

Enantioselective Synthesis of Both Enantiomers of Methyl Dihydrojasmonate Using Solid–Liquid Asymmetric Phase-Transfer Catalysis

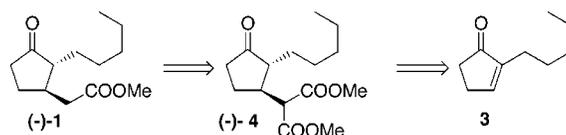
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ABSTRACT



Both enantiomers of methyl dihydrojasmonate (–)-1 and (+)-1 were obtained by a short route using asymmetric Michael addition of dimethyl malonate onto pentyl enone 3, followed by nonracemizing demethoxycarbonylation. The key enantioselective step involves a new system of asymmetric solid–liquid phase-transfer catalysis using solvent-free conditions. Enantiomeric excess as high as 90% (91% yield) was achieved.

(–)-Methyl dihydrojasmonate (–)-1 and its epimer (+)-2 are unnatural compounds, which have important olfactory properties (jasmine-like odor). Both compounds are constituents of famous fragrances.¹ Moreover, the natural parent compounds show hormonal activities in some plants.²

The compound (+)-2 epimerizes easily into (–)-1 under mild acidic or basic conditions.¹ The synthesis of *trans*-(–)-1 has often been realized by hydrogenation of the natural parent compound, i.e., *trans*-(–)-methyl jasmonate (see

Figure 1), which is a fragrance isolated from *Jasminum grandiflorum* L.³ Enantioselective syntheses of (–)-1 and (+)-2 have been published; the enantioselective steps described relying either on enamine alkylation of a chiral precursor,⁴ on catalytic asymmetric hydrogenation,⁵ or on a variant of the Claisen rearrangement.⁶

Our strategy consisted of building (–)-1 using as the key

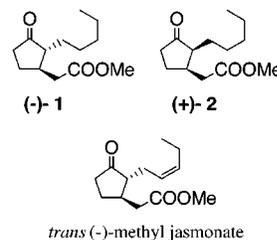


Figure 1. Structures of *trans*-methyl jasmonate and dihydrojasmonates.

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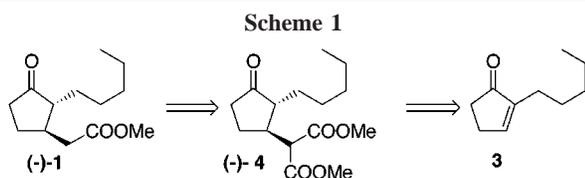
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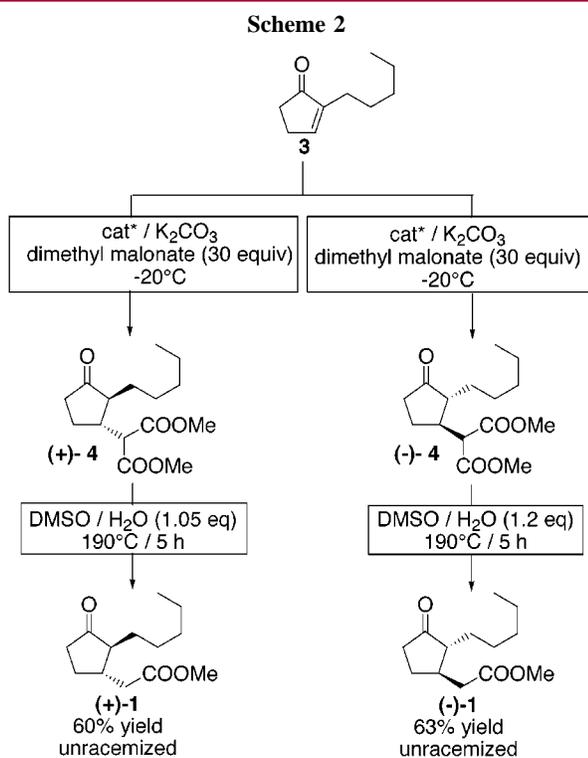
(1) Frater, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633.
(2) Ravid, U.; Ikan, R.; Sachs, R. M. *J. Agric. Food Chem.* **1975**, *23*, 835. Ishikawa, A.; Yoshihara, T.; Nakamura, K. *Biosci. Biotech. Biochem.* **1994**, *58*, 544 and references therein. Ishikawa, A.; Yoshihara, T.; Nakamura, K. *Plant Mol. Biol.* **1994**, *26*, 403. Zhang, Z.-P.; Krumm, T.; Baldwin, T. I. *J. Chem. Ecol.* **1997**, *23*, 2777. Koda Y. *Phytochemistry* **1991**, *30*, 1435. Bodnaryk, R.; Yoshihara, T. *J. Chem. Ecol.* **1995**, *21*, 1735. Seto, H.; Kamuro, Y.; Oian, Z.; Shimizu, T. *J. Pesticide Sci.* **1992**, *17*, 61.

(3) Demole, P. E. *Fragrance Chemistry*; Theimer, E. T., Ed.; Academic Press: Orlando, 1982.

step an asymmetric Michael addition of dimethyl malonate onto the enone **3** (Scheme 1).⁷



We decided to promote Michael addition under asymmetric phase-transfer catalysis and to use Krapcho conditions⁸ to achieve the demethoxycarbonylation of **4**, thus giving **1** (Scheme 2). This approach was inspired by recent advances



in the field of asymmetric phase-transfer catalysis using derivatives of *Cinchona* alkaloids.^{9,10}

We have tested the following chiral catalysts (Table 1), the structures of which are shown in Figure 2.

(4) Hill, R. K.; Edwards, A. G. *Tetrahedron* **1965**, *21*, 1501.

(5) Ets Roure-Bertrand Fils & Justin Dupont SA, no. US3978108, filed the 12/17/71. Hasegawa K. K., no. JP224916, filed the 10/11/85. Firmenich SA, no. CH96/2, 750, filed the 11/07/96. Firmenich SA, no. WO96/00206, filed the 21/06/95. Firmenich SA, no. US5874600, filed the 07/10/97. Firmenich SA, no. WO/9800776, filed the 05/19/98. See also: Dobbs, D A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J. Y.; Genêt, J. P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992.

(6) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 569.

(7) The enone is commercially available from Aldrich and can also be synthesized using Rhône Poulenc Industrialisation procedure.

(8) Krapcho, A. P. *Synthesis* **1982**, 805. Krapcho, A. P. *Synthesis* **1982**, 893.

Table 1. Michael Addition of Dimethyl Malonate onto Enone **3** (Potassium Carbonate as Base, 0.16 Equiv)

entry	catalyst (equiv)	malonate (equiv)	<i>T</i> (°C)	(+)- 4 ee (yield, ^a %)	(-)- 4 ee (yield, ^a %)
1	5 (0.10)	1	0	31	
2	5 (0.10)	2	0	32	
3	5 (0.10)	10	0	37	
4	5 (0.10)	20	0	42	
5	5 (0.10)	30	0	43	
6	5 (0.14)	30	-10	48	
7	5 (0.12)	30	-20	54 (75)	
8	6 (0.10)	30	-20	no reaction	
9	7 (0.12)	30	-20		80 (60)
10	8 (0.11)	30	-20	90 (91)	
11	9 (0.11)	30	-20	67 (21)	

^a ee was determined by NMR in the presence of Pr(hfc)₃ and confirmed by chiral HPLC. Absolute configuration of stereogenic centers was determined by chemical correlation after non racemic demethoxycarbonylation and yields quoted are after purification by flash-chromatography.

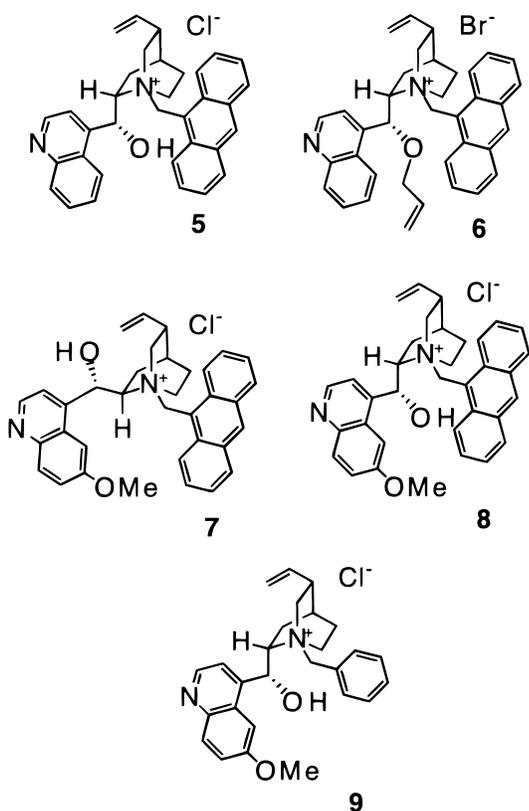
Optimization of experimental conditions led us to use simple inorganic bases such as potassium carbonate¹¹ and an excess of dimethyl malonate,¹² which played the dual role

(9) Corey, E. J.; Noe, M. C.; Xu, F.; *Tetrahedron Lett.* **1998**, *39*, 5347. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. O'Donnell, M. J. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publisher Inc.: New York, 1993; Chapter 8, p 389; *Tetrahedron, Symposia in print*, **1999**, *55* (20).

(10) For a previous description and structure determination of quinium derivatives, see: Stone, P. M. Ph.D. Thesis, Brandeis University, Waltham, Massachusetts, 1993. Pochapsky, T. C.; Stone, P. M. *J. Am. Chem. Soc.* **1991**, *113*, 1460. Hofstetter, C.; Stone Wilkinson, P.; Pochapsky, T. C. *J. Org. Chem.* **1999**, *64*, 8794. N-9-Antracenylnmethylquininium chloride **8**: To a suspension of quinine (2 g, 6.16 mmol) in toluene (40 mL) was added 9-(chloromethyl)anthracene (1.43 g, 6.29 mmol), and the mixture was stirred at reflux for 2.5 h. The mixture was cooled to room temperature, poured onto 100 mL of diethyl ether, and filtered. The solids were washed with diethyl ether and then dried in a vacuum at 50 °C. The yellow residue was collected in dichloromethane (100 mL), and the resulting suspension was refluxed for 2 h and then cooled to -15 °C. At this temperature was added diethyl ether (20 mL), and the suspension was filtered. The solids were collected and dried to give a light-brown solid (1.67 g, 49%). ¹H NMR (CDCl₃): δ = 1.40 (m, 2H); 1.84 (m, 1H); 2.16 (m, 3H); 2.62 (t, 1H, *J* = 10.5 Hz); 2.83 (m, 1H); 3.44 (m, 1H); 3.92 (s, 3H); 4.35 (t, 1H, *J* = 7.4 Hz); 4.91 (d, 1H, *J* = 3.8 Hz); 4.98 (d, 1H, *J* = 2.0 Hz); 5.12 (m, 1H); 5.50 (m, 1H); 6.24 (d, 1H, *J* = 13.6 Hz); 6.95 (d, 1H, *J* = 13.6 Hz); 7.05 (d, 1H, *J* = 5.1 Hz); 7.24–7.65 (m, 5H); 7.71 (d, 1H, *J* = 2.5 Hz); 7.83 (d, 1H, *J* = 8.2 Hz); 7.90–8.05 (m, 4H); 8.37 (s, 1H); 8.52 (d, 1H, *J* = 8.8 Hz); 8.58 (d, 1H, *J* = 4.5 Hz); 9.08 (d, 1H, *J* = 9.0 Hz). ¹³C NMR (CDCl₃): δ = 22.6; 25.4; 25.8; 38.3; 52.4; 56.3; 56.9; 61.0; 65.9; 70.8; 112.0; 117.6; 118.0; 120.9; 120.95; 123.9; 124.9; 125.6; 125.8; 126.3; 127.8; 128.5; 128.8; 129.8; 130.8; 131.1; 131.8; 132.0; 132.8; 133.2; 136.5; 143.5; 144.3; 147.5; 158.0. IR (cm⁻¹): 3014; 2952; 2398; 1620; 1509; 1471; 1450; 1428; 915. MS (FAB⁺): 515 (M⁺); 325; 191; 136. Mp: 190 °C dec. [α]_D²⁰ = -415 (c = 0.8, CHCl₃). Anal. Calcd: C, 76.28; H, 6.40; N, 5.08. Found: C, 75.98; H, 6.44; N, 5.36.

(11) Potassium carbonate can be replaced by either rubidium and cesium carbonate or by Schwesinger's bases as well as potassium *tert*-butoxide; on the other hand, lithium or sodium carbonate and potassium hydrogen carbonate failed to promote the reaction.

(12) The excess of dimethyl malonate was removed and easily recycled by simple distillation after workup. Methyl 1-carboxymethyl-1-((1*R*,2*S*)-2-pentyl-3-oxocyclopentyl)acetate ((+)-**4**): To a solution of 0.10 g of enone **3** (0.66 mmol, 1 equiv) in 2.50 mL of methyl malonate (20 mmol, 30 equiv), 40.2 mg of catalyst **8** (0.07 mmol, 0.11 equiv), and 12.4 mg of potassium carbonate (0.09 mmol, 0.14 equiv) were successively added. After magnetic stirring at -20 °C for 43 h, the reaction mixture was diluted with 20 mL of diethyl ether. The organic layer was washed successively by 2 × 5 mL of aqueous HCl (0.1 N), by 5 mL of water and 2 × 5 mL of brine. The



5 : *N*-methylantracenylninchonidinium chloride
6 : *N*-methylantracenyln O-allylcinchonidinium bromide
7 : *N*-methylantracenylnquinidinium chloride
8 : *N*-methylantracenylnquininium chloride¹⁰
9 : *N*-benzylquininium chloride

Figure 2. Structures of the catalysts.

of the reagent and the liquid organic phase. The use of an additional solvent (dichloromethane, diethyl ether, methyl *tert*-butyl ether, toluene, or THF) totally inhibited the Michael addition. Solid–liquid asymmetric phase-transfer catalysis has been previously studied by Loupy et al., who showed that both chemical yield and enantiomeric excess could be increased under such conditions.¹³

Entries 1–5 (Table 1) clearly showed that increasing the amount of dimethyl malonate up to 30 equiv increased the

organic layer was then dried over anhydrous magnesium sulfate, filtered, and evaporated. The crude pale yellow oil was distilled in a bulb-to-bulb apparatus (Kugelrohr distillation) to remove and recycle methyl malonate. Finally, flash chromatography on silica gel (eluant: heptane 70/diethyl ether 30) of the crude residue yielded 0.17 g (91%) of a colorless oil (after a treatment with charcoal). ¹H NMR (CDCl₃): δ = 0.80 (t, 3H, *J* = 6.7 Hz); 1.10–1.75 (m, 9H); 1.90–2.35 (m, 4H); 2.50–2.65 (m, 1H); 3.45 (d, 1H, *J* = 7.3 Hz); 3.70 (s, 6H). ¹³C NMR (CDCl₃): δ = 13.9; 22.4; 24.4; 25.8; 28.3; 31.9; 37.2; 40.2; 52.0; 52.4; 54.4; 168.3; 218.9. IR (cm⁻¹): 2920; 1736; 1436; 1140. GC/SM(EI): 284 (M⁺); 214; 153; 133; 109; 100; 95; 83; 69; 55. Bp: 127 °C (0.3 mmHg). ¹H NMR (CDCl₃ + 80% mol Pr-(hfc)₃) of methyl ester: 3.30 (s, integration: 5 mm); 3.18 (s, integration: 86 mm); 3.00 (s, integration: 86 mm); 2.93 (s, integration: 5 mm). 90% (± 2%) ee. [α]_D²⁰ = +19.7 (*c* = 3.0, CHCl₃). HPLC on chiral column CHIRALCEL OD (eluant: heptane 99/IPA 1; detection UV, λ = 226 nm; rate: 0.55 mL·min⁻¹): 32.53 and 35.15 min (90% ee). Anal. Calcd for C₁₅H₂₄O₅: C, 63.36; H, 8.51. Found: C, 63.58; H, 8.77.

ee. Entries 5–7 showed that the best conditions of temperature were about –20 °C. Entries 7–11 clearly demonstrated that the benzyl group (catalyst **9**) is less efficient than the *N*-9-methylantracenyln group and that the cinchonidine derivative (catalyst **5**) is less selective than quinine derivative (catalyst **8**). We also observed the pseudoenantiomeric effect when testing the *N*-alkylated quinidinium catalyst **7** in the reaction, compared to the stereoselectivity of the *N*-alkylated quininium catalyst **8**. Nevertheless, yield and ee were slightly lower. When the oxygen atom was protected with an allyl group (catalyst **6**, Corey's catalyst), no reaction took place. As previously assumed,¹⁴ we believe that a free hydroxyl function on the alkaloid is directly involved in the reactivity of the catalytic system.

Regarding the mechanism of asymmetric induction, we believe that the three-dimensional arrangement of the catalyst is similar to the conformation described by Corey.⁹ According to this hypothesis, the bulky substituents (*N*-9-anthracenyln and 6-methoxyquinoline) block two of the accessible faces to the ammonium ion and limit the area for the positioning of the dimethyl malonate anion. Thus, the approach of the electrophile could be directed by three criteria:

(1) hydrogen bonding between the free hydroxyl function of the catalyst and the carbonyl function of the electrophile, as indicated by the unreactivity of the O-allylated catalyst (Table 1, entry 8).

(2) van der Waals interactions between the methoxy group of the catalyst and the electron-deficient carbon atom of the polarized enone. The lack of methoxy group in the cinchonidine series thus explains the decrease in asymmetric induction (Table 1, entry 7).

(3) Steric interactions between the 6-methoxyquinoline and *N*-9-anthracenyln groups of the catalyst with the pentyl chain of the electrophile **3**. *N*-Benzyl catalyst **9** is thus less selective (Table 1, entry 11), and the use of 2-cyclopenten-1-one as electrophilic reagent gave only 50% ee (91% yield). For this

(13) Loupy, A.; Sansoulet, J.; Zaparucha, A.; Merienne, C. *Tetrahedron Lett.* **1989**, *30*, 333. Loupy, A.; Bram, G.; Sansoulet, J. *New J. Chem.* **1992**, *16*, 233. Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473. Mirza-Aghayan, M.; Etemad-Moghadam, G.; Zaparucha, A.; Berlan, J.; Loupy, A.; Koenig, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2643.

(14) Colonna, S.; Annunziata, R. *Afinidad* **1980**, *38*, 501. Loupy, A.; Bram, G.; Sansoulet, J. *New J. Chem.* **1992**, *16*, 233.

(15) (+)-Methyl dihydrojasmonate(+)-**1**: (*trans*-methyl ((1*S*,2*S*)-2-pentyl-3-oxocyclopentyl)acetate): To 3 mL of DMSO were added 0.15 g of (+)-**4** (0.53 mmol, 1 equiv) and 10 μL of distilled water (0.55 mmol, 1.05 equiv). The mixture was stirred for 5 h at 190 °C with a previously heated mineral oil bath. At room temperature, the reaction mixture was poured into 40 mL of ethyl ether. The organic layer was washed with 3 × 5 mL of water, 5 mL of brine, dried over anhydrous magnesium sulfate and concentrated. Traces of DMSO were removed under reduced pressure and residual oil was flash-chromatographed on silica gel (eluant: heptane 80/diethyl ether 20) to give 0.07 g of a colorless oil (60% yield). ¹H NMR (CDCl₃): δ = 0.84 (t, 3H, *J* = 6.5 Hz); 1.10–1.60 (m, 9H); 1.75 (m, 1H); 2.00–2.40 (m, 5H); 2.60 (qn, 1H, *J* = 10.4 Hz); 3.67 (s, 3H). ¹³C NMR (CDCl₃): δ = 13.9; 22.3; 26.2; 27.1; 27.6; 32.0; 37.6; 37.9; 38.8; 51.5; 54.1; 172.5; 219.6. IR (cm⁻¹): 2960; 2928; 1737; 1436; 1195; 1168. GC/SM(EI): 226 (M⁺); 195; 156; 109; 96; 83; 67; 55. Bp: 108 °C (0.3 mm Hg). GC on chiral column (Supelco β-dex 120 (15 m/0.25 mm) 1.3 mL·min⁻¹): 34.40 and 34.63 min and measurements of optical rotations clearly showed that the reaction occurred without any racemization, as checked on several samples starting with variously enriched (+)-**4** and (–)-**4** (lit. [α]_D²⁰ = +33.8 (*c* = 0.9, CHCl₃) Demole, E.; Lederer, E.; Mercier, D.; *Helv. Chim. Acta* **1962**, *45*, 675. Cross, B. E.; Webster, G. R. B.; *J. Chem. Soc. C* **1970**, 1839). Anal. Calcd for C₁₃H₂₂O₃: C, 68.99; H, 9.80. Found: C, 68.64; H, 9.98.

reason, we believe the enone **3** has few possible alternative orientations to fit in the catalyst. The most likely approach is shown in the Figure 3.

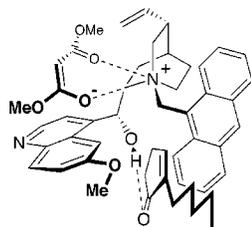
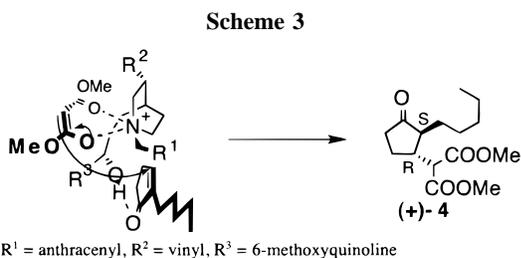


Figure 3. Model of asymmetric induction.

The hydrogen bonding ensures the proximity of the reactive centers and significantly stabilizes the model. The putative transition-state assembly shown in the Scheme 3 can explain the enantioselective addition of dimethyl mal-



onate. In this case, the Re face of the prochiral enone **3** is more accessible for the nucleophilic attack of dimethyl malonate. It leads to compound (+)-**4** with the observed absolute configuration (1*R*,2*S*).

Finally, having in hand compound **4** highly enantiomerically enriched, we achieved the synthesis of both enantiomers of methyl dihydrojasmonate **1** using the Krapcho procedure (Scheme 1). We observed no racemization during this demethoxycarbonylation step, as confirmed by optical rotations and GC analyses of compounds (+)-**1** and (–)-**1**.¹⁵ Moreover, this chemical correlation allowed us to assign the absolute configuration of the stereogenic centers of enantiomers (+)-**4** and (–)-**4**.

In conclusion, this solid–liquid asymmetric phase-transfer catalytic process constitutes a new and efficient method for access to both enantiomers of methyl dihydrojasmonate **1**. The main advantages of this procedure are the following: (1) the asymmetric Michael addition is solvent free. (2) Two contiguous stereogenic centers are built in the same step on the electrophilic substrate. (3) High enantioselectivities are reached even though no stereogenic center is created on the nucleophilic reagent (a common requirement for high enantioselection).¹⁶ (4) There is convenient access to both enantiomers of methyl dihydrojasmonate starting from the same precursor, taking advantage of the pseudoenantiomeric effect of *Cinchona* derivatives.

Extension of the method to other prochiral enones is in progress.

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(16) For a recent related example of highly enantioselective Michael reaction, see: Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.