Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4313–4319

TETRAHEDRON: *ASYMMETRY*

Stereochemistry of (3*E*)-3,7-dimethyl-3-octene-1,2,6,7-tetraol isolated from *Passiflora quadrangularis*

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Received 6 September 1999; accepted 6 October 1999

Abstract

3,7-Dimethyl-3(*E*)-octene-1,2,6,7-tetraol, a monoterpene recently isolated from *Passiflora quadrangularis* fruit pulp, has been established to be a 12:42:14:32 mixture of (2*R*,6*R*)-, (2R,6*S*)-, (2*S*,6*R*)- and (2*S*,6*S*)-stereoisomers, in that order, by HPLC analysis of the corresponding tri-(*R*)-MTPA ester in comparison with stereochemically defined synthetic samples. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the course of our studies on flavor chemistry of Colombian fruits, we isolated a polyhydroxylated monoterpene, 3,7-dimethyl-3(*E*)-octene-1,2,6,7-tetraol **1**.[1] The tetraol has two stereogenic centers at the C-2 and C-6 positions. In our preliminary study this compound was suggested to be an approximately 1:1 diastereoisomeric mixture by ^{13}C NMR analysis.[1] However, further stereochemical assessment of the natural tetraol remained to be established. We have now synthesized authentic samples of four stereoisomers at the C-2 and C-6 positions of 3,7-dimethyl-3(*E*)-octene-1,2,6,7-tetraol in the form of tri-(*R*)-MTPA esters and succeeded in determining the ratio of the stereoisomers of the natural monoterpene.

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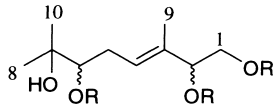
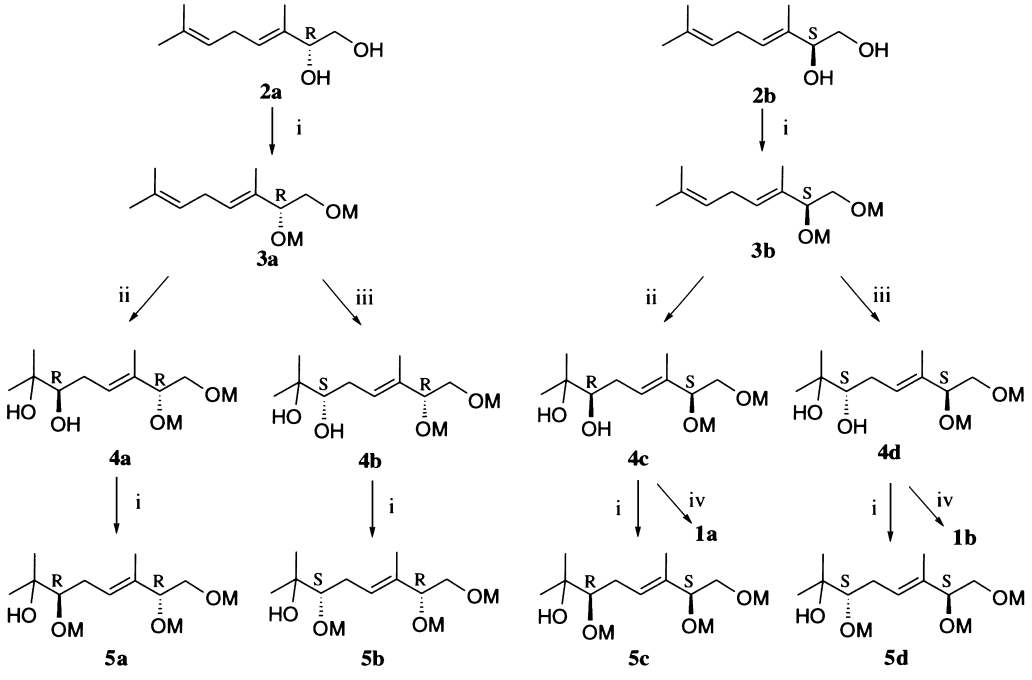
PII: S0957-4166(99)00461-9



1 : R=H natural sample
1a: R=H (2*S*,6*R*)
1b: R=H (2*S*,6*S*)
5a: R=(*R*)-MTPA (2*R*,6*R*)
5b: R=(*R*)-MTPA (2*R*,6*S*)
5c: R=(*R*)-MTPA (2*S*,6*R*)
5d: R=(*R*)-MTPA (2*S*,6*S*)

2. Results and discussion

Our approach relies on the HPLC profile analysis of the natural tetraol in the form of MTPA esters in comparison with stereochemically defined synthetic materials. The synthesis of the reference compounds, (2*R*,6*R*)-**5a** and (2*R*,6*S*)-**5b** 3,7-dimethyl-3(*E*)-octene-1,2,6,7-tetraols, was carried out according to Scheme 1, starting with the known (2*R*)-3,7-dimethyl-3(*E*),6-octadiene-1,2-diol **2a**,[2] which is readily obtained from geraniol. The di-(*R*)-MTPA ester **3a** derived from **2a** was subjected to Sharpless asymmetric dihydroxylation[3] using AD-mix β to afford (2*R*,6*R*)-tetraol diester **4a** in a moderate yield. The (2*R*,6*S*)-isomer **4b** was prepared by treating **3a** with AD-mix α in place of AD-mix β. The tetraol diesters **4a** and **4b** were converted into the tri-(*R*)-MTPA esters **5a** and **5b**, respectively.



Scheme 1. Synthesis of the stereochemically defined tetraols **5a**–**d**. Reagents: (i) (*S*)-MTPACl, py, (ii) AD-mix β, (iii) AD-mix α, (iv) $LiAlH_4$. Group M refers to (*R*)-MTPA

Table 1
^{13}C NMR data for (2*S*,6*R*)-**1a** and (2*S*,6*S*)-**1b** (100 MHz in CD_3OD)

C	1a	1b
1	65.69	65.65
2	78.92	78.95
3	137.21	137.22
4	126.30	126.32
5	30.87	30.88
6	79.61	79.60
7	73.71	73.70
8	24.86	24.85
9	12.46	12.40
10	25.88	25.87

The other two isomers, (2*S*,6*R*)- and (2*S*,6*S*)-tetraol tri-(*R*)-MTPA esters **5c** and **5d**, were synthesized in the same manner as described above starting with (2*S*)-diol **2b**.[2] Sharpless asymmetric dihydroxylation of the di-(*R*)-MTPA ester **3b** afforded (2*S*,6*R*)-tetraol diester **4c** and (2*S*,6*S*)-isomer **4d** depending on the reagents, AD-mix β and AD-mix α, respectively. Each isomer was converted into its respective tri-(*R*)-MTPA esters **5c** and **5d**. A part of the esters **4c** and **4d** was reduced with $LiAlH_4$ to give the diastereoisomeric tetraols, (2*S*,6*R*)-**1a** and (2*S*,6*S*)-**1b**.

The ^{1}H NMR spectra of the tetraols **1a** and **1b** were hardly distinguishable from each other. The ^{13}C NMR data of **1a** and **1b** are summarized in Table 1. Differences in the chemical shifts of most carbons were within the experimental error, although C-9 signal showed the maximum difference, $\Delta\delta_C$ 0.06. The ^{13}C NMR data of **1a** and **1b** confirmed that the natural tetraol is a mixture of the two diastereoisomers.

In contrast to the very close similarity of the ^{1}H and ^{13}C NMR spectra of **1a** and **1b**, the ^{1}H NMR spectra (Table 2) of the tri-(*R*)-MTPA ester derivatives **5a**–**d** were different from each other, and useful for the identification of the stereoisomers. Taking into consideration the notion of the advanced Moshers method,[4] one may notice the following characteristic ^{1}H chemical shifts among the isomers. The signals for 8-H3 and 10-H3 of (6*R*)-isomers **5a** and **5c** appeared downfield from those of (6*S*)-isomers **5b** and **5d**. This proved that Sharpless asymmetric dihydroxylation proceeded with the expected stereochemical course. The signals for H-5a of (2*R*,6*R*)-isomer **5a** appeared most upfield, while that of (2*S*,6*S*)-isomer **5d** resonated the most downfield. This can be reasonably explained by the combined effect of the chiral (*R*)-MTPA groups attached at the C-2 and C-6 positions. The signals of the 1-methylene protons of 2*S*-isomers are expected to be more upfield than those of (2*R*)-isomers provided that the effect of the 6-*O*-(*R*)-MTPA group is not significant. However, the observed chemical shifts for the methylene protons at C-1 were not systematic. The interaction of the vicinal *O*-MTPA groups at C-1 and C-2 positions may be the reason for this anomalous behavior.

In addition, a careful inspection of the ^{1}H NMR spectra of **5a**–**d**, in particular methyl and methoxy signals, revealed that (2*R*,6*R*)-**5a** and (2*R*,6*S*)-**5b** were accompanied by ca. 10% of **5c** and **5d**, respectively, which are apparently due to the presence of the antipode in starting material **2a**. Similarly, compounds **5c** and **5d** were found to be accompanied by ca. 10% of **5a** and **5b**, respectively. Thus, the Sharpless asymmetric dihydroxylation of **3a** and **3b** was found to be highly stereoselective.

HPLC trace of the tri-(*R*)-MTPA ester of the natural tetraol isolated from *P. quadrangularis* is

Table 2
^{1}H NMR data for tri-(*R*)-MTPA esters **5a–d** (400 MHz in $CDCl_3$)

No.	(2*R*,6*R*)-(**5a**)	(2*R*,6*S*)-(**5b**)	(2*S*,6*R*)-(**5c**)	(2*S*,6*S*)-(**5d**)
Ha-1	4.26 (dd, *J*=11.9, 8.7)	4.19 (dd, *J*=12.3, 8.9)	4.20 (dd, *J*=12.1, 7.8)	4.24 (dd, *J*=12.2, 7.4)
Hb-1	4.46 (dd, *J*=11.9, 2.6)	4.45 (dd, *J*=12.3, 3.0)	4.45 (dd, *J*=12.1, 3.6)	4.45 (dd, *J*=12.2, 3.4)
H-2	5.50 (dd, *J*=8.7, 2.6)	5.44 (dd, *J*=8.9, 3.0)	5.54 (dd, *J*=7.8, 3.6)	5.62 (m)
H-4	5.43 (t, *J*=7.2)	5.39 (t, *J*=6.6)	5.46 (t, *J*=7.1)	5.62 (m)
Ha-5	2.23 (m)	2.37 (t, *J*=6.6)	2.35 (m)	2.46 (m)
Hb-5	2.36 (m)	2.37 (t, *J*=6.6)	2.35 (m)	2.34 (m)
H-6	4.95 (dd, *J*=8.8, 4.0)	4.87 (t, *J*=6.6)	4.94 (dd, *J*=7.6, 4.9)	4.99 (dd, *J*=8.8, 4.0)
H_3-8	1.205 (s)	1.117 (s)	1.197 (s)	1.144 (s)
H_3-10	1.164 (s)	1.117 (s)	1.162 (s)	1.134 (s)
H_3-9	1.438 (s)	1.561 (s)	1.618 (s)	1.618 (s)
OMe	3.368 (s)	3.333 (s)	3.373 (s)	3.365 (s)
OMe	3.482 (s)	3.482 (s)	3.453 (s)	3.434 (s)
OMe	3.511 (s)	3.529 (s)	3.494 (s)	3.503 (s)

Coupling constants are expressed in Hz

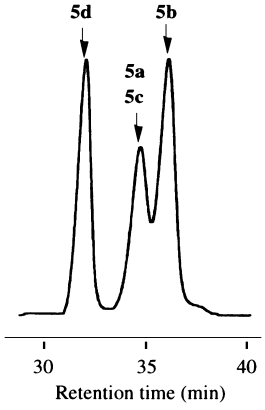


Figure 1. HPLC trace of tri-(*R*)-MTPA ester of the natural tetraol **1**. Conditions: solvent MeOH:H_2O 6:1, flow rate 0.7 ml/min, UV detection at 254 nm

illustrated in Fig. 1, which shows three peaks in a 32:26:42 ratio in the order of elution. The authentic tri-(*R*)-MTPA esters **5a–d** were eluted at 31.82 min for **5d**, 34.55 min for **5a** and **5c**, and 35.88 min for **5b**. Unfortunately, the two isomers **5a** and **5c** were eluted at the same retention time. To obtain an accurate ratio of the overlapped (2*R*,6*R*)- and (2*S*,6*R*)-isomers,[5] the second peak in the HPLC was separated and analyzed by ^{1}H NMR. Based on the intensities of the diagnostic signals of the methyl (δ 1.438 vs 1.618) and methoxy (δ 3.511 vs 3.453) groups (Table 2), this fraction was revealed to be composed of (2*R*,6*R*)- and (2*S*,6*R*)-isomers in a 6:7 ratio. Thus, it has been established that natural tetraol isolated from *P. quadrangularis* is a 12:42:14:32 mixture of **5a**, **5b**, **5c** and **5d**.

It is interesting to note that the other monoterpene, 3,7-dimethyl-1,3(*E*)-octadiene-6,7-diol (2,6-dimethyl-5(*E*),7-octadiene-2,3-diol), which was isolated together with the tetraol **1** in the same fruit pulp, is a 4:1 mixture of (6*S*)- and (6*R*)-antipodes.[1] The ratio of 6*S*:6*R* of **1** was 74:26 (=3:1). The fact

that (6*S*)-antipodes are predominant in the two compounds could support the biosynthetic correlation of the two oxygenated monoterpenes. The closely related olefinic isomer, 3,7-dimethyl-3(9)-octene-1,2,6,7-tetraol, was also isolated from the fruit of *Cnidium monnieri (Umbelliferae*)[6] and *Foeniculum vulgare* (*Umbelliferae*)[7] as a diastereoisomeric mixture whose stereochemical investigation has not yet been reported.

3. Experimental

3.1. General

^{1}H NMR spectra were obtained on a JEOL JNM LA-400 (400 MHz) spectrometer in $CDCl_3$ solutions or in CD_3OD solutions with tetramethylsilane as an internal reference. ^{13}C NMR spectra (100 MHz) were recorded on the same spectrometer in CD_3OD solutions and chemical shifts are referenced to the solvent signal (δ 49.0). HPLC was performed on a Shimadzu LC-6A with SPD-6A UV detector equipped with a Shimadzu Shim-Pack CLC-ODS column (15 cm×6 mm i.d.).

3.2. (2R)-3,7-Dimethyl-3(E),6-octadiene-1,2-diol di-(R)-MTPA ester **3a**

(*S*)-MTPACl (445 μl, 2.38 mmol) was added to a solution of the diol **2a** (163 mg, 0.959 mmol) in pyridine (0.30 ml) at 0°C and the mixture was stirred for 30 min at room temperature. Ice chips were added and the mixture was extracted with ether. The organic layer was washed with 2N HCl, satd aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel (hexane:AcOEt, 10:1) to give **3a** (376 mg, 65%) as a colorless oil. ^{1}H NMR δ: 1.55, 1.59, 1.68 (3H each, s, 9-H3, 8-H3, and 10-H3), 2.65 (2H, m, 5-H2), 3.36, 3.49 (3H each, s, OMe), 4.33 (1H, dd, J=12.1, 8.6 Hz, 1-Ha), 4.57 (1H, dd, J=12.1, 3.1 Hz, 1-Hb), 4.97 (1H, m, 4 or 6-H), 5.44 (1H, t, J=7.2 Hz, 6 or 4-H), 5.53 (1H, dd, J=8.6, 3.1 Hz, 2-H), 7.32–7.47 (10H, m, Ar). Anal. calcd for $C_{30}H_{32}F_6O_6$: C, 59.80; H, 5.35. Found: C, 59.85; H, 5.47. The e.e. of **3a** was determined to be 76% by ^{1}H NMR analysis.

3.3. (2S)-3,7-Dimethyl-3(E),6-octadiene-1,2-diol di-(R)-MTPA ester **3b**

Compound **2b** (425 mg, 2.50 mmol) was converted to **3b** (898 mg, 60%) as described for **2a**. Compound **3b**: colorless oil. ^{1}H NMR δ: 1.60, 1.67, 1.68 (3H each, s, 9-H3, 8-H3, and 10-H3), 2.70 (2H, t, J=7.0 Hz, 5-H2), 3.40, 3.46 (3H each, s, OMe), 4.30 (1H, dd, J=12.0, 7.4 Hz, 1-Ha), 4.54 (1H, dd, J=12.0, 4.1 Hz, 1-Hb), 5.00 (1H, t, J=7.0 Hz, 4 or 6-H), 5.59 (1H, t, J=7.0 Hz, 6 or 4-H), 5.66 (1H, dd, J=7.4, 4.1 Hz, 2-H), 7.33–7.45 (10H, m, Ar). Anal. calcd for $C_{30}H_{32}F_6O_6$: C, 59.80; H, 5.35. Found: C, 59.67; H, 5.29. The e.e. of **3b** was determined to be 74% by ^{1}H NMR analysis.

3.4. (2R,6R)-3,7-Dimethyl-3(E)-octene-1,2,6,7-tetraol 1,2-di-(R)-MTPA ester **4a**

AD-mix β (326 mg) was added to a mixture of **3a** (140 mg, 0.233 mmol), *t*-BuOH (1.5 ml) and H_2O (1.5 ml), and the mixture was stirred at room temperature for two days. $K_2OsO_2(OH)_4$ (0.2 mg) was added and stirring was continued for another day. Satd aq. $Na_2S_2O_3$ was added and the mixture was extracted with AcOEt repeatedly. The organic layer was washed with 2N HCl, satd aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel (hexane:AcOEt, 1:1) to give **4a** (48 mg, 32%) as white solid. ^{1}H NMR δ: 1.17, 1.22 (3H each, s, 8-H3,

10-H3), 1.57 (3H, s, 9-H3), 2.14 (2H, m, 5-H2), 3.31 (1H, dd, J=10.0, 2.8 Hz, 6-H), 3.38, 3.48 (3H each, s, OMe), 4.36 (1H, dd, J=12.0, 8.4 Hz, 1-Ha), 4.58 (1H, dd, J=12.0, 3.0 Hz, 1-Hb), 5.54 (1H, dd, J=8.4, 3.0 Hz, 2-H), 5.59 (1H, t, J=7.2 Hz, 4-H), 7.34–7.49 (10H, m, Ar). Anal. calcd for $C_{30}H_{34}F_6O_8$: C, 56.60; H, 5.38. Found: C, 56.48; H, 5.46.

*3.5. (2*R,*6*S*)-3,7-Dimethyl-3(*E*)-octene-1,2,6,7-tetraol 1,2-di-(*R*)-MTPA ester **4b***

AD-mix α (333 mg) was added to the mixture of **3a** (140 mg, 0.233 mmol), *t*-BuOH (1.5 ml), and H_2O (1.5 ml), and the mixture was stirred at room temperature for two days. Satd aq. $Na_2S_2O_3$ was added and the mixture was extracted with AcOEt repeatedly. The organic layer was washed with 2N HCl, satd aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel (hexane:AcOEt, 1:1) to give **4b** (91 mg, 61%) as white solid. ^{1}H NMR δ: 1.16, 1.21 (3H each, s, 8-H3, 10-H3), 1.56 (3H, s, 9-H3), 2.11 (2H, m, 5-H2), 3.25 (1H, dd, J=8.2, 4.5 Hz, 6-H), 3.38, 3.49 (3H each, s, OMe), 4.34 (1H, dd, J=12.0, 8.6 Hz, 1-Ha), 4.60 (1H, dd, J=12.0, 3.2 Hz, 1-Hb), 5.55 (2H, m, 2-H, 4-H), 7.33–7.49 (10H, m, Ar). Anal. calcd for $C_{30}H_{34}F_6O_8$: C, 56.60; H, 5.38. Found: C, 56.34; H, 5.47.

*3.6. (2*S,*6*R*)-3,7-Dimethyl-3(*E*)-octene-1,2,6,7-tetraol 1,2-di-(*R*)-MTPA ester **4c***

Compound **3b** (140 mg, 0.233 mmol) was treated with AD-mix β [576 mg; $K_2OsO_2(OH)_4$ (0.3 mg) was added after two days] as described for the conversion of **3a** to **4a** to give **4c** (69 mg, 46%) as white solid. ^{1}H NMR δ: 1.17, 1.22 (3H each, s, 8-H3, 10-H3), 1.66 (3H each, s, 9-H3), 2.17 (2H, t, J=6.7 Hz, 5-H2), 3.35 (1H, t, J=6.7 Hz, H-6), 3.40, 3.44 (3H each, s, OMe), 4.35 (1H, dd, J=12.0, 7.2 Hz, 1-Ha), 4.55 (1H, dd, J=12.0, 4.0 Hz, 1-Hb), 5.65 (1H, dd, J=7.2, 4.0 Hz, 2-H), 5.73 (1H, brt, J=6.7 Hz, 4-H), 7.35–7.47 (10H, m, Ar). Anal. calcd for $C_{30}H_{34}F_6O_8$: C, 56.60; H, 5.38. Found: C, 56.67; H, 5.51.

*3.7. (2*S,*6*S*)-3,7-Dimethyl-3(*E*)-octene-1,2,6,7-tetraol 1,2-di-(*R*)-MTPA ester **4d***

Compound **3b** (200 mg, 0.332 mmol) was treated with AD-mix α [465 mg; $K_2OsO_2(OH)_4$ (0.3 mg) was added after 24 h] as described for the conversion of **3a** to **4b** to give **4d** (159 mg, 75%) as white solid. ^{1}H NMR δ: 1.17, 1.21 (3H each, s, 8-H3, 10-H3), 1.67 (3H, s, 9-H3), 2.14 (2H, m, 5-H2), 3.29 (1H, dd, J=9.6, 2.8 Hz, 6-H), 3.41, 3.45 (3H each, s, OMe), 4.37 (1H, dd, J=11.9, 7.0 Hz, 1-Ha), 4.53 (1H, dd, J=11.9, 4.1 Hz, 1-Hb), 5.64 (1H, dd, J=7.0, 4.1 Hz, 2-H), 5.69 (1H, t, J=7.2 Hz, 4-H), 7.33–7.47 (10H, m, Ar). Anal. calcd for $C_{30}H_{34}F_6O_8$: C, 56.60; H, 5.38. Found: C, 56.64; H, 5.45.

*3.8. (2*R,*6*R*)-, (2*R,*6*S*)-, (2*S,*6*R*)- and (2*S,*6*S*)-3,7-Dimethyl-3(*E*)-octene-1,2,6,7-tetraol 1,2,6-tri-(*R*)-MTPA esters **5a**, **5b**, **5c** and **5d***

(*S*)-MTPACl (6 μl, 32 mmol) was added to a solution of **4a** (5 mg, 7.9 μmol) in pyridine (30 μl) and the mixture was stirred for 30 min. Ether (200 μl) was added to the mixture and the resulting solution was directly subjected to p-TLC (hexane:AcOEt, 2:1). The band having R_f=0.6 gave **5a** (6 mg, 90%) as a colorless oil. ^{1}H NMR δ: 7.36–7.57 (15H, m, Ar) and the data for the other protons are summarized in Table 2. HRFABMS 835.2551 $[M+H-H_2O]^+$. $C_{40}H_{40}F_9O_9$ requires 835.2529. The other (*R*)-MTPA esters **5b**, **5c** and **5d** were prepared in the same manner. The ^{1}H NMR data for these compounds are listed in Table 2. HRFABMS spectra of these samples displayed $[M+H-H_2O]^+$ ion within the experimental error.

3.9. (2S,6R)-3,7-Dimethyl-3(E)-octene-1,2,6,7-tetraol **1a**

$LiAlH_4$ (6.0 mg, 0.158 mmol) was added to a solution of **4c** (18 mg, 28.3 μmol) in dry THF (2 ml) under N_2, and the mixture was stirred at room temperature for 2 h. A small amount of water was added and the whole mixture was transferred onto a silica gel column using $CHCl_3$:MeOH (10:1). Elution of the column with $CHCl_3$:MeOH (4:1) furnished **1a** (3.6 mg, 62%) as a colorless oil. ^{1}H NMR (in CD_3OD) δ: 1.15, 1.18 (3H each, s, 8-H3, 10-H3), 1.63 (3H, s, 9-H3), 2.07 (1H, m, 5-Ha), 2.38 (1H, m, 5-Hb), 3.30 (1H, m, 6-H), 3.48 (1H, dd, J=11.2, 6.2 Hz, 1-Ha), 3.54 (1H, dd, J=11.2, 5.2 Hz, 1-Hb), 4.03 (1H, dd, J=6.2, 5.2 Hz, 2-H), 5.60 (1H, t, J=7.2 Hz, 4-H). The ^{13}C NMR data are listed in Table 1.

3.10. (2S,6S)-3,7-Dimethyl-3(E)-octene-1,2,6,7-tetraol **1b**

Compound **4d** (40 mg) was reduced with $LiAlH_4$ as described for **4c** to give **1b** (7.6 mg) as a colorless oil. ^{1}H NMR (in CD_3OD) δ: 1.15, 1.18 (3H each, s, 8-H3, 10-H3), 1.63 (3H, s, 9-H3), 2.07 (1H, m, 5-Ha), 2.38 (1H, m, 5-Hb), 3.30 (1H, m, 6-H), 3.48 (1H, dd, J=11.2, 7.2 Hz, 1-Ha), 3.54 (1H, dd, J=11.2, 5.2 Hz, 1-Hb), 4.02 (1H, dd, J=7.2, 5.2 Hz, 2-H), 5.60 (1H, t, J=6.8 Hz, 4-H). The ^{13}C NMR data are listed in Table 1.

Acknowledgements

Colciencias and IPICS (Uppsala University, Sweden) grants are greatly acknowledged.

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