

## Supplementary Information

### Regioselective Synthesis of $\alpha$ -Methyl 2-Methyleneglutarate via a Novel Lactonization-Elimination Rearrangement

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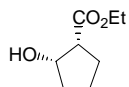
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#### Table of Contents

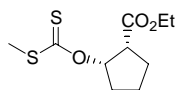
1. General Experimental Procedures	S1
2. Large-scale synthesis of <i>ent</i> -4.	S2
3. $^1\text{H}$ and $^{13}\text{C}$ NMR spectral data for compounds <b>5-7</b> .	S6

**General Experimental Procedures.** All reactions involving moisture-sensitive reagents were performed in flame-dried glassware under an atmosphere of nitrogen or argon. All solvents used in moisture-sensitive reactions were dried as follows: Tetrahydrofuran and  $\text{Et}_2\text{O}$  were freshly distilled from sodium/benzophenone.  $\text{CH}_2\text{Cl}_2$  was distilled from  $\text{CaH}_2$ . All flash chromatography was carried out using silica gel (0.04-0.06 mm, 230-400 mesh). Compound *ent*-4 was prepared using the procedure of Maeda et al.<sup>1</sup>  $^1\text{H}$  NMR spectra were recorded at 300 or 500 MHz and are reported as follows: chemical shifts in ppm downfield from internal tetramethylsilane (multiplicity, integrated intensity, coupling constant in Hz).  $^{13}\text{C}$  NMR spectra were obtained at 75 or 126 MHz and are referenced to d-solvent peak.

### Large-scale synthesis of *ent*-4.



**Ethyl (1*R*, 2*S*)-(+)-2-hydroxycyclopentanecarboxylate.** A suspension of baker's yeast (*S. cerevisiae*) (24.0 g), dextrose (304 g), MgSO<sub>4</sub> (2.0 g), KH<sub>2</sub>PO<sub>4</sub> (4.0 g), NH<sub>4</sub>H<sub>2</sub>PO<sub>4</sub> (4.0 g), and CaCO<sub>3</sub> (10 g) in 2 L dd H<sub>2</sub>O was shaken at 35 °C for 45 min in a rotary shaker. Ethyl 2-oxocyclopentanecarboxylate, (20 g, 128 mmol) was added. The reaction was shaken at 35 °C for 18h. The reaction progress was monitored via mini-workups in which 10 mL of the reaction mixture was extracted with Et<sub>2</sub>O (10 mL) and the organic layer monitored TLC. The reaction was centrifuged (8,000 rpm x 15 minutes) and the supernatant decanted. The pellets were each suspended in 100 mL H<sub>2</sub>O and centrifuged, this was repeated two more times. The combined aqueous supernatant was extracted with Et<sub>2</sub>O (3 x 1 L). The combined organic layers were dried over Mg SO<sub>4</sub> and concentrated. The crude product was purified by fractional distillation (short path, 5 mmHg, 110 °C) fractions condensing at 85-90 °C were pooled to give 15.6 g of Ethyl (1*R*, 2*S*)-(+)-2-hydroxycyclopentanecarboxylate as a clear, colorless oil (77%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.44 (m, 1H), 4.17 (q, 2H, J = 7.1 Hz), 3.12 (br s, 1H), 2.66 (m, 1H), 2.1-1.9 (overlapping m, 3H), 1.8-1.74 (overlapping m, 2H), 1.74-1.6 (m, 1H), 1.27 (t, 3H, J = 7.1 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 175.1, 73.8, 60.8, 49.6, 34.1, 26.6, 22.2, 14.4. [α]<sub>D</sub><sup>24</sup> +14.3° (c 1.0, CHCl<sub>3</sub>) (lit.<sup>2</sup> +14.1° (c 1.7, CHCl<sub>3</sub>)). MS (EI) *m/z* 101.1 (100), 159.2 ([M+H]<sup>+</sup>, 2). HRMS (EI) calcd for C<sub>8</sub>H<sub>15</sub>O<sub>3</sub> 159.1021 [M+H]<sup>+</sup>; found 159.1019.



**(1*R*, 2*S*)-2-methylsulfanylthiocarboxyoxycyclopentanecarboxylic acid ethyl ester.**

To a solution of Ethyl (1*R*, 2*S*)-(+)-2-hydroxycyclopentanecarboxylate (15.0 g, 94.8 mmol) in anhyd DMSO (50 mL) was added at rt DBU (15.7 mL, 105 mmol) and the reaction was stirred for 1 h. Carbon disulfide (37.7 mL, 626 mmol) was then added and the reaction was stirred for 1.5 h. Methyl iodide (11.8 mL, 190 mmol) was added and the reaction was stirred for 12 h. The reaction was concentrated by rotary evaporation (40 °C, 10 mmHg) and the resulting solution was diluted with CHCl<sub>3</sub> (800 mL) and washed with H<sub>2</sub>O (800 mL). The aqueous layer was extracted with CHCl<sub>3</sub> (800 mL). The organic layer was washed with brine (400 mL) and concentrated to ~250 mL, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 43 g of crude orange oil. The crude material was purified by silica gel chromatography (9:1 Hexanes/EtOAc) to give 22 g of (1*R*, 2*S*)-2-methylsulfanylthiocarboxyoxycyclopentanecarboxylic acid ethyl ester as an orange oil (94%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.14 (m, 1H), 4.14 (q, 2H, *J* = 7.1 Hz) 3.03 (m, 1H), 2.49 (s, 3H), 2.3-2.1 (m, 1H), 2.1-1.8 (m, 4H), 1.8-1.6 (m, 1H), 1.23 (t, 3H, *J* = 7.1 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 214.6, 171.4, 86.2, 60.9, 49.2, 32.3, 26.2, 22.4, 18.7, 14.4.



**Ethyl (*R*)-2-cyclopentene-1-carboxylate.** The above xanthate (22g, 89 mmol) was placed in a 50 mL round bottom flask equipped with a reflux condenser and was heated at 190 °C for 3.5 hours. The reaction was allowed to cool to rt. The product was purified by short path distillation (110°C, 40 mmHg) to give 11.3 g of ethyl (*R*)-2-cyclopentene-1-

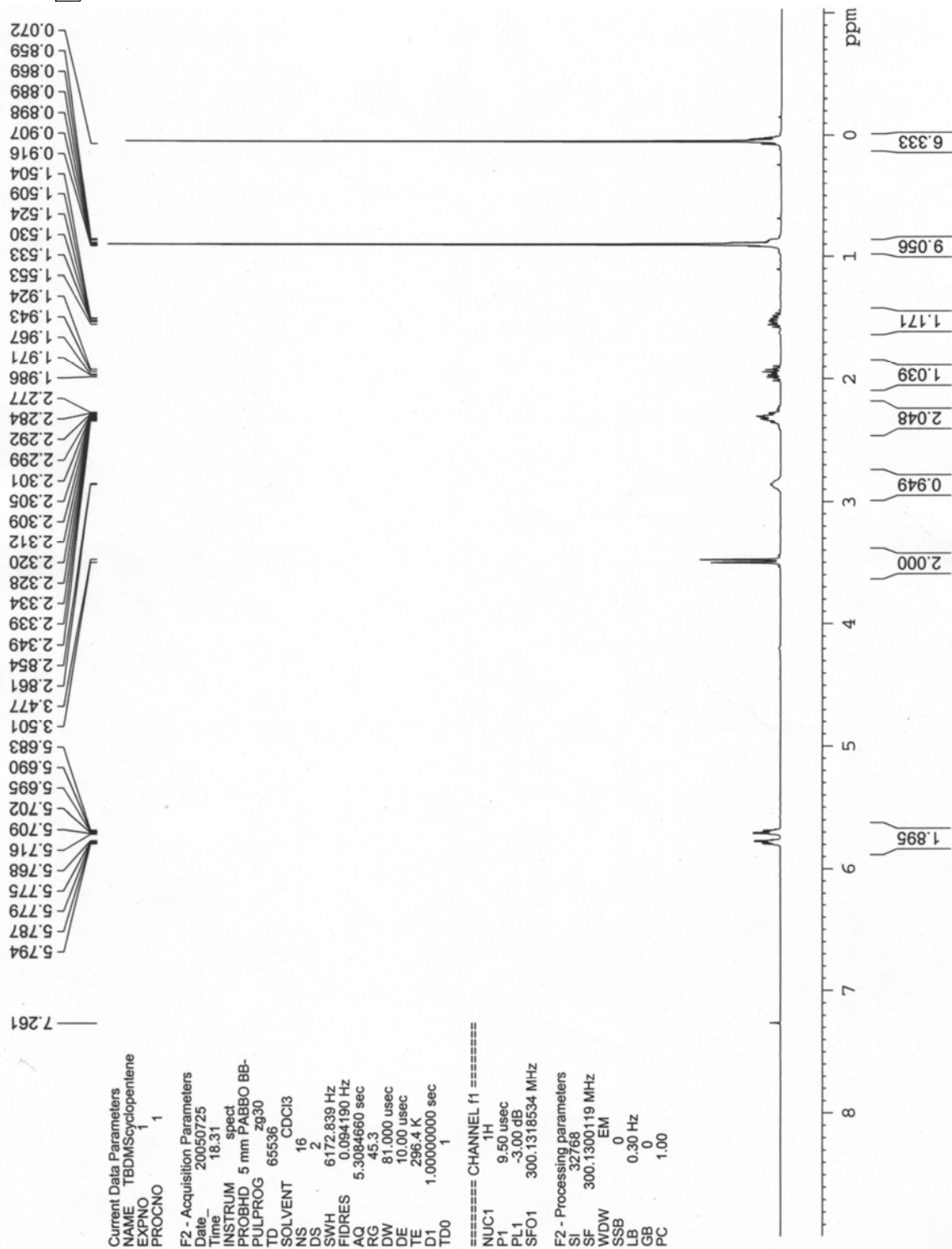
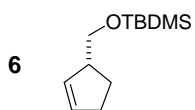
carboxylate as a clear oil. (90%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.88 (m, 1H), 5.72 (m, 1H), 4.13 (q, 2H,  $J = 7.1$  Hz), 3.53 (m, 1H), 2.6-2.3 (overlapping m, 2H), 2.13 (m, 2H), 1.26 (t, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  175.4, 134.2, 129.0, 60.9, 53.8, 51.1, 32.6, 26.9, 14.6.  $[\alpha]_{\text{D}}^{24} + 176.6^\circ$  ( $c$  1.0,  $\text{CHCl}_3$ ) (lit.<sup>1</sup>  $+188.5^\circ$  ( $c$  1.69,  $\text{CHCl}_3$ )).



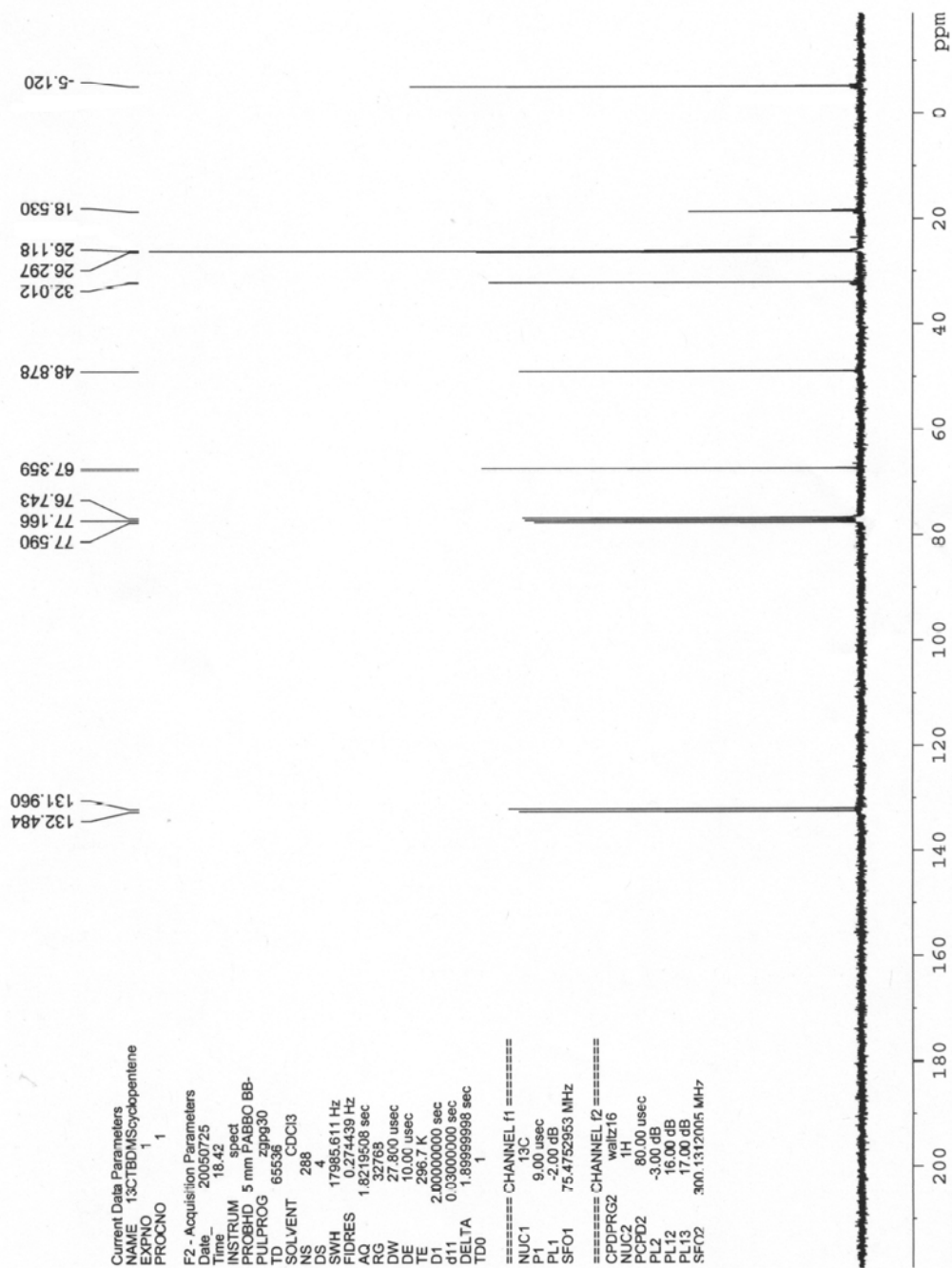
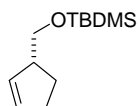
**(*R*)-3-(hydroxymethyl)cyclopent-1-ene, *ent*-4.** A solution of ethyl (*R*)-2-cyclopentene-1-carboxylate (11.3 g, 80.6 mmol) in  $\text{Et}_2\text{O}$  (25 mL) was added dropwise to a stirring suspension of LAH (4.3 g, 112.8 mmol) in  $\text{Et}_2\text{O}$  (250 mL) at  $0^\circ\text{C}$  under Ar. The reaction was allowed to warm to rt and stirred to 5 h. The reaction was quenched using standard workup conditions (4.3 mL  $\text{H}_2\text{O}$  was added followed by 4.3 mL 15% aq NaOH followed by 12.9 mL  $\text{H}_2\text{O}$  all at  $0^\circ\text{C}$ ).<sup>3</sup> The reaction was allowed to warm to rt and stirred until all of the excess LAH has reacted to form a solid, white precipitate of hydroxides. The precipitate was removed by filtration and washed with  $\text{Et}_2\text{O}$ . The filtrate was concentrated and the crude product was purified by Kugelrohr distillation (20 mmHg, 80-85  $^\circ\text{C}$ ) to give 6.5 g of *ent*-4 as a clear, slightly yellow oil (82%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.87 (m, 1H), 5.66 (m, 1H), 3.56 (t, 2H,  $J = 5.7$  Hz), 2.92 (m, 1H), 2.35 (m, 2H), 2.01 (m, 1H), 1.64 (m, 1H), 1.40 (t, 1H,  $J = 5.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  133.5, 131.2, 66.6, 48.6, 32.3, 26.1.  $[\alpha]_{\text{D}}^{24} +152.6^\circ$  ( $c$  1.45,  $\text{CHCl}_3$ ) (lit.<sup>1</sup>  $+158.9^\circ$  ( $c$  1.47,  $\text{CHCl}_3$ )). MS (EI)  $m/z$  98.1 ( $\text{M}^+$ , 5), 67.0 ( $[\text{M}-\text{CH}_2\text{OH}]^+$ , 100). HRMS (EI) calcd for  $\text{C}_6\text{H}_{10}\text{O}$  98.0732 [ $\text{M}^+$ ]; found 98.0731.

## References:

- (1) Maeda, K.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1994**, 67, 2880.
- (2) Deol, B. S.; Ridley, D. D.; W, S. G. *Aust. J. Chem.* **1976**, 29, 2459-2467.
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6





7

