Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1035–1038

TETRAHEDRON: *ASYMMETRY*

Lipase-catalyzed preparation of both enantiomers of methyl jasmonate

Hiromasa Kiyota,* Emi Higashi, Takanori Koike and Takayuki Oritani

Department of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

Received 12 March 2001; accepted 5 April 2001

Abstract—Preparation of both enantiomeric methyl jasmonates **1** was achieved via lipase-catalyzed resolution of (±)-methyl 7-epicucurbate **3**. Lipase P (Amano) provided good selectivity both for acylation of (±)-**3** ($E=370$) and hydrolysis of the corresponding acetate ($E=41$). Resolution of (±)-methyl 6,7-diepicucurbate **2** gave poor results. It was found that the (6*R*,7*S*)-configuration was suitable for the selective enzymatic reaction and the C-(3) stereochemistry of the substrate did not influence the enzymatic reaction.

1. Introduction

(−)-Methyl jasmonate (−)-**1** (Fig. 1) isolated from jasmine has been found to play important roles in plant growth regulation, including growth promotion and inhibition, potato tuber formation and signal transduction.[1] A recent development of the industrial production of (±)-methyl jasmonate (±)-**1** by Nippon Zeon Co., Ltd. has made it possible to use **1** as a plant growth regulator.[2] In addition, **1** is also an important perfumery constituent, being responsible for the familiar jasmine fragrance.[3] As is common for many natural products, the plant hormonal activities of the natural (−)-**1** are much higher than those of its enantiomer,[4] so a practical preparative method for the natural enantiomer is highly desirable. To date, preparative methods using asymmetric synthesis[1b,5] and resolution methods[6] to prepare (−)-**1** have been reported. However, none of these is especially practical. Since hydrolytic enzymes and microorganisms have been shown to be useful for the preparation of homochiral compounds on a large scale,[7] we examined the enzymatic resolution of (±)-**1**.

2. Results and discussion

2.1. Outline

Dart et al.[6a,b] reported the biocatalyst-mediated hydrolysis of the methoxycarbonyl group of (±)-**1** and its reduced derivative (±)-**2** and (±)-**3**,[8,9] which also showed

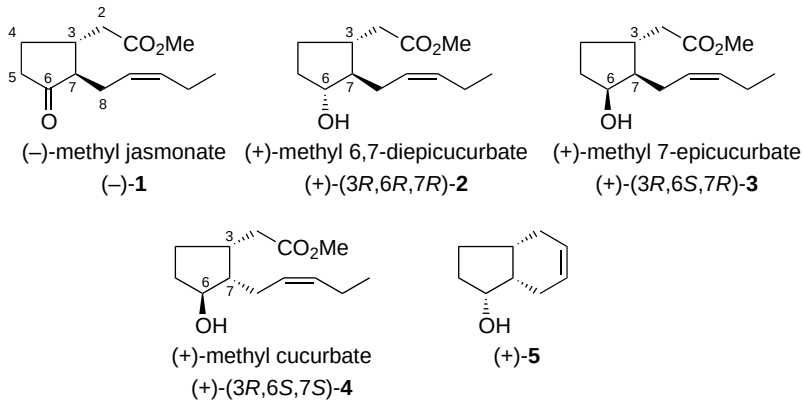


Figure 1. Methyl jasmonate and related compounds.

* Corresponding author. Tel./fax: +81-22-717-8783; e-mail: kiyota@biochem.tohoku.ac.jp

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00169-0

plant growth inhibitory activity.[9] However, the resulting carboxylic acids were formed with moderate e.e.s of <80%. We have previously reported the synthesis of (+)- and (−)-methyl cucurbate **4** via the enzymatic resolution of the bicyclic compound (±)-**5**.[10] We planned to resolve (±)-**2** and (±)-**3** by modifying the 6-hydroxyl group using a similar enzymatic strategy.

2.2. Synthesis of the substrates for enzymatic resolution

As shown in Scheme 1, commercially available methyl jasmonate [Jasmoneige®, (±)-**1** (*trans*/*cis*=20:1)] was treated with DBU in Et_2O to increase the purity of the *trans*-isomer. Using this procedure the purity of the *trans*-isomer was increased to >99%. The keto carbonyl group was then reduced with $NaBH_4$ to give two separable diastereomeric alcohols (±)-**2** and (±)-**3** in high yield.[8,9]

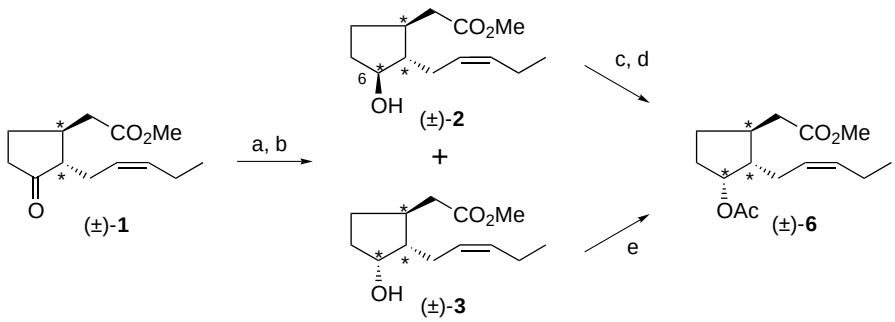
2.3. Enzymatic reaction

2.3.1. Resolution of (±)-methyl 6,7-diepicucurbate (±)-2. The enzyme-catalyzed resolution of (±)-**2** was first examined. Transesterification of (±)-**2** with vinyl acetate or vinyl chloroacetate gave poor results ($E=1\sim2$)[11] with all of the enzymes tested: lipase MY (Meito); P, PS30 (Amano); P, 2G and Rhilipase® (Nagase); immobilized lipase (TOYOBO); and CHIRAZYME® L-2 c.-f. C2 (Roche). Similarly, hydrolysis of the corresponding *O*-acetyl derivative[9a] of (±)-**2** using the same enzymes failed, with only lipase P (Amano) showing a moderate result ($E=3.6$).

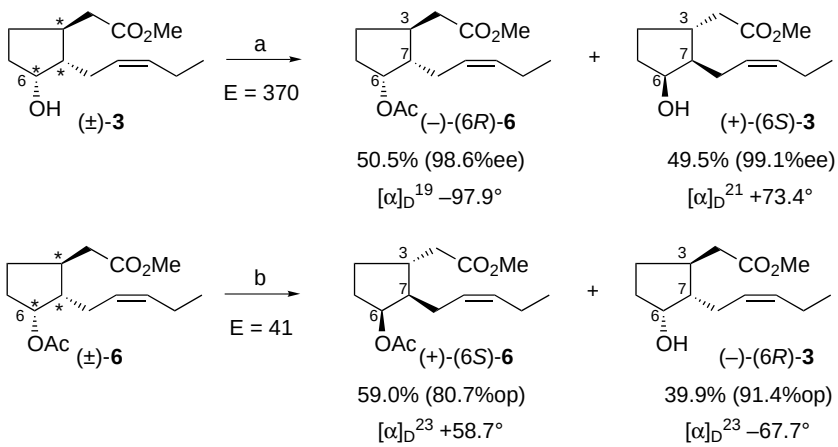
2.3.2. Resolution of (±)-methyl 7-epicucurbate (±)-3. As shown in Scheme 2 the reaction of (±)-**3** with vinyl acetate catalyzed by lipase P (Amano) occurred with good selectivity ($E=370$). The e.e. of (+)-(6*S*)-**3** was determined to be 99.1% by ^1H NMR analysis of the corresponding 6-*O*-MTPA esters. The (6*R*)-hydroxyl group was predominantly acylated in the reaction.

Hydrolysis of the corresponding acetate (±)-6[9a] was then investigated. In this case lipase P (Amano) also gave a good result ($E=41$), while lipase PS (Amano) showed moderate selectivity ($E=24$). Since (±)-**2** was shown to be a poor substrate for enzymatic resolution, it was converted to (±)-**6** with inversion at the 6-position for efficient preparation of the title compounds (Scheme 1). The combined (±)-**6** could be used in the enzymatic hydrolysis.

The results obtained indicate that the (6*R*,7*S*)-configuration is essential for resolution. This conclusion is in good accordance with our previous observations on **5**,[10] in which (+)-**5** with configuration corresponding to (6*R*,7*S*)-**3** and (6*R*,7*S*)-**6** was catalyzed selectively by hydrolytic enzymes. The configuration at the 3-position



Scheme 1. Preparation of the substrates for enzymatic reaction: (a) DBU, Et_2O (quant.); (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH [35.6% of (±)-**2** and 62.9% of (±)-**3**]; or $NaBH_4$, MeOH [68% of (±)-**2** and 23% of (±)-**3**]; (c) MsCl, pyridine, DMAP, $CHCl_3$; (d) KOAc, 18-c-6, toluene (78% in two steps); (e) Ac_2O, pyridine (94.3%).



Scheme 2. Lipase-catalyzed resolution of (±)-methyl 7-epicucurbate **3**: (a) lipase P (Amano), vinyl acetate, *i*-Pr_2O, 25°C; (b) lipase P (Amano), hexane, phosphate buffer (pH 7.0), 25°C.

does not appear to influence the affinity of the enzymes for the substrates.

2.4. Preparation of (+)- and (−)-methyl jasmonate

Oxidation of (+)-(6*S*)-**3** afforded (−)-methyl jasmonate, (−)-**1** (Scheme 3), the natural enantiomer, while (−)-(6*R*)-**6** was converted to (+)-methyl jasmonate unnatural, (+)-**1**. The total combined yields of (−)-**1** and (+)-**1** from enzymatic transesterification of the racemate were 41 and 21%, respectively.

3. Conclusion

Preparation of (−)-methyl jasmonate (−)-**1**, an important perfumery and plant growth regulatory compound, was achieved via the lipase-catalyzed resolution of (±)-methyl 7-epicucurbate **3**. Lipase P (Amano) provided good selectivity both for acylation of (±)-**3** ($E=370$) and hydrolysis of the corresponding acetate ($E=41$). The enzyme reacted preferentially with the (6*R*,7*S*)-substrate while the (6*S**,7*S**)-substrate was not accepted by the enzyme. The stereochemistry at the 3-position appears to be unimportant to the outcome of the reaction. The enzymatic method we have presented is thus an efficient method for the synthesis of both (−)-**1** and (+)-**1**, and provides a practical means for the supply of these compounds.

4. Experimental

4.1. General

Optical rotations were measured on HORIBA SEPA-300. ^{1}H NMR spectrum was recorded on Varian UNITY 500 (500 MHz) in $CDCl_3$ using Me_4Si as an internal standard. Column chromatography was performed with Merck silica gel 60, mesh size 0.063–0.200 mm. Preparative TLC plates (0.75 mm thickness) were made of Merck silica gel 60 PF_{254}.

4.2. (±)-Methyl 6-*O*-acetyl-7-epicucurbate (±)-6

A solution of (±)-**2** (0.730 g, 3.23 mmol), MsCl (1.2 mL, 16 mmol), pyridine (1.3 mL), DMAP (63 mg) in $CHCl_3$ (30 mL) was stirred at 20°C for 12 h. The reaction mixture was diluted with $CHCl_3$, washed with satd aq. $CuSO_4$ soln, satd aq. $NaHCO_3$ soln and brine, dried ($CaCl_2$) and concentrated in vacuo. The residual oil was used in the next step without further purification. The crude mesylate, AcOK (3.9 g, 40 mmol), 18-crown-6 ether (1.72 g, 6.51 mmol) in toluene (70 mL) was stirred under reflux for 7 days. The mixture was filtered and the filtrate concentrated in vacuo. The residue was diluted with H_2O and extracted with ether. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 9:1) to give (±)-**6** (0.686 g, 2.56 mmol, 79%).

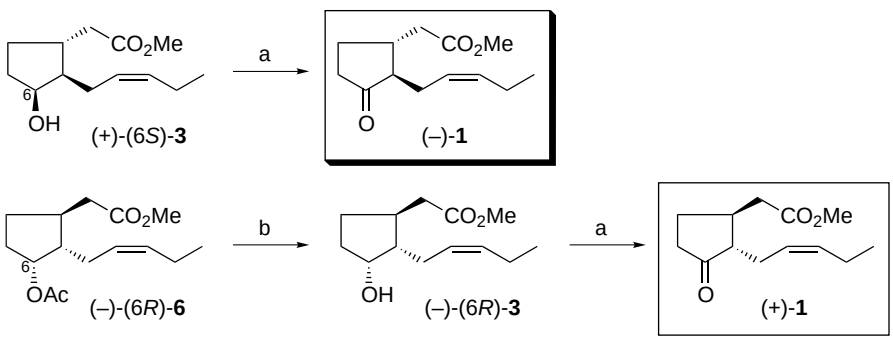
4.3. Enzymatic transesterification of (±)-3

A suspension of (±)-**3** (1.03 g, 4.55 mmol), vinyl acetate (5 mL), di-*iso*-propyl ether (10 mL) and lipase P (Amano, 1.0 g) was stirred vigorously at 25°C for 4 days. The reaction was monitored by TLC. The suspension was filtered through a Celite pad and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 6:1) afforded (−)-**6** (618 mg, 2.30 mmol, 50.5%) and (+)-**3** (510 mg, 2.25 mmol, 49.5%).

(+)-**3**: $[\alpha]_D^{21}=+73.4$ (*c* 1.20, $CHCl_3$), $[\alpha]_D^{23}=+81.9$ (*c* 1.07, MeOH) {lit.[8] $[\alpha]_D^{22.5}=+64.2$ (*c* 0.5, MeOH)}.

(−)-**6**: $[\alpha]_D^{19}=-97.9$ (*c* 0.985, $CHCl_3$). Alkaline hydrolysis (K_2CO_3, MeOH) of (−)-**6** gave (−)-**3** in 74% yield, $[\alpha]_D^{23}=-71.2$ (*c* 0.975, $CHCl_3$).

The e.e. of (+)-**3** was determined to be 99.1% by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester. A solution of (+)-**3** (19.4 mg, 0.0860 mmol), (*R*)-(−)-MTPACl (30 μL, 0.16 mmol), pyridine (0.150 mL), DMAP (8.5 mg) in CH_2Cl_2 (0.2 mL) was stirred at 20°C for 2 days. The reaction mixture was diluted with satd aq. $NaHCO_3$ soln and extracted with ether. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on preparative TLC (hexane/EtOAc = 3:1) to give the (*S*)-MTPA ester of (+)-**3** (37.3 mg, 0.0840 mmol, 98%). ^{1}H NMR (500 MHz) δ: 3.516 (pseudo q, CH_3OCCF_3, 99.55%) and 3.559 (0.45%). Consequently, the e.e. of (−)-**6** was estimated to be 98.6%.



Scheme 3. Preparation of (−)- and (+)-methyl jasmonates **1**: (a) Dess–Martin periodinane, CH_2Cl_2 [98.3% for (−)-**1**, 66.6% for (+)-**1**]; (b) K_2CO_3, MeOH (73.6%).

4.4. Enzymatic hydrolysis of (±)-6

A suspension of (±)-**6** (220 mg, 0.820 mmol) and lipase P (Amano, 200 mg) in hexane (2 mL) and 0.1 M phosphate buffer (pH 7.0, 2 mL) was stirred vigorously at 25°C for 5 days. The reaction was monitored by TLC. The suspension was filtered through a Celite pad. The filtrate was diluted with satd aq. $NaHCO_3$ soln, extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel column chromatography (hexane:EtOAc = 5/1) afforded (+)-**6** (130 mg, 0.484 mmol, 59.0%) and (−)-**3** (74.0 mg, 0.327 mmol, 39.9%).

(+)-**6**: $[\alpha]_D^{23} = +58.7$ (*c* 1.09, $CHCl_3$), e.e. = 80.7%.

(−)-**3**: $[\alpha]_D^{23} = -67.7$ (*c* 1.39, $CHCl_3$), e.e. = 91.4%.

The e.e. values were calculated from the specific rotation values of the compounds described in Section 4.3.

4.5. (−)-Methyl jasmonate [natural] (−)-1

A solution of (+)-**3** (273 mg, 1.21 mmol), Dess–Martin periodinane (667 mg, 1.58 mmol) in CH_2Cl_2 (5 mL) was stirred at 20°C for 1 h. The mixture was diluted with EtOAc, quenched with satd aq. $Na_2S_2O_3$ soln, washed with satd aq. $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 3:1) to afford (−)-**1** (268 mg, 1.19 mmol, 98%) as a colorless oil, $[\alpha]_D^{22} = -94.4$ (*c* 1.26, MeOH) {lit.[5] $[\alpha]_D^{23} = -90.2$ (*c* 1.03, MeOH)}.

4.6. (+)-Methyl jasmonate (+)-1

In the same manner as described for (−)-**1**, (−)-**3** (64.3 mg, 0.290 mmol) gave (+)-**1** (43.4 mg, 0.193 mmol, 67%), $[\alpha]_D^{23} = +86.3$ (*c* 0.985, MeOH) {lit.[5] $[\alpha]_D^{20} = +90.4$ (*c* 0.31, MeOH)}.

Acknowledgements

We thank Nippon Zeon Co., Ltd. for the gift of (±)-methyl jasmonate (Jasmoneige®). We also thank Amano Pharmaceutical Co., Ltd., Nagase & Co., Ltd., Roche Diagnostics K. K. and Toyobo Co., Ltd. for the gifts of various lipases.

References

1. Recent reviews: (a) Wasternack, C.; Miersch, O.; Kramell, R.; Hause, B.; Ward, J.; Beale, M.; Boland, W.; Parthier, B.; Feussner, I. *Fett/Lipid* **1998**, *100*, 139–146; (b) Beale, M. H.; Ward, J. L. *Nat. Prod. Rep.* **1998**, *15*, 533–548.
2. (a) Yoshioka, A.; Yamada, T. *J. Synth. Org. Chem. Jpn.* **1990**, *18*, 56–64 (in Japanese); (b) Kataoka, H.; Yamada, T.; Goto, K.; Tsuji, J. *Tetrahedron* **1987**, *43*, 4107–4112.
3. Demole, E.; Lederer, E.; Mercier, D. *Helv. Chim. Acta* **1962**, *45*, 675–685.
4. Koda, Y.; Kikuta, Y.; Kitahara, T.; Nishi, T.; Mori, K. *Phytochemistry* **1992**, *31*, 1111–1114.
5. Montforts, F.-P.; Gesing-Zibulak, I.; Grammenos, W. *Helv. Chim. Acta* **1989**, *72*, 1852–1859.
6. (a) Dart, R. K.; Kerry, S.; Marples, B. A. *Enzy. Microb. Technol.* **1992**, *14*, 954–958; (b) Kerry, S.; Dart, R. K.; Marples, B. A. *Enzy. Microb. Technol.* **1993**, *15*, 818–820; (c) Yamane, H.; Takahashi, N.; Ueda, J.; Kato, J. *Agric. Biol. Chem.* **1981**, *45*, 1709–1711; (d) Nishida, R.; Acree, T. E.; Fukami, H. *Agric. Biol. Chem.* **1985**, *49*, 769–772; (e) Okamoto, M.; Nakazawa, H. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1172–1173.
7. Recent reviews: (a) Mori, K. *Synlett* **1995**, 1097–1109; (b) Theil, F. *Chem. Rev.* **1995**, *95*, 2203–2227; (c) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769–3826; (d) Roberts, S. M.; Williamson, N. M. *Curr. Org. Chem.* **1997**, *1*, 1–20; (e) Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1608–1633.
8. Dathe, W.; Schindler, C.; Schneider, G.; Schmidt, J.; Porzel, A.; Jensen, E.; Yamaguchi, I. *Phytochemistry* **1991**, *30*, 1909–1914.
9. (a) Seto, H.; Kamuro, Y.; Qian, Z.-h.; Shimizu, T. *J. Pesticide Sci.* **1992**, *17*, 61–67; (b) Seto, H.; Nomura, E.; Fujioka, S.; Koshino, H.; Suenaga, T.; Yoshida, S. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 361–367.
10. Takehara, J.; Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1991**, *55*, 2939–2944.
11. Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695–707.