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THE ARENARANS, SESQUITERPENE ETHERS FROM THE MARINE SPONGE *DYSIDEA ARENARIA*

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ABSTRACT.—Two new cyclic sesquiterpenes, arenarans A [**1**] and B [**2**], were isolated from a Thai collection of *Dysidea arenaria*. Their chemical and cytotoxic properties are described.

Sponges of the genus *Dysidea* (family Dysideidae), abundant in all tropical reefs, are a reliable source of assorted terpenoids. The more than eighty terpenes from *Dysidea* exhibit a rich diversity in structures, bioactivities, and even in the names coined for these compounds. Highlights of this literature include: the monoterpene adriadysolide from *Dysidea* sp. (1), antiparasitic sesquiterpenes such as thiofurodysinin acetate (2) and the LTB4-agonist 15-acetyl thioxy furodysinin lactone (3) from *D. herbacea,* diterpenoids represented by shahamin E (4) and meroterpenoids exemplified by avarol (5), which modulates mRNA synthesis (6), from *D. avara*, and the protein tyrosine kinase inhibitor melemeleone B from *Dysidea* sp. (7).

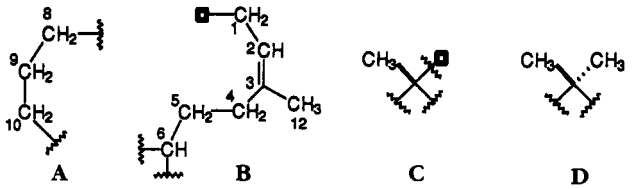
During an expedition to Phuket, Thailand, we encountered a bright blue colony of *D. arenaria* devoid of chlorophyll-containing organisms. Review of both our collection records and a personal literature database revealed two things. First no such sponges existed in our repository. Second, this species has been the subject of only one prior investigation by Schmitz *et al.* (8) who reported the presence of arenarol and arenarone. We began a chemical investigation of this organism to discover previously undescribed terpenoids. Outlined below are the isolation, structures, and cytotoxic properties of two new sesquiterpene ethers, arenarans A [**1**] and B [**2**].

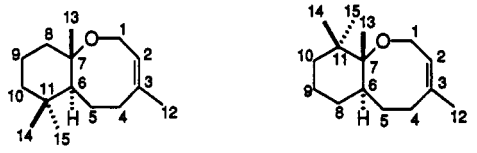
RESULTS AND DISCUSSION

Specimens of *D. arenaria* were preserved using our standard procedure followed by further extraction with MeOH (7). The crude extract was subjected to solvent partitioning, as outlined in the Experimental, and each solvent partition fraction was examined by APT ^{13}C-nmr spectroscopy. The nmr spectra of the hexanes fraction showed intense resonances beyond those observed for the normal lipids and steroids including peaks for double bonds (δ 124.8 and 133.0) and oxygen-bearing carbons (δ 79.5 and 61.7). Further purification of the hexane fraction by Sephadex cc followed by hplc (both silica and ODS columns) yielded arenarans A [**1**] and B [**2**].

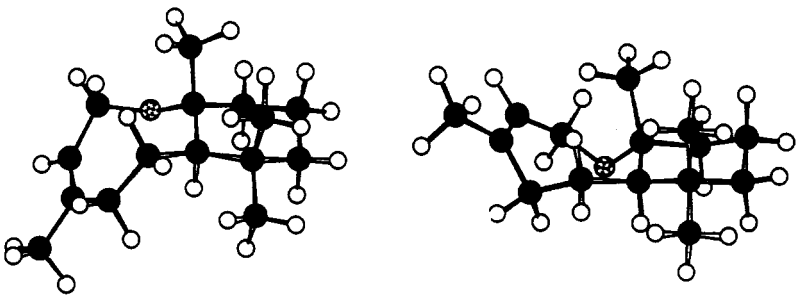
The ^{13}C-nmr spectrum of arenaran A [**1**] showed clearly fifteen distinct resonances, and an APT formula of $C_{15}H_{26}$ was deduced based on the data shown in Tables 1 and 2. There were four methyl groups which each gave a singlet ^{1}H-nmr resonance in CD_3OD. The lrcims (positive ion) *m/z* 223 $[M+H]^+$ was consistent with a molecular formula of $C_{15}H_{26}O$. It was apparent from the preceding data that the functionality consisted of an ether, a trisubstituted double bond, and two rings. Various ^{1}H-^{1}H COSY nmr correlations identified isolated spin-systems for substructures **A** and **B**. The three remaining Me groups were proposed to be attached to two quaternary carbons (δ 79.3 and 34.3) as in substructures **C** and **D**, and the Me ^{1}H-nmr shifts (CD_3OD) of δ 1.66, 0.90, and 0.87 indicated that the remaining oxygen atom must be geminal to the Me at δ 1.26 as shown in substructure **C**. Overall, these structural fragments could be merged in just two different ways as depicted in **1** and **1a**.

Long range ^{1}H-^{13}C COSY (J=9 Hz) nmr correlations were used to establish the final





1 **1a**



1′
mm E_{calcd}=36.2 kcal/mol
J_{calcd}=4.0 Hz

1″
mmx E_{calcd}=39.5 kcal/mol
J_{calcd}=5.5 Hz

J_{obs}=4.1

structure as **1**. The key correlations from both H_3-14 and H_3-15 to C-11 and C-6 further showed C-11 as the carbon bearing the *gem*-dimethyls, and C-11 as adjacent to C-6. These data were consistent only with structure **1** whose trans bicyclic ring junction was assigned based on the diagnostic ^{13}C-nmr shift of Me-13 (9,10).

The second sesquiterpene [**2**] exhibited an hreims (positive ion) M^+ 238.1928 for $C_{15}H_{26}O_2$ (Δ 0.6 mmu of calcd) and nmr spectra (see Tables 1 and 2) which were analogous to those of **1**. The most notable differences included the lack of olefin carbons and the presence of four oxygenated carbons at δ 58.2 (t), 60.8 (s), 64.1 (d), and 80.0 (s). The identical H_{26} count in the ms molecular formula and the APT formula suggested that the oxygens were a part of two ether residues. The constitution of the three rings was established based on ^{1}H-^{13}C (J=140 Hz) and ^{1}H-^{1}H COSY correlations which first revealed that substructures **A** and **B** (with an oxygen at the C-2–C-3 bond) were present in **2**. The relatively upfield chemical shifts of C-2 and C-3 (Table 2) were further consistent with the presence of an epoxide moiety (11). Substructures **C** and **D** were also recognized. Evidence in support of merging these four substructures to give the final structure **2** came from ^{1}H-^{13}C COSY (J=9 Hz) data. The key correlations included C-1/H-2; C-2/H_3-12; C-3/H_3-12; C-6/H_2-4, H_2-5, H_3-14, H_3-15; C-7/H-1, H_3-13; C-10/H_3-14, H_3-15; and C-11/H_3-14, H_3-15.

Chemical evidence for the presence of the epoxide functionality was obtained next. Treatment of arenaran B [**2**] with lithium triethylborohydride (12) afforded the alcohol **3** as shown in Scheme 1. The ^{1}H- and ^{13}C-nmr shifts (Tables 1 and 2) at C-2 (42.0, t),

TABLE 1. ^{1}H-Nmr Assignments for Compounds **1–3**, **6**, and **7**.

Proton	Compound					
	1[a,b]	**1**[c]	**2**[a,d]	**3**[d]	**6**[d]	**7**[d]
1	4.06 (br s)	4.27 (dd, J=18.5, 2.1) 3.96 (br d, J=18.5)	4.02 (dd, J=15.6, 2.1) 3.89 (d, J=15.6)	3.86 (m) 3.60 (m)	3.66 (d, J=13.3) 3.36 (d, J=13.3)	3.68 (m) 3.33 (m)
2	5.06 (br s)	5.15 (br s)	2.79 (d, J=2.1)	1.90 (m)	3.63 (d, J=10.8) 3.44 (d, J=10.8)	9.47 (s)
4	3.67 (ddd, J=19.9, 11.5, 1.3) 1.62 (m)	3.37 (m) 1.82 (m)	1.67 (m) 1.35 (m)	1.63 (m)	1.58 (m)	1.43 (m)
5	1.51 (m)	1.60 (m)	1.45 (m)	1.47 (m)	1.45 (m)	1.31 (m)
6	1.63 (m)	1.65 (m)	1.50 (m)	1.55 (m)	1.65 (m)	1.48 (m)
8	1.68 (m), 1.31 (m)	1.68 (m) 1.26 (m)	2.41 (dt, 13.5, 5.1) 1.86 (dt, 13.5, 3.6)	1.64 (m)	1.70 (m)	1.56 (m)
9	1.35 (m)	1.34 (m)	1.58 (m)	1.59 (m)	1.41 (m)	1.33 (m)
10	1.25 (m)	1.21 (m)	1.40 (m), 1.21 (m)	1.41 (m)	1.34 (m)	1.13 (m)
12	1.67 (s)	1.66 (s)	1.21 (s)	1.60 (s)	1.16 (s)	1.05 (s)
13	1.26 (s)	1.24 (s)	1.16 (s)	1.22 (s)	0.95 (s)	1.01 (s)
14	0.85 (s)	0.90 (s)	0.97 (s)	0.97 (s)	0.78 (s)	0.89 (s)
15	0.79 (s)	0.87 (s)	0.84 (s)	0.81 (s)	0.72 (s)	0.78 (s)

[a]Proton assignments established by ^{1}H-^{13}C COSY (J=140 and J=9 Hz) and ^{1}H-^{1}H COSY experiments.
[b]Recorded at 300 MHz in C_6D_6; ^{1}H-nmr signals referenced to residual C_6H_6 (7.15 ppm).
[c]Recorded at 300 MHz in CD_3OD; ^{1}H-nmr signals referenced to residual CH_3OH (3.30 ppm).
[d]Recorded at 250 MHz in $CDCl_3$; ^{1}H-nmr signals referenced to residual $CHCl_3$ (7.26 ppm).

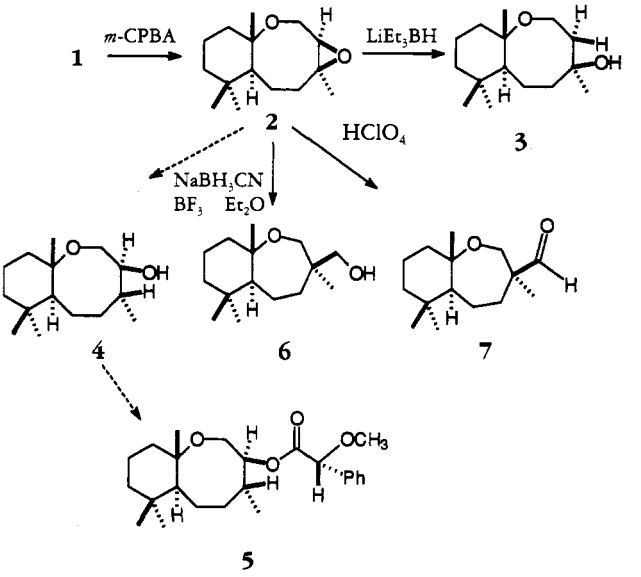
TABLE 2. ^{13}C-Nmr Assignments for Compounds **1**, **2**, **3**, and **6**.[a]

Carbon	Compound			
	1[b]	**2**[c]	**3**[b]	**6**[c]
1	61.5 (t)	58.2 (t)	57.2 (t)	71.3 (t)
2	124.5 (d)	64.1 (d)	42.0 (t)	67.3 (t)
3	132.8 (s)	60.8 (s)	72.2 (s)	38.4 (s)
4	29.5 (t)	36.0 (t)	41.2 (t)	39.3 (t)
5	24.7 (t)	20.0 (t)	19.8 (t)	20.0 (t)
6	45.9 (d)	45.0 (d)	51.4 (d)	53.7 (d)
7	79.3 (s)	80.0 (s)	78.9 (s)	79.0 (s)
8	35.5 (t)	32.7 (t)	36.3 (t)	38.0 (t)
9	20.5 (t)	22.1 (t)	20.5 (t)	21.1 (t)
10	42.4 (t)	42.4 (t)	43.0 (t)	41.1 (t)
11	34.3 (s)	35.5 (s)	35.9 (t)	35.7 (s)
12	26.1 (q)	23.0 (q)	31.8 (q)	22.9 (q)
13	23.0 (q)	22.6 (q)	23.2 (q)	22.2 (q)
14	33.1 (q)	33.3 (q)	33.2 (q)	32.9 (q)
15	21.9 (q)	21.9 (q)	20.8 (q)	21.0 (q)

[a]Multiplicities established by APT experiment.
[b]Recorded at 75.5 MHz in C_6D_6; ^{13}C-nmr signals referenced to C_6D_6 (128.0 ppm).
[c]Recorded at 62.7 MHz in $CDCl_3$; ^{13}C-nmr signals referenced to $CDCl_3$ (77.0 ppm).

H_2-2 (1.90, d), and C-3 (72.2, s) of this product were consistent with the expected course of the reaction. In addition, arenaran A [**1**] was converted into arenaran B [**2**] by treatment with *m*-chloroperoxybenzoic acid (*m*-CPBA). The resulting epoxide was identical to the natural material based upon the ^{1}H-nmr, hrfabms, and optical rotation data ($[\alpha]_D$ −24.4° (natural) vs. $[\alpha]_D$ −24.8° (synthetic)).

The stereochemical features of arenaran B [**2**] were assigned utilizing the following general strategy. First, the trans ring junction in **2** was evident because of the similarity of the ^{13}C-nmr chemical shift of Me-13 in **1** and **2**. Second, the stereochemistry of the



SCHEME 1. Synthetic interconversions.

epoxide functionality was based on the interesting observation that epoxidation of **1** yielded a single stereoisomer of **2**. It would appear that the eight-membered ring of **1** presents a solution conformation that allows for preferential access to one face of the olefin by *m*-CPBA. To gain additional insight on this point two possible conformations, **1′** and **1″** were entered into a molecular modeling program and energy minimizations were carried out. Coupling constants were then calculated for the minimized structures and compared with the experimental data. In CD_3OD the diastereotopic protons H-1 and H-1′ appeared as separate resonances and coupling values of $^3J_{1-2}=4.1$ and $^3J_{1'-2}=0$ Hz were measured. The experimental data was in better agreement with the calculated value of $^3J_{1-2}=4.0$ Hz for conformer **1′** vs. that of $^3J_{1-2}=5.5$ Hz for conformer **1″**. Additionally, an extensive conformational search was conducted which substantiated the conformation of **1′** as the global minimum, 3 kcal/mole lower in energy than conformer **1″**. Based upon the chemical interconversion of **1** (via **1′**) to **2**, the relative stereochemistry of **2** can now be defined as 2*R**, 3*S**, 6*S**, 7*S**.

With the relative stereochemistry of epoxide **2** established, an attempt was made to use Mosher's method to establish its absolute stereochemistry (13). Our idea was to convert the epoxide **2** to the secondary alcohol **4** which would then be transformed to an *O*-methylmandelate ester [**5**]. Unfortunately, treatment of **2** with cyanoborohydride and boron trifluoride etherate did not afford **4**, but instead gave **6**, characterized by nmr resonances δ 67.3 (t) and 38.4 (s) of the primary alcohol. Apparently, an aldehyde intermediate **7** had been formed and was reduced during the reaction to generate **6**. Aldehyde **7** was separately prepared by using $HClO_4/H_2O$ to open the epoxide moiety of **2** and provided material whose ^{1}H-nmr data contained upfield resonances analogous to those of compound **6** along with the δ 9.57 (s), which documented the presence of the aldehyde functionality.

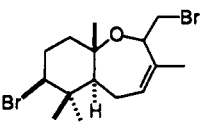
Both arenaran A [**1**] and arenaran B [**2**] were evaluated for their potential cytotoxicity properties in several whole-cell assays. Arenaran A was in vitro-active against several types of cancer cells [activity is defined as $IC_{50}<10$ μg/ml (14)] as shown by the following IC_{50}s in μg/ml (cell type); 9.51 (A549, human lung carcinoma), 9.11 (HT-29, human colon adenocarcinoma), 5.28 (HCT-29, human colon adenocarcinoma), 3.17 (P-388 murine leukemia); areneran B was inactive against each of these cell lines.

The arenarans have ring systems which are without prior precedent. The closest analogies are palisadin B [**8**], reported from the red alga *Laurencia* cf. *palisada* (10), aplysistatin [**9**], isolated from the sea hare *Aplysia angasi* (15), and 3,4-epoxypalisadin A as well as related compounds from *L. flexilis* (16). Outlined in Scheme 2 are biosynthetic relationships evident between the hypothetical monocyclofarnesane derivatives **10**, **11**, and **12** vs. the natural products arenarans A [**1**], B [**2**], and palisadin B [**8**].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The nmr spectra were recorded at 250.13 or 300.1 MHz for ^{1}H and 62.7 and 75.5 for ^{13}C. Multiplicities of ^{13}C-nmr resonances were determined from APT data, DEPT data, or COSY experiments. Hreims and lreims data were obtained on a magnetic sector instrument. Hplc was done using 10 μm ODS or 10 μm Si gel columns.

ANIMAL MATERIAL.—The sponge *D. arenaria* (coll. no. 88013) was collected offshore of Phuket, Thailand, and it was identified by Ms. M.C. Diaz, University of California, Santa Cruz (UCSC), and Prof.



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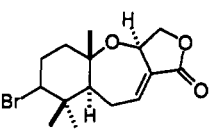

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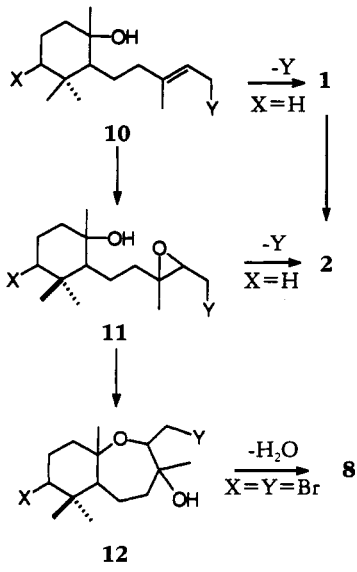

SCHEME 2. Proposed biogenesis of sesquiterpenes **1**, **2** and **8**.

R. van Soest (University of Amsterdam). A voucher specimen as well as an underwater photograph are in the UCSC sponge collection archives and are available from P.C. It was preserved as described below. The properties of this specimen were found to be similar to those of an Indonesian sponge previously described by van Soest (17). The dark-blue sponge was massive-encrusting with a vary conulose surface. The conules were big and loose and were formed clearly by terminating fibers. The choanosome consisted of dendritic fibers, 250 and 500 μm in diameter, densely packed with foreign spicules including asterose, tetractineas, oxeas, and tylotes.

EXTRACTION AND ISOLATION.—The freshly collected sponge (135 g dry wt) was preserved by immersion in EtOH-H_2O (50:50). After approximately 24 h the preserving solution was decanted and discarded. The damp organisms were placed in Nalgene bottles and shipped from the collection site to the laboratory at room temperature. Next, 100% MeOH was added and the organisms were soaked for 48 h. This procedure was repeated two more times. The combined organic extract yielded 4.79 g of a crude oil, which was successively partitioned between equal volumes of aqueous MeOH, percent adjusted to produce a biphasic solution, and a solvent series of hexanes (yield 3.98 g), CCl_4 (yield 0.02 g), and CH_2Cl_2 (yield 0.45 g). The remaining H_2O solubles were extracted but did not contain compounds of interest. A portion of the hexanes fraction (2.11 g) was then chromatographed over Sephadex LH-20 with CH_2Cl_2-MeOH (1:1) yielding a mixture of **1** and **2**. Further purification was by hplc over a reversed-phase ODS column with MeOH-H_2O (9:1) to yield pure arenaran A [**1**] (0.098 g) and impure arenaran B [**2**]. Final purification via hplc using a Si gel column with EtOAc-hexanes (5:95) gave **2** (0.053 g).

Arenaran A [**1**].—Amorphous colorless solid: mp 54.2°; $[\alpha]_D$ +154.0° (c=0.01, $CHCl_3$); ir (C_6H_6-d_6) ν max 2919 (s), 2355 (m), 2272 (s), 1449 (w), 1378 (m), 1102 (s), 1049 (m) cm^{-1}; lreims *m/z* $C_{15}H_{26}O$, 222 (10), 204 (16), 124 (15), 109 (100), 96 (45), 81 (41), 78 (57); lrcims (isobutane) *m/z* 223 (14), 205 (37), 149 (19), 137 (13), 123 (15), 109 (100), 95 (45), 81 (17); ^{1}H- and ^{13}C-nmr data are shown in Tables 1 and 2.

Arenaran B [**2**].—Amorphous colorless solid: mp 31.0°; $[\alpha]_D$ −24.4° (c=0.23, $CHCl_3$); ir ($CDCl_3$) ν max 2931 (s), 2249 (m), 1460 (s), 1384 (s), 1210 (w), 1160 (w), 1102 (m) cm^{-1}; hreims *m/z* 238.1928 ($C_{15}H_{26}O_2$ requires 238.1934, Δ −0.6 mmu of calcd); lreims *m/z* 223 ($[M-15]^+$, 2), 215 (9), 177 (16), 153 (20), 109 (58), 84 (100); lrcims (isobutane) *m/z* 239 ($[M+H]^+$, 8), 221 (21), 203 (13), 191 (80), 163 (30), 137 (86), 95 (100); ^{1}H- and ^{13}C-nmr data are shown in Tables 1 and 2.

Conversion of **1** *to* **2**.—A solution of *m*-CPBA (13.6 mg in 3 ml of dry CH_2Cl_2) was added dropwise to a solution of **1** (7.4 mg in 5 ml of dry CH_2Cl_2), and then cooled in an ice bath. The reaction mixture was stirred in an ice bath for 3 h and washed with 10% $NaHCO_3$ (2×10 ml). The organic solution was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by reversed-phase hplc (ODS column, MeOH-H_2O (9:1)) yielding 5.3 mg (67% yield) of synthetic **2**. The ^{1}H-nmr data of the synthetic product were identical to those of natural **2**. Additional physical data: hrfabms [positive ion, glycerol/thioglycerol matrix) *m/z* 239.204 $[M+H]^+$ (Δ 3.9 mmu of calcd)]; $[\alpha]_D$ −24.8° (c=0.20, $CHCl_3$).

Conversion of **2** *to* **3**.—To a solution of **2** (5.4 mg in 2 ml THF) was added $LiEt_3BH$ (0.06 ml 1.2 M in THF). The reaction was stirred for 20 min under N_2 at room temperature before quenching with H_2O (15 ml). The aqueous phase was saturated with anhydrous K_2CO_3 and then extracted with Et_2O (2×10 ml). Combined Et_2O extracts were dried over Na_2SO_4, filtered, and reduced to dryness. Purification by reversed-phase hplc (ODS column, MeOH-H_2O, 9:1) yielded 2.4 mg (44% yield) of pure **3**: $C_{15}H_{28}O_2$, $[\alpha]_D$ −36.8° (c=0.20, $CHCl_3$); ^1H- and ^{13}C-nmr data are shown in Tables 1 and 2; hrfabms [positive ion, glycerol/thioglycerol matrix *m/z* 241.2179 $[M+H]^+$ (Δ 1.1 mmu of calcd)].

Conversion of **2** *to* **6**.—The epoxide **2** (4.9 mg) was dissolved in dry THF (15 ml) and $NaBH_3CN$ (6.2 mg) was added to this solution. A small amount of bromocresol green/THF solution was added next. Finally, BF_3-etherate in THF was added until the color was a pale yellow. The reaction mixture was stirred for 24 h at room temperature. An equal volume of brine was added and the solution was then extracted with Et_2O. The Et_2O was dried over Na_2SO_4 and removed under vacuum. The product was purified by reversed-phase hplc (ODS, H_2O-MeOH, 1:4) yielding 3.1 mg of **6** (62.9% yield): $C_{15}H_{28}O_2$, $[\alpha]_D$ −64.6° (c=0.10, $CHCl_3$); ^1H- and ^{13}C-nmr data are shown in Tables 1 and 2; hrfabms [positive ion, glycerol/thioglycerol matrix *m/z* 241.2193 $[M+H]^+$ (Δ 2.5 mmu of calcd)].

Conversion of **2** *to* **7**.—The epoxide **2** (5.0 mg) was dissolved in dry THF (10 ml) to which was added 30% $HClO_4$ (0.05 ml). The reaction mixture was stirred for 15 h at room temperature, then quenched with 10% $NaHCO_3$ (10 ml), and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), gravity filtered, and removed under vacuum. The product was purified by reversed-phase hplc (ODS, H_2O-MeOH, 1:4), to afford 2.2 mg of **7** (44% yield): $C_{15}H_{26}O_2$, $[\alpha]_D$ −15.1° (c=0.05, $CHCl_3$); ^1H-nmr data are shown in Table 1; hrfabms [positive ion, glycerol/thioglycerol matrix *m/z* 239.2012 $[M+H]^+$ (Δ 3.3 mmu of calcd)].

COMPUTATIONAL METHODS.—Computer modeling was carried out with the PCMODEL program on a Silicon Graphics Personal Iris workstation. Molecular mechanics calculations were performed with the MMX force field including pi-VESCF calculations. Vicinal coupling constants (^3J) in the candidate conformations were calculated in PCMODEL with the Altona coupling equation (H-C(sp^3)-C(sp^3)-H) or the Garbisch coupling equation (H-C(sp^2)-C(sp^3)-H) (18).

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