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Enzyme-mediated preparation of enantioenriched forms of *trans*- and *cis*-*p*-menthan-1,8-dien-5-ol

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Abstract—The synthesis of the *trans*-*p*-menthan-5-ol (±)-**1** was carried out by Diels–Alder cycloaddition of 3-keto-1-butenyl-acetate **3** with isoprene followed by Wittig methylenation. PS lipase resolution of the alcohol afforded acetate (−)-**5** with 98% ee, which was hydrolysed to give (−)-**1**. Alternatively, enzymatic hydrolysis of a keto ester followed by Wittig methylenation and hydrolysis afforded the same alcohol with an ee of 86%. The *cis*-*p*-menthan-5-ol (−)-**2** was obtained by Swern oxidation of (−)-**1**, followed by diastereoselective reduction with L-Selectride without lost of enantiomeric excess.

1. Introduction

Recently, we have described a new preparation of several monoterpenic alcohols in their enantiomerically enriched forms. Our synthetic approach consisted of the enzyme-catalysed resolution of racemic *p*-menthane alcohols leading to the access of each enantiomer with good to excellent ee.[1] In continuation of this previous work, we herein report the selective synthesis of the *trans*- and *cis*-*p*-mentha-1,8-dien-5-ols, that is, (4*S*,5*R*)-**1** and (4*S*,5*S*)-**2** (Fig. 1).[2]

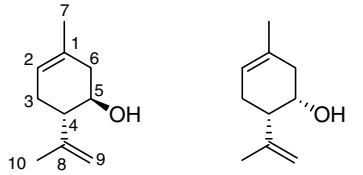

Figure 1. *trans*- and *cis*-*p*-menthan-1,8-5-ol with the *p*-menthane numbering.

In spite of its natural occurrence[3] and relatively simple structure, there has been only one selective synthesis of these monoterpenes reported in the literature. Builarm et al. described a synthetic route consisting of a three step sequence starting from *trans*-verbenol leading to the *trans*-*p*-mentha-1,8-dien-5-ol (4*S*,5*R*)-**1** in an overall yield of 30% with a discrete ee = 78%, whereas, the cis-isomer (4*S*,5*S*)-**2** was obtained with an identical ee by oxidation of the *trans*-alcohol to the corresponding ketone followed by diastereoselective reduction to give the *cis*-alcohol.[4]

2. Results and discussion

The preparation of (±)-**1** is outlined in Scheme 1. Our strategy is based on the Diels–Alder cycloaddition of the easily available dienophile 3-keto-1-butenyl-acetate,[5] that is, **3** (*E*/*Z*, 9:1), to the isoprene to give the *trans*-keto ester (±)-**4**. This reaction, which was tested using different Lewis[6a] acids and temperatures, always gave a complex mixture, mainly composed of polymeric side-products and (±)-**4** with excellent diastereoselectivity. After optimisation studies, which are summarised in Table 1, the best results were obtained using $BF_3{\cdot}Et_2O$ at −40 °C. Attempts to carry out the thermal cycloaddition gave (±)-**4** in a modest yield.[6b] The expected trans-relative configuration of **4** was unambiguously confirmed by analysis of the NMR coupling constants of protons H–C(6) and H–C(1). Indeed, the presence of two large ($J \approx 9$ and 10 Hz) and just one small

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Table 1. Cycloaddition of **3** with isoprene in CH_2Cl_2

Entry	Catalyst	Temperature (°C)	Time	Ratio[c]	Yield (%)
1	BF_3	−78	16 h	99:1	28[a]
2	BF_3	−30	8 h	99:2	43[a]
3	$SnCl_4$	rt	8 h	94:6	16[b]
4	$ZnCl_2$	rt	3 d	94:6	10[b]
5	$LiClO_4$	rt	10 d	95:5	3[b]
6		45	2 d	82:18	10[b]

[a] Yield of isolated product after crystallisation.
[b] Yield determined by GC–MS.
[c] Ratio of diastereoisomers determined by GC–MS.

($J \approx 6$ Hz) coupling constants for both protons is typical of a diaxial conformation.

Since, the keto-ester eliminates easily under either basic or acid conditions, the reaction was quenched with a 7.2 pH phosphate buffer. The purification was carried out by simple filtration on a pad of silica gel, followed by crystallisation in hexane to give pure (±)-**4**.

Finally, Wittig methylenation of (±)-**4**, followed by hydrolysis in MeOH with K_2CO_3 gave alcohol (±)-**1** in an overall yield of 70%.

Since, in our previous investigation on enzymatic resolution of monoterpenic alcohols, PS lipase proved to be the best enzyme, either in terms of efficiency or in terms of enantioselectivity, the resolution of (±)-**1** was carried out under similar conditions using TBME as a solvent and vinyl acetate, as an acyl donor.[1] Thus, after 2 weeks, corresponding to a conversion of 42% (detected by GC), the acetate (4*S*,5*R*)-**5** (ee 98%, by chiral GC) and the residual alcohol (4*R*,5*S*)-**1** {$[\alpha]_D = +43.1$, ee = 81%, by chiral GC of the corresponding acetate (4*R*,5*S*)-**5**} were separated by column chromatography. Hydrolysis of (*R*,*S*)-**5** with K_2CO_3 in MeOH gave (4*S*,5*R*)-**1** {$[\alpha]_D = -53.0$, vs lit.[4] ($[\alpha]_D = -41$, ee = 78%}.

Alternatively, a second strategy was based on the enzymatic hydrolysis of the racemic keto-ester. Thus, a solution of (±)-**4** in a mixture of a THF/7.2 pH phosphate buffer (9:1) was subjected to enzymatic hydrolysis catalysed by PS lipase. After 3 days, corresponding to a conversion of 48%, the remaining acetate (1*S*,6*S*)-**4** was separated from the hydrolysed alcohol (1*R*,6*R*)-**6**.[7] It is noteworthy, that after the separation, the keto-alcohol resulted in a solid, whereas, any attempt of recrystallising the resolved keto-ester failed, this is likely due to a low enantiomeric imbalance. Indeed, the corresponding acetate (4*S*,5*R*)-**5**, which was obtained by acetylation of (1*R*,6*R*)-**6** in pyridine with Ac_2O followed by Wittig methylenation, shown a good ee of 86%, whereas, the acetate (4*R*,5*S*)-**5** obtained by methylenation of the remaining acetate (1*S*,6*S*)-**4** showed a modest ee of 70%.

The resolution of racemic alcohol (±)-**6** was not possible, since any attempt at removing the acetate group, either by hydrolysis (NaOH, K_2CO_3), or by transesterification with MeONa in MeOH always gave partial elimination or isomerisation.

Finally, the *cis*-*p*-mentha-1,8-dien-5-ol (1*S*,5*S*)-**2** was obtained following the same synthetic approach adopted by Builarm. Thus, Swern oxidation of alcohol (4*S*,5*R*)-**1**, followed by reduction of the ketone (*S*)-**7** with L-Selectride[8] gave (4*S*,5*S*)-**2** {$[\alpha]_D = -5.4$, vs lit.[4] $[\alpha]_D = -4.1$} in an overall yield of 33%, without any loss of enantiomeric purity (Scheme 1).

3. Conclusion

We have succeeded in the preparation of (4*S*,5*R*)-**1** and (4*S*,5*S*)-**2** by simplifying the synthesis and improving significantly the ee of the previous reported synthesis. The PS-lipase catalysed acetylation gave better ee compared to the enzyme hydrolysis of its precursor. Finally, it should be noted that these kinds of synthons might be the precursors for an alternative synthesis of several natural products, such as all the Δ^8-tetrahydro-cannabinol or cannabidiol derivatives.[9,10]

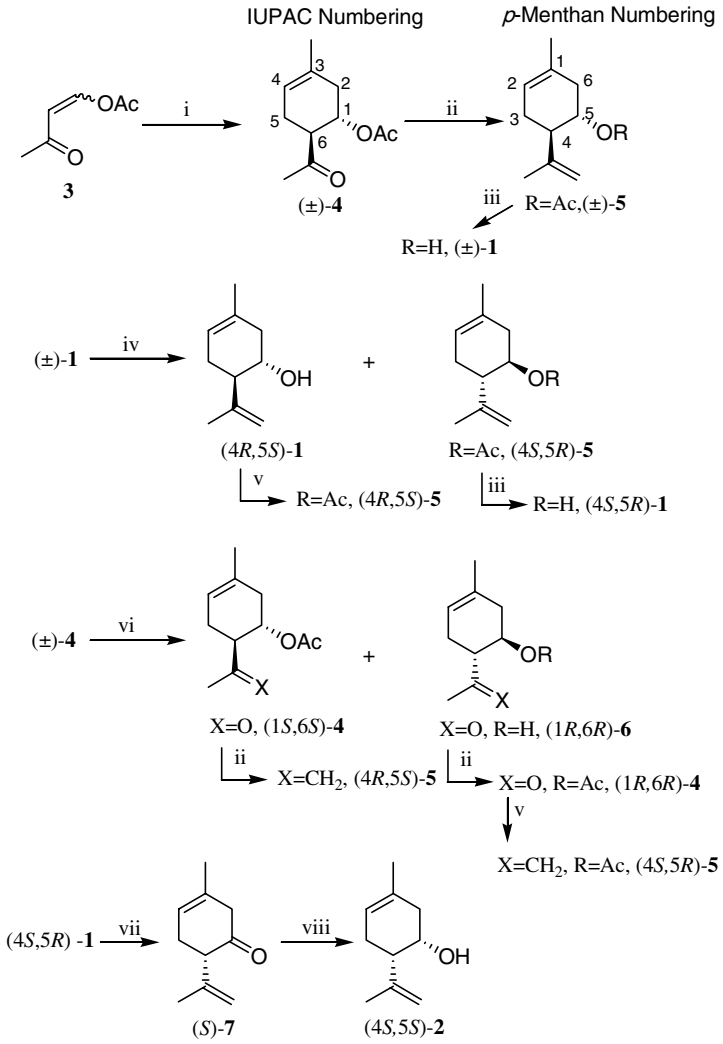
4. Experimental

4.1. General methods

All solvents and reagents were purchased by the suppliers and used without further purification. *Burkholderia cepacia* lipase (Lipase PS, Amano Pharmaceuticals Co., Japan) was employed in this work. GC/MS analyses were performed on an HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 mm). The following temperature program was employed: 60 °C (1 min)/6 °C/min/150 °C (1 min)/12 °C/min/280 °C (5 min). Chiral GC: DANI-HT-86.19 gas chromatograph; enantiomer excess determined on a Chirasil DEX-CB column (25 m × 0.25 mm; Chromopack) with the following temperature program: 50 °C (3 min)–0.5 °C/min–70–20 °C/min–180 °C. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions, on Bruker spectrometers; DMX (400 ^{1}H MHz). The chemical shift scale was based on internal TMS. *J* values are in hertz. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates.

4.2. Synthesis of (±)-*trans*-*p*-menthan-1,8-dien-5-ol (±)-1

4.2.1. (1*RS*,6*RS*)-6-Acetyl-3-methylacetate-cyclohex-3-enyl (±)-4. To a solution of **3** (40 g, 0.31 mol) in dry CH_2Cl_2 (200 mL) and isoprene at −40 °C was added dropwise $BF_3{\cdot}Et_2O$ (86 mL, 0.68 mol) under nitrogen. After the addition was complete, the stirring was continued until the complete conversion of **3**, usually after 8–10 h. The reaction mixture was then quenched with a phosphate buffer (7.2 pH) and extracted with Et_2O (2 × 0.4 L). The organic solvent was removed under reduced vacuum and the crude mixture decanted in methanol in order to remove the polymeric by-products. After evaporation of MeOH the crude was purified on a silica gel pad and crystallised in hexane at −20 °C to obtain pure (±)-**4** as a white spongy solid, which was



Scheme 1. Reagents and conditions: (i) 1 equiv $BF_3{\cdot}Et_2O$, −40 °C, isoprene/CH_2Cl_2 (1:2); (ii) $PhH_3P{=}CH_2$, THF; 0 °C; (iii) K_2CO_3, MeOH; (iv) PS Lipase, vinyl acetate, *t*-butylmethylether; (v) Ac_2O pyridine; (vi) PS-lipase, phosphate buffer/THF; (vii) DMSO, $(COCl)_2$, CH_2Cl_2, −60 °C, NEt_3, −60 °C to rt; (viii) L-Selectride, THF.

washed with cold hexane (26.1 g, 43%); ^{1}H NMR, $\delta = 5.31$, (m, 1H, H–C(4)), 5.18 (ddd, $J = 10.0$, 8.5, 5.8 Hz, 1H, H–C(1)), 2.85 (dt, $J = 10$, 5.9 Hz, 1H, H–C(6)), 2.47 (dd, $J = 17.2$, 5.8 Hz, 1H, H′–C(2), 2.10–2.25 (m, 6H, H″–C(2)+H–C(5)+Me), 2.01 (s, 3H, Me), 1.65 (s, 3H, Me–C(3)); ^{13}C NMR, $\delta = 209.1$, 170.0, 131.5, 118.3, 70.8, 50.9, 35.1, 29.0, 27.0, 22.7, 20.9; GC/MS: $t_R = 14.71$ min; *m*/*z*: 136 (M^+−60, 20), 121(40), 93(100).

4.2.2. (±)-*trans*-*p*-Menthan-1,8-dien-5-acetate (±)-5. To an ice cooled and well stirred suspension of $(Ph_3PMe)I$ (52 g, 0.13 mol) in THF (300 mL) was added dropwise BuLi (13 mL, 10 M). After 30 min was added a solution of (±)-**4** (19.6 g, 0.1 mol) in THF (40 mL). After 3 h the reaction mixture was quenched in cool water (200 mL). The quenched mixture was extracted with Et_2O (2 × 200 mL), and the combined organic phase was washed successively with satd NH_4Cl and with brine, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was dissolved in hexane/Et_2O 3:1, and the triphenyloxide eliminated by crystallisation (ice-bath cooling). The liquid phase was evaporated and the residue was purified by column chromatography using hexane/AcOEt (9:1) affording (±)-**5** as a colorless liquid (15.1 g, 78%). ^{1}H NMR, $\delta = 5.34$, (m, 1H, H–C(2)), 5.05 (ddd, $J = 11.0$, 8.9, 5.9 Hz, 1H, H–C(5)), 4.75 (m, 2H, CH_2–C(8)), 2.32–2.45 (m, 2H, H–C(6), 2.10–2.15 (m, 2H, H–C(4)+H–C(H3)), 1.96–2.08 (m, 4H, H–C(3)+AcO), 1.65–1.72 (m, 6H, C(8)–Me+C(1)–Me); ^{13}C NMR, $\delta = 171.2$, 146.2, 120.63, 112.7, 72.0, 46.8, 36.6, 32.2, 30.8, 23.5, 20.1; GC/MS: $t_R =$ 12.55 min; *m*/*z*: 134 (M^+−60, 70), 119(100).

4.2.3. (±)-*trans*-*p*-Menthan-1,8-dien-5-ol (±)-1. To a suspension of K_2CO_3 (21.3 g, 154.6 mmol) in MeOH (150 mL) was added (±)-**5** (15.0 g, 77.3 mmol) and after 2 h, the mixture was concentrated under reduced pressure. The residue was then dissolved in Et_2O (50 mL) and washed with brine (2 × 100 mL), the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled to give pure (±)-**1** as a colourless liquid (11.8 g, 90%). ^{1}H NMR, $\delta = 5.34$, (m, 1H, H–C(2)), 4.96 (m, 1H, H′–C(10)), 4.90 (s, 1H, H″–

C(10)), 3.80 (dt, $J = 9.6$, 5.8 Hz, 1H, H–C(5)), 2.35 (dd, $J = 16.3$, 5.3 Hz, 1H, H′–C(6))), 2.19–1.95 (m, 4H, H′–C(4)+H″–C(6)+H–C(3)), 1.75 (s, 3H, Me), 1.68 (s, 3H, Me); ^{13}C NMR, $\delta = 146.0$, 131.8, 119.8, 113.3, 68.2, 50.0, 38.7, 30.2, 23.0, 19.3; GC/MS: $t_R = 9.60$ min; m/z: 152 (M^+, 5), 137(90), 84(100).

4.3. Lipase resolutions

4.3.1. Enzymatic acetylation of (±)-*trans-p*-menthan-1,8-dien-5-ol (±)-1: (4*R*,5*S*)-*trans-p*-menthan-1,8-dien-5-ol (4*R*,5*S*)-1 and (4*R*,5*S*)-*trans-p*-menthan-1,8-dien-5-acetate (4*S*,5*R*)-5. A mixture of (±)-**1** (10.0 g, 65.7 mmol), PS lipase (7 g), vinyl acetate (5 mL) and ^{t}BuOMe (70 mL) was stirred at rt until the formation of the acetate (monitored by GC) reached a conversion of around 43% (2 weeks). The reaction was stopped by filtration of enzyme and evaporation of the solvent at reduced pressure. Column chromatography of the residue in gradient of eluent (hexane/AcOEt , 95:5–80:20) afforded in order: the acetate (4*S*,5*R*)-**5** (5.2 g, 41%); $[\alpha]_D = -29.3$ (c 1.1, $CHCl_3$); ee 98%, by chiral GC, $t_R = 36.4$ min; and the alcohol (4*R*,5*S*)-**1** (5.2 g, 52%), $[\alpha]_D = +43.1$ (c 0.9, $CHCl_3$. Hydrolysis of (4*S*,5*R*)-**5** (5.2 g, 26.8 mmol) using the above described procedure gave pure (4*S*,5*R*)-**1** (3.9 g, 95%); $[\alpha]_D = -53.0$ (c 1.0, $CHCl_3$), lit. $[\alpha]_D = -41$. Acetylation of alcohol (4*R*,5*S*)-**1** (5.2 g, 34.2 mmol) in pyridine (10 mL) with Ac_2O (5 mL) gave, after usual work-up and bulb–bulb distillation, (4*R*,5*S*)-**5** (5.6 g, 85%); $[\alpha]_D = +24.1$ (c 1.3, $CHCl_3$), ee 81%, by chiral GC: $t_R = 38.4$ min.

4.3.2. Enzymatic hydrolysis of (1*RS*,6*RS*)-6-acetyl-3-methylacetate-cyclohex-3-enyl (±)-4: (1*S*,6*S*)-6-acetyl-3-methylacetate-cyclohex-3-enyl (1*S*,6*S*)-4 and 1-((1*R*,6*R*)-6-hydroxy-4-methyl-cyclohex-3-enyl)ethanone (1*R*,6*R*)-6. A mixture of (±)-**4** (10 g, 51 mmol), phosphate buffer (7.2 pH)/THF (200 mL, 9:1), and PS lipase (4 g) was stirred at rt until the formation of alcohol reached a conversion around 50% (3 days). Then, the reaction was stopped by filtration through a pad of Celite, and the liquid was extracted with Et_2O (2×100 mL), the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated at reduced pressure. Column chromatography of the residue in gradient of eluent (hexane/AcOEt, 95:5–80:20) afforded in order: the keto-ester (1*S*,6*S*)-**4** (4.4 g, 45%) as a pale yellow oil; $[\alpha]_D = +107.3$ (c 0.9, $CHCl_3$); and the alcohol (1*R*,6*R*)-**6** (3.3 g, 42%) as white solid; $[\alpha]_D = -158.4$ (c 1.0, $CHCl_3$); ^{1}H NMR, $\delta = 5.33$, (m, 1H, H–C(4)), 4.11 (br q, 1H, H–C(1)), 2.80 (s, 1H, OH), 2.62 (ddd, $J = 10$, 5.9 Hz, 1H, H–C(6)), 2.42 (m, 1H, H′–C(2)), 2.42 (dd, $J = 17.2$, 5.8 Hz, 1H, H″–C(2)), 2.21 (s, 3H, Me–CO), 1.90–2.12 (m, 2H, H–C(5), 1.69 (s, 3H, Me–C(3));^{13}C NMR, $\delta = 212.4$, 132.6, 118.2, 67.9, 54.2, 37.8, 29.1, 27.9, 22.9; GC/MS: t_R=11.26 min; m/z: 154(M^+, 30), 136(50), 121(40), 93(100).

4.4. Determination of ee of each enantiomer of 5

4.4.1. (1*R*,6*R*)-6-Acetyl-3-methylacetate-cyclohex-3-enyl (1*R*,6*R*)-4. To a solution of Ac_2O (5 mL) in pyridine/CH_2Cl_2 (15 mL, 2:1) was added (1*R*,6*R*)-**6** (3.0 g, 19.5 mmol). After 3 h the reaction mixture was concentrated at reduced pressure, and the residue purified by column chromatography using hexane/AcOEt (9:1) followed by bulb-to-bulb distillation afforded (1*R*,6*R*)-**4** (3.4 g, 90%) as colourless oil; $[\alpha]_D = -131.8$ (c 1.0, $CHCl_3$).

4.4.2. (4*R*,5*S*)-*trans-p*-Menthan-1,8-dien-5-acetate (4*R*,5*S*)-5 and (4*S*,5*R*)-*trans-p*-menthan-1,8-dien-5-acetate (4*S*,5*R*)-5. A sample of both enantiomers of **4**, obtained from enzymatic hydrolysis of **4**, was methylenated following the same procedure adopted above.

Selected data of (4*R*,5*S*)-**5**: $[\alpha]_D = +21.1$ (c 1.0, $CHCl_3$); ee = 70% by chiral GC.

Selected data of (4*S*,5*R*)-**5**: $[\alpha]_D = -25.3$ (c 1.1, $CHCl_3$); ee = 86% by chiral GC.

4.5. Synthesis of (4*S*,5*S*)-*cis-p*-menthan-1,8-dien-5-ol (4*S*,5*S*)-2

4.5.1. (*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-enone (*S*)-7. To a solution of $(COCl)_2$ (2.2 g, 17.2 mmol) in CH_2Cl_2 (40 mL) under a nitrogen atmosphere and at −60 °C was added DMSO (2.0 g, 26.4 mmol). After 10 min was added quickly a solution of (4*S*,5*R*)-**1** (2.0 g, 13.2 mmol) in CH_2Cl_2 (10 mL). After 30 min, the reaction was treated with NEt_3 (8.0 g, 79.9 mmol), and left to reach the rt. Then, the reaction mixture was quenched with H_2O (20 mL) and washed with brine (2×30 mL). The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by column chromatography using hexane/EtOAc gave the ketone (*S*)-**7** (1.4 g, 54%); $[\alpha]_D = -127.2$ (c 1.2, $CHCl_3$), lit. $[\alpha]_D = -97$. ^{1}H NMR, $\delta = 5.62$, (1H, m, H–C(4)), 4.96 (s, 1H, H′-C(9)), 4.83 (s, 1H, H″-C(9)), 3.18 (t, $J = 7.8$ Hz, 1H, H–C(6)), 2.40–2.89 (m, 2H+2H, H–C(2)+H–C(5)), 1.76 (s, 3H, Me), 1.71 (br q, 3H, Me); ^{13}C NMR, $\delta = 208.9$, 142.7, 132.1, 20.2, 113.0, 55.0, 44.7, 30.2, 22.6, 21.3; GC/MS: $t_R = 8.45$ min; m/z: 150 (M^+, 50), 135(20), 94(100).

4.5.2. (4*S*,5*S*)-*cis-p*-Menthan-1,8-dien-5-ol (4*S*,5*S*)-2. To a solution of (*S*)-**7** (1.0 g, 6.7 mmol) in THF (20 mL), under a nitrogen atmosphere and at 0 °C, was added a 1 M solution of lithium tri-*sec*-butylborohydride (10 mL, 10 mmol). After complete reduction of the ketone the reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL) and washed with Et_2O (3×20 mL). The combined organic phase was washed with a solution of HCl (0.1 M, 2×10 mL), with a saturated solution of Na_2CO_3 (1×10 mL) and finally with brine (1×10 mL). The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by column chromatography using hexane/EtOAc (8:2) gave the alcohol (4*S*,5*S*)-**2** (0.6 g, 62%); $[\alpha]_D = -5.4$ (c 1.0, $CHCl_3$), lit. $[\alpha]_D = -5.3$. ^{1}H NMR, $\delta = 5.45$, (m, 1H, H–C(2)), 4.92 (s, 1H, H′–C(10)), 4.82 (s, 1H, H″–C(10)), 4.10 (m, 1H, H–C(5)), 1.95–2.3 (m, 5H, H–C(3)+H–C(4)+H–C(6)), 1.79 (s, 3H, Me), 1.65 (s, 3H, Me); ^{13}C NMR, $\delta = 146.4$, 130.0, 120.1, 110.8, 66.1, 44.2, 38.2, 24.1,

23.4, 22.7; GC/MS: $t_R = 9.60$ min; m/z: 152 (M^+, 5), 137(90), 84(100).

Acknowledgements

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