Lipase-Catalyzed Asymmetric Dealkoxylcarbonylation of σ-Symmetrical β-Ketodiesters and Its Application to the Synthesis of (–)-Podocarpic Acid

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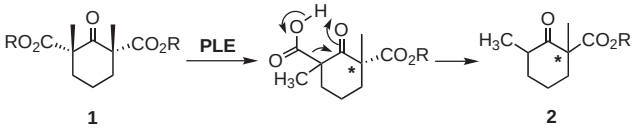
Abstract: Optically active 2,6-dimethylcyclohexanone-2-carboxylate was prepared by PLE-catalyzed dealkoxycarbonylation of σ-symmetrical β-ketodiesters, which possess quarternary carbons at α- and α′-positions. Moreover, (–)-podocarpic acid was prepared in a short sequence from 2,6-dimethylcyclohexanone-2-carboxylate.

Key words: dealkoxycarbonylation, PLE catalysis, β-ketodiesters, hydrolysis

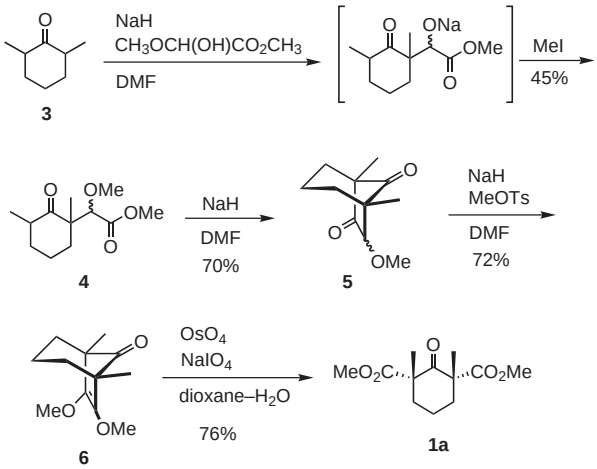
σ-Symmetrical β-ketodiesters can be easily converted to chiral β-ketoesters by esterase-catalyzed reactions since one of the two prochiral esters is selectively hydrolyzed to a β-ketocarboxylic acid and spontaneous decarboxylation proceeds by acid treatment of the reaction medium. We have recently succeeded in the formal total synthesis of (+)-carbacyclin and (+)-ferruginine by applying porcine pancreatic lipase (PPL)- or porcine liver esterase (PLE)-catalyzed reactions to σ-symmetrical β-ketodiesters as a key step to prepare chiral synthons.[1]



Scheme 1

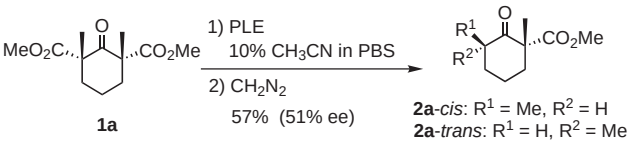
Herein, we would like to report a new type of PLE-catalyzed dealkoxycarbonylation, in which σ-symmetrical substrates of β-ketodiesters **1** with quarternary carbons at α- and α′-positions afford optically active methyl 2,6-dimethylcyclohexanone-2-carboxylate **2** (Scheme 1). Furthermore, (–)-podocarpic acid was prepared from **2** in a short sequence to show its usefulness as a chiral synthon for the synthesis of diterpenoids.

Preparation of the substrate **1a** by a PLE-catalyzed reaction posed some problems – the introduction of a pair of substituents on the α- and α′-carbons of cyclohexanone might not proceed, but O-alkylation could occur due to steric hindrance; in addition, the synthetic strategy would require tight stereochemical control to avoid production of the *trans* isomer of **1a**. Therefore, we prepared **1a** from commercially available 2,6-dimethylcyclohexanone (**3**) by taking advantage of a Dieckmann-type condensation. Treatment of **3** with sodium hydride and methyl 2-hydroxy-2-methoxyacetate and quenching of the reaction with methyl iodide afforded methyl 2-(1,3-dimethyl-2-oxocyclohexyl)-2-methoxyacetate (**4**). The Dieckmann-type condensation of **4** with sodium hydride gave [3.2.1]-bicyclic ketone **5**, which was transformed to **6** with sodium hydride and methyl tosylate. The double bond of **6** was oxidatively cleaved with osmium tetroxide in the presence of sodium periodate[2] to yield the desired dimethyl ester **1a**.



Scheme 2

Next, σ-symmetrical β-ketoester **1a** was treated with PLE (3,000 units/mmol of substrate) in phosphate buffer solution (PBS: 100 mM, pH 8) and a range of organic solvents were tested. The reaction using 10% acetonitrile as co-solvent in PBS (Scheme 3) was more successful than those using other solvents, such as ethanol, isopropanol, and DMSO.



Scheme 3

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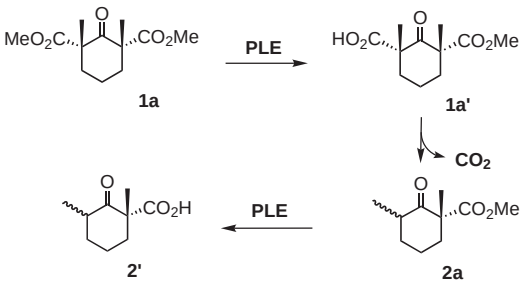
Unexpectedly, however, production of **2a** was not observed by TLC during the reaction, but extraction of the acidified reaction medium with diethyl ether followed by treatment of the extracted residue with diazomethane afforded a mixture of *cis* and *trans* isomers of **2a** (vide infra).

This result meant that β-ketocarboxylic acid **2′** isolated as methyl ester **2a** seemed to be stable and did not undergo decarboxylation even under acidic conditions while decarboxylation of plausible intermediate **1a′** proceeded readily (Scheme 4).



Scheme 4

X-ray crystallography of **1a** and the PM3 calculation could explain the stability difference between the products **2′** and the intermediates **1a′** toward dealkoxycarbonylation. Since the two ester groups of **1a** in a stable conformation take up an axial position (Figure 1), the carboxylic acid generated by hydrolysis of one of the two methyl esters should be held in the axial position. Thus, the favored interaction between the bonding orbital of the σ-bond on the α-carbon and the anti-bonding orbital of the π-bond (π*) of the ketone on the cyclohexanone moiety

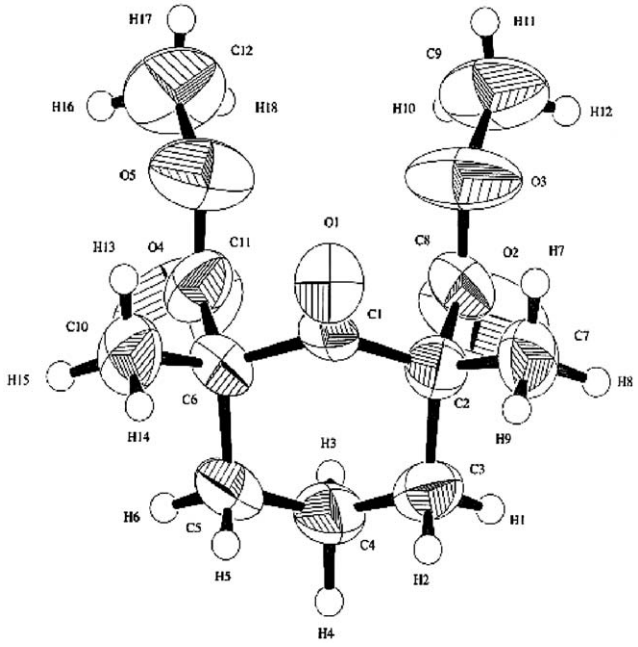
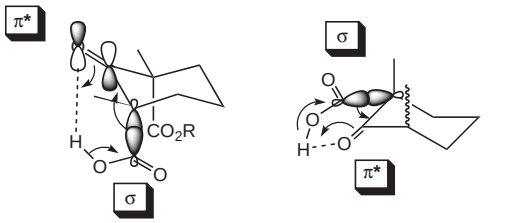


Figure 1 ORTEP of **1a**

accelerated decarboxylation (Figure 2, left), which afforded **2a**.

On the other hand, the PM3 calculation revealed that the conformation of **2′**, the final product of the PLE-catalyzed reaction, was stabilized (1.519 kcal/mol) by forming a hydrogen bond even in the case of the *cis*-dimethyl isomer. The lack of σ–π* interaction accounted for the stability of **2′** toward decarboxylation (Figure 2, right).

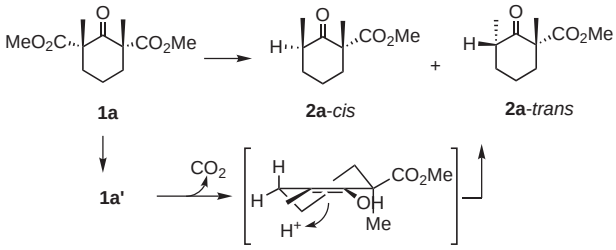
It was noteworthy that dealkoxycarbonylation of **1a** under non-enzymatic conditions using lithium hydroxide followed by methylation with diazomethane afforded (±)-**2a**-*trans* prior to (±)-**2a**-*cis*. The PM3 calculation exposed a stable enolate intermediate conformation generated by decarboxylation of **1a′**, which after protonation yielded **2a**-*trans* due to the stereoelectronic effect (Table 1). Since the PLE-catalyzed reaction mainly afforded **2a**-*cis*, it was suggested that PLE might effect decarboxylation and protonation as well as hydrolysis of ester bonds.



axial carboxylic acid *equatorial* carboxylic acid

Figure 2

Table 1 Dealkoxycarbonylation of **1a**



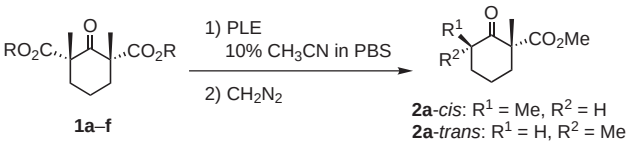
Method	Conditions	*cis*/*trans*
Enzymatic	PLE, 10% CH_3CN–PBS (pH 8.0), 48 h; CH_2N_2	**3**:1
Chemical	LiOH, THF–H_2O, 16 h; CH_2N_2	2:**15**

Next, the methyl ester groups of **1a** were replaced with ethyl **1b**, propyl **1c**, butyl **1d**, pentyl **1e**, and benzyl groups **1f** by ester exchange reaction with titanium tetraethoxide[3] to yield improved substrates for the reaction under the above conditions. Products of the reaction were isolated as methyl ester **2a** above.

Further optimization of the reaction conditions was achieved by changing the adding method of enzyme addition and the reaction time using dipropyl ester **1c** as substrate. After running the reaction under several conditions, the reaction in which PLE was added in two portions

(1,500 units/mmol of substrate were added twice within 48 hours) gave increased chemical yield (62%) and higher ee (**2a**-*cis* 88% ee, **2a**-*trans* 87% ee) (Table 2, entry 4). The product was isolated after treatment with diazomethane as a mixture of *cis* and *trans* isomers (**2a**-*cis*, **2a**-*trans*) (3:1). This result could be explained as follows: the conformation of PLE was gradually damaged by acetonitrile leading to decreased activity and selectivity, thus, adding the fresh enzyme in two parts increased the yield.

Table 2 Dealkoxycarbonylation of a Range of Substrates



1a–f

2a-*cis*: R^1 = Me, R^2 = H
2a-*trans*: R^1 = H, R^2 = Me

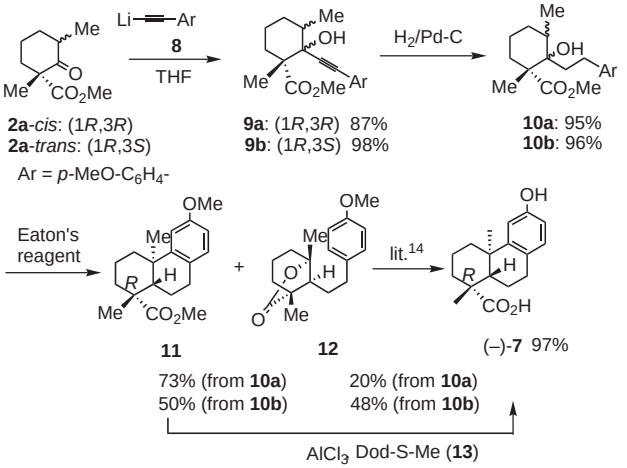
Entry	Compound	R	Time (h)	Yield (%)	ee (%)[b]
1	**1a**	Me	24	57	51
2	**1b**	Et	48	69	69
3	**1c**	Pr	24	33	76
4	**1c**	Pr	48[a]	62	87
5	**1d**	Bu	24	33	90
6	**1e**	Pentyl	24	13	94
7	**1f**	Bn	24	11	77

[a] Addition method: 1,500 units/mmol of substrate were added twice within 48 hours
[b] **2a**-*trans*: Daicel Chiralcel OJ (hexane–*i*-PrOH, 200:1), 230 nm.

The relative configurations of **2a**-*cis* and **2a**-*trans* were determined by comparison of their ^{1}H NMR spectra,[4] while the absolute configurations were established by the preparation of **2a**-*cis* and **2a**-*trans* from (1*R*)-(1-methyl-2-oxocyclohexyl)carboxylic acid[5] and comparison of their directions of optical rotation.[6]

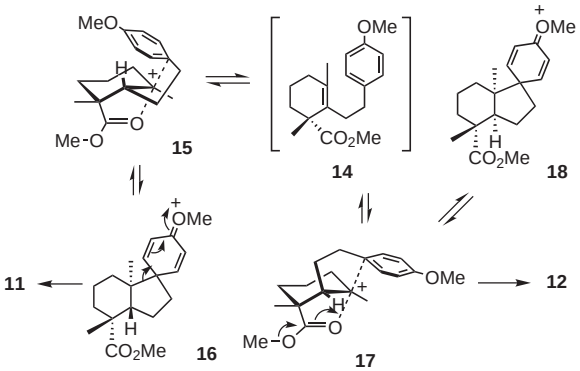
Finally, we attempted to synthesize optically active (–)-podocarpic acid [(–)-**7**] isolated from *Podocarpus cupressina var. imbricate* by using **2a** as a key chiral synthon. While racemic **7** has been synthesized by many groups due to its wide application as the starting material of many naturally occurring compounds,[7] only a few papers have reported the synthesis of (–)-**7**.[8]

(+)-β-Ketoester **2a**-*cis* was treated with lithium acetylide (**8**)[9] according to King's method[10] to give propargyl alcohol **9a**. The triple bond was reduced by conventional catalytic hydrogenation with Pd/C to afford **10a** as a mixture of diastereomers. Treatment of **10a** with Eaton's reagent[11] gave methyl (–)-*O*-methylpodocarpate (**11**), which can be obtained in enantiomerically pure form (>99% ee) and good yield after recrystallization,[12] as well as lactone **12**. Demethylation was carried out with $AlCl_3$ and odorless sulfide **13**[13] resulting in (–)-podocarpic acid [(–)-**7**]. The facile conversion of **12** to (–)-**7** had been reported previously[14] (Scheme 5).



Scheme 5

Thus, **10b** derived from **2a**-*trans* was treated with Eaton's reagent, the lactone **12** was obtained with a higher de than the reaction from **10e**. Currently the difference in product ratios is difficult to explain; however, this may be attributed to the difference in the two reaction pathways to **11** and **12**. Namely, protonation from the opposite side of the methoxycarbonyl group of the dehydrated intermediate **14** gave **15**, which was transformed to **11** by a dienone-phenol-type rearrangement via **16**, which resulted from the potent ring strain of the unstable *trans*-fused [3.2.0]-bicyclic system (Scheme 6). Meanwhile, protonation from the same face with the methoxycarbonyl group resulted in formation of a lactone ring via intermediate **17**. The intermediate could equilibrate with intermediate **18**; however, its stable *cis*-fused [3.2.0]-bicyclic system did not have sufficient ring strain to accelerate the dienone-phenol-type rearrangement.



Scheme 6

As shown above, we have succeeded in preparing optically active methyl 2,6-dimethylcyclohexanone-2-carboxylate **2** by PLE-catalyzed dealkoxycarbonylation of σ-symmetrical β-ketodiester **1c** and were able to show the usefulness of **2** as a chiral synthon in the synthesis of diterpenes. The method is applicable to the synthesis of many biologically active natural products.

Acknowledgment

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References

(1) (a) Node, M.; Inoue, T.; Araki, M.; Nakamura, D.; Nishide, K. *Tetrahedron Lett.* **1995**, *36*, 2255. (b) Katoh, T.; Kakiya, K.; Nakai, T.; Nakamura, S.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2351. (c) Node, M.; Inoue, T.; Araki, M.; Nakamura, D.; Nishide, K. *Tetrahedron: Asymmetry* **1998**, *9*, 157. (d) Node, M.; Nakamura, S.; Nakamura, D.; Katoh, T.; Nishide, K. *Tetrahedron Lett.* **1999**, *40*, 5357.

(2) Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(3) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.

(4) As shown below, the singlet signal assigned to the α-methyl group of **2a**-*cis* appeared at lower magnetic field than that of **2a**-*trans*, while methyl signals as doublets were observed at almost the same chemical shift.
2a-***cis***: $[\alpha]_D$ +69.6 (*c* 1.19, $CHCl_3$, 84% ee); IR ($CHCl_3$): 2951, 1736, 1705, 1458, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 2.71–2.59 (m, 1 H), 2.46–2.45 (m, 1 H), 2.10–2.00 (m, 1 H), 1.90–1.78 (m, 3 H), 1.55–1.47 (m, 1 H), 1.47 (s, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H); MS (20 eV): *m*/*z* (%) = 184 (M^+, 20), 152 (20), 124 (37), 101 (100), 58 (34); HRMS: *m*/*z* calcd for $C_{10}H_{16}O_3$ (M^+): 184.1099, found: 184.1103.
2a-***trans***: $[\alpha]_D$ –153 (*c* 0.80, $CHCl_3$, 89% ee); IR ($CHCl_3$): 2939, 1709, 1454, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.72 (s, 3 H), 2.59 (m, 2 H), 2.08–2.00 (m, 1 H), 1.76–1.67 (m, 2 H), 1.46–1.30 (m, 2 H), 1.28 (s, 3 H), 1.05 (d, *J* = 6.4 Hz, 3 H); MS (20 eV): *m*/*z* (%) = 184 (M^+, 59), 152 (35), 124 (56), 101 (100), 58 (62); HRMS: *m*/*z* calcd for $C_{10}H_{16}O_3$ (M^+): 184.1099, found: 184.1094.

(5) (a) Westerman, B.; Scharman, H. G.; Kortman, I. *Tetrahedron: Asymmetry* **1993**, *10*, 2119. (b) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718.

(6) (1*R*)-(1-Methyl-2-oxocyclohexyl)carboxylic acid (60% ee) prepared by PLE-catalyzed optical resolution of ethyl (1-methyl-2-oxocyclohexyl)carboxylate[5] was derivatized to (1*R*,3*R*)- and (1*R*,3*S*)-methyl (1-methyl-2-oxocyclohexyl)carboxylate; the direction of optical rotation [(+) for *cis* isomer, and (–) for *trans* isomer] implied that the **2a**-*cis* and **2a**-*trans* should have an *R* configuration at C-1.

(7) (a) Haworth, R. D.; Moore, B. P. *J. Chem. Soc.* **1946**, 633. (b) Mancini, V.; Fringuelli, F.; Taticci, A. *Gazz. Chim. Ital.* **1969**, *99*, 953. (c) Kanjilal, R. D.; Alam, S. K.; Ghatak, U. R. *Synth. Commun.* **1981**, 795. (d) Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (e) Meyer, W. L.; Maheshwari, K. K. *Tetrahedron Lett.* **1964**, 2175. (f) Roy, A.; Paul, T.; Drew, M. G. B.; Mukherjee, D. *Tetrahedron Lett.* **2003**, *44*, 4835.

(8) Hao, X.-J.; Node, M.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1505.

(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(10) King, F. E.; King, T. J.; Topliss, J. G. *J. Chem. Soc.* **1957**, *9*, 719.

(11) Eaton P. E., Carlson G. R., Lee J. T.; *J. Org. Chem.;* **1973**, 573.

(12) Recrystallization of **12** (258 mg, 84% ee) from *n*-hexane afforded the optically pure compound (61.0 mg, >99.5%).

(13) (a) Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177. (b) Ohsugi, S.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron* **2003**, *59*, 8393. (c) Nishide, K.; Ohsugi, S.; Miyamoto, T.; Kumar, K.; Node, M. *Monatsh. Chem.* **2004**, *135*, 189.

(14) Mancini, V.; Fringuelli, F.; Taticchi, A. *Gazz. Chim. Ital.* **1969**, *99*, 953.