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Asymmetric Synthesis of (7a*S*)-7a-Methyl-4,5,7,7a-tetrahydro-1*H*-indene-2,6-dione and Useful Derivatives Thereof

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Abstract: The enantioselective synthesis of the title compound, using Meyers' bicyclic lactam methodology, is described. This compound and a few of its derivatives are useful intermediates in natural product synthesis.

Keywords: Asymmetric synthesis, Meyers' bicyclic lactam template, hydrindenones.

Introduction

In the context of the development of structural analogs of calcitriol, the hormonally active metabolite of vitamin D_3 [1], we required the *cis*-fused perhydrindanone **7** (Scheme 1) [2]. We herein describe in detail the enantioselective synthesis of the potentially useful dione **5** and its further conversion to **7**.

Results and Discussion

The synthesis of **7**, a *cis*-fused angularly substituted perhydrindane dione, in which one of the carbonyl groups is protected as cyclic ketal, involves two phases. First Meyers' methodology for the enantioselective synthesis of hydrindenones is applied in the preparation of **5** [3]. In a second phase, the cyclohexanone carbonyl group of **5** is protected as an ethylene ketal and the *cis*-fusion in **7** is obtained by stereoselective catalytic hydrogenation of **6**.

Meyers' approach for the asymmetric synthesis of angularly substituted hydrinden-2-ones proceeds in 3 stages: (i) the asymmetric introduction of the quaternary center using a chiral bicyclic lactam such as **1**; (ii) the reductive intramolecular alkylation in which the 1,4-diketone is generated; (iii) the intramolecular aldolisation of the latter to the hydrinden-2-one. We chose to introduce the second carbonyl group in **5** via oxidative cleavage of the exocyclic double bond in **4**. Following Meyers' methodology the latter is obtained from diastereomer **2a**.

To stereoselectively obtain the correct configuration at the 6-position in **2a**, the methyl group and the unsaturated side chain need to be introduced sequentially and in that precise order. Indeed, the prior introduction of the unsaturated side chain could eventually lead to the formation of spirocyclic derivatives [4]. On the other hand, the preferred *endo*-alkylation of Meyers' bicyclic lactam template has been well documented [5]. Hence, enantiomerically pure (+)-**1** was required as starting material [6].

Scheme 1. Synthetic pathway to tetrahydro-1*H*-inden-2,6-dione **5** and derivatives.
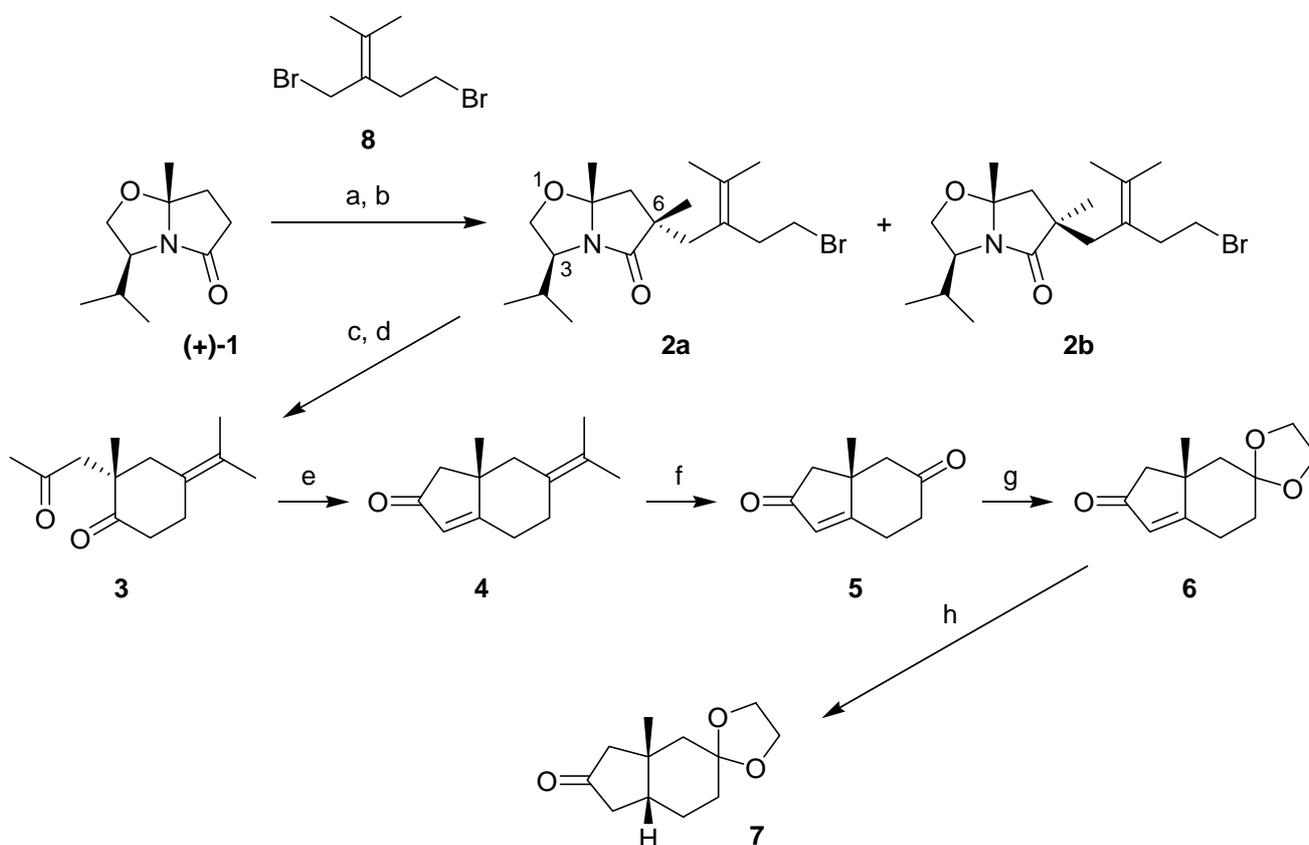
(a) (i) LDA, THF, –78 °C; (ii) MeI, –78 °C, 2 h (96%); (b) (i) LDA, DMPU, THF, –78 °C; (ii) **8**, –78 °C; 3 h (84%); (c) *t*-BuLi, KH, THF, –78 °C, 45 min; (d) *n*-Bu$_4$NH$_2$PO$_4$, EtOH, 75 °C, 12 h (68% from **2a**); (e) KOH, EtOH, rt, 16 h (89%); (f) O$_3$, CH$_2$Cl$_2$, –78 °C (73%); (g) HO(CH$_2$)$_2$OH, TsOH, toluene, reflux, 2 h (92%); (h) H$_2$, Pd/C, EtOAc, rt, 2.5 h (100%).

The methylation of **1** led to a 9:1 diastereomeric mixture, which was not separated. After further deprotonation with LDA (DMPU, THF) and alkylation with the known dibromide **8** [7], a 7:3 mixture of **2a** and **2b** was obtained, which was separated by chromatography. The preferred formation of the *endo*-isomer **2a** was proven by ^{1}H-NMR nOe signal-enhancement studies establishing the relative positions of the Me groups and H atoms indicated in Figure 1. The major isomer **2a** was subjected to

Meyers' protocol (KH, *t*-BuLi) yielding diketone **3**. Basic treatment (KOH, EtOH) led to hydrinden-2-one **4**. Selective cleavage of the exocyclic double bond in **4** (ozone, Me₂S) gave diketone **5** in which the saturated carbonyl group was further protected to afford the ketal **6**. Finally, catalytic hydrogenation of the latter occurred exclusively from the convex side of the bicyclic molecule leading to the *cis*-fused perhydrindanone **7**, the structure of which was confirmed by ^{1}H-NMR structural analysis: upon irradiation of the angular Me group a clear nOe enhancement of the signal of the bridgehead hydrogen was observed, confirming the *cis*-fusion of the hydrindane (Figure 1).

Figure 1. ^{1}H-NMR nOe signal-enhancement studies of **2a** and **7**.
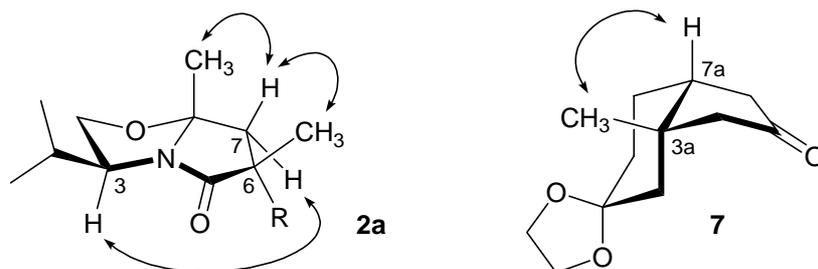
Conclusions

Angularly substituted perhydrindanones are useful intermediates in synthesis. The asymmetric synthesis of **7**, in which an additional carbonyl group in protected ketal form is present (overall yield 33%), following a sequence of 7 steps starting from commercially available **(+)-1** provides a useful example of the general applicability of Meyers' methodology.

Experimental

General

Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Dichloromethane (DCM) was distilled from CaH₂. Toluene was distilled from sodium. TLC were run on glass plates precoated with silica gel (Merck, 60F-254). Column chromatography was performed on silica gel (Merck, 230-400 mesh). IR spectra were recorded on a Perkin–Elmer series 1600 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-500 spectrometer. Hydrogen chemical shifts δ are reported in ppm relative to CDCl₃ (7.26 ppm) as an internal reference. *J* values are given in Hz. Carbon chemical shifts δ are reported in ppm relative to CDCl₃ (77.16 ppm) as an internal reference. Mass spectra (EI) were recorded on a Hewlett–Packard 5898A spectrometer at 70 eV.

(3S,6S,7aR)-6-[2-(2-Bromoethyl)-3-methylbut-2-en-1-yl]-3-isopropyl-6,7a-dimethyltetrahydro-pyrrolo[2,1-b][1,3]oxazol-5(6H)-one (**(+)-2a**) [8]

To *i*-Pr₂NLi (LDA, 2 M solution in THF; 110 mL, 0.22 mol) was added dry THF (1100 mL) and the solution was cooled to –78 °C. (3*S*,7a*R*)-3-Isopropyl-7a-methyltetrahydropyrrolo[2,1-*b*][1,3]-oxazol-5(6*H*)-one (**(+)-1**; 20 g, 0.11 mol) was added dropwise and the mixture was stirred for 30 min. MeI (46.74 g, 20.5 mL, 0.33 mol) was then added dropwise, the reaction mixture was stirred for 2 h and then allowed to warm to rt. An aqueous saturated NH₄Cl solution (50 mL) was added and the

mixture was stirred for 1 h. H_2O was added, the aqueous layer was extracted with Et_2O (3×), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (isooctane/EtOAc, 7:3) to afford a 9:1 mixture of the (6*R*/6*S*)-diastereomers of the methylated bicyclic lactam (20.8 g, 96%).

To LDA (2 M solution in THF; 7.5 mL, 20 mmol) was added dry THF (100 mL) and the solution was cooled to –78 °C. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 11 mL) was added and the mixture was stirred for 10 min. The above mixture of methylated bicyclic lactams (2.0 g, 10.1 mmol) in dry THF (10 mL) was added dropwise and the reaction mixture was stirred for 2 h. 5-Bromo-3-(bromomethyl)-2-methylpent-2-ene (**8**; 5.12 g, 20 mmol) in dry THF (10 mL) was then added dropwise and stirring was continued for 1 h. An aqueous saturated NH_4Cl solution (20 mL) was added and the mixture was allowed to warm to rt. H_2O was added, the aqueous layer was extracted with Et_2O, the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained 7:3 mixture of isomers of the dialkylated bicyclic lactam (3.1 g, 84%) was separated by column chromatography on silica gel (isooctane/ EtOAc, 7:3) to give the major (6*S*)-isomer (+)-**2a** as a solid: mp 45 °C; R_f (isooctane/EtOAc, 95:5) 0.22; $[\alpha]_D^{rt}$ +106.5 (*c* 1.15, CHCl₃); IR (KBr pellet) ν 2963, 2871, 1708, 1463, 1376, 1381, 1298, 1252, 1218, 1176, 1130, 1037, 1006), 967, 903, 842, 808, 771, 684, 650 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl₃) δ 4.18 (1 H, dd, *J* = 8.8, 8.8 Hz), 3.77 (1 H, dd, *J* = 7.9, 7.9 Hz), 3.59–3.54 (1 H, m), 3.39–3.34 (1 H, m), 3.28–3.22 (1 H, m), 2.39 (2 H, s), 2.68–2.62 (1 H, m), 2.29–2.23 (1 H, m), 2.24 (1 H, d, *J* = 13.5 Hz), 1.88 (1 H, d, *J* = 13.3 Hz), 1.71 (3 H, s), 1.66–1.63 (1 H, m), 1.63 (3 H, s), 1.50 (3 H, s), 1.29 (3 H, s), 1.04 (3 H, d, *J* = 6.6 Hz), 0.88 (3 H, d, *J* = 6.6 Hz) ppm; ^{13}C-NMR/DEPT (50 MHz, CDCl₃) δ 183.7 (C), 132.9 (C), 126.8 (C), 96.8 (C), 70.6 (CH₂), 61.6 (CH), 48.3 (C), 45.5 (CH₂), 38.2 (CH₂), 35.6 (CH₂), 34.2 (CH), 30.9 (CH₂), 27.5 (CH₃), 25.8 (CH₃), 21.4 (CH₃), 20.7 (CH₃), 20.6 (CH₃), 18.9 (CH₃) ppm; MS *m/z* (%) 372 (M$^+$, 17), 359 (17), 358 (88), 357 (20), 356 (88), 341 (14), 331 (11), 330 (60), 328 (100), 326 (46), 310 (7), 300 (21). Anal. Calcd for $C_{18}H_{30}BrNO_2$: C, 58.10; H, 8.06; N, 3.76. Found: C, 57.95; H, 8.25, N, 3.70.

(2S)-2-Methyl-4-(1-methylethylidene)-2-(2-oxopropyl)cyclohexanone ((+)-**3**)

To a solution of dialkylated bicyclic lactam (+)-**2a** (1.0 g, 2.7 mmol) in dry THF (54 mL) were added *t*-BuLi (1.7 M solution in pentane; 3.32 mL, 5.6 mmol) and KH (0.324 g, 8.1 mmol) at –78 °C and the reaction mixture was stirred for 45 min. H_2O (20 mL) was added and the mixture was allowed to warm to rt under stirring for 20 min. The solution was concentrated under reduced pressure to 1/3 of its volume and EtOH (20 mL) was added to obtain a homogeneous solution. A 1 M *n*-Bu₄NH₂PO₄ solution (26.5 mL, 0.081 mmol) was added and the mixture was refluxed for 12 h. After cooling, H_2O was added, the aqueous layer was extracted with Et_2O (2×), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (isooctane/EtOAc, 8:2) to give diketone (+)-**3** (0.388 g, 68%): R_f (isooctane/EtOAc, 8:2) 0.33; $[\alpha]_D^{rt}$ +20.5 (*c* 1.10, CHCl₃); IR (KBr film) ν 2963, 2921, 1710, 1456, 1360, 1167, 1104 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl₃) δ 2.98 (1 H, A<u>B</u>, *J* = 17.7 Hz), 2.69–2.63 (2 H, m), 2.56–2.47 (2 H, m), 2.49 (1 H, <u>A</u>B, *J* = 17.7 Hz), 2.44–2.38 (1 H, m), 2.34 (1 H, d, *J* = 14.1 Hz), 2.10 (3 H, s), 1.71 (3 H, s), 1.70 (3 H, s), 1.03 (3 H, s) ppm; ^{13}C-NMR/APT (125 MHz, CDCl₃) δ 206.9 (C), 206.9 (C), 126.1 (C), 125.3 (C), 52.2 (CH₂), 47.0 (C), 38.6 (CH₂), 38.6 (CH₂), 30.7 (CH₃), 27.2 (CH₂), 24.1 (CH₃), 20.4 (CH₃), 20.3 (CH₃); MS *m/z* (%) 208 (M$^+$, 1), 150 (49), 135 (34), 107 (43),

93 (21), 79 (26), 67 (21), 43 (100).

(7aS)-7a-Methyl-6-(1-methylethylidene)-1,4,5,6,7,7a-hexahydro-2H-inden-2-one ((+)**-4**)

To a solution of diketone (+)**-3** (2.5 g, 12 mmol) in EtOH (12 mL) was added KOH (0.64 g, 12 mmol) and the reaction mixture was stirred at rt for 16 h. H_2O was added and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (isooctane/EtOAc, 9:1) to give enone (+)**-4** (2.0 g, 89%) as yellow crystals: mp 84 °C; R_f (isooctane/EtOAc, 8:2) 0.37; $[\alpha]_D^{rt}$ +53.15 (*c* 0.75, $CHCl_3$); IR (KBr film) ν 2956, 2916, 2860, 2358, 1709, 1620, 1437, 1409, 1372, 1274, 1220, 1171, 840, 750, 670 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.79 (1 H, d, *J* = 1.6 Hz), 2.96 (1 H, m), 2.89 (1 H, dd, *J* = 13.0, 2.3 Hz), 2.72 (1 H, ddd, *J* = 13.6, 4.6, 2.3 Hz), 2.36 (1 H, ddd, *J* = 13.5, 13.5, 6.3 Hz), 2.33 (1 H, A<u>B</u>, *J* = 18.4 Hz), 2.28 (1 H, A<u>B</u>, *J* = 18.4 Hz), 1.82–1.75 (2 H, m), 1.77 (3 H, s), 1.72 (3 H, s), 1.13 (3H, s) ppm; ^{13}C-NMR/APT (125 MHz, $CDCl_3$) δ 208.2 (C), 188.0 (C), 126.8 (C), 126.2 (C), 126.0 (CH), 51.1 (CH_2), 45.2 (C), 43.9 (CH_2), 30.6 (CH_2), 28.9 (CH_2), 24.2 (CH_3), 20.5 (CH_3), 20.4 (CH_3) ppm; MS *m/z* (%) 190 (M$^+$, 100), 175 (32), 162 (10), 147 (76), 133 (15), 119 (57), 105 (44), 91 (47), 79 (38), 55 (28), 41 (45).

(7aS)-7a-Methyl-4,5,7,7a-tetrahydro-1H-indene-2,6-dione ((–)**-5**)

O_3 was bubbled through a solution of alkene (+)**-4** (0.48 g, 2.5 mmol) in DCM (126 mL) at –78 °C for 8 min. Me_2S (0.3 mL, 3.4 mmol) was added, the reaction mixture was allowed to warm to 0 °C, stirred for 1 h and then allowed to warm to rt. The solvent was evaporated and the residue was purified by column chromatography on silica gel (Et_2O/isooctane, 9:1) to give ketone (–)**-5** (0.298 g, 73%): R_f (Et_2O/isooctane, 9:1) 0.23; $[\alpha]_D^{rt}$ –62.0 (*c* 1.10, $CHCl_3$); IR (KBr film) ν 3070, 2953, 1710, 1678, 1622, 1432, 1337, 1296, 1198, 1090, 1070, 902 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.02 (1 H, d, *J* = 1.7 Hz), 3.06 (1 H, ddd, *J* = 14.6, 7.5, 1.4 Hz), 2.83 (1 H, dddd, *J* = 14.6, 13.1, 6.7, 1.7 Hz), 2.67–2.61 (2 H, m), 2.52–2.44 (2 H, m), 2.43 (1 H, A<u>B</u>, *J* = 18.6 Hz), 2.39 (1 H, A<u>B</u>, *J* = 18.6 Hz), 1.25 (3 H, s) ppm; ^{13}C-NMR/APT (125 MHz, $CDCl_3$) δ 207.2 (C), 206.4 (C), 181.2 (C), 128.3 (C), 54.2 CH_2), 51.2 (CH_2), 45.4 CH), 40.0 (CH_2), 26.09 (CH_2), 25.5 (CH_3) ppm; MS *m/z* (%) 164 (M$^+$, 86), 149 (18), 136 (14), 121 (39), 107 (44), 93 (56), 79 (100), 55 (25), 53 (30).

(3a'S)-3a'-Methyl-3a',4',6',7'-tetrahydrospiro[1,3-dioxolane-2,5'-inden]-2'(3'H)-one ((+)**-6**)

To a solution of ketone (–)**-5** (0.77 g, 4.7 mmol) in dry toluene (47 mL) were added $HOCH_2CH_2OH$ (0.3 g, 0.27 mL, 4.7 mmol) and TsOH (90 mg, 0.47 mmol). The reaction mixture was refluxed for 2 h with azeotropic removal of the generated H_2O (Dean–Stark). The solution was allowed to cool, concentrated under reduced pressure and an aqueous saturated $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/isooctane, 9:1) to give ketal (+)**-6** (0.9 g, 92%) as white-yellow crystals: mp 72 °C; R_f (Et_2O/isooctane, 9:1) 0.46; $[\alpha]_D^{rt}$ +6.28 (*c* 1.03, $CHCl_3$); IR (KBr pellet)

ν 2989, 2965, 2925, 1707, 1621, 1448, 1363, 1290, 1262, 1181, 1105, 1069, 1010, 952, 934, 907), 866, 844, 716 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 5.83 (1 H, s), 4.05–4.00 (2 H, m), 3.92 (2 H, t, *J* = 6.09 Hz), 2.69 (2 H, dd, *J* = 8.8, 3.2 Hz), 2.31 (1 H, A<u>B</u>, *J* = 18.3 Hz), 2.24 (1 H, <u>A</u>B, *J* = 18.3 Hz), 2.07–2.00 (2 H, m), 1.70–1.62 (2 H, m), 1.37 (3 H, s) ppm; ^{13}C-NMR/APT (125 MHz, CDCl$_3$) δ 185.97 (C), 126.8 (CH), 107.9 (C), 107.9 (C), 64.9 (CH$_2$), 64.0 (CH$_2$), 53.3 (CH$_2$), 47.3 (CH$_2$), 43.5 (C), 35.7 (CH$_2$), 26.3 (CH$_3$), 25.2 (CH$_2$) ppm; MS *m/z* (%) 208 (M$^+$, 26), 193 (34), 152 (13), 121 (13), 107 (26), 86 (100), 79 (35), 55 (18), 53 (21). Anal. Calcd for C$_{12}$H$_{16}$O$_3$: C, 69.21; H, 7.74. Found: C, 68.86; H, 7.95.

(3a'S,7a'R)-3a'-Methylhexahydrospiro[1,3-dioxolane-2,5'-inden]-2'(3'H)-one ((+)-**7**)

To a solution of enone (+)-**6** (1.0 g, 4.8 mmol) in EtOAc (96 mL) was added Pd/C (10%; 0.5 g, 0.48 mmol) and the reaction mixture was shaken under 4 bar H$_2$ pressure (Parr apparatus) at rt for 2.5 h. The mixture was filtered through Celite® and the solvent was evaporated under reduced pressure to afford saturated ketone (+)-**7** (1.0 g, 100%): R_f (isooctane/EtOAc, 9:1) 0.09; $[α]_D^{rt}$ +43.4 (*c* 1.5, CHCl$_3$); IR (KBr film) ν 2931, 2884, 2250, 1736, 1453, 1407, 1364, 1256, 1211, 1145, 1098, 1068, 1018, 994, 911, 732, 648, 608 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.93–3.90 (4 H, m), 2.73 (1 H, A<u>B</u>, *J* = 18.4 Hz), 2.47 (1 H, dd, *J* = 18.8, 7.7 Hz), 2.04 (1 H, dd, *J* = 18.8, 4.2 Hz), 1.95–1.93 (1 H, m), 1.87 (1 H, <u>A</u>B, *J* = 18.4 Hz), 1.85–1.80 (1 H, m), 1.71–1.66 (2 H, m), 1.59–1.48 (3 H, m), 1.12 (3 H, s) ppm; ^{13}C NMR/APT (125 MHz, CDCl$_3$) δ 219.4 (C), 108.4 (C), 64.2 (CH$_2$), 63.9 (CH$_2$), 49.9 (CH$_2$), 43.0 (CH$_2$), 42.0 (CH$_2$), 40.8 (CH), 39.7 (CH$_2$), 32.0 (C), 28.8 (CH$_3$), 26.0 (CH$_2$) ppm; MS *m/z* (%) 210 (M$^+$, 3), 153 (9), 126 (28), 99 (100), 86 (30), 55 (18), 42 (15).

Acknowledgements

References and Notes

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6. The enantiomeric purity of commercial (+)-**1**, purchased from Aldrich, was established by chiral GC (0.25-μm SUPELCO β-DEX 120 column, 30 m × 0.25 mm, 120 °C). Comparison with

racemic **(±)-1**, prepared from DL-valinol and levulinic acid according to Meyers, showed virtually 100% ee. See: Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663–5676.

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8. The ACD/I-Lab Web service (ACD/IUPAC Name Free 8.05) was used to generate the chemical names of compounds **1**–**8**.

Sample Availability: No samples available.