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An Efficient and Simple Synthesis of Optically Pure Tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron

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A Simple and Efficient Synthesis of Optically Pure Tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron

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Attachment of a (tricarbonyl)iron adjunct to an acyclic diene has been shown to effect diastereoselective bond formation at unsaturated centers *adjacent* to the (diene).[1] This diastereoselectivity can be translated into enantioselectivity if the precursor (diene)$Fe(CO)_3$ complex is optically active. For example, the enantiomers of tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron (**1**) have proven to be especially useful in asymmetric synthesis; (−)-**1** has been utilized in the synthesis of (−)-verbenalol,[2a] the leukotrienes 5-HETE,[2b] 11,12-DiHETE,[2c] LTB_4,[2d] and 2-(2`-carboxycyclopropyl)glycines,[2f] while (+)-**1**

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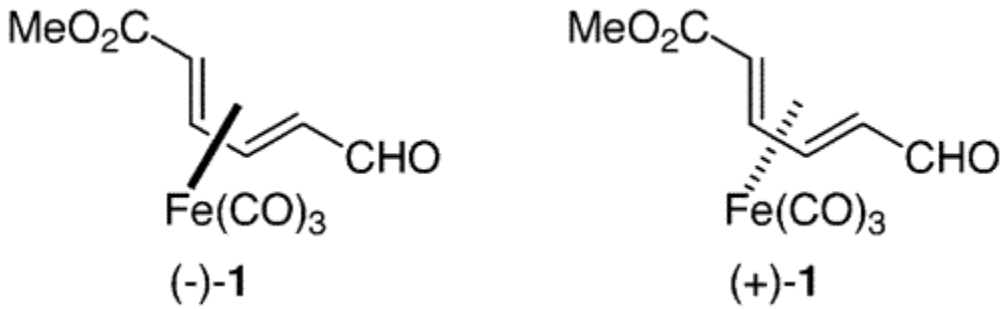
has been utilized in the synthesis of AF toxin IIa, IIb, and IIc.[2e,g] The enantiomers of **1** have been separated by classical resolution,[3a] by HPLC using β-cyclodextrin bonded columns,[3b] and by kinetic resolution via chiral allylboration[3c] or via baker's yeast mediated reduction.[3d] The enantiomers of the corresponding carboxylic acid, (6-oxo-2,4-hexadienoic acid)$Fe(CO)_3$, have also been separated by classical resolution.[3e] We herein report on a short, simple method for the preparation of optically pure (−)-**1** and (+)-**1**.



The reaction of (*R*)-glyceraldehyde acetonide[4] with the anion generated from trimethyl phosphonocrotonate gave the known[5] dienoate **2** as a mixture of *E,E* and *E,Z* isomers (ca. 3:1 ratio, 83%, Scheme 1). Complexation of **2** [$Fe_2(CO)_9$/toluene/reflux] gave a mixture of diene complexes **3**, (−)-**4**, and (+)-**5** (70−90%). Under these conditions, *E/Z* isomerization can occur and the *E,E*-diene is preferentially complexed; only a minor amount of **3** is observed in the ^{1}H NMR spectrum of the crude product. Use of other complexation conditions (e.g., $Fe(CO)_5$/TMANO or $Fe_2(CO)_9/C_6H_6$/reflux) gave significantly lower yields with little improvement in the diastereoselectivity. Notably, complexation of other chiral *acyclic E,E*-dienes generally proceeds with only modest diastereoselectivity.[6,7] Subjecting this mixture to careful column chromatography [SiO_2, hexanes−ethyl acetate (30:1 → 4:1 gradient)] gave only minor amounts of pure **4** and **5**; the majority of the material was recovered as a mixture. On the basis of an empirical relationship between the optical rotation sign and the absolute configuration of (diene)$Fe(CO)_3$ complexes bearing terminal electron withdrawing groups,[8] complex (−)-**4** was assigned the (2*R*) absolute configuration and (+)-**5** was assigned the (2*S*) absolute configuration.

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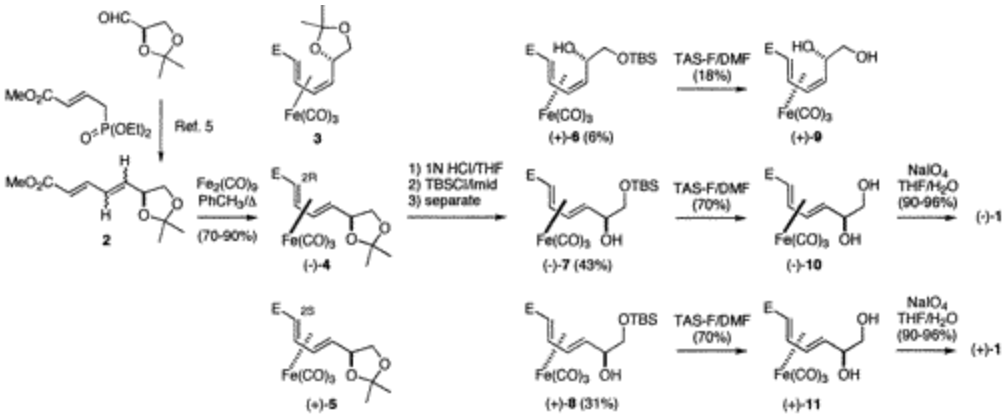

Scheme 1[a]
[a] E = CO_2Me.

Since the isolation of pure **4** and **5** was not practical on a preparative scale, derivatives more amenable to separation were sought. To this end, hydrolysis of the *crude* mixture (1 N HCl/THF) and protection of the mixture of glycols with 1 equiv of TBSCl/imidazole gave a mixture of monoprotected complexes (+)-**6**, (−)-**7**, and (+)-**8**. This mixture was cleanly separable on a preparative scale.[9] The gross structural assignments of **6**, **7**, and **8** were made on the basis of their ^{1}H NMR spectra. In particular, for **7** and **8** the H2, H3, H4, and H5 signals appear at ca. δ 0.90, 5.84, 5.47, and 1.15 ppm (**7**) and δ 1.05, 5.88, 5.55, and 1.15 ppm (**8**), respectively.[2] These chemical shifts are characteristic of 2*E*,4*E*-dienoate complexes. In comparison, for **6** the H2, H3, H4, and H5 signals appear at ca. δ 2.26, 6.00, 5.22, and 2.53 ppm, respectively. These chemical shifts are characteristic of 2*E*,4*Z*-dienoate complexes.[2b] The relative stereochemistry of **7** and **8** was *tentatively* assigned as ψ-endo and ψ-exo, respectively, on the basis of their relative chromatographic mobility (**8** more polar than **7**). It has been empirically found that ψ-exo diastereomeric alcohols are in general less mobile than their ψ-endo counterparts.[1b,10] In addition, the absolute configuration at the diene-iron segment of (+)-**6**, (−)-**7**, and (+)-**8** could be *tentatively* assigned in accord with the empirical relationship between the sign for the optical rotation and absolute configuration for (diene)$Fe(CO)_3$ complexes bearing electron-withdrawing groups.[8] These tentative assignments were eventually corroborated by separate transformation of (−)-**7** into (−)-**1** and transformation of (+)-**8** into (+)-**1**.

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Separate deprotection of (−)-**7** with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F)[11] gave (−)-**10,** while deprotection of (+)-**8** with TAS-F gave (+)-**11**, both in good yield. Deprotection of *E*,*Z*-diene complex (+)-**6** gave (+)-**9**, albeit in a only 18% yield. While (diene)iron complexes are susceptible to oxidative decomplexation, we have previously demonstrated that the (diene)$Fe(CO)_3$ group survives $NaIO_4$ oxidation.[12] Thus, glycol cleavage of (−)-**10** gave (−)-**1**, while (+)-**11** gave (+)-**1**, both in excellent yields.[13] The complexes prepared in this fashion were determined to be >96% ee on the basis of their specific rotation[3] while analysis of the ^1H NMR spectra of (−)-**1** and of (+)-**1** with a chiral shift reagent [$Eu(hfc)_3/CDCl_3$][14] indicated each to be >94% ee.

In summary, the above preparation of (−)-**1** (21%) and (+)-**1** (15%) was accomplished in five steps from glyceraldehyde acetonide. This sequence requires one distillation (**2**), and two chromatographic purifications (one for separation of the mixture of **6**, **7**, and **8**, and a second to purify the final products **1**).

Experimental Section

General Data.

Unless otherwise noted, reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Spectrograde solvents were used without purification with the exception of tetrahydrofuran which was distilled from sodium benzophenone ketyl; and CH_2Cl_2 which was distilled from P_2O_5. Anhydrous toluene was purchased from the Aldrich Chemical Co. Elemental analyses were obtained from Midwest Microlabs, LTD, Indianapolis and high-resolution mass spectral determinations were made at the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry. Melting points were determined for samples in open capillaries and are uncorrected and ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz respectively. The resonance signals for the Fe−CO were not observed due to their long relaxation times. Methyl 6,7-di-*O*-isopropylidene-6(*R*),7-dihydroxyhepta-2,4-dienoate (**2**) was prepared as described in the literature.[5]

Tricarbonyl(methyl 6,7-di-O-isopropylidene-6(R),7-dihydroxyhepta-2,4-dienoate)iron (3, 4, 5).

To a solution of methyl 6,7-di-*O*-isopropylidene-6(*R*),7-dihydroxyhepta-2,4-dienoate (**2**) (1.60 g, 7.41 mmol) in anhydrous toluene (25 mL) was added $Fe_2(CO)_9$ (3.23 g, 8.89 mmol). The mixture was heated at reflux for 1.5 h. After the mixture was cooled to room temperature, additional $Fe_2(CO)_9$ (0.81 g, 2.22 mmol) was added, and the resulting mixture was heated at reflux for 1.5 h. The latter step was repeated once more. After being cooled to room temperature, the solution was filtered through filter-aid, and the filter bed was washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure, and the residue was flash filtered through a bed of silica gel (silica gel 62, 60−200 mesh, 150 Å) with hexanes followed by hexanes−ethyl acetate (1:1). The hexanes−ethyl acetate fraction was concentrated under reduced pressure to afford the crude mixture of diene complexes **3**, **4**, and **5** (2.21 g, 84%). Generally, this mixture was used in the next step without further purification; however, subjecting this mixture to further chromatography (SiO_2, 0.35−0.07 mm, hexanes−ethyl acetate (5:1)) gave minor amounts of the pure diastereomers **4** and **5**.

(−)-**4**: R_f 0.34 (hexanes−ethyl acetate (2:1)); $[\alpha]_D$ = −182 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.81 (dd, *J* = 5.1, 8.0 Hz, 1H), 5.34 (dd, *J* = 5.1, 8.5 Hz, 1H), 4.13 (dd, *J* = 6.0, 8.0 Hz, 1H), 3.90 (q, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 3.58 (t, *J* = 7.4 Hz, 1H), 1.44 and 1.32 (2 x s, 6H), 1.23 (t, *J* = 8.4 Hz, 1H), 1.01 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.5, 109.3, 84.7, 83.9, 78.1, 70.6, 62.3, 51.7, 45.9, 26.6, 25.4; EI-HRMS *m/z* 352.0246 (calcd. for $C_{14}H_{16}O_7Fe$ *m/z* 352.0245).

(+)-**5**: R_f 0.41 (hexanes−ethyl acetate (2:1)); $[\alpha]_D$ = +134 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.88 (ddd, *J* = 1.2, 5.2, 8.3 Hz, 1H), 5.45 (dd, *J* = 5.2, 8.3 Hz, 1H), 4.11 (dd, *J* = 5.9, 8.1 Hz, 1H), 3.88 (dt, *J* = 5.8, 8.0 Hz, 1H), 3.75−3.63 (m, 1H), 3.67 (s, 3H), 1.40 and 1.37 (2 x s, 6H), 1.16 (d, *J* = 8.2 Hz, 1H), 1.09 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.2, 110.5, 86.0, 85.5, 78.2, 70.2, 59.0, 51.8, 46.8, 26.7, 26.1; EI-HRMS *m/z* 352.0244 (calcd. for $C_{14}H_{16}O_7Fe$ *m/z* 352.0245).

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Tricarbonyl(methyl 6(R)-hydroxy-7-(tertbutyldimethyl)siloxyhepta-2,4-dienoate)iron (6, 7, 8).

To a solution of the mixture of **3**, **4**, and **5** (29.57 g, 0.0840 mol) in THF (100 mL) was added 1 M HCl (100 mL). The cloudy solution was stirred at room temperature for 24 h with monitoring by TLC. During this time, the solution became clear. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give a mixture of diol complexes. The crude mixture of diols (24.38 g, 78.13 mmol) was dissolved in CH_2Cl_2 (100 mL), and imidazole (5.85 g, 85.9 mmol) was added. After all of the imidazole had dissolved, *tert*-butyldimethylsilyl chloride (11.78 g, 78.13 mmol) was added in small portions. Formation of a fine white precipitate was observed, and the mixture was stirred for 16 h. The mixture was filtered through filter-aid and the filter bed washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue (32.92 g) was purified by column chromatography in ca. 4 g batches (SiO_2 0.35−0.07 mm, hexanes−ethyl acetate (10:1)) to give (+)-**6** as a yellow solid (2.10 g, 6%), followed by (−)-**7** (15.43 g, 43%), and finally (+)-**8** (11.25 g, 31%) both as yellow oils.

(+)-**6**: mp 66−67 °C; R_f 0.54 (hexanes−ethyl acetate (5:1)); $[\alpha]_D$= +75 (*c* = 0.50 in $CHCl_3$); ^{1}H NMR δ 6.06 (ddd, *J* = 1.2, 5.3, 8.6 Hz, 1H), 5.27 (dd, *J* = 5.2, 7.7 Hz, 1H), 3.69 (s, 3H), 3.37 (m, 2H), 2.30 (m, 1H), 2.65 (d, *J* = 2.1 Hz, OH), 2.53 (dd, *J* = 8.0, 9.4 Hz, 1H), 2.26 (d, *J* = 8.6 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 173.2, 93.7, 84.0, 69.4, 68.5, 59.7, 51.7, 45.6, 25.8, 18.2, −5.4, −5.5. Anal. Calcd for $C_{17}H_{26}O_7SiFe$: C, 47.89; H, 6.14. Found: C, 47.91; H, 6.16.

(−)-**7**: R_f 0.44 (hexanes−ethyl acetate (5:1)); $[\alpha]_D$ = −116 (*c* = 0.50, $CHCl_3$); ^{1}H NMR δ 5.84 (dd, *J* = 5.1, 8.0 Hz, 1H), 5.47 (dd, *J* = 5.0, 8.5 Hz, 1H), 3.67 and 3.66 (m & s, 5H), 3.41 (t, *J* = 9.1 Hz, 1H), 2.52 (s, OH), 1.15 (t, *J* = 7.5 Hz, 1H), 0.90 (m & s, 10 H), 0.08 (s, 6H); ^{13}C NMR δ 172.5, 84.1, 83.3, 72.8, 68.7, 63.6, 51.6, 45.7, 25.8, 18.3, −5.4.

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(+)-**8**: R_f 0.27 (hexanes−ethyl acetate (5:1)); $[\alpha]_D$ = +134 (*c* = 0.50, $CHCl_3$); ^{1}H NMR δ 5.88 (dd, *J* = 5.0, 8.2 Hz, 1H), 5.55 (dd, *J* = 5.1, 8.6 Hz, 1H), 3.73 (m, 2H), 3.67 (s, 3H), 3.47 (m, 1H), 2.81 (s, OH), 1.15 (t, *J* = 7.5 Hz, 1H), 1.05 (d, *J* = 8.0 Hz, 1H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR δ 172.4, 85.6, 84.4, 73.1, 67.5, 61.0, 51.6, 46.3, 25.8, 18.3, −5.4.

Tricarbonyl((2R,5S) methyl 6(R),7-dihydroxyhepta-2(E),4(E)-dienoate)iron (−)-10.

To a solution of (−)-**7** (196.7 mg, 0.46 mmol) in DMF (5 mL) was added TAS-F (140.8 mg, 0.46 mmol). The mixture was stirred for 16 h and then poured into brine (5 mL) and extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 62, 60−200 mesh, 150 Å, hexanes−ethyl acetate (5:1 → 2:1 gradient)) to give (−)-**10** as a yellow oil (101.1 mg, 70%).

(−)-**10**: R_f 0.44 (ether); $[\alpha]_D$ = −168 (*c* = 0.5, $CHCl_3$); ^{1}H NMR δ 5.86 (ddd, *J* = 1.1, 4.8, 8.1 Hz, 1H), 5.47 (dd, *J* = 4.7, 8.9 Hz, 1H), 3.78 (br m, 2H), 3.67 (s, 3H), 3.50 (br t, *J* = 9.1 Hz, 1H), 2.47 (OH), 2.11 (OH), 1.20 (br t, *J* = 7.5 Hz, 1H), 0.97 (dd, *J* = 0.8, 8.0 Hz, 1H); ^{13}C NMR δ 172.5, 84.0, 83.6, 73.2, 68.2, 63.6, 51.7, 46.0; EI-HRMS *m/z* 311.9937 (calcd for $C_{11}H_{12}O_7Fe$ *m/z* 311.9932).

Tricarbonyl((2S,5R) methyl 6(R),7-dihydroxyhepta-2(E),4(E)-dienoate)iron (+)-11.

Reaction of (+)-**8** (163.7 mg, 0.38 mmol) with TAS-F was carried out in a fashion similar to the preparation of (−)-**10** from (−)-**7** to give (+)-**11** as a yellow oil (87.6 mg, 73%).

(+)-**11**: R_f 0.41 (ether); $[\alpha]_D$ = +182 (*c* = 0.50, $CHCl_3$); ^{1}H NMR δ 5.88 (dd, *J* = 5.0, 8.2 Hz, 1H), 5.52 (dd, *J* = 4.9, 8.6 Hz, 1H), 3.78 (d, *J* = 10.3 Hz, 1H), 3.66 (s, 3H), 3.57 (br m, 4H), 2.60 (s, OH), 2.17 (s, OH), 1.16 (t, *J* = 9.1 Hz, 1H), 1.08 (d, *J* = 8.4 Hz, 1H); ^{13}C

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NMR δ 172.5, 85.6, 84.5, 73.6, 67.0, 60.7, 51.7, 46.4; EI-HRMS *m*/*z* 311.9937 (calcd for $C_{11}H_{12}O_7Fe$ *m*/*z* 311.9932).

Tricarbonyl((2S,5S) methyl 6(R),7-dihydroxyhepta-2(E),4(Z)-dienoate)iron (+)-9.

Reaction of (+)-**6** (500 mg, 1.17 mmol) with TAS-F was carried out in a fashion similar to the preparation of (−)-**10** from (−)-**7**, to give (+)-**9** as a yellow solid (64.5 mg, 18%).

(+)-**9**: mp 103−105 °C; R_f 0.41 (ether); $[\alpha]_D$ = +62 (*c* = 0.50, $CHCl_3$); ^{1}H NMR δ 6.08 (ddd, *J* = 1.0, 5.2, 8.6 Hz, 1H), 5.29 (dd, *J* = 5.3, 7.9 Hz, 1H), 3.70 (s, 3H), 3.43 (br m, 2 H), 3.04 (br m, 1 H), 2.63 (ddd, *J* = 1.2, 8.1, 9.6 Hz, 1H), 2.54 (d, *J* = 0.5 Hz, OH), 2.15 (d, *J* = 9.1 Hz, 1H), 2.09 (s, OH); ^{13}C NMR δ 173.0, 93.9, 83.8, 69.1, 69.0, 60.2, 51.8, 45.8. Anal. Calcd for $C_{11}H_{12}O_7Fe$: C, 42.34; H, 3.88. Found: C, 42.63; H, 3.99.

Tricarbonyl((2R,5S) methyl 6-oxohexa-2(E),4(E)-di-enoate)iron (−)-1.

To a solution of (−)-**10** (368.2 mg, 1.18 mmol) in THF (5 mL) was added distilled water (5 mL). Solid $NaIO_4$ (378.4 mg, 1.77 mmol) was added to the clear yellow solution. The formation of a fine white precipitate was observed. The reaction mixture was stirred for 1.5 h at room temperature, at which time TLC monitoring indicated no remaining starting material. The mixture was filtered through filter-aid, and the filtrate was poured into brine. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 0.35−0.07 mm, hexanes−ethyl acetate (5:1)) to afford (−)-**1** as a yellow oil (318.3 mg, 96.3%): $[\alpha]_D$= −61 (*c* = 0.1, CH_3OH) [lit.[3] −62 (*c* = 0.1, CH_3OH)]; ^{1}H NMR δ 9.43 (d, *J* = 3.4 Hz, 1H), 6.03 (m, 2H), 3.70 (s, 3H), 1.52 (dd, *J* = 3.5, 8.1 Hz, 1H), 1.47 (d, *J* = 7.7 Hz, 1H). The ^{1}H NMR spectral data for this product was identical to the literature spectral data.[2b]

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Tricarbonyl((2S,5R) methyl 6-oxohexa-2(E),4(E)-dienoate)iron (+)-1.

The glycol cleavage of (+)-**11** (119.0 mg, 0.38 mmol) was carried out in a fashion similar to the preparation of (−)-**1** from (−)-**10** to give (+)-**1** (102.2 mg, 95.9%): $[\alpha]_D$= +61 (*c* = 0.1, CH_3OH) [lit.[3] +62 (*c* = 0.1, CH_3OH)]. The ^1H NMR spectral data for this product were identical to the literature spectral data.[2b]

Acknowledgment

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Supporting Information Available

Copies of the ^1H and ^{13}C NMR spectra of **4**, **5**, **7**, **8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9]From the *crude mixture* of **3**, **4**, and **5** (29.57 g), hydrolysis, TBS protection, and separation gave pure (+)-**6** (2.10 g, R_f 0.54), pure (−)-**7** (15.43 g, R_f 0.44), and pure (+)-**8** (11.25 g, R_f 0.27, hexanes−ethyl acetate = 5:1).

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