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ADDITIONAL DOLABELLANE DITERPENES FROM THE CARIBBEAN GORGONIAN OCTOCORAL *EUNICEA LACINIATA*

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ABSTRACT.—The Caribbean gorgonian octocoral *Eunicea laciniata* from the coasts of Palomino Island, Puerto Rico, has yielded four known and five new diterpenes based on the dolabellane ring system. The structures of the novel compounds **3–7** were established by interpretation of their spectral data. Some of these new compounds showed weak cytotoxicity against HeLa cells.

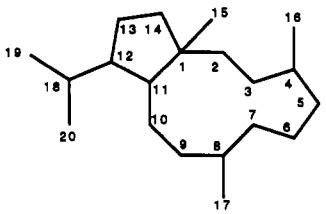
Gorgonians of the genus *Eunicea* are known to elaborate diterpenoids of five main structural types, namely, cembrane and cubitane diterpenoids, diterpenoids of the dilophol and fuscoside classes, and dolabellanes (1). Previous investigations of the gorgonian octocoral *Eunicea laciniata* Duchassaing and Michelotti (family Plexauridae) collected from Caribbean waters have revealed eight dolabellane-type diterpenes (2–5). Recently, we re-investigated the chemical content of the same gorgonian species collected at a different location near Puerto Rico and now report the results of this investigation. Although the structures of several of the compounds found are known (**2**, **8**, **9**, and **10**), five new representatives of the dolabellane class (**3–7**) are reported for the first time.

RESULTS AND DISCUSSION

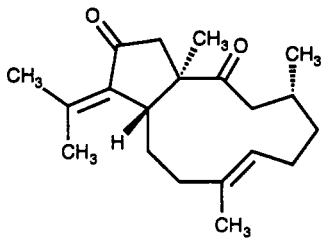
A sample (829.5 g) of freeze-dried *E. laciniata* was blended with MeOH-$CHCl_3$ (1:1), with the extract obtained concentrated, and the resulting crude extract partitioned against hexane and H_2O. The hexane solubles were filtered and evaporated, giving an oil which was subsequently fractionated by successive size-exclusion and adsorption cc. In most cases final compound purification was achieved by normal-phase hplc.

Edunone [**3**], a colorless oil that analyzed for $C_{20}H_{32}O$ by hreims and ^{13}C nmr, was recognized, from its ^1H- and ^{13}C-nmr data (Tables 1 and 2) as a 13-deoxo derivative of **1**, a previously described compound from *E. laciniata* (4). Comparison of nmr data showed many similarities between metabolites **1** and **3**, and revealed that **3** has the same eleven-membered ring as compound **1**. However, there were several significant differences that indicated the absence of a conjugated carbonyl functional group in the five-membered ring of **3**. ^{13}C-Nmr signals at δ 204.8 (s), 147.9 (s), and 135.8 (s), which corresponded to an enone functionality in **1**, were shifted in **3** to δ 30.17 (t), 121.60 (s), and 141.17 (s), respectively (Table 2). In their ^1H-nmr spectra, two methyl signals at δ 2.15 (3H, s) and 1.85 (3H, s), assigned in **1** as vinyl methyls at the terminal carbon of the conjugated exocyclic enone, were shifted to δ 1.61 (6H, s) in **3**.

In addition, the absorption at 254 nm (ε 3300) in the uv spectrum of **1** was absent in **3**, for which only end absorption was evident. All of these changes can be accommodated by replacement of the C-13 carbonyl functionality in **1** by a methylene group in **3**. The relative spatial arrangement of the angular methyl and the bridgehead proton on the β-face of the molecule was clearly established by a 2D NOESY nmr experiment. The absence of an nOe connecting H-11 and the associated methyl resonance at C-1 indicated that these groups could be assigned as trans. The stereochemistry of the remaining chiral center at C-4 in **3** could not be assigned by 2D NOESY experiments since the C-16 methyl protons failed to correlate with any key proton signals. The configuration of this



Dolabellane Skeleton



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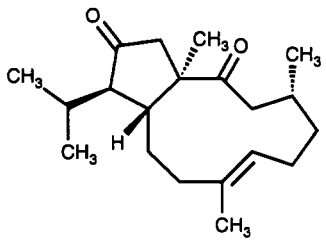

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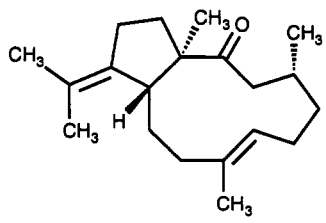

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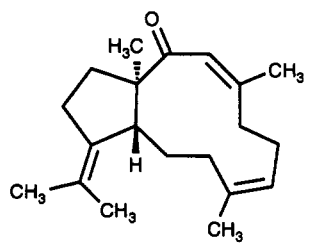

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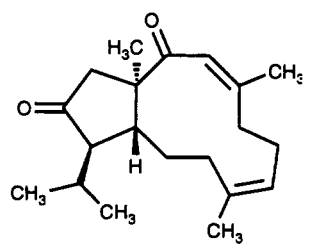

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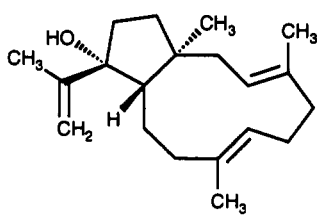

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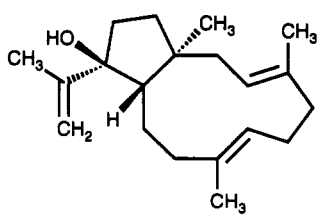

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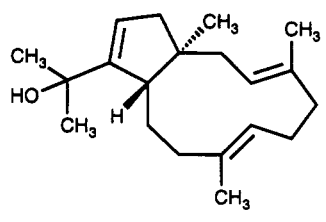

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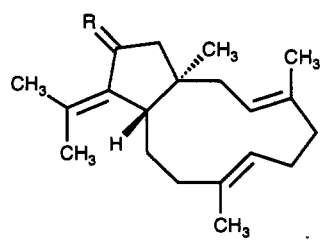

9 R=O
10 R=H,H

TABLE 1. ^{1}H-Nmr Data of Compounds **3**–**7**.[a]

Proton	Compound				
	3	**4**	**5**	**6**	**7**
	δ, mult., *J* (Hz), int.	δ, mult., *J* (Hz), int.	δ, mult., *J* (Hz), int.	δ, mult., *J* (Hz), int.	δ, mult., *J* (Hz), int.
1	—	—	—	—	—
2′	—	—	—	2.46, dd, 10.5, 13.2, 1H	2.15, m, 1H
2″	—	—	—	1.84, m, 1H	1.74, m, 1H
3′	2.49, dd, 10.2, 18.9, 1H	6.30, br s, 1H	6.35, br s, 1H	5.08, dd, 5.1, 10.8, 1H	4.99, dd, 3.0, 10.8, 1H
3″	2.22, dd, 3.0, 18.9, 1H	—	—	—	—
4	2.13, m, 1H	—	—	—	—
5′	1.93, m, 1H	3.09, m, 1H	3.20, dd, 5.7, 12.9, 1H	2.20, m, 1H	2.09, m, 1H
5″	1.41, m, 1H	1.93, m, 1H	1.99, m, 1H	2.10, m, 1H	2.07, m, 1H
6′	1.98, m, 1H	2.65, m, 1H	2.74, m, 1H	2.27, m, 1H	2.16, m, 1H
6″	1.89, m, 1H	1.79, m, 1H	1.82, m, 1H	2.12, m, 1H	2.12, m, 1H
7	4.95, m, 1H	5.02 br d, 12.0, 1H	4.99, br d, 10.8, 1H	4.89, m, 1H	4.91, br t, 6.5, 1H
8	—	—	—	—	—
9′	2.03, br t, 6.3, 1H	2.17, m, 1H	1.84, m, 1H	2.05, m, 1H	1.96, m, 1H
9″	2.03, br t, 6.3, 1H	1.63, m, 1H	1.50, m, 1H	1.54, m, 1H	1.44, m, 1H
10′	1.61, m, 1H	1.98, m, 1H	2.34, m, 1H	1.25, m, 1H	1.66, m, 1H
10″	1.61, m, 1H	1.32, m, 1H	1.67, m, 1H	1.25, m, 1H	1.28, m, 1H
11	2.73, br m, 1H	2.99, br d, 12.0, 1H	2.35, m, 1H	1.77, m, 1H	1.66, m, 1H
12	—	—	1.80, m, 1H	—	—
13′	2.35, dd, 7.2, 14.4, 1H	2.44, dd, 7.0, 14.7, 1H	—	2.07, m, 1H	1.95, m, 1H
13″	2.13, m, 1H	2.32, m, 1H	—	1.88, m, 1H	1.73, m, 1H
14′	1.78, dd, 5.5, 12.5, 1H	1.89, m, 1H	2.64, d, 17.7, 1H	1.83, m, 1H	1.74, m, 1H
14″	1.41, m, 1H	1.45, m, 1H	2.11, dd, 1.8, 17.7, 1H	1.46, dd, 4.2, 8.4, 1H	1.51, m, 1H
15	1.15, s, 3H	1.14, s, 3H	1.08, s, 3H	0.98, s, 3H	1.01, s, 3H
16	0.94, d, 6.9, 3H	1.80, s, 3H	1.83, s, 3H	1.57, s, 3H	1.52, s, 3H
17	1.61, s, 3H	1.69, s, 3H	1.62, s, 3H	1.59, s, 3H	1.54, s, 3H
18	—	—	1.97, m, 1H	—	—
19	1.61, s, 3H	1.67, s, 3H[b]	1.11, d, 6.9, 3H[b]	1.83, s, 3H	1.81, s, 3H
20′	1.61 s, 3H	1.61, s, 3H[b]	0.98, d, 6.9, 3H[b]	5.01, br s, 1H[b]	5.12, br s, 1H[b]
20″	—	—	—	4.93, br s, 1H[b]	4.84, br s, 1H[b]

[a]Spectra were recorded at room temperature in $CDCl_3$ using a proton observation frequency of 300.11 MHz. Assignments were aided by ^{1}H-^{1}H COSY, CSCM, and NOESY nmr experiments, spin-splitting patterns, and the comparison of *J* values. Chemical shifts are in ppm and are referenced to the residual $CHCl_3$ signal (7.26 ppm).

[b]Values with identical superscripts in each column may be interchanged.

TABLE 2. ^{13}C-Nmr Data of Compounds **3**–**7**.[a]

Carbon	Compound				
	3	**4**	**5**	**6**	**7**
	δ (m)	δ (m)	δ (m)	δ (m)	δ (m)
1	57.06 (s)	57.55 (s)	51.49 (s)	45.82 (s)	44.10 (s)
2	215.98 (s)	209.54 (s)	205.05 (s)	43.59 (t)	42.65 (t)
3	43.83 (t)	122.03 (d)	119.86 (d)	124.81 (d)	123.93 (d)
4	27.58 (d)	152.97 (s)	157.27 (s)	134.62 (s)	135.66 (s)
5	31.61 (t)	32.07 (t)	32.15 (t)	39.53 (t)	39.17 (t)
6	23.66 (t)	22.47 (t)	21.23 (t)	24.50 (t)	23.97 (t)
7	130.20 (d)	125.21 (d)	124.55 (d)	126.37 (t)	124.17 (t)
8	132.27 (s)	134.88 (s)	134.69 (s)	134.39 (s)	134.26 (s)
9	39.99 (t)	29.07 (t)	27.61 (t)	37.63 (t)	37.07 (t)
10	27.63 (t)	26.28 (t)	27.36 (t)	27.62 (t)	23.75 (t)
11	50.21 (d)	45.97 (d)	42.02 (d)	51.22 (d)	47.60 (d)
12	141.17 (s)	139.23 (s)	57.70 (d)	88.64 (s)	85.62 (s)
13	30.17 (t)	30.88 (t)	217.35 (s)	37.01 (d)	36.26 (d)
14	41.25 (t)	39.22 (t)	53.11 (t)	40.44 (t)	40.53 (t)
15	19.33 (q)	16.64 (q)	20.67 (q)	23.79 (q)	24.24 (q)
16	22.12 (q)	29.89 (q)	30.51 (q)	15.64 (q)	15.46 (q)
17	16.50 (q)	20.92 (q)	22.27 (q)	17.80 (q)	17.96 (q)
18	121.60 (s)	122.76 (s)	28.88 (d)	149.19 (s)	150.17 (s)
19	22.35 (q)[b]	22.91 (q)[b]	18.70 (q)[b]	21.22 (q)	20.11 (q)
20	21.00 (q)[b]	22.91 (q)[b]	16.81 (q)[b]	111.57 (t)	109.76 (t)

[a]Spectra were recorded at room temperature in $CDCl_3$ using a carbon observation frequency of 75 MHz. Resonance multiplicities were determined using the APT experiment. Carbon assignments were established by comparison with known model compounds and from CSCM, COSY, and selective INEPT nmr experiments.

[b]Values with the same superscript in each column may be interchanged.

center, however, seems likely to be as depicted in **3** based on the observation that dolabellanes **1** and **3** show almost identical nmr chemical shift values for all the hydrogen and carbon atoms near that position.

Eduenone [**4**] was isolated as a colorless oil that analyzed for $C_{20}H_{30}O$ by hreims and ^{13}C nmr. Compound **4** possessed a mass spectral molecular ion which was two mass units smaller than that of **3**. Comparison of relevant nmr spectra revealed that **4** has the same five-membered ring as compound **3**, thus the minor structural variations evident must be in the 11-membered ring. At first, a new olefinic proton signal at δ 6.30 (1H, br s), which showed long-range coupling in the COSY spectrum to a vinyl methyl signal at δ 1.80 (3H, s), suggested that **4** was the 3,4-dehydro derivative of edunone [**3**]. This contention was supported by the appearance of a conjugated enone absorption at 244 nm (ε 4391) in the uv spectrum of **4**, and a strong ir absorption at 1681 cm^{-1} [the *Z* configuration assigned for the Δ^3 double bond was based on the ^{1}H- and ^{13}C-nmr chemical shift values for Me-16 (δ 1.80 and δ 29.89, respectively) (6), and the intense nOe response observed between the Me-16 protons and H-3]. However, more careful inspection of the ^{13}C-nmr spectrum revealed that, contrary to **3**, the Δ^7 double bond in **4** also possessed the *Z* configuration. This was argued on the basis that in the ^{13}C-nmr spectrum the Me-17 signal (δ 20.92) was at low field and also as a result of a strong nOe response observed in the NOESY spectrum between H-7 and its associated methyl resonance at δ 1.69.

Dolabellane **5**, named edudione, was isolated as a uv-active [λ max 246 nm (ε 6421)], colorless semisolid that analyzed for $C_{20}H_{30}O_2$ by hreims and ^{13}C nmr. While

compound **5** possessed a mass spectral molecular ion that was 16 mass units larger than that of **4**, the nmr spectral data for both these compounds were very similar. Thus, in the ^{13}C-nmr spectra (Table 2), the two exocyclic olefin carbon signals in **4** (C-12, -18) were replaced by two high-field carbon resonances at δ 57.70 (d) and 28.88 (d) in **5**. Also, an additional carbonyl resonance at δ 217.35, not present in **4**, was observed for **5**. This analysis revealed **5** to possess a five-membered ring with identical substitution to dolabellane **2**, a previously described compound which was also found in this specimen of *E. laciniata* (4). Further analysis of its nmr data revealed edudione to possess an 11-membered ring identical with that of eduenone [**4**]. The relative stereochemistry of the chiral carbon at C-12 was assigned based on a weak nOe between the proton at δ 2.35 (H-11) and the methyl at δ 1.11 (C-19 or -20). It also seemed very likely that the orientation of the C-12 proton was α-, since the nmr spectral data ascribable to the five-membered ring for **5** were very similar to those reported for dolabellane **2** (4). Thus, the structure of **5** was defined as the 13-oxo-12,18-dihydro derivative of dolabellane **4**. All of the key protons and carbons of **5** were unambiguously assigned by ^{1}H-nmr COSY, NOESY, CSCM, and selective INEPT nmr experiments (Tables 1 and 2).

The dolabellane alcohols **6** and **7**, named, respectively, edunol and isoedunol, were isolated as oils that analyzed for $C_{20}H_{32}O$ by hreims and ^{13}C nmr. The ^{1}H- and ^{13}C-nmr spectra of these metabolites were virtually superimposable. In both isomers the presence of a tertiary hydroxyl was evident from a strong ir band near 3500 cm^{-1} and a ^{13}C-nmr resonance at δ 88.64 (s) in **6** and 85.62 (s) in **7**. Analysis of nmr data revealed alcohols **6** and **7** to possess an 11-membered ring identical to those of the known dolabellanes **8**, **9**, and **10** [the latter compounds were also isolated from the same specimen of *E. laciniata* and their structures were defined by comparison of ir, ^{1}H-nmr, ^{13}C-nmr, and ms data with values reported elsewhere (2–5)]. Differences were found, however, in their five-membered rings. For instance, in the ^{13}C-nmr spectrum, the olefinic resonances at δ 153.91 (s) and 122.55 (d) in **8**, due, respectively, to the cyclopentene carbon signals C-12 and C-13 (5), were replaced in **6** by a quaternary carbon signal (δ 88.64) and a methylene signal (δ 37.01). Corresponding changes were also found in the ^{1}H-nmr spectrum in which the vinyl proton signal at δ 5.46 (1H, br t, H-13) in **8** was replaced in **6** by two signals at δ 5.01 (1H, br s) and 4.93 (1H, br s). Also, the two tertiary carbinol methyl signals at δ 1.40 and 1.36 in palominol [**8**] were replaced by a new methyl signal at δ 1.83 (3H, s). ^{1}H-^{1}H COSY and selective INEPT nmr experiments allowed these new spectral features to be interpreted. The vinyl methyl signals at δ 1.83 and 1.81 in **6** and **7**, respectively, were found to be coupled to their respective terminal methylene protons. Moreover, the ^{13}C-nmr signals at δ 88.64 and 85.62, assigned to the carbon bearing the isopropylene and hydroxyl groups in **6** and **7** (C-12), showed enhancements during the selective irradiation of each of the terminal methylene protons. These results demonstrated that long-range carbon-proton coupling occurs between these atoms. The chemical shift of the carbon at C-12 in each epimer was at significantly lower field than C-18 in **8**, indicating that the hydroxyl groups in edunol and isoedunol are attached to the cyclopentane moiety at that position.

The proposed α- orientation for the 12-OH substituent in edunol [**6**] is based on the observation that H-11, which lies on the opposite β- face of the cyclopentane skeletal moiety to the 12-OH substituent, resonates at lower field than in epimer **7** (δ 1.77 vs. 1.66) (5). The proposed β- orientation for the 12-OH substituent in isoedunol [**7**] is also in agreement with the observation that in **6**, the C-10 methylene signal at δ 27.62 appears shifted to δ 23.75 in isoedunol, a fact that can be explained only if the C-10 methylene and the C-12 isopropylene group are in close proximity to each other. Careful examination of Dreiding models indicated that this condition is met when the

isopropylene group lies on the α face of the cyclopentane moiety. Information on the stereochemical orientation of the C-12 isopropylene substituent in both edunol [**6**] and isoedunol [**7**] could also be obtained via NOESY experiments. In **6**, a weak nOe between the proton at δ 1.77 (H-11) and both the methyl group at δ 1.83 (Me-19) and the terminal methylene proton resonating at δ 4.93 (H-20″), agreed with the proposed β-orientation for the 12-isopropylene substituent. These nOes were not detected in isoedunol, thus suggesting the α- orientation for the same substituent in **7**.

Some of the new dolabellanes displayed weak cytotoxicity against HeLa cells. The cytotoxic activity of these compounds was as follows: edunone [**3**] (IC_{50} 25 μg/ml), eduenone [**4**] (IC_{50} 50 μg/ml), edudione [**5**] (IC_{50} >100 μg/ml), and edunol [**6**] (IC_{50} 25 μg/ml).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All nmr spectra were recorded with a General Electric Multinuclear QE-300 instrument using $CDCl_3$ as solvent and TMS as internal standard. Ir spectra were recorded on a Nicolet 600 Ft-ir spectrophotometer and uv spectra on a Hewlett-Packard Chem Station 8452A spectrophotometer. Optical rotations were recorded on a Perkin-Elmer model 243B polarimeter. Hreims were determined by the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln. Cc was performed using Analtech Si gel (35–75 mesh) and all spectral grade hplc solvents were filtered prior to use.

ANIMAL MATERIAL.—The Caribbean gorgonian *Eunicea laciniata* (phylum Cnidaria) was collected by hand using scuba at depths of 5–10 m from Palomino Island, Puerto Rico. A voucher specimen is stored at the Chemistry Department of the University of Puerto Rico.

ISOLATION AND EXTRACTION.—The freeze-dried gorgonian (829.5 g) was blended in 1:1 MeOH-$CHCl_3$ (3×2 liters) and, after concentration, the crude extract (47.2 g) was partitioned against H_2O and hexane. The hexane extract (26.1 g) was purified by size-exclusion chromatography on a Bio-Beads SX-2 column (toluene) and the diterpene-enriched fractions were combined and purified subsequently by cc on Si gel (450 g), using mixtures of hexane/EtOAc as eluent. Twelve fractions were obtained on the basis of tlc analysis, and fraction 1 was identified as the known dolabellane hydrocarbon **10** (444.7 mg) (4). Fraction 2 (325.9 mg) was purified by hplc [Partisil-10/50 with hexane-*i*-PrOH (99.8:0.2)] to yield edunone [**3**] (55.3 mg). Fraction 3 (110.0 mg) gave analytically pure eduenone [**4**] (10.2 mg) after purification by hplc [Partisil-10/50 with hexane-*i*-PrOH (99.7:0.3)]. Fraction 6 (82.9 mg) consisted of a mixture of two compounds that, after subsequent separation by hplc [Partisil-10/50 with hexane-*i*-PrOH (99.5:0.5)], gave pure edunol [**6**] and isoedunol [**7**] (32.9 and 16.6 mg, respectively). Fraction 7 was identified as the known dolabellane enone **9** (151.5 mg) (2,3). Fraction 9 consisted of pure palominol [**8**] (1.01 g) (3–5) and fraction 11 consisted of the known dolabellane diketone **2** (2.15 g) (4). Fraction 12 (158.3 mg) was purified by hplc [Partisil-10/50 with hexane-*i*-PrOH (98:2)] to yield edudione [**5**] (26.2 mg).

Edunone [**3**].—Colorless oil; $[\alpha]^{25}D$ +17.0° (*c*=8.45, $CHCl_3$); ir (neat) ν max 2957, 2922, 2852, 1695, 1453, 1373, 1260, 1104, 1023, 796 cm^{-1}; hreims *m/z* $[M]^+$ 288.24462 (6.9) ($C_{20}H_{32}O$ requires 288.24530), 255 (6), 215 (13), 136 (41), 121 (99), 107 (55), 83 (8), 69 (66); ^1H- nmr data (300 MHz, $CDCl_3$), see Table 1; ^{13}C-nmr data (75 MHz, $CDCl_3$), see Table 2.

Eduenone [**4**].—Colorless oil: $[\alpha]^{25}D$ −54.0° (*c*=4.0, $CHCl_3$); ir (neat) ν max 2942, 1681, 1630, 1377, 1260, 1093, 1021, 799 cm^{-1}; uv (MeOH) λ max 244 nm (ε 4391); hreims *m/z* $[M]^+$ 286.23022 (1.8) ($C_{20}H_{30}O$ requires 286.22965), 258 (4), 215 (8), 175 (19), 159 (19), 136 (33), 121 (100), 107 (61), 81 (49), 67 (33), 55 (48); ^1H-nmr data (300 MHz, $CDCl_3$), see Table 1; ^{13}C-nmr data (75 mHz, $CDCl_3$), see Table 2.

Edudione [**5**].—Colorless semisolid: $[\alpha]^{25}D$ −92.4° (*c*=9.0, $CHCl_3$); ir (neat) ν max 2961, 2929, 2856, 1735, 1678, 1622, 1456, 1262, 1129, 1054, 1016 cm^{-1}; uv (MeOH) λ max 246 nm (ε 6421); hreims *m/z* $[M]^+$ 302.22397 (0.6) ($C_{20}H_{30}O_2$ requires 302.22456), 287 (0.9), 241 (1), 222 (76), 207 (22), 165 (25), 149 (35), 107 (41), 82 (100), 67 (48), 55 (62); ^1H-nmr data (300 MHz, $CDCl_3$), see Table 1; ^{13}C-nmr data (75 MHz, $CDCl_3$), see Table 2.

Edunol [**6**].—Colorless oil: $[\alpha]^{25}D$ −18.5° (*c*=7.9, $CHCl_3$); ir (neat) ν max 3420, 2962, 2924, 1456, 1378, 1261, 1092, 1022, 801 cm^{-1}; hreims *m/z* $[M]^+$ 288.24445 (15.3) ($C_{20}H_{32}O$ requires 288.24530), 270 (29), 255 (12), 242 (3), 213 (8), 201 (11), 189 (25), 161 (30), 145 (61), 134 (51), 107 (63), 95 (8), 81 (100), 69 (73), 55 (68); ^1H-nmr data (300 MHz, $CDCl_3$), see Table 1; ^{13}C-nmr data (75 MHz, $CDCl_3$), see Table 2.

Isoedunol [7].—Colorless oil: $[\alpha]^{25}D$ −60.2° (c=6.0, $CHCl_3$); ir (neat) ν max 3502, 2999, 2900, 2852, 1666, 1638, 1620, 1453, 1384, 1260, 1228, 1187, 1127, 1092, 1059, 985, 954, 894, 865, 826, 805 cm^{-1}; hreims m/z $[M]^+$ 288.24492 (26.3) ($C_{20}H_{32}O$ requires 288.24530), 270 (10), 227 (6), 204 (13), 189 (2), 175 (14), 161 (39), 135 (58), 121 (81), 93 (71), 81 (100), 69 (75), 55 (10); ^1H-nmr data (300 MHz, $CDCl_3$), see Table 1; ^{13}C-nmr data (75 MHz, $CDCl_3$), see Table 2.

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