Stereochemical Assignment at C-24 and C-25 of Marine 24-Ethyl-26-hydroxy Steroids through Comparison with Synthetic (24*S*,25*S*)-, (24*S*,25*R*)-, (24*R*,25*R*)-, and (24*R*,25*S*)-Models

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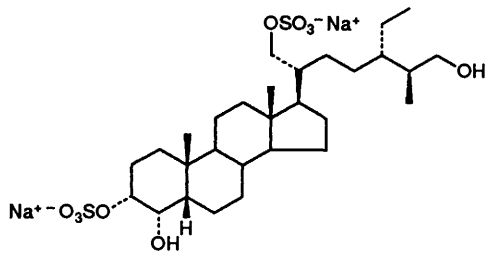
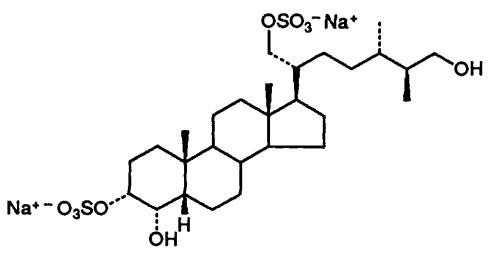
Stereoisomeric Δ^{22E}-24-ethyl-26-hydroxy steroids (**7a**), (**7b**), (**8a**), and (**8b**) and the corresponding 22,23-dihydro derivatives (**9a**), (**9b**), (**10a**), and (**10b**) were synthesized. Analysis of ^1H and ^{13}C NMR spectra of the synthetic model compounds and of their MTPA derivatives provided data suitable for the assignment of configuration at C-24 and C-25 in 24-ethyl-26-hydroxy steroids. From those models and the related spectral data, the stereochemistry (24*S*,25*S*) has been assigned to 24-ethyl-5β-cholestane-3α,4α,21,26-tetraol 3,21-disulphate, recently isolated from the marine ophiuroid *Ophiolepis superba*.

During our continuing work on polyhydroxysteroids and steroidal glycosides from echinoderms, we have recently isolated 24-ethyl-5β-cholestane-3α,4α,21,26-tetraol 3,21-disulphate (**1**) from the ophiuroid *Ophiolepsis superba*.[1] Structure (**1**) and those of related polyhydroxylated sulphated sterols, having the same 3α,4α,21,26-tetraol 3,21-disulphate structure in a 5β-H steroid and different side-chains, have been determined from spectral data, but the stereochemistry of compound (**1**) at C-24 and C-25 remained to be defined. In a previous paper[2] we have reported the synthesis of the C-24 and C-25 stereoisomeric pairs of 6β-methoxy-3α,5-cyclo-24-methyl-5α-cholestan-26-ols, and have assigned the stereochemistry at C-24 and C-25 of marine polyhydroxysteroids having 24-methyl-26-hydroxy side-chains, including the steroid (**2**) isolated from *O. superba*. This paper concerns the synthesis of all possible configurations of the 24-ethyl-26-hydroxy side-chain so that the stereochemistry at C-24 and C-25 of compound (**1**) could be determined.



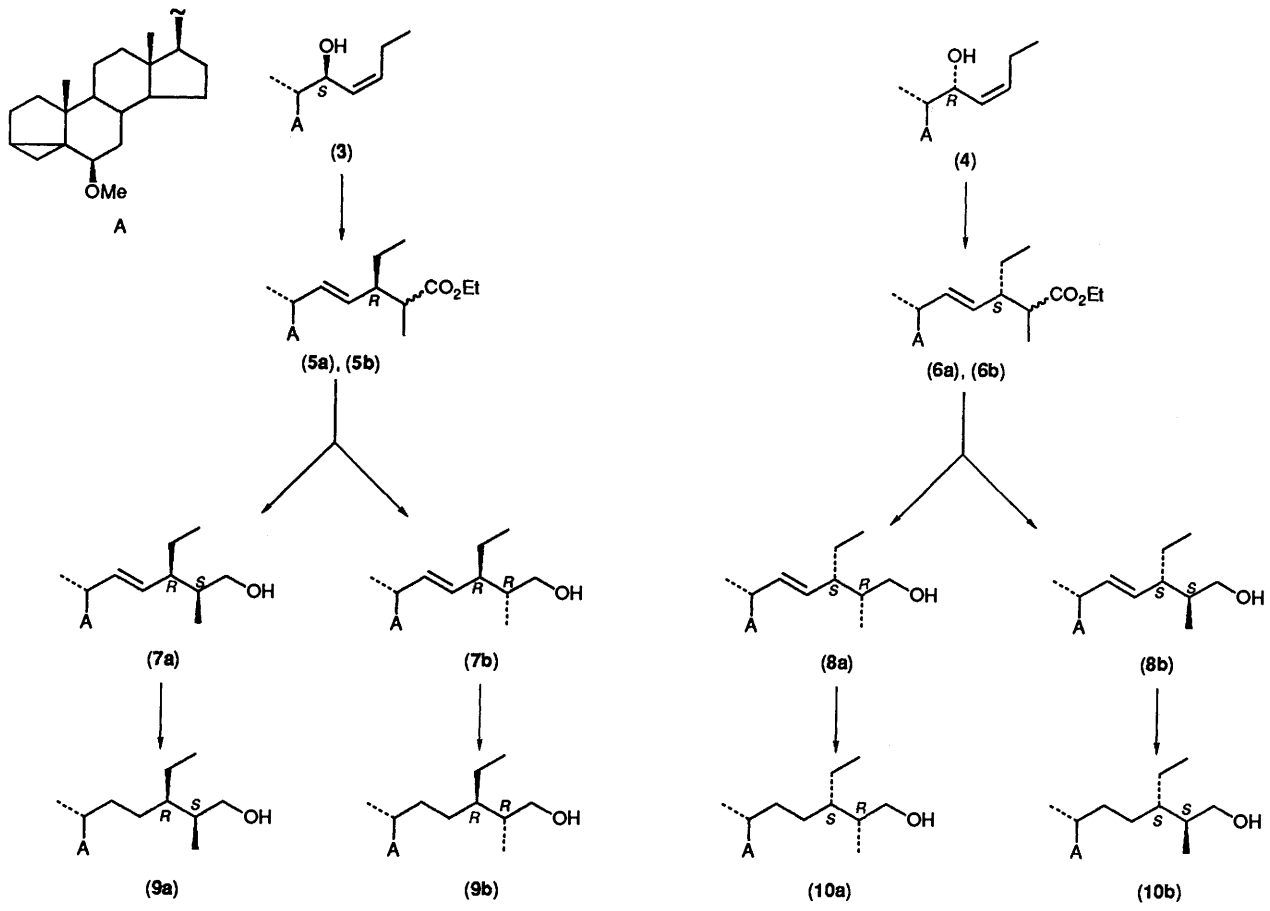
(**1**)



(**2**)

In the synthesis of the steroid (**1**) side-chain, we have used the Claisen rearrangement, which Sucrow *et al.*[3] have specifically applied to steroidal side-chain allylic alcohols. The method permits the construction of the stereogenic centre at C-24 in a predictable way by exposing the Δ^{23}-22-ol steroids to triethyl orthopropionate.[4–7]

The starting materials, the (22*S*)-*cis*-allylic alcohol (**3**) and the (22*R*)-epimer (**4**),[7] were independently used in the Claisen rearrangement with triethyl orthopropionate to give in both cases a mixture of two olefinic esters, which were epimeric at C-25 [(**5a** and **b**) and (**6a** and **b**), respectively] and which resisted attempts at separation.[4] Lithium aluminium hydride (LAH) reduction of each mixture afforded the corresponding mixture of two olefinic alcohols [(**7a** and **b**) and (**8a** and **b**), respectively], which were separated by HPLC. ^1H NMR analysis of the four stereoisomers revealed related pairs showing almost identical spectra, which obviously had to be the pairs with the same relative configuration, *i.e.* (**7a**)–(**8a**) and (**7b**)–(**8b**). The configuration at C-24 of each pair is derived from the stereoselectivity of the Claisen rearrangement, while the configuration at C-25 could be assigned by application to the corresponding saturated pair (**9b**) (24*R*-series)–(**10b**) (24*S*-series) the method for the determination of absolute configuration of primary alcohols, with the stereogenic centre at the C-2 position, based on the use of shift reagents with MTPA derivatives in ^1H NMR spectroscopy, described by Yasuhara and Yamaguchi.[8] Thus we prepared (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, Mosher's reagent[9]) esters of alcohols (**9b**) and (**10b**) and then compared the lanthanide shifts of the methoxy-group signals of the 1:2 mixture. Since a larger LIS_{OMe} was observed for the minor component, the 25*R* configuration was assigned to compound (**9b**) (24*R* series) and the 25*S* configuration to compound (**10b**) (24*S* series). The 24*R*,25*S* and 24*S*,25*R* configuration assigned to the pair (**9a**)–(**10a**), as well as the configuration assigned to the Δ^{22}-epimers (Scheme 1) followed accordingly. Thus the synthesis of the four side-chain models of the natural steroid (**1**) could now be concluded. When this work was finished, a paper by Horibe *et al.*[10] appeared describing the synthesis of the C-24 and C-25 stereoisomeric pairs of 24-ethyl-26-hydroxy steroids and their Δ^{22}-derivatives. These authors used Ireland's enolate-Claisen rearrangement,[11] which also permits control of the stereochemistry at C-25, and confirmed the absolute configurations, estimated from the reaction mechanism, by X-ray crystallography on the olefinic ester (**6b**) and on the corresponding acid of the ester (**5b**). A detailed comparison of the ^1H and ^{13}C NMR data (in $CDCl_3$) of our samples with those of the corresponding synthetic compounds described by Horibe *et al.*[10] confirmed our stereochemical assignments as those shown in Scheme 1.



Scheme 1.

Table 1. Selected NMR data of the model steroids and the natural product (**1**).[a]

Δ^{22}-Series	^{1}H 26-H_2,27-H_3	^{13}C C-24, -27, -28	^{1}H (*R*)-(+)-MTPA esters 26-H_2
(**7a**) (24*R*,25*S*)	3.25dd–3.64dd, 0.93d	48.7, 15.2, 25.5	4.10dd–4.32dd
(**8a**) (24*S*,25*R*)	3.25dd–3.63dd, 0.94d	48.7, 15.2, 25.5	4.04dd–4.38dd
(**8b**) (24*S*,25*S*)	3.32dd–3.48dd, 0.83d	47.1, 12.9, 26.9	4.15br d
(**7b**) (24*R*,25*R*)	3.34dd–3.48dd, 0.85d	47.1, 12.9, 26.9	4.08dd–4.19dd
Saturated side-chain series	^{1}H 26-H_2, 27-H_3	^{13}C C-23, -28	^{1}H (*R*)-(+)-MTPA esters 26-H_2
(**9a**) (24*R*,25*S*)	3.37dd–3.56dd, 0.89d	28.3, 23.6	4.17dd–4.26dd
(**10a**) (24*S*,25*R*)	3.38dd–3.52dd, 0.84d	28.4, 23.7	4.11dd–4.32dd
(**10b**) (24*S*,25*S*)	3.37dd–3.55dd, 0.89d	27.3, 25.2	4.22br d
(**9b**) (24*R*,25*R*)	3.39dd–3.53dd, 0.87d	27.0, 24.9	4.12dd–4.31dd
Natural (**1**) (24*S*,25*S*)	3.35dd–3.58dd, 0.92d	27.6, 25.1	4.26d (+)-MTPA ester 4.16dd–4.39dd (−)-MTPA ester

[a] Spectra were run in CD_3OD except those of the MTPA esters of the model steroids ($CDCl_3$).

For reason of direct comparison [natural (**1**) is soluble only in methanol] we needed to record the ^{1}H NMR and the ^{13}C NMR spectra of synthetic models for solutions in CD_3OD, and the chemical shifts of selected signals are listed in Table 1 (other signals are given in the Experimental section). In the Δ^{22}-series ^{1}H and ^{13}C NMR spectra of the pair (**7a**)–(**8a**) are significantly different from those of the pair (**7b**)–(**8b**). The major differences relate to the shifts of the C-26 methylene and C-27 methyl protons in the ^{1}H NMR and the shifts of the C-24, C-25, and C-27 carbons in the ^{13}C NMR spectrum. In the saturated side-chain series the ^{1}H NMR spectra of all isomers were very similar, while the ^{13}C NMR spectra of the pair (**9a**)–(**10a**) were significantly different from those of the pair (**9b**)–(**10b**) (major differences in the shift of C-23 and C-28 signals, Table 1). Thus NMR analysis allowed distinction of the (24*R*,25*S*)-, (24*S*,25*R*) pair from the (24*R*,25*R*)-, (24*S*,25*S*) pair. Differentiation within each pair, *i.e.* (**7a**) (25*S*) from (**8a**) (25*R*), (**7b**) from (**8b**), (**9a**) from (**10a**), and (**9b**) and (**10b**) could be obtained by ^{1}H NMR spectroscopic analysis of their (+)-MTPA esters* (Table 1).

* The term (+)- or (−)-MTPA ester refers to an ester obtained using the acid chloride prepared from (*R*)-(+) or (*S*)-(−) acid, respectively.

Within each pair the 26-methylene protons of the 25*S*-isomer appear as signals resonating much closer than do those in the corresponding 25*R*-isomer.

The ^{13}C NMR spectrum of the natural compound (**1**) and comparison with those of the synthetic models (Table 1) established its relative stereochemistry at C-24 and C-25 (24*R*,25*R* or 24*S*,25*S*). The ^{13}C NMR values of natural (**1**) (C-23: δ_C 27.6; C-24: 43.4; C-27: 13.4; C-28: 25.1) compare better with those of compound (**10b**) (24*S*,25*S*) (C-23: 27.3; C-24: 43.2; C-27: 13.5; C-28: 25.2) than with those of its isomer (**9b**) (24*R*,25*R*) (C-23: 27.0; C-24: 42.5; C-27: 13.0; C-28: 24.9), but differences between the two synthetic isomers are too small for an unambiguous assignment. Thus we prepared the 26-(+) and 26-(−)-MTPA esters of compound (**1**). The appearance of the 26-methylene protons as a doublet at δ 4.26 in the (+)-MTPA ester, and as two double doublets at δ 4.16 and 4.39 in the (−)-MTPA ester, established the 25*S* and accordingly the 24*S* stereochemistry for the natural sulphated steroid (**1**). Thus the complete structure for compound (**1**) has now been determined as (24*S*,25*S*)-24-ethyl-5β-cholestane-3α,4α,21,26-tetraol 3,21-disulphate.

Experimental

General Methods.—NMR spectra (^1H and ^{13}C) were recorded with a Bruker WM 250 Fourier Transform Spectrometer. The ^{13}C NMR spectra were recorded at 62.9 MHz, and the assignments were aided by DEPT pulse sequence experiments[12] using a polarization transfer pulse of 135°, obtaining positive signals for CH and CH_3 and negative ones for CH_2 groups. Polarization-transfer delays were adjusted to an average CH coupling of 135 Hz. Mass spectra were recorded on a AEI MS-30 instrument by direct inlet. Semipreparative HPLC was performed on a Whatman Partisil M9 10/50 column with a Waters Model 6000 A pump equipped with a U6K injector and a differential refractometer Model 401 detector.

Ethyl (22E,24R,25ζ)- *and Ethyl* (22E,24S,25ζ)-6β-*Methoxy*-3α,5-*cyclo*-5α-*stigmast*-22-*en*-26-*oate* (**5a** *and* **b**) *and* (**6a** *and* **b**).—The 22*S*-alcohol (**3**)[7] (0.4 g), triethyl orthopropionate (2 g), and propionic acid (two drops) were heated under reflux in dry xylene (10 ml) for 3 h.[4–7] Removal of the solvent and excess of reagent under reduced pressure gave an epimeric mixture of the esters (**5a**) and (**5b**).[4]

The 22*R* alcohol (**4**)[7] (0.7 g) when treated as above afforded an epimeric mixture of the esters (**6a**) and (**6b**).[4]

(22E,24R,25S)- *and* (22E,24R,25R)-6β-*Methoxy*-3α,5-*cyclo*-5α-*stigmast*-22-*en*-26*ol* (**7a** *and* **b**).—The (24*R*)-ester mixture epimeric at C-25 (**5a** and **b**) (0.42 g) was dissolved in anhydrous diethyl ether (30 ml) and LAH (500 mg) was slowly added. After being stirred at 25 °C for 5 h, the mixture was cooled at 0 °C and ice was cautiously added. Usual work-up afforded a mixture (0.35 g) of the oily olefinic alcohols (**7a**) and (**7b**), which were separated by HPLC on a Whatman Partisil M9 10/50 column with hexane–ethyl acetate (92:8) as eluting solvent (flow 10 ml min^{-1}) to give the less polar compound (**7a**) (24*R*,25*S*) (112 mg), t_R 8.2 min; *m/z* 442 (M^+); $\delta_H(CD_3OD)$ 0.48 (1 H, m, 4-H), 0.68 (1 H, m, 4-H), 0.79 (3 H, s, 18-H_3), 0.85 (3 H, t, *J* 7.5 Hz, 29-H_3), 0.93 (3 H, d, *J* 6.5 Hz, 27-H_3), 0.93 (1 H, m, 3-H), 1.04 (3 H, s, 19-H_3), 1.06 (3 H, d, *J* 6.2 Hz, 21-H_3), 2.84 (1 H, br t, 6-H), 3.25 (1 H, dd, *J* 11.2, 7.2 Hz)–3.64 (1 H, dd, *J* 11.2, 6.2 Hz, 26-H_2), 3.34 (3 H, s, OMe), 5.08 (1 H, dd, *J* 15, 8.8 Hz, 23-H), and 5.24 (1 H, dd, *J* 15, 8.8 Hz, 22-H); $\delta_C(CD_3OD)$ C-1: 34.5, C-2:, 25.8, C-3: 22.8, C-4: 13.8, C-5: 36.5, C-6: 84.0, C-7: 36.1, C-8: 31.8, C-9: 49.4, C-10: 44.6, C-11: 23.8, C-12: 41.5, C-13: 43.9, C-14: 57.6, C-15: 25.3: C-16: 30.0, C-17: 57.9, C-18: 12.9, C-19: 19.8, C-20: 41.5, C-21: 21.6, C-22: 139.6, C-23: 131.1, C-24: 48.7, C-25: 41.3, C-26: 66.6, C-27: 15.2, C-28: 25.5, C-29: 12.4, and OMe: 57.6; and the more polar isomer (**7b**) (24*R*,25*R*) 168 mg), t_R 8.5 min; *m/z* 442 (M^+); $\delta_H(CD_3OD)$ 0.85 (3 H, d, *J* 7.5 Hz, 27-H_3), 1.07 (3 H, d, *J* 6.2 Hz, 21-H_3), 3.34 (1 H, dd, *J* 11.2, 7.2 Hz)–3.48 (1 H, dd, *J* 11.2, 6.2 Hz, 26-H_2), 5.07 (1 H, dd, *J* 15, 8.8 Hz, 23-H), and 5.26 (1 H, dd, *J* 15, 8.8 Hz, 22-H); the remaining signals were identical with those of compound (**7a**); $\delta_C(CD_3OD)$ C-22: 140.2, C-23: 129.5, C-24: 47.1, C-25: 40.9, C-26: 67.3, C-27: 12.9, C-28: 26.9, and C-29: 12.5; signals for C-1–C-21 were identical with those of compound (**7a**).

(22E,24S,25R)- *and*(22E,24S,25S)-6β-*Methoxy*-3α,5-*cyclo*-5α-*stigmast*-22-*en*-26-*ol* (**8a** *and* **8b**).—The (24*S*)-ester mixture epimeric at C-25 (**6a** and **b**) (0.7 g), when treated with LAH as above, afforded a mixture (0.65 g) of the oily olefinic alcohols (**8a**) and (**8b**), which were separated by HPLC under the same conditions as above to yield compound (**8a**) (24*S*,25*R*) (180 mg), t_R 10.5 min; *m/z* 442 (M^+); with ^1H and ^{13}C NMR spectra virtually identical with those of compound (**7a**) (24*R*,25*S*); and isomer (**8b**) (24*S*,25*S*) (340 mg), t_R 10.2 min; with ^1H and ^{13}C NMR specta virtually identical with those of isomer (**7b**) (24*R*,25*R*).

(24R,25S)-, (24R,25R)-, (24S,25R)-, *and* (24S,25S)-6β-*Methoxy*-3α,5-*Cyclo*-5α-*stigmastan*-26-*ol* (**9a**), (**9b**), (**10a**) *and* (**10b**).—Each of the above olefinic alcohols (50 mg each) was hydrogenated at atmospheric pressure over Pt/C (20 mg) in ethanol (15 ml) for 12 h. After the catalyst was removed by filtration, the solvent was evaporated off to leave the saturated, non-crystalline alcohols: (**9a**) (24*R*,25*S*), *m/z* 444 (M^+); $\delta_H(CD_3OD)$ 0.78 (3 H, s, 18-H_3), 0.89 (3 H, d, *J* 7.5 Hz, 27-H_3), 0.93 (3 H, t, *J* 7.5, 29-H_3), 0.99 (3 H, d, *J* 6.2 Hz, 21-H_3), 1.05 (3 H, s, 19-H_3), and 3.37 (1 H, dd, *J* 10, 3 Hz)–3.56 (1 H, dd, *J* 10, 5 Hz, 26-H_2); $\delta_C(CD_3OD)$ C-16: 29.3, C-17: 56.8, C-18: 12.6, C-20: 37.5, C-21: 19.4, C-22: 35.2, C-23: 28.3, C-24: 43.1, C-25: 40.0, C-26: 66.7, C-27: 13.6, C-28: 23.6, and C-29: 12.5; the remaining nuclear signals were identical with those of compound (**7a**) and the other Δ^{22}-isomers.

Compound (**9b**) (24*R*,25*R*), *m/z* 444 (M^+); $\delta_H(CD_3OD)$ 0.78 (3 H, s, 18-H_3), 0.87 (3 H, d, *J* 7.5 Hz, 27-H_3), 0.92 (3 H, t, *J* 7.5, 29-H_3), 0.97 (3 H, d, *J* 6.2 Hz, 21-H_3), 1.05 (3 H, s, 19-H_3), and 3.34 (1 H, dd, *J* 10, 3 Hz)–3.53 (1 H, dd, *J* 10, 5 Hz, 26-H_2); $\delta_C(CD_3OD)$ C-23: 27.0, C-24: 42.5, C-25: 38.5, C-26: 66.9, C-27: 13.0, C-28: 24.9, and C-29: 12.3, the remaining nuclear signals were identical with those of compound (**9a**).

Compound (**10a**) (24*S*,25*R*), *m/z* 444 (M^+); $\delta_H(CD_3OD)$ 0.77 (3 H, s, 18-H_3), 0.84 (3 H, d, *J* 1.5 Hz, 27-H_3), 0.92 (3 H, t, *J* 7.5, 29-H_3), 0.98 (3 H, d, *J* 6.2 Hz, 21-H_3), 1.04 (3 H, s, 19-H_3), and 3.38 (1 H, dd, *J* 11.2, 3.8 Hz)–3.52 (1 H, dd, *J* 11.2, 5 Hz, 26-H_2); $\delta_C(CD_3OD)$ C-24: 42.8, C-25: 38.7, C-26: 67.0, C-27: 13.0, C-28: 23.7, and C-29: 12.7; the remaining nuclear signals were identical with those of compound (**9a**).

Compound (**10b**) (24*S*,25*S*), *m/z* 444 (M^+); $\delta_H(CD_3OD)$, 0.78 (3 H, s, 18-H_3), 0.89 (3 H, d, *J* 7.5 Hz, 27-H_3), 0.93 (3 H, t, *J* 7.5, 29-H_3), 0.98 (3 H, d, *J* 6.2 Hz, 21-H_3), 1.05 (3 H, s, 19-H_3), and 3.37 (1 H, dd, *J* 10, 3 Hz)–3.55 (1 H, dd, *J* 10, 6.2 Hz, 26-H_2); $\delta_C(CD_3OD)$ C-20: 37.6, C-21: 19.4, C-22: 35.4, C-23: 27.3, C-24: 43.2, C-25: 38.7, C-26: 66.8, C-27: 13.5, C-28: 25.2, and C-29: 12.6; the remaining signals were identical with those of compound (**9a**).

Preparation of (+)-*MTPA Esters of the Model Steroids* (**7a**)–(**10b**).—The required alcohol (5 mg) was treated with a solution of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride (3 μl) in dry pyridine (100 μl) for 1–3 h at room temperature. The reaction is followed by TLC. After disappearance of the starting material the solvent was removed and the product was purified by passage through a Pasteur

pipette filled (2 cm) with a slurry of silica gel in methylene dichloride. ^{1}H NMR ($CDCl_3$) signals for 26-H_2 protons are in Table 1; other significant signals are those due to 27-H_3; (**7a**) 0.95 (d), (**7b**) 0.82 (d), (**8a**) 0.91 (d), **8b**) 0.81 (d), (**9a**) 0.86 (d), (**9b**) 0.84 (d), (**10a**) 0.83 (d), **10b**), 0.85 (d).

26-(+)-*MTPA Ester and* 26-(−)-*MTPA Ester of the Natural Product* (**1**).—Compound (**1**) (3 mg) was treated with a solution of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (3 μl) in dry pyridine (0.2 ml) at room temperature for 3 h. After removal of solvent, the product, the (+)-MTPA ester of compound (**1**), was purified by reverse-phase HPLC on a C_{18} μ-Bondapak column in MeOH–water (55:45); δ_H(CD_3OD) 0.73 (3 H, s, 18-H_3), 0.87 (3 H, t, *J* 7 Hz, 29-H_3), 0.90 (3 H, d, *J* 7 Hz, 27-H_3), 0.95 (3 H, s, 19-H_3), 3.92 (1 H, dd, *J* 10.5, 6.5, 21-H), 4.18–4.23 (3 H, m, 21-, 3β- and 4β-H), and 4.28 (2 H, d, *J* 6.5 Hz, 26-H_2). The (−)-MTPA ester of compound (**1**) was similarly prepared from compound (**1**) (3 mg) and freshly distilled (−)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride and purified as above; the ^{1}H NMR (CD_3OD) data were very similar to those of the above (+)-MTPA ester except for the signal for the 26-methylene protons which resonated as two well separated dd at δ 4.16 (overlapping with 21-, 3β-, and 4β-H signals) and 4.39 (*J* 10.2, 6.5 Hz).

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