Alloaromadendrene. **4**, 40 mg, $[\alpha]_D -12$ ($CHCl_3$; *c* 1.65); IR ν_{max}^{film} cm^{-1}: 3080, 1675, 1460, 1375 and 890; EIMS *m/z* (rel. int.): 204 $[M]^+$ (64), 189 (41), 161 (100), 147 (71), 133 (68), 119 (93), 107 (86) and 105 (100); ^1H NMR: δ0.25 (1H, *dd*, *J*=11.0 and 9.6 Hz, H-6), 0.56 (1H, *m*, H-7), 0.94 (3H, *d*, *J*=7.2 Hz, H-14), 0.96 (3H, *s*, H-13), 1.00 (3H, *s*, H-12), 1.26 (1H, *m*, H-8), 1.32 (1H, *m*, H-3), 1.73 (2H, *m*, H-2), 1.80–1.90 (3H, *m*, H-3; H-5 and H-8), 2.07 (1H, *m*, H-4), 2.32 (2H, *m*, H-9), 2.67 (1H, *m*, H-1), 4.71 (1H, *br s*, H-15) and 4.73 (1H, *br s*, H-15); ^{13}C NMR: δ 152.5 (*s*, C-10), 109.6 (*t*, C-15), 51.0 (*d*, C-1), 42.3 (*d*, C-5), 37.8 (*d*, C-4), 35.8 (*t*, C-9), 31.3 (*t*, C-3), 28.7 (*q*, C-12), 28.3 (*t*, C-2), 25.0 (*d*, C-7), 23.7 (*d*, C-6), 22.2 (*t*, C-8), 17.3 (*s*, C-11), 16.4 (*q*, C-14) and 15.8 (*q*, C-13).

Bioassay. In the *Artemia salina* shrimp assay technique [10] samples of **1**–**4** (5 mg) were dissolved in DMSO (500 μl). Appropiate amounts of solns were transferred into vials, to obtain three vials for each concn (5, 10, 20 and 50 μl/ml) and artificial sea water was added to make 5 ml. Ten shrimps were then added to each vial. Survivors were counted after 24 hr exposure and the percent deaths at each dose and control were determined. LC_{50} were determined using the probit analysis method described in ref. [12].

Acknowledgements—This work is part of an Italian–Yugoslav programme on mutual research of the Adriatic Sea and has been performed with financial support of CNR Roma and SIZ III S. R. Croatia, Zagreb. Bioassays have been carried out with financial support of 'Progetti Strategici' of CNR. We thank Mrs R. Sankovic' and Mr C. Iodice for technical assistance. The authors are also obliged to Dr A. De Giulio for bioassays.

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Phytochemistry, Vol. 27, No. 6, pp. 1878–1881, 1988.
Printed in Great Britain.

0031-9422/88 $3.00+0.00
Pergamon Press plc.

THE ABSOLUTE CONFIGURATION OF GRINDELIC ACID

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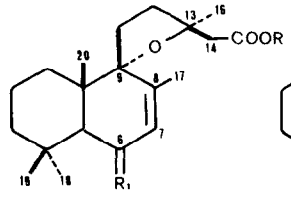
(*Received* 30 *July* 1987)

Key Word Index—*Grindelia*; Compositae; grindelic acid; 6-oxogrindelic acid; 7α,8α-epoxygrindelic acid; grindelane diterpenoids.

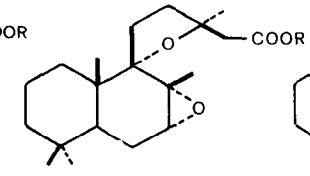
Abstract—Contrary to recent assignments, the labdane absolute configuration of grindelic acid, 6-oxogrindelic acid and 7α-8α-epoxygrindelic acid is confirmed through application of the CD exciton chirality method.

We have been interested in the structure of the grindelane diterpenoids isolated from the resin of *Grindelia robusta*, namely grindelic acid **1a**, 6-oxogrindelic acid **2a** and 7α,8α-epoxygrindelic acid **3a** [1–3] for some years. Their stereochemistry was defined by chemical correlation to sclareol **4** [4, 5] and was confirmed by total synthesis from sclareol itself [6]. More recently, the diterpenoid content of several *Grindelia* species has been investigated and many functional derivatives of grindelic acid have been isolated [7–16]. In one of the most recent reports [14] the isolation of grindelic acid from the aerial parts of *G. perennis*, *G. aphanactis*, *G. boliviana* and *G. chiloensis* is described and the *ent*-labdane structure **5a** is proposed for the compound. This was deduced on the grounds of

(a R = H; b R = Me)



1 $R^1 = H_2$
2 $R^1 = O$



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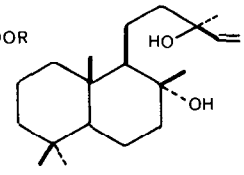

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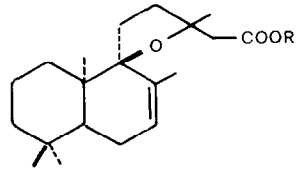

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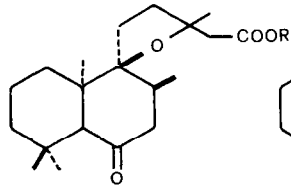

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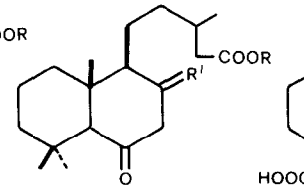
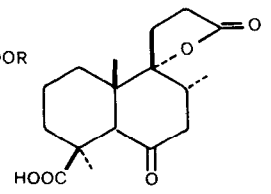


7 $R^1 = \beta$-H, α-Me
8 $R^1 = \beta$-Me, α-H



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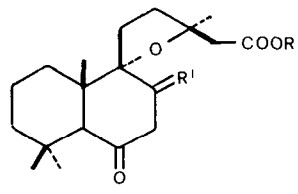
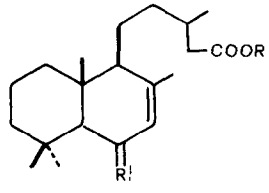
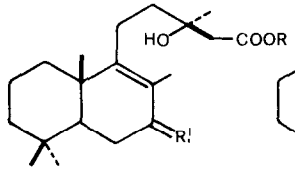


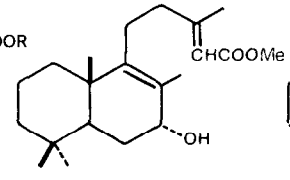
10 $R^1 = \beta$-H, α-Me
11 $R^1 = \beta$-Me, α-H



12 $R^1 = O$
24 $R^1 = H_2$



13 $R^1 = O$
14 $R^1 = \beta$-OH, α-H
15 $R^1 = \beta$-OCOϕ, α-H



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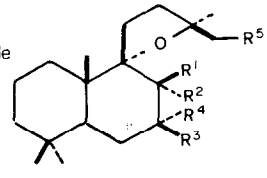
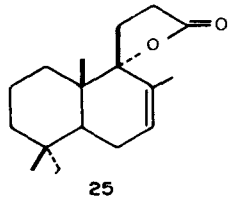


	R^1	R^2	R^3	R^4	R^5
17	Me	OH	H	OH	COOR
18	Me	$O_2C\phi Br$	H	$O_2C\phi Br$	COOR
19	OH	Me	OH	H	COOR
20	OH	Me	$O_2C\phi Br$	H	COOR
21		$=CH_2$	$O_2C\phi Br$	H	COOR
22		$=CH_2$	OH	H	COOR
23		$=CH_2$	H	OH	COOR
27	Me	OH	H	H	CH_2OH



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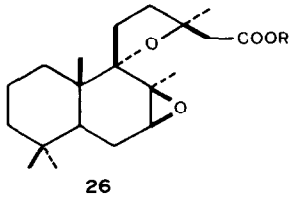

26

the conversion of the methyl ester of the acid to the 6-oxo-7,8-dihydroderivative, that was assigned the *ent*-labdane configuration **6b** on account of the interpretation, according to the octant rule, of the positive sign of the Cotton effect ($\Delta\varepsilon_{295} = +0.61$) exhibited by the compound. In addition, the suggestion is given that all labdanes from *Grindelia* species also have the same *ent*-labdane absolute configuration. These inferences appear to be inconsistent with the previous attribution [17] of the labdane configuration to 6-oxo-7,8-dihydrocativic acids **7a** and **8a** just based on the application of the octant rule to the interpretation of the positive sign of the Cotton effect exhibited by both compounds. In addition, a positive Cotton effect is exhibited [17] by the oxoacid **9**, that may be obtained from marrubiin [18], and by the 6-oxo-7,8-dihydrogrindelic acids **10a** and **11a** [2] obtained by hydrogenation of the 6-oxogrindelic acid that may be either isolated from *G. robusta* or prepared by chromic oxidation of the grindelic acid from the same source [2]. This 6-oxogrindelic acid, in turn, displays [2] a positive Cotton effect just like 6-oxocativic acid **12** [17].

In our opinion, these considerations do not allow us to question the labdane absolute configuration of grindelic, 6-oxogrindelic and 7α,8α-epoxygrindelic acid. However, because of the considerable number of grindelane diterpenoids isolated so far, in this paper additional independent evidence in support of the stereostructures **1a**, **2a** and **3a** is provided.

Methyl 7α,8α-epoxygrindelate **3b**, obtained by peracid epoxydation of methyl grindelate **1b** [3], was converted into the α,β-unsaturated ketone **13b** [3, 19] by

H^+–THF–H_2O treatment. Reduction ($NaBH_4$–MeOH) of **13b** to **14b** and subsequent benzoylation (C_6H_5COCl–C_5H_5N) of this latter gave **15b**. In the ^1H NMR spectra of both **14b** and **15b** the signal of the proton at the position 7 appears as a multiplet with $W_{1/2}$ = 17.2 Hz, indicating the α-pseudoaxial orientation of the 7-proton. Accordingly, in the ^1H NMR spectrum of **16** the signal of the 7β-pseudoequatorial proton appears as a multiplet with $W_{1/2}$ = 6 Hz [6]. In the region of the $\pi \rightarrow \pi^*$ intramolecular charge transfer transition at 229 nm, the CD spectrum of **15b** exhibits a negative Cotton effect (λ_{ext} 229 nm, $\Delta\varepsilon = -8.25$). According to the allylic benzoate chirality method [20], the negative sign of the effect indicates the negative exciton chirality between the benzoate and double bond chromophores. Consequently, allylic benzoate possesses the chirality depicted in **15b** and, therefore, 7α,8α-epoxygrindelic acid, 6-oxogrindelic acid and grindelic acid possess the labdane chirality depicted by structures **3a**, **2a** and **1a**, respectively.

For support of the stereochemistry of grindelic acid, the exciton chirality method [20] could have been applied alternatively to di-*p*-bromobenzoate **18b** if this compound could have been prepared from diol **17b**, that had been obtained by oxidation (OsO_4) of methyl grindelate **1b** and was assigned the 7α,8α-orientation of the hydroxyl groups on the supposition that the osmylation of the 7,8-double bond of **1b** occurred from the α-side [1]. Although any attempt to obtain the diester from the diol (*N*, *N*-dimethylaniline, *p*-bromobenzoylchloride; *N*,*N*-dimethylformamide, sodium hydride, *p*-bromobenzoylchloride; 4-(*N*,*N*-dimethylamino)pyridine, pyridine, *p*-bromobenzoylchloride [21, 22]) failed owing to the tertiary nature of the hydroxyl group at the position 8 but gave the 7-*p*-bromobenzoate monoester, opportunity offered to revise the structure of the diol. The ^1H NMR spectrum of the monoester displayed the 7-proton signal at δ5.19 as a multiplet with $W_{1/2}$ = 17.5 Hz, indicative of α-axial orientation. Analogously, in the spectrum of the diol the corresponding signal appears as a multiplet with $W_{1/2}$ = 20.1 Hz. Thus the diol and its 7-monoester derivative should rather possess stereostructures **19b** and **20b**, respectively. On the other hand, the methyl signal at δ1.31 in the spectrum of the diol may be safely assigned to the 17-protons since the chemical shift of the remaining signal that may be ascribed to a Me–C–O group [δ1.38, (16)Me] is unchanged in the spectrum of the monoester, owing to the distance between the benzoyl and (16)Me groups. The NOE measured for the (14)CH_2 signal at δ2.68 upon irradiation of the signal at δ1.31 of the diol indicated the spatial proximity of the involved protons and, therefore, the α-equatorial orientation of the (17)methyl group. Chemical evidence for structures **19b** and **20b** was obtained as follows. The monoester was dehydrated (thionyl chloride, pyridine) to **21b** and then converted by hydrolysis and subsequent re-esterification with diazomethane to alcohol **22b**, whose physical behaviour (mp, $[\alpha]_D$, ^1H NMR) was quite different from that of the known 7-epimer **23b** [8]. Thus, the osmylation of **1b** occurs preferentially from the β-side, clearly owing to the presence of the 9α-axial oxygen atom that hinders the α-side. On the other hand, this effect has already been invoked to account for the catalytic hydrogenation of both **1b** [1, 24] and lactone **25** [24] from the β-side, contrary to the behaviour of cativic acid **24** [23].

These results might doubt the configuration at the positions 7 and 8 of 7,8-epoxygrindelic acid, isolated from *G. robusta* and synthesized by peracid treatment of grindelic acid **1a** [3]. In fact, the α-orientation of the oxirane ring rested initially [3] on the belief that epoxidation of **1a** occurred from the α-side because of the minor crowding of this face of the molecule. Following some reports [8, 9] that described 7,8-epoxygrindelic acid as possessing the 7β,8β-configuration **26a**,* more recently [10] structure **3a** has been confirmed by ^{13}C NMR spectroscopy and the result of the epoxidation of **1a** has been accounted for the directing effect of the 9α-axial oxygen atom on the peracid by hydrogen bonding. Further support for structure **3a** can now be given through NOE measurements with alcohol **27**, obtained from **3b** by lithium aluminium hydride reduction [3]. The two methyl proton NMR signals of **27** at lower field (δ1.21 and 1.46) may be safely assigned to the (17)- and (16)methyl groups bonded to oxygen-bearing carbon atoms. The methyl signal at δ0.94 must be assigned to the (20)methyl protons because of the results of a 2D carbon-proton shift correlation experiment that showed connectivity between these protons and the carbon signal at δ18.4, previously assigned to the (20) carbon atom [10].† A NOE enhancement of the signal at δ0.94 measured upon irradiation at δ1.21 showed the spatial proximity of the (20)methyl group and one of the Me–C–O groups, necessarily the (17)methyl group. Thus this latter must be β-oriented in the alcohol **27** and, therefore, 7,8-epoxygrindelic acid does possess structure **3a** with the α-oriented oxirane ring.

EXPERIMENTAL

General. ^{13}C and ^1H NMR spectra were recorded at 30° and 75.47/300.14 MHz with an AM-300 FT NMR Bruker spectrometer equipped with a dual-probe. 1D spectra were typically obtained with 3000 Hz (^1H) and 13 000 Hz (^{13}C) spectral widths. The shifts are given for solns in $CDCl_3$ as ppm downfield from TMS (δ). The one-bond 2D carbon–proton shift correlation experiment was performed with the Bruker XHCORR microprogram using delay D_3 = 3.8 msec, corresponding to $J_{C,H}$ = 130 Hz. The NOE difference FID's were obtained by gated decoupling. For CC Merck silica gel 60 (0.063–0.200 mm) was used. For TLC and PLC, Merck silica gel 60 F-254 (0.25 and 2 mm, respectively) was used.

Ketone **13b**. A soln of methyl 7α,8α-epoxygrindelate **3b** (110 mg) and 70% $HClO_4$ (1 drop) in THF–H_2O (6:1; 1.5 ml) was heated at 40° for 40 min. The reaction mixture was diluted with AcOEt and washed with H_2O. After evapn of the solvent, PLC (3:1 C_6H_6–Et_2O, 2 runs) of the residue afforded pure **13b** (72 mg) [3, 19], mp 78–79° (from hexane). ^1H NMR: 0.86 (3H, *s*), 0.90 (3H, *s*), 1.07 (3H, *s*), 1.28 (3H, *s*, 16-H_3), 1.73 (3H, *s*, 17-H_3), 2.48 (2H, ABq, $J_{A,B}$ = 12.8 Hz, 14-H_2), 3.71 (3H, *s*, COOMe).

*Some confusion seems to arise from the fact that in Devon and Scott's Handbook [25] the 7,8-epoxygrindelic acid isolated from *G. robusta* has been erroneously depicted as in **26a** instead of **3a**. In addition, the Handbook quotes a mistaken reference [24] instead of the correct one [3].

†As a result of the correlation experiment, the assignments of the lines of the 3- and the 14-carbons reported in ref. [10] should be reversed.

Allylic alcohol **14b**. A soln of **13b** (55 mg) in MeOH (5 ml) was treated with $NaBH_4$ (10 mg) at room temp. for 1 hr. Usual work-up and CC (elution with C_6H_6–Et_2O) of the crude product gave **14b** (50 mg, oil) [6]. ^1H NMR: 0.85 (3H, *s*), 0.89 (3H, *s*), 1.03 (3H, *s*), 1.28 (3H, *s*, 16-H_3), 1.69 (3H, *s*, 17-H_3), 2.52 (2H, ABq, $J_{A,B}$ = 14.0 Hz, 14-H_2), 3.71 (3H, *s*, COOMe), 4.07 (1H, m, $W_{1/2}$ = 17.2 Hz, 7α-H).

Allylic benzoate **15b**. A soln of **14b** (40 mg) in dry pyridine (1 ml) was treated with benzoyl chloride (0.1 ml) at room temp. for 4 hr. Usual work-up and PLC (7:3 $CHCl_3$–Et_2O, 1 run) gave **15b** (40 mg, oil). ^1H NMR: 0.85 (3H, *s*), 0.92 (3H, *s*), 1.09 (3H, *s*), 1.29 (3H, *s*, 16-H_3), 1.59 (3H, *s*, 17-H_3), 2.54 (2H, ABq, $J_{A,B}$ = 15.7 Hz, 14-H_2), 3.72 (3H, *s*, COOMe), 5.57 (1H, *m*, $W_{1/2}$ = 17.2 Hz, 7α-H), 7.3–8.1 (5H, C_6H_5COO–). *CD* (CH_3CN): λ_{ext} 229 nm, $\Delta\varepsilon = -8.25$.

Diol **19b**. Diol **19b** was obtained from methyl grindelate **1b** by reaction with OsO_4 [1]. ^1H NMR: 0.83 (3H, *s*), 0.89 (3H, *s*), 1.05 (3H, *s*), 1.31 (3H, *s*, 17-H_3), 1.38 (3H, *s*, 16-H_3), 2.68 (2H, ABq, $J_{A,B}$ = 12.9 Hz, 14-H_2), 3.61 (1H, *m*, $W_{1/2}$ = 20.1 Hz, 7α-H), 3.67 (3H, *s*, COOMe).

p-*Bromobenzoate* **20b**. A soln of diol **19b** [1] (60 mg) and *p*-bromobenzoyl chloride (40 mg) in *N*,*N*-dimethylaniline (3 ml) was kept at 80° for 4 hr. Usual work-up and PLC (7:3 C_6H_6–AcOEt, 1 run) afforded **20b** (56 mg, oil). ^1H NMR: 0.81 (3H, *s*), 0.88 (3H, *s*), 1.09 (3H, *s*), 1.22 (3H, *s*, 17-H_3), 1.38 (3H, *s*, 16-H_3), 2.72 (2H, ABq, $J_{A,B}$ = 12.6 Hz, 14-H_2), 3.67 (3H, *s*, $COOCH_3$), 5.19 (1H, *m*, $W_{1/2}$ = 17.5 Hz, 7α-H), 7.6–7.9 (4H, A_2B_2q, BrC_6H_4COO–). ^{13}C NMR: 36.7 (C-1), 18.8 (C-2), 41.2 (C-3 or C-12), 33.1 (C-4), 49.7 (C-5), 22.4 (C-6), 76.1 (C-7), 146.3 (C-8), 125.2 (C-9), 39.8 (C-10), 25.9 (C-11), 41.6 (C-12 or C-3), 71.1 (C-13), 44.5 (C-14), 173.3 (C-15), 26.4 (C-16), 20.1 (C-17 or C-19), 33.1 (C-18), 21.6 (C-19 or C-17), 14.8 (C-20), 51.7 (OMe), 130.8 (C-1'), 129.6 (C-2' and C-6'), 128.3 (C-3' and C-5'), 132.7 (C-4'), 166.6 ($OCOC_6H_5$). *p*-Bromobenzoaate **20b** was also obtained from diol **19b** by reaction with *p*-bromobenzoyl chloride and 4-(*N*,*N*-dimethylamino)pyridine in dry pyridine at room temp. for 24 hr and by reaction with NaH and then *p*-bromobenzoyl chloride in *N*,*N*-dimethylformamide at room temp. for 3 hr.

p-*Bromobenzoate* **21b**. A soln of **20b** (40 mg) in dry pyridine (1 ml) was treated with thionyl chloride (2 drops) at 0° for 30 min. The reaction mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ and H_2O and evapd. CC (elution with C_6H_6) of the residue afforded **21b** (31 mg, oil). ^1H NMR: 0.79 (3H, *s*), 0.80 (3H, *s*), 0.91 (3H, *s*), 1.30 (3H, *s*, 16-H_3), 2.66 (2H, ABq, $J_{A,B}$ = 12.9 Hz, 14-H_2), 3.62 (3H, *s*, COOMe), 4.82 (1H, *d*, *J* = 1.4 Hz, 17-H), 4.94 (1H, *d*, *J* = 1.7 Hz, 17-H'), 5.82 (1H, *q*, $J_{6\alpha,7\alpha} + J_{6\beta,7\alpha} = 17.5$ Hz, 7α-H), 7.5–8.0 (4H, A_2B_2q, BrC_6H_4COO–).

Alcohol **22b**. A soln of **21b** (20 mg) in 5% KOH–EtOH (1 ml) was kept at room temp. for 30 min. The reaction mixture was neutralized with Amberlite IR 120, filtered and evapd. The residue, that was constituted mainly by **22a** (TLC), was esterified with ethereal CH_2N_2 and then purified by PLC (9:1 C_6H_6–Et_2O, 3 runs) to give alcohol **22b** (16 mg), mp 98–99° (from hexane), $[\alpha]_D + 27°$ ($CHCl_3$; *c* = 0.7). ^{13}C NMR: 36.9 (C-1), 19.3 (C-2), 41.9 (C-3), 33.6 (C-4), 44.8 (C-5), 32.8 (C-6 or C-12), 70.7 (C-7), 153.3 (C-8), 92.1 (C-9), 41.9 (C-10), 26.2 (C-11), 32.2 (C-12 or C-6), 81.9 (C-13), 46.9 (C-14), 171.7 (C-15), 27.3 (C-16), 103.6 (C-17), 33.5 (C-18), 22.0 (C-19), 17.2 (C-20), 51.4 (OMe). ^1H NMR: 0.75 (3H, *s*), 0.80 (3H, *s*), 0.92 (3H, *s*), 1.29 (3H, *s*, 16-H_3), 2.51 (2H, ABq, $J_{A,B}$ = 13.9 Hz, 14-H_2), 3.64 (3H, *s*, COOMe), 4.52 (1H, *q*, $J_{6\alpha,7\alpha} + J_{6\beta,7\alpha} = 17.6$ Hz, 7α-H), 4.88 (1H, *d*, *J* = 1.5 Hz, 17-H), 5.16 (1H, *d*, *J* = 1.8 Hz, 17-H').

Alcohol **27**. Alcohol 27 was prepared from methyl 7α,8α-epoxygrindelate by $LiAlH_4$ reduction [3]. ^{13}C NMR: the chemical shifts were identical to those reported and assigned in ref. [10]. ^1H NMR: 0.79 (3H, *s*), 0.87 (3H, *s*), 0.94 (3H, *s*, 20-H_3), 1.21 (3H, *s*, 17-H_3), 1.3 (1H, *m*, 14-H), 1.46 (3H, *s*, 16-H_3), 2.24 (1H, *m*, 11-H), 2.44 (1H, *ddd*, $J_{14\text{-H},14\text{-H}'} = 14.7$ Hz, $J_{14\text{-H}',15\text{-H}'} = 11.8$ Hz, $J_{14\text{-H}',15\text{-H}} = 4.4$ Hz, 14-H'), 3.75 (1H, *ddd*, $J_{15\text{-H},15\text{-H}'} = 11.8$ Hz, $J_{14\text{-H}',15\text{-H}} = 4.4$ Hz, $J_{14\text{-H},15\text{-H}} = 2.9$ Hz, 15-H), 4.12 (1H, *ddd*, $J_{15\text{-H},15\text{-H}'} = 11.8$ Hz, $J_{14\text{-H}',15\text{-H}'} = 11.8$ Hz, $J_{14\text{-H},15\text{-H}'} = 2.2$ Hz, 15-H'); the proton chemical shift assignments are based on H,H decoupling and a 2D C–H shift correlation experiment (see General).

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