{gem} = 13			2.18 q (2)	
4	3.82 d	3.61 ddd, 3.38 ddt, 3.18 ddd, 3.06 m	3.05 m	5.97 d	2.80 dd, 1.78 dd	4.28 s	3.74 s (3)	1.11 t (3)	
	J = 2			J = 5	J_{gem} = 13			2.18 m, 2.30 m	
								J_{gem} = 18	
5	2.88 d[a], 3.19	4.0 m, 3.4 m, 3.5 m, 2.8 m[a]	2.9[a]	6.06 m	~2.9[a], 2.04 d	-	3.88 s (3)	1.13 t (3)	-
	J_{gem} = 6				J_{gem} = 13			2.48 m, 2.35 m	
								J_{gem} = 18	
6	3.17 dt, 2.50 d	3.99 dd, 3.58 dd, 3.41 dd	2.7 m[a]	5.98 d	2.7[a], 1.87 d	4.62 s	3.64 s (3)	1.12 t (3)	
	J_{gem} = 8				J_{gem} = 11			2.2 m, 2.3 m	
7	2.95[a], 3.44 d	3.55 t, 3.35 dd, 3.05 dd, 3.0 m	-	5.67 s	2.08 d, 1.23 d	3.95 s	3.62 s (3)	1.10 t (3)	
	J_{gem} = 14				J_{gem} = 5			2.25 m, 2.17 m	
								J_{gem} = 18	
8	3.19 d, 2.9 d[a]	2.95 m (2)[a], 3.35 dd, 3.7 m[a]	-	5.42 bs	2.01 d[a], 1.12 d	3.76 d, 3.04 d[a]	3.62 s (3)	1.03 t (3)	
	J_{gem} = 14				J_{gem} = 5	J_{gem} = 17		1.98 q (2)[a]	
9[d]	7.90 d	3.05 dd, 2.85 dd, 2.75 dd, 0.65 dd	-	5.83 s	6.25 s	5.22	3.46 s (3)	1.06 t (3)	
	J = 1	C-5 J_{gem} = 13, C-6 J_{gem} = 14						2.09 q[c] (2)	
10	-	4.8 m[a], 3.15 m[a], 2.8 m (2)[a]	-	6.35 d	2.46 d, 1.81 d	4.08 d	3.59 s (3)	1.15 t (3)	
				J = 1	J_{gem} = 6	J = 1		2.5 m[a] (2)	

[a] Overlaps another signal. [b] Assignments may be interchanged. [c] Additional fine coupling. [d] In benzene-d_6.

Table II. Carbon-13 NMR Data

	3	5	6	14	15	16	17	18	19	20[a]	21	O=C	OCH_3	other
1	53.7	50.0	22.0	31.3	124.2	56.0	39.0	11.3	26.8	149.8	62.4	174.7	52.9	-
2	55.8	43.8	15.8	34.0	131.6	67.6	44.6	13.0	23.7	b	102.8	173.8	52.8	54.0[c] (OMe)
3	55.6	43.9	15.8	33.3	149.2	67.4	44.6	13.1	23.1	141.9	190.7	174.4	53.0	-
4	51.9	51.7	21.0	34.4	120.7	54.5	36.9	11.0	26.5	151.6	60.0	173.1	52.5	120.2 (CN)
5	49.8[c]	49.8[c]	20.5	29.3	124.9	61.1	36.8	11.3	25.7	145.5	64.9	172.0	53.3	117.8 (CN)
6	54.9	53.0	26.8	31.8	122.9	54.0	39.0	11.7	27.1	148.4	55.4	173.8	51.9	121.5 (CN)
7	48.9	48.8	25.8	34.9	125.1	31.4	23.8	12.2	26.7	b	56.6	171.5	53.2	118.5 (CN)
8	51.7	47.9	25.8	26.4	119.4	34.6	23.4	12.3	27.6	141.2	56.9	171.5	52.4	
9[d]	139.6	57.6	28.6	b	132.7	b	137.2	15.3	25.5	b	43.0	169.6	51.9	
10	165.2	49.4	24.9	35.5	132.9	36.1	23.9	12.9	25.6	143.2	53.6	169.6	53.6	116.9 (CN)

[a] The C-20 signal is assigned as the unprotonated carbon distinctly downfield of the C2, C8, and C13 carbons of the indole ring. For **2**, **7**, and **9** this assignment is ambiguous. [b] Not assigned. [c] Not resolved. [d] In benzene.

pound **8** shows the characteristic C17 methylene peaks at 2.01 and 1.12 ppm with J_{gem} = 5 Hz and other features of the spectrum are also consistent with the assigned structure. Use of sodium borodeuteride as the reductant gives **8-*21-d***. Compounds **7** and **8** would be the products expected to be formed from the intermediate G by addition at C21 of the nucleophiles cyanide and hydride, respectively. Oxidation of **8** by DDQ in the presence of TMSCN gives **7**.

Reaction of **1** with DDQ in anhydrous tetrahydrofuran, followed by KCN/18-crown-6 (5 equiv) gave 3-cyanocatharanthine, **4** (20% yield). An additional minor product **10** was also isolated.[8] When the reaction mixture from the DDQ oxidation in dry THF is treated with $NaBD_4$ the main product is partially dideuterated **8** (25%). The extent of deuteration is >80% at C21 and ≈70% at C3. The undeuterated compound was isolated in 21% yield when $NaBH_4$ was used. The dideuterated portion of **8** must arise by reduction of intermediate derived from D or G by a subsequent oxidation, but the identity of the intermediate is unknown.

DDQ is known to be able to oxidize both aromatic rings and heteroatomic functional groups by one-electron transfer in addition to the conventional hydride transfer mechanism.[9] Previous DDQ oxidations of 16-*O*-acetylvindoline and other *vinca* alkaloids have given

(8) The 21-cyano-3-oxo structure is preferred to the 3-cyano-21-oxo alternative on the basis of the absence of a large downfield shift for the C15 carbon signal; a downfield shift of the β-carbon of an unsaturated amide to about 140 ppm would expected for the 21-oxo structure as is observed for other unsaturated amides, cf. Boll, P. M.; Hansen, J.; Simonsen, O.; Thorup, N. *Tetrahedron* **1984**, *40*, 171.

(9) (a) Buckley, D.; Dunstan, S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4880. (b) Kosower, E. M. *Prog. Phys. Org. Chem.* **1965**, *3*, 81. (c) Lai, C. C.; Colter, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 1115. (d) Nishida, S.; Murakami, M.; Oda, H.; Tsuji, T.; Mizuno, T.; Matsubara, M.; Kikai, N. *J. Org. Chem.* **1989**, *54*, 3859. (e) Bhattacharya, A.; DiMichele, L. M.; Dolling, U.-H.; Grabowski, E. J. J.; Grenda, V. J. *J. Org. Chem.* **1989**, *54*, 6118.

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.

(10) Sariaslani, F. S.; Eckenrode, F. M.; Beale, J. M., Jr.; Rosazza, J. P. *J. Med. Chem.* **1984**, *27*, 749; Goswami, A.; Schaumberg, J. P.; Duffel, M. W.; Rosazza, J. P. *J. Org. Chem.* **1987**, *52*, 1500.
(11) Nelsen, S. F.; Ippoliti, J. T. *J. Am. Chem. Soc.* **1986**, *108*, 4879. Pandey, G.; Kumaraswamy, G. *Tetrahedron Lett.* **1988**, *29*, 4153.
(12) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325.

Synthesis of the Angular Anthraquinone Subunit of Dynemicin A

Hidenori Chikashita,[†] John A. Porco, Jr.,[†] Thomas J. Stout,[‡] Jon Clardy,[‡] and Stuart L. Schreiber*[,†]

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, and Department of Chemistry, Cornell University, Ithaca, New York 14853-1301

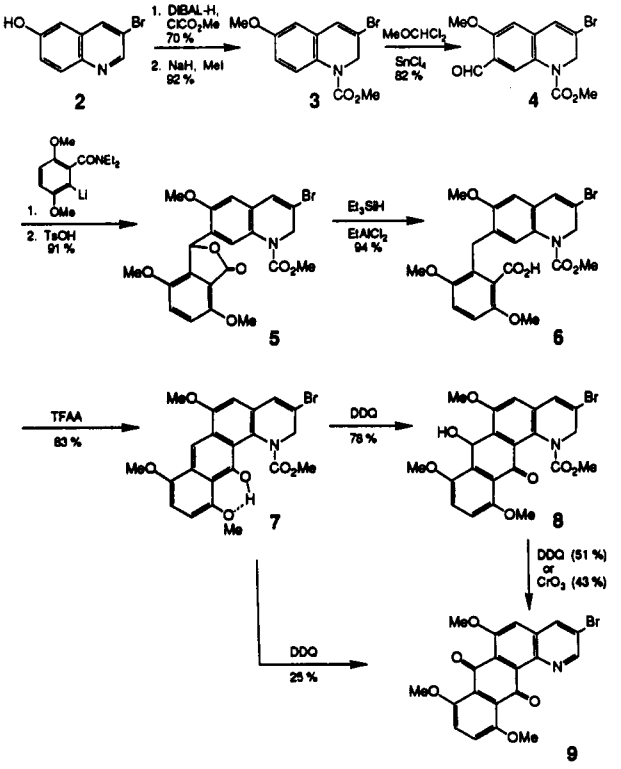
Received December 14, 1990

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



[†] Harvard University.
[‡] Cornell University.

(1) (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

0022-3263/91/1956-1692$02.50/0