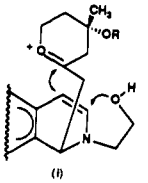
cyclization between enol ether **2** and salt **9**, prepared from pyrido[3,4-*g*]isoquinoline (**3**)[18] and 2-bromoethanol (CH_3CN, 82 °C; 84%), in the presence of the acid scavenger $CaCO_3$[19] and concomitant intramolecular interception[20] of the resultant iminium ion by the N-tethered oxygen 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.

(18) Bolitt, V.; Mioskowski, C.; Reddy, S. P.; Falck, J. R. *Synthesis* **1988**, 388.
(19) Manna, S.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1982**, *47*, 5021.
(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)

(21) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
(22) A two-step mechanism for Bradsher cyclizations allowing isomerization has been proposed: Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393. Bradsher, C. K.; Stone, J. A. *J. Org. Chem.* **1969**, *34*, 1700.
(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.
(24) Hageman, H. A. *Org. React. (N.Y.)* **1953**, *7*, 198.
(25) Syper, L. *Synthesis* **1989**, 167.
(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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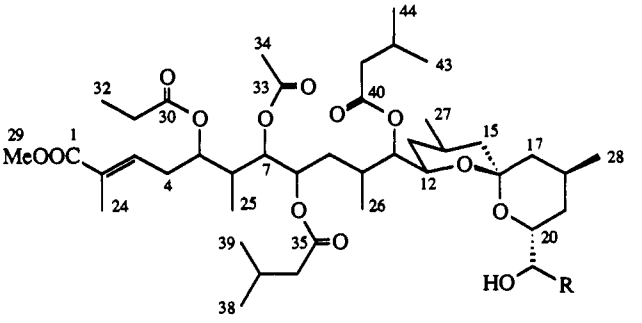
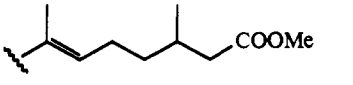
Replication of human immunodeficiency virus (HIV) entails expression of several viral polyproteins which require the presence of a virus-specific protease for their maturation. Inhibition of this enzyme results in immature viral particles and inhibition of viral replication in vitro.[1] HIV-1 protease 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.

(1) Lambert, D. M.; Meek, T. D.; Dreyer, G. B.; Hart, T. K.; Mathews, T. J.; Leary, J. J.; Bugelski, P. J.; Metcalf, B. W.; Petteway, S. R., Jr. *Ann. N.Y. Acad. Sci.* **1990**, *616*, 552.
(2) Hyland, L. J.; Dayton, B. D.; Moore, M. L.; Shu, A. Y. L.; Heys, J. R.; Meek, T. D. *Anal. Biochem.* **1990**, *188*, 408.
(3) A curve fit of the dose-response data was accomplished by using the equations of De Lean et al.: De Lean, A.; Munson, P. J.; Rodbard, D. *Am. J. Physiol.* **1978**, *235*(2), E97.

0002-7863/91/1513-6321$02.50/0

Table I. Didemnaketal A: ^1H and ^{13}C NMR Data

C no.	^{13}C ppm (mult)	^1H ppm (mult, J (Hz))	long-range ^1H–^{13}C correlations
1	168.1 (s)		
2	130.2 (s)		
3	136.1 (d)	6.71 (ddd, 5, 7, 2)	C1, C2, C5, C24
4	30.8 (t)	2.49 (ddd, 16, 5, 5)	C2, C3, C5
		2.53 (ddd, 16, 7, 7)	C2, C3, C5
5	72.2 (d)	4.83 (m)	C3, C6, C30
6	36.7 (d)	2.09 (m)	C5
7	72.9 (d)	5.16 (dd, 9, 2)	C5, C6, C8, C25, C33
8	70.6 (d)	5.22 (br t, 10)	C7, C9, C10, C35
9	32.2 (t)	1.24 (m)	
		1.61 (m)	
10	29.4 (d)	1.84 (m)	
11	78.2 (d)	4.78 (dd, 6, 6)	C9, C10, C12, C26, C40
12	69.2 (d)	3.69 (m)	C10, C11, C14, C16
13	34.5 (t)	0.81 (ddd, 12, 12, 12)	C12, C27
		1.45 (br d, 13)	
14	24.9 (d)	1.93 (m)	
15	43.9 (t)	0.98 (br m)	
		1.67 (dd, 14, 3)	C13, C16, C17
16	98.4 (s)		
17	40.0 (t)	1.45 (br d, 13)	C16, C19
		1.59 (br d, 13)	C15, C16, C18, C28
18	24.3 (d)	1.99 (m)	
19	31.8 (t)	1.34 (br dd, 14, 3)	
		1.71 (ddd, 14, 11, 5)	C18, C20, C21, C28
20	67.5 (d)	3.89 (ddd, 11, 5, 3)	
21	79.1 (d)	4.14 (dd, 5, 5)	C19, C20, C22
22	209.3 (s)		
23	28.1 (q)	2.32 (s)	C21, C22
24	12.5 (q)	1.82 (s)	C1, C2, C3
25	9.8 (q)	0.98 (d)	C5
26	16.1 (q)	0.98 (d)	
27	22.0 (q)	0.86 (d, 7)	C13, C14, C15
28	20.6 (q)	1.08 (m)	C17, C18, C19
29	51.8 (q)	3.72 (s)	C1
30	173.8 (s)		
31	27.5 (t)	2.28 (br m)	C30, C32
32	8.3 (q)	1.08 (m)	C30, C31
33	170.2 (s)		
34	20.8 (q)	1.98 (s)	C33
35	172.4 (s)		
36	43.1 (t)	2.13 (m)	C35
37[a]	25.2 (d)	2.04 (m)	
38[b]	22.3 (q)	0.93 (d)	
39[b]	22.4 (q)	0.93 (d)	
40	172.7 (s)		
41	43.6 (t)	2.24 (m)	C40
42[a]	25.5 (d)	2.08 (m)	
43[b]	22.5 (q)	0.98 (d)	
44[b]	22.5 (q)	0.98 (d)	
O–H		3.34 (d, 5)	C21, C22

[a,b] Signals are interchangeable.

The ^1H and ^{13}C NMR data were assigned as shown in Table I by interpretation of the ^1H–^1H COSY, HMQC (J = 135 Hz), and HMBC (J = 8 Hz) experiments. The unsaturated ester at the head of the isoprenoid chain was defined by the HMBC cross peaks [3.72 (OMe): 168.2 (C-1)], [6.71 (H-3): 168.2], and [6.71: 12.3 (C-24)], and the *E* geometry was assigned on the basis of the chemical shifts of C-24 (δ 12.3) and H-3 (δ 6.71). The COSY data revealed two contiguous carbon chains from C-3 to C-15 and C-17 to C-21 with branching methyl groups at C-6, C-10, C-14, and C-18. Both the chemical shift values and HMBC data required ester functionality at C-5, C-7, C-8, and C-11. Since the H-21 signal was coupled to a hydroxyl proton signal, the oxygens attached at C-12 and C-20 must both be joined to the ketal carbon at C-16. This proposal was supported by HMBC cross peaks at [3.69 (H-11): 98.4 (C-16)], [1.45 (H-15): 98.4], and [1.59 (H-17): 98.4]. The terminal methyl ketone was assigned on the basis of the HMBC cross peaks at [2.32 (H-23): 209.3 (C-22)] and [2.32: 79.1 (C-21)]. The remaining ^1H and ^{13}C NMR signals were assigned to one acetate, one propionate, and two isovalerate esters, although the signals for the two isovalerate groups could not be differentiated into two sets. The positions of the acetate and propionate groups were defined by HMBC cross peaks at [1.98 (H-34): 170.2 (C-33)] and [5.16 (H-7): 170.2] and [1.08 (H-32): 173.8 (C-30)] and [4.83 (H-5): 173.8]; the isovalerate esters are therefore at C-8 and C-11. The stereochemistry of the substituents about the pyran rings was determined by interpretation of ^1H NMR coupling constants and the observation of two nuclear Overhauser enhancements between H-20 and Me-28 and between H-12 and H-20.

Didemnaketal B (**2**) is a clear oil of molecular formula $C_{52}H_{86}O_{15}$. Comparison of the ^1H and ^{13}C NMR spectra[4] of ketal **2** with those of ketal **1** revealed that the compounds were identical in the C-1 to C-20 region. The differences in NMR spectra are consistent with the proposed structure **2** in which the additional carbon atoms constitute an extension of the polyisoprenoid chain such that oxidative cleavage of the C-22 olefinic bond of didemnaketal B (**2**) produces didemnaketal A (**1**). In the ^1H COSY spectrum of **2**, the additional olefinic signal at δ 5.48 (t, 1 H, J = 6.9 Hz) is coupled to methylene signals at ca. 2.1 and shows long-range coupling to the methyl signal at 1.61 (s, 3 H) and the H-21 signal at 4.05 (d, 1 H, J = 3.5 Hz), which was in turn coupled to the H-20 signal at 3.86 (overlaps with H-12). The methyl signal at δ 1.61 was correlated with a ^{13}C NMR signal at 13.3 (q), the chemical shift of which indicated the 22*E* geometry. After locating the ^{13}C NMR signals for all carbons attached to the C-1 to C-23 portion of the molecule, the remaining signals at δ 173.5 (s), 51.3 (q), 41.5 (t), 36.5 (t), 30.0 (d), 24.9 (t), and 19.6 (q) were assigned to an isoprenoid carbon chain terminating at the methyl ester.

Didemnaketal B (**2**) is a linear heptaprenoid, which is a very rare terpenoid class. The isolation of terpenoids from ascidians is unusual since most ascidian metabolites are amino acid derived.[5] Although didemnaketal A (**1**) is probably an oxidation product of didemnaketal B (**2**), it was not among the decomposition products of ketal **2**, which did not survive prolonged storage. The well-established lability of esters under physiological conditions precluded further development of these compounds as drug candidates.

Acknowledgment. We thank Dr. Françoise, Monniot, Muséum National d'Histoire Naturelle, Paris, for identifying the ascidian that was collected by Dr. Brad Cartê. We also thank the Government and people of the Republic of Palau for facilitating the field research. The research at UCSD was supported by grants from the National Institutes of Health (CA49084 and RR07433 (500-MHz NMR instrument grant) and the California Sea Grant College Program (R/MP-46).

Supplementary Material Available: ^1H and ^{13}C NMR, HMQC, and HMBC spectra of didemnaketal A, a table containing ^1H and ^{13}C NMR spectral data for didemnaketal B, and ^1H and ^{13}C NMR spectra of didemnaketal B (11 pages). Ordering information is given on any current masthead page.

(4) Didemnaketal B (**2**): IR ($CHCl_3$) 3500, 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.69 (t, 1 H, J = 7 Hz), 5.48 (t, 1 H, J = 7 Hz), 5.23 (dd, 1 H, J = 9, 8 Hz), 5.13 (dd, 1 H, J = 8, 3 Hz), 4.83 (m, 1 H), 4.77 (dd, 1 H, J = 6, 5 Hz), 4.05 (d, 1 H, J = 3 Hz), 3.87 (m, 1 H), 3.85 (m, 1 H), 3.73 (s, 3 H), 3.66 (s, 3 H), 2.51 (dt, 1 H, J = 16, 5 Hz), 2.47 (dt, 1 H, J = 16, 7 Hz), 2.35 (m, 2 H), 2.29 (dd, 1 H, J = 7, 5 Hz), 2.25 (d, 2 H, J = 7 Hz), 2.13 (d, 2 H, J = 7 Hz), 2.13 (m, 1 H), 2.12 (m, 1 H), 2.08 (m, 2 H), 2.06 (m, 2 H), 2.00 (m, 1 H), 1.98 (s, 3 H), 1.96 (m, 1 H), 1.91 (m, 1 H), 1.90 (m, 1 H), 1.84 (s, 3 H), 1.67 (m, 1 H), 1.66 (m, 1 H), 1.64 (m, 1 H), 1.62 (s, 3 H), 1.58 (br d, 1 H, J = 14 Hz), 1.54 (br d, 1 H, J = 14 Hz), 1.44 (m, 1 H), 1.38 (m, 1 H), 1.25 (m, 1 H), 1.22 (m, 1 H), 1.12 (m, 1 H), 1.09 (t, 3 H, J = 7 Hz), 1.07 (d, 3 H, J = 6 Hz), 1.00 (d, 1 H, J = 7 Hz), 0.99 (d, 6 H, J = 7 Hz), 0.98 (d, 3 H, J = 7 Hz), 0.97 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 0.94 (d, 6 H, J = 6 Hz), 0.86 (d, 3 H, J = 7 Hz), 0.80 (q, 1 H, J = 14 Hz); ^{13}C NMR ($CDCl_3$) δ 173.7 (s), 173.5 (s), 172.7 (s), 172.3 (s) 170.1 (s), 168.0 (s), 135.9 (d), 133.0 (s), 130.3 (s), 126.3 (d), 98.3 (s), 78.6 (d), 78.0 (d), 72.7 (d), 72.3 (d), 70.6 (d), 69.1 (d), 66.6 (d), 51.8 (q), 51.3 (q), 44.3 (t), 43.7 (t), 43.1 (t), 41.5 (t), 40.7 (t), 37.0 (d), 36.5 (t), 35.1 (t), 32.9 (t), 30.9 (t), 30.0 (d), 30.0 (t), 29.5 (d), 27.6 (t), 25.6 (d), 25.3 (d), 24.9 (t), 24.8 (d), 24.5 (d), 22.6 (2 q), 22.5 (2 q), 22.1 (q). 20.8 (q), 20.7 (q), 19.6 (q), 16.2 (q), 13.3 (q), 12.6 (q), 9.9 (q), 8.9 (q); HRFABMS obsd. m/z 933.5951, $C_{52}H_{85}O_{14}$ $(M - OH)^+$ requires m/z 933.5939.

(5) For recent reviews, see: Faulkner, D. J. *Nat. Prod. Rep.* **1991**, *8*, 97 and previous reviews in this series.