Supplementary Material Available: Experimental details for the preparation and physical and spectral data of **4a,b, 1** and its sodium salt, and **6**, general procedure for the preparation of CFPA derivatives, all X-ray crystallographic data for compound **4a**, and tables of atomic coordinates and anisotropic thermal parameters (6 pages); observed and calculated structure factors for **4a** (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of Vineomycinone B_2 Methyl Ester via Double Bradsher Cyclization[1]

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Vineomycin B_2[2] is a secondary metabolite of *Streptomyces matensis* subsp. *vineus* and displays potent antitumor/antibiotic activity with a pharmacologic profile similar to that of the clinically important anthracyclines.[3] Its chemical degradation[2] in acidic methanol yields an aglycon subunit, vineomycinone B_2 methyl ester (**1**), bearing several salient structural features shared in part by other anthraquinone antibiotics,[4] inter alia, an olivose-type β-C-glycoside and a 3(*R*)-hydroxyisovaleryl side chain situated on opposing sides of an anthrarufin nucleus. Accordingly, vineomycin B_2 has engendered much synthetic interest[5] and provided a forum for the demonstration of new methodology resulting in recent total syntheses[6,7] of the aglycon moiety **1**. Herein, we describe a conceptually distinct approach to **1** utilizing a convergent strategy of consecutive Bradsher cycloadditions[8] of the electron-rich dienophiles **2** and **4** with the heterodienes implicit in **3** (eq 1).

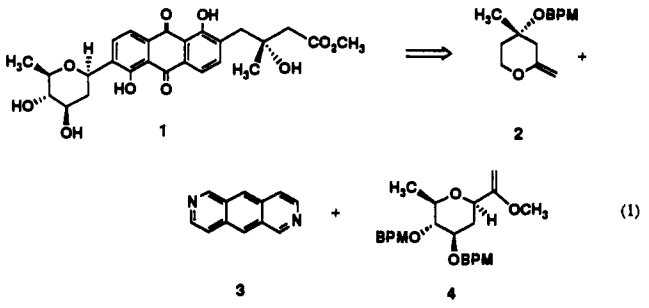
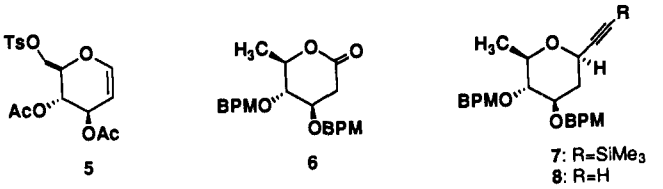
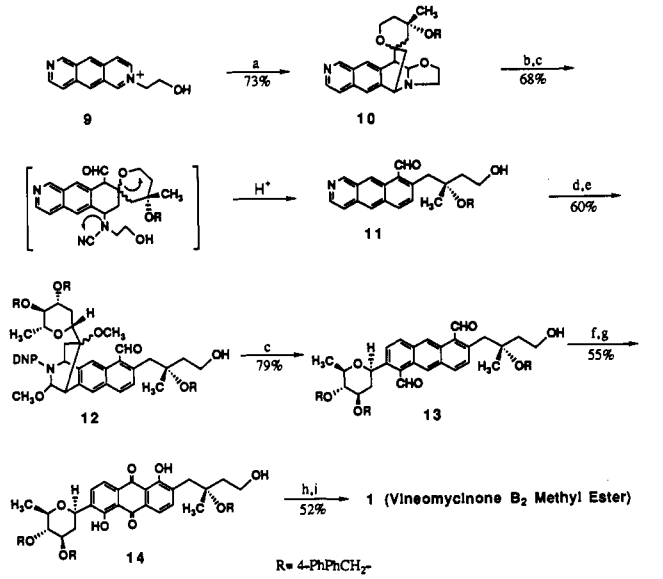


Chart I



Scheme I[a]



[a] (a) **2**, $CaCO_3$, $MeOH/CH_2Cl_2$, 24 °C, 2 h; (b) CNBr, $NaHCO_3$, MeOH, 0 °C, 0.5 h; (c) 3 N HCl/THF, 40 °C, 12 h; (d) DNP-Br, CH_3CN, 65 °C, 10 h; (e) **4**, $CaCO_3$, MeOH, 10 °C, 6 h; (f) $PhSeO_2H$, H_2O_2, H_2O/CH_2Cl_2, 25 °C, 20 h; NH_4OH; (g) $^1O_2$, CH_2Cl_2; $NaBH_4$, MeOH; O_2 (workup); (h) PDC, DMF, 25 °C, 10 h; CH_2N_2; (i) H_2 (1 atm), 5% Pd/C, EtOAc, 6 h.

As envisaged above, the acyclic side chain is introduced in the latent form embodied in **2**,[9] readily available from the vinylidene analogue[10] of (*S*)-mevalonolactone by etherification of the tertiary alcohol with *p*-biphenylmethyl (BPM) bromide[11] (72%). Access to the β-C-glycoside precursor **4** from glucal **5**[12] (Chart I) was realized by sequential lithium aluminum hydride reduction in Et_2O (80%), protection of the liberated C(3) and C(4) alcohols as BPM ethers (86%), and pyridinium chlorochromate oxidation of the cyclic enol ether[13] (76%). Addition of the cerium(III) chloride salt[14] of (trimethylsilyl)acetylide to the resultant lactone **6** (mp 118-120°C) at -78 °C in tetrahydrofuran (THF) provided an anomeric mixture of hemiketals (90%), which was reduced[15] with excess $Et_3SiH/BF_3{\cdot}Et_2O$ (10 equiv each) in CH_3CN/CH_2Cl_2 (1:1) at -40 °C. Chromatographic purification on silica gel (ethyl acetate/hexane, 1:4) afforded **7** and its α-epimer (89%, 3:1), R_f ~ 0.56 and 0.49, respectively. Desilylation[14] to **8** (90%, mp 91 °C) and methoxymercuration/demercuration according to Hudrlik[16] furnished **4** (58%, mp 70-71 °C).

Attachment of both appendages to the polycyclic core and final elaboration to **1** are summarized in Scheme I. Facile[17] Bradsher

(1) (a) Presented at the 199th National Meeting of the American Chemical Society, Boston, MA, 1990. (b) Taken in part from the Ph.D. Thesis of V.B., Universite Louis Pasteur, Strasbourg, France.
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cyclization between enol ether **2** and salt **9**, prepared from pyrido[3,4-*g*]isoquinoline (**3**)[18] and 2-bromoethanol (CH_3CN, 82 °C; 84%), in the presence of the acid scavenger $CaCO_3$[19] and concomitant intramolecular interception[20] of the resultant iminium ion by the N-tethered oxygen nucleophile[23] gave adduct **10** as a diastereomeric mixture arising from endo and exo addition.[22] Careful spectroscopic analysis revealed no regioisomeric products. Although separable chromatographically, in practice, the crude mixture was directly transformed to aldehyde **11** by selective von Braun cleavage[24] of the mixed azaacetal using methanolic cyanogen bromide, mild acidic hydrolysis, and subsequent in situ aromatization.[19] A second Bradsher cyclization of the 2,4-dinitrophenyl (DNP) salt[17] of **11** with **4** in methanol yielded adduct **12**, also as a mixture of diastereomers. Acidic hydrolysis/aromatization as above smoothly evolved anthracene **13** containing the complete carbon framework of the target molecule. The residual aldehydes were profitably exploited for introduction of the phenolic oxygens by subjecting **13** to modified Dakin oxidation.[25] Singlet oxygen addition across the central aromatic ring[26] with reductive workup and aerial oxidation during isolation generated anthraquinone **14**. Pyridinium dichromate (PDC) oxidation of the primary alcohol in dimethylformamide (DMF), diazomethane esterification of the resultant carboxylate, and selective hydrogenolysis[27] of the BMP protecting groups led to **1**, mp 183-184 °C (lit.[7] mp 183-184 °C), spectrally and chromatographically comparable to authentic material.

The foregoing synthesis highlights the potential of polar [4+ + 2] cycloadditions for the construction of complex polycyclic systems containing highly functionalized appendages and expands the repertoire of aza aromatics capable of Bradsher annulation. Extensions of the scope and preparative applications of this methodology will be reported in due course.

Acknowledgment. Supported financially by the USPHS NIH (GM36465) and the Robert A. Welch Foundation (I-782). The Association pour la Recherche sur le Cancer provided a student fellowship to V.B. The purchase of a mass spectrometer was assisted by a grant from the NIH Biomedical Research Support Program (RR05922). We express our appreciation to Dr. Samuel J. Danishefsky (Yale University) for spectra of **1** and to Dr. Satoshi Omura (Kitasato Institute) for a sample of vineomycin B_2.

Supplementary Material Available: Analytical data for **1**, **4**, **6**, **8**, **11**, and **13** (1 page). Ordering information is given on any current masthead page.

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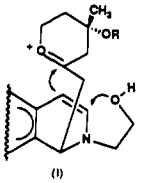
(20) Generally, *5-endo-trigonal* ring closures are disfavored (ref 21). Alternatively, this annulation may involve addition of the oxygen nucleophile to the initially formed one-bond product i (ref 22).



(i)

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(23) For the salt prepared from 3-bromopropanol, addition of a second molecule of **2** to the iminium ion was nearly equally competitive with ring closure. See: Day, F. H.; Bradsher, C. K.; Chen, T.-K. *J. Org. Chem.* **1975**, *40*, 1195.
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(26) Rigaudy, J. *Pure Appl. Chem.* **1968**, *16*, 169.
(27) BPM ethers undergo hydrogenolysis over Pd catalysts 2-4 times faster than the corresponding benzyl ethers. Additionally, they are cleaved by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), albeit slowly (8-15 h): Abdali, A.; Falck, J. R., unpublished results.

Didemnaketals A and B, HIV-1 Protease Inhibitors from the Ascidian *Didemnum* sp.

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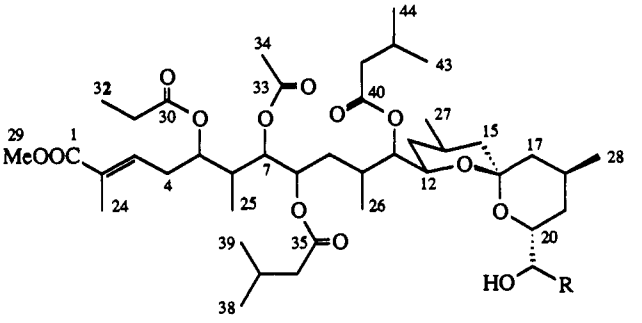
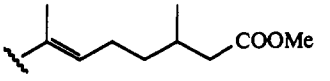
Replication of human immunodeficiency virus (HIV) entails expression of several viral polyproteins which require the presence of a virus-specific protease for their maturation. Inhibition of this enzyme results in immature viral particles and inhibition of viral replication in vitro.[1] HIV-1 protease is therefore an exciting target for mechanism-based natural product screening in order to identify candidates for development of chemotherapeutics for AIDS. The magenta ascidian *Didemnum* sp. was collected by hand (-1 m) at Auluptagel Island, Palau. The sample was stored at -20 °C for several years until the HIV-1 protease inhibition assay[2] revealed bioactivity in a crude extract. Using bioassay-guided fractionation, the hexane-soluble material from a 1:1 methanol-dichloromethane extract (15 g) was chromatographed on Sephadex LH-20 (5:5:1 CH_2Cl_2-MeOH-H_2O) to obtain two active fractions, which were further purified by reversed-phase HPLC to obtain didemnaketals A (**1**, 4 mg) and B (**2**, 12 mg). Inhibition of HIV-1 protease by didemnaketals A (**1**, IC_{50} = 2 μM) and B (**2**, IC_{50} = 10 μM) was measured by using a peptidolysis assay.[2,3]



1 R = $^{23}COCH_3$ **2** R = 

Didemnaketal A (**1**), $[\alpha]_D$ = -11.0° (*c* 0.8, $CHCl_3$), was isolated as a clear oil. The molecular formula, $C_{44}H_{72}O_{14}$, was deduced from the ^{13}C NMR data and the $(M + H)^+$ peak at m/z = 825.5030 in the HRFABMS spectrum. The IR spectrum contained bands at 3490, 1735, and 1712 cm^{-1} that were assigned to hydroxyl, ester, unsaturated ester, and ketone groups. The ^{13}C NMR spectrum (Table I) contained signals assigned to a ketone carbonyl, five ester carbonyls, two olefinic carbons, a ketal carbon, seven -CH(OR)- carbons, a methoxy group, six aliphatic methine carbons, nine methylene carbons, and 12 methyl carbons. From these data it was concluded that **1** was a bicyclic ketal with no other rings present.

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