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Synthesis, stereochemistry and absolute configuration of deodarols and deodarones

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Abstract—The stereochemistry and absolute configuration of the four deodarols and two deodarones derived from *R*-(+)-limonene is described.

1. Introduction

The widely studied sesquiterpene constituents of the *Cedrus deodara* Loud[1–4] essential oil appear to derive from *cis*-farnesyl pyrophosphate[1] either by a 1,6-cyclization to give bisabolane derivatives, or a 1,11-cyclization, to give himachalane or longibornane derivatives. Atlantones are the major sesquiterpene ketones of this essential oil and its characteristic wood odor is due to deodarones **4**, which are present as approximately 2% of the oil.[1] This oil is also interesting from a medicinal point of view owing to its anti-inflammatory activity against various experimental models of inflammation.[5]

Deodarones **4** are tetrahydropyranyl sesquiterpenes originally isolated from the wood of *C. deodara*.[1] They have been prepared synthetically by several methods although, in all cases, as diastereoisomeric mixtures.[6,7] Consequently, there are no data published for the individual deodarones and the ^{1}H NMR data reported for the mixture of diastereomers have been only partially assigned.[8] On the other hand, deodarols **3** have not yet been found in nature and have never been obtained synthetically. As part of our synthesis of deodarones, we have prepared and characterized each diastereoisomeric deodarol **3a**–**d**. Herein, we report the preparation and absolute configuration of the four possible deodarols **3** and the two possible deodarones **4** obtained synthetically from (*R*)-(+)-limonene, as is shown in Scheme 1.

2. Results and discussion

The synthetic pathway involved the selective metallation of (*R*)-(+)-limonene **1** which was condensed with senecialdehyde to give the corresponding atlantols **2**, which in turn were converted into deodarols **3** by a mercuration–demercuration-catalyzed cyclization. As the metallation of optically active limonene occurs without altering the C(4)[9] stereogenic center, four diastereoisomeric deodarols **3a**–**d** and subsequently, two diastereoisomeric deodarones **4a** and **4b** were obtained. The four diastereomeric deodarols **3a**–**d** were obtained in a 18:36:25:21 ratio and were readily separated by reverse phase high pressure liquid chromatography (RP-HPLC).

The ^{1}H NMR spectra of the four deodarols **3** showed the C(11)H signal around δ 4.1 as a triple-triplet (J= 11.0, 4.5 Hz) evidencing that the hydroxyl group was equatorial in the four diastereoisomers. *W*-Type couplings between C(10)H$_{eq}$ and C(12)H$_{eq}$ were also evident in the ^{1}H NMR spectra of the four deodarols. The critical assignments of C(10) and C(12) were easily made using the HMBC contour as are shown in Figs. 2–4 for deodarols **3a**–**c**. The total ^{1}H and ^{13}C NMR

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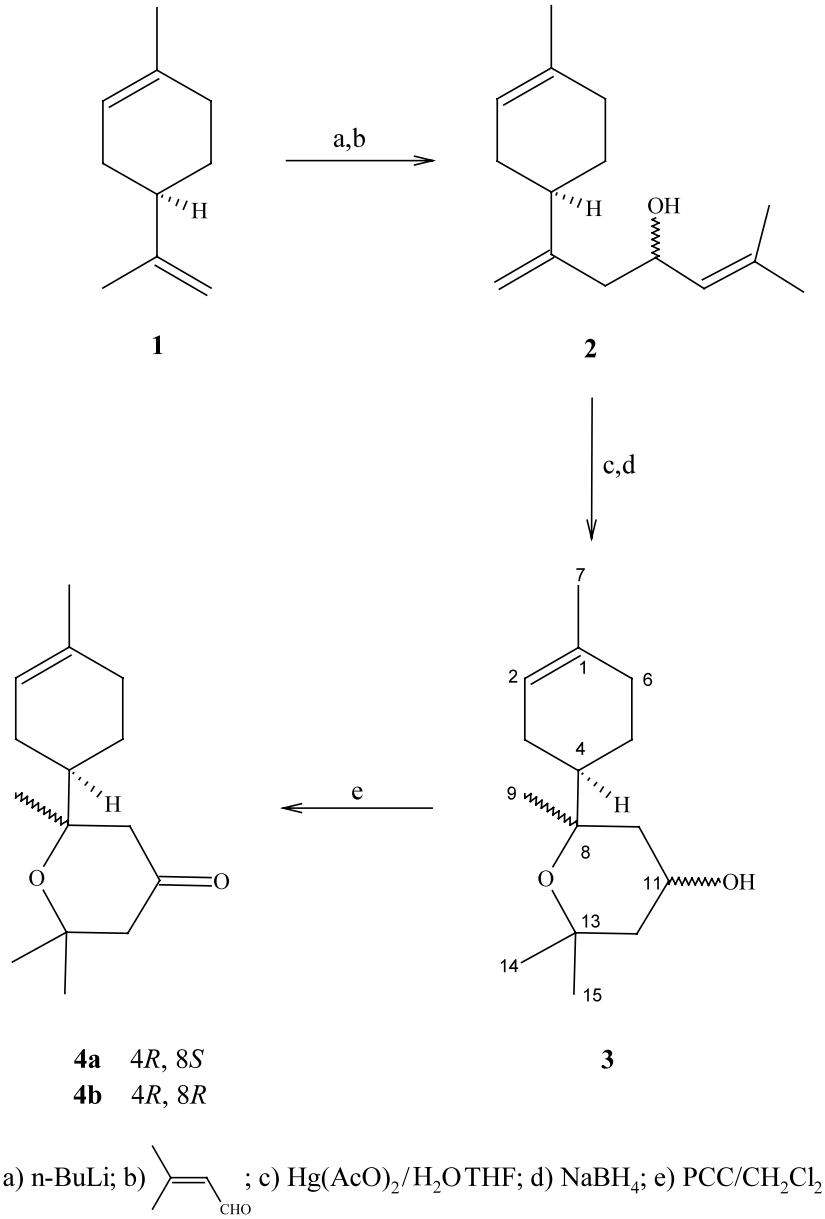


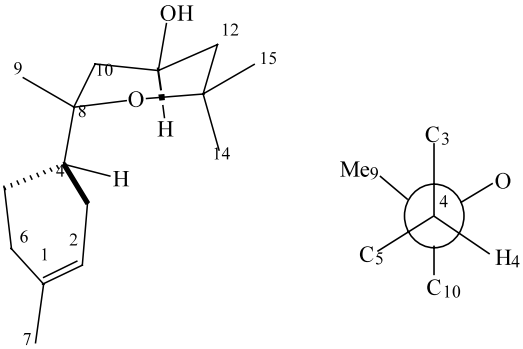
Scheme 1. Synthetic pathway for the preparation of deodarols and deodarones.

assignments (Tables 1 and 2) were made with the aid of spin–spin decoupling, COSY, NOESY, DEPT, HETCOR, and HMBC experiments.

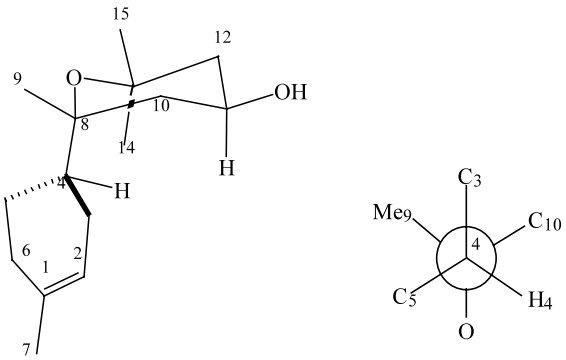
Two conformations of the tetrahydropyran ring, both having the hydroxyl group in an equatorial disposition are possible, i.e. a chair- or boat-like conformation. Molecular modeling, using the PCMODEL[10] program, were performed to calculate the minimum energy conformation of each deodarol **3a**–**d**, the results being depicted in Fig. 1.

The ^{13}C NMR spectra of the four deodarols **3a**–**d** were, as expected, very similar (Table 2). However, careful evaluation of the chemical shifts for C(3) and C(5) of each stereoisomer reveals that C(5) in **3a** and C(3) in **3b** are shifted downfield some 2.4 ppm in comparison to the remaining three compounds. Evaluation of Newman projections by looking through the C(4)/C(8) bond (see Fig. 1) reveals that only isomer **3b** has a different neighborhood for C(3), with the oxygen in an *anti*-position. Following a similar reasoning and observing the C(5) chemical shift, it can be seen that **3a** is the only isomer having the oxygen in an *anti*-position to C(5). It therefore follows that (4*R*,8*S*,11*S*)- and (4*R*,8*R*,11*R*)-configurations can be assigned to **3a** and **3b**, respectively. In addition, oxidation of **3a** and **3c** gave a single deodarone **4a**, while oxidation of **3b** and **3d** gave the other deodarone **4b**. These results indicated that the pairs of diastereoisomeric deodarols **3a**/**3c** and **3b**/**3d** had the same configuration at C(8) and, therefore, **3c** and **3d** have the (4*R*,8*S*,11*R*)- and (4*R*,8*R*,11*S*)-configurations, respectively.

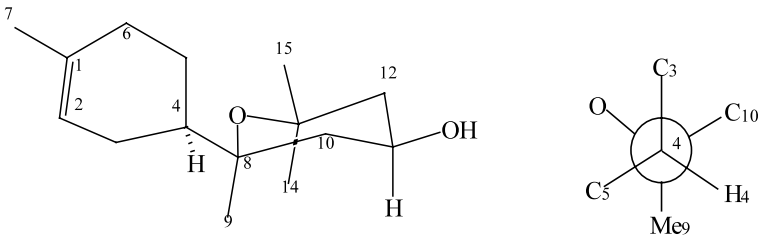
The absolute configuration at C(11) of the four deodarols (**3a**–**d**) was further confirmed by the prepara-



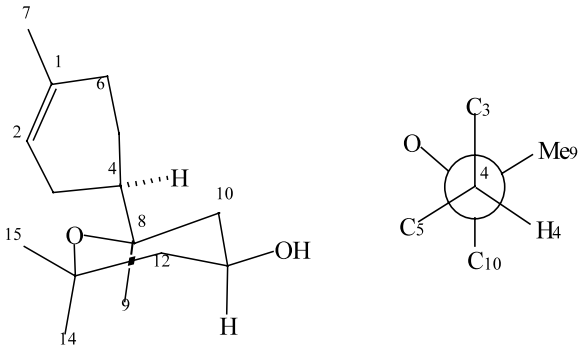
3a 4*R*,8*S*,11*S*



3b 4*R*,8*R*,11*R*



3c 4*R*,8*S*,11*R*



3d 4*R*,8*R*,11*S*

Figure 1. Minimal energy conformation of deodarols and C(4)–C(8) bond Newman projections.

tion of their Mosher esters[11] as shown in Tables 3 and 4 where the ^{1}H NMR chemical shifts differences for selected signals in the spectra of the (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate ester derived from each deodarol are compared.

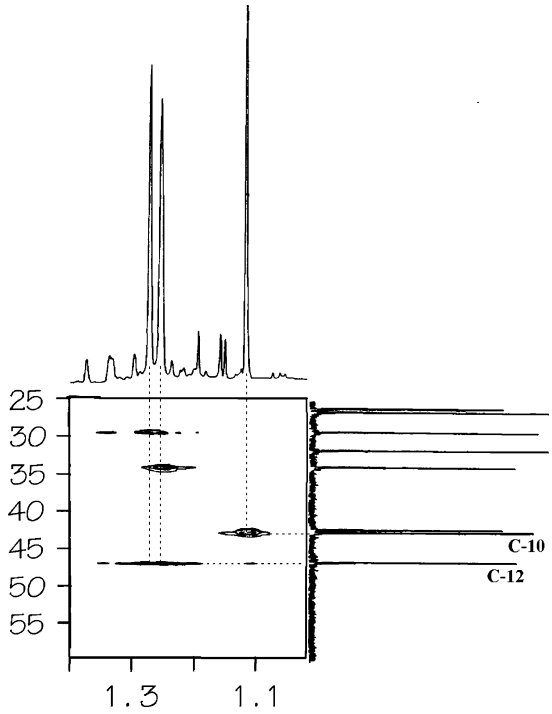


Figure 2. HMBC contour of Me-9, Me-14, and Me-15 region of deodarol **3a**.

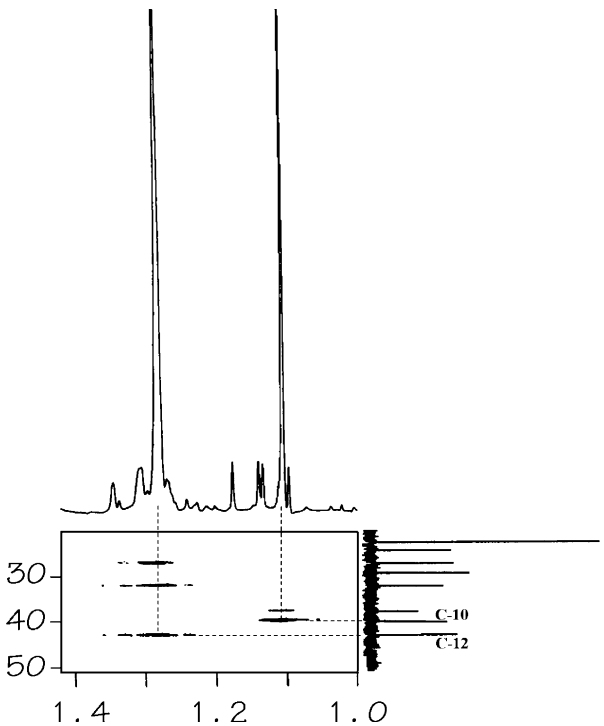


Figure 3. HMBC contour of Me-9, Me-14, and Me-15 region of deodarol **3b**.

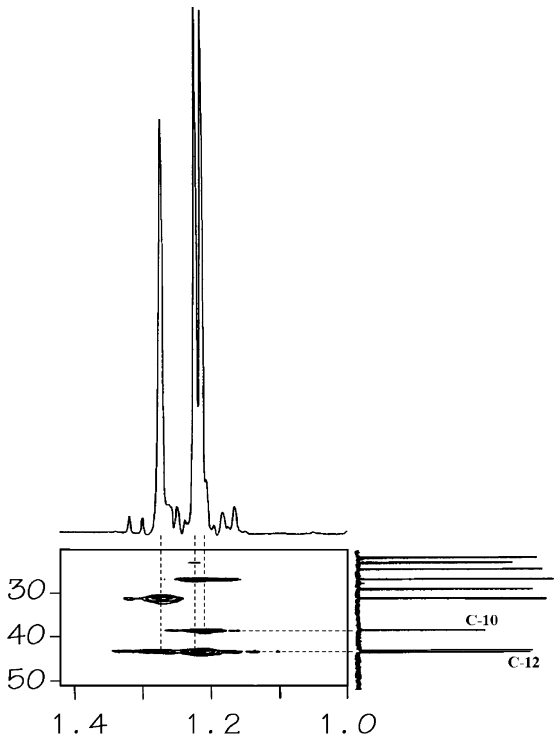


Figure 4. HMBC contour of Me-9, Me-14, and Me-15 region of deodarol **3c**.

Deodarones **4a** and **4b** were obtained by oxidation of the respective deodarols. These deodarones have identical retention time in gas chromatography using a 30 m HP-5 column. However, their mass spectra consistently show slight differences in the relative abundance of the ions at *m*/*z* 119, 120, 121, 134, and 141. Thus, in **4a** the ion at *m*/*z* 121 was always of lower intensity than its neighbors of essentially identical intensity at *m*/*z* 134, 120, and 119, while in **4b** the same occurred with the ion at *m*/*z* 134 in relation to the ions at *m*/*z* 121, 120, and 119. The ^{1}H and ^{13}C NMR data of each diastereoisomer are given in Tables 5 and 6, respectively. The assignments were made with the aid of DEPT, HSQC experiments, and by comparison with the corresponding deodarol spectra.

It is interesting to note that natural deodarone was claimed[3] to be a mixture of two diastereoisomers having the same configuration at C(4) supported by the similarity of the natural deodarone specific rotation value ($[\alpha]_D$=ca. +6) and that of the deodarone obtained by the hydration of *trans*-atlantone. However, the essential oil from *C. deodara* mainly contains *trans*-atlantone,[2] the possible biogenetic precursor of deodarone, in near-racemic form.[9] These facts, along with the $[\alpha]_D$ values measured in this work for deodarones **4a** and **4b** of +46.3 and +67.0, respectively, are indicative that natural deodarone and the deodarone described in Ref. 3 is a mixture of the four possible stereoisomers with a slight excess of the positive antipodes.

Table 1. ^{1}H NMR data for deodarols **3a–d**[a,b]

H	3a	3b	3c	3d	
2	5.41	5.36	5.37	5.36	br d (4.2)
3	2.16	1.94	2.09	2.03	m
	1.95	1.72	1.80	1.78	m
4	1.78	1.89	1.48	1.48	dddd (11.2, 11.2, 4.0, 2.0)
5_{eq}	1.74	2.05	1.92	1.88	ddd (12.0, 5.1, 2.2)
5_{ax}	1.27	1.28	1.22	1.21	dddd (12.0, 12.0, 12.0, 4.8)
6	1.96	1.94	1.96	1.95	m
7	1.63	1.65	1.63	1.63	br s
9	1.11	1.09	1.19	1.18	s
10_{eq}	2.29	2.18	1.80	1.73	ddd (13.0, 4.5, 2.1)
10_{ax}	1.16	1.13	1.22	1.20	dd (13.0, 11.0)
11	4.06	4.05	4.13	4.13	tt (11.0, 4.5)
12_{eq}	1.89	1.91	1.91	1.90	ddd (12.3, 4.5, 2.1)
12_{ax}	1.34	1.30	1.19	1.18	dd (12.3, 4.5)
14	1.25	1.27	1.25	1.24	s
15	1.27	1.27	1.21	1.19	s

[a] 300 MHz, $CDCl_3$, TMS as internal standard.
[b] J values are the same for the four diastereoisomers.

3. Experimental

For separations, a Gilson HPLC machine with refractive index detector was used. The column employed was a Beckmann C-18 (5μ, 10×250 mm). Retention times (t_R) were measured from the solvent peak. ^{1}H, ^{13}C, COSY-^{1}H/^{1}H, HMBC and HSQC spectra: Mercury 300. ^{1}H measured at 300 MHz, ^{13}C at 75.4 MHz, TMS as internal standard, solvent $CDCl_3$. IR spectra: Perkin–Elmer 16F PC FT-IR spectrophotometer. Specific rotations: Perkin–Elmer 241 or Horiba SEPA-300 polarimeters. Column chromatography (CC) Merck silica gel, particle size 0.040–0.063 mm (230–400 mesh, ASTM). (*R*)-(+)-Limonene, *n*-butyllithium in hexane, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and 3-methyl-2-butenal were commercially available (Aldrich). The concentration of active *n*-butyllithium was checked using the 4-biphenylmethanol method.[12] TMEDA was dried immediately prior to use by distillation from calcium hydride.

3.1. Atlantols 2

n-Butyllithium (0.025 mol), TMEDA (0.025 mol) and (*R*)-(+)-limonene (0.05 mol) were reacted as in Ref. 9 to give atlantols **2** (3.3 g, 60%, based on *n*-butyllithium). Spectroscopic data were in agreement to those reported.[9]

3.2. Deodarols 3

A mixture of atlantols **2** (3 g), $Hg(AcO)_2$ (9.5 g), H_2O (14 mL) and THF (14 mL) was magnetic stirred overnight at room temperature. A solution of aqueous NaOH (3 M, 20 mL) followed by a solution of $NaBH_4$ (700 mg) in aqueous NaOH (3 M, 20 mL) were added and the mixture stirred 0.5 h after which the mixture was saturated with NaCl and extracted twice with ethyl ether. The combined ethereal phases were washed with water, dried and evaporated. The residue (2.9 g) was purified by column chromatography over silica gel (hexane–EtOAc 9:1) to yield a mixture of the four diastereoisomeric deodarols **3** (1.3 g, 40%). This mixture was separated by HPLC using a C-18 column, MeOH–H_2O 72:28 as solvent, and a flow of 2.5 mL min^{-1} to give **3a** (t_R 18.5 min, 213 mg), **3b** (t_R 20.7 min, 414 mg), **3c** (t_R 29 min, 296 mg), and **3d** (t_R 32.8 min, 245 mg):

3.2.1. (4*R*,8*S*,11*S*)-Deodarol 3a. $[\alpha]_{589}$ +98.3, $[\alpha]_{578}$ +102.2, $[\alpha]_{546}$ +115.9, $[\alpha]_{436}$ +196.3, $[\alpha]_{365}$ +302.9 (*c* 1.36, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3608, 3016, 1522, 1376, 1206. EIMS 70 eV *m*/*z* (rel. int.): 187 (1), 164 (2), 159 (1), 146 (5), 143 (56), 131 (8), 125 (73), 119 (9), 107 (34), 95 (16), 87 (45), 85 (12), 79 (13), 67 (14), 57 (16), 43 (100). ^{1}H and ^{13}C NMR data in Tables 1 and 2, respectively.

3.2.2. (4*R*,8*R*,11*R*)-Deodarol 3b. $[\alpha]_{589}$ +13.3, $[\alpha]_{578}$ +13.8, $[\alpha]_{546}$ +15.9, $[\alpha]_{436}$ +28.0, $[\alpha]_{365}$ +46.4 (*c* 3.97, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3608, 3452, 3014, 1522, 1376, 1206. EIMS 70 eV *m*/*z* (rel. int.): 220 $[M-H_2O]^+$ (0.5),

Table 2. ^{13}C NMR data for deodarols **3a–d**[a]

C	3a	3b	3c	3d
1	133.5	134.5	133.8	133.8
2	121.2	120.6	120.8	120.8
3	26.3	28.5	26.1	26.0
4	42.0	40.6	46.8	46.8
5	25.9	23.3	23.3	23.4
6	31.4	30.9	31.1	31.1
7	23.2	23.3	23.2	23.3
8	78.0	77.9	76.7	76.5
9	26.2	25.3	24.5	23.8
10	42.3	43.0	41.3	41.8
11	63.4	63.1	63.8	63.9
12	46.3	46.5	46.6	46.5
13	73.1	72.9	72.7	72.7
14	29.0	28.6	28.6	28.5
15	33.6	34.1	33.5	33.5

[a] 75.4 MHz, $CDCl_3$, TMS as internal standard.

Table 3. Selected ^{1}H NMR chemical shift values for (*R*)- and (*S*)-MTPA esters of **3a** and **3b**

H	**3a**			**3b**		
	(*R*)-MTPA	(*S*)-MTPA	$\Delta\delta_{R-S}$	(*R*)-MTPA	(*S*)-MTPA	$\Delta\delta_{R-S}$
9	1.05	1.12	−0.07	1.10	1.05	+0.05
10α	2.26	2.32	−0.06	2.31	2.22	+0.09
10β	1.35	1.44	−0.09	1.40	1.29	+0.11
12α	1.97	1.90	+0.07	1.94	1.99	−0.05
12β	1.64	1.54	+0.10	1.53	1.59	−0.06
14	1.29	1.28	+0.01	1.31	1.33	−0.02
15	1.26	1.20	+0.06	1.23	1.27	−0.04

Table 4. Selected ^{1}H NMR chemical shift values for (*R*)- and (*S*)-MTPA esters of **3c** and **3d**

H	**3c**			**3d**		
	(*R*)-MTPA	(*S*)-MTPA	$\Delta\delta_{R-S}$	(*R*)-MTPA	(*S*)-MTPA	$\Delta\delta_{R-S}$
9	1.28	1.27	+0.01	1.25	1.26	−0.01
10α	1.89	1.87	+0.02	1.75	1.82	−0.07
10β	1.47	1.43	+0.04	1.43	1.47	−0.04
12α	1.95	2.08	−0.13	2.02	1.94	+0.08
12β	1.35	1.50	−0.15	1.37	1.34	+0.03
14	1.33	1.34	−0.01	1.32	1.31	+0.01
15	1.20	1.23	−0.03	1.21	1.18	+0.03

Table 5. ^{1}H NMR data for deodarones **4a** and **4b**[a,b]

H	**4a**	**4b**	
2	5.38	5.36	m
3a	2.10	1.95–2.10	m
3b	1.98	1.79	m
4	1.86	1.93	dddd (12.0, 12.0, 5.5, 2.2)
5a	1.79	1.95–2.10	m
5b	1.59	1.60	m
6a,b	1.98	1.95–2.10	m
7	1.65	1.65	br s
9	1.22	1.21	s
10a	2.56	2.54	d (15.6)
10b	2.29	2.23	d (15.6)
12a,b	2.43	2.42	s
14	1.31	1.30	s
15	1.31	1.30	s

[a] 300 MHz, $CDCl_3$, TMS as internal standard.
[b] *J* values are the same for the two diastereoisomers.

Table 6. ^{13}C NMR data for deodarones **4a** and **4b**[a]

C	**4a**	**4b**
1	133.9	134.1
2	120.5	120.4
3	26.3	26.5
4	46.0	45.9
5	23.8	23.6
6	31.0	31.0
7	23.3	23.3
8	78.4	78.4
9	26.1	25.4
10	47.0	47.7
11	209.3	209.3
12	51.4	51.6
13	74.2	74.3
14	30.7	30.7
15	33.2	32.2

[a] 75.4 MHz, $CDCl_3$, TMS as internal standard.

187 (1), 164 (2), 159 (1), 146 (5), 143 (72), 131 (8), 125 (93), 119 (9), 107 (40), 95 (17), 87 (54), 85 (15), 79 (13), 67 (15), 57 (18), 43 (100). ^{1}H and ^{13}C NMR data in Tables 1 and 2, respectively.

3.2.3. (4*R*,8*S*,11*R*)-Deodarol 3c. $[\alpha]_{589}$ +75.0, $[\alpha]_{578}$ +78.2, $[\alpha]_{546}$ +89.0, $[\alpha]_{436}$ +151.9, $[\alpha]_{365}$ +239.8 (*c* 3.37, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3608, 3452, 3014, 1522, 1374, 1206. EIMS 70 eV *m*/*z* (rel. int.): 220 $[M-H_2O]^+$ (1), 187 (2), 164 (6), 159 (2), 146 (12), 143 (45), 131 (18), 125 (71), 119 (20), 107 (34), 95 (22), 87 (45), 85 (15), 79 (15), 67 (16), 57 (16), 43 (100). ^{1}H and ^{13}C NMR data in Tables 1 and 2, respectively.

3.2.4. (4*R*,8*R*,11*S*)-Deodarol 3d. $[\alpha]_{589}$ +46.6, $[\alpha]_{578}$ +48.2, $[\alpha]_{546}$ +54.3, $[\alpha]_{436}$ +91.1, $[\alpha]_{365}$ +145.5 (*c* 2.24, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3620, 3016, 1522, 1376, 1210. EIMS 70 eV *m*/*z* (rel. int.): 220 $[M-H_2O]^+$ (1), 187 (2), 164 (5), 159 (2), 146 (11), 143 (46), 131 (16), 125 (68), 119 (18), 107 (33), 95 (21), 87 (45), 85 (15), 79 (14), 67 (16), 57 (17), 43 (100). ^{1}H and ^{13}C NMR data in Tables 1 and 2, respectively.

3.3. (*R*)- and (*S*)-MTPA esters of deodarols

A solution of each of the deodarols **3a**–**d** (10 mg, 42 μmol) in CH_2Cl_2 (2 mL) was treated with a solution of dicyclohexylcarbodiimide (78 mg, 0.38 mmol), 4-

(dimethylamino)pyridine (11.6 mg, 95 μmol) and either (*R*)- or (*S*)-α-methoxy-α-trifluoromethyl)phenylacetic acid (38.8 mg, 0.17 mmol) in CH_2Cl_2 (2 mL), at room temperature for 24 h. The mixture was concentrated and the residue was suspended in EtOAc (3 mL), successively washed with aqueous HCl (10%, 1 mL), H_2O, saturated aqueous $NaHCO_3$ (1 mL) and brine, dried over Na_2SO_4 and evaporated at reduced pressure. In each case, the Mosher esters were purified by flash column chromatography on silica gel using hexane–EtOAc (33:1) as eluent.

3.4. Deodarones 4

To a stirred suspension of pyridinium chlorochromate (37 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (0.5 mL) a solution of deodarol (24 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was added. After 1.5 h, dry Et_2O (1.0 mL) was added and the supernatant liquid was decanted from a black gummy residue. The residue was washed with dry Et_2O (3×0.5 mL). The combined organic solution was percolated through a short pad of Florisil and the solvent was evaporated. In each case, the deodarone was purified by flash column chromatography on silica gel using hexane–EtOAc (33:1) as eluent. Yield 87–91%.

3.4.1. (4*R*,8*S*)-Deodarone 4a. $[\alpha]_{680}$ +34.1, $[\alpha]_{650}$ +38.0, $[\alpha]_{600}$ +44.2, $[\alpha]_{589}$ +46.3, $[\alpha]_{577}$ +48.2, $[\alpha]_{546}$ +53.3, $[\alpha]_{492}$ +64.2 (*c* 3.48, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3016, 1712, 1378. MS (EI) *m*/*z*: 236 (M^+, 1), 218 (2), 162 (15), 141 (68), 134 (24), 121 (22), 120 (25), 119 (25), 105 (16), 95 (22), 93 (15), 85 (32), 83 (100), 79 (14), 77 (10), 67 (16), 55 (15), 43 (48), 41 (11).

3.4.2. (4*R*,8*R*)-Deodarone 4b. $[\alpha]_{680}$ +47.6, $[\alpha]_{650}$ +52.7, $[\alpha]_{600}$ +63.2, $[\alpha]_{589}$ +67.0, $[\alpha]_{577}$ +70.6, $[\alpha]_{546}$ +79.6, $[\alpha]_{492}$ +102.2 (*c* 4.28, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3016, 1712, 1380. MS (EI) *m*/*z*: 236 (M^+, 1), 218 (2), 162 (13), 141 (78), 134 (18), 121 (22), 120 (22), 119 (21), 105 (14), 95 (22), 93 (15), 85 (32), 83 (100), 79 (14), 77 (10), 67 (16), 55 (15), 43 (48), 41 (11).

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