73. Synthesis of (+)-(4*S*,8*R*)-8-Epi- and (−)-(4*R*,8*S*)-4-Epi-β-bisabolol

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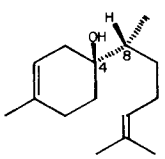
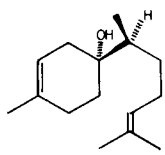
The first total enantioselective synthesis of (+)-(4*S*,8*R*)-8-epi-β-bisabolol ((+)-**1**) and of (−)-(4*R*,8*S*)-4-epi-β-bisabolol ((−)-**1**) is reported. The key step in the synthesis is the kinetic resolution of (±)-**5** by means of the *Sharpless* epoxidation yielding (−)- and (+)-**6**, respectively. Reduction of the epoxides with $LiAlH_4$ gave the diols (+)- and (−)-**7** which were transformed into (+)- and (−)-**8**, respectively, *via* the corresponding mesylate. Reaction of these epoxides with the *Grignard* reagent derived from homoprenylbromide, assisted by Li_2CuCl_4, finished the synthesis of the target compounds **1** with high diastereo- and enantioselectivity.

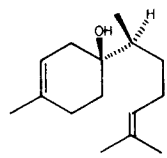
Introduction. – 'β-Bisabolol' has been first isolated from the essential oil of the cotton plant [1]. It showed some attractive activity towards boll weevil [2]. Subsequently, 'β-bisabolol' of unknown configuration was also found in corn oil [3], vanilla [4], camphor oil [5], and olibanum oil [6]. Recently, *Ohloff et al.* [7] isolated (−)-4-epi-β-bisabolol[1]) ((−)-**1**) in bergamot oil and established its (4*R*,8*S*)-configuration.



(+)-**1** (4*S*,8*R*)



(−)-**1** (4*R*,8*S*)



(+)-**2** (4*S*,8*S*)

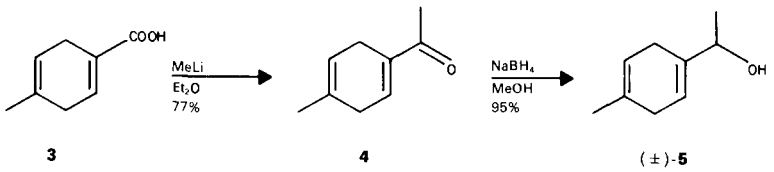
'β-Bisabolol', *i.e.* the corresponding carbonium ion, is of interest as a biosynthetic intermediate to the tricyclic cedrene family [8–10]. Surprisingly, β-bisabolol[1]) and its stereoisomers have been more or less neglected as a synthetic target. Besides two reports on the synthesis of racemic diastereoisomeric mixtures [8] [11], the only notable exception is the above mentioned work [7] in which the synthesis of (+)-(4*S*,8*R*)-8-epi-β-bisabolol[1]) ((+)-**1**) and (+)-(4*S*,8*S*)-β-bisabolol[1]) ((+)-**2**) is reported.

In this communication, we describe an enantioselective synthesis of (+)-(4*S*,8*R*)-8-epi-β-bisabolol ((+)-**1**) and (−)-(4*R*,8*S*)-4-epi-β-bisabolol ((−)-**1**)[1]).

Results. – The synthesis started with 4-methylcyclohexa-1,4-dienecarboxylic acid (**3**) which was easily available from isoprene and propynoic acid (*cf.* [12]). Reaction of **3** with

[1]) The numbering given in *Formula* (+)-**1** is generally employed. The trivial names of (+)-**1**, (−)-**1**, and (+)-**2** do not reflect enantiomeric relationships, since they are based on the name β-bisabolol which implies (4*S*,8*S*) configuration. Systematic names and numbering are given in the *Exper. Part.*

Scheme 1

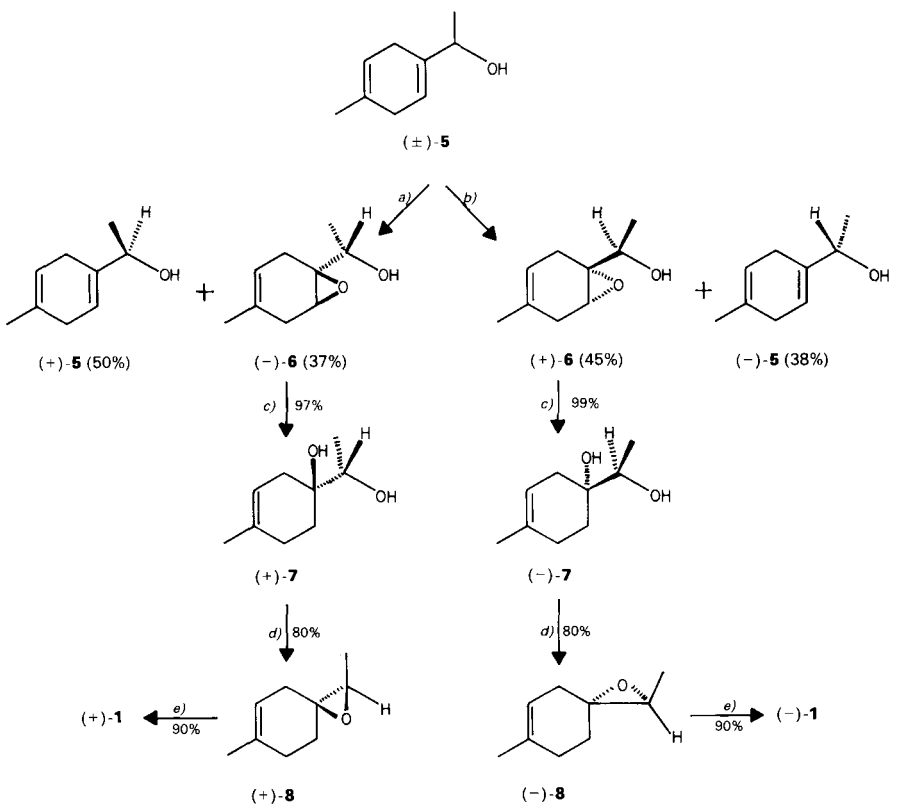


3 **4** (±)-**5**

MeLi yielded ketone **4** and reduction with $NaBH_4$ the secondary alcohol (±)-**5**[2] *(Scheme 1)*.

The kinetic resolution of (±)-**5** was carried out according to *Sharpless'* protocol [14a][3] with catalytic amounts (0.1 equiv.) of $Ti(i\text{-}PrO)_4$ and diisopropyl tartrate and 0.45 equiv. of *tert*-butyl hydroperoxide. Epoxidation with (+)-L-tartrate as the catalyst furnished

Scheme 2



a) Diisopropyl L-tartrate, $Ti(i\text{-}PrO)_4$, (*t*-Bu)OOH; *b)* diisopropyl D-tartrate, $Ti(i\text{-}PrO)_4$, (*t*-Bu)OOH; *c)* $LiAlH_4$, THF; *d)* 1. MsCl, Py; 2. KOH, MeOH; *e)* $[(CH_3)_2C{=}CHCH_2CH_2]MgBr$, Li_2CuCl_4, THF.

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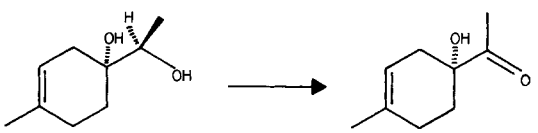
[2]) This alcohol has previously been prepared by *Birch* reduction of the corresponding aromatic alcohol [13].

[3]) There are already innumerable accounts on the use of the very powerful *Sharpless* epoxidation. For a review on the synthetic aspects, see [14c], and for a discussion on the mechanism, see [14d].

(−)-**6** in 37% yield *(Scheme 2)*; the diastereoselectivity could be estimated by ^{1}H-NMR and the final products to be 98.5:1.5, the enantioselectivity 97.5:2.5 *(vide infra)*. The remaining less reactive allylic alcohol (+)-**5** was isolated in 50% yield with *ca.* 65% e.e. (*cf.* [14b] and *Exper. Part*). Analogous epoxidation of (±)-**5** with (−)-D-tartrate as catalyst gave (+)-**6** in 45% yield, with 98.5:1.5 diastereoselectivity and > 99% enantioselectivity *(vide infra)*.

Subsequent treatment of (−)- and (+)-**6** with $LiAlH_4$ produced (+)- and (−)-**7**, respectively, in nearly quantitative yield. The nucleophilic attack of the hydride proceeded with complete selectivity on the secondary center of the epoxide as anticipated[4]). In order to check the optical purity, diol (−)-**7** was oxidized to the known [18] ketone (−)-**9** of (*R*)-configuration (*Scheme 3*; $[\alpha]_D^{20} = -30.2$ (EtOH, $c = 1.0$), $[\alpha]_D^{20} = -35.3$ (CCl_4, $c = 1.3$)). NMR experiments in the presence of chiral shift reagent showed this compound to have > 98% e.e. (signal of the vinyl proton).

Scheme 3



(−)-**7** (−)-**9**

The diols (+)- and (−)-**7** were transformed to the epoxides (+)- and (−)-**8**, respectively, by first preparing *in situ* the secondary monomesylate and then subjecting the latter to KOH in MeOH. In the final step, (+)- and (−)-**8** were treated with the *Grignard* reagent derived from homoprenyl bromide in the presence of Li_2CuCl_4 (*cf.* [19] [20]). In both cases, the reaction proceeded cleanly and gave the target compounds (+)-(4*S*,8*R*)-8-epi-β-bisabolol ((+)-**1**) and (−)-(4*R*,8*S*)-4-epi-β-bisabolol ((−)-**1**) in 80–90% yield. The diastereoselectivity of both products was determined to be 98.5:1.5 by ^{1}H-NMR *d* for CH_3 of the (4*SR*,8*SR*)-**2** isomer at 0.915 ppm (see [7][5])). The enantiomeric excess was checked during the synthesis to be > 98% for (−)-**7** *(vide supra)*. With the final products, ^{1}H-NMR experiments with chiral shift reagent were again performed, and though this method is not very accurate, we judge (−)-**1** to have 98% e.e. and (+)-**1** 95% e.e.

The odour of (+)-**1**, (−)-**1**, and (±)-**2** has been determined by smelling the main peak on the end of a capillary column. The odour sensation caused by the enantiomers (+)-**1** and (−)-**1** on the one side and by the racemic diastereoisomer (±)-**2** on the other side was very similar and can be described as floral, green, fresh, privet, and reminiscent of dimethylbenzyl alcohol. The three compounds differed, however, in the intensity of odour. The relation of the threshold values of (+)-**1**/(−)-**1**/(±)-**2** was determined by use of an olfactometer [21] and was equal to 4:8.5:1[6]).

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[4]) See, however, [15] for the $LiAlH_4$ reduction of epoxymethylmyrtanol, [16] for the hydride reduction of allyl-alcohol epoxides with two secondary centers, and [17] for nucleophilic openings of chiral 2,3-epoxy alcohols.

[5]) We synthesized this isomer *via* a different route.

[6]) These relatively small differences are sufficient to differentiate the compounds in a blind test.

In conclusion, we described a highly diastereo- and enantioselective seven-step synthesis of the natural [7] (4*R*,8*S*)-4-epi-β-bisabolol ((−)-**1**) and its enantiomer (4*S*,8*R*)-8-epi-β-bisabolol ((+)-**1**).

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Experimental Part

General. See [22]. $[\alpha]_D$: *Perkin-Elmer*, Model *141*.

4-Methylcyclohexa-1,4-diene-1-carboxylic Acid (**3**) (*cf.* [12]). A soln. of propynoic acid (38 g, 0.45 mol) and isoprene (40 g, 0.58 mol) in toluene (100 ml) was heated in an autoclave to 140°. When this temp. was reached, the exothermic reaction raised the temp. to 185–190° without any external heating within 5 min (*ca.* 12 atm.). After *ca.* 5–10 min, the reaction eased off, and the mixture was slowly cooled down over night. Filtration of the mixture yielded 39 g (50%) of **3** with m.p. 186°. The mother liquor was evaporated and the remaining thick oil (30 g) crystallized from hexane at −20° to give 10.5 g of crystals. M.p. 102–115°. This material consisted of 80% of the 5-methyl isomer of **3** and 20% of **3** (by NMR: 5.5–5.46 (*m*, H−C(5) of **3**); 5.39–5.35 (*m*, H−C(4) of isomer).

Methyl 4-Methylcyclohexa-1,4-dien-1-yl Ketone (**4**). A soln. of **3** (60 g, 0.43 mol) in Et_2O (500 ml) was slowly treated with 1.6M MeLi (1 mol) in Et_2O at −30° and not above 0° for 1.5 h. Then, the mixture was poured into 2 l of ice-cold 1N AcOH and extracted with pentane, the pentane phase dried and evaporated, and the oily residue (66 g) distilled at 30–40°/0.5 Torr: 53 g of oil. The residue of the distillation solidified: *ca.* 5 g of **3**. The distilled oil was taken up in hexane (250 ml) and crystallized at −10°: 30.5 g of highly pure **4**, low-melting (m.p. *ca.* 10°) crystals. The mother liquor (25 g) was chromatographed on silica gel with hexane/Et_2O 9:1: 16 g of **4** (*ca.* 95% pure) and 5.4 g of the corresponding tertiary alcohol. Total yield of **4**: 46 g (77%). NMR: 6.9–6.88 (*m*, H−C(2)); 5.5–5.47 (*m*, H−C(5)); 2.87–2.83 (*m*, CH_2(3), CH_2(6)); 2.32 (*s*, CH_3CO); 1.70 (*s*, CH_3−C(4)).

α,4-Dimethylcyclohexa-1,4-diene-1-methanol (**5**). To a soln. of **4** (60 g, 0.44 mol) in MeOH (600 ml), $NaBH_4$ (10 g) was added in portions at 25–35° within *ca.* 40 min. After usual workup, the crude oil (63 g) was bulb-to-bulb distilled at *ca.* 40°/0.1 Torr: 56.7 g (93%) of **5**, purity > 96%. ^{1}H-NMR: 5.72–5.68, 5.48–5.44 (*m*, H−C(2), H−C(5)); 4.27–4.20 (*m*, H−C(α)); 2.74–2.57 (*m*, CH_2(3), CH_2(6)); 1.70–1.67 (*m*, CH_3−C(4)); 1.28 (*d*, CH_3−C(α)).

(αS,1S,6S)-α,4-Dimethyl-7-oxabicyclo[4.1.0]hept-3-ene-1-methanol ((−)-**6**). To the soln. of (±)-**5** (28 g, 0.2 mol) and (+)-diisopropyl L-tartrate (5.9 g, 25 mmol) in CH_2Cl_2 (80 ml) were added at −20°, activated and powdered molecular sieves 3 Å (10 g) and freshly distilled Ti(i-PrO)$_4$ (5.6 g, 6 ml, 20 mmol). The stirred mixture was cooled to −30° and treated dropwise with 3M (*t*-Bu)OOH in toluene (30 ml, 0.09 mol) and kept at −30° for 15 h. The mixture was worked up with the soln. of $FeSO_4$ (30 g) and citric acid (20 g) in H_2O (200 ml) at 0°. After drying and evaporation of the org. phase, 36 g of an oil were isolated. Chromatography on silica gel (*t*-BuOMe/hexane 2:1) yielded 18 g of starting material/tartrate and 12.3 g of product. Bulb-to-bulb distillation at *ca.* 50°/0.1 Torr furnished 11.3 g (37%) of (−)-**6**. $[\alpha]_D^{20} = -50.0$ (EtOH, $c = 1.0$). IR: 3420. ^{1}H-NMR: 5.24–5.19 (*m*, H−C(3)); 3.85–3.79 (*dq*, H−C(α)); 3.37–3.35 (*d*, OH); 2.52–2.32 (*m*, 5 H); 1.68–1.65 (*m*, CH_3−C(4)); 1.25 (*d*, CH_3−C(α)). MS: 154 (0.5, M^+), 136 (28), 121 (24), 111 (56), 93 (86), 81 (56), 67 (66), 45 (100).

The mixture starting material/tartrate (18 g) was dissolved in 300 ml of hexane and washed extensively with H_2O. Drying, evaporation, and bulb-to-bulb distillation yielded 14.1 g (50%) of (+)-**5**, 96% pure by GLC. $[\alpha]_D^{20} = +10.8$ (EtOH, $c = 1.0$), *ca.* 65% e.e.

(αR,1R,6R)-α,4-Dimethyl-7-oxabicyclo[4.1.0]hept-3-ene-1-methanol ((+)-**6**) was obtained as (−)-**6** from (±)-**5** (42 g, 0.3 mol), 0.13 equiv. of (−)-diisopropyl D-tartrate, and 0.1 equiv. of Ti(i-PrO)$_4$: 20.8 g (45%) of (+)-**6**. $[\alpha]_D^{20} = -53.0$ (EtOH, $c = 1.0$).

The remaining slower-reacting (−)-**5** was isolated in 38% yield (16 g): $[\alpha]_D^{20} = -9.0$ (EtOH, $c = 1.15$), *ca.* 60% e.e.

*Optical Purity of (+)- and (−)-***5**. To a soln. of (−)-**5** (12.8 g, 92 mmol; $[\alpha]_D^{20} = -9.0$ (EtOH, $c = 1.16$)) in pyridine (40 ml) and THF (20 ml), (−)-camphanoyl chloride (21.6 g, 0.1 mol) was slowly added at 0° within *ca.* 30 min (pyridinium hydrochloride precipitated). The mixture was stirred, until the temp. reached 20°, and worked up as usual (H_2O, Et_2O): 22 g (75%) of a crude product. A first crop of crystals (7.3 g, m.p. 76–78°) was obtained by crystallization from hexane. These crystals were recrystallized from hexane (*ca.* 3% Et_2O): 3.4 g of a camphanoate with m.p. 78–80°. $LiAlH_4$ reduction of this camphanoate produced, in 95% yield, (−)-**5**, b.p. 80°/0.5 Torr (bulb-to-bulb dist.), $[\alpha]_D^{20} = -15.2$ (EtOH, $c = 1.0$). GLC (β-cyclodextrin column) showed a 99:1 ratio, whereas in the NMR of the corresponding *Mosher* ester, no impurity could be detected.

(αS,1S)-1-Hydroxy-α,4-dimethylcyclohex-3-ene-1-methanol ((+)-7). The soln. of (−)-**6** (11 g, 71 mmol) in THF (20 ml) was slowly added to the slurry of $LiAlH_4$ (3 g, 79 mmol) in THF (50 ml) at ≤ 50°. After 30 min, the reduction was complete. Workup with $NaOH/H_2O$ as usual and bulb-to-bulb distillation at 70°/0.05 Torr yielded 10.8 g (97%) of (+)-7. $[\alpha]_D^{20} = +38.6$ (EtOH, $c = 1.16$). IR (film): 3400. ^{1}H-NMR: 5.32–5.28 (*m*, H–C(3)); 3.70–3.62 (*dq*, H–C(α)); 2.73 (*d*, OH–C(α)); 2.41 (*s*, OH–C(1)); 2.29–1.89 (*m*, 4 H); 1.77–1.68 (*m*, 1 H); 1.69–1.67 (*m*, CH_3–C(4)); 1.58–1.49 (*ddd*, 1 H); 1.18 (*d*, CH_3–C(α)). MS: 156 (1, M^+), 138 (22), 111 (100), 93 (70), 77 (18), 67 (30), 55 (33).

(αR,1R)-1-Hydroxy-α,4-dimethylcyclohex-3-ene-1-methanol ((−)-7). As for (+)-**7**, (+)-**6** (20 g, 0.13 mol) was reduced: 20 g (99%) of (−)-7. $[\alpha]_D^{20} = -39.44$ (EtOH, $c = 1.07$).

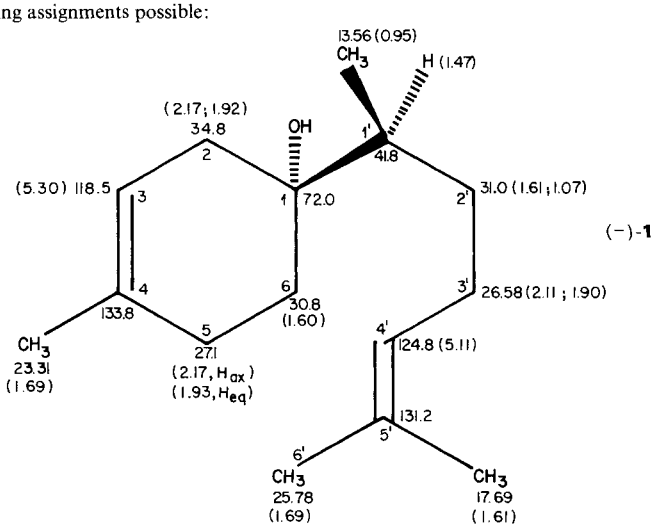
(2S,3R)-2,6-Dimethyl-1-oxaspiro[2.5]oct-5-ene ((−)-**8**). To the soln. of (−)-**7** (18 g, 0.11 mol) in pyridine (80 ml) methanesulfonyl chloride (10.5 ml, 0.13 mol) was slowly added (temp. rise to *ca.* 40°). After 1 h further stirring, workup with H_2O and *t*-BuOMe furnished 30 g of crude methanesulfonate. The crude methanesulfonate was added to the soln. of KOH (18 g) in MeOH (400 ml) at 40° and stirred at 60° for 10 min. Usual workup yielded, after bulb-to-bulb distillation at 50–60°/10 Torr, 11.9 g (78%) of (−)-**8**. $[\alpha]_D^{20} = -47$ (EtOH, $c = 1.3$). ^{1}H-NMR: 5.41–5.37 (*m*, H–C(5)); 2.92 (*q*, $J = 5.5$, H–C(2)); 2.32–2.18 (*m* 2 H); 2.11–1.97 (*m*, 2 H); 1.72–1.70 (*m*, CH_3–C(6)); 1.78–1.70 (*m*, H–C(8)); 1.64–1.56 (*m*, H–C(8)); 1.29 (*d*, $J = 5.0$, CH_3–C(2)). MS: 138 (45, M^+), 110 (30), 95 (34), 79 (100), 67 (18), 39 (25).

(2R,3S)-2,6-Dimethyl-1-oxaspiro[2.5]oct-5-ene ((+)-**8**). As for (−)-**8**, with 10 g (64 mmol) of (+)-**7**: 7 g (79%) of (+)-**8**. $[\alpha]_D^{20} = +45$ (EtOH, $c = 1.3$).

(+)-(1S)-1-[(1R)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-3-en-1-ol ((+)-**1**). To the soln. of $CuCl_2$ (670 mg, 5 mmol) and LiCl (420 mg, 10 mmol) in THF (50 ml) at −30°, the soln. of (+)-**8** (5,6 g, 40 mmol) in THF (10 ml) and 100 ml of 1M *Grignard* reagent in THF, prepared from 5-bromo-2-methylpent-2-ene, were added successively. The mixture was stirred for 3 h at −15° (less than 10% of (+)-**8** left). Usual workup, chromatography (silica gel; removal of a minor hydrocarbon) of the oily residue (10.2 g), and bulb-to-bulb distillation afforded 7.1 g (80%) of (+)-**1**. GLC (*SE-54*, 25 m): > 99,9%. $[\alpha]_D^{20} = +59.7$ (EtOH, $c = 1.0$), $[\alpha]_D^{20} = +66.6$ ($CHCl_3$, $c = 0.5$).

(−)-(1R)-1-[(1S)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-3-en-1-ol ((−)-**1**) was isolated in 90% (6.1 g) yield from 4.2 g (30 mmol) of (−)-**8**. GLC (*SE-54*, 25 m): > 99.9%. $[\alpha]_D^{20} = -61.7$ (EtOH, $c = 1.7$), $[\alpha]_D^{20} = -70$ ($CHCl_3$, $c = 0.5$). ^{1}H-NMR: 5.31–5.275 (*m*, H–C(3)); 5.14–5.08 (*m*, H–C(4′)); 2.2–2.06 (*m*, 3 H); 1.98–1.85 (*m*, 3 H); 1.70–1.67 (*m*, CH_3–C(5′), CH_3(6′)); 1.66–1.57 (*m*, 3 H); 1.62–1.60 (*m*, CH_3–C(4)); 1.51 (*s*, OH); 1.475 (*ddq*, $J = 10, 3$, H–C(1′)); 1.07 (*ddd*, H–C(2′)); 0.95 (*d*, $J = 7$, CH_3–C(1′)). ^{13}C-NMR: 133.8 (*s*, C(4)); 131.25 (*s*, C(5′)); 124.84 (*d*, C(4′)); 118.56 (*d*, C(3)); 72.04 (*s*, C(1)); 41.85 (*d*, C(1′)); 34.81 (*t*, C(2)); 30.99 (*t*, C(2′)); 30.81 (*t*, C(6)); 27.09 (*t*, C(5)); 26.58 (*t*, C(3′)); 25.73 (*q*, C(6′)); 23.31 (*q*, CH_3–C(4)); 17.68 (*q*, CH_3–C(5′)); 13.55 (*q*, CH_3–C(1′)). MS: 228 (0, M^+), 204 (40), 161 (4), 154 (2), 140 (9), 121 (40), 111 (50), 93 (66), 82 (100), 72 (32), 69 (50), 55 (38), 41 (76).

The combination of an inadequate 2D ^{13}C-NMR spectrum and a heteronuclear ^{13}C,^{1}H correlation of (−)-**1** made the following assignments possible:



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