Structural and Stereochemical Studies of C-21 Terpenoids from Mediterranean Spongiidae Sponges

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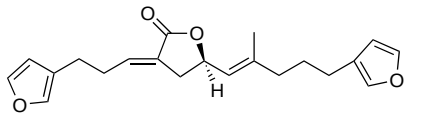
The degraded C-21 sesterterpenoid (+)-**3,** enantiomeric with (−)-untenospongin B, has been isolated from the Mediterranean sponge *Spongia virgultosa*. The absolute stereochemistry of **3** was assigned by applying Mosher's method. On the basis of this work, the absolute stereochemistry at C-11 of nitenin (**1**) and dihydronitenin (**2**) has been reanalyzed by applying Mosher's method, whereas the *R* chirality at C-8 of **2** was determined by recording NOE spectra.The structures of two known C-21 furanoterpenes, tetradehydrofurospongin-1 (**8**) and **7**, have been revised as (+)-**3** (named "revised tetradehydrofurospongin-1") and its acetyl derivative **5**, respectively. Finally, a comparison between the Mosher and Horeau methods was carried out, paying attention to the reliability of the stereochemical predictions obtained by the two approaches applied to compounds (+)-**3**, nitenin (**1**), and dihydronitenin (**2**), containing aliphatic-type alcohols.

Many sponges belonging to the family Spongiidae are chemically characterized by a series of terpenoids containing 21 carbons and displaying two β-substituted furan moieties at the ends of the molecule.[1−9] These unusual compounds are probably biogenetically derived from higher terpenoids. In our study of benthic organisms from Spanish coasts we have studied two sponges, *Spongia agaricina* Pallas (1766) and *Spongia virgultosa* Schmidt (1868), showing similar secondary metabolism and have isolated nitenin (**1**) and dihydronitenin (**2**) from *S. agaricina* and compound (+)-**3** from *S. virgultosa*. All three degraded terpenoids were previously characterized from marine sources,[1,5,8] although aspects of their structures needed still further analysis.

Here we describe the chemical characterization of **1**, **2**, and **3**; the complete determination of the absolute stereochemistry of **2**; and, finally, the reanalysis of the absolute stereochemistry, previously assigned by Horeau's method, of **1** and **3** by applying high resolution ^{1}H-NMR to Mosher's approach as suggested by Kakisawa's group.[10−12] This study also enabled us to compare the Horeau and Mosher methods for assigning absolute stereochemistry as applied to furospongin-like compounds.

S. virgultosa (15 g dry wt) and *S. agaricina* (250 g dry wt) were collected off Blanes (NE of Spain). The Et_2O-soluble fraction from the Me_2CO extract of *S. virgultosa* was characterized by an abundant Ehrlich's reagent positive metabolite (TLC, Et_2O/light petroleum, 4:6; $R_f = 0.4$). The ^{1}H-NMR data of (+)-**3** were identical to those already reported for (−)-untenospongin-B (**6**) isolated from a Japanese *Hippospongia* sp.,[8] although the reported optical rotation was very different [(−)-untenospongin-B $[\alpha]_D = -1.5°$; (+)-**3** $[\alpha]_D = +21.8°$].

The chemical shifts of all protons and carbons were assigned by an extensive 1D- and 2D-NMR analysis.



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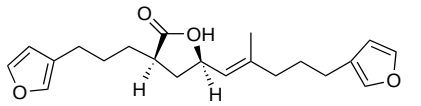

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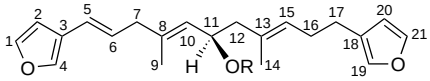
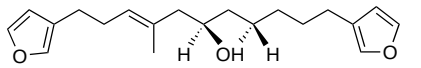


3 R = H
5 R = Ac



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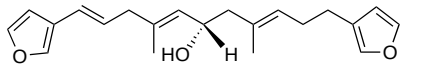
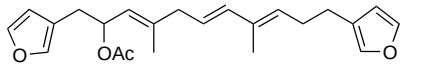


6 (–)-untenospongin B



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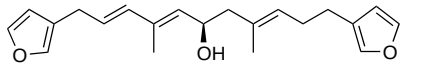

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The *E* stereochemistry at Δ^5 was supported by the coupling constants ($J = 15.8$ Hz) between H-5 ($\delta = 6.24$) and H-6 ($\delta = 5.89$). In the same way, the *E* configuration of the other two double bonds was suggested both by comparison of NMR data with reported values[8] and by a strong NOEs between Me-9 ($\delta = 1.70$) and H-11 ($\delta = 4.44$) and between Me-14 (1.64) and H-16 (2.29).

In order to overcome the ambiguity about the stereochemistry of untenospongin-B (**6**), (+)-**3** was treated with (*R*)- and (*S*)-MTPA chlorides. The $\Delta\delta$ analysis (Table 1) of (*S*)- and (*R*)-esters led to assignment of the *R* absolute stereochemistry at C-11. This result is consistent with revised data on (−)-untenospongin B,[13]

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Table 1. NMR Data in $CDCl_3$ for (+)-(**3**) and Its MTPA Esters[a]

	δ ^{1}H m[b]	δ ^{13}C	δ ^{1}H m[b] (*S*)-MTPA ester	δ ^{1}H m[b] (*R*)-MTPA ester	$\Delta\delta = \delta_H(S) - \delta_H(R)$
1	7.34 s	143.32			
2	6.49 s	107.56	6.46	6.47	−0.01
3		124.26			
4	7.36 s	139.62			
5	6.24 d	121.14	6.22	6.24	−0.02
6	5.89 dt	127.60	5.80	5.83	−0.03
7	2.82 d	42.86	2.80	2.84	−0.04
8		136.90			
9	1.70 s	16.69	1.78	1.79	−0.01
10	5.23 d	128.23	5.10	5.24	−0.14
11	4.44 dt	65.82	5.85	5.87	−0.02
12	2.16 d	48.09	2.26	2.21	+0.05
			2.46	2.40	+0.06
13		132.26			
14	1.64 s	16.22	1.64	1.57	+0.07
15	5.27 dd	128.04	5.25	5.16	+0.09
16	2.29 dt	28.46	2.23	2.16	+0.07
17	2.48 dd	24.79	2.41	2.36	+0.05
18		124.64			
19	7.20 s	138.87	7.18	7.16	+0.02
20	6.26 s	110.90	6.24	6.23	+0.01
21	7.34 s	142.72			
-OCH_3			3.52	3.51	+0.01
Ph-MTPA			7.33−7.52	7.33−7.52	

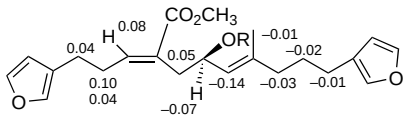
[a] In ppm from internal TMS in $CDCl_3$ solution. [b] Assignments aided by ^{1}H−^{1}H COSY and decoupling experiments.

which indicates that it has $[\alpha]_D$ −20.1° (*c* 1.02, $CHCl_3$). In addition, the acid chlorides giving the (*R*)- and (*S*)-MTPA esters[9] were reported with their stereochemistry reversed.[13] Compound (−)-**3** thus has the *S* absolute stereochemistry.

A comparison of the NMR data of (+)-**3** and of its acetyl derivative **5** with those reported in the literature for tetradehydrofurospongin-1 (**8**), isolated from *Spongia* sp.,[5,6] and for **7**, found in the digestive glands of the Mediterranean *Dendrodoris grandiflora*,[14] led to the revision of both previously suggested structures. Tetradehydrofurospongin-1 (**8**) [(+) isomer][15] and **7** must be reassigned as (+)-**3** and its acetyl derivative **5**. It is interesting that the *R* chirality at C-11 for **8**, suggested by applying Horeau's method,[6] is consistent with our results obtained by Mosher's methodology.

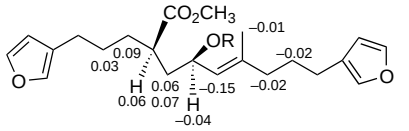
The Et_2O-soluble fraction from the Me_2CO extracts of *S. agaricina* contained large amounts of **1** and **2**, previously isolated from a Spongiidae sponge reported as *Spongia nitens*.[1] However, a recent analysis of a specimen of *Spongia nitens*, collected in the Bay of Naples, showed neither chemical nor taxonomic differences from *S. agaricina*. In order to confirm the proposed stereochemistry at C-11, the lactone ring of **1** was opened by alkaline hydrolysis, and the resulting hydroxy acid was immediately methylated with CH_2N_2 to give the ester **9**. Esterification with (*R*)- and (*S*)-MTPA chloride led, respectively, to (*S*)- (**9a**) and (*R*)-MTPA (**9b**) esters. The ^{1}H-NMR analysis of the esters confirmed the *R* absolute stereochemistry at C-11 (Figure 1a) previously predicted by applying Horeau's method.[1] The same procedure was carried out to determine the absolute configuration at C-11 of **2**; analogously with **1**, it was assigned as *R* (Figure 1b). Moreover, a cis relationship between H-8 and H-11 was demonstrated by a series of NOE measurements, leading to assignment of the chirality *8R,11R* to dihydronitenin (**2**).

a)



9 R = H
9a R = (*S*)-MTPA
9b R = (*R*)-MTPA

b)



10 R = H
10a R = (*S*)-MTPA
10b R = (*R*)-MTPA

Figure 1. $\Delta\delta$ (δ^1H (*S*)-MTPA ester−δ^1H (*R*)-MTPA ester) values observed by analyzing the ^{1}H-NMR spectra of the MTPA derivatives of **9** (a) and **10** (b).

As already stated, our results on compounds **1**, **2**, and **3** confirm the previous stereochemical assignments obtained by Horeau's method.[1,6] These conclusions seem to disagree with data reported for furospongin-1 (**4**),[16] for which Mosher's and Horeau's methods reach different conclusions. Nevertheless, a careful analysis of structures **1**−**3** points out some structural aspects that explain this apparent anomaly. In particular, the distance between the chiral carbinol center and the double bond seems to play a key role for the reliability of Horeau's method applied to **1**−**3**. In fact, the hydroxy function is α to the double bond (allylic position) for compounds **1**−**3**, whereas it is *β* for furospongin (**4**). Horeau's method is based on the unequal esterification rates of the chiral alcohol with racemic 2-phenylbutyric anhydride (or the corresponding chloride). As the kinetic resolution depends on the chemical diversity of the two substituents connected to the chiral secondary alcohol, it can be concluded that the position of the double bond of compounds **1**−**3**, for steric or stereoelectronic effects, is able to influence the degree of differentiation of the two groups. On the other hand, Mosher's method, as modified by Kakisawa, is based on the effect that the aromatic ring of MTPA has on the two substituents and is, in theory, independent of the structural features of the two groups.

In conclusion, Horeau's method can be used with confidence when the chemical nature of the two substituents connected to the chiral center is different. In practice, in the case of the C-21 furan products studied, only compounds **1**, **2**, and **3** show these structural requirements, whereas the two groups connected to the chiral center of furospongin (**4**) are presumably too similar to allow rigorous application of Horeau's method.

Experimental Section

General Experimental Procedures. HPLC was performed on a Spherisorb ODS-2 S5 (250 × 5 mm) column with a Waters Liquid Chromatography unit, using a Waters R41 differential refractometer. MS were recorded on a Kratos MS 50. Precoated TLC plates Merck Si gel 60 F254 were used for analytical TLC, and Merck Kieselgel 60 powder was used for preparative column chromatography. ^{1}H- and ^{13}C-NMR spectra were recorded by Bruker AMX500 (500 MHz) spectrom-

eter. Chemical shifts are expressed in ppm referred to $CHCl_3$ used as an internal standard. Coupling constants (*J* values) are reported in Hz. Optical rotations were determined by JASCO DIP 370 polarimeter. IR and UV spectra were measured with a BIO-RAD FTS-7 FTIR and a Varian DMS 90 spectrophotometer, respectively.

Biological Material. All sponges were collected off Blanes (NE Spain) and classified by one of us (M. U.). Voucher specimens (*S. agaricina* no. CEAB.POR.CH001 and *S. Virgultosa* no. CEAB.POR.CH002) are deposited at the Centre d'Estudios Avanzados, Blanes.

Isolation and Characterization of Nitenin (1) and Dihydronitenin (2). The Et_2O-soluble material (3.5 g) from the CH_3COCH_3 extract of the frozen *S. agaricina* (dry wt, 250 g) was fractionated by Si gel column eluting with light petroleum−Et_2O (90:10 v/v) to afford nitenin (**1**, 56 mg) together with a second fraction (40 mg) containing **2** as main component. Dihydronitenin (**2**) was further purified by washing this fraction with light petroleum. A complete assignment of ^{1}H- and ^{13}C-NMR values of **1** and **2** was carried out by 1D and 2D NMR experiments (^{1}H−^{1}H COSY, ^{1}H−^{13}C HETCOR, HOHAHA).

Nitenin (**1**): obtained as a yellow oil (light petroleum−Et_2O 9:1); $[\alpha]_D$ −42.5° ($CHCl_3$, *c* 1.86); *m/z* (%) 340 (M^+, 15), 325 (25), 177 (100), 161 (70), 135 (80), 81 (95), 53 (80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, s, H-1 and H-21), 7.24 (1H, s, H-4), 7.20 (1H, s, H-19), 6.30 (1H, s, H-2), 6.26 (1H, s, H-20), 6.16 (1H, dd, J = 7.2 Hz, H-7), 5.22 (1H, d, J = 8.8 Hz, H-12), 5.15 (1H, m, H-11), 2.99 (2H, m, H-10a and H-6), 2.57 (2H, m, H-10b and H-5), 2.39 (2H, t, J = 7.6 Hz, H-17), 2.06 (2H, t, J = 7.6 Hz, H-15), 1.72 (3H, s, CH_3-14), 1.68 (3H, s, CH_3-16); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.74 (C-9), 142.87 (C-1), 142.76 (C-21), 142.64 (C-13), 142.07 (C-7), 139.06 (C-4), 138.87 (C-19), 125.67 (C-8), 124.66 (C-18), 123.87 (C-3), 123.38 (C-12), 110.93 (C-2), 110.89 (C-20), 74.05 (C-11), 38.84 (C-15), 36.46 (C-10), 27.69 (C-16), 27.51 (C-6), 24.23 (C-5 and C-17), 16.71 (C-14).

Dihydronitenin (**2**): obtained as a yellow oil (light petroleum−Et_2O 9:1); $[\alpha]_D$ −30.1° ($CHCl_3$, *c* 18.1); *m/z* (%) 342 (M^+, 10), 327 (20), 233 (25), 135 (90), 95 (90), 81 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (2H, s, H-1 and H-21), 7.22 (1H, s, H-4), 7.20 (1H, s, H-19), 6.26 (2H, s, H-2 and H-20), 5.20 (1H, d, J = 8.5 Hz, H-12), 5.06 (1H, ddd, J = 8.5, 5.6, 5.6 Hz, H-11), 2.61 (1H, m, H-8), 2.47 (3H, m, H-10a and H-5), 2.40 (2H, m, H-17), 2.07 (2H, t, J = 7.6 Hz, H-15), 2.00 (1H, m, H-7a), 1.72 (3H, s, CH_3-14), 1.67 (2H, m, H-16), 1.65 (2H, m, H-6), 1.60 (1H, m, H-10b), 1.50 (1H, m, H-7b); ^{13}C NMR (500 MHz, $CDCl_3$) δ 178.75 (C-9), 143.96 (C-13), 142.83 (C-1 and C-21), 138.89 (C-4 and C-19), 124.67 (C-3 or C-18), 124.46 (C-18 or C-3), 122.86 (C-12), 110.85 (C-2 and C-20), 75.34 (C-11), 41.03 (C-8), 38.85 (C-15), 36.11 (C-10), 29.87 (C-7), 27.81 (C-6), 27.68 (C-16), 24.61 (C-5), 24.22 (C-17), 16.79 (C-14).

Isolation and Characterization of (+)-3. *Spongia virgultosa* (15 g dry wt) was extracted with CH_3COCH_3 (500 mL). After removing the organic solvent, the residual H_2O was extracted with Et_2O three times. The upper layers were recombined and concentrated to give 450 mg of crude material that was fractionated on a Si gel column using light petroleum with increasing amounts of Et_2O as eluent to afford (+)-**3** (60 mg) as the main metabolite.

(+)-Tetradehydrofurospongin-1 (**3**): obtained as a colorless oil (light petroleum−Et_2O); $[\alpha]_D$ +21.8° ($CHCl_3$, *c* 0.78); $(\theta)_{218.5}$ 7240 (EtOH); UV (EtOH) λ_{max} 209 (ϵ 30270); IR (EtOH solution) ν_{max} 3433, 3128, 2916, 2853; EIMS (70 eV) *m/z* (%) 326 (M^+, 7), 308 ($M^+ - H_2O$, 20), 176 (60), 150 (60), 97 (84), 81 (100). HREIMS *m/z* (%) 326.1913 (required 326.1882 for $C_{21}H_{26}O_3$); ^{1}H- and ^{13}C-NMR values are reported in Table 1.

(*S*)- and (*R*)-Methyl Esters of (+)-3. A solution of (+)-**3** (8 mg) was divided into two fractions containing 5 mg and 3 mg, respectively. The two fractions were treated with (*S*)- and (*R*)-MTPA chloride and worked up in the usual way, in order to obtain, after chromatographic purification, (*S*)-MTPA ester (**3a**, 2.4 mg) from the fraction of 5 mg, and (*R*)-MTPA ester (**3b**, 1.5 mg) from the fraction of 3 mg. ^{1}H-NMR data are reported in Table 1.

Acetylation of (+)-3. To a solution of (+)-**3** (6 mg, 0.018 mmol) in pyridine (0.5 mL), Ac_2O (20 μL) was added, and the mixture was stirred at room temperature for 2 h. After concentration *in vacuo*, chromatographic purification gave **5** (6 mg, 0.016 mmol, 90%) $[\alpha]_D$ +28.9° ($CHCl_3$, *c* 1.5). Spectral data were identical to those previously reported.[14]

Niteninic Acid Methyl Ester (9). A solution of nitenin (**1**, 200 mg, 0.588 mmol) in 40 mL of MeOH−H_2O (1:1 v/v) containing 1 g of KOH was heated with stirring at 60 °C for 1 h. The reaction mixture was cooled, and the organic solvent was removed *in vacuo*. The H_2O suspension was acidified with 0.5 N HCl and then extracted with Et_2O (3 × 15 mL). The combined extracts were washed with H_2O and dried over Na_2SO_4. CH_2N_2 (5mL in Et_2O) was added dropwise to the Et_2O solution at 0 °C. After 15 min at 0 °C, the reaction mixture was quenched with MeOH; the solvent was removed under reduced pressure, and **9** (35 mg, 0.094 mmol, 32%) was purified by chromatography on Si gel. ^{1}H-NMR data are identical to those reported.[1]

Dihydroniteninic Acid Methyl Ester (10). To **2** (21 mg, 0.062 mmol) was added 2 mL of a solution of MeOH−H_2O (1:1 v/v) containing 2.5% of KOH. The reaction mixture was stirred at room temperature for 1 h, and then worked up as previously discussed for niteninic acid to give pure **10** (15.8 mg, 0.043 mmol, 69%). ^{1}H-NMR data are identical to those reported.[1]

(*S*)- and (*R*)-Methyl Esters of 9. (*S*)-MTPA chloride was added at 0 °C to a solution of **9** (4 mg) in CH_2Cl_2 (1.5 mL) containing DMAP (9.5 mg) and Et_3N (8 mL). The solution was stirred under N_2 at room temperature for 2 h. After concentration *in vacuo*, the (*R*)-MTPA ester (**9b**) was purified by HPLC using a reversed-phase column (MeOH−H_2O, 8:2 v/v). The (*S*)-MTPA ester (**9a**) was obtained in the same way by (*R*)-MTPA chloride.

(*S*)-MTPA Ester of Niteninic Acid Methyl Ester (9a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (1H, MTPA), 7.34 (7H, m, MTPA, H-4 and H-19), 7.18 (2H, s, H-1 and H-21), 6.23 (2H, s, H-2 and H-20), 6.00 (1H, t, J = 7.1 Hz, H-7), 5.82 (1H, m, H-11), 5.00 (1H, d, J = 9.3 Hz, H-12), 3.75 (3H, s, $-CO_2CH_3$), 3.49 (3H, br s, $-OCH_3$), 2.76 (1H, m, H-6a), 2.64 (1H, m, H-6b), 2.60 (2H, t, J = 6.9 Hz, H-10), 2.46 (2H, t, J = 7.3 Hz, H-5), 2.35 (2H, t, J = 7.5 Hz, H-17), 2.01 (2H, t, J = 7.3 Hz,

H-15), 1.74 (3H, d, J = 1.0 Hz, CH_3-14), 1.63 (2H, t, J = 7.5 Hz, H-16).

(*R*)-MTPA Ester of Niteninic Acid Methyl Ester (9b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (1H, MTPA), 7.35 (7H, m, MTPA, H-4 and H-19), 7.18 (2H, s, H-1 or H-21), 6.24 (2H, s, H-2 and H-20), 5.92 (1H, m, H-7), 5.89 (1H, m, H-11), 5.14 (1H, d J = 9.4 Hz, H-12), 3.74 (3H, s, $-CO_2CH_3$), 3.50 (3H, br s, $-OCH_3$), 2.72 (1H, m, H-6a), 2.56 (2H, m, H-10), 2.54 (1H, m, H-6b), 2.42 (2H, t, J = 7.0 Hz, H-5), 2.36 (2H, t, J = 7.4 Hz, H-17), 2.04 (2H, t, J = 7.3 Hz, H-15), 1.75 (3H, sd, J = 1.2 Hz, CH_3-14), 1.65 (2H, t, J = 7.7 Hz, H-16).

(*S*)- and (*R*)-Methyl Esters of 10. A solution of **10** (16 mg) in dry pyridine (2 mL) was divided into two aliquots. Under N_2, (*R*)- or (*S*)-MTPA chlorides were separately added to each fraction. The two reactions were kept at room temperature for 48 h. Then the pyridine was removed under reduced pressure, and the oily residue was partitioned between H_2O and Et_2O (3 × 3 mL). The combined Et_2O extracts were washed with H_2O and dried over Na_2SO_4, and the solvent was evaporated to obtain a residue that was chromatographed by HPLC on ODS-2 with MeOH−H_2O (88:12, v/v) to give, respectively, (*S*)-MTPA ester (**10a**) and (*R*)-MTPA-ester (**10b**).

(*S*)-MTPA Ester of Dihydroniteninic Acid Methyl Ester (10a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (1H, MTPA), 7.35 (7H, m, MTPA, H-4 and H-19), 7.18 (2H, s, H-1 and H-21), 6.23 (2H, s, H-2 and H-20), 5.67 (1H, m, H-11), 4.95 (1H, d, J = 9.5 Hz, H-12), 3.68 (3H, s, $-CO_2CH_3$), 3.52 (3H, br s, $-OCH_3$), 2.37 (5H, m, H-5, H-17 and H-8)*, 2.14 (1H, m, H-10a), 2.04 (2H, t, J = 7.5 Hz, H-15), 1.75 (3H, br s, CH_3-14), 1.70 (1H, m, H-10b), 1.64 (2H, t, J = 8.0 Hz, H-16)*, 1.64 (2H, m, H-7)*, 1.51 (2H, m, H-6)*. (*Chemical shifts designated with an asterisk were assigned by COSY.)

(*R*)-MTPA Ester of Dihydroniteninic Acid Methyl Ester (10b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (1H, MTPA), 7.37 (7H, m, MTPA, H-4 and H-19), 7.18 (2H, s, H-1 and H-21), 6.23 (2H, s, H-2 and H-20), 5.71 (1H, m, H-11), 5.10 (1H, bd, J = 9.5 Hz, H-12), 3.65 (3H, s, $-CO_2CH_3$), 3.52 (3H, br s, $-OCH_3$), 2.37 (4H, t, J = 7.5 Hz, H-5 and H-17), 2.31 (1H, m, H-8), 2.08 (1H, m, H-10a)*, 2.06 (2H, t, J = 7.5 Hz, H-15), 1.76 (3H, bs, CH_3-14), 1.66 (2H, t, J = 7.3 Hz, H-16),1.63 (1H, m, H-10b)*, 1.55 (2H, m, H-7)*, 1.48 (2H, m, H-6)*. (*Chemical shifts designated with an asterisk were assigned by COSY.)

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Supporting Information Available: Copies of ^{1}H-NMR of compounds **1**, **2**, and (+)-**3** (3 pages). Ordering information is given on any current masthead page.

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