the mixture was poured directly over a column of silica gel maintained below -40 °C, and the product was eluted with dichloromethane into a flask held at -40 °C. Removal of solvent below -30 °C gave the dimethyl-*syn*-cyclophane **50** (340 mg, 100%) as a white solid: ^{1}H NMR (-30 °C) δ 6.79, 6.74, 6.50, 6.27, 6.24, 6.19 (6 s, 1 H each, H-4,6,8,12,14,16), 4.37 (dd, J = 9.6, 6.6 Hz, 1 H, H-9), 4.13 (dd, J = 9.5, 3.8 Hz, 1 H, H-1), 3.69 (m, 1 H, H-10$_{ax}$), 3.32 (dd, J = 13.4, 9.5 Hz, 1 H, H-2$_{ax}$), 2.78 (dd, J = 13.6, 3.8 Hz, 1 H, H-2$_{eq}$), 2.35 (m, 1 H, H-10$_{eq}$), 2.19 and 2.08 and 2.01 and 1.95 (s, 3 H each, C-5-CH$_3$, C-13-CH$_3$, and -SCH$_3$'s).

Acknowledgment. We wish to thank the Natural Sciences and Engineering Research Council of Canada and the University of Victoria for financial support.

Supplementary Material Available: General experimental conditions, crystal structure determination (including labeling schemes, tables of fractional atomic coordinates, isotropic thermal parameters, bonded atomic distances, bond angles, mean planes and torsion angles, and intermolecular distances), and X-ray experimental details for syn complex **22** and anti complex **28** (26 pages). Ordering information is given on any current masthead page.

Total Syntheses of (+)- and (-)-Didemnenones A and B. Antiselectivity in the Intramolecular Carbomercuration Reaction[1a]

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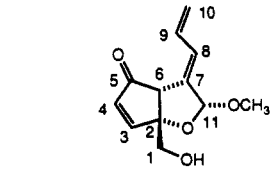
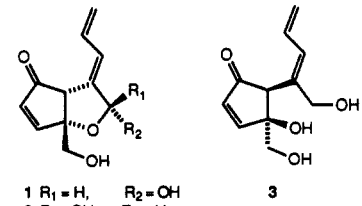
Abstract: Total syntheses of the title compounds were achieved in 11 steps and ca. 7% overall yield from the chiral synthon **10**. In conjunction with previous chiroptical studies, this work allowed the assignment of absolute configurations to didemnenones A-D (**1-4**, respectively), a series of cytotoxic cyclopentanoid marine natural products isolated from the tunicates *Trididemnum* cf. *cyanophorum* and *Didemnum voeltzkowi*. Thus, **1** and **2** were shown to have the 2*R*,6*R* configuration; **3** was shown to have the 2*S*,6*S*, and **4**, most plausibly, the 2*S*,6*R* configurations. Featured in the syntheses are an efficient 1,3 chirality transfer to establish the C2 configuration, one-pot mercuric chloride induced intramolecular cyclization/iodination reactions of an ϵ-alkynyl silyl enol ether to form a *cis*-6-oxabicyclo[3.3.0]oct-3-en-2-one system bearing an exocyclic C8-vinyl iodide and an installation of the C11 oxidation level and diene moiety by sequential SeO_2/*t*-BuOOH oxidation and Pd-mediated vinyl cross-coupling with *n*-$Bu_3SnCHCH_2$. In examining the intramolecular carbomercurations of cyclopentenone silyl enol ethers bearing β-(2-propynyloxy) side chains, an apparently exclusive and unexpected antiselectivity was revealed.

The didemnid tunicates have proven to be a particularly rich source of structurally diverse, biologically potent compounds including the depsipeptides didemnins A-C,[2] heteroaromatic ascididemin,[3] and didemnenones A-D.[4] The didemnenones are a series of at least four C_{11} cyclopentanoid natural products that have recently been isolated from the Caribbean tunicate *Trididemnum* cf. *cyanophorum*, didemnenones A (**1**) and B (**2**), and the South Pacific tunicate *Didemnum voeltzkowi*, didemnenones C (**3**) and D (**4**). The didemnenones display a rich abundance and variety of functionality; every carbon atom in these compounds is functionalized. In addition to their intriguing structural features, the broad-range antimicrobial and antileukemic activities displayed by the didemnenones[4] make them ideal synthetic targets. Reported herein are the full details of our synthetic studies on didemnenones A and B,[5] which culminated in their enantioselective total syntheses and the assignment of the absolute configurations to didemnenones A-D depicted in **1-4**.

Isolated along with didemnenones A and B from *T.* cf. *cyanophorum* extracts were the anomeric acetals **5** and **6**, which, rather than being natural products, are believed to have been formed from the inseparable hemiacetals **1** and **2** upon chromatography in the presence of methanol. The structure determination

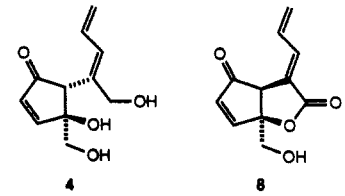


5



1 R_1 = H, R_2 = OH
2 R_1 = OH, R_2 = H
6 R_1 = OCH_3, R_2 = H
7 R_1, R_2 = O

3



4 **8**

of major acetal **5** by X-ray crystallography proved to be instrumental to the elucidation of the relative stereostructures of **1-6** through spectral correlations and chemical interconversions. In particular, allylic oxidations of **1-4** provided pivotal correlations

(1) (a) Taken in part from the Ph.D. Thesis of C.J.F., Cornell University, 1989. (b) Present address: Department of Chemistry, Harvard University, Cambridge, MA 01238.
(2) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857-1859.
(3) Kobayashi, J.; Cheng, J.; Nakamura, H.; Ohizumi, Y. *Tetrahedron Lett.* **1988**, *29*, 1177-1180.
(4) Lindquist, N.; Fenical, W.; Sesin, D. F.; Ireland, C. M.; Van Duyne, G. D.; Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 1308-1309.
(5) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 5911-5912.

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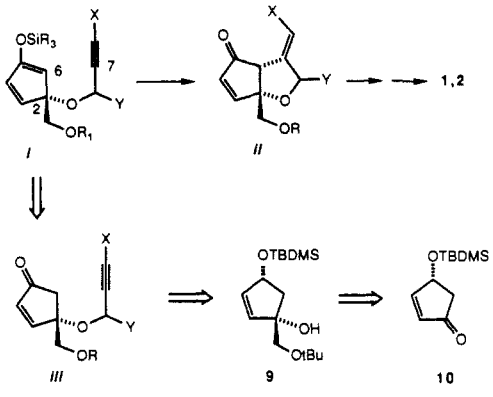
Scheme I



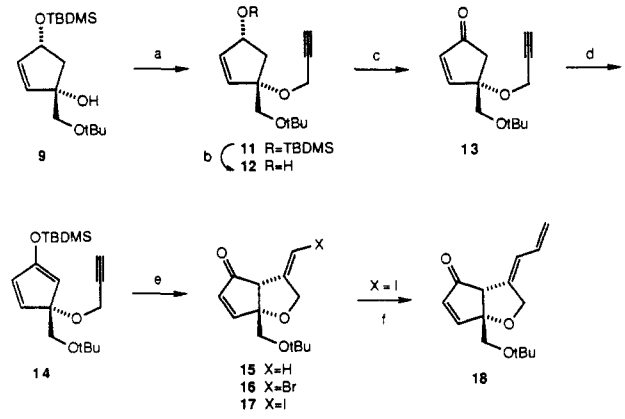
that, interestingly, demonstrated that the two hemispherically separated tunicates contain similar, but enantiomeric metabolites. MnO_2 oxidation of Caribbean-derived hemiacetals **1** and **2** gave lactone **7**, which appeared to be identical with lactone **8** that was similarly obtained from the South Pacific derived triol **3**. Chiroptical comparison of the two lactones, however, revealed that they were in fact optical antipodes. Allylic oxidation of **4** yielded a C_{11} aldehyde that did not form a γ-lactol, but rather yielded a δ-lactol in methanol-d_4, indicating a trans disposition between the cyclopentenone's C2-hydroxyl and C6 substituents. Thus, **3** has the opposite absolute configurations of **1** and **2** at C2 and C6, while **4** is, most plausibly, a C6 epimer of **3**.[4] Although these experiments established the relative stereostructures of the didemnenones, the absolute configurations remained unknown.

The opportunities to explore new methods for the construction and elaboration of the densely functionalized *cis*-6-oxabicyclo[3.3.0]oct-3-en-2-one skeleton of didemnenones A and B, to provide an alternative source of these compounds for further biological evaluation, and to determine the absolute stereochemistries of each member of this new class of natural products prompted us to undertake the synthetic studies reported here. Additionally, in exploiting the application of the intramolecular cycloalkenylation reaction of Drouin et al.[6] for the construction of such bicyclic ring systems, we have uncovered an apparent antiselective carbomercuration that necessitates a revision of the cyclization stereochemistry previously reported.[5]

Results and Discussion

Synthetic Strategy. In view of its central role in the structure determinations and its ease of conversion into natural products **1** and **2**, acetal **5** was chosen as the initial synthetic target. Examination of **5** revealed three central synthetic issues that would have to be addressed: establishment of the C7 diene *E* configuration, installation of the correct relative and absolute configurations at C2 and C6, and formation of the C6–C7 bond. In addressing each of these issues, we based our synthetic strategy on an intramolecular C6–C7 bond formation by the 5-exo-dig[7] cyclization of cyclopentenones bearing β-(2-propynyl)oxy side chains, a transformation well precedented in simple ϵ-alkynyl ketone systems via thermal[8] and catalyzed[9] ene-type reactions, and in recently reported free-radical-based reactions.[10] Because

Scheme II[a]



[a] Conditions are as follows: (a) 3-bromo-1-propyne, NaH, THF, 0 °C to room temperature, 40 h, 96%; (b) *n*-Bu_4NF, THF, room temperature, 3.5 h, 96%; (c) pyridinium dichromate, CH_2Cl_2, room temperature, 16 h, 94%; (d) tBDMSOTf, Et_3N, CH_2Cl_2, 0 °C to room temperature, 30–90 min; (e) (*i*) $HgCl_2$, HMDS, CH_2Cl_2, 15–90 min, 23–35 °C; (*ii*) 5 N HCl, NaI, 0 °C to room temperature, 16 h, 83% **15**; or (*ii*) NBS, DMAP, 0 °C to room temperature, 4 h, 78% **16**; or (*ii*) NIS, NaI, 0 °C to room temperature, 4 h, 91% **17**; (f) *n*-$Bu_3SnCHCH_2$, $(Ph_3P)_4Pd$, LiCl, THF, reflux, 5 h, 75%; or *n*-$Bu_3SnCHCH_2$, $(Ph_3P)_2PdCl_2$, DMF, room temperature, 12 h, 68%.

Drouin et al. reported that $HgCl_2$-induced cyclization of an acyclic ϵ-alkynyl silyl enol ether gave a carbocyclic product bearing an exocyclic β-keto vinyl group substituted with a mercuric salt exclusively syn to the carbonyl,[6] we envisioned that mercuric salt treatment of an ϵ-alkynyl silyl enol ether **i** (X = H) might similarly undergo such a synselective carbomercuration to form a bicyclic vinyl mercurial intermediate **ii** (X = HgCl; Scheme I). Such a stereochemically defined intermediate might then be elaborated into the (*E*)-diene moiety of the didemnenones by a two-step sequence involving electrophilic substitution of the vinyl mercurial with halogen[6,11] and a transition-metal-mediated vinyl cross-coupling. Because retention of configuration could be expected in both steps, intermediate **ii** would lead directly to the natural products' (*E*)-diene. Additionally, since the configuration at C6 in cis-fused cyclization product **ii** would be defined by that at C2 in cyclization precursor **i**, only a single stereogenic center at C2 would need to be incorporated. Requisite enol ether cyclization precursor **i** could be obtained from corresponding enone **iii**, which in turn would be available from cyclopentene **9**. The key stereogenic center in **9** could be established by 1,3 chirality transfer in the diastereofacial selective nucleophilic addition reaction of a hydroxymethyl anion equivalent to enone **10**.

Preliminary Cyclization Studies. When enone **10** was added to an excess of (*tert*-butoxymethyl)lithium,[12] the 1,2-addition product (**9**) resulting from approach of the nucleophile on the less sterically hindered face of the enone was obtained in a 7:1 ratio over the diastereomer arising from nucleophilic attack on the face of the enone cis to the C4-silyloxy group (80–85% combined yields). Room-temperature treatment of tertiary alcohol **9** with propargyl bromide and sodium hydride in THF afforded propargyl ether **11**, which was desilylated to secondary alcohol **12** (Scheme II). Pyridinium dichromate oxidation then gave enone **13** in 87% overall yield from **9**. After exploring various methods to form and isolate the trimethylsilyl or *tert*-butyldimethylsilyl enol ethers derived from **13**, we found that cyclopentadiene **14** could be obtained in essentially quantitative yield by simple treatment of enone **13** with a slight excess of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and triethylamine in CH_2Cl_2,[13] followed by a nonaqueous, extractive workup. While

(6) Drouin, J.; Boaventura, M. A.; Conia, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1726–1729.
(7) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(8) For a review on thermal intramolecular ene reactions see: (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. Also see: (b) Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1975**, *40*, 1699–1701.
(9) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801.
(10) For some related cyclizations involving radical-mediated intramolecular addition to alkynes see: (a) Okabe, M.; Abe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 1775–1777. (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720–3722. (c) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959–3971. (d) Curran, D. P.; Kuo, S.-C. *Tetrahedron* **1987**, *43*, 5653–5661. (e) Dulcere, J. P.; Rodriguez, J.; Santelli, M.; Zahra, J. P. *Tetrahedron Lett.* **1987**, *28*, 2009–2012. (f) Srikrishna, A.; Krishnan, K. *Tetrahedron Lett.* **1988**, *29*, 4995–4996. (g) Moriya, O.; Okawara, M.; Ueno, Y. *Chem. Lett.* **1984**, 1437–1440. (h) Dulcere, J. P.; Mihoubi, M. N.; Rodriguez, J. *J. Chem. Soc., Chem. Commun.* **1988**, 237–239.
(11) (a) Jensen, F. R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*; McGraw-Hill: New York, 1968; pp 64 and 89. (b) Riedicker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842–5844.
(12) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165–3168.
(13) Emde, H.; Gotz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1982**, 1643–1657.

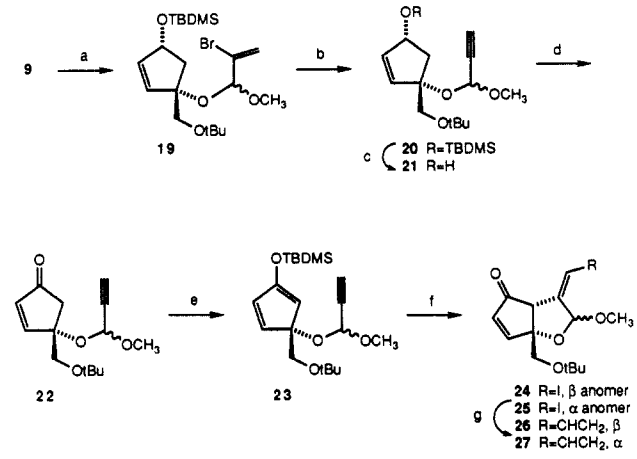
crude **14** would not withstand purification, it was sufficiently pure for ensuing cyclization reactions.

In a preliminary experiment analogous to that reported by Drouin et al.,[6] mercuric chloride was added to a sample of **14** in $CDCl_3$ in an NMR tube. Signals corresponding to the silyl enol ether and the terminal alkyne quickly (<10 min) disappeared and were replaced by α,β-enone and ring junction methine resonances, as well as an additional vinyl resonance (see the Experimental Section, **13** → **17**), indicating that a facile reaction had occurred. When a solution of **14** and the acid scavenger hexamethyldisilazane (0.2 equiv; HMDS) in CH_2Cl_2 was added to a stirred suspension of dry $HgCl_2$ (1 equiv) in CH_2Cl_2 at room temperature, the resulting mixture was stirred for 1 h and then treated with 5 M HCl (2 equiv of HCl) and NaI (2 equiv) for a total of 16 h; workup and chromatography gave exocyclic methylene product **15** (ca. 83% yield from enone **13**). The hydrolysis time could be shortened from ca. 12–16 h to <2 h at room temperature by employing a THF–H_2O cosolvent system for the HCl–NaI treatment.

A simple variation on the two-step carbomercuration–demercuration sequence sufficed to deliver either an exocyclic vinyl bromide or an iodide.[6,11] After cyclopentadiene **14** was submitted to an initial 30–70-min $HgCl_2$ cyclization step, the intermediate vinyl mercurial could be intercepted with *N*-bromo- or *N*-iodosuccinimide (1.1 equiv of NBS, 2 equiv of DMAP; or 1.1 of equiv NIS, 2 equiv of NaI; 0 °C to room temperature; 4–16 h) to afford, after workup and chromatography, an isomerically homogeneous vinyl bromide (**16**) or iodide (**17**) in 78–91% yields from enone **13**. On the basis of our misinterpretation of the results of the isotopic substitution experiments described below, the single vinyl halide isomers obtained in each case were originally assigned the same stereochemistry as the monocarbocyclic adducts reported by Drouin et al.[6]—with the vinyl substituent syn to the carbonyl. However, as detailed later, the opposite stereochemistry actually resulted.[14]

At this stage in our effort, existing synthetic technology suggested that elaboration of the presumptive (*E*)-vinyl iodide **17** into the diene moiety of the didemnenones could be accomplished by a transition-metal-catalyzed coupling with an organometallic reagent such as a vinylmagnesium,[15] -zinc,[16] or -cuprate[17] species. However, the unique mildness and low nucleophilicity generally associated with palladium-catalyzed reactions employing alkenylstannanes[18] seemed to offer a potential for executing a direct cross-coupling without recourse to enone protection. When vinyl iodide **17** was subjected to palladium-catalyzed vinyl coupling under enol trifluoromethanesulfonate–vinyl tin cross-coupling conditions (tri-*n*-butylvinylstannane, catalytic $(Ph_3P)_4Pd$, and LiCl in refluxing THF for 5 h),[19] a single diene (**18**) was obtained in 75% yield after workup and silica gel chromatography. Subsequent to this early study, Stille and Groh[20] reported that similar palladium-catalyzed couplings could be accomplished with complete retention of configuration in both coupling partners at room temperature using various Pd catalysts and DMF as solvent. Consequently, when these milder conditions were employed (tri-*n*-butylvinylstannane, catalytic $(Ph_3P)_2PdCl_2$, DMF, 23–24 °C, 12 h), the same single diene **18** was obtained.[21] Considering that **18** bore the complete and stereochemically correct carbon framework of the didemnenones, two synthetic tasks appeared to remain: liberation of the primary alcohol and introduction of the

Scheme III[a]



[a] Conditions are as follows: (a) 1-methoxy-1,2-propadiene, NBS, CH_2Cl_2, −25 °C to room temperature, 4 h, 81%; (b) $NaNH_2$, NH_3, 31% **20**, 40% **21**; (c) *n*-Bu_4NF, THF, room temperature, 16 h, 76%; (d) pyridinium dichromate, CH_2Cl_2, room temperature, 6 h, 98%; (e) tBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 30 min; (f) (*i*) $HgCl_2$, HMDS, CH_2Cl_2, room temperature, 40 min; (*ii*) NIS, NaI, −20 °C to room temperature, 12 h, 57%, **24**:**25** (ca. 1:1); (g) *n*-$Bu_3SnCHCH_2$, $(Ph_3P)_2PdCl_2$, DMF, 23–24 °C, 18 h, 71–78%.

C11-acetal oxidation level of didemnenones A and B. While the former transformation could be smoothly effected by treatment of **18** with $FeCl_3$–Ac_2O[22] followed by cleavage of the resulting primary acetate (K_2CO_3 or TsOH, MeOH), accomplishing the latter task proved to be more problematic.

C11 Oxidation Level: Mixed-Acetal Approaches. All attempts to introduce the C11 oxidation level of didemnenones A and B by direct oxidation of diene **18** to an allylic acetal or hemiacetal, including allylic bromination–methanolysis/hydrolysis; thermal, photolytic, and metal initiated *tert*-butyl perbenzoate;[23] selenium dioxide;[24] and ceric triethylammonium nitrate–alcohol[25] reactions, were unsuccessful. In considering alternatives to direct oxidation, we pondered whether the silyl enol ether of a cyclopentenone bearing a β'-propargyl *acetal* would also undergo the key C6–C7 bond-forming reaction. If so, cyclization, iodinolysis, and vinyl cross-coupling as already performed should afford the fully elaborated didemnenone skeleton.

Attempts to form a mixed acetal by mineral acid, acidic ion-exchange resin, or lanthanide[26]-catalyzed trans-acetalizations between diethoxy or dimethoxy propynal acetals and tertiary alcohol **9** were only marginally effective. However, tertiary alcohol **9** added to methoxyallene[27] under the influence of *N*-bromosuccinimide (CH_2Cl_2, −25 °C to room temperature, 4 h) to afford the sensitive, epimeric vinyl bromide acetals **19** in 81% yield after chromatography (Scheme III). Attempted dehydrodehalogenations under phase-transfer conditions[28] gave unsatisfactory results, but treatment of **19** with sodium amide in liquid ammonia, followed by workup and chromatography, gave acetylenic silyl ether **20** (31%) and alcohol **21** (40%). Subsequent fluoride treatment of **20** yielded **21** in 76% isolated yield. Pyridinium dichromate oxidation provided anomeric mixed-acetal enones **22**, which upon conversion to corresponding silyl enol ether **23** and subsequent intramolecular alkyne carbomercuration and

(14) The structures of **17** and the corresponding primary acetate **39** were incorrectly assigned in ref 5. As described in this paper, they have been shown to be the corresponding (*Z*)-vinyl iodides, rather than the *E* isomers depicted as compounds **10** and **11** in ref 5.

(15) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191–194.

(16) Negishi, E. I.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.

(17) Jabri, N.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1983**, *11–12*, 321–333.

(18) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

(19) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

(20) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.

(21) Overlap of the C4, C8, and C9 proton resonances in the ^1H NMR spectrum of **18** precluded NOE measurements to substantiate the diene configuration.

(22) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728–3730.

(23) Lawesson, S. O.; Berglund, C. *Ark. Kemi* **1961**, *17*, 475–484; Sosnovsky, G. *Tetrahedron* **1965**, *21*, 871–880.

(24) (a) Substoiciometric SeO_2 oxidations were attempted: Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528. (b) Stoichiometric SeO_2 oxidations were attempted: Bhalerano, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835–4840.

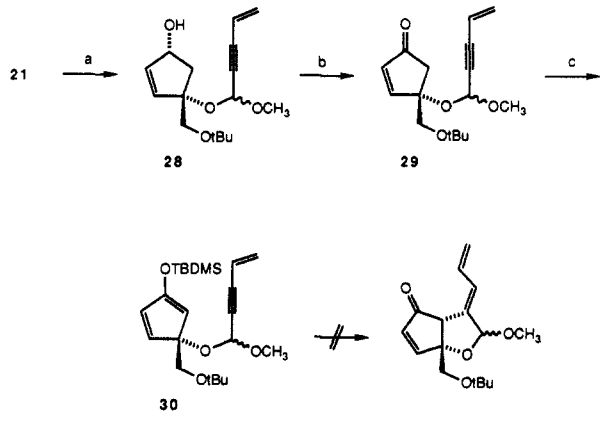
(25) Maione, A. M.; Romeo, A. *Synthesis* **1987**, *3*, 250–251.

(26) Luche, J. M.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976–977.

(27) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916–924. For similar additions to alkoxyallenes see refs 10g and 10h.

(28) Gorgues, A.; Le Coq, A. *Tetrahedron Lett.* **1976**, 4723–4724.

Scheme IV[a]



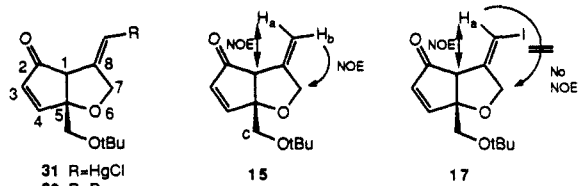
[a] Conditions are as follows: (a) CH_2CHBr, $(Ph_3P)_4Pd$, *n*-$PrNH_2$, CuI, C_6H_6, 10 °C to room temperature, 16 h, 96%; (b) pyridinium dichromate, CH_2Cl_2, room temperature, 18 h, 70%; (c) tBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 30–60 min.

iodinolysis gave (*Z*)-acetals **24** and **25** (ca. 1:1 ratio and 57% combined yield from **22**) as well as several unidentified minor products. Palladium-mediated vinyl cross-couplings of **24** and **25** with tri-*n*-butylvinylstannane[20] separately delivered corresponding (*Z*)-dienes **26** and **27** whose C8 and C11 geometries were determined by comparison with **5** and **6**.[29] Thus, although the mixed-acetal cyclization approach successfully introduced the desired C11 oxidation level, the stereochemical course of the cyclization and halogenation sequence was opposite that reported for the monocarbocyclic case[6] and gave bicyclic adducts that could not be directly elaborated into the (*E*)-diene moiety of the didemnenones. The present result was initially ascribed to a dual coordination of the mercuric salt with the alkyne and acetal oxygen that directed the cyclization through a trans addition to the alkyne side chain. However, the same stereochemical result was also actually obtained in the absence of the acetal methoxyl group (e.g., **14** → **17**).

In an attempt to exploit this apparent α-oxygen-directing effect for the synthesis of the didemnenones, and to further explore the scope and stereochemistry of the intramolecular alkyne carbomercuration reaction, mixed enyne acetal cyclization precursors were briefly examined. It was reasoned that if cyclization of a terminally substituted propargylic acetal could be effected, the stereochemistry of enol ether addition to the metal-coordinated alkyne observed for **23** would result in a tetrasubstituted exocyclic methylene group bearing a terminal substituent syn to the carbonyl and a mercuric salt anti to the α-keto carbon. Protolytic demercuration would then lead to the desired *E*-substituted alkene. The potential for succinctly installing the complete C7–C11 fragment containing the correct C11 oxidation state in a single C6–C7 bond-forming process prompted the initial choice of a vinyl group as the terminal alkyne substituent.

Anomeric enyne acetals **28** were prepared in excellent isolated yield (96%) by Pd/CuI-catalyzed coupling of alkyne **21** with vinyl bromide (Scheme IV).[30] Oxidation to enone **29** followed by silyl enol ether formation gave fully functionalized putative cyclization precursor **30**, which embodied all of the functionality present in the target molecules. This enol ether, however, could not be induced to add to the disubstituted alkyne under the influence of mercuric chloride or more electrophilic mercuric salts. After 1–16 h was allowed for a cyclization of **30** to occur in the presence of either mercuric chloride, acetate, or trifluoroacetate, the CH_2Cl_2 reaction mixtures were treated with H_2O and Et_3N, with or without NaI and DMAP. Parent enone **29** and acetal hydrolysis product 4-(*tert*-butoxymethyl)-4-hydroxy-2-cyclopentenone were the major identifiable products isolated from these sequential carbomercuration–demercuration attempts. While the presence of an α-acetal alone significantly diminished the efficiency of the cyclization–halogenation sequence (cf. **14** vs **23**), the combination of terminal vinyl and α-methoxy substitution totally extinguished the alkyne's reactivity toward intramolecular carbomercuration.

Mercuric Salt Induced Cyclization: Stereochemistry and Scope. As alluded to above, the actual stereochemical course of the central mercuric chloride induced cyclization reaction of **14** is opposite of what was anticipated and initially assigned.[5,14] A combination of ^1H NMR and vinyl mercurial–deuterium exchange experiments served to unambiguously establish the exocyclic methylene stereochemistry of the cyclization products. First, the exocyclic vinyl proton resonances of cyclization product **15** were identified by their relative chemical shifts and the following difference NOE results. Irradiation of the vinyl proton resonance at δ 5.16 (H_a) gave a 1.9% NOE enhancement of the bridgehead methine resonance at δ 3.15 (H1),[31] while irradiation of the δ 5.00 (H_b) alkene resonance enhanced the allylic ether methylene resonance at δ 4.42 (H7) by 1.4%, and irradiation at δ 3.15 (H1) increased both the δ 5.16 (δ 5.27 in $CDCl_3$, H_a, 1.2%) and the (*tert*-butoxymethyl)methylene δ 3.67 (H_c, 2.1%) resonances (acetone-d_6). Thus, consistent with their relative chemical shifts, H_a and H_b are the respective (*E*)- and (*Z*)-vinyl protons. Second, when silyl enol ether **14** was subjected to the same mercuric chloride cyclization reaction as performed in the preparation of **15** (1.0 equiv of $HgCl_2$, 0.2 equiv of HMDS, CH_2Cl_2, room temperature, 1 h), but presumptive intermediate vinyl mercurial **31** was treated with



a mixture of DCl and NaI in D_2O (ca. 2 equiv each of DCl and NaI, 0 °C 4 h, room temperature 12 h), single bicyclic deuteriomethylene product **32** was obtained in 84% yield after workup and chromatography. Examination of the ^1H NMR spectrum of **32** ($CDCl_3$) revealed that the terminal vinyl proton resonance at δ 5.00 (H_b) was diminished to <4% of its original value in **15**, while the δ 5.27 (H_a) resonance maintained its original integral value, indicating a stereospecific deuterium substitution for the *(Z)-vinyl proton* H_b. Third, since electrophilic iodinolysis and deuterolysis of vinyl mercurial **31** should both occur with retention of configuration,[11a] it could be presumed that mercurial **31** and iodide **17** share the same C8 configuration with deuteriomethylene **32**. NOE measurements substantiated this presumption in the case of crystalline vinyl iodide **17**. Irradiation of the bridgehead methine resonance at δ 3.20 (H1) of **17** gave an NOE enhancement of the iodovinyl proton resonance at δ 6.35 (H_a), and the *reverse irradiation at δ 6.35 enhanced only the δ 3.20 resonance*, confirming the syn disposition of vinyl proton H_a with respect to the bridgehead methine H1, a *Z* configuration in **17**, and implicating (*Z*)-vinyl mercurial cyclization product **31**.

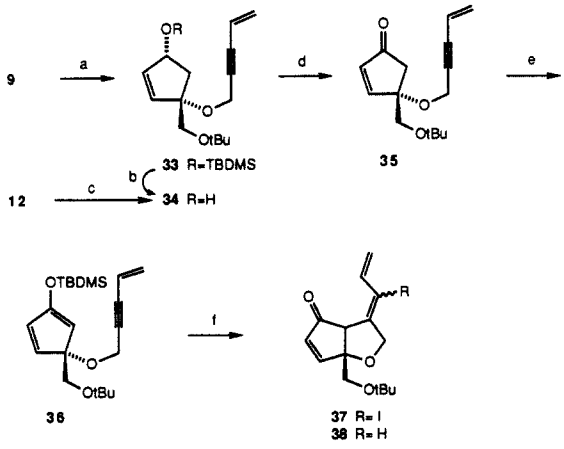
The results obtained here are in direct contrast with those reported for the monocarbocyclic case[6] and suggest a different mechanistic course. The present results are consistent with an intramolecular trans addition of the α-keto carbon to a metal-coordinated alkyne to afford (*Z*)-vinylmercurial **31**, which then may undergo electrophilic substitution with retention of configuration. In light of the previous work,[6] the most surprising feature of this antiselective intramolecular alkyne carbomercuration is the total exclusion of syn addition products. Several factors may be operative in excluding the alternative syn addition, including

(29) The ^1H NMR spectrum of **6**, as well as authentic samples of **1**, **2**, and **5**, was provided by Prof. W. Fenical and N. Lindquist, Scripps Institute of Oceanography.

(30) (a) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917–923. (b) Sonogashira, K.; Tohada, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (c) Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984**, *106*, 5734–5736.

(31) Numbering based on 8-methylene-6-oxa-*cis*-bicyclo[3.3.0]oct-3-en-2-one skeleton.

Scheme V[a]



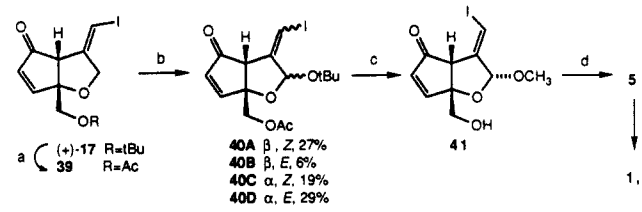
[a] Conditions are as follows: (a) 5-bromopent-1-en-3-yne, NaH, THF, 0 °C to room temperature, 19 h, 82%; (b) n-Bu_4NF, THF, room temperature, 10 h, 94%; (c) CH_2CHBr, $(Ph_3P)_4Pd$, CuI, t-$BuNH_2$ (1.2 equiv), C_6H_6, 10 °C to room temperature, 6 h, 93%; (d) pyridinium dichromate, CH_2Cl_2, room temperature, 6–12 h, 91–98%; (e) tBDMSOTf, Et_3N, CH_2Cl_2; 0 °C to room temperature, 30 min; (f) (*i*) $HgCl_2$, HMDS, CH_2Cl_2, 30–240 min, 23–35 °C; (*ii*) 5 M aqueous HCl, NaI, 0 °C to room temperature, 4–16 h, 20–26% **37**, 0% **38**.

an inhibition of mercuric coordination with the enol ether/carbonyl system due to structural/steric constraints in forming the *cis*-bicyclo[3.3.0]oct-3-en-2-one system, the presence of a potentially competitive Hg^{2+} coordinating propargylic oxygen, and the steric influence of the bulky *tert*-butyldimethylsilyl group. The instability of the trimethylsilyl enol ether analogue of **14** precluded its use in the cyclization reaction. Although the stereodirecting influence of an acetal oxygen–mercury coordination has been cited in an alkene oxymercuration,[32] such coordination does not enhance the carbomercuration of mixed propynal acetal **23** relative to **14**. The actual stereochemical course of the intramolecular carbomercuration–halogenation sequence involving **14** was masked by the randomization of alkene configuration that accompanied the introduction of the C11 oxidation level discussed below.

Once it was uncovered that propargyl ether **14** underwent the cyclization–halogenation sequence with anti selectivity, the tactic of employing a terminally substituted propargyl ether cyclization precursor (cf. enyne acetals **30**) was briefly explored. Although the combination of terminal and α-alkynyl substitution virtually eliminated the alkyne's reactivity toward cyclization in the case of **30**, the absence of the deactivating α-methoxy group (cf. **23** vs **14**) might have allowed a disubstituted acetylenic side chain to undergo intramolecular anticarbomercuration to afford the desired *E* adduct after protolytic demercuration.

Mirroring the preparation of **14**, the requisite enyne ether could be prepared by sequential alkylation of **9** with 5-bromopent-1-en-3-yne[33] to give ether **33**, desilylation to alcohol **34**, and oxidation to the unstable enone **35** in ca. 72% overall yield (Scheme V). Alternatively, treatment of alcohol **12** with vinyl bromide and $(Ph_3P)_4Pd$/CuI in benzene with a slight excess of dry *tert*-butylamine gave enyne **34** in 93% yield.[30c] Standard enol ether formation (TBDMSOTf, Et_3N, CH_2Cl_2) smoothly provided cyclopentadiene **36** from **35**, but subsequent sequential mercuric salt and hydrolysis treatments (5 M HCl, NaI, 0 °C to room temperature, 4–16 h) afforded mixtures of intractable compounds, although a single bicyclic adduct could be chromatographically isolated in minimal yields (ca. 20%). This compound was tenatively identified as C8 iodo diene **37**; conspicuously absent was corresponding protonated diene **38**. The presence of the terminal vinyl substituent alone was sufficient to severely inhibit the alkyne's

Scheme VI[a]



[a] Conditions are as follows: (a) $FeCl_3$, AcO_2, 0 °C, 1 h, 93%; (b) SeO_2, t-BuOOH, $ClCH_2CH_2Cl$, 83 °C, 8 h, 81% combined; (c) (*i*) MeOH, TsOH, room temperature, 84 h; (*ii*) chromatography, 24% from **39**; (d) n-BuSnCHCH$_2$, $(Ph_3P)_2PdCl_2$, DMF, 23–24 °C, 16 h, 72%; (e) HCl, THF/H_2O (2:1), 0 °C to room temperature, 2.75 h, 70%.

reactivity toward intramolecular carbomercuration.

The remaining problem of obtaining both the correct C11 oxidation level and C7-alkene configuration of the natural products **1** and **2** was finally resolved at the level of bicyclic vinyl iodide **17**, as outlined below.

Total Synthesis. We recognized that establishing the absolute configuration at the stereogenic tertiary center in cyclization precursor **14** would suffice for the enantiospecific construction of the *cis*-6-oxabicyclo[3.3.0]oct-3-en-2-one skeleton of didemnenones A and B through a cis ring fusion C6–C7 bond-forming cyclization. As previously noted, the key stereocenter could, in turn, be established in adduct **9** by 1,3 chirality transfer in the diastereofacial selective nucleophilic addition of (*tert*-butoxymethyl)lithium to nonracemic enone **10**. Since both enantiomers of **10** are available from the corresponding alcohols,[34] either enantiomer of **9**, and hence didemnenones A and B, would be accessible.

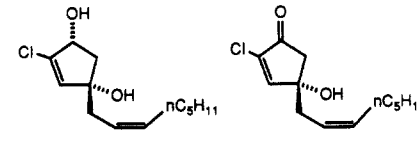
Silylation of *R*-enriched 4-hydroxy-2-cyclopentenone, obtained from (2*S*,3*S*)-(−)-tartaric acid by slight modification[1a] of the published procedure,[34a] gave (*R*)-**10** (ca. 94% ee). Reaction of (*R*)-**10** with (*tert*-butoxymethyl)lithium yielded the key chiral intermediate (1*S*,4*R*)-(+)-**9** in 75% yield, as well as the chromatographically separable but impure 1*R*,4*R*-enriched diastereomer (ca. 10%). As outlined in Scheme II, (1*S*,4*R*)-(+)-**9** was sequentially transformed into (+)-propargyl ether **11**, secondary alcohol **12**, and enone **13** ($[\alpha]^{21}_D$ +40.7° (*c* 0.988, $CHCl_3$)). The assigned stereochemistries of (+)-**9**–**13** are supported by comparison with compounds of known relative and absolute configurations.[35] Enone (*R*)-**13** was converted[13] into silyl enol ether **14**, which when subjected to successive one-pot intramolecular

(32) Carceller, E.; Castello, A.; Garcia, M. L.; Moyano, A.; Serratosa, F. *Chem. Lett.* **1984**, 775–778.

(33) Prepared in two steps from propargyl alcohol: (1) vinyl bromide, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, 0 °C, 7 h, 90% (ref 30b); (2) PBr_3, pyridine, Et_2O, 0 °C to room temperature, 2 h, 50%.

(34) (a) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1976**, 759–763. (b) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708–710. (c) Gill, M.; Rickards, R. W. *Tetrahedron Lett.* **1979**, 1539–1542. (*R*)-**10** is reportedly commercially available from Teijin Co. and Sumitomo Chemical Co., Japan. See also footnote 6 in ref 5 for additional references.

(35) (a) For example, the ^1H NMR and chiroptical data for (+)-(1*S*,4*R*)-**9** and enone (+)-**13** are in accord with that of the homochiral *cis*-1,4-dihydroxy-2-cyclopentene **iv** and the derived enone **v**, whose absolute stereo-



iv *v*

$[\alpha]_D^{15}$ +59.9°

chemistries have been secured by correlation to X-ray analysis: Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B. J.; Scheuer, P. J.; Noyori, R. *J. Org. Chem.* **1988**, *53*, 286–295. Conversely, the spectral data of minor diastereomer (1*R*,2*R*)-**9** and chiroptical data of enone (−)-**13** are incongruous with **iv** and **v**, respectively. Enone (−)-**13** was prepared from the major adduct ((−)-(1*R*,4*S*)-**9**) between (*tert*-butoxymethyl)lithium and (*S*)-(−)-**10** as described for (+)-**13** (see the Experimental Section). (b) For ^1H NMR analyses of *cis*- and *trans*-1,4-dihydroxy-2-cyclopentenes see: Cocu, F. G.; Wolczuniwicz, G.; Bors, L.; Posternak, Th. *Helv. Chim. Acta* **1970**, *53*, 739–749. (c) Haubenstock, H.; Mennit, P. G.; Butler, P. E. *J. Org. Chem.* **1970**, *35*, 3208–3210. Also see the supplementary material.

carbomercuration–iodinolysis reactions gave, after workup and chromatography, the crystalline bicyclic (*Z*)-vinyl iodide (2*R*,3*R*)-**17** ($[\alpha]^{21}_D$ +200.8° (*c* 0.779, $CHCl_3$)) in 91% overall yield from (*R*)-**13**. To reiterate, subsequent to the completion of the synthesis, the assigned C7-alkene stereochemistry was confirmed directly by NOE measurements and indirectly by deuterolysis of the intermediate vinylmercurial. Thus, although this advanced intermediate was prepared in a highly efficient manner from enone **10** (63% overall yield), its exocyclic methylene configuration was, unbeknown at the time, opposite of that of the didemnenones. Fortuitously, however, this bicyclic compound would still serve as a viable intermediate due to an unplanned randomization of the C7-alkene stereochemistry that occurred upon introduction of the C11-acetal oxidation level through direct allylic oxidation.

Preliminary work indicated that removal of the *tert*-butyl group from vinyl iodide **17** was best performed prior to allylic oxidation. Accordingly, smooth conversion of *tert*-butyl ether **17** into corresponding acetate **39** (93% yield) was accomplished with $FeCl_3$ in acetic anhydride (Scheme VI).[22] Extensive experimentation revealed that substoichiometric selenium dioxide oxidation[24a] of allylic ether **39** in the presence of excess dry *tert*-butyl hydroperoxide would yield a mixture of four (*E*,*Z*)-*tert*-butoxy acetals **40A–D** (81% combined yield, ^1H NMR). Although acetals **40A–D** could not be completely separated by repeated chromatography, pure samples of the two anomeric (*Z*)-vinyl iodides **40A** and **40C** were obtained, and, on the basis of chemical interconversions and spectral comparison with dienes 5 and 6,[29] the following stereochemical assignments were made: **40A**, β-anomer, (*Z*)-vinyl, 27% yield; **40B**, β, *E*, 6%; **40C**, α, *Z*, 19%; **40D**, α, *E*, 29%.

This oxidation was always accompanied by *E*–*Z* isomerization of the exocyclic methylene. Approximately the same distribution of products resulted regardless of the extent of reaction; however, at shorter reaction times and with the omission of an aqueous base wash in the workup, small amounts of the corresponding hemiacetals could also be isolated along with the acetals and starting allylic ether **39**. In situ formation of the *tert*-butoxy acetal would prevent further oxidation of a hemiacetal to a lactone[36] and protect the molecule from the base workup. No endocyclic alkene isomers were identified in the product mixtures, and no *E*–*Z* isomerization of the unoxidized starting allylic ether under the reaction conditions was ever detected in that only the original vinyl configuration prevailed in the recovered starting material.

Room-temperature treatment of the mixture of oxidation products **40** with catalytic *p*-toluenesulfonic acid in methanol effected both trans-acetalization and acetate cleavage (Scheme VI). The major (*E*)-methoxy acetal **41** (24% yield from **39**) could be separated from the methanolysis product mixture by careful chromatography. While iodo acetal **41** was quite unstable at room temperature, the corresponding diene (2*R*,6*R*,11*R*)-(+)-**5** ($[\alpha]^{21}_D$ +346.9° (*c* 0.179, $CHCl_3$, ca. 93% ee); natural product derivative **5**,[4] $[\alpha]_D$ +371.8° (*c* 0.86, $CHCl_3$)), obtained in 72% yield from the room-temperature $(Ph_3P)_2PdCl_2$-catalyzed coupling of **41** with tri-*n*-butylvinyltin in DMF,[20] formed a stable crystalline solid that matched (^1H NMR, ^{13}C NMR,[37] IR, UV, HRMS, TLC, melting point, sign of specific rotation, and crystallographic unit cell constants) acetal **5** derived from naturally occurring didemnenones A and B. Similar coupling with a bis(acetonitrile)palladium(II) chloride catalyst consumed all of the vinyl iodide present within 30 min but afforded **5** in a considerably lower yield. To complete the synthesis of (+)-didemnenones A and B, synthetic acetal (+)-**5** was subjected to acid-catalyzed hydrolysis to afford, after careful workup and Sephadex LH-20 chromatography, the base-sensitive hemiacetals (2*R*,6*R*)-(+)-**1** and **-2** as a 1:1 mixture of anomers and in 70% yield ($[\alpha]^{22}_D$ +515° (*c* 0.081, DMSO, ca. 89% ee); natural products **1** and **2**,[4] $[\alpha]_D$ +576.1° (*c* 0.49, DMSO)). The synthetic (+)-hemiacetals matched the natural product mixture by ^1H NMR, IR, UV, HRMS, TLC, and sign of specific rotation. The hemiacetals enriched in the opposite enantiomer ((2*S*,6*S*)-(−)-**1** and **-2**) were obtained from (*S*)-(−)-**10** via (2*S*,6*S*,11*S*)-(−)-**5** by the same route.

The excess enantiomers of synthetic (+)-**1** and **-2** and (+)-**5** have the same absolute configurations as their naturally derived counterparts. The absolute configurations at C2 and C6 are defined by the synthesis and are 2*R*,6*R* for (+)-**1** and **-2** and (+)-**5**. Since chiroptical comparison of lactone **7** derived from a mixture of **1** and **2** indicated that it is enantiomeric with lactone **8** similarly obtained from **3**,[4] it follows that triol **3** is 2*S*,6*S*, whereas **4** is most plausibly the α-keto epimer of **3** and has the 2*S*,6*R* configuration.

Conclusion

An efficient, flexible enantioselective synthetic route to didemnenones A and B was developed, which allowed assignment of the absolute configurations to didemnenones A–D. In the course of these studies, the scope of the mercuric chloride induced cyclization reaction[6] was further delineated. In contrast to previous reports,[5,6] it was found that, in forming a *cis*-6-oxabicyclo[3.3.0]oct-3-en-2-one system, cyclopentadienyl silyl enol ethers bearing ϵ-alkynes in the form of terminally unsubstituted propargylic ethers or acetals would undergo the reaction with apparently exclusive anti selectivity. Although the mechanism of this transformation was not investigated, the present results are consistent with an intramolecular trans addition of the α-keto carbon and mercuric chloride to the terminal ϵ-alkyne, rather than a syn-selective cyclization involving the intermediacy of a transient α-keto mercurial.[6] The only conditions that were found that would efficiently and regiospecifically oxidize the *Z* allylic ether cyclization products directly to an acetal or hemiacetal would only do so with concomitant *Z*–*E* isomerization of the exocyclic methylene. An efficient 1,3 chirality transfer in the diastereofacial selective 1,2-addition to nonracemic enone **10**, the remarkably mild palladium-mediated vinyl cross-coupling of Stille,[20] and the direct oxidation of an allylic ether to an acetal via modified Sharpless conditions[24a] contributed to the brevity of the natural products' synthesis, which spanned 11 steps from enone **10**. The enantiomeric flexibility of the synthesis was demonstrated by the separate preparations of antipodally enriched (+)- and (−)-didemnenones A and B; optically pure products could be obtained by the same route with homochiral **10**.

Experimental Section

(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopentenone ((+)-10). To a stirred solution of (*R*)-(+)-4-hydroxy-2-cyclopentenone[34a] (2.60 g, 26.5 mmol; $[\alpha]^{21}_D$ +79.9° (*c* 0.6835 g/100 mL, $CHCl_3$), $[\alpha]^{21}_D$ +93° (*c* 0.837 g/100 mL, MeOH)) in DMF (25 mL) at 0 °C and under argon were sequentially added diisopropylethylamine (10.17 mL, 58.4 mmol), *tert*-butyldimethylsilyl chloride (7.965 g, 53.1 mmol), and 4-(dimethylamino)pyridine (1.070 g, 8.75 mmol). The resulting solution was allowed to warm to room temperature and stir for 12 h, at which time TLC showed no remaining starting material. The clear, yellow-brown reaction mixture was diluted with diethyl ether (200 mL) and washed with H_2O (100 mL), saturated aqueous NH_4Cl (100 mL), and saturated aqueous NaCl (100 mL) before being dried over Na_2SO_4, filtered, and concentrated to a yellow oil. Chromatography (100 g SiO_2, hexanes–ethyl acetate, 9:1) and subsequent fractional vacuum distillation yielded (+)-**10** (3.03 g, 14.3 mmol, 54%) as a white solid that matched previously reported material:[38,34c] mp 28–29 °C; $[\alpha]^{21}_D$ +62.8° (*c* 2.495 g/100 mL, MeOH, ca. 94% ee) [lit.[34c] mp 30–31 °C, $[\alpha]^{22}_D$ +67° (*c* 0.117, MeOH, 100% ee)].

Silylation of (*S*)-(−)-4-hydroxy-2-cyclopentenone[34a] ($[\alpha]^{24}_D$ −68.7° (*c* 0.184 g/100 mL, $CHCl_3$, ca. 85% ee)) with *tert*-butyldimethylsilyl trifluoromethanesulfonate and diisopropylethylamine gave (−)-**10** of lower optical purity; $[\alpha]^{23}_D$ −43.6° (*c* 0.184 g/100 mL, MeOH, ca. 65% ee).

(1*S*,4*R*)-1-(*tert*-Butoxymethyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-ol ((+)-9). A solution of *sec*-butyllithium in cyclohexane (24.84 mL of 0.93 M, 23.1 mmol) was added dropwise over 30 min to a well-stirred suspension of potassium *tert*-butoxide (2.67 g of 97%, 23.1 mmol) in *tert*-butyl methyl ether (120 mL) under argon at −78 °C. The

(36) SeO_2 oxidation (according to ref 24a) reportedly gave only an α-methylene-γ-butyrolactone from the corresponding ether: Hanessian, S.; Beaulieu, P.; Dube, D. *Tetrahedron Lett.* **1986**, *27*, 5071–5074.

(37) The ^{13}C assignments for C4 and C9 of compound **5** reported in footnote 6 of ref 4 should be reversed.

(38) Tanaka, T.; Kurozumi, S.; Toru, T.; Miura, S.; Kobayshi, M.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1713–1718.

resulting bright yellow-orange mixture was stirred for 2 h at −78 °C before a solution of 2 M LiBr in THF (23.10 mL, 46.20 mmol) was added. The resulting yellow suspension was warmed to −10 °C, stirred at that temperature for 30 min, and then recooled to −78 °C. A solution of (+)-**10** (3.50 g, 16.5 mmol) in THF (10 mL) was added, and the resulting white suspension was stirred at −78 °C for 5 min before a saturated aqueous solution of NH_4Cl (20 mL), adjusted to pH 8.0 with NH_4OH, was added and the mixture allowed to warm to room temperature. The clear, colorless organic phase was separated, and the aqueous phase was extracted with diethyl ether (20 mL). The combined organic fractions were washed with H_2O (2 × 100 mL) and saturated aqueous NaCl (100 mL) before being dried over $MgSO_4$, filtered, and concentrated to a pale yellow oil (5.21 g). ^1H NMR analysis of this material indicated a 7:1 ratio of diastereomeric adducts (CH_2O-*t*-Bu at δ 3.21 ((1*S*,4*R*)-(+)-**9**) and δ 3.40 ((1*R*,4*R*)-**9**). Simple column chromatography (240 g of SiO_2, hexanes–ethyl acetate, 5:1) afforded (1*S*,4*R*)-(+)-**9** (3.69 g, 12.3 mmol, 75%) as a white solid, and repeated chromatography (SiO_2, CH_2Cl_2) gave the impure 1*R*,4*R* diastereomer (0.512 g, ca. 1.71 mmol, 10%) as a colorless oil.

(1*S*,4*R*)-(+)-**9**: mp 39.5–40 °C; $[\alpha]^{21}_D$ +79.6° (*c* 0.950 g/100 mL, $CHCl_3$); IR ($CHCl_3$) 3625–3100, 2860, 1475, 1464, 1367, 1255, 1135, 940 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.82 (s, 2 H, C2,3-H), 4.68 (m, 1 H, C4-H), 3.21 (s, 2 H, OCH_2), 2.46 (dd, *J* = 13.3, 7.0 Hz, 1 H, C5-H*β*), 2.4–2.1 (br s, 1 H, OH), 1.71 (dd, *J* = 13.3, 5.1 Hz, 1 H, C5-H*α*), 1.16 (s, 9 H, O-*t*-Bu), 0.87 (s, 9 H, Si-*t*-Bu), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 136.8 (C2), 136.2 (C3), 82.4 (C1), 75.1 (C4), 73.1 ($OC(CH_3)_3$), 67.8 (OCH_2), 46.3 (C5), 27.5 ($OC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.6 ($Si(CH_3)_2$); EIMS 299 (M − 1, 1.3%), 283 (M + 1 − H_2O, 1.4), 243 (M − C_4H_9, 1.6), 227 (M − C_4H_9O, 6.5), 213 (8.9), 75 (50.0), 57 (C_4H_9, 100); CIMS 283 (0.5), 245 (0.4), 243 (0.1), 227 (3.3), 95 (100); HRMS exact mass for $C_{12}H_{23}O_3Si$ (M − C_4H_9), calcd 243.1416, found 243.1419. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.43; H, 10.86.

(1*R*,4*R*)-**9**: IR ($CDCl_3$) 3560, 3060, 2995, 2965, 2940, 2870, 1475, 1315, 1250, 1065, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.82–5.93 (m, 2 H, C2,3-H), 4.97–5.07 (m, 1 H, C4-H), 3.40 (s, 2 H, OCH_2), 2.19 (dd, *J* = 14.8, 7 Hz, 1 H, C5-H*β*), 1.72 (dd, *J* = 14.8, 4 Hz, 1 H, C5-H*α*), 1.18 (s, 9 H, O-*t*-Bu), 0.88 (s, 9 H, Si-*t*-Bu), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 137.1 (C2), 136.3 (C3), 83.4 (C1), 76.0 (C4), 73.1 ($OC(CH_3)_3$), 68.4 (OCH_2), 45.6 (C5), 27.5 ($OC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.7 ($Si(CH_3)_2$); EIMS 243 (1.4), 241 (6.2), 227 (0.5), 213 (23.3), 75 (97.3), 73 (72.3), 57 (100).

(1*R*,4*S*)-(−)-**9** was similarly prepared from (*S*)-(−)-**10** and (*tert*-butoxymethyl)lithium; $[\alpha]^{23}_D$ −47.9° (*c* 0.7265 g/100 mL, $CHCl_3$).

(1*S*,4*R*)-1-(*tert*-Butoxymethyl)-4-[(*tert*-butyldimethylsilyl)oxy]-1-(2-propynyloxy)-2-cyclopentene ((+)-11). To a stirred solution of (1*S*,4*R*)-(+)-**9** (4.70 g, 15.8 mmol) in THF (150 mL) at 0 °C was added NaH (1.520 g, 63.2 mmol). The resulting mixture was allowed to warm to room temperature over 20 min. Propargyl bromide (11.75 g of 80% solution in toluene, 79.0 mmol) was added, and the mixture was stirred at room temperature for 40 h. H_2O (5 mL) was cautiously added over 20 min, and then the mixture was diluted with hexane (300 mL) and washed with H_2O (2 × 200 mL) and saturated aqueous NaCl (200 mL). Drying over Na_2SO_4, filtration, and concentration gave a dark oil that was chromatographed (120 g SiO_2, hexanes–ethyl acetate, 9:1) to give (+)-**11** as a clear oil (5.125 g, 15.16 mmol, 96%): $[\alpha]^{21}_D$ +37.6° (*c* 0.593 g/100 mL, $CHCl_3$); IR (neat) 3280, 2940, 2915, 2845, 1368, 1315, 1050, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.96 (dd, *J* = 6, 2 Hz, 1 H, C2-H), 5.76 (d, *J* = 6 Hz, 1 H, C3-H), 4.68 (m, 1 H, C4-H), 4.14 (t, *J* = 3 Hz, 2 H, C1′-H,H), 3.40 (d, *J* = 9.2 Hz, 1 H, CH_2O-*t*-Bu), 3.34 (d, *J* = 9.2 Hz, 1 H, CH_2O-*t*-Bu), 2.38 (dd, *J* = 14, 7 Hz, 1 H, C5-H), 2.37 (t, *J* = 3 Hz, 1 H, C3′-H), 1.76 (dd, *J* = 14, 4 Hz, 1 H, C5-H), 1.13 (s, 9 H, O-*t*-Bu), 0.89 (s, 9 H, Si-*t*-Bu), 0.08 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 139.2 (C2), 134.1 (C3), 89.9 (C2′), 81.7 (C1), 75.0 (C4), 73.1 ($OC(CH_3)_3$), 72.8 (C3′), 66.9 (CH_2O-*t*-Bu), 51.6 (C1′), 41.5 (C5), 27.4 ($OC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −5.2 ($SiCH_3$), −4.2 ($SiCH_3$); EIMS 338 (M^+, 0.3), 283 (M − C_3H_3O, 2.0), 282 (1.9), 281 (M − C_4H_9, 5.15), 251 (M − $C_5H_{11}O$, 100); HRMS exact mass for $C_{15}H_{25}O_3Si$ (M − C_4H_9) calcd 281.1573, found 281.1589.

Ether formation with (1*R*,4*S*)-(−)-**9** under the same conditions gave (−)-**11**, $[\alpha]^{23}_D$ −32° (*c* 0.27 g/100 mL, $CHCl_3$).

(1*S*,4*R*)-1-(*tert*-Butoxymethyl)-1-(2-propynyloxy)-2-cyclopenten-4-ol ((+)-12). To a stirred solution of (+)-**11** (2.590 g, 7.663 mmol) in THF (75 mL) at room temperature was added a solution of tetra-*n*-butylammonium fluoride in THF (8.36 mL of 1.1 M, 9.20 mmol). The resulting solution was stirred at room temperature for 3.5 h before the solvent was removed by rotary evaporation. The residue was suspended in diethyl ether (100 mL) and washed with H_2O (2 × 100 mL) and then saturated aqueous NaCl (100 mL). Drying over Na_2SO_4, filtration, and concentration gave an orange oil that was chromatographed (60 g of SiO_2, hexane–ethyl acetate, 2:1) to provide (+)-**12** (1.651 g, 7.371 mmol, 96%) as a clear, pale yellow oil: $[\alpha]^{21}_D$ +40.9° (*c* 1.437 g/100 mL, $CHCl_3$); IR (neat) 3640–3110, 3290, 3055, 2120, 1780, 1465, 1385, 1365, 1248, 1197, 1050, 620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.08 (dd, *J* = 6, 3 Hz, 1 H, C2-H), 5.90 (d, *J* = 6 Hz, 1 H, C3-H), 4.69 (m, 1 H, C4-H), 4.18 (d, *J* = 3 Hz, 2 H, C1-H,H′), 3.42 (d, *J* = 9 Hz, 1 H, CH_2O-*t*-Bu), 3.34 (d, 9, 1 H, CH_2O-*t*-Bu), 3.0–2.8 (br s, 1 H, OH), 2.46 (dd, *J* = 14, 7 Hz, 1 H, C5-H*β*), 2.39 (t, *J* = 3 Hz, 1 H, C3′-H), 1.82 (dd, *J* = 14, 4 Hz, 1 H, C5-H*α*), 1.13 (s, 9 H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 138.5 (C2), 135.4 (C3), 89.8 (C2′), 81.6 (C1), 75.0 (C4), 73.6 ($C(CH_3)_3$), 72.9 (C3′), 66.7 (CH_2O-*t*-Bu), 51.8 (C1′), 41.7 (C5), 27.4 ($C(CH_3)_3$); EIMS 167 (M − C_4H_9, 0.9), 137 (M − $C_5H_{11}O$, 100), 57 (C_4H_9, 64.8); CIMS 224 (M^+, 0.1), 223 (1.2), 207 (22.4), 95 (100); HRMS exact mass for $C_9H_{11}O_3$ (M − C_4H_9), calcd 167.0708, found 167.0705.

Desilylation of (−)-**11** similarly gave (−)-**12**, $[\alpha]^{23}_D$ −34.8° (*c* 0.3305 g/100 mL, $CHCl_3$).

(4*R*)-4-(*tert*-Butoxymethyl)-4-(2-propynyloxy)-2-cyclopentenone ((+)-13). Pyridinium dichromate (5.531 g, 14.41 mmol) was added to a solution of (+)-**12** (2.934 g, 13.10 mmol) in CH_2Cl_2 (100 mL), and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through SiO_2 (25 g) under partial aspirator vacuum along with additional CH_2Cl_2 (3 × 100 mL) washes. The combined filtrate and washes were concentrated, and the residual oil was chromatographed on SiO_2 (100 g, hexane–ethyl acetate, 4:1) to yield (+)-**13** (2.743 g, 12.36 mmol, 94%) as a clear, colorless oil: $[\alpha]^{21}_D$ +40.7° (*c* 0.988 g/100 mL, $CHCl_3$); IR (neat) 3262, 3065, 2112, 1715, 1584, 1460, 1385, 1360, 1233, 1189, 1054, 620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.50 (d, *J* = 5.8 Hz, 1 H, C3-H), 6.29 (d, *J* = 5.8 Hz, 1 H, C2-H), 4.15 (d, *J* = 3.0 Hz, 2 H, C1′-H,H′), 3.59 (d, *J* = 9.6 Hz, 1 H, CH_2O-*t*-Bu), 3.47 (d, *J* = 9.6 Hz, 1 H, CH_2O-*t*-Bu), 2.59 (d, *J* = 18.4 Hz, 1 H, C5-H), 2.50 (d, *J* = 18.4 Hz, 1 H, C5-H′), 2.43 (t, *J* = 3.0 Hz, 1 H, C3′-H), 1.14 (s, 9 H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 205.8 (C1), 162.4 (C3), 136.5 (C2), 84.8 (C2′), 80.5 (C4), 74.6 (C3′), 73.5 ($C(CH_3)_3$), 65.7 (CH_2O-*t*-Bu), 52.6 (C1′), 42.5 (C5), 27.3 ($C(CH_3)_3$); EIMS 149 (M − C_4H_9O, 4.9), 136 (M − $C_5H_{10}O$, 67.8), 135 (M − $C_5H_{11}O$, 30.8), 97 (100), 57 (C_4H_9, 94.5); CIMS 221 (M − 1, 1.2), 183 (M − C_3H_3, 4.7), 167 (M − C_3H_3O, 4.9), 165 (M − C_4H_9, 3.7), 149 (6.3), 95 (100); HRMS exact mass for $C_9H_9O_2$ (M − C_4H_9O), calcd 149.0603, found 149.0606.

Oxidation of (−)-**12** under the same conditions gave (−)-**13**, $[\alpha]^{23}_D$ −31.4° (*c* 0.7715 g/100 mL, $CHCl_3$).

(1*R*,5*R*)-5-(*tert*-Butoxymethyl)-8(*Z*)-(iodomethylene)-6-oxa-*cis*-bicyclo[3.3.0]oct-3-en-2-one ((+)-17). Triethylamine (2.49 mL, 17.8 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.28 mL, 3.77 g, 14.3 mmol) were sequentially added to a stirred, 0 °C solution of (+)-**13** (2.640 g, 11.89 mmol) in CH_2Cl_2 (50 mL) under argon. The clear, yellow solution was stirred at 0 °C for 15 min and then allowed to warm to room temperature with continued stirring for an additional 45 min. Removal of the volatile components under vacuum left a biphasic liquid residue that was extracted with anhydrous diethyl ether (2 × 10 mL) under dry argon. Concentration of the ether extracts provided (*R*)-**14** (3.877 g) as an orange oil: IR ($CHCl_3$) 3310, 1620, 1475, 1365, 1295, 1250, 1175, 1055, 1028, 945, 840, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.25 (dd, *J* = 5.6, 2 Hz, 1 H, C3-H), 6.04 (d, *J* = 5.6 Hz, 1 H, C4-H), 4.99 (br s, 1 H, C1-H), 4.00 (d, *J* = 2.4 Hz, 2 H, OCH_2CCH), 3.53 (d, *J* = 10 Hz, 1 H, CH_2O-*t*-Bu), 3.41 (d, *J* = 10 Hz, 1 H, CH_2O-*t*-Bu), 2.37 (t, *J* = 2.4 Hz, 1 H, OCH_2CCH), 1.15 (s, 9 H, O-*t*-Bu), 0.93 (s, 9 H, Si-*t*-Bu), 0.20 (s, 6 H, $Si(CH_3)_2$).

A solution of crude (*R*)-**14** (3.852 g, ca. 11.46 mmol) and hexamethyldisilazane (0.502 mL, 384 mg, 2.38 mmol) in CH_2Cl_2 (10 mL) was added to a well-stirred suspension of $HgCl_2$ (3.122 g, 11.50 mmol) in CH_2Cl_2 (40 mL) at 30 °C under argon. After 5 min all of the suspended $HgCl_2$ had dissolved to afford a clear, red-brown solution, which was stirred at 30–32 °C for a total of 70 min under argon. ^1H NMR analysis in a separate experiment indicated that **14** was completely converted within 10 min into the presumptive bicyclic intermediate 5-(*tert*-butoxymethyl)-8-(mercurivinyl)-6-oxa-*cis*-bicyclo[3.3.0]oct-3-en-2-one (**31**): ($CDCl_3$, 200 MHz) δ 7.46 (d, *J* = 6 Hz, 1 H, C4-H), 6.29 (m, 1 H, C=C*H*HgCl), 6.23 (d, *J* = 6 Hz, 1 H, C3-H), 4.46 (apparent d, *J* = 1 Hz, 2 H, C7-H,H′), 3.67 (d, *J* = 9 Hz, 1 H, CH_2O-*t*-Bu), 3.59 (d, *J* = 9 Hz, 1 H, CH_2O-*t*-Bu), 3.30 (br s, 1 H, C1-H), 1.14 (s, 9 H, *t*-Bu). The reaction mixture was cooled to 0 °C, and *N*-iodosuccinimide (2.675 g, 11.89 mmol) and powdered NaI (3.564 g, 23.78 mmol) were added. The resulting suspension was allowed to warm to room temperature, and stirring was continued for 4.0 h under argon. Solid 4-(dimethylamino)pyridine (1.453 g, 11.89 mmol) was added, and the mixture was stirred for an additional 15 min before it was filtered through a fritted glass funnel under aspirator vacuum. The remaining solids were washed with CH_2Cl_2 (3 × 50 mL), and the combined filtrate and washings were washed with 1% aqueous HCl (2 × 100 mL), H_2O (100

mL), and saturated aqueous NaCl (100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to a yellow oil. Chromatography (120 g SiO_2, hexanes–ethyl acetate, 4:1) and removal of residual silanol under vacuum afforded (+)-**17** (3.749 g, 10.77 mmol, 91% from **13**) as a crystalline solid: mp 94–96 °C (EtOH); $[\alpha]^{21}_D$ +200.8° (*c* 0.779 g/100 mL, $CHCl_3$); IR ($CHCl_3$) 2967, 1724, 1640, 1367, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41 (d, *J* = 5.72 Hz, 1 H, C4-H), 6.35 (dd, *J* = 4, 2 Hz, 1 H, C9-H), 6.16 (d, *J* = 5.72 Hz, 1 H, C3-H), 4.53 (dd, *J* = 14.2, 2.2 Hz, 1 H, C7-H), 4.26 (apparent dt, *J* = 14.2, 2.2 Hz, 1 H, C7-H′), 3.63 (d, *J* = 9.2 Hz, 1 H, C10-H), 3.57 (d, *J* = 9.2 Hz, 1 H, C10-H′), 3.20 (apparent t, *J* = 2 Hz, 1 H, C1-H), 1.13 (s, 9 H, *t*-Bu), irradiation at δ 3.20 enhanced the δ 6.35 peak, and irradiation at δ 6.35 enhanced only the δ 3.20 resonance; ^{13}C NMR ($CDCl_3$) δ 201.6 (C2), 161.9 (C4), 146.2 (C8), 134.1 (C3), 93.7 (C5), 76.0 (C=*C*HI), 73.5 (*C*(CH_3)$_3$), 70.8 (C7), 64.6 (*C*H_2O-*t*-Bu), 57.6 (C1), 27.3 (C(*C*H_3)$_3$); EIMS 292 (M − C_4H_8, 12.1), 291 (M − C_4H_9, 9.7), 57 (C_4H_9, 100); CIMS 349 (M + 1, 27.4), 348 (M^+, 7.3), 347 (M − 1, 42.5), 293 (100); HRMS exact mass for $C_9H_8IO_3$ (M − C_4H_9), calcd 290.9520, found 290.9592. Anal. Calcd for $C_{13}H_{17}IO_3$: C, 44.85; H, 4.92; I, 36.45. Found: C, 44.60; H, 4.83; I, 36.32.

Successive enol ether formation, $HgCl_2$-induced cyclization, and iodinolysis of (−)-**13** similarly afforded (−)-**17**, $[\alpha]^{23}_D$ −198.1° (*c* 1.669 g/100 mL, $CHCl_3$).

(1*R*,5*R*)-5-(Acetoxymethyl)-8(*Z*)-(iodomethylene)-6-oxa-*cis*-bicyclo[3.3.0]oct-3-en-2-one ((+)-39). To a stirred 0 °C solution of (+)-**17** (3.700 g, 10.63 mmol) in acetic anhydride (20.0 mL) under argon was added anhydrous ferric chloride (50 mg). The resulting deep red-purple mixture was stirred for 1 h at 0 °C under argon. The reaction mixture was then diluted with diethyl ether (200 mL) and poured into an ice–water mixture (200 mL). The separated organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 200 mL), H_2O (200 mL), and saturated aqueous NaCl (100 mL) before being dried over $MgSO_4$. Filtration and concentration gave an oil that was chromatographed repeatedly on silica gel (hexanes–ethyl acetate, 3:1) to afford (+)-**39** (3.147 g, 9.896 mmol, 93%) as pale yellow solid: mp 63 °C; $[\alpha]^{21}_D$ +194.8° (*c* 0.854 g/100 mL, $CHCl_3$); IR ($CHCl_3$) 1748, 1725, 1640, 1080–1025, 1455, 1342, 1380, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41 (d, *J* = 5.71 Hz, 1 H, C4-H), 6.42 (dd, *J* = 4, 2 Hz, 1 H, C9-H), 6.24 (d, *J* = 5.71 Hz, 1 H, C3-H), 4.57 (dd, *J* = 14.4, 2.4 Hz, 1 H, C7-H), 4.37 (d, *J* = 15.6 Hz, 1 H, C*H*$_2$OAc), 4.28 (d, *J* = 15.6 Hz, 1 H, C*H*$_2$OAc), 4.26 (d m, *J* = 14.4 Hz, 1 H, C7-H′), 3.28 (m, 1 H, C1-H), 2.07 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 205.5 (C2), 170.4 (*C*(O)CH_3, 160.0 (C4), 145.3 (C8), 134.9 (C3), 92.4 (C5), 76.0 (C=*C*HI), 71.5 (C7), 65.5 (*C*H_2OAc), 57.3 (C1), 20.7 (CH_3); EIMS 334 (M^+, 1.4), 292 (5.4), 275 (4.5), 274 (34.6), 261 (15.9), 147 (74.0), 134 (55.0), 127 (1.4), 43 (100); CIMS 335 (M + 1, 100), 334 (M^+, 2.4), 333 (8.7), 293 (56.4), 275 (81.5), 207 (38.7), 128 (0.6), 127 (0.1); HRMS exact mass for $C_{11}H_{11}IO_4$, calcd 333.9704, found 333.9571.

Similar treatment of (−)-**17** yielded (−)-**39**: $[\alpha]^{23}_D$ −157.4° (*c* 1.006 g/100 mL, $CHCl_3$).

(1*R*,5*R*,7*R*)-5-(Hydroxymethyl)-8(*E*)-(iodomethylene)-7-methoxy-6-oxa-*cis*-bicyclo[3.3.0]oct-3-en-2-one ((+)-41). *tert*-Butyl hydroperoxide (0.810 g of 90% in *tert*-butyl alcohol–H_2O; ca. 0.729 g, 6.63 mmol peroxide) was dissolved in 1,2-dichloroethane (5.0 mL), and the solution was stirred over $MgSO_4$ (0.5 g) for 30 min. The clear solution was then filtered through glass wool into a well-stirred suspension of SeO_2 (0.1416 g, 1.276 mmol) in 1,2-dichloroethane (15.0 mL), and the resulting mixture was stirred for 30 min at room temperature. A solution of (+)-**39** (580 mg, 1.824 mmol) in 1,2-dichloroethane (5.0 mL) was then added, and the resulting clear, yellow suspension was heated at reflux in the dark for 8 h under a $CaSO_4$ drying tube. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL), and washed with 5% aqueous NaOH (2 × 25 mL), H_2O (2 × 25 mL), and saturated aqueous NaCl (25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to a clear, yellow oil (0.632 g). ^1H NMR analysis of this mixture showed four major oxidation products ((1*R*,5*R*,7*R*,*S*)-5-(acetoxymethyl)-8(*E*,*Z*)-(iodomethylene)-7-*tert*-butoxy-6-oxa-*cis*-bicyclo-[3.3.0]oct-3-en-2-ones, **40A–D**) and starting material, listed in order of chromatographic elution: **40A** (7*S*,8*Z*, 27%), **40B** (7*S*,8*E*, 6%), **39** (19%), **40D** (7*R*,8*E*, 29%), and **40C** (7*R*,8*Z*, 19%). Repetitive chromatography (SiO_2, hexane–ethyl acetate, 9:1 to 4:1) afforded pure samples of **40A** and **40C**. The remaining product mixture containing **40A–D** (427 mg) was dissolved in anhydrous methanol (20 mL). *p*-Toluenesulfonic acid monohydrate (50 mg) was added, and the resultant solution was stirred for 84 h at room temperature, while it was monitored by TLC. Addition of solid $NaHCO_3$ (50 mg) and careful rotary evaporation at room temperature gave a residue that was immediately applied to a SiO_2 column (40 g of SiO_2, hexanes–ethyl acetate, 3:1) and chromatographed to afford, in order of elution, 5-OH-**39**, (+)-**41** (138.6 mg, 0.4304 mmol, 24% from **39**), and (8*Z*)-**41** (impure) as colorless oils. Acetals **41** readily decompose upon standing at room temperature.

(+)-**41**: $[\alpha]^{21}_D$ +242.3° (*c* 0.456 g/100 mL, $CHCl_3$); IR ($CHCl_3$) 3610–3065, 1727, 1645, 1180–1107 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.52 (d, *J* = 6.3 Hz, 1 H, C4-H), 6.72 (d, *J* = 1.9 Hz, 1 H, vinyl-H), 6.18 (d, *J* = 6.3 Hz, 1 H, C3-H), 5.24 (s, 1 H, C7-H), 3.86 (d, *J* = 11.7 Hz, 1 H, OCH_2), 3.71 (d, *J* = 11.7 Hz, 1 H, OCH_2), 3.46 (d, *J* = 1.9 Hz, 1 H, C1-H), 3.25 (s, 3 H, OCH_3), 2.0–1.7 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 207.1 (C2), 160.3 (C4), 147.9 (C8), 135.1 (C3), 106.8 (C7), 92.8 (C5), 79.2 (C=*C*HI), 65.3 (*C*H_2OH), 55.7 (C1), 54.3 (OCH_3); EIMS 322 (M^+, 17.2), 195 (M − iodine, 23.5), 136 (100), 135 (56.9), 127 (4.8); HRMS exact mass for $C_{10}H_{11}IO_4$, calcd 321.9704, found 321.9715.

(8*Z*)-**41**: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.54 (d, *J* = 6.3 Hz, 1 H), 6.67 (apparent t, *J* = 1.6 Hz, 1 H), 6.19 (d, *J* = 6.3 Hz, 1 H), 5.36 (d, *J* = 1.6 Hz, 1 H), 3.87 (d, *J* = 11.8 Hz, 1 H), 3.64 (d, *J* = 11.8 Hz, 1 H), 3.41 (s, 3 H), 3.32 (t, *J* = 1.6 Hz, 1 H), 1.6–1.9 (br, 1 H). Upon palladium-catalyzed coupling with tri-*n*-butylvinyltin as described for **5** below, this compound gave (7*Z*)-**5**: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55 (d, *J* = 6 Hz, 1 H, C3-H), 6.20–6.48 (m; *J* = 11, 9 Hz, 2 H; C8,9-H), 6.17 (d, *J* = 6 Hz, 1 H, C4-H), 5.62 (s, 1 H, C11-H), 5.29 (d, *J* = 18 Hz, 1 H, C10-H$_Z$), 5.23 (d, *J* = 9 Hz, 1 H, C10-H$_E$), 3.88 (d, *J* = 11 Hz, 1 H, C1-H), 3.68 (d, *J* = 11 Hz, 1 H, C1-H′), 3.34 (s, 3 H, OCH_3), 3.31 (br s, 1 H, C6-H), 1.73 (br s, 1 H, OH).

(8*Z*)-**40A**: mp 120–121 °C; IR ($CDCl_3$) 3450, 3070, 2990, 2950, 1735, 1645, 1595, 1450, 1315, 1005, 920, 810, 795 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.50 (d, *J* = 5.7 Hz, 1 H), 6.89 (m, 1 H), 6.09 (d, *J* = 5.7 Hz, 1 H), 5.85 (apparent t, *J* = 1.6 Hz, 1 H), 4.60 (d, *J* = 10.9 Hz, 1 H), 4.43 (d, *J* = 10.9 Hz, 1 H), 3.31 (m, 1 H), 2.03 (s, 3 H), 1.29 (s, 9 H); ^{13}C NMR ($CDCl_3$) 200.8 (s, C5), 170.2 (s, *C*(O)CH_3), 160.6 (d, C3), 141.7 (s, C7), 133.1 (d, C4), 110.7 (d, C11), 91.9 (s, C2), 80.3 (d, C8), 77.1 (s, C12), 65.6 (t, C1), 55.0 (d, C6), 26.6 (q, C13), 20.6 (q, C(O)*C*H_3); EIMS 333 (M − C_4H_9O, 100), 291 (84.0), 273 (17.1), 164 (76.4), 146 (62.0), 128 (11.5), 127 (9.6); HRMS exact mass for $C_{11}H_{10}IO_4$ (M − C_4H_9O), calcd 332.9624, found 332.9615. This compound gave (8*Z*)-**41** upon treatment with methanol and TsOH.

(8*E*)-**40B**: ^1H NMR ($CDCl_3$, 200 MHz, mixture) δ 7.51 (d, *J* = 5.7 Hz, 1 H), 6.87 (apparent t, *J* = 1.6 Hz, 1 H), 6.21 (d, *J* = 5.7 Hz, 1 H), 5.80 (apparent t, *J* = 1.6 Hz, 1 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.33 (d, *J* = 11.4 Hz, 1 H), 3.54 (apparent t, *J* = 1.5 Hz, 1 H), 2.07 (s, 3 H), 1.25 (s, 9 H). In a separate experiment, a mixture of **40B** and **40D** devoid of **40A** and **40C** gave **41** upon acidic methanol treatment.

(8*Z*)-**40C**: IR ($CDCl_3$) 3050, 2990, 2945, 1735, 1645, 1605, 1465, 1315, 1005, 815, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.57 (d, *J* = 6 Hz, 1 H), 6.80 (m, 1 H), 6.19 (d, *J* = 6 Hz, 1 H), 5.89 (d, *J* = 1.1 Hz, 1 H), 4.37 (d, *J* = 13 Hz, 1 H), 4.27 (d, *J* = 13 Hz, 1 H), 3.26 (d, *J* = 2.0 Hz, 1 H), 2.04 (s, 3 H), 1.21 (s, 9 H); ^{13}C NMR ($CDCl_3$) 200.6 (C5), 170.3 (*C*(O)CH_3), 161.2 (C3), 143.0 (C7), 134.5 (C4), 109.5 (C11), 91.4 (C2), 81.1 (C8), 79.1 (C12), 65.3 (C1), 56.5 (C6), 26.6 (C13), 20.6 (C(O)*C*H_3); EIMS 334 (M + 1 − C_4H_9O, 13.1), 333 (M − C_4H_9O, 87.1), 332 (13.3), 291 (77.3), 273 (12.5), 164 (37.2), 146 (32.2), 128 (5.7), 127 (6.0), 57 (26.5), 43 (100); CIMS 333 (100), 307 (8.0), 291 (3.5), 89 (68.6), 73 (87.2). Anal. Calcd for $C_{15}H_{19}IO_5$: C, 44.35; H, 4.71. Found: C, 44.15; H, 4.61. This compound gave (8*Z*)-**41** upon methanolysis.

(8*E*)-**40D**: ^1H NMR ($CDCl_3$, 200 MHz, mixture) δ 7.53 (d, *J* = 5.7 Hz, 1 H), 6.88 (m, 1 H), 6.20 (d, *J* = 5.7 Hz, 1 H), 5.80 (d, *J* = 1.2 Hz, 1 H), 4.41 (d, *J* = 11 Hz, 1 H), 4.23 (d, *J* = 11 Hz, 1 H), 3.43 (d, *J* = 2 Hz, 1 H), 2.06 (s, 3 H), 1.15 (s, 9 H).

Successive SeO_2 and methanolysis treatment of (−)-**39** similarly gave (−)-**41**, $[\alpha]^{23}_D$ −183.1° (*c* 0.284 g/100 mL, $CHCl_3$).

(2*R*,6*R*,11*R*)-11-Methoxydidemnenone A ((+)-5). Bis(triphenylphosphine)palladium(II) chloride (3.5 mg, 50 μmol) was added to a magnetically stirred solution of (+)-**41** (32.2 mg, 100 μmol) in DMF (2.0 mL) at room temperature and under argon. The resulting yellow mixture was stirred for 15 min at room temperature before tri-*n*-butylvinyltin (76.2 μL, 253 μmol) was added. After the mixture was stirred for 16 h at room temperature under argon, 10% aqueous NH_4OH (2.0 mL) was added and the resultant mixture was stirred for an additional 15 min. The mixture was then extracted with diethyl ether (4 × 2 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to a yellow oil. Chromatography of this material on SiO_2 (10 g, hexanes–ethyl acetate, 3:1) gave (+)-**5** (16.02 mg, 72.16 μmol, 72%) as a crystalline solid that matched the natural product derivative.

Synthetic (+)-5: mp 127–128 °C; $[\alpha]^{21}_D$ +346.9° (*c* 0.179 g/100 mL, $CHCl_3$, ca. 93% ee); IR ($CDCl_3$) 3690, 3620-3180, 1724, 1605, 1250, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55 (d, *J* = 6 Hz, 1 H, C3-H), 6.85 (ddd, *J* = 17, 11, 10 Hz, 1 H, C9-H), 6.30 (dd, *J* = 11, 2 Hz, 1 H, C8-H), 6.17 (d, *J* = 6 Hz, 1 H, C4-H), 5.39 (d, *J* = 17 Hz, 1 H, C10-H), 5.36 (d, *J* = 10 Hz, 1 H, C10-H), 5.33 (s, 1 H, C11-H), 3.89 (dd, *J* = 12, 4 Hz, 1 H, C1-H), 3.70 (dd, *J* = 12, 8 Hz, 1 H, C1-H′),

3.61 (d, J = 2 Hz, 1 H, C6-H), 3.31 (s, 3 H, C12-H), 2.03 (m, 1 H, OH); ^{13}C NMR[37] (acetone-d_6) δ 203.5 (C5), 163.8 (C3), 139.0 (C7), 135.3 (C8), 134.4 (C4), 128.5 (C9), 120.2 (C10), 108.6 (C11), 94.7 (C2), 65.3 (C1), 54.2 (C12), 53.0 (C6); EIMS 222 (M^+, 15.1), 191 (M - OCH_3, 100), 160 (77.1), 103 (65.1), 77 (75.9); HRMS exact mass for $C_{12}H_{14}O_4$, calcd 222.0892, found 222.0889; UV (MeOH) λ_{max} 234 nm (ϵ = 19000); TLC (diethyl ether) R_f = 0.24, coelutes with natural product derivative; crystallographic unit cell constants a = 7.6658 (33) Å, b = 7.7295 (20) Å, c = 9.8184 (39) Å, β = 104.279 (32)°.

Natural product derivative 5:[4] mp 126-128 °C; $[\alpha]_D$ +371.8° (c 0.86, $CHCl_3$); IR ($CDCl_3$) 3690, 3550, 1720, 1215, 1075, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 5.5 Hz, 1 H), 6.85 (ddd, J = 17.0, 10.5, 10.5 Hz, 1 H), 6.30 (dd, J = 10.5, 2.0 Hz, 1 H), 6.17 (d, J = 5.5 Hz, 1 H), 5.39 (d, J = 17.0 Hz, 1 H), 5.36 (d, J = 10.5 Hz, 1 H), 5.33 (s, 1 H), 3.90 (dd, J = 11.0, 3.0 Hz, 1 H), 3.71 (dd, J = 11.0, 7.0 Hz, 1 H), 3.61 (d, J = 2.0 Hz, 1 H), 3.34 (s, 3 H), 2.03 (dd, J = 7.0, 3.0 Hz, exchangeable, 1 H); ^{13}C NMR (acetone-d_6) δ 203.5 (s), 163.7 (d), 138.8 (s), 135.2 (d), 134.4 (d), 128.4 (d), 120.2 (t), 108.6 (d), 94.7 (s), 65.3 (t), 54.2 (q), 52.9 (d); HREIMS 222.0877 (21), 191.0703 ($C_{11}H_{11}O_3$, 100), 160.0525 ($C_{10}H_8O_2$, 78); UV (MeOH) λ_{max} 236 nm (ϵ = 21000); crystallographic unit cell constants a = 7.662 (1) Å, b = 7.709 (1) Å, c = 9.808 (1) Å, β = 104.308 (13)°.

Palladium-mediated tri-*n*-butylvinyltin coupling with (-)-**41** similarly gave (-)-**5**, $[\alpha]^{23}_D$ -245.9° (c 0.270 g/100 mL, $CHCl_3$, ca. 66% ee).

(2*R*,6*R*)-Didemnenones A and B ((+)-1 and -2). Synthetic acetal (+)-**5** (4.31 mg, 19.4 μmol) was dissolved in a mixture of THF (1.00 mL) and H_2O (0.50 mL). The solution was cooled to 0 °C, and 1 M HCl (30 μL) was added. The solution was allowed to warm to room temperature with continued stirring for 2.75 h, at which time TLC showed no remaining **5**. The reaction mixture was recooled to 0 °C, and 0.50 M NaOH (60 μL) was slowly added to the vigorously stirred solution. Concentration by rotary evaporation at room temperature gave an aqueous suspension that was extracted with ethyl acetate (3 × 1 mL). The combined extracts were concentrated, and the residue was chromatographed on Sephadex LH-20 (2 g, ethyl acetate), to afford (+)-**1** and -**2** (1:1 mixture, 2.82 mg, 13.6 μmol, 70%) as an amorphous solid that matched the natural products.

Synthetic (+)-1 and -2: $[\alpha]^{22}_D$ +515° (c 0.081 g/100 mL, DMSO, ca. 89% ee); IR (CH_3CN) 3100-3550, 1720, 1205, 995 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.62 (d, J = 6 Hz, 1 H), 7.55 (d, J = 6 Hz, 1 H), 6.90 (ddd, J = 17, 12, 9 Hz, 2 H), 6.28 (br d, J = 12 Hz, 2 H), 6.21 (d, J = 6 Hz, 1 H), 6.11 (d, J = 6 Hz, 1 H), 5.73 (s, 1 H), 5.50 (br s, 1 H), 5.34 (d, J = 17 Hz, 2 H), 5.28 (d, J = 9 Hz, 2 H), 3.81-3.63 (m, 6 H); EIMS 208 (M^+, 1.7), 190 (M - H_2O, 5.8), 177 (6.0), 160 (21.7), 103 (48.9), 77 (100); HRMS exact mass for $C_{11}H_{10}O_3$ (M - H_2O), calcd 190.0630, found 190.0626; UV (CH_3CN) λ_{max} 234 nm (ϵ = 13000); TLC (diethyl ether) R_f = 0.09, coelutes with natural product mixture.

Natural products 1 and 2:[4] $[\alpha]_D$ +576.1° (c 0.49 g/100 mL, DMSO); IR (Nujol) 3100-3500, 1710, 1272, 1255, 1203, 1083, 1045, 1005, 995 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.62 (d, J = 5.5 Hz, 1 H), 7.55 (d, J = 5.5 Hz, 1 H), 6.90 (ddd, J = 17.0, 10.8, 9.8 Hz, 2 H), 6.28 (br d, J = 10.8 Hz, 2 H), 6.21 (d, J = 5.5 Hz, 1 H), 6.12 (d, J = 5.5 Hz, 1 H), 5.73 (s, 1 H), 5.51 (br s, 1 H), 5.35 (d, J = 17.0 Hz, 2 H), 5.28 (d, J = 9.8 Hz, 2 H), 3.81-3.62 (m, 6 H); HREIMS 208.0747 ($C_{11}H_{12}O_4$ requires 208.0736, 11.1%), 190.0616 ($C_{11}H_{10}O_3$, 14.8%), 177.0549 ($C_{10}H_9O_3$, 55.7%); UV (CH_3CN) λ_{max} 238 nm (ϵ = 13000).

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Supplementary Material Available: General experimental procedures, full experimental details, and spectral data for compounds **15**, **18-29**, and **32-37**, copies of ^{1}H and ^{13}C NMR spectra of compounds **15** and **32**, ^{1}H NMR spectra of synthetic **1**, **2**, and **5**, difference NOE spectra of **17**, and stereochemical correlation data for **9** (29 pages). Ordering information is given on any current masthead page.

Incisterols, a New Class of Highly Degraded Sterols from the Marine Sponge *Dictyonella incisa*

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Abstract: Four new sterols (**1-4**) with an unprecedented highly degraded skeleton were isolated from the Mediterranean sponge *Dictyonella incisa*. The structures of these new compounds were assigned on the basis of spectral studies, particularly NMR and mass spectrometry. A plausible pathway for the biogenesis of these compounds starting from cholestatrien-3β-ols through a unique in vivo oxidative process is proposed. The entire sterol content of the sponge and the structural elucidation of two new polyhydroxy sterols (**6b** and **6d**) are also reported.

Marine sponges are the richest source of unusual sterols with a bewildering variety of remarkable variations both in the side chain and nucleus, many of which have no terrestrial counterpart.[1-3] Most marine sterols possess novel side-chain alkylation patterns including the exceedingly rare in nature cyclopropene ring. A second class of unusual sterols is characterized by a great variety of oxygenated functionalities, including polyhydroxy, epoxide, and mono- and polyenone systems. Several other sterols include structural modification of the basic carbon skeleton, such as *B*- and *C*-secosterols and (hydroxymethyl)-*A*-norsteranes, the latter composing the entire sterol content of some sponges. A further small class of unusual sterols are the 19-norsterols, which, until now, represent the only example of biodegradation leading

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