

New Scalaranes from the Nudibranch *Glossodoris atromarginata* and Its Sponge Prey

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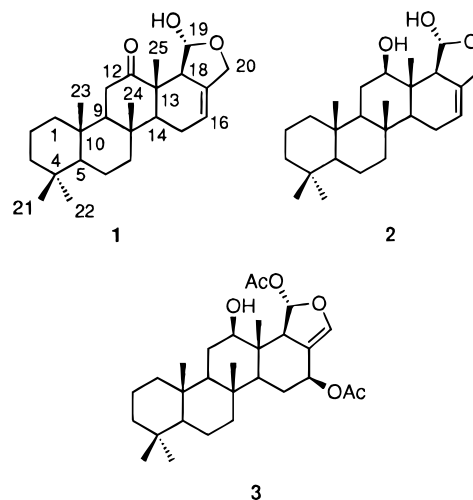
Two new scalaranes (**1** and **2**) have been isolated from the dorid nudibranch *Glossodoris atromarginata* and its prey. The structures were determined by spectral techniques and confirmed by chemical methods. Compounds **1** and **3** showed selective cytotoxic activity against human thyroid carcinoma.

Scalarane compounds have been isolated from many marine organisms including molluscs^{2–4} and sponges.⁵ The pharmacological properties of this class of natural products are of special interest. In fact, many scalaranes have been shown to exert antiinflammatory activity^{6,7} and antiproliferative effects against several tumor cell lines.^{8–10} In Nature it has been also demonstrated that these sesterterpenoids have an ecological role as defense chemicals in opisthobranch molluscs and sponges.^{11,12} In this paper we describe two new scalaranes (**1** and **2**) isolated together with heteronemin (**3**) from the Indo-Pacific nudibranch *Glossodoris atromarginata* (Cuvier, 1804) (Chromodorididae) and its prey, an uncharacterized sponge probably belonging to the genus *Spongia*. Moreover, the structure elucidation of **2** led us to revise the spectral data of a sesterterpene recently reported from a Japanese sponge *Hirtios erecta*.¹⁰

Results and Discussion

The dorid *G. atromarginata* (5 specimens) was collected upon an unidentified sponge off Mandapan (India) in July 1998. The molluscs showed round, white formations along the mantle border. Although these structures resembled the mantle dermal formations (MDF) of Mediterranean *Hypselodoris*¹³ in appearance, they were very different in consistency. In fact, differently from MDFs of *Hypselodoris*, the skin structures of *G. atromarginata* were soft and the content was very easily removed by syringe. This substance was dissolved in CHCl₃/MeOH 2:1 and chromatographically compared with the EtOAc-soluble material of the acetone extracts from the skin and from the inner organs of the mollusc. As expected, the content of MDF-like structures proved to be a mixture of almost pure Ehrlich-positive compounds later identified as **1–3**. The same compounds were present in the anatomical sections of the nudibranch, whereas the sponge extract was shown to contain only **2**. Accordingly, fractionation of the mollusc extracts (88 mg) gave compound **1–3**, whereas SiO₂ chromatography, followed by reversed-phase HPLC purification of the sponge material (126 mg) yielded **2**.

The molecular formula of 12-deacetoxy-12-oxo-deoxoscalarin (**1**), [α]_D +32.6° (c 0.5, CHCl₃) was deduced as C₂₅H₃₈O₃ by the EIMS highest fragment at *m/z* 386. The IR absorptions at 1706 and 3421 cm⁻¹ indicated the



presence of carbonyl and hydroxy groups. The ¹³C NMR spectrum of **1** showed twenty-five signals accounting for one ketone (δ 219.1), two olefinic carbons (δ 136.3 and 116.3), one ketal (δ 99.2), five methyl groups (δ 33.2, 21.3, 16.2, 15.7 and 13.5), and one carbon bearing oxygen (δ 68.5). In accordance with the scalarane skeleton, the ¹H NMR spectrum of **1** featured five angular methyl groups (δ 0.85, H₃-21; δ 0.82, H₃-22; δ 0.88, H₃-23; δ 1.12, H₃-24; δ 1.06, H₃-25), together with an acetal hydrogen at δ 5.23 (H-19), an olefin proton at δ 5.49 (H-16) and a downshifted methylene system at δ 4.53 and 4.20 (H₂-20). The keto function was assigned at C-12 in analogy with other related compounds on the basis of the chemical shifts both of H₃-25 (δ 1.06) and of the methylene system at C-11 (δ 2.62 and 2.37), in turn coupled to the methine proton at δ 1.24 (H-9). The structure elucidation was completed by 2D-NMR experiments that confirmed the all trans stereochemistries of the A, B and C rings and allowed all resonances to be assigned (Table 1).

Compound **2** (12-deacetyl-12-epi-deoxoscalarin), [α]_D +13.5° (c 0.5, CHCl₃), showed a ¹H NMR spectrum very similar to that of **1**. In fact, compound **2** mainly differed from **1** by the presence of a carbinolic proton at δ 3.52 (H-12) and by the upfield shift of H₂-11 (δ 1.72 and 1.49), H₃-24 (δ 0.93), and H₃-25 (δ 0.85). These data, on the whole, indicated the presence of the hydroxy group at C-12 and a molecular arrangement very close to that of deoxoscalarin (**4**) or epi-deoxoscalarin (**5**). Accordingly, the ¹³C NMR data showed twenty-five signals including one acetal and two carbons bearing oxygen. The C-25 shift has been described

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Table 1. NMR Data (CDCl₃) for Compounds **1** and **2**

	compound 1			compound 2		
	δ_{H} , <i>m</i> , <i>J</i> (Hz)	δ_{C} (m)	selected NOEs	δ_{H} , <i>m</i> , <i>J</i> (Hz)	δ_{C} (m)	selected NOEs
1	1.60–1.54, <i>m</i>	39.3 (t)		1.45–1.70, <i>m</i>	39.9 (t)	
2	1.60–1.54, <i>m</i>	18.0 (t)		1.45–1.70, <i>m</i>	18.1 (t)	
3	1.44, <i>m</i>	41.4 (t) ^a		1.42, <i>m</i>	41.7 (t)	
	1.12, <i>m</i>			1.12, <i>m</i>		
4	–			–	33.3 (s)	
5	0.81, <i>m</i>	56.4 (d) ^b		1.12, <i>m</i>	56.5 (d)	
6	1.57, <i>m</i>	18.3 (t)		1.61, <i>m</i>	18.6 (t)	
	1.44, <i>m</i>			1.42, <i>m</i>		
7	1.83, <i>dt</i> , 12.7, 3.3, and 3.3	41.8 (t) ^a		1.71, <i>m</i>	42.1 (t)	
	1.00, <i>ddd</i> , 12.7, 12.7, and 3.7			0.90, <i>m</i>		
8	–	37.8 (s)		–	37.4 (s)	
9	1.24, <i>dd</i> , 14.3 and 2.2	55.8 (d) ^b		1.12, <i>m</i>	58.8 (d)	
10	–	38.1 (s)		–	37.4 (s)	
11	2.62, <i>t</i> , 14.3	35.7 (t)		1.72, <i>m</i>	26.0 (t)	
	2.37, <i>dd</i> , 14.3 and 2.2			1.49, <i>m</i>		
12	–	219.1 (s)		3.52, <i>dt</i> , 11.4, 4.0, and 4.0	81.2 (d)	H-18, H-14
13	–	49.1 (s)		–	39.9 (s)	
14	1.53, <i>dd</i> , 11.0 and 5.4	55.7 (d) ^b	H-18	1.12, <i>m</i>	53.4 (d)	H-12, H-18
15	2.14, <i>bm</i>	22.4 (t)	H ₃ –24	2.04, <i>m</i>	22.2 (t)	H ₃ –24
16	5.49, <i>bs</i>	116.3 (d)		5.50, <i>bs</i>	117.2 (d)	
17	–	136.3 (s)		–	135.2 (d)	
18	2.65, <i>bs</i>	59.6 (d)	H-14, H-20a	2.22, <i>bs</i>	61.0 (d)	H-14, H-20a
19	5.23, <i>bd</i> , 5.4	99.2 (d)	H ₃ –25, H-20	5.27, <i>bd</i> , 6.5	99.6 (d)	H ₃ –25, H-20b
20	4.53, <i>bd</i> , 12.0	68.5 (t)	H-18, H-19	4.53, <i>d</i> , 12.0	68.7 (t)	H-18
	4.20, <i>d</i> , 12.0			4.23, <i>d</i> , 12.0		
21	0.85, <i>s</i>	33.2 (q)		0.80, <i>s</i>	33.3 (q)	
22	0.82, <i>s</i>	21.3 (q)		0.84, <i>s</i>	21.3 (q)	
23	0.88, <i>s</i>	16.2 (q)		0.84, <i>s</i>	16.6 (q) ^c	
24	1.12, <i>s</i>	15.7 (q)	H-15	0.93, <i>s</i>	17.0 (q) ^c	H-15
25	1.06, <i>s</i>	13.5 (q)	H-19	0.85, <i>s</i>	8.7 (q)	H-19

^{a–c} Assignments with the same superscripted letters are interchangeable.

Table 2. Selected ¹³C NMR Data of Sesterterpenes 1–6 and 9–12.

	1	2	2^a	3	4^b	5^c	6	9^c	10^c	11^d	12^d
C-12	219.1	81.2	81.2	80.5	74.8	82.7	39.9	74.6	82.1	81.5	82.7
C-13	41.5	39.9	49.5	42.7	36.8	37.7	31.9	36.9	38.6	37.3	37.5
C-18	60.5	61.0	59.2	64.2	53.4	61.2	61.3	50.8	58.8	58.9	58.1
C-19	99.7	99.6	106.3	101.7	98.5	99.8	99.4	98.9	99.8	102.1	103.8
C-25	13.8	8.7	8.8	8.8	14.7	9.8	14.1	15.1	10.2	8.8	9.8

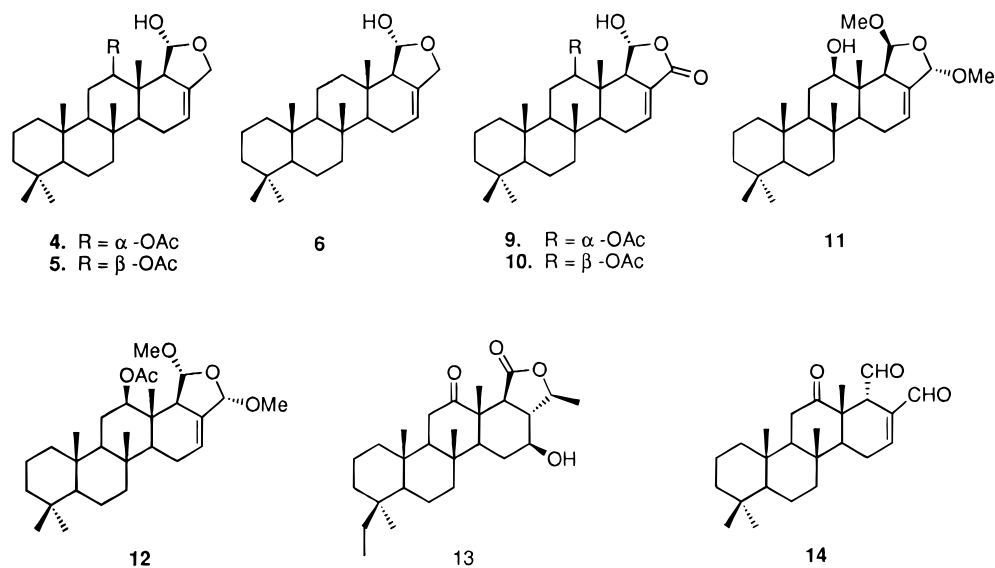
^a Data from ref 10. ^b Data from ref 4. ^c Data from ref 14. ^d Data from ref 7.

by many authors as diagnostic to determine the relative stereochemistry at C-12 and C-18 in the scalarane series.^{7,11,14} In fact, there is an additive γ -effect that induces the upfield shift of C-25 moving from 12 α ,18 α - to 12 β ,18 β -substituted scalaranes. The chemical shift value of C-25 (δ 8.7) in **2** was very similar to that found in 12-*epi*-deoxoscalarin (**5**) (δ 9.8),¹⁴ thus supporting a β stereochemistry at both C-12 and C-18 (Table 1).

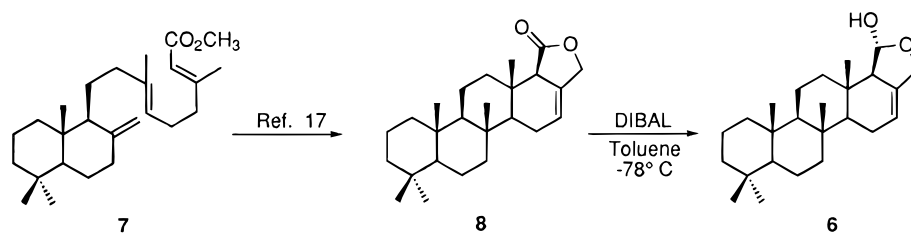
Products **1** and **2** had a five-membered heterocyclic ring of which the hemiacetal stereochemistry seemed to be similar to that found in deoxoscalarin (**4**) and other related compounds. The relative stereochemistry of **1** was fully determined by NOESY experiments (mixing time at 400 or 800 ms). In particular, cross-peaks between H-19 (δ 5.23) and H₃-25 (1.06), as well as between H-14 (δ 1.53) and H-18 (δ 2.65) supported unambiguously the trans relationship between H-18 and H-19, thus confirming the relative geometry previously suggested for deoxoscalarin and related products. Likewise, conformational analysis of **2** led us to the same conclusion featured by the all *anti* stereochemistry of the ring junctions and the β -orientation of H-19. In fact, NOESY and 1D-NOE experiments showed correlation among H-12 (δ 3.52), H-14 (δ 1.12), and H-18 (δ 2.22), as well as H-19 (δ 5.27) and H₃-25 (δ 0.85). Compound **2** had the same structure as a scalarane

derivative recently reported from the Japanese sponge *H. erecta*.¹⁰ However, a comparison of the ¹³C NMR data of **2** with those of the *H. erecta* metabolite put in evidence some significant differences. In fact, particularly misleading were the chemical shifts of C-13 and C-19 that fell at δ 49.5 and 106.3 in the sesterterpenoid isolated from *H. erecta*¹⁰ and at δ 39.9 and 99.6 in **2**. To clarify this incongruence, we carried out the synthesis of 12-deacetoxy-deoxoscalarin (**6**), a non-natural derivative of deoxoscalarin (**4**) with relative configuration of the sesterterpenoid skeleton similar to that of **2**. To obtain **6**, we took advantage of a recent stereoselective synthesis of scalarane compounds by superacidic cyclizations of chiral precursors.¹⁵ According to the procedure reported by Ungur et al.,¹⁶ the chiral ester **7** was transformed into the lactone **8**. Reduction of this latter compound with DIBAL gave the hemiacetal **6** in 33% yield (100% of conversion). Despite the absence of the hydroxy group at C-12, the NMR data of **6** were very similar to those of **2**. In particular, the chemical shifts values of both C-13 and C-19 in **6** were in good agreement with those found for **2**, **4**, **5**, and related compounds (**9**, **11**, **12**) (Table 2, Chart 1).^{4,7,10,14} As no stereochemical studies have been mentioned to support the assignment of the product from *H. erecta*,¹⁰ we have to conclude that either this metabolite

Chart 1



Scheme 1. Synthesis of 12-Deacetoxydeoxoscalarin (**6**)



has a different structure or the values shown in the paper are misrepresented.

Conclusion

The presence of **2** in both *G. atromarginata* and the sponge supports their prey-predator relationship. On the other hand, the keto moiety at C-12 of **1** is quite common in natural products belonging to the homoscalarane series (e.g. **13**),¹⁷ but, except for the 12-ketoscalaradiol (**14**),² it has never been described for products having the scalarane skeleton. This fact, together with the co-occurrence of **2**, led us to suggest that *G. atromarginata* may bio-transform the sponge metabolite **2** by selective oxidation of the hydroxy group at C-12. However, the finding of heteronemin (**3**) in the nudibranch could also indicate that the mollusc preys upon different sponges from which it may bio-accumulate **1** and **3**.

We have previously reported the presence of spongiane diterpenoids from an Egyptian (Red Sea) collection of *G. atromarginata*.¹⁸ The apparent occurring of scalarane and spongiane compounds from the same nudibranch led us to reconsider the taxonomy of the Red Sea mollusc. On the basis of a further analysis the species of this latter mollusc was revised as *Glossodoris cincta* (Bergh, 1888) (Chromodorididae).

Finally, it is noteworthy that the reduction of the lactone **8** proceeds in a stereospecific manner to give only the hemiacetal **6**. There are two possible explanations for the reaction to proceed in this way. The first hypothesis is *anti*-Cram attack of the hydride to the carbonyl group from the more hindered face; the second possibility is that the reduction of **8** first gives the hydroxyaldehyde **15**, that, under the reaction conditions, can cyclize to the more stable hemiacetal **6** (Schemes 1 and 2). This latter way seems to us much more conceivable and, moreover, could account

for the experimental observation that the rare scalaranes with syn geometry between H-18 and H-19 isomerized to *anti* isomers on standing for several days in CDCl₃.⁷

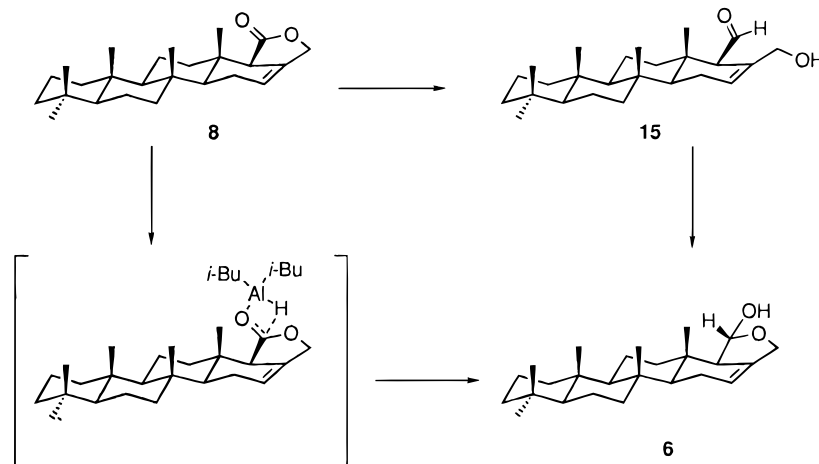
In a preliminary assay, 12-ketodeoxoscalarin (**1**) and heteronemin (**3**) showed specific cytotoxicity against human thyroid carcinoma (25 and 30% of mortality, respectively), but 12-deacetyl-12-*epi*-deoxoscalarin (**2**) was inactive in this test. Further details will be the subject of a forthcoming paper.

Experimental Section

General Methods. 1D and 2D NMR spectra were recorded on Bruker AMX-500. The CHCl₃ resonances at δ 7.26 and 77.0 were used as internal references. MS spectra were obtained on a Kratos MS 50 spectrometer operating at 70 eV. Infrared data were recorded by Bio-Rad FTS-7 FT/IR spectrophotometer. Optical rotations were determined by JASCO DIP-370 polarimeter. HPLC was performed by Waters Liquid Chromatography apparatus equipped with two 510 pump units and a JASCO Uvidec 100 III spectrophotometer.

Biological Material. The first population of *G. atromarginata* (5 specimens, 3 cm long) and the sponge upon which the nudibranchs grazed were collected while SCUBA diving off Mandapam (India) during the April of 1998. The molluscs were identified by Prof. J. Ortea of the University of Oviedo. Voucher specimen of *G. atromarginata* (MAN23-98) is kept at ICMIB (Italy).

Extraction of Nudibranch and Fractionation of Extracts. After collection, the nudibranchs were immediately frozen and transferred to Italy. The content of some MDF's from different nudibranchs was removed by syringe, dissolved in CHCl₃/MeOH 2:1 (1 mL) and directly analyzed by SiO₂ TLC. The nudibranchs were carefully dissected to separate the skin from the inner organs. The anatomical section and the mucus released by the animals were exhaustively extracted with acetone. After removing the volatile solvent, the aqueous residues were diluted by freshwater and separately partitioned

Scheme 2. Hypothetical Mechanism for the Stereoselective Reduction of the Lactone **8** to the Hemiacetal **6**

with EtOAc. The organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated at reduced pressure to give 38 mg of mantle extract, 50 mg of gland extract, and 2.2 mg of mucus extract. The EtOAc-soluble materials were compared by TLC in different eluant systems (light ether/ Et_2O 4:6, light ether/ Et_2O 2:8; $\text{CHCl}_3/\text{MeOH}$ 95:5). Mantle and gland extracts were combined and fractionated on a Si gel column (1×25 cm) by eluting with a gradient of petroleum ether/diethyl ether to give **1** (11.2 mg, 12.7% of the EtOAc extract), **2** (0.5 mg, 0.5% of the EtOAc extract), and **3** (2.6 mg, 2.9% of the EtOAc extract).

Extraction of the Sponge and Fractionation of the Extract. The sponge (600 mg wet weight) collected together with this population of nudibranchs was extracted as above-reported for the nudibranch sections. Si gel column chromatography of the EtOAc-soluble material, followed by reversed-phase HPLC (ODS-2 10×250 mm column; isocratic elution with 10% of H_2O in MeOH, at a flow of 1 mL/min; detector UV at 208 nm) gave 2.8 mg of **2** (0.46% of the wet wt).

12-Deacetoxy-12-oxodeoxoscalarin (1): 11.2 mg, white powder; $[\alpha]_D +32.6^\circ$ (c 0.5, CHCl_3); IR (film) 3421, 2919, 2846, 1706, 1390 cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 1; EIMS (m/z): 386 (M^+ , 3), 368 (35, $\text{M} - \text{H}_2\text{O}$), 192 (70), 70 (100); HREIMS m/z 368.2727 [$\text{C}_{25}\text{H}_{36}\text{O}_2$, ($\text{M} - 18$) $^+$ requires 368.2715].

12-Deacetyl-12-*epi*-deoxoscalarin (2): 3.3 mg, white powder; $[\alpha]_D +13.5^\circ$ (c 0.5, CHCl_3); IR (film) 3367, 2919, 2850, 1382 cm^{-1} ; ^1H NMR and ^{13}C NMR data, see Table 1; EIMS (m/z): 370 ($\text{M} - \text{H}_2\text{O}$, 13), 355 (5), 192 (40), 96 (60), 70 (100); HREIMS m/z 370.2874 [$\text{C}_{25}\text{H}_{38}\text{O}_2$, ($\text{M} - 18$) $^+$ requires 370.2872].

Synthesis of 12-Deacetoxydeoxoscalarin (6). Compound **8** (11.0 mg, 0.03 mmol) was dissolved in 1.5 mL of toluene and reacted with DIBAL in THF (8.5 mg, 0.06 mmol) at -78°C under N_2 atmosphere. The reaction was allowed to stir for 2 h, and then it was acidified with 5% H_2SO_4 (2 mL). The reaction mixture was extracted with Et_2O (3×2.5 mL). The organic layers were combined, dried at reduced pressure, and purified on Si gel column to give 3.6 mg of **6**.

12-Deacetoxydeoxoscalarin (6): 3.6 mg, white crystalline powder; $[\alpha]_D -6.9^\circ$ (c 0.2, CHCl_3); IR (film) 3395, 2915, 2866, 1445 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.49 (1H, bs), 5.26 (1H, bt), 4.47 (1H, bd, $J = 11.3$ Hz), 4.17 (1H, d, $J = 11.3$ Hz), 2.16 (1H, bs), 2.10–1.80 (2H), 1.75–1.50 (8H), 1.45–1.00 (10H), 0.90 (3H, s), 0.83 (6H, s), 0.80 (3H, s), 0.76 (3H, s); ^{13}C NMR (CDCl_3) δ 14.8 (q), 16.4 (q), 17.3 (q), 18.1 (t), 18.6 (t), 21.4 (q), 22.7 (t), 31.9 (s), 33.3 (q), 37.5 (s), 37.7 (s), 39.9 (t), 41.2 (t), 41.6 (t), 42.2 (t), 55.0 (d), 56.4 (d), 61.3 (d), 62.1 (d), 68.9 (t), 99.4 (d), 116.9 (d), 136.1 (s); EIMS (m/z): 354 ($\text{M} - \text{H}_2\text{O}$, 20), 192 (30), 96 (80), 70 (100); HREIMS m/z 354.2924 [$\text{C}_{25}\text{H}_{38}\text{O}$, ($\text{M} - 18$) $^+$ requires 354.2923].

Compound 8: spectroscopic data (IR, optical rotation, ^1H NMR) were identical to those previously reported.¹⁶ ^{13}C NMR (CDCl_3) δ 14.8 (q), 16.4 (q), 17.1 (q), 18.1 (t), 18.6 (t), 21.4 (q), 22.4 (t), 33.3 (q), 33.3 (s), 34.3 (s), 37.5 (s), 37.8 (s), 39.9 (t), 40.0 (t), 41.7 (t), 42.1 (t), 54.2 (d), 54.7 (d), 56.6 (d), 61.3 (d), 69.8 (t), 121.7 (d), 129.5 (s), 175.4 (s).

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