Triterpenoid total synthesis. Part 5.[1] Synthetic disproof of the triterpene structure proposed for naurol A, a cytotoxic metabolite of a Pacific sponge

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Naurol A is a cytotoxic metabolite isolated from a Pacific sponge, and **1** has been proposed as its structure. A mixture of (±)-**1** and *meso*-**1′** was synthesized from 4-*tert*-butyldimethylsilyloxy-3-methylcyclohex-2-en-1-one (**6**) employing the Stille coupling (**10** + **11**→**1** + **1′**) as the key step. Although the synthetic sample (**1** + **1′**) was a diastereomeric mixture at C-11, its spectral data (IR, UV, ^{1}H and ^{13}C NMR and MS) were significantly different from those reported for naurol A. It was therefore concluded that the structure **1** proposed for naurol A was in error.

Introduction

In 1991 De Guzman and Schmitz isolated naurol A and B as the metabolites of Pacific sponge collected at Nauru Island.[2] Naurol A and B showed mild cytotoxicity against murine lymphocytic leukemia cells, and their structures were proposed as **1** and **2**, respectively, primarily on the basis of ^{1}H and ^{13}C NMR data. The structures **1** and **2** are unique, because they are triterpene alcohols with C_2 symmetry. The unusual partially cyclized squalene skeleton present in **1** and **2** (Chart 1) has also been reported in the case of (±)- and *meso*-limatulone (**3** and **3′**), the defensive metabolites of a limpet *Achmeia* (*Collisella*) *limatula*,[3] and is also found in a rapidly growing group of new marine triterpenes such as (+)-testudinariol A (**4**).[4]

In continuation of our synthesis of limatulones (**3** and **3′**),[5] we attempted to synthesize the proposed **1** as a racemic and diastereomeric mixture at C-11. As detailed below, the present synthesis of **1** disproved the correctness of the structure **1** assigned to naurol A.

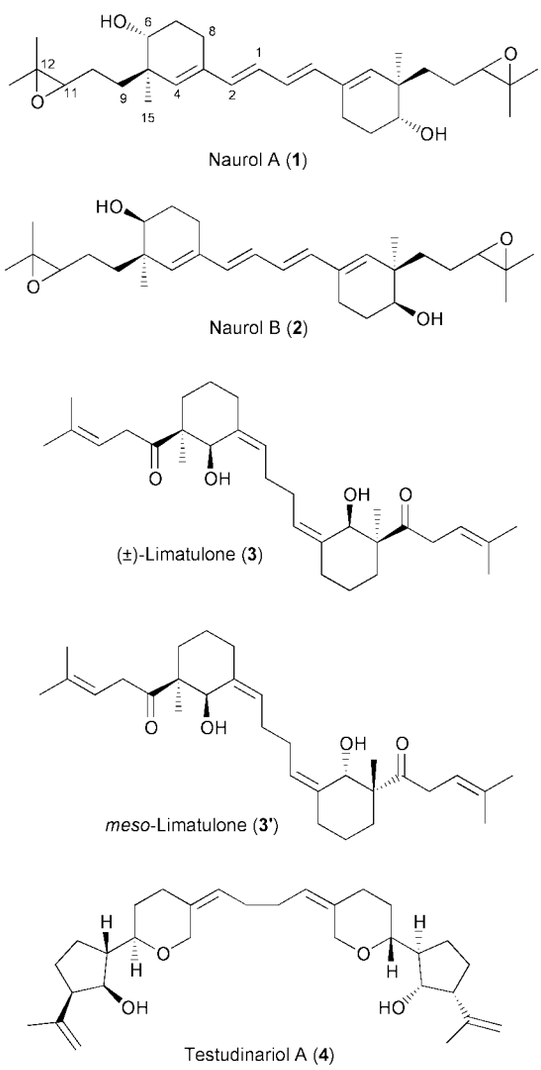

Chart 1 Structures of naurol A, B and related metabolites.

Results and discussion

Synthetic plan

Scheme 1 shows our synthetic plan for **1**. The major challenge in this synthesis was how to construct the *E*,*E*-tetraene system in the centre of the molecule. To construct this tetraene system, we adopted Stille coupling[6] that can couple the key intermediate **A** and the known distannane **B**.[7] Preparation of the key intermediate **A** would be accomplished by a diastereoselective Michael addition of a homoprenyl group to **D** followed by several steps. Because the preparation of optically active **D** is known,[8] this synthetic plan might be applicable for enantioselective synthesis of **1**. However, we initially attempted the synthesis of **1** as a diastereomeric mixture to establish our synthetic route.

Synthesis of a compound with proposed structure 1

First we synthesized the known enone **6** (=**D**) from *m*-cresol methyl ether (**5**).[8] The enone **6** was treated with homoprenylmagnesium bromide (Scheme 2) in the presence of TMSCl and $CuBr{\cdot}SMe_2$ to give the enol ether **7** as a single isomer (quant.).[8,9] The resulting **7** was then treated with MeLi followed by *N*-phenyltrifluoromethanesulfonimide (Tf_2NPh) to afford the triflate **8** (=**C**) in 74% yield.[10] Selective epoxidation of **8** with MCPBA afforded the epoxide **9** as an inseparable mixture of two diastereomers (*ca.* 1:1) in 96% yield. Since the

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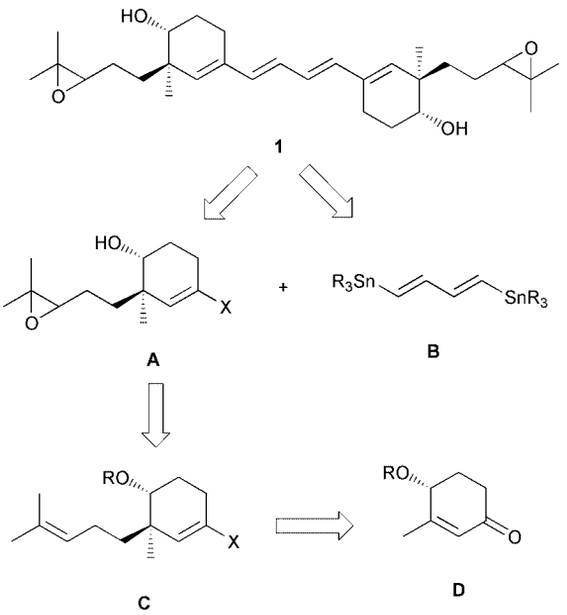


Scheme 1 Synthetic plan for **1**.

configuration at C-11 relative to C-5 had not been clarified,[2] no care was taken to control the stereochemistry of this epoxidation. Deprotection of the TBDMS group by treatment with TBAF yielded the alcohol **10** (=**A**) in 82% yield.

The known distannane **11**[7] (=**B**) [1,4-bis(trimethylstannyl)-buta-1,3-diene, *E*,*E*:*E*,*Z* = *ca.* 2:1] was prepared according to the reported procedure.[7] The final Stille coupling of **10** and **11** was the key step of our synthesis, and therefore the reaction conditions were carefully optimized. Only the *E*-configured trimethylstannyl group of **11** could react with **10** in the presence of tetrakis(triphenylphosphine)palladium $[Pd(PPh_3)_4]$[6] at room temperature, while the *Z*-configured trimethylstannyl group could also react at 60 °C. This difference in reactivity enabled us to obtain only the *E*,*E*-products (**1** and **1′**), even when **11** was employed as a mixture of geometrical isomers (*E*,*E*:*E*,*Z* = *ca.* 2:1). The remaining problem was the improvement of the conversion yield. The greater the excess of **11**, the more the "mono-coupled" by-products (**12**) were generated. (The structures of these by-products (**12**) were tentative. Because of their instability, we could not fully characterize them.) After optimization, treatment of 2.0 eq. of **10** with 1.2 eq. of **11** was found to give the best result. Finally, the triflate **10** was coupled with **11** to give a mixture of **1** and **1′** as pure *E*,*E*-isomers in 72% yield based on **10**. The overall yield was 42% based on **6** in 5 steps.

Conclusion

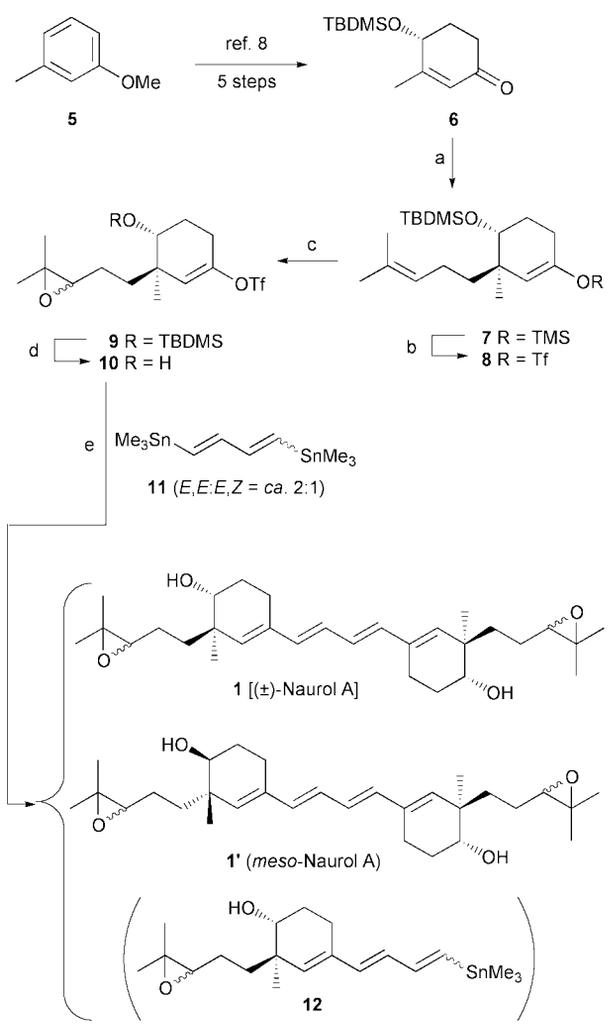
The synthesis of a compound with structure **1** was accomplished in a partially stereocontrolled manner to give correct *E*,*E*-geometry and relative configuration between C-5 and C-6. Since the key intermediate **10** was the racemate, a mixture of (±)-**1** and *meso*-**1′** was obtained as a diastereomeric mixture at C-11. The various spectral data of the synthetic mixture of **1** and **1′** are much simpler than expected and rather easy to analyze. With respect to the side-chain portion, the NMR data of synthetic **1** and **1′** are in good accord with those reported. Those of the cyclohexene moiety including the tetraene system, however, are significantly different from those reported for naurol A,[2] as shown in Tables 1 and 2. In addition to various 1D and 2D NMR spectra, HRFAB-MS, IR and UV spectra of the synthetic sample also support the fact that our synthetic mixture of **1** and **1′** possesses the proposed structure. We therefore conclude that the proposed structure **1** for natural naurol A is incorrect.

The correct structures of naurol A and B must be elucidated in future after their reisolation.

Table 1 ^{1}H NMR data[a] for naurol A and a mixture of **1** and **1′** (δ_H, ppm)

Proton	Naurol A[b]	A mixture of **1** and **1′**[c]
1-H	6.71 (d, 13.2)	6.10–6.25 (m)[d]
2-H	6.52 (d, 13.2)	
4-H	5.64 (br s)	5.39 (s) and 5.40 (s)
6-H	4.09 (dd, 10, 4)	3.71 (br d, 12.2)
7-H_2	2.17 (m)	1.75–1.90 (m)
8-H_{ax}	2.33 (m)[e]	2.18 (quintet like, 8.4)
8-H_{eq}		2.33 (d like, 16.8)
9-H_2	1.83 (m) and 1.44 (m)	1.38–1.73 (m)[f]
10-H_2	1.57 (m) and 1.36 (m)	
11-H	2.69 (m)	2.68 (t, 6.1)
13-H_3	1.25 (s)	1.25 (s)
14-H_3	1.30 (s)	1.29 (s)
15-H	1.13 (s)	1.00 (s)

[a] In $CDCl_3$; splitting patterns and *J*-values (Hz) are given in parentheses. [b] Measured at 300 MHz. [c] Measured at 500 MHz. [d] 1-H and 2-H. [e] 8-H_2. [f] 9-H_2 and 10-H_2.



Scheme 2 Synthesis of a mixture of **1** and **1′**. *Reagents*: (a) $(Me)_2C{=}CH(CH_2)_2MgBr$, $CuBr{\cdot}SMe_2$, TMEDA, TMSCl–THF (quant.); (b) MeLi–DME then $PhNTf_2$–THF (74%); (c) MCPBA–$CHCl_3$ (96%); (d) TBAF·2.5H_2O–THF (82%); (e) **11** (1.2 eq.), $Pd(PPh_3)_4$, LiCl–DMF (72%).

Experimental

IR spectra were measured as films for oils on a JASCO A-102 spectrometer. UV spectra were measured on a Shimadzu UV-260 spectrometer. ^{1}H-NMR spectra were recorded at 90 MHz on a JEOL JNM-EX 90A spectrometer, at 400 MHz on a JEOL JNM-LA400 spectrometer and at 500 MHz on a JEOL JNM-

Table 2 ^{13}C NMR data[a] for naurol A and a mixture of **1** and **1′** (δ_C, ppm)

Carbon	Naurol A[b]	A mixture of **1** and **1′**[c]
1-C	130.1	127.27
2-C	136.9	134.61
3-C	133.0	134.34 and 134.42
4-C	141.0	136.57
5-C	41.4	40.17 and 40.26
6-C	63.8	71.68 and 71.93
7-C	28.9	26.94 and 27.08
8-C	24.9	23.36 and 23.40
9-C	36.8	36.37 and 36.44
10-C	24.2	23.81
11-C	64.5	64.69 and 64.79
12-C	58.7	58.46 and 58.58
13-C	19.0	18.62 and 18.66
14-C	25.2	24.84
15-C	23.0	20.97 and 21.09

[a] In $CDCl_3$. [b] Measured at 75 MHz. [c] Measured at 126 MHz.

LA500 spectrometer. The peak for TMS or $CHCl_3$ in $CDCl_3$ (at δ 7.26) was used for the internal standard. Chemical shifts are reported in ppm on the δ scale and *J*-values are given in Hz. ^{13}C-NMR spectra were recorded at 126 MHz on a JEOL JNM-LA500 spectrometer. The peak for $CDCl_3$ (at δ 77.0) was used as the internal standard. Mass spectra were measured with a JEOL JMS-SX102A spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734. TLC analyses were performed on Merck silica gel plates 60F–254.

4-(*tert*-Butyldimethylsilyloxy)-3-methylcyclohex-2-en-1-one 6

The known enone **6** was prepared by the reported procedure.[8] n_D^{27} 1.4730; ν_{max}(film)/cm^{-1} 1675s (C=O), 1630w (C=C), 1250s (TBDMS), 1105s (C–O); δ_H(90 MHz; $CDCl_3$) 0.13 (6H, s, $SiMe_2$), 0.89 (9H, s, SiBu^t), 1.91–2.60 (4H, m, 5- and 6-H_2), 1.98 (3H, s, 3-Me), 4.35 (1H, m, 4-H), 5.82 (1H, br s, 2-H). These spectral data were in good accord with those reported.[8]

(3*R,4*R**)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(4′-methylpent-3′-enyl)-1-(trimethylsilyloxy)cyclohex-1-ene 7**

To a stirred solution of $CuBr{\cdot}SMe_2$ (5.36 g, 26.0 mmol) in dry THF (50 cm^3) was added a solution of $(Me)_2C{=}CH(CH_2)_2$-MgBr in dry THF (1.04 mol dm^{-3}; 50 cm^3, 52.0 mmol) at −78 °C under Ar. After having been stirred at −40 °C for 30 min, TMEDA (7.83 cm^3, 52.0 mmol), TMSCl (8.28 cm^3, 65.0 mmol) and a solution of **6** (3.00 g, 12.5 mmol) in dry THF (30 cm^3) were added successively at −78 °C. The solution was then allowed to warm to room temperature with stirring overnight. This reaction mixture was diluted with hexane, washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the *crude* **7** (4.95 g, quant.) as a colorless oil, ν_{max}(film)/cm^{-1} 1670m (C=C), 1255s (TBDMS), 1205m (enol C–O), 1105s (C–O); δ_H(90 MHz; $CDCl_3$) 0.05 (6H, s, $SiMe_2$), 0.18 (9H, s, $SiMe_3$), 0.89 (9H, s, SiBu^t), 0.92 (3H, s, 3-Me), 1.20–1.40 (2H, m, 1′-H_2), 1.50–1.80 (2H, m, 5-H_2), 1.59 and 1.67 (total 6H, each s, $Me_2C{=}C$), 1.80–2.10 (4H, m, 6- and 2′-H_2), 3.61 (1H, m, 4-H), 4.60 (1H, s, 2-H), 4.95–5.15 (1H, m, 3′-H). This was employed in the next step without further purification.

(3*R,4*R**)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(4′-methylpent-3′-enyl)-1-(trifluoromethylsulfonyloxy)cyclohex-1-ene 8**

To a stirred solution of **7** (4.95 g, 12.5 mmol) in dry DME (60 cm^3) was added MeLi (1.14 mol dm^{-3} in Et_2O; 11.4 cm^3, 13.0 mmol) dropwise at −70 °C under Ar. After having been stirred at −10 °C for 2 h, a solution of Tf_2NPh (5.10 g, 14.3 mmol) in dry THF (50 cm^3) was added at −70 °C. After the reaction mixture was stirred at −30 °C for 1 h, it was diluted with hexane, washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **8** (4.35 g, 74%) as a colorless oil, n_D^{26} 1.4492 (Found: C, 52.74; H, 7.92. $C_{20}H_{35}O_4SSiF_3$ requires C, 52.61; H, 7.73%); ν_{max}(film)/cm^{-1} 1685w (C=C), 1420s, 1250s (TBDMS), 1210s (enol C–O), 1145s (S–O), 1115s (C–O); δ_H(90 MHz; $CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.89 (9H, s, SiBu^t), 1.01 (3H, s, 3-Me), 1.30–1.70 (4H, m, 5- and 1′-H_2), 1.59 and 1.67 (total 6H, each s, $Me_2C{=}C$), 1.88 (2H, t , *J* 6.3, 2′-H_2), 2.37 (2H, t, *J* 6.5, 6-H_2), 3.68 (1H, t, *J* 6.5, 4-H), 4.95–5.15 (1H, m, 3′-H), 5.47 (1H, s, 2-H).

(3*R,4*R**,3′*RS*)-4-(*tert*-Butyldimethylsilyloxy)-3-(3′,4′-epoxy-4′-methylpentyl)-3-methyl-1-(trifluoromethylsulfonyloxy)-cyclohex-1-ene 9**

To a stirred solution of **8** (100 mg, 0.219 mmol) in $CHCl_3$ (1 cm^3) was added MCPBA (70% purity; 82 mg, 0.33 mmol) at 0 °C. After having been stirred at room temperature for 30 min, the reaction mixture was poured into 10% aq. Na_2SO_3 and extracted with $CHCl_3$. The extract was washed with saturated aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give a diastereomeric mixture of the *epoxide* **6** (99 mg, 96%) as a colorless oil. The ratio of the diastereomers was determined to be 1 : 1 based on ^1H NMR analysis of **10**, n_D^{25} 1.4469 (Found: C, 50.91; H, 7.10. $C_{20}H_{35}O_5SSiF_3$ requires C, 50.83; H, 7.46%); ν_{max}(film)/cm^{-1} 1690w (C=C), 1420s, 1250s (TBDMS), 1215s (enol C–O), 1150s (S–O), 1120m (C–O); δ_H(400 MHz; $CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.88 (9H, s, SiBu^t), 1.01 and 1.02 (total 3H, each s, 3-Me), 1.25 and 1.30 (total 6H, each s, 4′-Me_2), 1.32–1.71 (4H, m, 1′- and 2′-H_2), 1.84 (2H, m, 5-H_2), 2.35 (2H, m, 6-H_2), 2.64 (1H, m, 3′-H), 3.64 (1H, m, 4-H), 5.43 (1H, s, 2-H).

(3*R,4*R**,3′*RS*)-3-(3′,4′-Epoxy-4′-methylpentyl)-4-hydroxy-3-methyl-1-(trifluoromethylsulfonyloxy)cyclohex-1-ene 10**

To a solution of **9** (1.50 g, 3.17 mmol) in THF (15 cm^3) was added $TBAF{\cdot}2.5H_2O$ (*ca.* 1 g) at 0 °C. After having been stirred at room temperature for 3 h, the reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **10** (921 mg, 82%) as a colorless oil, n_D^{25} 1.4535 (Found: C, 46.70; H, 6.05. $C_{14}H_{21}O_5SF_3$ requires C, 46.92; H, 5.91%); ν_{max}(film)/cm^{-1} 3430s (O–H), 1680w (C=C), 1410s, 1245m, 1205s (enol C–O), 1140s (S–O), 1060m (C–O); δ_H(400 MHz; $CDCl_3$) 1.05 and 1.06 (total 3H, each s, 3-Me), 1.25, 1.29 and 1.30 (6H, each s, 4′-Me_2), 1.38–1.78 (4H, m, 1′- and 2′-H_2), 1.87–1.95 (2H, m, 5-H_2), 2.06 (0.5H, d, *J* 5.6, one of OH), 2.39 (2.5H, m, 6-H_2 and one of OH), 2.70 (1H, m, 3′-H), 3.69 (1H, m, 4-H), 5.45 and 5.46 (total 1H, each s, 2-H).

1,4-Bis(trimethylstannyl)buta-1,3-diene 11

The known distannane **11** was prepared by the reported procedure.[7] ν_{max}(film)/cm^{-1} 3000s, 2930m, 1535s; δ_H(400 MHz; $CDCl_3$) 0.14 (6H, s, *E*,*E*-$SnMe_3$), 0.15 and 0.21 (total 3H, each s, *E*,*Z*-$SnMe_3$), 6.05–6.65 (total 4H, m, 1-, 2-, 3- and 4-H). The ratio of *E*,*E*-**11** and *E*,*Z*-**11** was determined to be 2 : 1 based on ^1H NMR analysis. These spectral data were in good accord with those reported.[7]

The mixture of (1*E*,3*E*,3′*R,4′*R**,3″*RS*)-1,4-bis[3′-(3″,4″-epoxy-4″-methylpentyl)-4′-hydroxy-3′-methylcyclohex-1′-enyl]buta-1,3-diene (1)† and its *meso*-type isomer (1′)**

To a slurry of LiCl (309 mg, 7.28 mmol) and $Pd(PPh_3)_4$ (84 mg,

† This numbering follows the IUPAC nomenclature. It is not the same as used for text and tables, which use that reported in the isolation paper.[2]

0.073 mmol) in DMF (5 cm^3) was added a solution of **10** (257 mg, 0.717 mmol) and **11** (166 mg, 0.437 mmol) in DMF (5 cm^3). After having been stirred at room temperature for 3 h, the reaction mixture was diluted with EtOAc, washed with water, 10% ammonium hydroxide solution, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give an inseparable mixture of the *target compounds* **1** and **1′** (121 mg, 72%) as a colorless foam (Found: C, 76.60; H, 9.80. $C_{30}H_{46}O_4$ requires C, 76.55; H, 9.85%); λ_{max} (ε) ($CHCl_3$)/nm 293 (0.69), 306 (1.00), 321 (0.83); ν_{max}(film)/cm^{-1} 3450m (O–H), 2970s, 2940s, 1630w (C=C), 1460m, 1430m, 1375m, 1320m, 1250m, 1210m, 1120m, 1050s (C–O), 980s, 950w, 925w, 895m, 870m, 790m, 755s; δ_H(500 MHz; $CDCl_3$) 1.00 (6H, s, 3′-Me), 1.25 and 1.29 (total 12H, each s, 4″-Me_2), 1.38–1.73 (10H, m, 1″- and 2″-H_2 and OH), 1.75–1.90 (4H, m, 5′-H_2), 2.18 (2H, quintet like, *J* 8.4, 6′-H_{ax}), 2.33 (2H, d like, *J* 16.8, 6′-H_{eq}), 2.68 (2H, t, *J* 6.1, 3″-H), 3.71 (2H, br d, *J* 12.2, 4′-H), 5.39 and 5.40 (total 2H, each s, 2′-H), 6.10–6.25 (4H, m, 1-, 2-, 3- and 4-H); δ_C(126 MHz; $CDCl_3$) 18.62 and 18.66 [4″-Me(a)], 20.97 and 21.09 (3′-Me), 23.36 and 23.40 (6′-C), 23.81 (2″-C), 24.84 [4″-Me(b)], 26.94 and 27.08 (5′-C), 36.37 and 36.44 (1″-C), 40.17 and 40.26 (3′-C), 58.46 and 58.58 (4″-C), 64.69 and 64.79 (3″-C), 71.68 and 71.93 (4′-C), 127.27 (2- and 3-C), 134.34 and 134.42 (1′-C), 134.61 (1- and 4-C), 136.57 (2′-C), HMBC cross peaks (selected): 2′-H/1-, 4′-, 6′- and 1″-C and 3′-Me; 4′-H/3′-Me, 6′- and 1″-C; 5′-H/1′-, 3′ -, 4′- and 6′-C; 6′-H_{ax}/1-, 1′-, 2′-, 4′- and 5′-C; 6′-H_{eq}/1-, 1′-, 2′-, 4′- and 5′-C; 3″-H/1″-, 2″- and 4″-C; 4″-Me(a)/3″- and 4″-C and 4″-Me(b); 4″-Me(b)/3″- and 4″-C and 4″-Me(a); 3′-Me/2′-, 3′-, 4′- and 1″-C; NOE correlations (selected): 3′-Me/2′-H and 5′-H; 6′-H_{ax}/4′-H; 6′-H_{eq}/5′-H [Found: (HRFAB-MS) $(M-H)^+$ 470.3401 $C_{30}H_{46}O_4$ requires *m*/*z* 470.3396].

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