Grob-type fragmentation of a carvone derived β-hydroxymesylate: application to the synthesis of chiral lavandulol derivatives

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Abstract—Grob-type fragmentation of the carvone derived diol-monosulphonate **5** has been utilised for the enantioselective synthesis of various lavandulol derivatives

1. Introduction

Although the cyclic template of the monoterpene carvone has been extensively utilised as a chiral-pool material for the asymmetric synthesis of diverse cyclic structures of interest, its application in the synthesis of acyclic chiral molecules is somewhat less documented.[1] During the course of our studies[2] towards the construction of taxoids from carvone, we were attracted to the possibility of developing new routes to some acyclic chiral molecules of interest from carvone using suitable ring-opening protocol. Herein, we describe our efforts towards the synthesis of various chiral lavandulol derivatives from carvone. Our strategy relied on the identification of the stereogenic center at C-5 of carvone as identical to that of lavandulol at C-2 and some restructuring plans for the synthesis of various lavandulol derivatives could also be envisioned (Fig. 1).

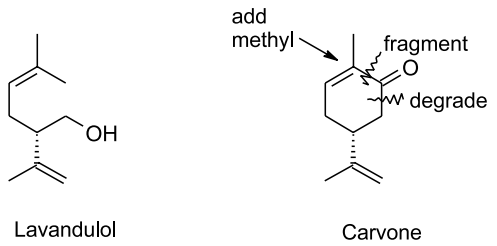

Figure 1. Structural correlation of lavandulol with carvone.

Keywords: Fragmentation; Carvone; Lavandulol; Enatioselective.

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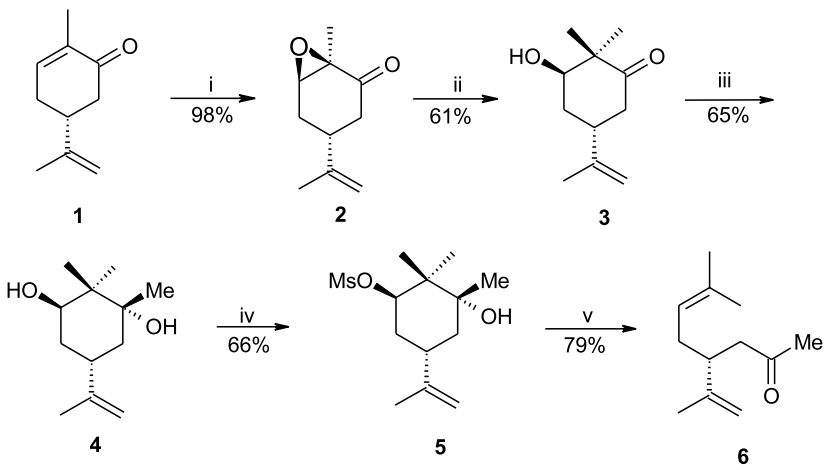
2. Results and discussion

Our synthetic approach commenced from the cheaper, more abundant *R*(−)-carvone (**1**) which was readily elaborated to the hydroxyketone **3** via a two step sequence involving reductive methylation of the derived epoxyketone **2** as described previously.[3] In line with our earlier observation,[2] addition of methylmagnesium iodide to **3** proceeded with high diastereoselectivity and the diol **4** was obtained in good yield after removal of the minor isomer (5%). Selective mesylation of the secondary hydroxy group in the diol **4** could easily be accomplished using conventional conditions to yield the hydroxymesylate **5** in good yield (Scheme 1).

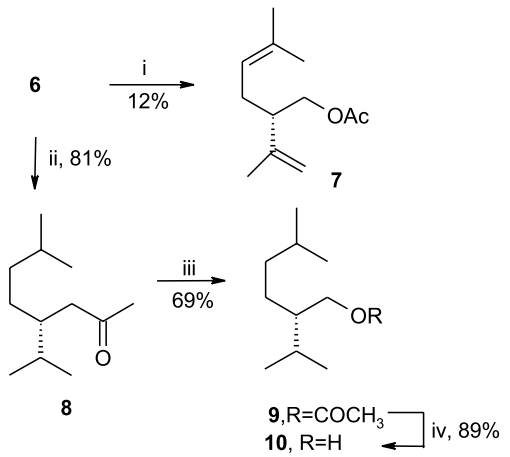
The Grob-type fragmentation of 1,3-diolmonosulphonates has evolved[4] into an outstanding piece and its utility in the construction of functionalised alkenes with defined regio- and/or stereospecificity has rendered it a valuable tool in organic synthesis. Recently an elegant example of this reaction, for the synthesis of some musk compounds, has been reported.[5] We considered application of this type of fragmentation of the hydroxymesylate **5** to unravel the framework of the lavandulyl system. Pleasingly, the hydroxymesylate **5** underwent smooth conversion in refluxing tetrahydrofuran in the presence of sodium hydride to the unsaturated ketone **6** which was obtained as a pleasant smelling colourless liquid.

The ketone **6** contains most of the structural features of the important irregular mono-terpene alcohol lavandulol, therefore, a further degradation to lavandulol[6] was then considered. Although several possibilities exist for this seemingly simple transformation, we argued that a successful Bayer–Villiger oxidation[7] would convert the ketone **6**



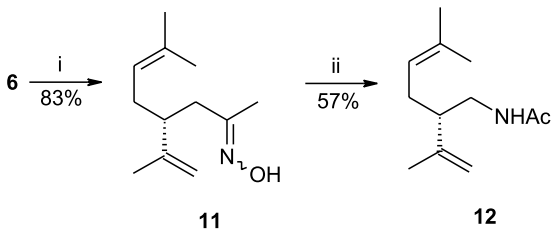
Scheme 1. Reagents and conditions: (i) H_2O_2, NaOH, 0 °C, 4 h, 98%; (ii) Li, NH_3, MeI, −33 °C to room temperature, 3 h, 61%; (iii) MeMgI, 0 °C to room temperature, 12 h, 65%; (iv) MsCl, pyridine, 0 °C to room temperature, 8 h, 66%; (v) NaH, THF, reflux, 8 h, 79%.

into lavandulol acetate. We were aware of the possibility of competing oxidation of the two somewhat activated double bonds present in the molecule, but ample literature precedence in analogous cyclic substrates prompted us to try some of these fruitful conditions. In all of the experiments with *meta*-chloroperbenzoic acid (using sodium bicarbonate, *para*-toluenesulphonic acid, trifluoroacetic acid, etc. as additives) or hydrogen peroxide (in conjunction with acetic or trifluoroacetic acid) epoxidation of the C_6–C_7 double bond was the major phenomenon observed, while from basic conditions (H_2O_2/NaOH) the starting material was recovered unchanged, even after prolonged heating. Bis-trimethylsilyl peroxide has been reported[8] to carry-out Bayer–Villiger oxidation of unsaturated ketones but moderate yields have been recorded in most cases. This reagent in conjunction with $SnCl_4$ did indeed afforded lavandulol acetate, but in poor yield (Scheme 2). On the other-hand, the saturated ketone **8**, obtained by hydrogenation of **6**, underwent smooth Bayer–Villiger oxidation with sodium percarbonate[9] in the presence of trifluoroacetic anhydride[10] to give the acetate **9** in good yield. Hydrolysis of the latter with aqueous potassium carbonate afforded tetrahydrolavandulol in high yield. Tetrahydrolavandulol has been utilised as a key intermediate in the synthesis[11] of tetradesoxybacterioruberin and recently, some interesting biotransformation of the former has also been reported.[12]



Scheme 2. Reagents and conditions: (i) TMS_2O_2, $SnCl_4$, CH_2Cl_2, 24 h, 12%; (ii) H_2, Pd–C, EtOH, room temperature, 4 h, 81% (iii) SPC, TFAA, room temperature, 16 h, 69%; (iv) potassium carbonate, methanol, room temperature, 2 h, 89%.

We also considered the Beckmann-type rearrangement of the oxime of the ketone **6** as an additional possibility. Thus, the ketone **6** was converted into its oxime **11** (~7:1 mixture of E- and Z-) by treatment with hydroxylamine hydrochloride under conventional conditions.[13] Treatment[14] of this mixture with *para*-toluenesulfonyl chloride in pyridine led to smooth formation of the rearranged product **12** as the only isolable product (Scheme 3).



Scheme 3. Reagents and conditions: (i) NH_2OH·HCl, pyridine, ethanol, rt, 6 h, 83%; (ii) *p*-TsCl, pyridine, benzene, rt, 12 h, 57%.

3. Conclusion

In short, we have demonstrated that various chiral lavandulol derivatives could be prepared from carvone through a fragmentation-based approach. Some of the compounds reported here have the potential to find applications in perfumery.

4. Experimental

4.1. General details

Optical rotations were recorded in spectroscopic grade chloroform or dichloromethane on a Jasco DIP-370 polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were obtained using a Perkin–Elmer 1600 series spectrometer as liquid films or

dilute solutions in spectroscopic grade dichloromethane. Proton NMR spectra were recorded on a Bruker DRX-300 spectrometer as dilute solutions in deuterochloroform. The chemical shifts are quoted in parts per million (ppm) relative to tetramethylsilane as the internal standard and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants are quoted in Hertz. Carbon-13 NMR spectra were recorded on Bruker DPX-300 spectrometer as dilute solutions in deuterochloroform. Chemical shifts are recorded relative to internal chloroform (δ 77.2) or TMS as standard on a broad band decoupled mode, and the multiplicities determined using a DEPT sequence. Mass spectra were recorded on a JEOL-JMS 600 instrument and elemental analyses were obtained on a Perkin–Elmer 204b elemental analyzer.

4.1.1. (1*R*,3*R*,5*R*)-5-isopropenyl-1, 2, 2-trimethylcyclohexane-1,3-diol (4). A solution of methylmagnesium iodide (2 M in THF, 10 ml, 20 mmol) was added dropwise over 20 min to a stirred solution of the hydroxyketone **3**[3] (1.64 g, 9.11 mmol) in dry THF under nitrogen at 0 °C and the resulting yellowish solution was allowed to come to room temperature over 20 h. It was quenched with saturated aqueous NH_4Cl solution (10 ml) and then extracted with ether (2×50 ml). The combined organic extract was washed successively with water (2×50 ml), brine (20 ml) and then dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 7:1) afforded the product as a colourless oil (1.17 g, 65%). $[\alpha]_D$ +8.54 (*c*, 0.82 in $CHCl_3$). ν_{max} (neat) 3340, 2920, 1665, 1080 and 885 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (1H, s), 4.70 (1H, s), 3.62 (1H, t, *J*=9.1 Hz), 3.12 (1H, bs), 2.98–2.64 (1H, m), 1.72 (3H, s), 1.69–1.57 (4H, m), 1.13 (3H, s), 1.10 (3H, s), 0.88 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (s), 108.8 (t), 78.6 (d), 76.0 (s), 40.7 (t), 39.4 (s), 33.9 (t), 33.8 (d), 25.3 (q), 24.0 (q), 21.0 (q), 20.6 (q). Elemental analyses: C, 72.49%; H, 11.04%; $C_{12}H_{22}O_2$ requires C, 72.68%; H, 11.18%. *m/z* (EI, 70 eV) 180 (M^+-H_2O), 145.

4.1.2. (1*R*,3*R*,5*R*)-3-hydroxy-5-isopropenyl-2,2,3-trimethylcyclohexyl methanesulfonate (5). Methanesulfonyl chloride (0.85 ml, 11 mmol) was added in one portion to a stirred solution of the diol **4** (375 mg, 1.89 mmol) in dry pyridine (10 ml) at 0 °C under nitrogen. It was allowed to come to room temperature and stirring continued for 14 h. The brownish mixture was diluted with water (50 ml) and then extracted with ether (3×50 ml). The combined ether extract was washed successively with water (3×25 ml) and saturated aqueous copper sulfate solution (2×25 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated to leave the crude product as a brownish oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 6:1) afforded the product as a colourless oil (343 mg, 66%). $[\alpha]_D$ −19.58 (*c*, 2.72 in $CHCl_3$). ν_{max} (neat) 3560, 1660, 1330, 1165 and 880 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (1H, s), 4.64 (1H, s), 3.26–3.06 (1H, m), 3.03 (3H, s), 2.54 (1H, tt, *J*=8.7, 4.2 Hz), 2.11–2.02 (1H, m), 1.82–1.77 (2H, m), 1.73 (3H, s), 1.63–1.48 (1H, m), 1.15 (3H, s), 1.12 (3H, s), 0.99 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8 (s), 109.6 (t), 90.3 (d), 74.4 (s), 40.5 (t), 40.4 (s), 38.9 (d), 33.7 (q), 32.2 (t), 24.7 (q), 24.3 (q), 21.0 (q), 20.5 (q). Elemental analyses: C, 56.27%; H, 8.44%; S, 11.31%; $C_{13}H_{24}SO_4$ requires C, 56.49%; H, 8.75%; S, 11.60%.

4.1.3. (4*R*)-4-isopropenyl-7-methyl-6-octen-2-one (6). Sodium hydride (130 mg, excess) was added in one portion to a solution of the hydroxymesylate **5** (114 mg, 0.41 mmol) in dry tetrahydrofuran (8 ml) under nitrogen atmosphere and the resulting mixture was heated to reflux for 8 h. It was then cooled in an ice-bath and quenched by slow addition of methanol (1 ml) followed by saturated aqueous ammonium chloride (5 ml). It was then extracted with ether (2×25 ml) and the combined ether extract was washed with water (2×20 ml), brine (1×10 ml) and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 20:1) afforded the product as a colourless oil (58 mg, 79%). $[\alpha]_D$ +12.1 (*c*, 2.1 in $CHCl_3$). ν_{max} (neat) 2920, 1720, 1665 and 1645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (1H, t, *J*=7.2 Hz), 4.73 (1H, s), 4.67 (1H, s), 2.60 (1H, quin., *J*=6.9 Hz), 2.46–2.44 (2H, m), 2.08 (3H, s), 2.03 (2H, t, *J*=7.2 Hz), 1.66 (6H, s), 1.54 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4 (s), 147.1 (s), 133.0 (s), 122.0 (d), 111.0 (t), 47.5 (t), 42.8 (d), 30.1 (q), 32.0 (t), 25.8 (q), 19.8 (q), 17.8 (q). Elemental analyses: C, 79.69%; H, 10.98%; $C_{12}H_{20}O$ requires C, 79.95%; H, 11.18%. *m/z* (EI, 70 eV) 180 (M^+), 165, 137 (100%).

4.1.4. (2*S*)-2-isopropenyl-5-methyl-4-hexenyl acetate (7). Stannic chloride (130 mg, 0.5 mmol) was added dropwise to a stirred solution of the ketone (90 mg, 0.5 mmol) and bis(trimethylsilyl)peroxide[15] (90 mg, 0.5 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen atmosphere. After stirring for 1 h at that temperature it was allowed to come to room temperature and stirring continued for 24 h. It was then diluted with dichloromethane (25 ml) and then poured into an aqueous solution of sodium thiosulfate (10 ml). The organic layer was separated and washed successively with water (2×10 ml), saturated sodium bicarbonate solution (1×10 ml), water (1×10 ml) and brine (1×10 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated to leave the crude product as a brownish oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 12:1) afforded lavandulol acetate as a colourless oil (11 mg, 12%). $[\alpha]_D$ 6.3 (*c*, 1.5 in $CHCl_3$). ν_{max} (neat) 2910, 1708, 1670 and 1645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05 (1H, t, *J*=7.5 Hz), 4.82 (1H, d, *J*=1.5 Hz), 4.73 (1H, bs), 4.03 (2H, d, *J*=6.9 Hz) 2.39 (1H, quin., *J*=6.9 Hz), 2.17–2.05 (2H, m), 2.02 (3H, s), 1.69–1.64 (6H, overlapping singlets), 1.59 (3H, s).^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (s), 144.9 (s), 132.9 (s), 121.6 (d), 112.4 (t), 65.8 (t), 46.0 (d), 28.5 (t), 25.7 (q), 20.9 (q), 19.9 (q), 17.8 (q). Elemental analyses: C, 73.66%; H, 10.49%; $C_{12}H_{20}O_2$ requires C, 73.43%; H, 10.27%. *m/z* (EI, 70 eV) 196 (M^+), 153, 59 (100%).

4.1.5. (4*R*)-4-isopropyl-7-methyloctan-2-one (8). A solution of the ketone **6** (72 mg, 0.4 mmol) in methanol (5 ml) was vigorously stirred under hydrogen atmosphere in the presence of Pd–C (10%, 5 mg) for 3 h at room temperature. The heterogeneous mixture was then filtered through celite and the filter cake was washed with ether. The combined organic solution was then concentrated to leave the crude

product as a colourless liquid, which was purified by chromatography over silica gel using a mixture of petroleum ether and ethyl acetate (20:1) as eluent. The product was obtained as a colourless liquid (59 mg, 81%). $[\alpha]_D$ +2.1 (*c*, 1.2 in $CHCl_3$). ν_{max} (neat) 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (1H, dd, *J*=15.9, 5.7 Hz), 2.15 (1H, dd, *J*=15.9, 5.7 Hz), 2.03 (3H, s), 1.75 (1H, m), 1.65 (1H, m), 1.36 (1H, m), 1.21 (2H, m), 1.12 (2H, m), 0.8 (12H, overlapping doublets). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.8 (s), 45.4 (d), 39.6 (t), 36.5 (t), 30.3 (t), 29.5 (q), 28.9 (d), 28.2 (d), 22.6 (q), 22.4 (q), 19.5 (q), 18.4 (q). Elemental analyses: C, 77.88%; H, 12.90%; $C_{12}H_{24}O$ requires C, 78.19%; H, 13.12%. *m/z* (EI, 70 eV) 184 (M^+), 169, 141 (100%), 126.

4.1.6. (2*S*)-2-isopropyl-5-methylhexyl acetate (9). Trifluoroacetic anhydride (0.085 ml) was added to a stirred heterogeneous mixture of the ketone **8** (35 mg, 0.2 mmol) and sodium percarbonate (64 mg, 0.4 mmol) in dry dichloromethane (2 ml) at 0 °C under nitrogen atmosphere. The mixture was allowed to come to room temperature and stirred for 16 h. It was then diluted with dichloromethane (20 ml) and filtered. The filtrate was concentrated in vacuo and the residue was partitioned between ether (20 ml) and water (20 ml). The organic layer was washed successively with saturated sodium bicarbonate solution (2×10 ml), water (10 ml), brine and then dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 10:1) afforded tetrahydrolavandulol acetate as a colourless oil (27 mg, 69%). ν_{max} (neat) 1708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.99–3.84 (2H, m), 2.03 (3H, s), 1.75–1.66 (1H, m), 1.46–1.40 (2H, m), 1.37–1.30 (1H, m), 1.24–1.16 (2H, m), 1.12–1.00 (2H, m), 0.88–0.82 (12H, overlapping doublets), 0.76–0.71 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 (s), 65.5 (t), 43.2 (d), 36.7 (t), 28.3 (d), 25.7 (t), 22.6 (d), 22.8 (q), 22.4 (q), 21.0 (q), 19.8 (q), 19.3 (q). Elemental analyses: C, 71.70%; H, 11.89%; $C_{12}H_{24}O_2$ requires C, 71.95%; H, 12.07%.

4.1.7. (2*S*)-2-isopropyl-5-methylhexan-1-ol (10). A solution of the acetate **9** (99 mg, 0.5 mmol) in methanol (5 ml) and saturated aqueous potassium carbonate (2 ml) was stirred at room temperature for 2 h. It was then diluted with water (20 ml) and extracted with ether (2×20 ml). The combined ether extract was washed with brine (1×10 ml) and dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 10:1) afforded tetrahydrolavandulol as a colourless oil (71 mg, 89%). $[\alpha]_D$ −9.6 (*c*, 1.4 in $CHCl_3$). ν_{max} (neat) 3320 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.96–3.58 (2H, m), 1.82–1.78 (1H, m), 1.53–1.30 (5H, m), 0.91–0.87 (12H, overlapping doublets). ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.2 (t), 47.3 (d), 37.5 (t), 28.8 (d), 28.3 (d), 25.8 (t), 23.1 (q), 22.9 (q), 20.1 (q), 19.6 (q). Elemental analyses: C, 75.69%; H, 13.82%; $C_{10}H_{22}O$ requires C, 75.88%; H, 14.01%.

4.1.8. (4*R*)-4-isopropenyl-7-methyl-6-octen-2-one oxime (11). Hydroxylamine hydrochloride (232 mg, 3.34 mmol) was added in one portion to a stirred solution of the ketone **6** (500 mg, 2.78 mmol) in pyridine (1.25 ml) and ethanol (1 ml) and the resulting mixture was stirred for 6 h at ambient temperature. It was then cooled to 0 °C, diluted with water (5 ml) and extracted with ethyl acetate (2×10 ml). The combined organic extract was washed successively with aqueous hydrochloric acid (5%, 1×10 ml), sodium bicarbonate solution (5%, 1×10 ml), water (1×10 ml) and then brine (1×10 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a pale yellow oil which was purified by chromatography (SiO_2) (petroleum ether/ethyl acetate, 10:1) to leave the product as a colourless oil (0.451 g, 83%). ν_{max} (neat) 3200, 2890, 1625, 1430 and 1360 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): data for the mixture (~7:1 by GC) (data in [] refer to the possible *syn*-isomer) δ 5.05 (1H, br t), 4.75 (1H, s) [4.72, s], 2.43–2.33 (2H, m), [2.10–2.07 (m)], 1.85 (3H, s) [1.84, s], 1.68 (3H, s), 1.65 (3H, s), 1.59 (3H, s). Elemental analyses: C, 73.62%; H, 10.89%; N, 7.46%; $C_{12}H_{21}NO$ requires C, 73.80%; H, 10.84%, N, 7.17%.

4.1.9. N 1-[(2*S*)-2-isopropenyl-5-methyl-4-hexenyl]acetamide (12). *p*-Toluenesulfonyl chloride (341 mg, 1.79 mmol) was added in one portion to a solution of the oxime **11** (350 mg, 1.79 mmol) in a mixture of benzene (1.5 ml) and pyridine (0.4 ml).The resulting homogeneous mixture was stirred at room temperature for 12 h and then diluted with water (10 ml) and ethyl acetate (20 ml). The aqueous phase was extracted with ethyl acetate (2×10 ml) and the combined organic extract was washed successively with aqueous hydrochloric acid solution (5%, 2×10 ml), sodium bicarbonate solution (5%, 1×10 ml), water (2×10 ml) and brine (1×10 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave the crude product as a brownish oil which was purified by chromatography (SiO_2) (petroleum ether/ethyl acetate, 4:1) to give the product as a colourless oil (202 mg, 57%). $[\alpha]_D$ −7.6 (*c*, 1.4 in $CHCl_3$). ν_{max}(neat) 3280, 2900, 1635 and 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.41 (1H, bs), 5.03 (1H, t, *J*=6 Hz), 4.87 (1H, s), 4.77 (1H, s), 3.42 (1H, dt, *J*=12.6, 5.5 Hz), 3.02 (1H, ddd, *J*=13.4, 9.5, 4.2 Hz), 2.24–2.16 (2H, m), 2.04 (1H, broad t, *J*=6.6 Hz), 1.95 (3H, s), 1.68 (3H, s) 1.65 (3H, s), 1.58 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (s), 145.6 (s), 132.9 (s), 121.5 (d), 113.0 (t), 47.1 (d), 40.9 (t), 29.7 (t), 25.6 (q), 23.2 (q), 18.6 (q), 17.8 (q). Elemental analyses: C, 73.53%; H, 11.09%; N, 7.42%; $C_{12}H_{21}NO$ requires C, 73.80%; H, 10.84%; N, 7.17%. *m/z* (EI, 70 eV) 196 (M^+ +1), 123, 69 (100%).

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