

## Synthesis of (+)- and (–)-isocarvone

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**Abstract**—The first synthesis of 5-isopropenyl-3-methyl-cyclohex-2-enone, (isocarvone) (**2**), in enantiomerically pure form is reported. Both enantiomers of **2** can be produced by manipulation of carboxylic acid **5**, which is available from *R*-(–)-carvone (**1**). These materials provide new chiral building blocks that could be used in total synthesis of natural products and related optically active compounds.

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Carvone (**1**), commercially available in both enantiomeric forms, is one of the most common natural monoterpenes, used in the food and perfume industries, and as chiral starting material in the synthesis of natural products.<sup>1</sup> A scan of the past years' chemical literature reveals over 4000 hits for the keyword 'carvone', many of which exemplify and validate its use in synthesis as a chiral building block. Despite the plethora of chemical transformations based on **1**, the chemistry of its methyl positional isomer, referred to herein as isocarvone (**2**: 5-isopropenyl-3-methyl-cyclohex-2-enone), remains virtually unknown (Fig. 1). In fact, only one racemic synthesis of isocarvone (**2**) has been described by Stetter and Simons in 1985 using an aldol condensation as key step,<sup>2</sup> and there are no reported syntheses of **2** in enantiomerically pure form. Herein, we describe an efficient synthesis of both (–)-**2** and (+)-**2** using as a common starting material the readily available *R*-(–)-carvone.

The retrosynthetic analysis toward (–)- and (+)-isocarvone is highlighted in Figure 2. We anticipated that intramolecular olefination of ketophosphonate **3** would produce (–)-**2**, while methylation of ketone **4**,<sup>3</sup> followed by an oxidative carbonyl transposition would form (+)-**2**. Both **3** and **4** could be available from acid **5**, which is

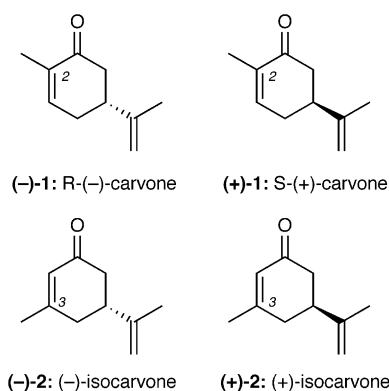


Figure 1. Chemical structures of carvone (**1**) and isocarvone (**2**).

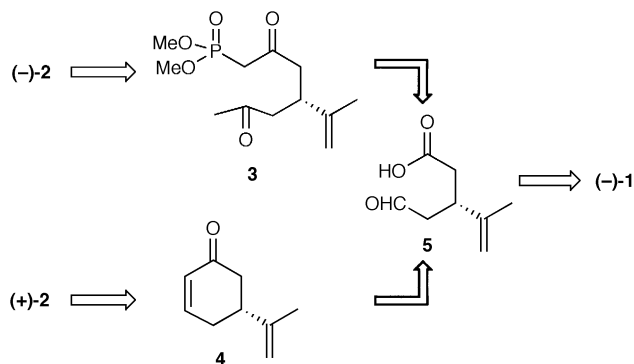
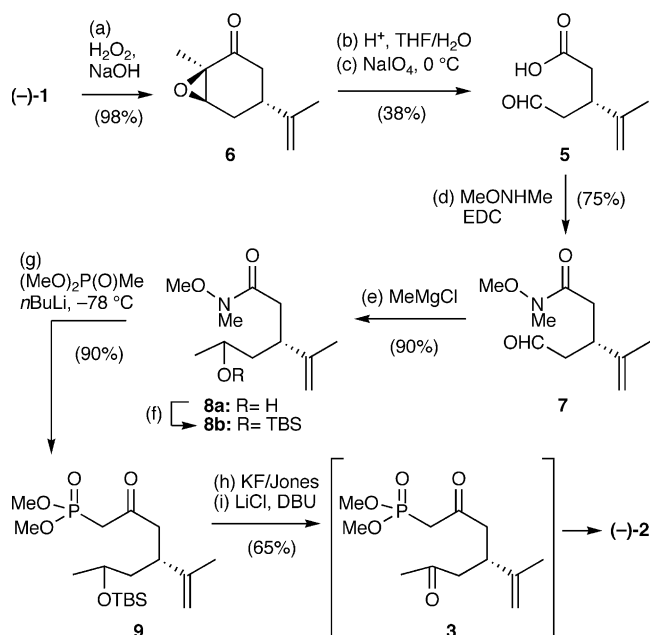


Figure 2. Retrosynthetic analysis of isocarvones (–)-**2** and (+)-**2**.

**Keywords:** Terpenes; Natural products; Synthetic methods; Chiral synthon.

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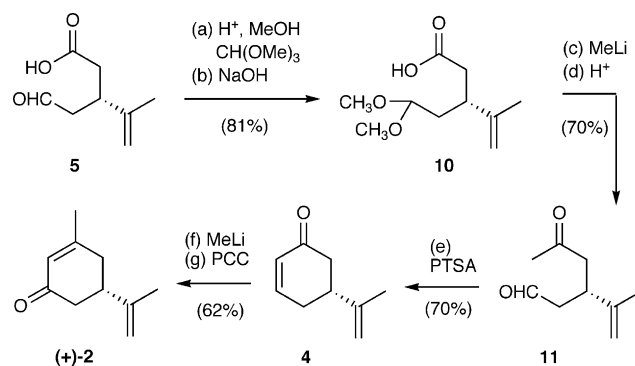


**Scheme 1.** Synthesis of (-)-isocarvone (-)-2. Reagents and conditions: (a) H<sub>2</sub>O<sub>2</sub>, NaOH, 0 °C, 3 h, 98%; (b) H<sub>2</sub>SO<sub>4</sub>, THF–H<sub>2</sub>O, reflux, 3 h, 50%; (c) NaIO<sub>4</sub> (2.0 equiv), MeOH–H<sub>2</sub>O, 0 °C, 3 h, 75%; (d) (MeO)NHMe·HCl (1.2 equiv), Et<sub>3</sub>N (1.2 equiv), EDC·HCl (1 equiv), –30 to 25 °C, 16 h, 75%; (e) MeMgCl (1.3 equiv), THF, –50 to –10 °C, 2.5 h, 90%; (f) TBSCl (1.5 equiv), Et<sub>3</sub>N (2 equiv), DMAP (0.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0–25 °C, 16 h, 75%; (g) (MeO)<sub>2</sub>P(O)CH<sub>3</sub> (3.0 equiv), *n*-BuLi (3.0 equiv), THF, –78 to 25 °C, 16 h, 90%; (h) KF/Jones (2.0 equiv), acetone, 0–25 °C, 5 h; (i) LiCl (1.0 equiv), DBU (1.0 equiv), THF, –78 to 25 °C, 16 h, 65% (two steps).

known to derive from manipulation of *R*-(-)-carvone as reported by the Deslongchamp and co-workers.<sup>4</sup>

The synthesis of (-)-isocarvone began with epoxidation of (-)-1, in the presence of basic hydrogen peroxide, to produce epoxide 6 in 98% yield (Scheme 1).<sup>4,5</sup> Compound 6 was treated with aqueous H<sub>2</sub>SO<sub>4</sub> in THF to produce a 1:1 mixture of *cis* and *trans* diols that were separated by column chromatography. The *cis* diol was subjected to oxidative cleavage with NaIO<sub>4</sub> to produce the known carboxylic acid 5<sup>6</sup> in 38% combined yield (from (-)-1). Coupling of 5 with MeONHMe·HCl proceeded in best yields using EDC·HCl and Et<sub>3</sub>N and afforded Weinreb amide 7 (75% yield). Alkylation of 7 with MeMgCl in THF proceeded selectively at low temperature (–50 to –10 °C) and generated the secondary alcohol 8a,<sup>7</sup> which was converted to the corresponding silyl ether 8b in 68% combined yield. Treatment of 8b with the anion of dimethoxymethylphosphonate at –78 °C formed ketophosphonate 9 in 90% yield.

Deprotection of silyl ether 9 was found to be unexpectedly difficult. Several reagents were tried (TBAF·THF, TBAF on alumina, PTSA, CSA, HCl) but led in most cases to decomposition. After much experimentation, a one-pot procedure using KF and Jones' reagent as oxidant<sup>8</sup> gave the required methyl ketone 3. Without purification, compound 3,<sup>9</sup> was subjected to an intermolecular Horner–Wadsworth–Emmons olefination



**Scheme 2.** Synthesis of isocarvone (+)-2. Reagents and conditions: (a) PTSA (0.1 equiv), CH(OMe)<sub>3</sub> (5.0 equiv), MeOH, reflux, 2 h, 90%; (b) 3 N NaOH (3.0 equiv), MeOH–THF (1:2), 5 h, 25 °C, 90%; (c) MeLi (2.5 equiv), TMSCl (1.0 equiv), THF, 0–25 °C, 1 h; (d) 0.5 M HCl, 30 min, THF, 25 °C; 70% (two steps); (e) PTSA (0.1 equiv), PhCH<sub>3</sub>, reflux, 1 h, 70%; (f) MeLi (1.5 equiv), Et<sub>2</sub>O, 2 h, 0 °C; (g) PCC (2.0 equiv), MS 4 Å, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 3 h, 62% (two steps).

under Masamune–Roush conditions (LiCl, DBU)<sup>10</sup> to afford the desired isocarvone (-)-2<sup>11</sup> in 65% combined yield (Scheme 1).

The synthesis of (+)-2 isocarvone is highlighted in Scheme 2. Acid 5 was treated with (MeO)<sub>3</sub>CH in MeOH under acid catalysis to produce, after hydrolysis of the resulting methylester, ketal 10 in 81% combined yield. Alkylation of acid 10 using MeLi/TMSCl followed by deprotection of the carbonyl group afforded ketoaldehyde 11 (70% yield), which was subjected to an acid-catalyzed intramolecular aldol condensation reaction to form enone 4 (70% yield). Treatment of 4 with MeLi produced the corresponding tertiary alcohol, which underwent a PCC induced oxidative rearrangement to form (+)-2 isocarvone<sup>11</sup> in 62% combined yield.

In conclusion, we present herein an efficient approach for the synthesis of both enantiomers of 5-isopropenyl-3-methyl-cyclohex-2-enone, (isocarvone) (2). Both synthetic sequences depart from carboxylic acid 5, which is readily available from *R*-(-)-carvone. This approach represents the first entry into both enantiomers of isocarvone and opens the way for their application as chiral building blocks in organic synthesis.<sup>12</sup>

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  - Selected data for compounds **3**, **5**, and **7–9**. Compound **3**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.77–4.75 (2H, m,  $\text{C}=\text{CH}_2$ ), 3.79 (3H, s, *MeO*), 3.75 (3H, s, *MeO*), 3.11–3.04 (3H, m,  $\text{CH}_2\text{P}=\text{O}$  and  $\text{CHC}=\text{CH}_2$ ), 2.74–2.68 (2H, m), 2.52 (2H, d,  $J = 6.9$  Hz), 2.11 (3H, s, *Me*), 1.71 (3H, s, *Me*). Compound **5**: yellow oil;  $[\alpha]_{\text{D}}^{25} -7.1$  ( $c$  0.8,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.70 (1H, dd,  $J = 2.4$ , 2.5 Hz, *CHO*), 4.86–4.84 (2H, m,  $\text{C}=\text{CH}_2$ ), 3.15 (1H, m), 2.60–2.20 (4H, m), 1.74 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  201.0, 144.9, 112.7, 46.6, 37.8, 37.2, 19.9. Compound **7**: light yellow-orange oil;  $R_f = 0.3$  (50% ethyl acetate in hexanes);  $[\alpha]_{\text{D}}^{25} -1.7$  ( $c$  0.7,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.65 (1H, br s, *CHO*), 4.80 (2H, m,  $\text{C}=\text{CH}_2$ ), 3.68 (3H, s, *MeO*), 3.16 (3H, s, *MeN*), 2.57–2.44 (4H, m), 1.74 (3H, s, *Me*);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  201.2, 171.9, 145.6, 111.6, 61.1, 46.7, 36.8, 35.7, 31.9, 20.3; IR (film)  $\nu_{\text{max}}$  2940, 1721, 1652, 1457, 1420, 1177, 1001, 898; HRMS calcd for  $\text{C}_{10}\text{H}_{17}\text{NO}_3$  ( $\text{M}+\text{Na}^+$ ) 222.1106, found 222.1126. Compound **8a**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.81 (1H, br s,  $\text{C}=\text{CH}_2$ ), 4.76 (1H, br s,  $\text{C}=\text{CH}_2$ ), 3.68 (3H, s, *MeO*), 3.18 (3H, s, *MeN*), 2.84 (1H, m), 2.50 (2H, m), 1.74 (3H, s, *Me*), 1.62 (1H, m), 1.45 (1H, m), 1.16 (3H, d,  $J = 6.0$  Hz, *CHMe*);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  148.3, 111.1, 65.7, 61.2, 43.7, 39.1, 36.3, 23.2, 19.9; IR (film)  $\nu_{\text{max}}$  3500–3300, 2970, 2937, 1732, 1647, 1441, 1383. Compound **8b**: colorless oil,  $R_f = 0.4$  (20% ethyl acetate in hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.75 (2H, m), 3.66 (3H, s, *MeO*), 3.14 (3H, s, *MeN*), 1.70 (3H, s, *Me*) and 1.67 (s, *Me* diastereomer), 1.15 (3H, d,  $J = 5.7$  Hz, *CHMe*) and 1.13 (d,  $J = 5.7$ , *CHMe* diastereomer), 0.87 (9H, br s,  $\text{SiCMe}_3$ ), 0.02 (6H, br s,  $\text{SiMe}_2$ ); IR (film)  $\nu_{\text{max}}$  2957, 2932, 2857, 1737, 1670, 1380, 1253. Compound **9**: colorless oil,  $R_f = 0.3$  (50% ethyl acetate in hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.73 (2H, m), 3.76 (3H, s, *MeO*), 3.73 (3H, s, *MeO*), 3.68 (1H, m), 3.05 (2H, m), 1.66 (3H, s, *Me*) and 1.62 (s, *Me* diastereomer), 1.10 (3H, d,  $J = 6.0$  Hz, *CHMe*) and 1.08 (d,  $J = 6.0$  Hz, *CHMe* diastereomer), 0.86 (9H, s,  $\text{SiCMe}_3$ ) and 0.84 (s,  $\text{SiCMe}_3$  diastereomer), 0.02 (6H, s,  $\text{SiMe}_2$ ) and 0.00 (s,  $\text{SiMe}_2$  diastereomer).
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