Two Novel Polyhydroxysteroids with a 24-Ethyl-25-hydroxy-26-sulfoxy Side Chain from the Deep Water Starfish *Styracaster caroli*

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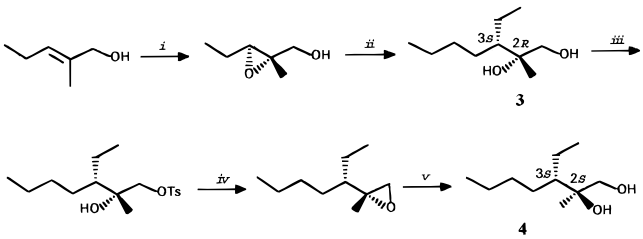
The structure of two minor polyhydroxysteroids isolated from the deep water starfish *Styracaster caroli* were determined as (22*E*,24*R*,25*R*)-24-ethyl-5α-cholest-22-en-3*β*,5,6*β*,8,15α,25,26-heptol 26-sulfate (**1**) and (24*R*,25*R*)-24-ethyl-5α-cholestane-3*β*,5,6*β*,15α,16*β*,25,26-heptol 26-sulfate (**2**). The stereochemistry at the C-24 and C-25 positions was determined by enantioselective synthesis of 2-methyl-3-ethylheptane-1,2-diols as models and by comparison of the ^{1}H-NMR data of their (+)- and (−)-MTPA esters with those of the 26-MTPA esters of the 22,23-dihydro derivative of the naturally occurring **1** and of **2**.

The starfish *Styracaster caroli* Ludwig (family Porcellanasteridae), collected at a depth of 200 m between the islands of Thio and Lifou, New Caledonia, contains a very complex mixture of unprecedented polyhydroxysteroids. We have hitherto identified 13 compounds, three of which, carolisterols A−C, are a novel group of polyhydroxysteroid constituents possessing an amido function in the side chain with a D-(−)-cysteinolic acid linked to a C-24 carboxy group.[1] The remaining 10 constituents have a common 3*β*,5,6*β*-trihydroxy functionality with additional hydroxyl groups at position 8, 15α (or *β*) and 16*β* and a side chain with multiple functionalities and different alkylation patterns.[2] In the present paper we report the structures of two new polyhydroxysteroids (**1** and **2**) with a novel 24-ethyl-25-hydroxy-26-sulfoxycholestane skeleton.

Results and Discussion

Droplet counter-current chromatography (DCCC) followed by reversed-phase HPLC of the sulfated polyhydroxysteroid fractions, obtained from the MeOH extracts of *S. caroli* (2.0 kg., fresh wt) by chromatography on Sephadex LH-60, gave compound **1** (4.0 mg), $[\alpha]_D$ +4.6° (MeOH), and compound **2** (3.5 mg), $[\alpha]_D$ +15.4° (MeOH). Examination of their spectral data (^{1}H and ^{13}C NMR) indicated that the steroid **1** contained the 3*β*,5α,6*β*,8,15α-pentahydroxytetracyclic nucleus as in the previous (22*E*,24*S*)-5α-ergost-22-en-3*β*,5,6*β*,8,15α,28-hexol 28-sulfate and (22*E*,24*R*,28*S*)-5α-stigmast-22-ene-3*β*,5,6*β*,8,15α,28,29-heptol 28-sulfate from *S. caroli*.[2] Steroid **2** contained the 3*β*,5α,6*β*,15α,16*β*-pentahydroxytetracyclic nucleus as in 5α-cholestane-3*β*,5,6*β*,15α,16*β*,26-hexol from *S. caroli*[2] (also previously isolated from *Luidia maculata*[3] and *Tremaster novaecaledoniae*[4]). Negative ion FABMS of **1** and **2** showed molecular anion peaks at *m/z* 589 [MSO_3^-] and 591 [MSO_3^-], respectively. Upon solvolysis with dioxane-pyridine, **1** and **2** were converted to **1a** and **2a**, desulfated derivatives of lower polarity. The FABMS of these products showed pseudomolecular ions at *m/z* 509 [M − H$^-$] (**1a**) and 511 [M − H$^-$] (**2a**) corresponding to the loss of 80 mass units (SO_3) from **1** and **2,** respectively. The ^{13}C NMR of both compounds accounted for a total of 29 carbon atoms, and DEPT measurements revealed the presence in both compounds of a C-10 side chain containing three methyl groups, two methines, one methylene, one CH_2−O−, and one C−OH, together with two olefinic methines in **1**, replaced in **2** by two methylenes. An analysis of ^{1}H-NMR data for compound **1**, two doublets at *δ* 3.88 and 3.97 (each 1H, *J* = 9.0 Hz, H_2-26), indicated a CH_2−O− grouping linked to a quaternary carbon. The spectrum also showed the signals of one secondary methyl at *δ* 1.04 (d, *J* = 7.0 Hz, H_3-21), one tertiary methyl geminal to oxygen at *δ* 1.22 (s, H_3-27), one primary methyl at *δ* 0.86 (t, *J* = 7.0 Hz, H_3-29), and two well separated olefinic double doublets at *δ* 5.30 (*J* = 15.0, 8.0 Hz, H-22) and 5.20 (*J* = 15.0, 8.5 Hz, H-23), indicative of a 22*E*-double bond. The signals associated with the CH_2−O− grouping were observed shifted to *δ* 3.47 (d, *J* = 9.0 Hz) and 3.40 (d, *J* = 9.0 Hz) in the desulfated derivative **1a**, indicating that the sulfate is located there. ^{1}H−^{1}H COSY experiment confirmed the ^{1}H coupling networks C_{20}−C_{24}. Thus, the structure of compound **1** was determined as 24-ethyl-5α-cholest-22-en-3*β*,5,6*β*,8,15α,25,26-heptol 26-sulfate.

Scheme 1. Synthesis of 2-Methyl-3-ethylheptane-1,2-diols (**3** and **4**)[a]



[a] Reagents and conditions: *i*, Ti(i-OPr)$_4$, TBHP, L-(+)-diethyltartrate, CH_2Cl_2 dry, −25 °C; *ii*, Lithium di-*n*-butylcuprate, ethyl ether, −30 °C, *iii*, *p*-toluenesulfonyl chloride 0 °C, pyridine, *iv*, KOH in EtOH, *v*, $HClO_4$ 60%, THF−H_2O (4:1), 25 °C.

The ^{1}H-NMR data of compound **2** revealed signals for one secondary methyl at *δ* 1.01 (d, *J* = 7.0 Hz, H_3-21), one tertiary methyl geminal to oxygen at *δ* 1.16 (s, H_3-27), and one primary methyl at *δ* 1.00 (t, *J* = 7.0 Hz, H_3-29), indicative of the presence of an ethyl group. The

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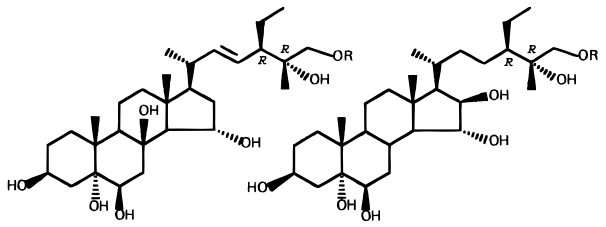
spectrum also showed an AB quartet (separation between the inner lines $J = 9.5$ Hz, H_2-26) centered at δ 3.94, shifted upfield to δ 3.47 br s in the desulfated material **2a**, indicative of a $CH_2-OSO_3^-$ grouping. These features can be arranged in a 25-hydroxy-26-sulfoxy-24-ethylcholestane side chain, and the structure of compound **2** can be assigned as 24-ethyl-5α-cholestane-3β,5,6β,15α,16β,25,26-heptol 26-sulfate. The remaining features needed to establish the structures fully are the configurations at C-24 and C-25. This required the synthesis of model compounds, and we decided to synthesize enantioselectively simpler side-chain models, that is, 2-methyl-3-ethylheptane-1,2-diols, and compare their spectral data with those of 22,23-dihydro derivative of the desulfated **1a** (**1b**) and with those of desulfated **2a**.



The models were synthesized by application of the asymmetric epoxidation method developed by Katsuki and Sharpless[5] to (*E*)-2-methyl-2-pentenol using L-(+)-diethyltartrate as the chiral catalyst, followed by reaction with lithium di-*n*-butylcuprate[6,7] to give (2*R*,3*S*)-2-methyl-3-ethylheptane-1,2-diol (**3**), which was then converted to the diastereomer (2*S*,3*S*) **4** by tosylation, alkaline treatment, and opening of the resulting 1,2-epoxide with 60% perchloric acid. In the ^{1}H-NMR spectrum (CD_3OD) of the dihydro derivative **1b**, the diastereotopic 26-methylene protons resonated as an AB quartet at δ 3.46 (separation between the inner lines J = 8.5 Hz), in better accord with the values measured for the diastereomer **4** (2*S*,3*S*) at δ 3.46 (2H, separation between the inner lines of the ABq $J = 8.5$ Hz, H_2-1), as compared with the corresponding signals measured at δ 3.46 for the diastereomer **3** (2*R*,3*S*), which appear closer (separation between inner lines of the AB quartet $J = 3.5$ Hz). This allowed us to propose the relative stereochemistry at C-24 and C-25, as either 24*S*,25*S* or 24*R*,25*R* in **1**. The absolute configuration was then derived by ^{1}H-NMR analysis of the (*R*)-(+)- and (*S*)-(−)-MTPA esters[8] of the model compounds and by comparison with values of the MTPA derivatives of the naturally derived **1b** (Figure 1). The C-1 proton signals appear as two well separated doublets ($J = 11$ Hz) at δ 4.23 and 4.27 in the spectrum (CD_3OD) of the 1-(−)-MTPA ester of the 2*S*-model (**4**) and much closer, br s at δ 4.25, in that of the (+)-MTPA ester. Of course such behavior is reversed in the 2*R*-model compound **3**, the signals being now closer in the spectrum of the 1-(−)-MTPA (δ 4.25, br s) and well separated in that of the 1-(+)-MTPA ester (δ 4.23 and 4.27, $J = 10$ Hz). Similarly to the 2*R* model **3**, the C-26 methylene proton signals of the 3β,15α,26-*O*-(+)-MTPA ester of **1b** appear as well separated doublets at δ 4.21 and 4.28 ($J = 10$ Hz) in the ^{1}H-NMR spectrum (CD_3OD) of the (+)-MTPA ester and as a broad singlet at δ 4.25 in that of the (−)-MTPA ester, thus indicating the 25*R* stereochemistry for **1b** and, accordingly, the 24*R*,25*R* configuration for the naturally occurring **1**. We note that in $CDCl_3$ the behavior of the C-26 methylene proton signals in the NMR spectra of the (+)- and (−)-MTPA esters of both the models and the naturally derived **1b** is reversed; that is, in the (2*R*)- or (25*R*)-isomers the methylene proton signals of the (+)-MTPA esters appear closer than those of the (−)-MTPA esters, which appear as two separated doublets; the opposite occurs with the (2*S*)- or (25*S*)-isomers. We would also note that this last trend is the same as that observed by Koizumi *et al.* with the synthetic (25*R*)- and (25*S*)-25,26-dihydroxycholestane when the spectra of the corresponding 26-MTPA esters were run in $CDCl_3$,[10] as well as by Riccio *et al.* with the synthetic 2,3-dimethylpentane-1,2-diols, when the spectra of the corresponding 1-(+)-MTPA were run in $CDCl_3$.[11]

Table 1. ^{1}H- and ^{13}C-NMR Spectral Data of Natural Compounds **1** and **2** (CD_3OD)[a]

	1		2	
Position	δ_H	δ_C	δ_H	δ_C
1		34.3		31.6
2		30.8		33.4
3	4.10 m	68.1	4.03 m	68.2
4		42.0		41.8
5		76.3		76.5
6	3.58 t (2.5)	77.8	3.49 t (2.5)	76.3
7	2.20 dd (15.0, 2.5)	40.9		35.0
8		77.2		31.0
9		49.1		46.4
10		39.0		39.2
11		19.6		21.8
12		42.6		41.3
13		45.2		44.5
14		66.4		60.6
15	4.28 td (10.0, 3.0)	69.8	3.75 dd (11.0, 2.5)	84.8
16		40.2	4.05 dd (8.0, 2.5)	82.8
17		55.6		60.0
18	1.01 s	15.4	0.93 s	15.0
19	1.34 s	17.9	1.21 s	17.3
20		40.8		31.7
21	1.04 d (7.0)	21.1	1.01 d (7.0)	18.6
22	5.30 dd (15.0, 8)	141.2		27.4
23	5.20 dd (15.0, 8.5)	128.3		37.5
24		54.5		47.8
25		74.2		75.6
26	3.97 d (9.0) 3.88 d (9.0)	74.3	3.94 ABq (3.5)	74.5
27	1.22 s	23.5	1.16 s	21.2
28		22.0		24.5
29	0.86 t (7.0)	12.9	1.00 t (7.0)	13.7

[a] The coupling constants are given in Hz and are enclosed in parentheses.

The ^{1}H-NMR spectrum of the desulfated **2a** showed the C-26 methylene protons resonating as a broad singlet at δ 3.47, but because of the presence of the 16β-OH, we were not confident in assigning the relative stereochemistry based on the chemical shift of 26-methylene protons and have preferred to use the small differences observed in the ^{13}C-NMR spectra of the diastereomeric models. The chemical shift of C-28 of the natural **2** at δ_C 24.5 is very close to that at δ_C 24.4 of C-9 in **4** and differs from the value of δ_C 23.7 observed for the corresponding carbon in **3**. On this basis we propose the same relative stereochemistry for **2** as for the model (24*S*,25*S* or 24*R*,25*R*) **4**. The ^{1}H-NMR ($CDCl_3$) pattern of the 26-methylene proton signals in 3β,6β,15α,26-tetra-(+)-MTPA of **2a**, consisting of two

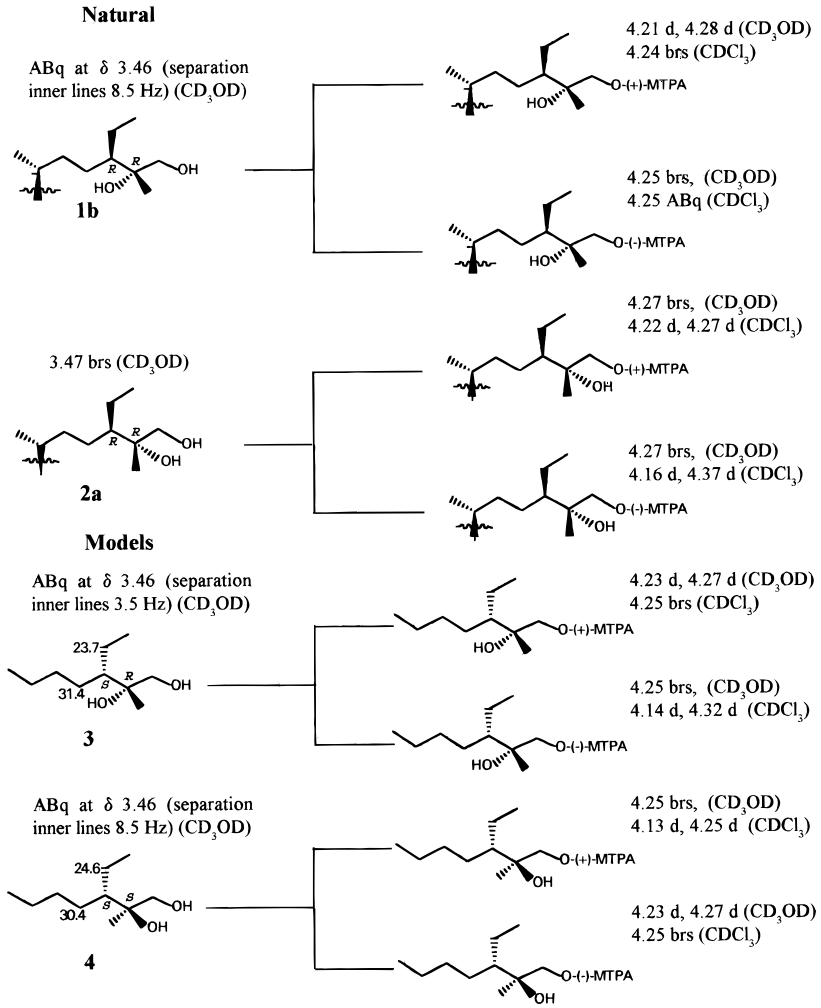


Figure 1. Configuration at C-24 and C25 in 24-ethyl-25,26-dihydroxysteroids: ^{1}H NMR data in CD_3OD and in $CDCl_3$ of C-26 methylene protons of synthetic models (**3** and **4**), natural products (**1b** and **2a**) and their (+)- and (−)-MTPA derivatives.

doublets at δ 4.22 and 4.27 (each 1H, $J = 10$ Hz, H_2-26) pointed to the 25*R*-configuration,[10] when compared with the same signals in 3β,6β,15α,26-tetra-(−)-MTPA of **2a**, which consisted of well separated doublets at δ 4.16 and 4.37 (each 1H, $J = 10$ Hz, H-26 and H′-26). Thus, the configuration of **2a**, and accordingly of naturally occurring **2**, can be assigned as 24*R*,25*R*.

Experimental Section

General Experimental Procedures. NMR measurements were performed on a Bruker AMX-500 spectrometer equipped with a Bruker X-32 computer, using the UXNMR software package. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using a sodium lamp operating at 589 nm. FABMS were recorded in a glycerol−thioglycerol matrix in the negative ion mode on a VG AUTOSPEC instrument (Cs^+ ion bombardment). Reversed-phase HPLC, C_{18} μ-Bondapak column (30 cm × 7.8 mm i.d., flow rate 5 mL/min), Waters Model 6000 A or 510 pump equipped with a U6K injector and a differential refractometer model 401. Droplet counter-current chromatography (DCCC): DCC-A apparatus manufactures by Tokio Rikakikai Co., equipped with 250 tubes and Büchi apparatus equipped with 300 tubes. In the NMR spectra, triplets designated with a asterisk (t*) were distorted.

Animal Material. *Styracaster caroli* Ludwig (family Porcellanasteridae) were collected between Thio and Lifou, New Caledonia, at depth of 2000 m during the Biogeocal oceanographic campaign and identified by Dr. Catharine Vadon, Museum Nationale d'Histoire Naturelle, Paris, where a voucher specimen (EA282) is preserved.

Extraction and Isolation. The MeOH extracts of starfish *Styracaster caroli* were chromatographed on a column of Sephadex LH-60 (4 × 100 cm) with MeOH-H_2O (2:1) as eluent and partitioned in three major fractions. Fractions 50−59 (0.5 g) mainly cointained very polar polyhydroxysteroids, fractions 60−65 (0.7 g) contained a crude mixture of sulfated steroids, and fractions 70−118 (1.0 g) mainly contained the polyhydroxysteroids.[3] Fractions 60−65 were submitted to DCCC using *n*-BuOH−MeOH−H_2O (3:1:5) in the ascending mode. Four fractions were eluted: 87−150 (400 mg), 161−165 (32.4 mg), 166−188 (38.4 mg), and 189−220 (19.1 mg). Fractions 166−188 contained the steroid (22*E*,24*R*,28*S*)-5α-stigmast-22-en-3β,5,6β,8,15α,28,29-heptol 26-sulfate, along with two minor sulfated compounds **1** and **2**. The purification was pursued by HPLC with MeOH:H_2O (45:55) on a C_{18} μ-Bondapak column (30 cm × 7.8 mm i.d.) to give pure compounds.

Solvolysis of 1 and 2. Solutions of **1** (3.5 mg) and **2** (3.0 mg) in pyridine (100 μL) and dioxane (100 μL) were heated at 130° for 2 h in stoppered reaction vials. The residue of each solvolysis was evaporated to dryness and purified by HPLC (C_{18}-μ-Bondapak column 30 cm × 3.9 mm i.d., flow rate 2mL/min) with MeOH-H_2O (7:3) as

eluent to give desulfated **1a** and **2a**. Data of **1a**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 5.28 (1H, dd, J = 14.0, 8.0 Hz, H-22), 5.18 (1H, dd, J = 14.0, 8.0 Hz, H-23), 4.28 (1H, dt, J = 10.0, 3.0 Hz, H-15β), 4.10 (1H, m, H-3α), 3.60 (1H, t, J = 2.5 Hz, H-6α), 3.40−3.47 (each 1H, d, J = 9.0 Hz, H_2-26), 2.22 (1H, dd, J = 15.0, 2.5 Hz, H-7β), 1.34 (3H, s, H_3-19), 1.16 (3H, s, H_3-27), 1.04 (3H, d, J = 7.0 Hz, H_3-21), 1.01 (3H, s, H_3-18), 0.86 (3H, t, J = 7.0 Hz, H_3-29). Data of **2a**: ^{1}H NMR; δ_H (CD_3-OD, 500 MHz): 4.03 (1H, dd, J = 8.0, 2.5 Hz, H-16α), 4.03 (1H, m, H-3α), 3.77 (1H, dd, J = 11.0, 2.5 Hz, H-15β), 3.50 (1H, t, J = 2.5 Hz, H-6α), 3.47 (2H, brs, H_2-26), 1.21 (3H, s, H_3-19), 1.10 (3H, s, H_3-27), 1.01 (3H, d, J = 7.0 Hz, H_3-21), 1.00 (3H, t, J = 7.0 Hz, H_3-29), 0.94 (3H, s, H_3-18).

Hydrogenation of 1a to 1b. Compound **1a** (2.5 mg) was hydrogenated at atmospheric pressure over 10% Pt/C in 2 mL of MeOH for 48 h. Removal of the catalyst by filtration and evaporation of the solvent gave the saturated compound **1b**. Compound **1b** was purified by HPLC with MeOH-H_2O (7:3) on a C_{18} μ-Bondapak column (30 cm × 3.9 mm i.d.); FABMS (−ve ion) m/z 511 [M − H$^-$]; ^{1}H NMR; δ_H (CD_3OD, 500 MHz), 4.30 (1H, dt, J = 10.0, 3.0 Hz, H-15β), 4.11 (1H, m, H-3α), 3.61 (1H, t, J = 2.5 Hz, H-6α), 3.46 (2H, ABq, separation between the inner lines, J = 8.5 Hz, H_2-26), 2.22 (1H, dd, J = 15.0, 2.5 Hz, H-7β), 1.34 (3H, s, H_3-19), 1.10 (3H, s, H_3-27), 0.98 (3H, s, H_3-18), 0.98 (3H, t, J = 7.0 Hz, H_3-29), 0.97 (3H, d, J = 7.0 Hz, H_3-21).

MTPA Esters of the Steroids 1b and 2a. Steroids **1b** (1.0 mg) and **2**a (1.0 mg) were treated with freshly distilled (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (4 μL), obtained from the *R*-(+)-acid, in dry pyridine (100 μL) for 1 h at room temperature to give, after removal of the solvent, the 3β,15α,26-tri-(+)-MTPA esters. Steroid **1b**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 5.51 (1H, m, H-3α), 5.32 (1H, dt, J = 10.0, 3.0 Hz, H-15β), 4.28 (1H, d, J = 10.0 Hz, H-26), 4.21 (1H, d, J = 10.0 Hz, H-26), 3.48 (1H, t, J = 2.5 Hz, H-6α), 1.28 (3H, s, H_3-19), 1.15 (3H, s, H_3-27), 1.02 (3H, s, H_3-18), 0.95 (3H, d, J = 7.0 Hz, H_3-21), 0.89 (3H, t, J = 7.0 Hz, H_3-29); ^{1}H NMR, δ_H ($CDCl_3$, 500 MHz), 5.46 (1H, m, H-3α), 5.24 (1H, dt, J = 10.0, 3.0 Hz, H-15β), 4.24 (2H, brs, H_2-26), 1.24 (3H, s, H_3-19), 1.10 (3H, s, H_3-27), 0.96 (3H, s, H_3-18), 0.89 (3H, d, J = 7.0 Hz, H_3-21), 0.88 (3H, t, J = 7.0 Hz, H_3-29). Steroid **2a**: ^{1}H NMR, δ_H (CD_3-OD, 500 MHz), 5.45 (1H, m, H-3α), 4.27 (2H, brs, H_2-26), 4.15 (1H, dd, J = 8.0, 2.5 Hz, H-16α), 3.49 (1H, t, J = 2.5 Hz, H-6α), 1.21 (3H, s, H_3-27), 1.20 (3H, s, H_3-19), 1.00 (3H, s, H_3-18), 0.95 (3H, d, J = 7.0 Hz, H_3-21), 0.94 (3H, t, J = 7.0 Hz, H_3-29); ^{1}H NMR, δ_H ($CDCl_3$ 500 MHz), 5.42 (1H, m, H-3α), 4.58 (1H, dd, J = 10.0, 3.0 Hz, H-15β), 4.22−4.27 (each 1H, d, J = 10.0, H_2-26), 4.08 (1H, dd, J = 8.0, 2.5 Hz, H-16), 1.12 (3H, s, H_3-27), 1.09 (3H, s, H_3-19), 0.95 (3H, s, H_3-18), 0.93 (3H, t, J = 7.0 Hz, H_3-29), 0.92 (3H, d, J = 7.0 Hz, H_3-21).

The 3β,15α,26-tri-(−)-MTPA ester of **1b** (1.0 mg) and **2a** (1.0 mg) were prepared using (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (4 μL), obtained from the S-(−)-acid. Steroid **1b**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 5.54 (1H, m, H-3α), 5.39 (1H, dt, J = 10.0, 3.0 Hz, H-15β), 4.25 (2H,br s, H_2-26), 1.31 (3H, s, H_3-19), 1.12 (3H, s, H_3-27), 1.02 (3H, s, H_3-18), 0.91 (3H, d, J = 7.0 Hz, H_3-21), 0.87 (3H, t, J = 7.0 Hz, H_3-29); ^{1}H NMR, δ_H ($CDCl_3$, 500 MHz): 5.46 (1H, m, H-3α), 5.24 (1H, dt, J = 10.0, 3.0 Hz, H-15β), 4.25 (2H, ABq, separation between the inner lines, J = 8.5 Hz, H_2-26), 1.24 (3H, s, H_3-19), 1.10 (3H, s, H_3-27), 0.96 (3H, s, H_3-18), 0.89 (3H, t, J = 7.0 Hz, H_3-29), 0.89 (3H, d, J = 7.0 Hz, H_3-21). Steroid **2a**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 5.50 (1H, m, H-3α), 5.02 (1H, dd, J = 11.0, 2.5, H-15β), 4.27 (2H, brs, H_2-26), 4.00 (1H, dd, J = 8.0, 2.5 Hz, H-16α), 3.48 (1H, t, J = 2.5 Hz, H-6α), 1.21 (3H, s, H_3-27), 1.11 (3H, s, H_3-19), 1.00 (3H, s, H_3-18), 0.93 (3H, d, J = 7.0 Hz, H_3-21), 0.89 (3H, t, J = 7.0 Hz, H_3-29); ^{1}H NMR, δ_H ($CDCl_3$ 500 MHz), 5.42 (1H, m, H-3α), 4.65 (1H, dd, J = 10.0, 3.0 Hz, H-15β), 4.37 (1H, d, J = 10.0, H-26), 4.16 (1H, d, J = 10.0, H-26), 3.98 (1H, dd, J = 8.0, 2.5 Hz, H-16β), 1.12 (3H, s, H_3-27), 1.11 (3H, s, H_3-19), 0.95 (3H, t, J = 7.0 Hz, H_3-29), 0.95 (3H, s, H_3-18), 0.94 (3H, d, J = 7.0 Hz, H_3-27).

(2*R*,3*R*)-2,3-Epoxy-2-methylpentan-1-ol. To dry dichlorometane (15 mL) cooled at 25 °C were added sequentially the following liquids: titanium tetraisopropoxide (Aldrich, 370 μL), L-(+)-diethyltartrate (Aldrich, 250 μL), *t*-butyl hydroperoxide (freshly distilled in dry dichloromethane, 300 μL), and finally a solution of (*E*)-2-methylpent-2-en-1-ol (600 mg) in dry dichloromethane (10 mL). The resulting homogenous solution was then stored overnight (*ca.* 18 h) in the freezer at −25 °C and finally 10% aqueous tartaric acid (3 mL), was added at −25 °C to the stirred mixture. After 30 min the cooling bath was removed and the mixture was stirred at room temperature for 2 h. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a pale yellow oil, which was purified by Si gel (30 g) column chromatography with hexane and increasing amounts of Et_2O to give 340 mg of (2*R*,3*R*)-2,3-epoxy-2-methylpentan-1-ol $[\alpha]_D$ =+11.0°. ^{1}H-NMR: δ_H ($CDCl_3$ 500 MHz), 3.66 (1H, dd, J = 12.5, 5.0 Hz, H′-1), 3.55 (1H, dd, J = 12.5, 7.5 Hz, H-1), 2.99 (1H, t, J = 5.0 Hz, H-3); 1.56 (2H, m, H_2-4), 1.27 (3H, s, H_3-6), 1.02 (3H, t, J = 7.0 Hz, H_3-5); ^{13}C NMR, δ_C ($CDCl_3$, 125.76 MHz), 65.49 (C-1); 61.12 (C-2); 61.33 (C-3); 21.07 (C-6), 13.51 (C-4); 10.07 (C-5).

(2*R*,3*S*)-2-Methyl-3-ethylheptane-1,2-diol (3). To a stirred solution of 9 mmol of lithium di-*n*-butylcuprate in 15 mL of ethyl ether, at −30 °C, were added dropwise 170 mg (1.46 mmol) of (2*R*,3*R*)-2,3-epoxy-2-methylpentan-1-ol dissolved in 3 mL of Et_2O. The mixture was stirred at −20 °C for 3 h, then hydrolyzed by addition of 50 mL of saturated ammonium chloride solution. The mixture was stirred for 1 h at room temperature, then the aqueous layer was separated and extracted with two 50-mL portions of EtOAc. The combined organic extracts were washed with 30 mL of saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to yield 200 mg of crude product. The diol was purified by column chromatography (Si gel, 8 g) using hexane-ethyl ether (1:1) as eluent, to afford 155 mg of pure (2*R*,3*S*)-2-methyl-3-ethylheptane-1,2-diol (61% yield): ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 3.46 (2H, ABq, separation between the inner lines, J = 3.5 Hz, H_2-1), 1.09 (3H, s, H-8), 0.99 (3H, t, J = 6.8 Hz, H-7); 0.95 (3H, t*, J = 6.8 Hz, H-10); ^{1}H NMR, δ_H ($CDCl_3$, 500 MHz), 3.53 (1H, d, J = 10.1 Hz, H′-1), 3.40 (1H, d, J = 10.1 Hz, H-1), 1.06 (3H, s, H-8), 0.94 (3H, t, J = 7.0 Hz, H-7), 0.87 (3H, t*, J = 7.0 Hz, H-10); ^{13}C NMR, δ_C (CD_3OD, 125.76 MHz), 76.7 (C-2), 69.3 (C-1), 47.8 (C-3), 32.8 (C-

5), 31.4 (C-4), 24.4 (C-6), 23.7 (C-9), 20.8 (C-8), 14.5 (C-7), 14.3 (C-10).

(2*R*,3*S*)-2-Methyl-3-ethylheptane-1,2-diol 1-*p*-Toluenesulfonate. (2*R*,3*S*)-2-Methyl-3-ethylheptane-1,2-diol (36 mg, 0.2 mmol) was dissolved in dry CH_2Cl_2 (250 μL) and cooled in an ice bath. Pyridine (50 μL, 3 mmol) was then added, followed by a slow addition of *p*-toluensulfonyl chloride (79 mg, 0.4 mmol) dissolved in dry CH_2Cl_2 (100 μL). After 20 minutes, the cooling bath was removed and, after 5 hours, the mixture was diluted with 3 mL of ethyl ether and washed successively with HCl 1 N, $NaHCO_3$ saturated solution, and H_2O. The organic phase was then dried ($MgSO_4$) and evaporated to yield 74 mg of crude product. The tosylate was purified by column chromatography (Si gel, 8 g) using hexane-ethyl ether (7:3) as eluent to afford 61 mg of pure (2*R*,3*S*)-2-methyl-3-ethyleptane-1,2-diol 1-*p*-toluenesulfonate (90% yield): ^{1}H NMR, δ_H ($CDCl_3$, 500 MHz), 7.80 (2H, d, J = 8.2 Hz, aromatic protons), 7.35 (2H, d, J = 8.2 Hz, aromatic protons); 3.95 (1H, d, J = 9.6 Hz, H′-1), 3.87 (1H, d, J = 9.6 Hz, H-1), 2.45 (3H, s, CH_3-Ph), 1.07 (3H, s, H-8), 0.92 (3H, t, J = 7.7 Hz, H-7), 0.86 (3H, t*, J = 7.0 Hz, H-10).

(2*R*,3*S*)-1,2-Epoxy-2-methyl-3-ethylheptane. To a cooled solution (0 °C) of (2*R*,3*S*)-2-methyl-3-ethyleptane-1,2-diol 1-*p*-toluenesulfonate (12 mg, 0.036 mmol) in absolute EtOH (300 μL) was added a solution of KOH (3 mg, 0.044 mmol) in absolute EtOH (40 μL). During the addition of base a white precipitate was noted. After ten minutes the mixture was poured into H_2O (2 mL) and extracted four times with hexane-ethyl ether (95:5) (3 mL). The combined organic extracts were washed with 4 mL of H_2O, dried over anhydrous Na_2SO_4 and evaporated with a stream of N_2 (in a bath at 15 °C) to yield 4.3 mg of highly volatile (2*R*,3*S*)-1,2-epoxy-2-methyl-3-ethylheptane (67% yield): ^{1}H NMR, δ_H ($CDCl_3$, 500 MHz), 2.56 (1H, d, J = 5.0 Hz, H′-1), 2.52 (1H, d, J = 5.0 Hz, H-1), 1.18 (3H, s, H-8), 0.94 (3H, t, J = 7.5 Hz, H-7), 0.89 (3H, t*, J = 7.0 Hz, H-10).

(2*S*,3*S*)-2-Methyl-3-ethylheptane-1,2-diol (4). To a solution of (2*R*,3*S*)-1,2-epoxy-2-methyl-3-ethyleptane (8 mg, 0.046 mmol) in 1 mL of THF-H_2O (4:1) at room temperature, were added 10 μL of $HClO_4$ 60%. After 24 h, 1 mL of saturated solution of $NaHCO_3$ was added, and the excess of THF was removed under reduced pressure. The H_2O layer was extracted three times with EtOAc. The organic phase was then dried ($MgSO_4$) and evaporated to yield 5.0 mg of crude product. The diol was purified by column chromatography (Si gel) using hexane-ethyl ether (4:6) as eluent to afford 4.0 mg of pure (2*S*,3*S*)-2-methyl-3-ethylheptane-1,2-diol (45% yield): ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 3.46 (2H, ABq, separation between the inner lines, J = 8.5 Hz, H_2-1), 1.09 (3H, s, H-8), 0.98 (3H, t, J = 6.8 Hz, H-7), 0.95 (3H, t*, J = 6.8 Hz, H-10); ^{1}H NMR, δ_H ($CDCl_3$, 500 MHz), 3.57 (1H, d, J = 10.1 Hz, H′-1), 3.43 (1H, d, J = 10.1 Hz, H-1), 1.10 (3H, s, H-8), 0.95 (3H, t, J = 7.0 Hz, H-7), 0.90 (3H, t*, J = 7.0 Hz, H-10); ^{13}C NMR, δ_C (CD_3OD, 125.76 MHz), 76.7 (C-2), 69.2 (C-1), 47.7 (C-3), 33.2 (C-5), 30.4 (C-4), 24.6 (C-5), 24.4 (C-9), 20.8 (C-8), 14.5 (C-7), 14.0 (C-10).

MTPA Esters of Compounds 3 and 4. Compound **3** (2 mg, 0.011 mmol) and compound **4** were esterified with α-(+)-methoxy-α-(trifluoromethyl)phenyacetyl chloride (5 μL) in 200 μL of dry pyridine to give 1-(+)-MTPA esters. Compound **3**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 4.27 (1H, d, J = 11.3 Hz, H′-1), 4.23 (1H, d, J = 11.3 Hz, H-1), 1.13 (3H, s, H-8), 0.94 (3H, t, J = 6.8 Hz, H-7); 0.92 (3H, t, J = 6.8 Hz, H-10); ^{1}H NMR, δ_H ($CDCl_3$ 500 MHz), 4.25 (2H, s, H-1), 1.10 (3H, s, H-8), 0.92 (3H, t, J = 7.0 Hz, H-7); 0.87 (3H, t*, J = 7.0 Hz, H-10). Compound **4**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 4.25 (2H, s, H-1), 1.13 (3H, s, H-8); 0.93 (3H, t, J = 6.8 Hz, H-7), 0.88 (3H, t*, J = 6.8 Hz, H-10); ^{1}H NMR, δ_H ($CDCl_3$ 500 MHz), 4.25 (1H, d, J = 11.1 Hz, H′-1), 4.13 (1H, d, J = 11.1 Hz, H-1), 1.10 (3H, s, H-8), 0.88 (6H, m, H-7 and H-10). The 1-(−)-MTPA ester of **3** (2 mg, 0.011 mmol) and **4** (2 mg, 0.011 mmol) were prepared using (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (5 μL), obtained from the (*S*)-(−)-acid. Compound **3**: ^{1}H NMR, δ_H (CD_3OD, 500 MHz), 4.25 (2H, s, H-1), 1.14 (3H, s, H-8); 0.95 (3H, t, J = 6.8 Hz, H-7); 0.90 (3H, t, J = 6.8 Hz, H-10); ^{1}H NMR, δ_H ($CDCl_3$ 500 MHz), 4.32 (1H, d, J = 11.1 Hz, H′-1), 4.14 (1H, d, J = 11.1 Hz, H-1), 1.10 (3H, s, H-8), 0.92 (3H, t, J = 7.0 Hz, H-7), 0.87 (3H, t, J = 7.0 Hz, H-10). Compound **4**: ^{1}H NMR, δ_H (CD_3OD,500 MHz), 4.27 (1H, d, J = 10.0 Hz, H′-1), 4.23 (1H, d, J = 10.0 Hz, H-1), 1.13 (3H, s, H-8), 0.92 (6H, m, H-7 and H-10); ^{1}H NMR, δ_H ($CDCl_3$ 500 MHz), 4.27 (1H, d, J = 11.1 Hz, H′-1), 4.22 (1H, d, J = 11.1 Hz, H-1), 1.10 (3H, s, H-8), 0.90 (6H, m, H-7 and H-10).

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