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Conformational analysis and absolute stereochemistry of 'spongian'-related metabolites

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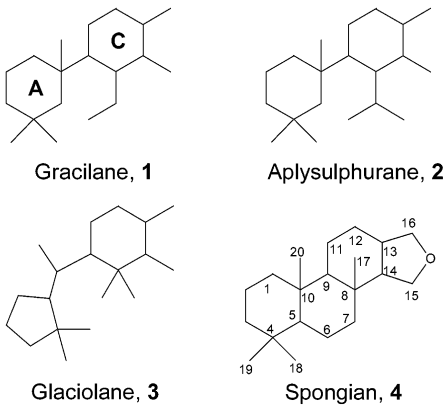
Abstract—New degraded and rearranged diterpenoids, **5**–**8**, have been isolated from the Antarctic sponge *Dendrilla membranosa*. The structure and relative stereochemistry of these compounds were determined by spectroscopic data. The absolute stereochemistry of **5** was determined by spectroscopic data using a chiral reagent. Conformational studies allowed us to assign also the absolute stereochemistry of **6**–**8**, as well as those previously isolated spongian-derived metabolites with known relative stereochemistries.

1. Introduction

Sponges are known to be a rich source of highly functionalized terpenoids[1] with degraded and rearranged carbobicyclic frameworks, such as **1**–**3**, hypothetically derived from a common spongian skeleton precursor **4**. Gracilin A[2] (isolated from *Spongionella gracilis*, Dictyoceratida), aplysillolides A and B, (*Aplysilla glacialis*, Dendroceratida) are examples[3] of naturally occurring diterpenoids belonging to the gracilane skeletal class; aplysulphurin,[4,5] tetrahydroaplysulphurins[5,6] (*Aplysilla sulphurea*), cadlinolides A and B[3] (*A. glacialis*) are aplysulphurane derivatives and glaciolide[7] (*A. glacialis*) is representative of the glaciolane skeleton. The gracilane skeleton is common to sponges of the orders Dictyoceratida and Dendroceratida while aplysulphurane and glaciolane-derived metabolites have only been found in species of the order Dendroceratida.

Dendrilla membranosa, a slow-growing sponge which has no spicules or mucus and that has not been observed to be preyed upon,[8] appears to be chemically defended,[8,9] and four related bioactive diterpenoids were previously isolated from it: 9,11-dihydrogracilin,[8,10] membranolide,[8,11] dendrillin,[9] and dendrinolide.[12]

Continuing with our interest in benthic organisms from the Antarctic[13–19] we have decided to restudy[11] the Antarctic sponge *D. membranosa* in order to isolate its minor metabolites. In this work we report on the structure of four new diterpenoids, **5**–**8**. Compound **5** is a nor-diterpene gracilane skeleton derivative while **6**–**8** are C-20 aplysulphurane-type diterpenes. The presence of a methyl butyrolactone moiety on **5** allowed us to apply a recently reported method[20] to determine the absolute configuration of **5**, and the conformational analysis of **5**–**8** allowed to establish the absolute stereochemistry of **6**–**8**, as well as that of the known spongian-derived metabolites related to gracilane **1** and aphysulphurane **2** backbone.



2. Results and discussion

D. membranosa was collected off King George Island (South Shetlands), Antarctic. From the crude extract the new compounds **5**–**8** were obtained together with the already described membranolide,[8,11] and polyrhaphin D,[21] after flash chromatography followed by gel filtration and successive HPLC.

Keywords: Sponges; Dendroceratida; Stereochemistries; Diterpenes.
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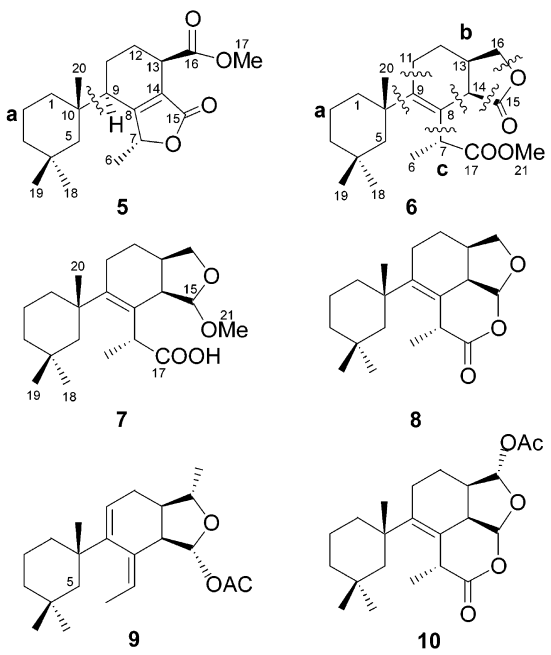


Compound **5** (HREIMS $[M+1]^+$ 335.2197 (calcd for $C_{20}H_{31}O_4$, 335.2222)) was isolated as a colorless oil. The ^{13}C NMR spectrum, Table 1, showed signals for 20 carbons, and DEPT spectral data indicated the presence of five methyl groups, one of them (C-17) attached to oxygen, six methylene groups, three methine carbons (one bearing oxygen), two quaternary olefinic carbons, two carbonyls, and two sp^3 quaternary carbons. ^1H NMR spectrum, Table 1, showed four methyl singlets, one of them as a methoxy group at δ 3.37, a signal for a secondary methyl group at δ 1.05 (d, J=6.5 Hz), a quartet at δ 4.92 (1H, q, J=6.5 Hz), a broad doublet of doubles at δ 3.50 (1H, dd, J=2.9, 2.9 Hz), and complex signals between δ 2.10 and 0.75.

The presence of a deshielded methylene carbon at around 52 ppm in **5** (entry 5, Table 1) called our attention, and the HMBC long-range correlations of this carbon with three angular methyl groups indicate that it corresponds to an isolated methylene. This led us to suspect that ring A contained in gracilane and aplysulphurane skeletons was present in **5**. A similar chemical shift of 52.7 ppm was observed[2] for the corresponding C-5 of gracilin A, **9**. The comparison of the ^{13}C NMR chemical shifts of the remaining carbon atoms of ring A of **5** with that of gracilin A[2] corroborated a fragment **a** moiety. These arguments are also applicable to compounds **6**–**8**. The C-5 chemical shift of naturally occurring metabolites related to gracilane and aplysulphurane skeletons seems very useful in assisting structural elucidation, and it is noteworthy that this has never been pointed out previously.

The presence of a methyl ester group was confirmed by the HMBC correlation between H_3-17 and C-16. One of the two remaining oxygens given by the molecular formula was a carbonyl and the other has to be attached to C-7, while both must be involved in a methyl substituted lactone ring. This lactone was established as α,β-unsaturated by the HMBC correlations between H_3-6/C-8 and H-7/C-8, C-14, which is

Table 1. ^1H and ^{13}C NMR data of compounds **5**–**8** (500 MHz, δ ppm, (J) Hz, $CDCl_3$)

No.	**5**		**6**		**7**		**8**	
	δ_H[a]	δ_C[a]	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	0.70 ddd (4.3, 13.0, 13.0) 1.30 m	35.9	β: 2.18 br d (12.8) α: 1.28 m	39.0	β: 2.17 m α: 1.30 m	39.1	1.89 m 1.08 m	39.9
2	1.38 m 1.31 m	18.9	β: 2.00 m α: 1.51 m	19.9	1.85 m 1.50 m	20.1	1.49 m	20.5
3	0.90 m 1.30 m	38.8	1.16 m 1.37 m	39.9	1.17 ddd (3.8, 13.1, 13.1) 1.35 ddd (3.8, 3.8, 13.0)	40.0	1.17 m 1.29 m	39.5
4		30.8		31.1		31.5		31.6
5	β: 1.12 d (13.5) α: 0.77 d (13.1)	51.7	β: 1.80 br d (14.1) α: 1.03 d (14.1)	50.9	β: 1.80 d (12.1) α: 1.00 m	50.8	β: 1.24 d (13.7) α: 1.78 d (13.7)	51.2
6	1.05 d (6.5)	19.2	1.18 d (7.0)	16.4	1.23 d (7.0)	15.7	1.37 d (7.4)	14.3
7	4.92 q (6.5)	79.7	4.28 q (7.0)	41.0	4.20 q (7.0)	41.5	4.14 d (7.4)	40.6
8		166.8		125.3		127.7		122.8
9	1.57 m	47.4		146.3		144.5		147.0
10		37.5		41.6		39.6		39.6
11	β: 1.50 m α: 1.30 m	21.6	β: 1.60 m α: 2.36 ddd (3.5, 3.5, 15.5)	27.1	β: 1.90 m α: 2.20 ddd (4.3, 4.3, 15.7)	27.7	β: 1.89 m α: 2.46 ddd (4.7, 4.7, 11.9)	26.8
12	1.16 m 2.07 dddd (2.8, 2.8, 5.7, 13.2)	25.4	1.43 m 1.74 m	31.3	1.30 m 1.60 m	30.7	0.89 m 1.89 m	25.5
13	3.50 dd (2.9, 2.9)	37.0	2.58 m	34.2	2.30 m	37.9	2.62 m	37.5
14		127.7	3.62 d (8.6)	41.0	2.70 dd (8.1, 2.9)	48.9	3.00 m	41.6
15		171.2		176.5	4.74 d (2.9)	113.0	6.00 d (5.8)	103.4
16		172.1	4.12 dd (1.0, 9.2) 4.39 dd (6.6, 9.1)	74.5	3.76 d (8.5) 4.10 dd (8.5, 5.4)	74.8	3.58 dd (8.9, 8.9) 4.15 dd (8.8, 8.8)	72.9
17	3.37s	51.4		175.2		178.1		172.4
18	0.83s	35.1	0.81s	26.2	0.88s	26.9	0.74s	27.5
19	0.86s	26.9	0.86s	33.0	0.86s	33.0	0.88s	32.8
20	0.74s	19.9	1.07s	31.2	1.03s	30.7	1.12s	31.8
21			3.71s	52.0	3.20s	54.9		

[a] C_6D_6.

consistent with the IR absorptions at 1757 and 1735 cm^{-1} for ester functionalities. Since the IR spectrum revealed no absorption for additional unsaturations, the molecule is tricyclic.

COSY correlated fragment H-9–H_2-11–H_2-12–H-13 and HMBC correlations of H-9 with C-8, C-14 fixed the position of the lactone ring and allowed us to link the ester appendage to C-13 in agreement with the deshielded chemical shift of H-13 and the HMBC long-range correlation between H-12 and C-16. The C-9/C-10 linkage of both six-membered rings was secured by the HMBC correlation of the downfield H-9 with C-20, C-10 and C-5. This completes the overall planar structure of **5**.

The relative stereochemistry of **5** was assigned on the basis of 2D NOESY experiments, coupling constants and molecular mechanics calculations, Figure 1. In 2D NOESY (C_6D_6) experiments H-7 shows NOE with H_3-20 and H-5β, while H-9 shows NOE with H_3-6 and H-5α. Additional NOE effects of H_3-20 with H-11β and H_3-19 were observed, establishing a β configuration for Me-20, Me-19 and H-7, and an α stereochemistry for H-9 and Me-6. The small *J*-value of H-13 (J=2.9 Hz) observed is an equatorial disposition for H-13. Thus, the stereochemistry of the carboxylate group on C-13 is axial.

Molecular mechanics calculations were performed[22] in order to find a minimized structure for **5** compatible with the NOEs observed. The minimized structure (Fig. 1) consists of a trimethylcyclohexane moiety, ring A, in a chair conformation equatorially linked at C-10 to a bicyclic system formed by a cyclohexene carboxylate ring C fused to a methyl γ-lactone residue. Conformation **5** is consistent with the observed NOEs and allowed us to establish the relative configuration as 7R^*, 9R^*, 10S^* and 13R^*. The configurations at C-9 and C-10 of **5** are coincident with those of the 9,11-dihydrogracilin A whose relative configurations were determined by X-ray analysis of an 8-keto derivative.[10]

Compound **5** is the first example of a degraded diterpenoid belonging to the gracilane skeleton that possesses a lactone function between C-7 and C-15 instead of the oxane ring between C-15 and C-16. The presence of a γ-methyl butenolide moiety on compound **5** allowed us to use the method described by Latypov et al.[20] to determine the absolute configuration of **5**. *R* and *S* 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) were used to form complexes with the γ-methyl butenolide moiety of compound **5**. NMR analysis of the Δδ of H-7 of the two complexes gave clear evidence to assign the absolute stereochemistry of C-7 as *R* (Table 2). This information, together with the NOESY data, implied that C-9 and C-13 are *R* and C-10 is *S*.

Table 2. $\delta_{H\text{-}7}$ of compound **5** with *R* and *S* TFAE at 233 K

n equiv. of (*R*) or (*S*)-TFAE	δ_R	δ_S	$\Delta(\delta_R-\delta_S)$
6	5.23509	5.26778	−0.03269
12	5.19413	5.24010	−0.04597
24	5.14964	5.21106	−0.06142

Compound **6** (HREIMS $[M]^+$ 348.2300 (calcd for $C_{21}H_{32}O_4$, 348.2300)) was isolated as a colorless oil. The ^{13}C NMR data, Table 1, indicated the presence of 21 carbons in the molecule, one of them being a methoxy group (C-21). As aforementioned, the ^1H and ^{13}C NMR spectroscopic data (Table 1) of **6** suggested that it possesses the same A ring (fragment **a**), which was corroborated by HMBC correlations.

COSY NMR experiments allowed the correlation H_2-11-H_2-12-H-13-H_2-16 and H-14-H-13 fragment **b**; and H_3-6-H-7 fragment **c**. The long-range HMBC correlation of the secondary methyl group H_3-6 with C-17 confirmed the presence of the methyl ester group at C-7 in fragment **c**. According to the degree of unsaturation, the molecule is tricyclic and, once again, taking into account the number of oxygens of the molecular formula, and the fact that molecule must possess an oxymethylene, this and the remaining oxygen must be involved in a lactone ring. From biogenetic considerations, HMBC correlations and comparison of the ^1H NMR and ^{13}C NMR data with those of the related compound tetrahydroaplysuphurin-1, **10**,[5] the structure was concluded to be as depicted in **6**.

The ^1H and ^{13}C NMR data of compound **7** are very similar to those of compound **6**, the main difference between them being the substitution of the carbonyl group of the lactone ring of **6** (δ_C 176.2, C-15) for a hemiketal carbon at δ_C 113.0. The presence of the methoxy group at C-15 was confirmed by HMBC correlation between H_3-21 and C-15. The downfield chemical shift of C-17 at δ 178.1 ppm and an IR broad absorption at 3100 cm^{-1} and a band at 1731 cm^{-1}

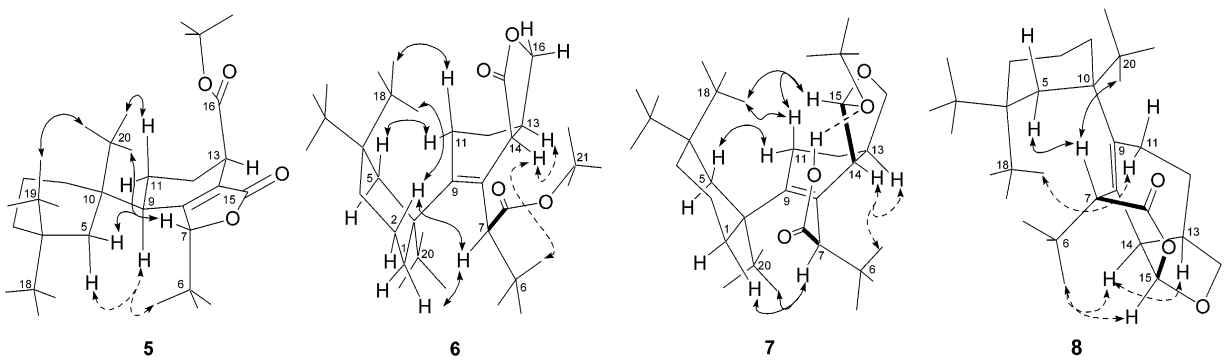


Figure 1. Selected NOEs of compounds **5**–**8**.

indicate that compound **7** must have a carboxylic acid instead of the methylester of **6**.

Compound **8** (HREIMS $[M]^+$ 318.21167 (calcd for $C_{20}H_{30}O_3$, 318.2194)) can be seen as a derivative of **7** by the loss of methanol as a consequence of an intramolecular displacement of the hemiketalic methoxy group by the free carboxylic acid to give the corresponding δ-lactone **8**. This was corroborated by the presence of a hemiketal proton at C-15 (δ_H 6.00; δ_C 103.4), one oxygen less in the molecular formula and the similarity between the ^1H and ^{13}C NMR data and those of **7**.

From the biogenetic point of view, the aplysulphurane and gracilane skeletons have been hypothesized[23] to arise from a common spongian skeleton precursor **4**, Scheme 1, by migration of the C-17 methyl group and cleavage of the C-5–C-6 bond. Assuming that the C-10 chiral centre of the related compounds **6**–**8** is not involved in that process, we could expect them to have an identical C-10 configuration.

2D NOESY experiments showed strong NOEs between H-7/H-1β and H-11α/H-5β for compounds **6** and **7**, whereas **5** and **8** shows NOE between H-7/H5β and H-7/H-5α, respectively. These NOEs indicate that ring A in compound **8** must adopt a different disposition, Figure 1, with respect to the bicyclic moiety from that of **6** and **7** in order to preserve the same configuration at C-10. This was corroborated by molecular mechanics calculations and a study of the coupling constants. The minimized structures **6**–**8**, as represented in Figure 1, were obtained, and the comparison of the well-resolved *J*-values of selected protons of these compounds with the theoretical coupling constants given by the program[22] proved to be in good agreement. For example, the *J*-values of H_2-16 (1.6, 6.4 Hz) and H-14 (8.6 Hz) of **6**; the *J*-values of H_2-16 (0.9, 4.3 Hz), H-14 (8.3 Hz) and H-15 (5.9 Hz) of **7**; and the *J*-values of H-15 (6.6 Hz) of **8** have to be compared with the *J*-values of the respective protons given in Table 1. The conformations **6**–**8**, Figure 1, fulfill additional observed NOEs H_3-6/H-14; H-13/H-14; H-7/H-2β; H_3-18/H-2β and H-11β/H_3-18 in **6**; H_3-6/H-14; H-14/H-13; H-15/H-11β, H_3-18; H-7/H_3-20 and H-11β/H_3-18 in **7**; H_3-6/H-14, H-15; H-14/H-13; H-7/H_3-20; and H-11α/H_3-18 in **8**.

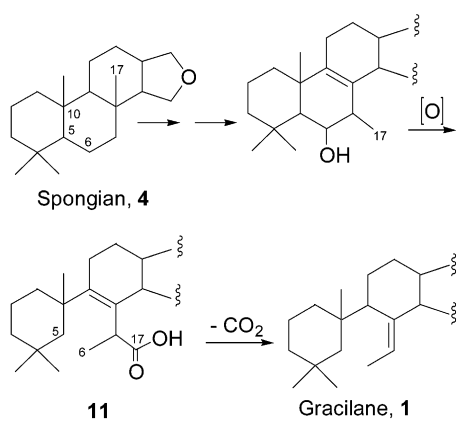
In compounds **6**–**8** the cyclohexane ring has a chair conformation with Me-18 and the bicyclic residues in axial positions. The *cis*-fused cyclohexene ring C of the bicyclic moiety of **6** and **7** adopted a similar twisted half boat arrangement. However, in **6**, the five-membered ring has an envelope conformation with the endocyclic atoms arranged in an almost ideal plane, whereas in compound **7**, that shows H-bond interaction of the proton of the acid with the oxygen of the methoxy group at C-15 on the furane ring, it was a partial envelope with C-16 out of the ideal plane through the remaining atoms of the ring.

In compound **5** ring A has a chair conformation with Me-19 and Me-20 in a 1,3-diaxial disposition. This change in the conformation of ring A of **5** with respect to that of ring A of compounds **6**–**8**, which places both H_3-19 and H_3-20 methyl groups in an equatorial configuration, explains a ^{13}C chemical shift (data in $CDCl_3$ in experimental) difference of about 7 ppm of Me-18 and Me-19 in these compounds: from $\delta_{C\text{-}18}$ 35.8 and $\delta_{C\text{-}19}$ 27.7 for compound **5** to values of δ 26.5 and 33.0 for C-18 and C-19, respectively, for compounds **6**–**8**, entries 18 and 19, Table 1.

The configuration at C-10 of compounds **6**–**8** is coincident with the *S* configuration at C-10 of **5**. All these considerations allowed us to propose the absolute stereochemistries: 7*R*,10*S*,13*R*,14*R* for **6**; 7*R*,10*S*,13*R*,14*R*,15*S* for **7**; and 7*R*,10*S*,13*R*,14*R*,15*R* for **8**, as depicted in Figure 1.

Compound **7** is biogenetically interesting because a free acid such as **11** has been proposed[22] as an intermediate in the biogenesis of the gracilane skeleton by the loss of CO_2, Scheme 1. The finding of the acid **7** as a naturally occurring metabolite supports this hypothesis, and the conservation of the chirality at C-10 as *S* in compounds **5**–**8**, which is coincident with that of the respective C-10 of spongian marine skeleton,[24] gives additional support for the biogenetic origin of these compounds from the spongian precursor, and suggests that most of the spongian-derived marine diterpenes with a given relative stereochemistry should have an absolute configuration identical with that of **5**. For instance, tetrahydroaplysulphurin-1, **10**,[4,6] and related compounds,[3–5,25] membranolide,[8,11] gracilin-A[2,10,26] and related compounds,[3,25] whose relative stereochemistries were solved by single-crystal X ray diffraction analysis or by other means.

Compound **5** is the first non-annonaceous naturally occurring metabolite containing a γ-methyl butenolide moiety to which the method described by Latypov et al.[20] was applied to solve the absolute configuration.



Scheme 1. Biogenesis of the gracilane skeleton via acid **11**.

3. Experimental

3.1. General procedures

Optical rotations were measured on a Perkin–Elmer model 343 Plus polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin–Elmer 1650/FTIR spectrometer in $CHCl_3$ solutions. ^1H NMR and ^{13}C NMR, HSQC, HMBC and COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR. Two-dimensional NMR spectra were obtained with the standard Bruker

software. EIMS and HRMS data were taken on a Micromass Autospec spectrometer. HPLC separations were performed with a Hewlett Packard 1050 (Jaigel-Sil semipreparative column, 10 μm, 20×250 mm) with hexane–EtOAc mixtures. The gel filtration column (Sephadex LH-20) used hexane–MeOH–CH_2Cl_2 (3:1:1) as solvent. Merck Si gels 7734 and 7729 were used in column chromatography. The spray reagent for TLC was H_2SO_4–H_2O–AcOH (1:4:20).

3.2. Biological material

D. membranosa (1.0 kg) was collected by SCUBA diving off King George Island (South Shetlands, Antarctic) at −35 m.

3.3. Extraction and isolation

Wet samples were extracted with acetone at room temperature, and were concentrated to give a dark residue (26.1 g). The extract was chromatographed by flash chromatography on silica gel. The fraction eluted with hexane–EtOAc (8:2) (1.19 g) was chromatographed on an LH-20 column to give a complex mixture that was further separated on HPLC to give compounds, **5** (4.1 mg), **6** (1.5 mg), and **8** (1.6 mg) and the known compounds membranolide[8,11] (53.0 mg), and polyrhaphin D[13] (0.8 mg). From the fraction eluted with hexane–EtOAc (6:4) (1.03 g) compound **7** (3.7 mg) was isolated after LH-20 column and HPLC.

3.3.1. Compound 5. Colorless oil; $[\alpha]_D^{25}$=+70 (*c*, 0.27, $CHCl_3$); IR ν_{max} (film) 1757, 1735 cm^{-1}; ^1H and ^{13}C NMR (C_6D_6), see Table 1; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (3H, s, H-18), 0.91 (3H, s, H-20), 0.97 (3H, s, H-19), 1.05 (1H, m, H-2), 1.09 (1H, m, H-3), 1.10 (1H, m, H-5α), 1.15 (1H, m, H-1), 1.40 (1H, m, H-5β), 1.41 (1H, m, H-3), 1.44 (3H, d, *J*=6.6 Hz, H-6), 1.50 (1H, m, H-1), 1.50 (1H, m, H-2), 1.57 (1H, dddd, *J*=2.9, 2.9, 2.9, 12.4 Hz, H-12), 1.69 (1H, m, H-11), 1.80 (1H, m, H-11), 2.19 (1H, m, H-9), 2.22 (1H, dddd, *J*=2.6, 2.9, 5.5, 13.1 Hz, H-12), 3.41 (1H, dd, *J*=2.8, 2.8 Hz, H-13), 3.69 (3H, s, H-17), 5.27 (1H, q, *J*=6.6 Hz, H-7); ^{13}C NMR ($CDCl_3$ 125.7 MHz) δ 19.4 (CH_3, C-6), 19.9 (CH_2, C-2), 20.8 (CH_3, C-20), 22.1 (CH_2, C-11), 25.8 (CH_2, C-12), 27.7 (CH_3, C-19), 31.5 (C, C-4), 35.8 (CH_3, C-18), 36.8 (CH_2, C-1), 37.2 (CH, C-13), 38.4 (C, C-10), 39.4 (CH_2, C-3), 48.5 (CH, C-9), 52.2 (CH_2, C-5), 52.6 (CH_3, C-17), 81.0 (CH, C-7), 127.2 (C, C-14), 168.9 (C, C-8), 172.7 (C, C-15), 172.9 (C, C-16); EIMS *m/z* 335 $[M+1]^+$ (<1), 319 $[(M-Me]^+$ (<1), 210 (100); HREIMS $[M+1]^+$ 335.2197 (calcd for $C_{20}H_{31}O_4$, 335.2222), $[M-Me]^+$ 319.1817 (calcd for $C_{19}H_{27}O_4$, 319.1909).

3.3.2. Compound 6. Colorless oil; $[\alpha]_D^{25}$=−30 (*c*, 0.10, $CHCl_3$); IR ν_{max} (film) 1768, 1730 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 348 $[M]^+$ (13), 316 $[M-MeOH]^+$ (100), 301 $[M-MeOH-Me]^+$ (41), 273 (87); HREIMS $[M]^+$ 348.2300 (calcd for $C_{21}H_{32}O_4$, 348.2300), $[M-MeOH]^+$ 316.1987 (calcd for $C_{20}H_{28}O_3$, 316.2038), $[M-MeOH-Me]^+$ 301.1799 (calcd for $C_{19}H_{25}O_3$, 301.1803).

3.3.3. Compound 7. Colorless oil; $[\alpha]_D^{25}$=+12 (*c*, 0.25, $CHCl_3$); IR ν_{max} (film) 3100, 1731 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$, see Table 1; EIMS *m/z* 318 $[M-CH_3OH]^+$ (6), 303 $[M-CH_3-CH_3OH]^+$ (3), 274 $[M-CO_2-CH_3OH]^+$ (18), 259 (16), 245 (14), 150 (56), 69 (100); HREIMS 318.2266 (calcd for $C_{20}H_{30}O_3$, 318.2195), 303.1995 (calcd for $C_{19}H_{27}O_3$, 303.1960), 274.2338 (calcd for $C_{19}H_{30}O$, 274.2297), 259.2140 (calcd for $C_{18}H_{27}O$, 259.2062), 245.1954 (calcd for $C_{17}H_{25}O$, 245.1905).

3.3.4. Compound 8. Unstable colorless oil; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 318 $[M]^+$ (1), 274 $[M-CO_2]^+$ (25), 259 (23), 245 (26) 69 (100); HREIMS $[M]^+$ 318.2116 (calcd for $C_{20}H_{30}O_3$, 318.2194), $[M-CO_2]^+$ 274.2293 (calcd for $C_{19}H_{30}O$, 274.2296).

3.3.5. Preparation of the 2,2,2-trifluoro-1-(9-anthryl) ethanol complexes of 5. Compound **5** (1.0 mg, 3.0 μmol) and $CDCl_3$ (0.5 mL) were placed in a 5 mm NMR tube with increasing amounts of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (0, 6, 12 and 24 equiv.). The same experimental procedure was followed for the production of the corresponding (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol complexes. The ^1H NMR spectrum for each complex with each concentration was recorded at 233 K.

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