Bisabolane- and Santalane-Type Sesquiterpenoids from *Santalum album* of Indian Origin

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Six new bisabolane-type (**1**−**3**) and santalane-type (**4**−**6**) sesquiterpenoids, together with (+)-α-nuciferol, (+)-citronellol, and geraniol, were isolated from the heartwood of *Santalum album* of Indian origin. Their structures, including two bisabolol diastereomers (**1**, **2**), were established on the basis of spectroscopic data interpretation.

Santalane-type sesquiterpenoids and their biogenetically related bisabolane- and campherenane-type analogues have been found in the plant species of the families Illiciaceae, Lauraceae, Rutaceae, and Santalaceae.[1−12] In particular, plants of the genus *Santalum* (Santalaceae), widely distributed in India, Indonesia, Malaysia, and Australia, have been reported as being rich in sesquiterpenoids.[7−12] Among these sesquiterpenoids, the tricyclic derivative, α-santalol, is attracting increasing attention because of its cancer chemopreventative and neuroleptic effects under both in vitro and in vivo conditions.[13−17] As part of a phytochemical survey of naturally occurring bioactive principles, we reported recently the isolation of new neolignans from the heartwood extract of *Santalum album* of Indian origin.[18] Further investigation of the terpenoid constituents of this biomass resulted in the isolation of six new compounds (**1**−**6**) along with three known terpenoids, geraniol, (+)-citronellol, and (+)-α-nuciferol. This paper deals with the structural elucidation of these new compounds.

Compound **1** was obtained as a colorless oil, $[\alpha]^{20}_D$ −5.2 ($CHCl_3$). Its molecular formula, $C_{15}H_{26}O_2$, was deduced from the molecular ion peak at *m/z* 238.1931 $[M]^+$ in the HREIMS and from the NMR data. The ^1H and ^{13}C NMR spectra of **1** (Tables 1 and 2) exhibited signals due to two vinyl methyls at δ_H 1.80 (δ_C 21.4) and 1.69 (δ_C 23.3), two olefins at δ_H 5.32 (δ_C 128.7) and 5.30 (δ_C 118.3), a secondary methyl at δ_H 0.90 (δ_C 13.8), and a hydroxymethylene group at δ_H 4.16, 4.10 (δ_C 61.6). The HSQC spectrum revealed, in addition to the above carbon resonances, the presence of five methylenes and one methine carbon as well as one tertiary carbon bearing an oxygen function (δ_C 72.3). These spectroscopic features along with four sp^2 carbon signals (two double bonds) in the ^{13}C NMR spectrum and the ^1H−^1H COSY correlations (H-3/H-2, -14, H-5/H-6, -14, H-8/H-9, -7, and H-10/H-13, -9) suggested that compound **1** is a monocyclic sesquiterpenoid with a *β*-bisabolol skeleton.[19] Extensive analysis of the HMBC correlations (H-15/C-8, -7, -1, H-14/C-5, -4, -3, H-13/C-12, -11, -10, H-8/C-10, -9, -7, -1, H-7/C-15, -8, -6, -2, -1, H-6/C-7, -5, -4, -2, and H-2/C-7, -4, -3, -1) supported this inference. The geometry of the Δ^{10} double bond was assigned as *Z* on the basis of salient cross-peaks between H-10/H-13 and H-9/H-12 in the NOESY spectrum. The upfield shift of C-12 ($-CH_2OH$) and downfield shift of C-13 (CH_3) provided additional evidence for the Δ^{10} geometry when compared with those of known *E*- and *Z*-isomeric analogues.[20,21] The stereochemistry of compound **1** required comparison with the structure of the closely related **2**.

The HREIMS of compound **2** showed an ion peak at *m/z* 238.1930 $[M]^+$, the same as that of **1**, indicating the molecular formula ($C_{15}H_{26}O_2$) of **2**. Most of the NMR signals in **2** were nearly identical to those of **1**, except for the different splitting patterns of the hydroxymethylene signals at δ_H 4.13 (2H, d, J = 1.2 Hz, H-12) and a slight upfield shift of H-8 (δ_H 1.64) in **2**. The geometry of the Δ^{10} double bond was shown to be *Z*, from the chemical shifts of the vinyl methyl (H-13) signal, similar to that of **1**, and by NOEs between H-10/H-13 and H-9/H-12.[20,21] Among the four possible diastereomers of *β*-bisabolol (**7**) synthesized from (+)-*cis*-1,2-epoxy-*p*-menth-8-ene,[19,22] the dextrorotatory compounds, (+)-**7**, were reported to possess the *S* configuration at the position of C-1 on the cyclohexene ring, independent of the stereochemistry at the asymmetric C-7, while the levorotatory congeners have the 1*R* configuration. The optical properties of **1** ($[\alpha]^{20}_D$ −5.2) and **2** ($[\alpha]^{20}_D$ −72.5) thus allowed us to assign the absolute configuration as 1*R* for both compounds. Moreover, the *cis*- or *trans*-orientation between the C-7 methyl and C-1 hydroxyl groups in (1*R*)-**7** was also shown to be distinguishable by diagnostic chemi-

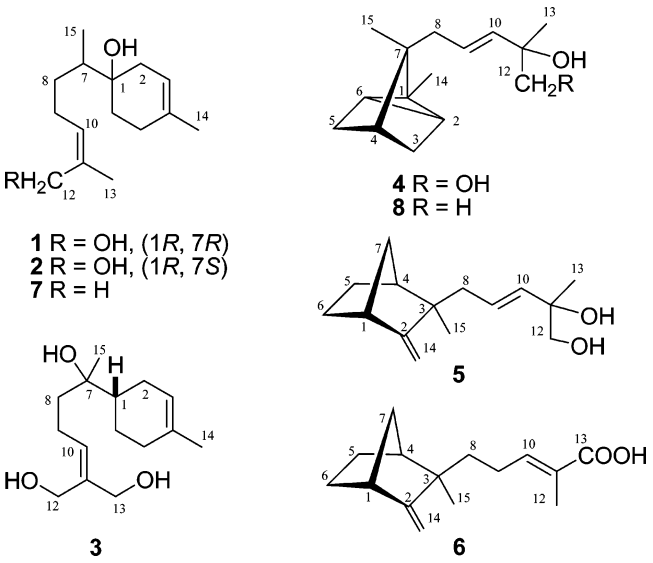

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Table 1. ^{1}H NMR Data for Compounds **1**−**6** in $CDCl_3$[a]

position	**1**[b]	**2**[b]	**3**[b]	**4**	**5**	**6**
1			1.57 m		2.68 d (4.2)	2.68 brd (4.2)
2β	2.17 m	2.18 m	1.97 m	0.87 m		
2α	1.86 m	1.89 m	1.75 m			
3β	5.30 m	5.29 m	5. 36 m	1.63 td (4.8, 1.8)		
3α				1.05 dd (10.6, 6.0)		
4				1.53 brs	2.06 brs	2.11 brd (4.2)
5β	2.16 m	2.14 m	2.00 m	1.61 brd (10.8)	1.62 m	1.69 m
5α	1.93 m	1.92 m	2.00 m	1.06 dd (10.6, 6.0)	1.41 m	1.42 m
6β	1.60 m	1.61 m	1.87 m	0.87 m	1.65 m	1.68 m
6α			1.23 m		1.23 m	1.26 m
7	1.47 tdd (9.6, 6.6, 2.4)	1.48 tdd (10.2, 4.2, 3.0)			1.69 m	1.66 m
					1.19 d (9.6)	1.20 m
8	1.73 m	1.64 m	1.54 m	2.00 dd (14.4, 7.8)	2.15 m	1.49 m
	1.08 m	1.10 m		1.89 dd (13.8, 7.8)	1.98 m	1.32 m
9	2.21 m	2.19 m	2.21 m	5.73 dt (15.8, 7.8)	5.78 m	2.18 m
	1.99 quint (7.2)	2.00 quint (7.2)				
10	5.32 brt (7.2)	5.30 brt (7.2)	5.60 brt (7.8)	5.49 dt (15.6, 1.2)	5.49 m	6.88 m
11						
12	4.16 d (12.0)	4.13 d (1.2)	4.30 brd (1.8)	3.48 dd (10.8, 1.2)	3.50 d (10.8)	1.84 d (0.6)
	4.10 d (12.0)			3.42 d (10.8)	3.43 d (10.8)	
13	1.80 d (1.2)	1.79 d (1.2)	4.18 s	1.27 s	1.28 s	
14	1.69 brs	1.68 brs	1.65 brs	1.02 s	4.77 s	4.76 s
					4.45 s	4.47 s
15	0.90 d (6.6)	0.94 d (6.6)	1.12 s	0.81 s	1.02 d (1.8)	1.06 s

[a] TMS was used as the internal standard. Chemical shifts are shown on the δ scale with J values (Hz) in parentheses. [b] α and β were not assigned.

Table 2. ^{13}C NMR Data for Compounds **1**−**6** in $CDCl_3$[a]

position	**1**	**2**	**3**	**4**	**5**	**6**
1	72.3	72.1	43.3	27.0	46.8	46.7
2	33.8	35.1	27.0	19.5	165.3	165.7
3	118.3	118.4	120.3	31.0	44.9	44.7
4	134.1	134.0	134.3	38.5	44.8	44.7
5	26.9	27.0	31.0	31.2	23.6	23.7
6	31.2	30.4	23.3	19.6	29.6	29.6
7	41.8	41.6	74.7	46.2	36.9	37.1
8	31.1	31.2	39.6	37.3	43.8	39.3
9	26.1	26.1	21.6	127.9	127.7	24.7
10	128.7	128.7	131.8	134.9	135.9	145.5
11	134.4	134.4	136.9	73.2	73.2	126.4
12	61.6	61.7	59.9	70.1	70.1	12.0
13	21.4	21.3	67.6	24.4	24.4	172.5
14	23.3	23.2	23.3	10.7	100.1	100.1
15	13.8	13.7	23.0	17.5	23.0	22.6

[a] TMS was used as the internal standard. Chemical shifts are shown on the δ scale.

cal shifts of the signals of the C-7 methyl signal in the ^{1}H NMR spectrum (δ_H 0.91 for 1*R*, 7*R*; δ_H 0.95 for 1*R*, 7*S*).[22,23] The chemical shifts observed for CH_3-7 in **1** and **2** of the 1*R* series clearly indicated the 7*R* and 7*S* configuration, respectively. The above configurational assignments were further supported by NOE correlations of H-6/H-7, -5 and H-15/H-2 for **1**, along with H-6/H-7, -5 and H-15/H-6 for **2**. Consequently, the most likely 1*R*, 7*R* and 1*R*, 7*S* configurations for compounds **1** and **2**, respectively, have been deduced.

The NMR data and optical rotation of compound **2** are similar to those of 6,13-dihydroxybisabola-2,10-diene ($[\alpha]_D$ −84.6), which was isolated from *Santalum austrocaledonicum* by Alpha et al.[24] However, they proposed the planar structure of *E* stereochemistry for the Δ^{10} double bond without discussion of the ^{13}C NMR signals for C-12 and -13 and NOESY correlations.[20,21] The structure of 6,13-dihydroxybisabola-2,10-diene from *S. austrocaledonicum* should thus be revised as **2**.

The HREIMS of compound **3** revealed the parent peak at *m/z* 254.1878 $[M]^+$, corresponding to the molecular formula of $C_{15}H_{26}O_3$, which is 16 mass units larger than that of **1** or **2**. Comparison of the NMR (^{1}H and ^{13}C) spectroscopic data (Tables 1 and 2) with those of **1** and **2** indicated that compound **3** is also a structurally related bisabolane-type analogue, in which one of the vinyl methyl groups of **1** or **2** is replaced by a hydroxymethylene group. The NMR spectra of **3** also showed the presence of a tertiary methyl group (δ_H 1.12, δ_C 23.0) instead of the secondary methyl in **1** or **2**, suggesting an α-bisabolol skeleton.[25,26] The absolute stereochemistry at the position of C-1 was deduced by comparison with those of synthetic analogues. Derivatives possessing the 1*R* configuration among the four stereoisomers of α-bisabolol have dextro rotations, while the 1*S* configuration has levo rotations.[27] Thus, the optical rotation values of compound **3** ($[\alpha]^{20}_D$ −52.7) showed the absolute configuration of C-1 to be *S*. Accordingly, compound **3** was assigned to 7,12,13-trihydroxybisabola-3,10-diene with a 1*S* configuration, although the absolute configuration at C-7 remained undetermined.

Compound **4** was obtained as a colorless oil, $[\alpha]^{20}_D$ −19.4 ($CHCl_3$). The HREIMS showed the molecular ion peak at *m/z* 236.1789 $[M]^+$ corresponding to the molecular formula $C_{15}H_{24}O_2$. The ^{1}H NMR spectrum of **4** (Table 1) exhibited signals due to two tertiary methyl groups at δ_H 1.02 (3H, s, H-14) and 0.81 (3H, s, H-15), three methines at δ_H 1.53 (1H, br s, H-4) and 0.87 (2H, m, H-2, −6), and two methylene groups at δ_H 1.63 (1H, td, J = 4.8, 1.8 Hz, H-3β), 1.61 (1H, br d, J = 10.8 Hz, H-5β), 1.06 (1H, dd, J = 10.6, 6.0 Hz, H-5α), and 1.05 (1H, dd, J = 10.6, 6.0 Hz, H-3α). The data suggest the presence of a tricyclo[2.2.1.0]heptane ring as a partial structure. The ring system proposed was evidenced by ^{13}C NMR resonances corresponding to those of α-santalol[13,28] and ^{1}H−^{1}H COSY cross-peaks (H-2/H-3, H-3/H-2, -4, H-4/H-3, -5, H-5/H-4, -6, and H-6/H-5). Furthermore, the ^{1}H NMR spectrum (Table 1) exhibited proton signals of the C-8−C-13 side chain, *trans* olefinic protons [δ_H 5.73 (1H, dt, J = 15.6, 7.8 Hz, H-9), 5.49 (1H, dt, J = 15.6, 1.2 Hz, H-10)], one hydroxymethylene [δ_H 3.48 (1H, dd, J = 10.8, 1.2 Hz, H-12), 3.42 (1H, d, J = 10.8 Hz, H-12)], and one tertiary methyl group [δ_H 1.27 (3H, s, H-13)]. In the HMBC spectrum of **4**, the long-range correlations of

H-9/C-11, -10, -8, H-10/C-11, -9, H-12/C-13, -11, -10, and H-13/C-12, -11, -10 allowed us to assign the location of one *trans* olefin at C-9 and C-10 positions, one hydroxymethylene at C-12, and one methyl group at C-11. These spectroscopic characteristics are comparable to those reported for α-photosantalol A (**8**),[2,4] except for the signals of a hydroxymethylene group (H-12) in **4**. On the basis of these findings, the structure **4** was assigned to 9(*E*)-11-hydroxy-α-santalol, although the absolute stereostructure is tentative and is in accordance with that of α-photosantalol A, from biogenetic considerations.

Compound **5** was isolated as a colorless oil, $[\alpha]^{20}_D$ −35.8 ($CHCl_3$), and the HREIMS showed the molecular ion peak at *m/z* 236.1775 $[M]^+$ corresponding to the molecular formula $C_{15}H_{24}O_2$, the same as that of **4**. The ^1H NMR spectrocsopic data of **5** (Table 1) were similar to those of **4**, except for the lack of cyclopropane methine protons and the presence of an extra exomethylene group [δ_H 4.77 (1H, s, H-14), 4.45 (1H, s, H-14), δ_C 100.1] instead of the tertiary methyl signals in **4**. These proton signals and the corresponding carbon resonances, assigned by 2D NMR techniques, showed the presence of a bicyclo[2.2.1]heptane (*β*-santalol)[1,13] skeleton with the same alkyl side chain in **4**. The relative stereochemistry at C-3 was determined by NOESY correlations of H-14/H-15, -1 and H-8/H-7 and was further confirmed by the comparison of NMR (^1H and ^{13}C) chemical shift data with the literature values for C-3 epimers.[29] Thus, compound **5** was assigned to 9(*E*)-11-hydroxy-*β*-santalol, which is a biosynthetic transformation product of **4**.

Compound **6** was obtained as a colorless oil, $[\alpha]^{20}_D$ −77.2 ($CHCl_3$). The HREIMS showed an ion peak at *m/z* 234.1618 $[M]^+$, corresponding to the molecular formula $C_{15}H_{22}O_2$. The ^1H NMR spectrum of **6** (Table 1) exhibited signals due to two methine protons at δ_H 2.68 (C-1) and 2.11 (C-4) and one exomethylene group at δ_H 4.76, 4.47 (C-14), as are found in compound **5**. Complete analysis of a combination of the ^1H−^1H COSY, HMQC, HMBC, and NOESY spectra suggested that compound **6** is a *β*-santalol derivative analogous to **5**. Distinguishable features of **6** from **5** are the presence of the only one vinyl proton signal at δ_H 6.88 (1H, m, H-10), δ_C 145.5 (C-10), and one conjugated carbonyl carbon at δ_C 172.5 (C-13). The presence of an α,*β*-unsaturated carbonyl function in **6** was elucidated by sp^2 carbon resonances at δ_C 126.4 (C-11), 145.5 (C-10), and 172.5 (carboxyl), which are characteristic of the double bond conjugated with the carboxyl group.[30] The *E* stereochemistry of the double bond was deduced from an explicit NOE correlation between H-12 and H-9. The relative configuration of **6** was also determined by NOESY correlations of H-14/H-1, -15 and H-8/H-7. Consequently, the structure of compound **6** was assigned to 10(*E*)-*β*-santalic acid, which is unknown in the literature.

Three known compounds, (+)-α-nuciferol,[31,32] (+)-citronellol,[33,34] and geraniol,[35] were identified by comparison of their physical properties and spectroscopic data with those of authentic samples and reported data.

In conclusion, we have isolated six new sesquiterpenes using officially imported Indian sandalwood chips, since a report in 1990.[36] The new compounds have been identified as genuine constituents of the wood.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. The ^1H and ^{13}C NMR spectra were taken on a Varian Unity Inova AS600NB instrument operating at 600 and 150 MHz, respectively. The chemical shifts are given in δ (ppm) values relative to that of the solvent $CDCl_3$ (δ_H 7.26; δ_C 77.0) on a tetramethylsilane (TMS) scale. The standard pulse sequences programmed into the instruments were used for each 2D measurement. The J_{CH} value was set at 8 Hz in the HMBC spectra. The HREIMS and EIMS were recorded on a Micromass AutoSpec OA-TOF spectrometer. Normal-phase HPLC was conducted on a YMC-Pack SIL A-003 column (4.6 mm i.d. × 250 mm; YMC Co., Ltd.) and developed at room temperature with a solvent of *n*-hexane−EtOH (15:1) (flow rate: 1.5 mL/min; detection: UV 205 or 220 nm). Reversed-phase HPLC was carried out on a YMC-Pack ODS A-302 column (4.6 mm i.d. × 150 mm; YMC Co., Ltd.) and developed at 40 °C with 10 mM H_3PO_4/10 mM KH_2PO_4/MeCN (7:3, flow rate: 1.0 mL/min). Column chromatography was carried out on silica gel 60 (Merck, 70−230 mesh), Toyopearl HW-40 (coarse grade; Tosoh Co.), YMC GEL ODS AQ 120-50S (YMC Co., Ltd.), MCI GEL CHP-20P (Mitsubishi Kasei Co.), and Sephadex LH-20 (Pharmacia Fine Chemicals Co., Ltd.). Preparative TLC was performed on Kieselgel 60 F_{254} plates (0.2 mm layer thickness, Merck).

Plant Material. Chips of *S. album* L. wood collected in Mysore District of India were used. The wood was officially imported from India in 2003 under a special treaty between the Indian and Japanese governments to sculpt a Buddhist image in a Japanese temple (Kannonshoji Temple) with a long and distinguished history.

Extraction and Isolation. Chips of *S. album* heartwood (1.53 kg) were extracted with MeOH at room temperature. The concentrated MeOH extract (73.1 g) was suspended in 20% MeOH (2 L) and then partitioned with *n*-hexane (3 × 2 L) and EtOAc (3 × 2 L) to afford *n*-hexane- (16.4 g), EtOAc- (27.1 g), and H_2O-soluble (17.5 g) residues. The *n*-hexane extract (10.0 g) was subjected to silica gel column chromatography (6.0 cm i.d. × 42 cm, 70−230 mesh), developed with *n*-hexane containing increasing amounts of EtOAc in a stepwise gradient mode, to give 12 fractions. The eluate of *n*-hexane−EtOAc (85:15) was subjected to preparative reversed-phase HPLC (YMC-Pack ODS-AM, 20.0 mm i.d. × 250 mm) with 70% aqueous MeCN to give (+)-α-nuciferol (59.4 mg). The *n*-hexane−EtOAc (3:2) eluate was similarly purified by preparative reversed-phase HPLC with 40% aqueous MeCN to afford pure (+)-citronellol (2.1 mg) and geraniol (1.8 mg), as well as the crude compounds **1**, **2**, **4**, **5**, and **6**. These crude materials were finally purified by preparative normal-phase HPLC (4.6 mm i.d. × 250 mm) eluted with *n*-hexane−EtOH (15:1) to yield pure compounds **1** (2.6 mg, t_R 14.9 min), **2** (16.5 mg, t_R 15.7 min), **4** (31.8 mg, t_R 3.5 min), **5** (2.2 mg, t_R 15.5 min), and **6** (7.6 mg, t_R 3.01 min). A part (7.0 g) of the EtOAc extract was chromatographed over Toyopearl HW-40 (coarse grade; 2.2 cm i.d. × 65 cm) with H_2O containing increasing amounts of MeOH in a stepwise gradient mode. The 40% MeOH eluate was subjected to column chromatography over YMC GEL ODS AQ 120-50S (1.1 cm i.d. × 41 cm) with aqueous MeOH and finally purified by preparative normal-phase HPLC (4.6 mm i.d. × 250 mm) eluted with *n*-hexane−EtOH (15:1) to yield pure compound **3** (6.8 mg, t_R 17.6 min).

(1*R*,7*R*)-1,12-Dihyroxybisabola-3,10-diene (1): colorless oil; $[\alpha]^{20}_D$ −5.2 (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 238 $[M]^+$ (17), 220 (23), 202 (57), 187 (9), 157 (42), 119 (72), 91 (32), 58 (100); HREIMS *m/z* 238.1931 $[M]^+$ (calcd for $C_{15}H_{26}O_2$, 238.1933).

(1*R*,7*S*)-1,12-Dihyroxybisabola-3,10-diene (2): colorless oil; $[\alpha]^{20}_D$ −72.5 (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 238 $[M]^+$ (13), 220 (20), 202 (23), 187 (7), 157 (33), 119 (47), 91 (21), 58 (100); HREIMS *m/z* 238.1930 $[M]^+$ (calcd for $C_{15}H_{26}O_2$, 238.1933).

7,12,13-Trihydroxybisabola-3,10-diene (3): colorless oil; $[\alpha]^{20}_D$ −52.7 (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 254 $[M]^+$ (37), 238 (21), 220 (13), 194 (42), 141 (53), 119 (62), 91 (100); HREIMS *m/z* 254.1878 $[M]^+$ (calcd for $C_{15}H_{26}O_3$, 254.1882).

9(*E*)-11-Hydroxy-α-santalol (4): colorless oil; $[\alpha]^{20}_D$ −19.4 (*c* 0.5, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS

m/z 236 $[M]^+$ (6), 218 (11), 205 (88), 187 (13), 155 (53), 121 (100), 105 (8), 93 (38); HREIMS *m/z* 236.1789 $[M]^+$ (calcd for $C_{15}H_{24}O_2$, 236.1776).

9(*E*)-11-Hydroxy-*β*-santalol (5): colorless oil; $[\alpha]^{20}_D$ −35.8 (*c* 0.5, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 236 $[M]^+$ (13), 218 (8), 205 (63), 187 (12), 155 (50), 121 (100), 105 (43), 91 (73); HREIMS *m/z* 236.1775 $[M]^+$ (calcd for $C_{15}H_{24}O_2$, 236.1776).

10(*E*)-*β*-Santalic acid (6): colorless oil; $[\alpha]^{20}_D$ −77.2 (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 234 $[M]^+$ (18), 155 (35), 119 (51), 105 (37), 91 (71), 58 (100); HREIMS *m/z* 234.1618 $[M]^+$ (calcd for $C_{15}H_{22}O_2$, 234.1620).

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