Pergamon

Tetrahedron 58 (2002) 147–151

TETRAHEDRON

# Enzymatic kinetic resolution of aromatic substituted norbornene mono-esters using pig's liver esterase

M. Mamaghani*

*Department of Chemistry, Faculty of Science, Guilan University, P.O. Box 1914, Rasht, Iran*

Received 6 May 2001; revised 17 October 2001; accepted 8 November 2001

**Abstract**—Pig's liver esterase (PLE) has been used as a chiral catalyst in the enzymatic kinetic resolution of aromatic substituted norbornene mono-esters, methyl 3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate and its *endo*-counterpart, methyl 3-*endo*-*p*-nitro-phenyl-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate and methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate. In this study a range of low to high enantioselectivities (83% ee) was observed. The effect of co-solvents has also been examined. 

## 1. Introduction

Enzymes as biocatalysts have captured an important place in organic synthesis. In particular hydrolases are effective catalysts and the large majority of esterase catalyzed reactions have been performed by pig liver esterase (PLE). The great potential of this enzyme has been utilized in asymmetric synthesis,[1] separation of stereoisomers,[2,3] hydrolysis of ester functions contained in hydrolytically sensitive compounds[4] and in the kinetic resolution of racemates.[5]

Following our continued studies of the kinetic resolution of norbornene type esters,[6,7] in order to examine the effect of aromatic substituents in the resolution of these systems by PLE, substrates **1**–**4** (Fig. 1) were synthesized and subjected to PLE hydrolysis.

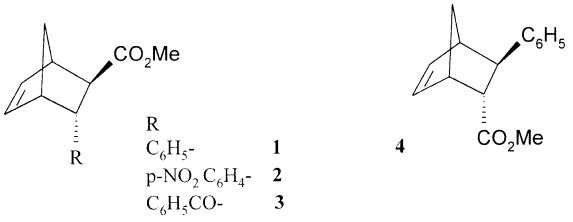



**Figure 1.**

## 2. Results and discussion

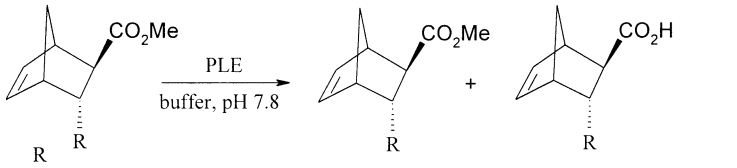
Substrates **1** and **4** were prepared using Diels–Alder methodology by refluxing methylcinnamate and cyclopentadiene. The mixture was distilled under reduced pressure to provide the desired adducts (*exo*/*endo* ratio 47:53, by GC) contaminated with 16% methylcinnamate which could not be removed by distillation. The mixture was purified by PLE, which preferably hydrolyzed methylcinnamate, to provide the adducts **1** and **4** as a ~1:1 *exo*/*endo* mixture (by GC). The adducts were hydrolyzed (KOH/MeOH) and separated by iodolactonization[8] which furnished the related acid products. Samples of pure 3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid and 3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid were methylated by diazomethane to give pure esters **1** and **4** (yields>98%). The adduct **1** was subjected to PLE hydrolysis (0.1 M phosphate buffer, pH=7.8, room temperature) (Scheme 1). The reaction was stopped at 50% conversion (12 days) and the products were purified by column chromatography (hexane/EtAc 5:1) which provided (−)-**1** and (+)-**5** with ees of 59.5 and 61.5% respectively, $E$=8.

A sample of *rac*-**1** was also subjected to PLE hydrolysis in the presence of 10% acetone as a co-solvent using identical conditions as for the earlier reaction. At 50% conversion (4 days), the reaction provided (−)-**1**, in 40% yield, $[\alpha]_D^{20}=-183.02$ ($c$ 0.67, in MeOH), ee=62.2%, and (+)-**5**, in 47% yield, which was methylated by $CH_2N_2$, to give the related methyl ester, $[\alpha]_D^{20}=+118$ ($c$ 0.7, in MeOH), ee=42%.

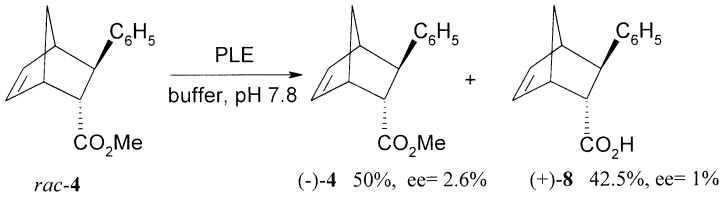
The *endo*-isomer *rac*-**4** was hydrolyzed slowly (14 days) with almost no enantioselectivity. Enantiomeric excesses of the acid product (+)-**8** and the remaining ester (−)-**4**

*Keywords*: kinetic resolution; aromatic substitution; pig's liver esterase.
* E-mail: m-chem41@cd.gu.ac.ir

0040–4020/02/$ - see front matter 
PII: S0040-4020(01)01115-2




**Scheme 1.**




**Scheme 2.**

calculated as 1 and 2.6%, respectively, $E<1$. A sample of (+)-**8** was transformed to the related methyl ester (+)-**4** by ethereal $CH_2N_2$ and the ee% of *endo*-acid (+)-**8** was calculated on the basis of enantiomeric excess of methyl ester (+)-**4** (Scheme 2).

In order to evaluate the possible effect of the nitro group in the PLE hydrolysis of cinnamic acid/cyclopentadiene adducts, a mixture of 3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic acid (**6**) and 3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid (**9**) (ratio of *exo*/*endo* isomers 64:36, by $^1$H NMR) (Fig. 2) were prepared and separated according to the literature.[8]

A sample of racemic 3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic acid **6** was transformed to the related methyl ester **2** by diazomethane and subjected to PLE hydrolysis, applying the procedure used in the resolution of **1**. Due to a longer reaction time (16 days), the reaction was stopped at 33% conversion to provide (+)-3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (+)-**6** in 31.6% yield, $[\alpha]_D^{20}=+21.4$ (*c* 0.51, in MeOH), ee=10.7% ($E=1.5$) and the unreacted methyl ester in 77.3% yield, $[\alpha]_D^{20}=-11.71$ (*c* 0.64, in MeOH), ee=4.5% (Scheme 1).

A sample of (+)-3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (+)-**6** was transformed to the related methyl ester using an ethereal solution of diazomethane to provide (+)-**2** in 97% yield, mp 59–60°C, $[\alpha]_D^{20}=+27.85$ (*c* 0.45, in MeOH), ee=10.7%.

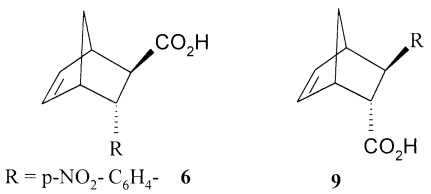
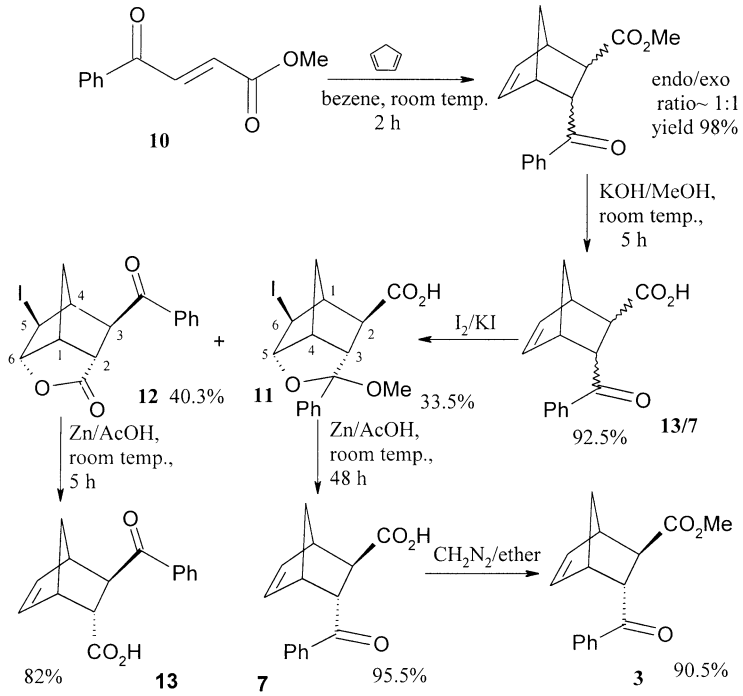



**Figure 2.**

The resolution of methyl 3-*endo*-*p*-nitro- phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate **2** was also conducted by PLE in the presence of 10% acetone as a co-solvent. The reaction was stopped at 10% conversion(7 days) to provide (+)3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic acid (+)-**6** in 9.8% yield, $[\alpha]_D^{20}=+34.2$ (*c* 0.25, in MeOH), ee=17% and (−)-methyl 3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (−)-**2**, $[\alpha]_D^{20}=-1.05$ (*c* 0.29, in MeOH), ee<1%.

In order to further substantiate the effect of benzoyl group on the efficiency of PLE hydrolysis in the norbornene system, racemic bicyclo[2.2.1]heptene ketone **3** was investigated. This new adduct along with the related *endo*-isomer was prepared from the reaction of methylbenzoylacrylate and freshly distilled cyclopentadiene in 98% yield (the ratio of *endo*/*exo* isomers ~1:1 by $^1$H NMR and GC) (Scheme 3). A sample of mixed ester adducts were hydrolyzed by methanolic potassium hydroxide and subjected to iodolactonization. The reaction gave crystalline 3-*exo*-benzoylbicyclo [2.2.1] heptanecarbolactone **12** and interestingly a ketal **11**, which also provides a convenient method for the protection of olefinic bond and keto group for further elaboration to the substrate **7** (Scheme 3). The ketal and lactone **12** on treatment with Zn/AcOH (room temperature), produced the desired 3-*endo*-benzoyl-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid **7** and 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid **13** in 95.5 and 82% yield, respectively. A sample of the *exo*-acid **7** was transformed to the related methyl ester by ethereal solution of diazomethane and subjected to PLE hydrolysis (0.1 M phosphate buffer solution/5% $CH_3CN$, room temperature, pH=7.8) (Scheme 1). The reaction was stopped at 20% conversion (7 days), to provide unreacted (+)-methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (+)-**3**, in 79.3% yield, $[\alpha]_D^{20}=+39.6$ (*c* 0.82, in MeOH), ee=19% and (−)-3-*endo*-benzoylbicyclo-[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (−)-**7** in 19.2% yield, $[\alpha]_D^{20}=-157$ (*c* 1, in MeOH), ee=83%, $E=13$.




**Scheme 3.**

A sample of (−)-*exo*-acid **7** was methylated by $CH_2N_2$ to give (−)-methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (−)-**3**, $[\alpha]_D^{20}=-171.3$ (*c* 0.44, in MeOH), ee=83%. The kinetic resolution of adduct **3** was also conducted in the absence of co-solvent which due to the high insolubility of the substrate and longer reaction time we did not pursue. No attempt was made to assess the resolution of the related methyl ester of *endo*-acid **13** by PLE, since *endo*-isomers in these systems are usually hydrolyzed much more slowely.[6,7]

The result of this research leads to the conclusion that the presence of aromatic substituents *trans* to the methyl-ester function in these systems, make them poor substrates for PLE. However the best result is obtained with the pheny1 group. The effect of co-solvent on the reaction time is impressive with no appreciable effect on the ees. These results are also entirely consistent with results obtained for the corresponding norbornene esters[6,9] and again nicely fit Tamm's PLE substrate model.[10] The optical purity of all the products were measured by $^1$H NMR spectroscopic analysis (400 MHz) using Eu(hfc)$_3$ as chiral shift reagent.

## 3. Experimental

### 3.1. General remarks

Melting points were measured with a Reichert Thermo pan microscope and are uncorrected. IR spectra were taken on Perkin–Elmer 298 infrared spectrophotometer. $^1$H NMR spectra were recorded on a Bruker AM-400, using TMS as an internal standard. For mass spectra a Bruker double focusing VG 7070 E mass spectrometer was used. Capillary GC analyses were performed using a Hewlett–Packard 5890 A gas chromatograph, containing a cross-linked methyl silicone column (25 m). Flash chromatography was carried out at a pressure of ca. 1.5 bar, a column length of 15–25 cm and a column diameter of 1–4 cm, using Merck Kieselgel 60 H, unless stated otherwise. All solvents used were dried and distilled following standard procedures.

### 3.2. Preparation of methyl 3-*endo*-phenylbicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylate and methyl 3-*exo*-phenyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate(1 and 4)

To a solution of *trans*-methylcinnamate (25 g, 154 mmol) in benzene (74 ml), freshly distilled cyclopentadiene (11 g, 167 mmol) was added. The reaction mixture was refluxed at 95°C and every 5 h freshly distilled cyclopentadiene (167 mmol) was added. After 21 h reflux, the reaction mixture was distilled under reduced pressure, using a short path distillation unit, to provide a 1:1 ratio of mixed adducts and methylcinnamate (21.17 g), bp=127/1.5 mmHg. The mixture was redistilled, bp=72°/0.06 mmHg, bath temperature <125°C (distillation at higher temperature led to the retro Diels–Alder reaction), in order to separate most of the methylcinnamate. The residue (11.1 g) was analyzed by GC which showed a 84:16 ratio of adducts and methylcinnamate. The adducts were purified by PLE and hydrolyzed by methanolic potassium hydroxide to provide the related *endo*- and *exo*-acid adducts, which were separated by iodolactonization.[8] The adducts were methylated using an ethereal solution of $CH_2N_2$[11] to give the related methyl esters **1** and **4** (yield, 98%). The structures of these products were confirmed by comparison of their spectroscopic data with those in the literature.[11]

### 3.3. General procedure for PLE catalyzed hydrolysis of the ester adducts

The ester adduct as a substrate was suspended in a 0.1 M

phosphate buffer solution (10 ml/mmol substrate) at pH=7.8 and incubated with PLE (50 μl/mmol) at room temperature. The pH was maintained by continuous addition of 0.25 M NaOH using an auto-burette. After reaching an appropriate reaction conversion the reaction was stopped by adding aqueous sodium carbonate until pH=10. The aqueous reaction mixture was extracted with ether and the combined ether extracts were dried ($MgSO_4$) and evaporated to give the unreacted ester product.

The remaining aqueous layer was acidified by dilute $H_2SO_4$ to pH=3 and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give the related acid product.

### 3.4. Large scale purification of methylcinnamate adducts (1 and 4) by use of PLE

Methyl cinnamate/cyclopentadiene adducts(**1** and **4**) (8 g), contaminated with methylcinnamate (ca. 16%), were suspended in 0.1 M phosphate buffer solution (100 ml) at pH=7.8 and incubated with PLE (300 μl) at room temperature. Following the general procedure and stopping the reaction after consumption of 44 ml NaOH, the reaction provided the mixed-ester adducts (*exo*/*endo* ratio 47:53 by GC) (5.5 g) with no trace of methyl cinnamate ($^1$H NMR and GC analysis).

**3.4.1. PLE catalyzed hydrolysis of methyl 3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 1.** Methyl 3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (1.14 g, 5 mmol), was subjected to PLE hydrolysis using the general procedure. After 12 days (50% conversion) the reaction gave: *(−)-methyl 3-endo-phenylbicyclo[2.2.1]-hept-5-ene-2-exo-carboxylate (−)*-**1** (0.53 g, 2.33 mmol); yield 46.7%; mp 40–42°C; $[\alpha]_D^{20}=-175.75°$ (*c* 0.85, in MeOH); ee=59.5% (after purification by column chromatography; hexane/EtOAc, 5:1; *E*=8; the $^1$H NMR and IR of this product was the same as starting methyl ester) and (+)-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (+)-**5** (0.42 g, 1.95 mmol); yield 39% (after purification by column chromatography; hexane/EtOAc, 3:2); mp 90–92°C; $[\alpha]_D^{20}=+172$ (*c* 0.63, in MeOH), ee=61.5%. The $^1$H NMR and IR spectra of this product were also the same as racemic *exo*-acid. A sample of this optically active acid was transformed to the related methyl ester using diazomethane,[11] mp 40–43°C; $[\alpha]_D^{20}=+172.7$ (*c* 0.55, in MeOH); ee=61.5%.

**3.4.2. PLE catalyzed hydrolysis of methyl 3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate 4.** Using the general procedure, racemic methyl 3-*exo*-phenylbicyclo-[2.2.1]hept-5-ene-2-*endo*-carboxylate (0.5 g, 2.19 mmol) was hydrolyzed by PLE (105 μl), reaction time 14 days (after 11 days 30 μl fresh PLE was added), 50% conversion, to provide: *(−)-methyl 3-exo-phenylbicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (+)*-**4** (0.25 g, 1.09 mmol), yield 50%; $[\alpha]_D^{20}=-3.54$ (*c* 1, in MeOH); ee=2.6% (the $^1$H NMR and IR were the same as racemic starting ester) and (+)-3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (+)-**8** (0.2 g, 0.93 mmol), yield 42.5%; $[\alpha]_D^{20}=+2.98$ (*c* 0.97, in MeOH), ee=1%; *E*<1; mp 107–108°C; the $^1$H NMR and IR were the same as racemic *endo*-acid. A sample of 3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (0.15 g, 0.67 mmol) was transformed to the related methyl ester using ethereal diazomethane,[11] yield 99.5%; $[\alpha]_D^{20}=+3.4°$ (*c* 0.58, in MeOH); ee=1%.

**3.4.3. PLE catalyzed hydrolysis of methyl 3-*endo*-*p*-nitrophenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 2.** Methyl 3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (1.0 g, 3.66 mmol) (prepared according to the literature)[8] was subjected to PLE hydrolysis, using the general procedure, reaction time 16 days (every 4 days fresh PLE, 100 μl, was added). The hydrolysis reaction was stopped at 33% conversion, to provide (−)-methyl 3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (−)-**2** (0.67 g, 2.83 mmol); yield 77.3%; mp 58–59°C; $[\alpha]_D^{20}=-11.71$ (*c* 0.64, in MeOH); ee=4.5% (the $^1$H NMR and IR were the same as starting racemate methyl ester) and (+)-3-*endo*-*p*-nitro-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (+)-**6** (0.30 g, 1.15 mmol); yield 31.6%; mp 176–177°C; $[\alpha]_D^{20}=+21.4$ (*c* 0.51, in MeOH); ee=10.7%; *E*=1.5. The $^1$H NMR and IR were the same as racemic *exo*-acid. A sample of *exo*-acid was transformed to the related methyl ester by ethereal solution of diazomethane (yield 97%), mp 59–60°C; $[\alpha]_D^{20}=+27.85$ (*c* 0.45, in MeOH); ee=10.7%.

**3.4.4. Preparation of methyl 3-*endo*-benzoylbicyclo-[2.2.1]hept-5-ene-2-*exo*-carboxylate and 3-*exo*-benzoyl bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid 3 and 13.** To a magnetically stirred solution of methyl benzoylacrylate[12] (5 g, 26.31 mmol) in benzene (13 ml), freshly distilled cyclopentadiene (1.87 g, 28.3 mmol) in benzene (5 ml) was added slowly. An immediate exothermic reaction occurred. The reaction mixture was stirred for 2 h and the solvent was removed under vacuum to provide the desired adducts (6.6 g, 25.8 mmol) in 98% yield, as a viscous liquid. It was shown by $^1$H NMR to be ~1:1 mixture of *endo*/*exo* isomers (Scheme 3).

A sample of the adduct mixture (5.8 g, 22.6 mmol) was hydrolyzed by methanolic potassium hydroxide (10 g KOH in 75 ml MeOH) at room temperature, reaction time 5 h, to give the related acid adducts **13/7** (5.1 g, 20.9 mmol), yield 92.5%. The mixture was subjected to iodolactonization[8] to provide: *3-exo-benzoylbicyclo[2.2.1]heptane carbolactone* **12** (3.1 g, 8.42 mmol) in 40.3% yield as a brown solid; mp 157–158°C (recrystalized from acetone/ethanol); $\nu_{max}$ (KBr) 1760, 1660 (C=O stretch), 1590, 1575, 1440 (C=C stretch of arom. ring) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.98 (2H, m, arom. H), 7.57 (3H, m, arom. H), 5.20 (1H, t, *J*=5.1 Hz, $H_6$), 4.08 (1H, d, *J*=2.5 Hz, $H_5$), 3.71 (1H, s, $H_1$), 3.22 (2H, m, $H_2$, $H_3$), 2.96 (1H, s, $H_4$), 2.30 (1H, d, *J*=9.5 Hz, $H_7$), 1.8 (1H, d, *J*=9.5 Hz, $H_7$); *m*/*z* (EI) (0.97, $M^+$, 0.30, M+1), 242 (13.3), 241 (77.9), 127 (1.2), 105 (100%); HRMS: $M^+$, found 367.99098±0.00073. $C_{16}H_{13}IO_3$ requires 367.99095 and *ketal* **11** (2.8 g, 7 mmol) in 33.5% yield, as a white solid, mp 185–186°C (recrystalized from methanol); $\nu_{max}$ ($CH_2Cl_2$) 3500–2500(O–H stretch), 1705 (C=O stretch) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$), 7.38 (5H, m, arom. H), 4.91 (1H, d, *J*=5.0 Hz, $H_5$), 3.81 (1H, d, *J*=2.5 Hz, $H_6$), 3.25 (1H, m, $H_1$), 3.05 (1H, t, *J*=4.8 Hz, $H_3$), 2.93 (3H, s, O*Me*), 2.75 (1H, s, $H_4$), 2.2 (1H, d, *J*=4.8 Hz, $H_2$), 2.04 (1H,

br s, $H_7$), 1.85 (1H, d, $J$=9.3 Hz, $H_7$); *m/z* (EI) (100, M–OMe), 370 (16.7), 273 (0.2), 197 (7.8), 242 (0.7), 241 (2.3), 127 (4.3), 105 (30.0%); HRMS: (M–OMe), found 368.99871±0.00073. $C_{15}H_{14}IO_3$ requires 368.99817.

The ketal **11** (0.97 g, 2.42 mmol) was treated with zinc (1.14 g) and glacial acetic acid (8 ml) and stirred magnetically at room temperature for 48 h. The reaction mixture was filtered and the residue was washed with hot water and ether. The filtrate was extracted with ether (3×70 ml), the combined ether extracts were dried ($MgSO_4$) and evaporated in a rotatory evaporator to give 3-*endo*-benzoylbicyclo[2.2.1] hept-5-ene-2-*exo*-carboxylic acid **7** (0.56 g, 2.31 mmol) in 95.5% yield as a colorless oil; $\nu_{max}$ ($CH_2Cl_2$) 3500–2500 (OH stretch), 1695, 1680 (C=O stretch) $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 10.35 (carboxylic H), 7.99 (2H, m, arom. H), 7.53 (3H, m, arom. H), 6.33 (1H, dd, $J$=2.8, 5.3 Hz, $H_5$ or $H_6$), 5.83 (1H, dd, $J$=2.6, 5.3 Hz, $H_5$ or $H_6$), 4.29 (1H, t, $J$=4.2 Hz, $H_3$), 3.30 (2H, br s, $H_1$, $H_4$), 3.10 (1H, dd, $J$=3.0, 4.2 Hz, $H_2$), 1.8 (1H, d, $J$=8.7 Hz, $H_7$), 1.53 (1H, m, $H_7$); HRMS: $M^+$, found 242.09419±0.00069. $C_{15}$ $H_{14}O_3$ requires 242.094229.

A sample of 3-*endo*-benzoylbicyclo[2.2.1] hept-5-ene-2-*exo*-carboxylic acid **7** (0.5 g, 2.06 mmol) was methylated by an ethereal solution of diazomethane at room temperature to provide methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate **3** (0.48 g, 1.87 mmol) in 90.5% yield as a colorless oil; $\nu_{max}$ (liquid film) 1720, 1675 (C=O stretch), 1595, 1580, 1445 (Aromatic C=C stretch), 1265, 1215 (C–O–C stretch)$cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.0 (2H, m, arom. H), 7.26 (3H, m, arom. H), 6.30 (1H, dd, $J$=2.8, 5.3 Hz, $H_5$ or $H_6$), 5.83 (1H, dd, $J$=2.7, 5.3 Hz, $H_5$ or $H_6$), 4.28 (1H, t, $J$=4.2 Hz, $H_3$), 3.71 (3H, s, O*Me*), 3.31 (2H, br s, $H_1$, $H_4$), 3.05 (1H, dd, $J$=3.2, 4.5 Hz, $H_2$), 1.75 (1H, d, $J$=8.6 Hz, $H_7$), 1.50 (1H, m, $H_7$); HRMS: $M^+$, found 256.10983±0.00065. $C_{16}H_{16}O_3$ requires 256.10986.

3-*exo*-Benzoylbicyclo[2.2.1]heptane carbolactone **12** (1.85 g, 5.03 mmol) was treated with zinc (2.01 g) and glacial acetic acid (14 ml) mixture at room temperature, reaction time 5 h, to give 3-*exo*-benzoylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid **13** (0.95 g, 4.13 mmol) in 82% yield as a colorless oil; $\nu_{max}$ ($CH_2Cl_2$), 3500–2500 (OH stretch), 1700, 1675 (C=O stretch), 1596, 1580, 1447 (aromatic C=C stretch), 1370, 1020, 910, 870 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 8.02 (2H, m, arom. H), 7.53 (3H, m, arom. H), 6.43 (1H, dd, $J$=2.9, 5.2 Hz, $H_5$ or $H_6$), 6.24 (1H, dd, $J$=2.7, 5.2 Hz, $H_5$ or $H_6$), 3.75 (1H, t, $J$=3.1 Hz, $H_1$), 3.62 (1H, dd, $J$=3.2, 5.1 Hz, $H_3$), 3.48 (1H, br s, $H_4$), 3.35 (1H, br s, $H_2$), 1.65 (1H, d, $J$=8.5 Hz, $H_7$), 1.42 (1H, m, $H_7$); *m/z* (EI) (6.0, $M^+$, 1.3, M+1), 224 (26.2), 197 (30.2), 178 (12.5), 177 (100), 159 (36.5), 137 (15.6), 105 (59.6%); HRMS: $M^+$, found 242.09419±0.00096. $C_{15}H_{14}O_3$ requires 242.09429.

**3.4.5. PLE catalyzed hydrolysis of methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 3.** (±)-Methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (0.275 g, 1.07 mmol) was subjected to PLE catalyzed hydrolysis in the presence of 5% acetonitrile as a co-solvent, using the general procedure. The reaction was stopped at 20% conversion, reaction time 7 days (after 6 days 113 μl fresh PLE was added), to give the unreacted (+)-methyl 3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (+)-**3** (0.22 g, 0.85 mmol), purified by column chromatography (hexane/EtOH, 10:1); yield 79.4%; $[\alpha]_D^{20}$=+39.60 (*c* 0.82, in MeOH); ee=19% (the $^1H$ NMR and IR of this product was the same as the starting racemic ester) and (−)-3-*endo*-benzoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (−)-**7** (0.05 g, 0.20 mmol); yield 19.2%; $[\alpha]_D^{20}$=−157 (*c* 1, in MeOH); ee=83%; $E$=13. The $^1H$ NMR and IR spectra of this acid were the same as the related racemic acid. A sample of the acid (−)-**7** was transformed to the related methyl ester by ethereal solution of diazomethane, $[\alpha]_D^{20}$=−171.3 (*c* 0.44, in MeOH); ee=83%.

## Acknowledgements

The author is grateful to Professor B. Zwanenburg, Dr A. J. H. Klunder (the Netherlands) and the Research Council of Guilan University.

## References

1. (a) Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1–55. (b) Santaniello, E.; Ferraboschi, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140. (c) Faber, K. *Pure Appl. Chem.* **1997**, *69*, 1613–1632. (d) Faber, K. *Biotransformation in Organic Chemistry, A Textbook*; 3rd ed; Springer: Heidelberg, 1997. (e) Pietruszka, J.; Wilhelm, T.; Witt, A. *Synlett* **1999**, *12*, 1981–1983. (f) Athawale, V.; Manjrekar, N. *Synlett* **2000**, *2*, 225–226.
2. Eberl, M.; Egli, M.; Seebach, D. *Helv. Chim. Acta.* **1988**, *71*, 1–23.
3. Sweers, H. M.; Wong, C. *J. Am. Chem. Soc.* **1986**, *108*, 6421–6422.
4. Sicic, S.; Lerroy, J.; Wakselman, C. *Synthesis* **1987**, 155–156.
5. (a) Kozikowski, A. P.; Simoni, D.; Baraldi, P. G.; Lampronti, I.; Manfredini, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 4441–4444. (b) Renold, P.; Tamm, C. *Tetrahedron: Asymmetry* **1993**, *4* (11), 2295–2298. (c) Klunder, A. J. H.; Huizinga, W. B.; Hulshof, A. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1986**, 2543–2546. (d) Whitesides, G. M.; Wong, C. *Aldrichim. Acta* **1983**, *16*, 27–32.
6. Mamaghani, M.; Namazi, A. *J. Sci. I. R. Iran* **1999**, *10* (3), 169–173.
7. Mamaghani, M.; Klunder, A. J. H.; Zwanenburg, B. *J. Sci. I. R. Iran* **2000**, *11* (3), 205–212.
8. Roundestveet, Jr., C. S.; Ver Nooy, C. D. *J. Am. Chem. Soc.* **1955**, *76*, 4878–4883.
9. Zhu, L. M.; Tedford, M. C. *Tetrahedron* **1990**, *46* (19), 6587–6611.
10. Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta.* **1983**, *66*, 2501–2511.
11. Nicolas, L.; Beuglmans-Verrier, M.; Guilhem, J. *Tetrahedron* **1981**, *37*, 3847–3860.
12. Lutz, R. E. *J. Am. Chem. Soc.* **1930**, *52*, 3423–3436.