AWARD LECTURE / CONFÉRENCE D'HONNEUR

Dauben–Michno oxidative transposition of allylic cyanohydrins — Enantiomeric switch of (–)-carvone to (+)-carvone*

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Abstract: Allylic cyanohydrins were subjected to Dauben–Michno oxidation at low temperatures to provide β-cyanoenones in good to excellent yields. The potential of this oxidative transposition as a means of an enantiomeric switch of enones containing a latent plane of symmetry was tested by conversion of (–)-carvone to its enantiomer.

Key words: Dauben–Michno reaction, oxidative 1,3-transposition of allylic alcohols, cyanoenones, enantiomeric switch of carvone.

Résumé : On a soumis des cyanohydrines allyliques à une oxydation de Dauben–Michno, à basse température, pour obtenir des β-cyanoénones avec des rendements allant de bons à excellents. Dans le but d'évaluer le potentiel de cette transposition oxydante comme méthode de réaliser une transposition énantiomère dans les énones contenant un plan de symétrie latent, on a transformer la (–)-carvone en son énantiomère.

Mots-clés : réaction de Dauben–Michno, transposition oxydante 1,3 d'alcools allyliques, cyanoénones, transposition énantiomère de la carvone.

[Traduit par la Rédaction]

Introduction

The Dauben–Michno oxidation constitutes a reliable protocol for oxidative transposition of tertiary allylic alcohols substituted with electron-donating groups.[1,2] The reaction proceeds by a [3,3] sigmatropic rearrangement of the initially formed chromate ester followed by further oxidation of the rearranged chromate ester to the final enone. The process is analogous to the well-known chromium(VI) oxidations of olefins to enones that proceed via an ene reaction of the chromium oxide followed by oxidation. The initially formed chromate ester is either oxidized to an enone or undergoes [3,3] sigmatropic rearrangement prior to the final oxidation. Thus, mixtures of regioisomeric enones are frequently encountered in the oxidation of cyclic olefins.[3,4] Because only one product can arise from the rearrangement of a tertiary allylic alcohol, the Dauben–Michno reaction does not suffer from regiochemical issues. Although well-documented for allylic alcohols flanked by electron-donating groups, this reaction has not been reported for allylic alcohols substituted with esters or nitriles. To our knowledge the first example of such oxidation was the conversion of allylic alcohol **1** to enone **2** during our recently completed synthesis of oseltamivir (**3**) (Tamiflu), Fig. 1.[5]

To establish whether the reaction is general for allylic alcohols substituted with other electron-withdrawing groups we investigated a series of cyanohydrins as means of synthesis of β-cyanoenones. In this paper we report the results of this investigation, along with a procedure for an enantiomeric switch of (–)-carvone to (+)-carvone.

Results and discussion

We began the investigation with a series of cyclic enones (Table 1, entries 1–3) and their conversion to cyanohydrins following a recently published procedure that uses proline catalysis for the formation of the intermediate trimethylsilyl ethers of cyanohydrins.[6] Following the hydrolysis, the free cyanohydrins were obtained in essentially quantitative yield and used without purification in the Dauben–Michno oxidation. The proline-catalyzed protocol is exceedingly efficient and cleanly affords the cyanohydrins, thus obviating any

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Fig. 1. Dauben–Michno oxidation of α-hydroxybutenoate.

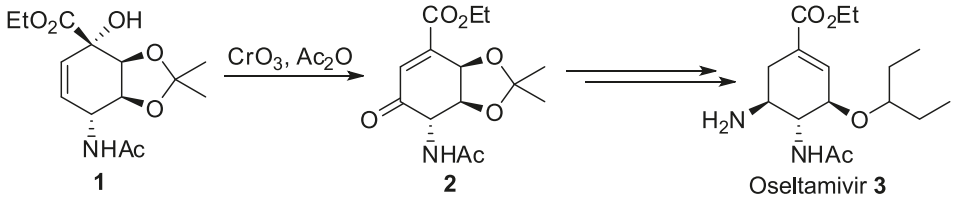
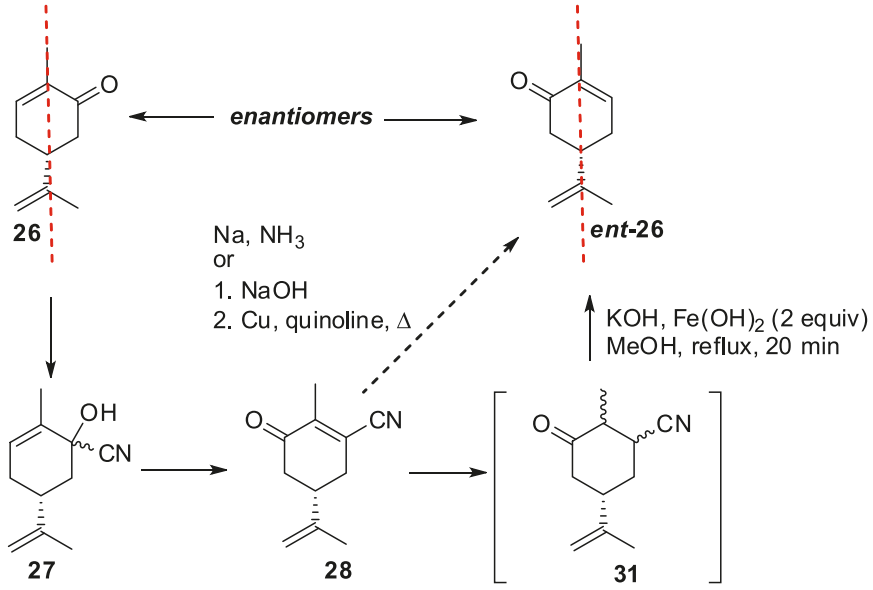


Fig. 2. Proposed enantiomeric switch of (–)-carvone via Dauben–Michno oxidation.



separation issues prior to subsequent reactions. In the case of cyclopentenone, the cyanohydrin was obtained in 60% yield at the expense of the competing 1,4-addition of the cyanide to the enone. Similarly, cyanohydrins were obtained from methylvinyl ketone (Table 1, entry 4), 3-penten-2-one (Table 1, entry 5), 4-phenylbutenone (Table 1, entry 6), acetophenone (Table 1, entry 7), and (–)-carvone (Table 1, entry 8).

The Dauben–Michno procedure required the treatment of CrO_3 with acetic anhydride at 80 °C before cooling and addition of the cyanohydrin at or below 0 °C. The best results were obtained by performing the oxidation below 0 °C to avoid competing reactions at the site of the double bond that may result from the generation of peroxyacetic acid during the reaction. Such competition is absent when the oxidation is performed at –40 °C or below. The yields of transposed cyanoenones were in the range of 70%–80% except in the case of cyclopentenone, where the conversion was excellent and essentially quantitative (vide NMR); however, the volatility of the product contributed to low isolated yields (Table 1).

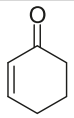
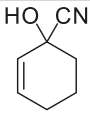
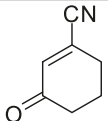
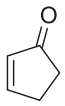
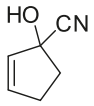
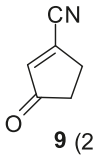
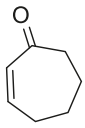
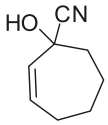
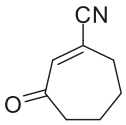
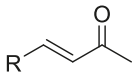
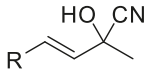
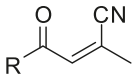
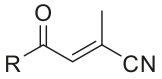
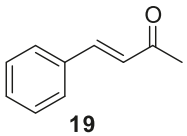
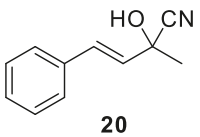
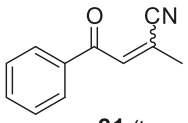
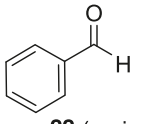
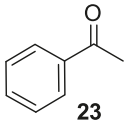
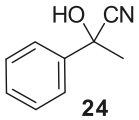
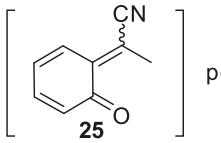
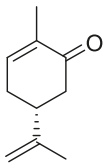
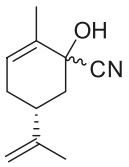
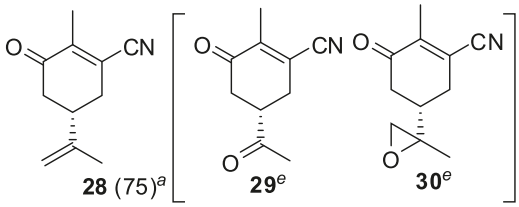
With acyclic enones the results were different; in the case of methylvinyl ketone the corresponding unsaturated aldehyde **15** (a consequence of the oxidation of a primary chromate ester formed by the sigmatropic rearrangement) was isolated as a mixture of *Z*- and *E*-isomers in the ratio of 7:1. (Note: On repetition of these experiments at higher temperatures or on a larger scale only the *Z*-isomer was detected.) The volatility of the product made the accurate determination of yield difficult. It was somewhat surprising that little or no over-oxidation took place whether 1 equiv or up to 3 equiv of the oxidant were used. We did not detect the corresponding acid even after careful repetition of the experiments; however, over-oxidation of an aldehyde to an acid requires the formation of a hydrate, which cannot take place under the conditions of the reaction. If the corresponding acid is desired, a simple dilution of the reaction with water and addition of an additional equivalent of chromium oxide should provide the corresponding carboxylic acid in high yield.

With pent-3-en-2-one (**16**) the corresponding cyanohydrin **17** was isolated in 76% yield and rearranged cleanly to the β-cyanoenone **18** in 84% yield (66% over two steps); only the *Z*-isomer **18a** was observed. In the case of 4-phenylbutenone (**19**), the rearrangement of the corresponding cyanohydrin **20** produced only traces of the transposed enone **21**, and the major product isolated was benzaldehyde (**22**). The formation of benzaldehyde may be rationalized by the oxidative cleavage of the intermediate 1,2-chromate diester formed from the styrene double bond in competition with the Dauben–Michno reaction.

For acetophenone (**23**) and the oxidation of its cyanohydrin **24**, only the formation of an intractable polymer was observed at prolonged reaction times or at higher temperatures. The cyanohydrin derived from acetophenone was still present in the reaction mixture after 16 h at room temperature. We expected the Dauben–Michno to proceed with disruption of aromaticity to provide **25**, in analogy with reported cases of reactivity of this type;[7] however, attempts at trapping intermediates of type **25** with external dienophiles such as maleic anhydride proved unsuccessful.

The oxidative 1,3-transposition could, in principle, be used

Table 1. Dauben–Michno oxidation of cyanohydrins.

Entry	Enone	Cyanohydrin	Product(s) (%)
1	 **4**	 **5**	 **6** (79)[a]
2	 **7**	 **8** (60)[b]	 **9** (25%)[c] (93%)[d]
3	 **10**	 **11**	 **12** (81)[a]
4	 **13** R = H	 **14** R = H (67%)[d]	 (Z:E = 7:1)  **15a** R = H **(Z-)** **15b** R = H **(E-)** (43)[a,c]
5	**16** R = Me	**17** R = Me (78%)	**18a** R = Me (84%)(66%)[a] **18b** R = Me
6	 **19**	 **20**	 **21** (trace)  **22** (major)
7	 **23**	 **24**	 polymer **25**
8	 **26**	 **27**	 **28** (75)[a] **29**[e] **30**[e]

[a]Isolated yield over two steps.
[b]Yield of 1,2-adduct, 1,4-adduct of cyanide was observed during the cyanohydrin synthesis.
[c]Isolated yield, product is volatile and losses occur on evaporation.
[d]Product content as estimated by NMR.
[e]Formed only in reactions above 0 °C.

to provide enantiomers of homochiral enones that contain a latent plane of symmetry, as shown in Fig. 2 with carvone. To test this idea we applied the Dauben–Michno protocol to carvone with the expectation that further manipulations of the β-cyanoenone **28** would lead to the formation of *ent*-carvone, as depicted in Fig. 2.

The Dauben–Michno oxidation of cyanohydrin **27** derived from carvone provided the corresponding β-cyanoenone **28** in 75% yield. At 0–4 °C, considerable amount of side products, such as the methyl ketone **29** and epoxide **30**, were isolated. The former compound is likely a result of the oxidative cleavage of the 1,2-diol, formed by the addition of CrO_3 to the isopropylidine double bond, whereas the latter is probably formed by epoxidation mediated by peroxyacetic acid generated by in situ oxidation of acetic acid. When the reaction was performed at –40 to –50 °C, only oxidative rearrangement took place, and no side products arising from over-oxidation were observed.

Fig. 3. Synthesis of *ent*-dihydrocarvone from enone **28**.

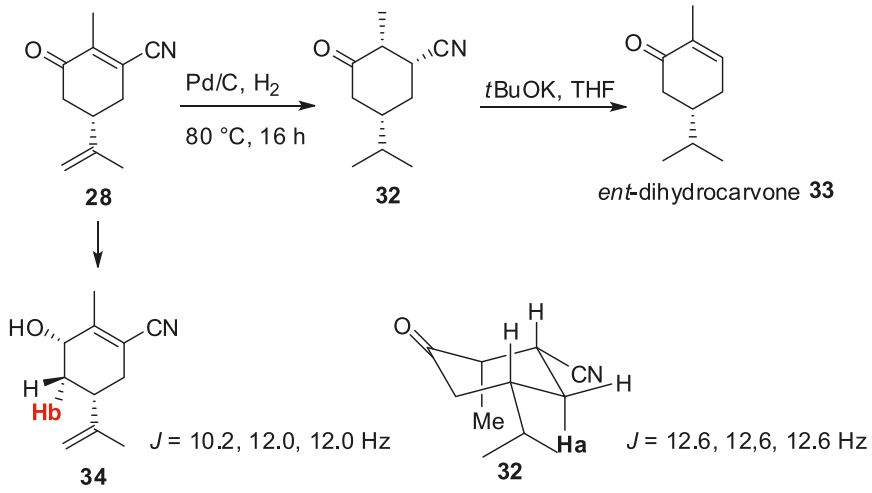


Fig. 4. Enantiomeric switch of (–)-carvone.

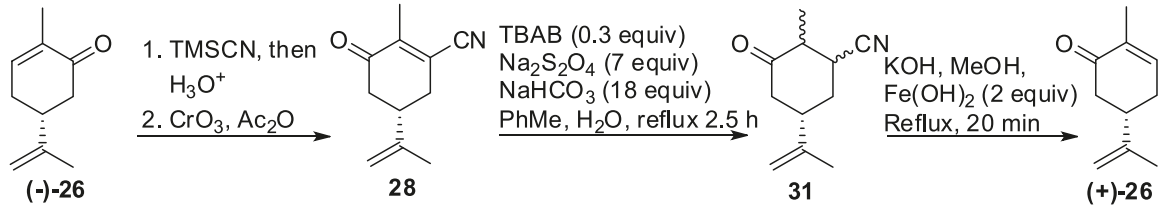
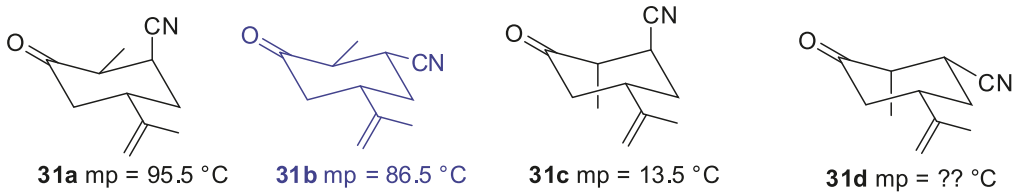


Fig. 5. Djerassi's assignment of diastereomeric dihydrocyanocarvone **31**.



The proof of principle for the enantiomeric switch was demonstrated on a small scale by the conversion of cyanoenone **28** to the fully saturated β-cyano ketone **32** as shown in Fig. 3. Hydrogenation of **28** at 1 atm (1 atm = 101.325 kPa) produced ketone **32** (34% yield), whose structure was assigned by the analysis of coupling constants of H_a, as shown in Fig. 3.

The low yield of the hydrogenation was attributed to the formation of a by-product (2-methyl-3-cyano-5-isopropylphenol) resulting from full aromatization under the conditions of the hydrogenation. Treatment of **32** with *t*-BuOK in THF provided *ent*-dihydrocarvone (**33**). Enone **28** was also reduced under Luche conditions to the allylic alcohol **34** in anticipation of a possible rhodium-catalyzed isomerization[8] ($RhCl_3$, EtOH) to the saturated ketone **31**; however, this isomerization proved unsuccessful. The stereochemistry assignment of **34** was evident from the large coupling constants of the axial H_b, as shown in Fig. 3.

For the direct conversion of cyanoenone **28** to *ent*-carvone (**26**) several methods were investigated, among them hydrolysis to the corresponding acid and thermal decarboxylation,[9] and Birch reduction,[10] as shown in Fig. 2. Neither method proved very efficient in our hands.

The enantiomeric switch of carvone was accomplished in two steps via a reduction–elimination sequence as shown in Fig. 4. The cyanoenone **28** was reduced with sodium dithionite[11] to a mixture of the saturated cyanoketones **31**. All four diastereomers of **31** are known compounds, generated over the years in investigations of various reactions of enones[12–14] that utilized carvone as a convenient starting material. The major product from the dithionite reduction turned out to be the diastereomer **31b** (Fig. 5), as evidenced by melting point as well as by detailed NMR analysis.

In the early 1900s Lapworth[15–17] studied the addition of cyanide to *ent*-carvone and isolated two diastereomers of **31**, one from the reaction of potassium cyanide in ethanol, water, and acetic acid conducted at room temperature, and the other from a reaction performed in refluxing ethanol without acetic acid. (These two compounds would later be identified as **31a** and **31b**, respectively; Fig. 5) When Djerassi et al.[18] repeated Lapworth's experiments in 1963 with (–)-carvone, they found that the physical constants of the two diastereomers matched Lapworth's results. They then studied the equilibration of the two isomers and isolated a third when **31a** was treated with *p*-TsOH in EtOAc at room temperature for 1 week. The third isomer, a much lower melting compound, was later assigned as structure **31c**, Fig. 4.

Fig. 6. Assignment of stereochemistry of **31b** by NMR methods. (A) Resolution enhanced ^{1}H spectrum. (B) Resolution enhanced ^{1}H spectrum selectively decoupled from H7 methyl.

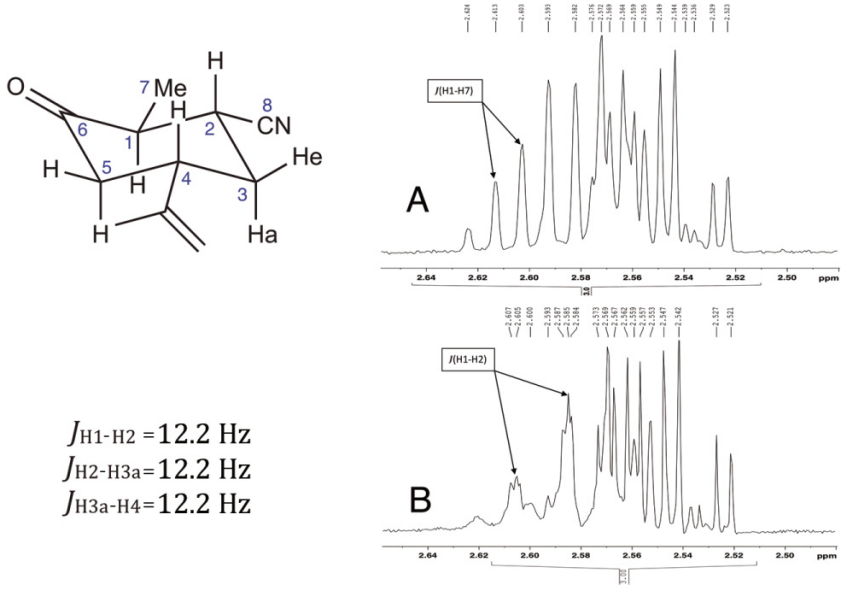
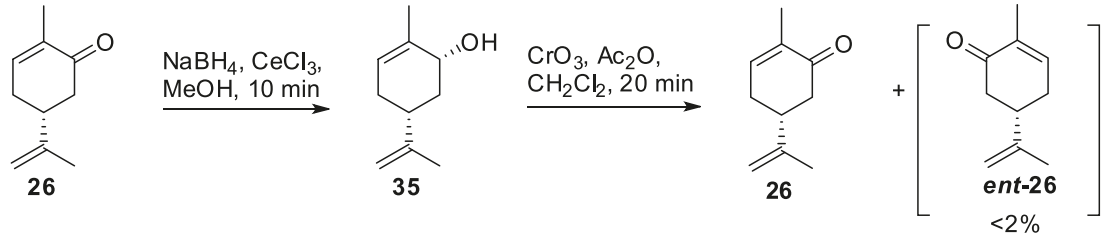


Fig. 7. Attempted Dauben–Michno synthesis of (+)-carvone from (–)-carvol **35**.



Attempted equilibration of **31b** was unsuccessful save for a trace amount of a new compound tentatively assigned as **31d**. Djerassi et al.[18] assigned the stereochemistry of the four diastereomers of **31** by use of detailed conformational analysis and optical rotary dispersion. In addition, they proved by simple yet ingenious experiments that the equilibration of **31a** occurs at C-2 and not at C-3 by conversion of nitriles to benzamides and equilibration of C-2 positions. The stereochemistry of **31b** was evident by matching the melting point with the compound identified by Djerassi et al.[18]

The assignment of **31b** by NMR methods proved to be nontrivial because of overlapping signals of the key protons and required the dispersion field of a 600 MHz spectrometer with advanced methods to separate the overlapping signals. The assignment of stereochemistry is shown in Fig. 6. In the normal proton spectrum, the six protons from the ring are all grouped at 1.9–2.6 ppm with one proton at 2.03 ppm, a multiplet at 2.37 ppm corresponding to three protons, and another multiplet at 2.57 ppm also corresponding to three protons. The proton at 2.03 ppm shows a d–d–d splitting pattern with three equal coupling constants (J = 12.2 Hz). Given the ring structure of cyclohexane there is only one possible case for the assignment of this proton, H3a. It is the only possible case with two large vicinal couplings (axial–axial) and one large geminal coupling. This also establishes that protons H4a and H2a are axial protons, implying that both the CN group and the propylene are in equatorial positions on the ring.

For the assignment of the H1 proton two-dimensional NMR methods had to be employed. From the H–C HSQC and COSY spectra, the locations of the other ring protons were determined. H1, H5, (H2a or H4a) are grouped at 2.6 ppm and H5 and H3e (H4a or H2a) are grouped at 2.37 ppm. H1 is identified from the coupling to the H7 methyl group in the COSY spectrum as being located on the left side of the multiplet, as shown in Fig. 6A. To increase spectral resolution, Gaussian line broadening was employed with a shift of 0.5 and a line-broadening factor of –1 Hz. From the proton spectrum a coupling constant of 6.2 Hz, corresponding to the vicinal coupling of H1 to H7 protons, was determined. This coupling alone would generate a quartet splitting pattern for H1. However, a more complicated pattern is observed for H1, therefore, the coupling H1 to H2 cannot be extracted directly from the proton 1-D NMR spectrum.

A homonuclear proton experiment was employed to measure the H1–H2 vicinal coupling constant. A proton spectrum was acquired selectively decoupling the H7 methyl group protons at 1.30 ppm from H1. As a result the H1 coupling pattern was simplified and reduced to H1–H2 vicinal coupling, as shown in Fig. 6B. By overlapping the normal proton spectrum with the selectively decoupled spectrum, the H1–H2 coupling constant of 12.2 Hz was extracted. This corresponds to an axial position for H1, confirming that the C-1 methyl group occupies an equatorial position. At this point the right side of the 2.57 ppm multiplet can be assigned as

H2a showing the d–d–d pattern expected for H2a, as H4a would generate a d–d–d–d pattern. As this spectral assignment for **31b** would, of course, not have been possible in the 1960s, one must admire the brilliant deductive logic employed by Djerassi et al.[18] in accurately assigning all four diastereomers of **31**.

In preliminary experiments the treatment of **31b** with NaOEt in ethanol provided (+)-carvone, identical in all respects to (–)-carvone except for the sign of optical rotation, thus accomplishing the intended enantiomeric switch. Under these conditions, however, the yields of carvone were low (~35%) at the expense of condensation products. The conditions that employ $Fe(OH)_2$ (shown in Fig. 4) provided the much improved yield of 79% for (+)-carvone.

Finally, we subjected carvol (**35**), obtained by Luche reduction of carvone according to literature protocol,[19] to the Dauben–Michno conditions at –50 °C to investigate the possibility of competition between chromate ester re-oxidation to (–)-carvone versus the Dauben–Michno transposition–oxidation to (+)-carvone (Fig. 7). The rate-determining step in chromium(VI) oxidation of alcohols is the collapse of the chromate ester[20] and not its formation. We speculated that at low temperature, the sigmatropic rearrangement of the initially formed chromate ester required for the transposition may compete with the oxidation even for secondary allylic alcohols.

If the transition state of the [3,3] rearrangement is not symmetrical along the latent plane of symmetry in carvone, then the Dauben–Michno protocol applied to carvol would provide the enantiomer directly. The initial experiment, performed at –55 °C, indeed provided a scalemic mixture of carvone with an optical rotation lower than that of the (–)-enantiomer, indicating that the two processes may indeed compete.

We performed three experiments at different temperatures (–55, –78, and –100 °C) and noted some decrease in the value of rotation for the (–)-enantiomer. However, verification of true *er* by HPLC (Daicel Chiralcel OB-H; flow = 0.6 mL/min (hexane–*i*-PrOH, 95:5; retention time for (*R*)-(–)-carvone = 9.56 min and for (*R*)-(–)-carvone = 10.41 min)[21] provided at best an indication of an ~1%–2% increase in the (+)-enantiomer. Thus, no conclusion can be drawn from these experiments. For now, the three-step high-yielding protocol for the enantiomeric switch via Dauben–Michno oxidation of cyanohydrins should suffice.

Conclusions

We have developed a reliable procedure for the conversion of enones to the corresponding β-cyanoenones with the attendant 1,3-functional transposition of the carbonyl group of the original enone. The possibility of using this transposition to generate enantiomers of enones that possess a latent plane of symmetry was tested and reduced to practice with the enantiomeric switch of (–)-carvone. Future attention should be given to a more detailed study of the Dauben–Michno oxidation of other allylic alcohols, including secondary ones, and the dependence of the outcome of such oxidation on conformational bias and stereochemical features of the substrates.

Experimental section

General procedure for the synthesis of cyanohydrins[6]

To a vial charged with the lithium salt of L-proline (0.1 mmol) was added the enone (1.0 mmol) followed by trimethylsilyl cyanide (1.0 mmol, 133 μL). After the suspension was stirred at room temperature for 12 h, an additional portion of trimethylsilyl cyanide (1.0 mmol, 133 μL) was added, and the reaction mixture was subsequently stirred for another 12 h. Upon completion, THF (2 mL) and 1 mol/L aq HCl (2 mL) were added, and the resulting solution was stirred for 1 h. Following the hydrolysis, the reaction mixture was washed with diethyl ether (30 mL) and water (5 mL), and the aqueous layer was re-extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried over magnesium sulfate with a spatula tip of sodium bicarbonate, then filtered and concentrated under reduced pressure to afford the essentially pure cyanohydrin, which was used without further purification.

General procedure for the Dauben–Michno oxidations[5]

Acetic anhydride (5.3 mmol, 0.5 mL) was added to a vial charged with chromium(VI) oxide (2.5 mmol). The mixture was stirred at 80 °C until complete dissolution (5 min). After cooling to room temperature, the solution was diluted with dichloromethane (2 mL) and added dropwise to a solution of cyanohydrin (1.0 mmol) in dichloromethane (3 mL) at 4 °C. The resulting solution was stirred for 10 min before addition of ethanol (3 mL). The solution was allowed to stir for 30 min at room temperature before concentration under reduced pressure and co-evaporated with toluene. The crude mixture was passed through a column of silica gel using dichloromethane as a solvent to yield β-cyanoenone.

1-Hydroxycyclohex-2-enecarbonitrile (5)[6,22]

^{1}H (300 MHz, $CDCl_3$) δ: 6.03–6.09 (m, 1H), 5.79 (d, 1H, J = 9.9 Hz), 1.79–2.21 (m, 6H).

3-Oxocyclohex-1-enecarbonitrile (6)[23,24]

^{1}H (300 MHz, $CDCl_3$) δ: 6.53 (s, 1H), 2.50–2.59 (m, 4H), 2.10–2.19 (m, 2H).

1-Hydroxycyclopent-2-enecarbonitrile (8)

^{1}H (300 MHz, $CDCl_3$) δ: 6.17 (dt, 1H, J= 2.3, 5.4 Hz), 5.82 (dt, 1H, J = 2.0, 5.4 Hz), 2.14–2.59 (m, 5H). ^{13}C (75 MHz, $CDCl_3$) δ: 138.81, 130.74, 120.88, 67.91, 31.01, 25.52. A by-product of this reaction was the 1,4-adduct, 3-oxocyclopentanecarbonitrile:[25] ^{1}H (300 MHz, $CDCl_3$) δ: 3.15–3.25 (m, 1H), 2.42–2.67 (m, 4H), 2.24–2.36 (m, 2H).

3-Oxocyclopent-1-enecarbonitrile (9)[26]

^{1}H (300 MHz, $CDCl_3$) δ: 6.74 (s, 1H), 2.58–2.91 (m, 2H), 2.53 (t, 2H, J = 4.8 Hz). ^{13}C (75 MHz, $CDCl_3$) δ: 206.24, 143.45, 143.04, 114.81, 34.10, 30.20.

1-Hydroxycyclohept-2-enecarbonitrile (11)

^{1}H (300 MHz, $CDCl_3$) δ: 5.99 (ddd, 1H, J = 6.3, 6.3, 11.4 Hz), 5.68 (ddd, 1H, J = 1.2, 1.2, 11.7 Hz), 3.65 (bs, 1H), 2.19–2.25 (m, 1H), 1.82–2.07 (m, 6H), 1.70–1.75 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ: 135.04, 133.16, 120.55, 71.39, 39.28, 27.50, 26.18, 25.21.

3-Oxocyclohept-1-enecarbonitrile (12)[27]

^{1}H (300 MHz, $CDCl_3$) δ: 6.56 (s, 1H), 2.63–2.67 (m, 4H), 1.82–1.93 (m, 4H). ^{13}C (300 MHz, $CDCl_3$) δ: 201.17, 142.81, 127.36, 118.95, 42.96, 32.14, 25.36, 21.14.

2-Hydroxy-2-methylbut-3-enenitrile (14)

^{1}H (300 MHz, $CDCl_3$) δ: 5.95 (dd, 1H, J = 10.2, 17.1 Hz), 5.67 (d, 1H, J = 16.8 Hz), 5.35 (d, 1H, J = 10.2 Hz), 1.67 (s, 3H). ^{13}C (300 MHz, k$CDCl_3$) δ: 137.49, 120.45, 116.77, 68.76, 28.06.

(Z)-2-Methyl-4-oxobut-2-enenitrile (15a) *(major)*

IR (film, cm^{-1}) ν: 2925, 2222, 1688, 1618, 1448, 1381, 1227, 1171, 1095, 1041, 1019, 861, 787, 665. ^{1}H (300 MHz, $CDCl_3$) δ: 10.02 (d, 1H, J = 7.8 Hz), 6.52 (dq, 1H, J = 1.5, 7.8 Hz), 2.25 (d, 3H, J = 1.5 Hz). ^{13}C (300 MHz, $CDCl_3$) δ: 189.62, 141.64, 129.26, 115.41, 21.68. MS (EI+) *m/z* % 94 (M^+ – H): 83 (15), 68 (63), 52 (29), 44 (100).

(E)-2-Methyl-4-oxobut-2-enenitrile (15b) *(minor)*

IR (film, cm^{-1}) ν: 2925, 2222, 1688, 1618, 1448, 1381, 1227, 1171, 1095, 1041, 1019, 861, 787, 665. ^{1}H (300 MHz, $CDCl_3$) δ: 10.07 (d, 1H, J = 7.8 Hz), 6.52 (dq, 1H, J = 1.5, 7.8 Hz), 2.38 (d, 3H, J = 1.5 Hz). ^{13}C (300 MHz, $CDCl_3$) δ: 189.62, 141.64, 129.26, 115.41, 21.68. MS (EI+) *m/z* % 94 (M^+ – H): 83 (15), 68 (63), 52 (29), 44 (100).

(E)-2-Hydroxy-2-methyl-3-pentenenitrile (17)

R_F = 0.76 (hexanes–EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.10 (dq, J = 15.3, 6.6 Hz, 1H), 5.55 (dd, J = 15.4, 1.7 Hz, 1H), 3.08 (brs, 1H), 1.76 (dd, J = 6.6, 1.7 Hz, 3H), 1.64 (s, 3H); –OH signal confirmed by D_2O exchange. ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 130.81, 129.02, 120.80, 68.42, 28.27, 17.26; NMR data are in agreement with those previously reported.[28]

(Z)-2-Methyl-4-oxopent-2-enenitrile (18)

R_F = 0.15 (hexanes–EtOAc, 5:1); mp 37–38 °C (white crystals, pentane–Et_2O). IR (KBr, cm^{-1}) ν: 2359, 1732, 1637, 1385. ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 6.60 (d, J = 1.5 Hz, 1H), 2.39 (s, 3H), 2.16 (d, J = 1.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ: 194.25, 140.10, 119.64, 117.12, 30.06, 22.18. MS (+EI) *m/z* (%): 109 (22), 94 (100), 66 (15), 43 (40). HRMS (+EI) calcd for C_6H_7NO: 109.05276; found: 109.05246.

1-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enecarbonitrile (27)

^{1}H (300 MHz, $CDCl_3$) δ: 5.70 (dd, 1H, J = 1.2, 3.0 Hz), 4.79 (d, 2H, J = 12.3 Hz), 3.24 (bs, 1H), 2.49–1.90 (m, 5H), 1.86 (s, 3H), 1.74 (s, 3H). ^{13}C (300 MHz, $CDCl_3$) δ: 146.85, 131.76, 128.40, 121.09, 110.18, 70.21, 41.27, 38.96, 30.67, 20.57, 17.01.

β-Cyanocarvone (28)

To a solution of crude cyanohydrin **27** (352 mg, 1.99 mmol) in dichloromethane (3 mL) cooled to –55 °C was added a solution of CrO_3 (499 mg, 4.99 mmol) and Ac_2O (2 mL) in dichloromethane (6 mL). After 30 min the reaction was quenched by the addition of methanol (10 mL) and allowed to warm to room temperature. The mixture was then concentrated and co-evaporated three times with toluene (10 mL). Chromatography of the residue (silica, 20 mL; dichloromethane–hexane, 1:1) afforded enone **28** as a light yellow solid; yield: 260 mg (75%). R_F = 0.6 (dichloromethane–hexane, 1:1). $[\alpha]_D^{20}$ = 82.8 (*c* 1, $CHCl_3$); mp 25–26 °C (neat). IR (KBr, cm^{-1}) ν: 3747, 30.85, 2970, 2925, 2218, 1688, 1648, 1439, 1383, 1318, 1295, 1140, 1108, 1070, 900. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.81 (s, 1H), 4.72 (s, 1H), 2.73–2.53 (m, 3 H), 2.45 (ddq, 1H, J = 3 × 2.4, 12.3, 17.4 Hz), 2.37 (dd, 1H, J= 12.9, 16.2 Hz), 2.00 (dd, 3H, J = 1.8, 2.4 Hz), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 196.66, 146.31, 144.74, 124.58, 116.95, 111.86, 42.60, 41.26, 33.07, 20.40, 14.86. MS (+FBA) *m/z* (%): 176 (100). HRMS could not be obtained; the compound proved to be too labile. Structure was confirmed by HRMS after reduction of the keto group.

Oxidation of 27 at elevated temperature

To a solution of crude cyanohydrin **27** (235 mg, 1.33 mmol) in dichloromethane (5 mL) cooled to 0 °C was added a solution of CrO_3 (332 mg, 3.33 mmol) and Ac_2O (0.78 mL) in dichloromethane (2.5 mL). After 20 min at 0 °C a new portion of CrO_3 (332 mg, 3.33 mmol) and Ac_2O (0.78 mL) in dichloromethane (2.5 mL) was added. After an additional 70 min, the reaction was quenched by the addition of ethanol (2 mL) and allowed to warm to room temperature over 45 min. The mixture was then concentrated. Chromatography of the residue (silica, 25 mL; Et_2O–hexane, 1:1) afforded diketone **29** (yield: 17.6 mg), epoxide **30** (yield: 73.2 mg), and a mixed fraction (yield: 61 mg).

5-Acetyl-2-methyl-3-oxocyclohex-1-enecarbonitrile (29)

$[\alpha]_D^{20}$ = 25.1 (*c* 1, $CHCl_3$). IR (film, cm^{-1}) ν: 3022, 2964, 2220, 1685, 1416, 1358, 1314, 1265, 1216, 1104, 752, 668, 629. ^{1}H (600 MHz, $CDCl_3$) δ: 3.23 (dddd, 1H, J = 4.2, 7.2, 10.5, 10.5 Hz), 2.82–2.78 (m, 3H), 2.65 (dd, 1H, J = 11.4, 16.8 Hz), 2.25 (s, 3H), 2.10 (s, 3H). ^{13}C (600 MHz, $CDCl_3$) δ: 205.98, 194.49, 146.66, 122.89, 116.56, 46.69, 38.99, 29.71, 27.88, 14.97. MS (EI+) *m/z* % 177 (M^+): 135 (45), 107 (6), 79 (7), 43 (100), HRMS calcd for $C_{10}H_{11}NO_2$: 177.1998; found: 177.0790.

2-Methyl-5-(2-methyloxiran-2-yl)-3-oxocyclohex-1-enecarbonitrile (30)

$[\alpha]_D^{20}$ = 57.5 (*c* 1, $CHCl_3$). IR (film, cm^{-1}) ν: 2927, 2218, 1686, 1436, 1386, 1313, 1140, 1070, 894, 820, 682, 622. ^{1}H (300 MHz, $CDCl_3$) δ: 2.70 (dd, 1H, J = 4.1, 14.2 Hz), 2.66–2.57 (m, 3H), 2.50–2.43 (m, 1H), 2.33–2.26 (m, 1H), 2.26–2.14 (m, 1H), 2.04 (s, 3H), 1.32 (d, 3H, J = 8.4 Hz). ^{13}C (300 MHz, $CDCl_3$) δ: 195.81, 146.45, 124.28, 116.78, 57.39, 52.64, 40.13, 39.41, 29.85, 18.82, 14.87. MS (EI+) *m/z* % 176 (M^+ – CH_3): 148 (51), 134 (100), 122 (53), 58 (81), 43 (96). HRMS calcd for $C_{11}H_{13}NO_2$: 191.2264; found: 176.0712.

(1R,2R,5S)-2-Methyl-3-oxo-5-(prop-1-en-2-yl) cyclohexanecarbonitrile (32)

A solution of enone **28** (0.1g, 0.57 mmol) with Pd/C (20 mg, 10%) in ethanol (3 mL, 95%) was hydrogenated in

an H_2 atmosphere at 80 °C for 16 h. The reaction mixture was then filtered through Celite and concentrated. Chromatography (silica, 8 mL; dichloromethane–hexane, 1:1) of crude product afforded 35 mg (34%) of fully saturated ketone **32** as a white solid. The remaining mass balance consisted of fully aromatized material identified as 2-methyl-3-cyano-5-isopropylphenol. R_F = 0.5 (dichloromethane–hexane, 1:1). $[\alpha]_D^{20}$ = –49.26 (*c* 1, $CHCl_3$); mp 77 °C (hexane). IR (KBr, cm^{-1}) *v*: 3412, 2979, 2959, 2938, 2916, 2874, 2241, 1713, 1477, 1469, 1448, 1429, 1381, 1369, 1346, 1313, 1245, 1231, 1218, 1147, 1076, 870, 628. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.58–2.44 (m, 3 H), 2.27 (dddd, 1H, *J* = 2.4, 2.7, 2.7, 13.5 Hz), 2.14 (dd, 1H, *J* =13.2, 12.9 Hz), 1.81 (ddd, 1H, *J* = 12.6, 12.6, 12.6 Hz), 1.63 (dd, 1H, *J* = 12.6, 14.1 Hz), 1.61 (m, 1H), 1.25 (d, 3H, *J* = 6.0 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 207.54, 120.28, 46.35, 44.53, 43.71, 36.13, 32.78, 32.36, 19.28, 19.06, 12.71. MS (+EI) *m/z* (%): 179 (100). HRMS (+EI) calcd for $C_{11}H_{17}N_1O_1$: 179.13101; found: 179.13136.

(3S,5S)-3-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-1-enecarbonitrile (34)

To the cooled (4 °C) solution of enone **28** (50 mg, 29 mmol) in methanol (2 mL) was added $CeCl_3{\cdot}7H_2O$ (106 mg, 29 mmol). After 5 min of stirring, $NaBH_4$ (11 mg, 29 mmol) was added portionwise. After an additional 10 min stirring, the reaction was quenched by the addition of a citric acid solution (0.5 mL, 5% *w*/*w*) and concentrated. The residue was dissolved in dichloromethane (25 mL) and washed with citric acid (5 mL, 5% *w*/*w*). The aqueous layer was re-extracted with additional dichloromethane (5 mL), the combined organic layers were dried over $MgSO_4$, and then concentrated to yield essentially pure product. Chromatography (silica, 5 mL, dichloromethane) yielded 48 mg (95%) of the allylic alcohol **34** as a colourless oil. R_F = 0.2 (dichloromethane). $[\alpha]_D^{20}$ = 40.42 (*c* 1, $CHCl_3$). IR (KBr, cm^{-1}) *v*: 3446, 3084, 2926, 2859, 2215, 1646, 1441, 1378, 1288, 1261, 1071, 1056, 1025, 895. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.81 (s, 1H), 4.76 (s, 1H), 4.24 (m, 1H), 2.36–2.13 (m, 5 H), 2.11 (s, 3H), 1.75 (s, 3H), 1.55 (ddd, 1H, *J* = 10.2, 12.0, 12.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.69, 146.75, 118.34, 110.52, 108.08, 70.25, 39.28, 36.62, 32.71, 20.43, 18.33. MS (+EI) *m/z* (%): 177 (3), 159 (100), 144 (33), 134 (59). HRMS (+EI) calcd for $C_{11}H_{15}N_1O_1$: 177.11536; found: 177.11525. HRMS (+EI) calcd for $C_{11}H_{13}N_1$: 159.10480; found: 159.10496.

Reduction of 28 to 31a, 31b, and 31c

To a round-bottomed flask containing water (5 mL) and tetrabutylammonium bromide (100 mg, 0.3 mmol) was added a solution of enone **28** (175 mg, 1.0 mmol) in toluene (5 mL). The emulsion was degassed in an ultrasonic bath for 20 min. A condenser was attached, and the system was flushed with nitrogen. Sodium bicarbonate (1.52 g, 18 mmol) was added, and the reaction mixture was heated to reflux. Sodium dithionite (7 × 200 mg, 85%, 6.95 mmol) was added in seven portions over 2 h. After an additional 30 min of stirring at reflux, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with 0.5 N HCl (5 mL), then water (5 mL), and dried over magnesium sulfate. After filtration and evaporation of the solvent, the crude mixture was purified via flash column chromatography (EtOAc in hexanes, 10%–25%) to yield 145 mg (82%) of the mixture consisting of three of the four isomers of cyanoketone **31**. This mixture was suitable for use in the elimination to (+)-carvone.

Identification of isomers 31a, 31b, and 31c

To a round-bottomed flask containing water (60 mL), sodium bicarbonate (4.31 g, 51.30 mmol), and tetrabutylammonium bromide (275 mg, 0.855 mmol) was added a solution of enone **28** (500 mg, 2.85 mmol) in toluene (60 mL). The reaction mixture was heated to reflux, and sodium dithionite (6 × 875 mg, 4.28 mmol) was added in six portions over 3 h. After an additional 1 h of stirring at reflux, the reaction mixture was allowed to cool to room temperature. The organic layer was separated from the aqueous layer and then dried over magnesium sulfate. After filtration and evaporation of solvent, the crude mixture was purified via flash column chromatography (hexane – diethyl ether, 7:1) to provide 75 mg (15%) of saturated ketone **31b** as a white solid. Further separation provided the remaining isomers **31a** and **31c**.

(1S,2S,5S)-2-Methyl-3-oxo-5-(prop-1-en-2-yl) cyclohexanecarbonitrile (31a)

R_F = 0.17 (hexanes–EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.86 (s, 1H), 4.80 (s, 1H), 3.34 (dt, *J* = 6.0, 3.7 Hz, 1H), 2.86–2.72 (m, 1H), 2.66–2.47 (m, 2H), 2.36–2.18 (m, 2H), 2.05–1.86 (m, 1H), 1.77 (s, 3H), 1.25 (d, *J* = 6.6 Hz, 3H).

^{1}H NMR data are in agreement with the literature.[14]

(1R,2S,5S)-2-Methyl-3-oxo-5-(prop-1-en-2-yl) cyclohexanecarbonitrile (31b)

White solid. R_F = 0.42 (hexane – ethyl acetate, 5:1). $[\alpha]_D^{20}$ = –56 (*c* 1, $CHCl_3$). mp 82–84 °C (first crystallization: hexanes – diethyl ether; second crystallization: mp 85–86 °C (lit.[18] mp 86.5). IR ($CHCl_3$, cm^{-1}) *v*: 2244, 1719, 1648, 1452, 901. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm) δ: 4.85 (s, 1H), 4.78 (s, 1H), 2.61–2.52 (m, 3 H), 2.40–2.36 (m, 3H), 2.01 (ddd, 1H, *J* = 10.9, 11.9, 12.4 Hz), 1.75 (s, 3H), 1.28 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz, ppm) δ: 206.66, 145.27, 119.98, 111.30, 46.28, 44.14, 36.00, 34.25, 20.23, 12.67. MS (+EI) *m/z* (%): 177 (12), 95 (55), 82 (54), 68 (100), 67 (74), 41 (41). HRMS (+EI) calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11509.

(1S,2R,5S)-2-Methyl-3-oxo-5-(prop-1-en-2-yl) cyclohexanecarbonitrile (31c)

Viscous oil; assignment is tentative (**31c** has a mp of 13 °C). IR (KBr, cm^{-1}) *v*: 2359, 1650, 1385, 1088. ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 4.87 (s, 1H), 4.79 (s, 1H), 3.14 (td, *J* = 5.1, 2.5 Hz, 1H), 2.64 (t, *J* = 12.8 Hz, 1H), 2.40 (dt, *J* = 12.8, 2.3 Hz, 1H), 1.87–1.80 (m, 1H), 1.78 (s, 1H), 1.61–1.49 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 1H). MS (+EI) *m/z* (%): 177 (27), 95 (72), 82 (52), 69 (29), 68 (100), 67 (70), 41 (42).; HRMS (+EI) calcd for $C_{11}H_{15}NO$: 177.11536; found: 177.11498.

ent-Carvone

The mixture of saturated ketones **31a**, **31b**, and **31c** obtained (445 mg, 2.5 mmol) was dissolved in MeOH (15 mL). The solution was degassed in an ultrasonic bath for 5 min (to avoid oxidation of Fe(II) by air). A condenser was attached, and $FeSO_4 \cdot 7H_2O$ (1.39 g, 5.0 mmol) was added. KOH (2.25 g, 35 mmol, 10 + 4 equiv) was added to a vigorously stirred suspension to generate $Fe(OH)_2$. The reaction flask was placed in a preheated oil bath, and the mixture heated at reflux for 20 min. The resulting dark black mixture was quickly cooled to room temperature and diluted with EtOAc (100 mL) and water (10 mL). The organic layer was washed with 0.2 N HCl (3 × 10 mL) and dried over magnesium sulfate. After filtration and evaporation of solvent, the crude product was filtered through a short pad of silica gel (eluted with 10% EtOAc in hexanes) to yield *S*-(+)-carvone (296 mg, 79%).

S-(+)-Carvone

$[\alpha]_D^{19} = +54.2$ (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.82–6.65 (m, 1H), 4.80 (s, 1H), 4.75 (s, 1H), 2.78–2.51 (m, 2H), 2.51–2.37 (m, 1H), 2.37–2.19 (m, 2H), 1.85–1.76 (m, 3H), 1.75 (s, 3H). (Commercially available (+)-carvone is 96% optically pure; (–)-carvone is 98% optically pure).

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