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# Lipase-catalyzed asymmetric demethoxycarbonylation: Formal syntheses of (+)-carbacyclin, (−)-ajmalicine, and (−)-tetrahydroalstonine †

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**Abstract**

Both enantiomers of $C_2$-symmetric dimethyl 3,7-dihydroxybicyclo[3.3.0]-octa-2,6-diene-2,6-dicarboxylate **3** were prepared in enantiomerically pure form from symmetric tetraester **1** by the lipase-catalyzed demethoxycarbonylation, respectively. Double asymmetric differentiation with lipase in the above demethoxycarbonylation was observed. Their applications to formal total syntheses of (+)-carbacyclin and (−)-ajmalicine including (−)-tetrahydroalstonine are also described. 

## 1. Introduction

Bicyclo[3.3.0]octane derivatives are useful synthetic intermediates for natural products having the polyquinane skeleton.[1] For example, asymmetric syntheses of the bicyclo[3.3.0]octane intermediates for the synthesis of capnellenes[2] have been developed by Shibasaki,[3] Fuji,[4] and our group.[5] On the other hand, utilizing enzymes or microbes for asymmetric synthesis has become common. While desymmetrization or kinetic resolution of esters or alcohols by enzyme-catalyzed hydrolysis or acylation has been widely studied,[6] the enzyme-catalyzed asymmetric dealkoxycarbonylation of esters has been limited. Only two studies have been reported on the enzyme-catalyzed dealkoxycarbonylation of esters for the syntheses of β-nitropropionate[7] and optically active bicyclo[3.3.0]octane derivatives.[8]

As shown in Scheme 1, σ-symmetric tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate **1** prepared from dimethyl 3-oxoglutarate and glyoxal by the one pot Weiss reaction[9] is an interesting substrate for the enzymic demethoxycarbonylation, because it is known that the keto

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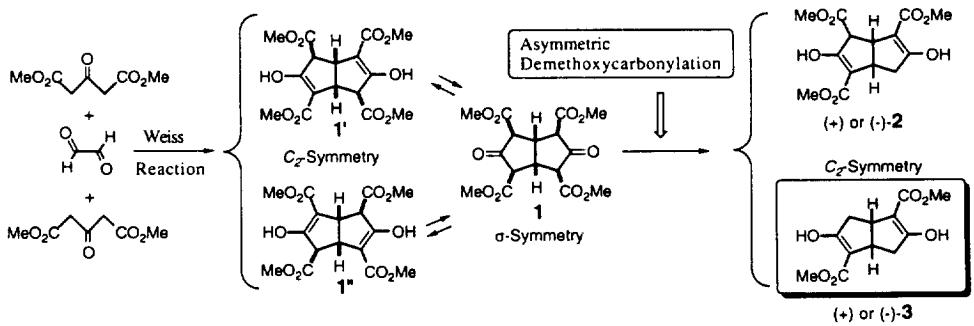
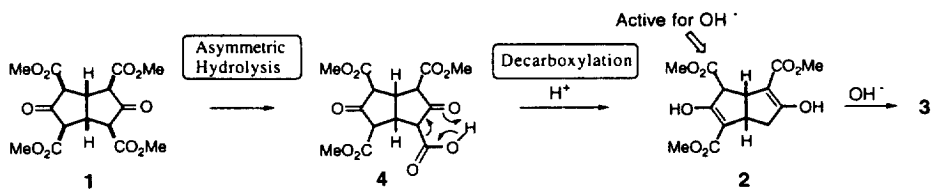
ester **1** exists as an equilibrium mixture of $C_2$-symmetric enol-forms **1′** and **1″**.[9] Therefore, a dynamic kinetic resolution with an enzymic demethoxycarbonylation through a keto–enol tautomerism should be possible to give an enantiomerically enriched triester **2** or diester **3** in a quantitative yield theoretically, even if any tautomer could be subjected to enzymic reaction. In the case of enzymic hydrolysis occurring in the tetraester **1**, the formed acid **4** could be spontaneously decarboxylated by the acidic treatment to give triester **2**, as shown in Scheme 2. Furthermore, the triester **2** could be partially hydrolyzed with an alkali to give an enantiomerically enriched diester **3**. On the synthesis of optically active diester **3**, only kinetic resolution of diester **3** by microbial reduction with *Rhizopus oryzae* was known.[7] Here we report a full account of the lipase-catalyzed asymmetric demethoxycarbonylation of tetraester **1** and its application to formal syntheses of (+)-carbacyclin and (−)-ajmalicine including (−)-tetrahydroalstonine.




Scheme 1. Synthetic strategy for optically active $C_2$-symmetric diester **3**




Scheme 2.

## 2. Results and discussion

The results of the demethoxycarbonylation of **1** with lipases are summarized in Table 1. The product and its enantioselectivity depended on the lipase used. The reaction with porcine pancreatic lipase (PPL, Sigma Type II) gave the triester (+)-**2**, while that with Lipase M Amano 10 afforded the diester (+)-**3**, in high enantioselectivities (runs 1 and 3). The reaction with lipase A Amano 6 afforded (+)-**2** in low enantioselectivity (run 2). On the other hand, the lipases derived from the *Candida* species afforded their enantiomers, triester (−)-**2** and/or diester (−)-**3** (runs 4 and 5). Lipase F-AP 15 gave the undesired racemic triester **2** (run 6). The yields of triester **2** and diester **3** should exceed 50% theoretically, but the isolated yields of them were less than 50%, regardless of the reaction conditions, except for the reaction with Lipase AY. The reasons of the low yields are that the substrate **1** remains (ca. 30% of tetraester **1** was recovered in the reaction with PPL) and the products are gradually decomposed to unidentified materials in the prolonged reaction time. The formation of the triester (−)-**2** along with the diester (−)-**3** in run 5 indicated that this lipase-catalyzed demethoxycarbonylation of the tetraester **1** might proceed stepwise.

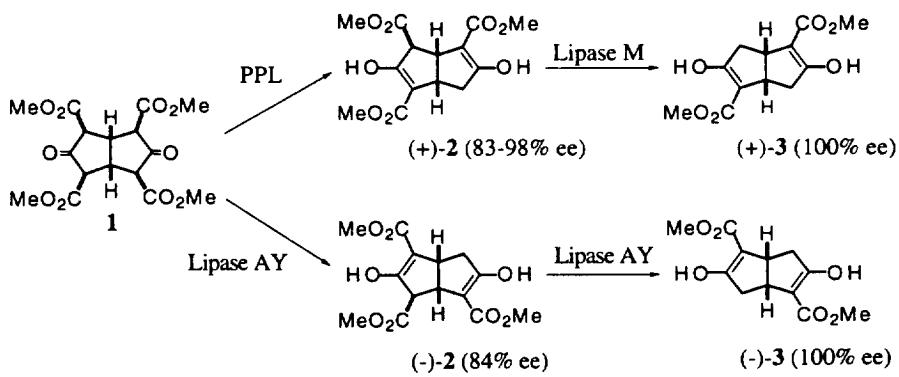
Table 1
Lipase-catalyzed asymmetric demethoxycarbonylation of tetraester **1**

| run | lipase | time (d) | product | yield (%)[a] | % ee[b] |
|---|---|---|---|---|---|
| 1 | Sigma Type II (*Porcine pancreas*) (PPL) | 14 | (+)-**2** | 43 | 83 - 98 |
| 2 | Lipase A Amano 6 (*Aspergillus niger*) | 18 | (+)-**2** | 10 | 24 |
| 3 | Lipase M Amano 10 (*Mucor javanicus*) | 7 | (+)-**3** | 20 | 90 |
| 4 | Sigma Type VII (*Candida rugosa*) | 6 | (-)-**2** | 33 | 90 |
| 5 | Lipase AY Amano 30 (*Candida rugosa*) | 5 | (-)-**2** | 35 | 84 |
| | | | (-)-**3** | 32 | 100 |
| 6 | Lipase F-AP 15 (*Rhizopus sp.*) | 11 | *rac*-**2** | 31 | 0 |

a) Isolated yield. b) HPLC analyses of (*S*)-bis-MTPA esters.

The reason for the extremely high enantioselectivity of (−)-**3** in run 5 might be attributable to double differentiation in the two step reactions.

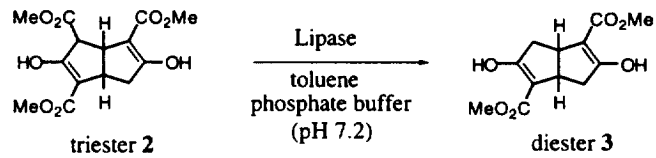
In order to confirm double differentiation of this lipase-catalyzed asymmetric demethoxycarbonylation, racemic and optically active triesters **2** were subjected to this enzymic reaction. The results are compiled in Table 2. One step asymmetric demethoxycarbonylation of racemic triester **2** with lipase M Amano 10 gave diester (+)-**3** in 77% ee (Table 2, run 1), whose ee was lower than that of the two step asymmetric demethoxycarbonylations from tetraester **1** with the same lipase (Table 1, run 3). The same trend was observed in the reaction with lipase AY Amano 30 (Table 2, run 2), in which the enantiomer (−)-**3** was obtained in 80% ee. On the other hand, enantiomerically pure diester (+)-**3** was obtained when the optically active triester (+)-**2** (83% ee) was treated with lipase M Amano 10 (Table 2, run 3). These results obviously suggested the double differentiation of the substrates **1** and **2** with lipases (lipase AY and lipase M) in the two step demethoxycarbonylations started from tetraester **1**. Therefore, we established the methods to obtain both optically pure diesters **3** from tetraester **1** by the lipase-catalyzed double demethoxycarbonylation, as shown in Scheme 3.




Scheme 3. Double demethoxycarbonylation by lipase

It was also possible to have diester **3** by chemical conversion of triester **2**, as planned in Scheme 2. Hydrolysis of the triester (+)-**2** with lithium hydroxide followed by the decarboxylation with hydrochloric acid gave the diester (+)-**3** in 80% yield. This selective demethoxycarbonylation is based on the high reactivity of the non-conjugated methyl ester moiety compared with the conjugated one, and on the fixation of the enol form **2** because it was known that a direction of enolization in tetraester **1** preferred diagonal geometry **1′** and **1″**.[9]

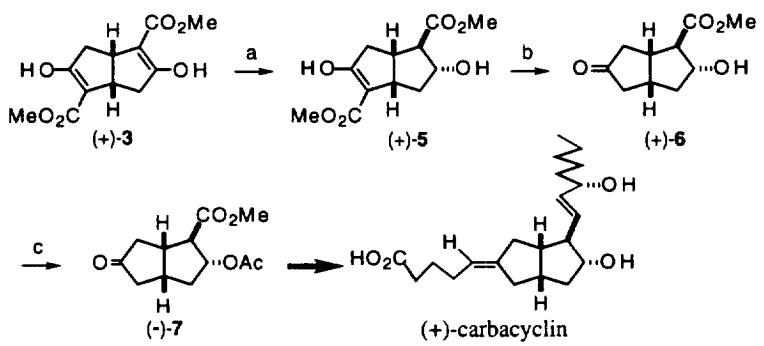
Table 2
Asymmetric demethoxycarbonylation of triester **2** by lipase




triester **2** diester **3**

| run | enantiomeric purity of **2** | lipase | time (d) | product | yield (%) | %ee |
|---|---|---|---|---|---|---|
| 1 | racemic | Lipase M | 6 | (+)-**3** | 17 | 77 |
| 2 | racemic | Lipase AY | 7 | (-)-**3** | 37 | 80 |
| 3 | 83 %ee (+) | Lipase M | 4 | (+)-**3** | 38 | 100 |

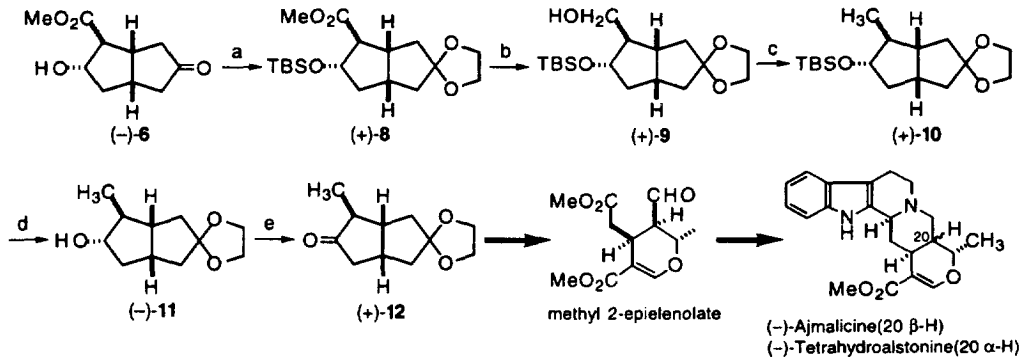
The relationship between specific rotation and the absolute configuration was not clear at this stage. In order to determine the absolute configuration of (+)-**3**, it was easily converted to an intermediate **7** for the synthesis of (+)-carbacyclin[10] as depicted in Scheme 4. The partial reduction of the $C_2$-symmetric bisketoester (+)-**3** with sodium triethoxyborohydride gave (+)-**5** as a sole product. Hydrolysis of two methoxycarbonyl group in (+)-**5** with lithium hydroxide, decarboxylation of the formed β-ketocarboxylic acid part with hydrochloric acid and the subsequent methylation of the remaining carboxylic acid afforded a monoester (+)-**6**. Since the reproducibility in the yield of the above stepwise demethoxycarbonylation (Method A) of (+)-**5** was poor, direct demethoxycarbonylation with hydrochloric acid (Method B) was conducted to have good reproducibility. Acetylation of the alcohol (+)-**6** gave a synthetic intermediate of (−)-**7**. The spectroscopic data and the specific rotation {$[\alpha]_D^{20}$ −25.7 (c 3.0, $CHCl_3$)} of (−)-**7** were consistent with those of the Sakai's intermediate,[10a] therefore, the absolute structure of $C_2$-symmetric diester (+)-**3** was clearly determined as shown in Scheme 3 and an expeditious formal total synthesis of (+)-carbacyclin was established.[10d,11]




a) $NaBH(OEt)_3$ (1 eq) THF, - 40°C to r.t., conv. 94% b) Method A: 1) LiOH, THF-$H_2O$, r.t.; 2) 1*N*-HCl, reflux ; 3) $CH_2N_2$, 73% (3 steps); or Method B: 1) 2*N*-HCl, reflux; 2) $CH_2N_2$, 77% (2 steps); c) $Ac_2O$-pyridine, r.t. 85%

Scheme 4. A formal synthesis of (+)-carbacyclin

Next we turned our efforts to a formal synthesis of *Rauwolfia* alkaloids (−)-ajmalicine[12] and (−)-tetrahydroalstonine[13] which are categorized to heteroyohimbine alkaloids, because they were synthesized from methyl 2-epielenolate[14] as a synthetic intermediate which was derived from methyl-7-ethylenedioxy-bicyclo[3.3.0]octan-3-one **12**.[15] Our synthetic route for a formal synthesis of (−)-ajmalicine and (−)-tetrahydroalstonine is depicted in Scheme 5.




a) 1) TBSCl, imidazole, $CH_2Cl_2$, r.t., 96 %, 2) $TMSOCH_2CH_2OTMS$, $Me_3SiOTf$, $CH_2Cl_2$, -78 °C, 78 %; b) DIBAH, THF, -50 °C, 93 %; c) 1) TsCl, pyridine, 2) $LiAlH_4$, 81 % (2 steps); d) TBAF, THF, r.t., 96 %; e) PCC, $CH_2Cl_2$, r.t., 70 %

Scheme 5. Formal synthesis of (−)-ajmalicine and (−)-tetrahydroalstonine

Enantiomerically pure diester (−)-**3** prepared from tetraester **1** with lipase AY through double asymmetric demethoxycarbonylation was treated with the same procedure described in Scheme 4 to afford an alcohol (−)-**6**. After protection of the hydroxyl group in (−)-**6** with *tert*-butyldimethylsilyl chloride the carbonyl group was converted into ethylenedioxy group to give (+)-**8** according to the Noyori's method.[16] The methyl ester of (+)-**8** was reduced with DIBAH to give an alcohol (+)-**9** in high yield. The hydroxylmethyl group in (+)-**9** was reduced with lithium aluminum hydride to the methyl group via its tosylate in 81% yield. Deprotection of the TBS group in (+)-**10** with tetrabutylammonium fluoride to alcohol and the subsequent oxidation to ketone afforded a synthetic intermediate (+)-**12** $\{[\alpha]_D^{22}$ +32.5 (1.80, $CHCl_3$)$\}$ in a reasonable yield. Therefore, a formal synthesis of (−)-ajmalicine and (−)-tetrahydroalstonine was accomplished.

## 3. Conclusion

We have demonstrated that tetraester **1** is a suitable starting material for the lipase-catalyzed asymmetric demethoxycarbonylation to give $C_2$-symmetric diester (+)-**3** and (−)-**3** in an enantiomerically pure form depending on the lipases used. This demethoxycarbonylation was proved to be a double asymmetric differentiating process by lipases (lipase AY and lipase M) via triester (−)-**2**. This process provides one of a few examples for dealkoxycarbonylation by lipase. The obtained $C_2$-symmetric diesters (+)-**3** and (−)-**3** were employed for formal synthesis of (+)-carbacyclin and (−)-ajmalicine including (−)-tetrahydroalstonine, respectively.

## 4. Experimental

### 4.1. General

Melting points were taken with a micro hot-stage apparatus (Yanagimoto) and are uncorrected. The infrared (IR) spectra were recorded with a JASCO IR-810 diffraction grating infrared spectrophotometer and $^1H$ NMR spectra were obtained with a Varian XL-300 or a JEOL JNM-EX-270 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL JMS SX-102A QQ or a Hitachi M-80 mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200

polarimeter in the indicated solvent. Combustion analyses were performed by a Yanaco CHN-corder MT-3. The HPLC analyses were performed with a Shimadzu LC-9A Liquid Chromatograph series using a LiChrosorb SI-60 column (10 μm, 4 ϕ×25 cm, temp: 40°C, UV detector: 254 nm, flow: 1 ml/min.). Their data were recorded with a Shimadzu C-R6A Chromatopac. Phosphate buffer was adjusted with a Horiba pH meter F-13. Wakogel C-200 (100–200 mesh, Wako Pure Chemical), and Wakogel C-300 (200–300 mesh, Wako Pure Chemical) were used for open column chromatography. Kieselgel 60 $F_{-254}$ plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was carried out with Kieselgel 60 $F_{-254}$ plates (0.25 mm, Merck). If necessary, compounds were purified by a recycle HPLC (LC-908, Japan Analytical Industry Co., Ltd) on GPC columns (JAIGEL 1H and 2H) after purification on silica gel.

### 4.2. Materials

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC HCl), (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), and 4-dimethylaminopyridine (DMAP) were purchased from Kokusan Chemical Works, Ltd, nacalai tesque, and Wako Pure Chemical Ind. Ltd, respectively. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere before use, after washing with water ten times to remove methanol and pre-drying over calcium chloride. Toluene was used after distillation.

### 4.3. A general procedure for lipase-catalyzed demethoxycarbonylation (Table 1)

A lipase (2 g) was added to a solution of tetramethyl-3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**1**) (200 mg, 0.54 mmol) in toluene (10 ml) and 0.1 M phosphate buffer solution (pH 7.2, 10 ml). The reaction mixture was stirred at room temperature for the indicated time in Table 1. The reaction mixture was filtered with celite. The filtrate was neutralized with 1 N hydrochloric acid to pH 4 and extracted with ethyl acetate. The extract was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=4:1) gave triester **2** and/or diester **3** in the yields indicated in Table 1.

The enantiomeric excesses were determined by HPLC analyses of their (*S*)-bis-MTPA esters of enols in triester **2** and diester **3**. (*S*)-Bis-MTPA ester of (+)-triester **2**; retention time: 14.9 min, (*S*)-bis-MTPA ester of (−)-triester **2**; retention time: 16.2 min, hexane:ethyl acetate=5:1. (*S*)-Bis-MTPA ester of (+)-diester **3**; retention time: 15.3 min, (*S*)-bis-MTPA ester of (−)-diester **3**; retention time: 16.8 min, hexane:ethyl acetate=8:1.

All (*S*)-bis-MTPA esters of triester **2** and diester **3** were prepared by the condensation of triester **2** or diester **3** (ca. 20 mg scale) with (*S*)-MTPA (5 eq.), WSC HCl (6 eq.) and a catalytic amount of DMAP in dichloromethane (2 ml) at room temperature for 2 h. The starting material triester **2** or diester **3** was monitored to be consumed completely by TLC analysis. After the usual extraction with dichloromethane and work-up, the samples for HPLC analysis were obtained by short column chromatography only to exclude polar components derived from the reagents.

### 4.4. Trimethyl (1S,4S,5R)-3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6-tricarboxylate (+)-2

Colorless crystals; mp 81–84°C (hexane:ethyl acetate); $[\alpha]_D^{23}$ +83 (c 0.65, MeOH) (98% ee); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 10.39 (br s, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 3.60–3.77 (m, 3H), 2.5–2.9 (m,

2H); IR ($CHCl_3$): 3630–3080, 1741, 1672, 1634 $cm^{-1}$; MS m/z 312 ($M^+$); anal. calcd for $C_{14}H_{16}O_8$: C, 53.84; H, 5.16. Found: C, 53.91; H, 5.09.

*4.5. Dimethyl (1S,5S)-3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,6-dicarboxylate (+)-3*

Colorless crystals; mp 77–80°C (hexane:ethyl acetate); $[\alpha]_D^{24}$ +138 (c 1.4, MeOH) (100% ee); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 10.46 (br s, 2H), 3.78 (s, 6H), 3.48–3.53 (m, 2H), 2.78–2.90 (m, 2H), 2.52–2.59 (m, 2H); IR ($CHCl_3$): 3710–3150, 1734, 1665, 1626 $cm^{-1}$; MS m/z 254 ($M^+$); anal. calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.62; H, 5.63.

*4.6. Trimethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6-tricarboxylate 2*

To a water (250 ml) solution of tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate disodium salt (20.14 g, 0.049 mol) was added a water (25 ml) solution of lithium hydroxide monohydrate (2.45 g, 0.058 mol, 1.2 eq.) at room temperature and the reaction mixture was stirred for 17.5 h. After acidification with 2 N hydrochloric acid to pH 4 and stirring for 12 h at room temperature, the reaction mixture was extracted with dichloromethane. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on silica gel column chromatography (eluent; hexane:ethyl acetate:dichloromethane=5:1:1.5) gave **2** (1.19 g, 8%) and diester **3**[9b] (1.92 g, 16%) accompanied by their mixture (7.61 g).

*4.7. A general procedure for lipase-catalyzed demethoxycarbonylation (Table 2)*

The same procedure as described previously for Table 1 using racemic or 83% ee triester **2** (100 mg, 0. 32 mmol) and lipase (1.5 g) was performed.

*4.8. Chemical conversion of triester (+)-2 into diester (+)-3*

To a solution of triester (+)-**2** (107 mg, 0.34 mmol) in THF (1 ml) and water (0.9 ml) was added a solution of lithium hydroxide monohydrate (35 mg, 0.82 mmol) in water (1 ml) at room temperature and stirred for 24 h. The reaction mixture was acidified with 1 N hydrochloric acid to pH 4 and stirred for additional 10 h, then extracted with ether. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on column chromatography (eluent; AcOEt:hexane=1:4) gave diester (+)-**3** in 80% yield.

*4.9. Dimethyl (1S,5S,6R,7R)-3,7-dihydroxybicyclo[3.3.0]octa-2-ene-2,6-dicarboxylate (+)-5*

To a dry THF solution (5 ml) of (+)-**3** (463 mg, 1.83 mmol) was added sodium triethoxyborohydride (0.38 M solution in EtOH, 5.69 ml) dropwise at −45°C and then stirred for 1 h at room temperature. The reaction mixture was quenched with 1 N HCl, then concentrated under reduced pressure. Water (30 ml) was added to the residue, then the aqueous layer was extracted with ether (50 ml×3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Silica gel chromatography (hexane:ethyl acetate:dichloromethane=3:1:2) of the residue gave (+)-**5** (192.9 mg, 41%; conversion yield: 94%) and the recovered (+)-**3** (259.5 mg, 56%) as colorless crystals. (+)-**5**: Mp 57.5–61.6°C (hexane:ethyl acetate); $[\alpha]_D^{25}$ +36.2 (c 1.19, MeOH); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 10.36 (br s, 0.6H), 4.57–4.48 (m, 0.4H), 4.33–4.24 (m, 0.6H), 3.77 (s, 1.8H), 3.76 (s, 3H), 3.75 (s, 1.2H),

3.31–3.12 (m, 1.4H), 3.02 (dq, *J*=9.1 and 3.7 Hz, 0.4H), 2.92–2.70 (m, 1H), 2.73 (dq, *J*=7.5 and 2.5 Hz, 0.6H), 2.58–2.43 (m, 3H), 2.40 (br s, 0.6H), 2.34 (br s, 0.4H), 1.67 (ddd, *J*=13.7, 7.1 and 5.7 Hz, 0.4H), 1.49 (ddd, *J*=12.9, 10.1 and 7.9 Hz, 0.6H); IR ($CHCl_3$): 3600 (br), 3480–3360, 3005, 2955, 1725, 1660, 1620, 1445, 1435, 1350 $cm^{-1}$; MS (70 eV) m/z: 256 ($M^+$, 69), 224 (77), 206 (78), 193 (55), 174 (67), 147 (100), 121 (60); anal. calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.25; H, 6.19.

### *4.10. Dimethyl (1R,5R,6S,7S)-3,7-dihydroxybicyclo[3.3.0]octa-2-ene-2,6-dicarboxylate (−)-5*

The same procedure as described above was carried out using diester (−)-**3**. (−)-**5**: $[\alpha]_D^{25}$ −37.9 (c 1.32, MeOH).

### *4.11. Methyl (1S,2R,3R,5R)-3-hydroxy-7-oxobicyclo[3.3.0]octane-2-carboxylate (+)-6*

(Method A): To a solution of (+)-**5** (1.51 g, 5.89 mmol) in THF (15 ml) and water (10 ml) was added a solution of lithium hydroxide monohydrate (0.99 g, 23.6 mmol) in water (10 ml) at room temperature and stirred for 3.5 h. The reaction mixture was acidified with 1 N hydrochloric acid at 0°C to pH 1 and refluxed for an additional 15.5 h. After cooling to room temperature, the reaction mixture was extracted with ether and then with ethyl acetate. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product (ketocarboxylic acid). To a solution of the crude product in ether (10 ml) and methanol (5 ml) was added a ethereal diazomethane solution at 0°C. After addition of acetic acid to decompose excess diazomethane, the reaction mixture was evaporated to give a crude product. Silica gel chromatography (hexane:ethyl acetate=2:1) of the residue gave (+)-**6** (848 mg, 73%) as a colorless oil. (+)-**6**: $[\alpha]_D^{20}$ +7.7 (c 1.09, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 4.46 (ddd, *J*=15.1, 8.2 and 3.3 Hz, 1H); 3.75 (s, 3H), 2.94 (dq, *J*=9.1 and 4.5 Hz, 1H), 2.87–2.75 (m, 1H), 2.65–2.29 (m, 6H), 2.24–2.14 (m, 1H), 1.56 (dt, *J*=12.9 and 7.9 Hz, 1H); IR ($CHCl_3$): 3680, 3610, 3550–3250, 3010, 2960, 1730, 1438, 1403, 1368 $cm^{-1}$; MS (70 eV) m/z 198 ($M^+$, 100), 180 (37), 167 (52), 154 (38), 138 (38), 121 (47), 100 (54), 97 (63), 96 (60); HRMS calcd for $C_{10}H_{14}O_4$ ($M^+$) 198.0892, found 198.0885.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-hydroxy-7-oxobicyclo[3.3.0]octane-2-carboxylate (−)-**6** was also prepared by the same procedure described above using (−)-**5**. (−)-**6**: $[\alpha]_D^{24}$ −7.7 (c 0.83, $CHCl_3$).

(Method B): A mixture of (+)-**5** (0.500 g, 1.95 mmol) in THF (5 ml) and 2 N hydrochloric acid (20 ml) was refluxed for 10 h. The reaction mixture was extracted with ethyl acetate (50 ml×5) by salting-out. The combined extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was diluted with ether (20 ml) and methanol (10 ml), then added an ethereal solution of diazomethane at 0°C. After consumption of the starting material was checked by TLC analysis, the reaction mixture was evaporated under reduced pressure. Silica gel chromatography (hexane:ethyl acetate=1:1) of the residue gave (+)-**6** (297 mg, 77%).

### *4.12. Methyl (1S,2R,3R,5R)-3-acetoxy-7-oxobicyclo[3.3.0]octane-2-carboxylate (−)-7*

Acetic anhydride (0.06 ml, 0.61 mmol) was added to a solution of (+)-**6** (30.5 mg, 0.15 mmol) in pyridine (0.1 ml) at 0°C. The reaction mixture was stirred for 3.5 h at room temperature. After addition of methanol at 0°C, the reaction mixture was concentrated in vacuo. The residue was diluted with dichloromethane, and the solution was washed with saturated ammonium chloride, then brine, dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on silica gel column chromatography (eluent; hexane:ethyl acetate=3:1) gave (−)-**7** (32 mg, 85%) as a colorless oil. (−)-**7**: $[\alpha]_D^{20}$ −25.7 (c 3.0, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 5.41 (q, *J*=6.2 Hz, 1H), 3.73 (s, 3H),

3.08–2.83 (m, 2H), 2.74 (t, *J*=6.1 Hz, 1H), 2.66–2.48 (m, 3H), 2.32 (dd, *J*=20.1 and 3.6 Hz, 1H), 2.17 (dd, *J*=19.8 and 5.3 Hz, 1H), 2.03 (s, 3H), 1.66 (dt, *J*=13.9 and 5.6 Hz, 1H); IR ($CHCl_3$): 3000, 2955, 2850, 1740, 1720, 1430, 1400, 1360 $cm^{-1}$; MS (70 eV) m/z 240 ($M^+$, 90), 198 (68), 180 (74), 148 (100), 138 (38), 121 (58); HRMS calcd for $C_{12}H_{16}O_5$ ($M^+$) 240.0998, found 240.1012.

### *4.13. Methyl (1R,2S,3S,5S)-3-*tert*-butyldimethylsilyloxy-7,7-ethylenedioxybicyclo[3.3.0]-octane-2-carboxylate (+)-8*

To a solution of *tert*-butyldimethylsilyl chloride (TBSCl, 92.8 mg, 0.62 mmol) and imidazole (87.3 mg, 1.28 mmol) in dichloromethane (5 ml), which was stirred at room temperature for 30 min, was added a solution of (−)-**6** (101.6 mg, 0.51 mmol) in dichloromethane (1 ml). After being stirred for 7 h, the reaction mixture was poured into a cooled brine solution, then extracted with dichloromethane. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=3:1) gave methyl (1*R*,2*S*,3*S*,5*R*)-3-*tert*-butyldimethylsilyloxy-7-oxobicyclo[3.3.0]octane-2-carboxylate (153.8 mg, 96%) as a colorless oil. $[\alpha]_D^{23}$ +21.8 (c 1.18, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 4.43 (q, *J*=6.2 Hz, 1H), 3.64 (s, 3H), 2.97–2.71 (m, 2H), 2.58–2.42 (m, 3H), 2.28–2.13 (m, 3H), 1.51 (dt, *J*=13.2 and 6.4 Hz, 1H), 0.80 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); IR ($CHCl_3$): 2990, 2950, 2925, 2890, 2850, 1730, 1465, 1460, 1430 $cm^{-1}$; MS (FAB) m/z 313 ($M^+$+H, 28); HRMS (FAB) calcd for $C_{16}H_{29}O_4Si$ ($M^+$+H) 313.1835, found 313.1842.

To a solution of trimethylsilyl triflate (TMSOTf, 6 μl, 0.03 mmol) in dichloromethane (3 ml) were added 1,2-bis(trimethylsilyloxy)ethane (1.08 ml, 4.39 mmol) and a solution of methyl (1*R*,2*S*,3*S*,5*R*)-3-*tert*-butyldimethylsilyloxy-7-oxobicyclo[3.3.0]octane-2-carboxylate (1.054 g, 3.38 mmol) in dichloromethane (3 ml) at −78°C under a nitrogen atmosphere. After the reaction mixture was stirred for 30 min, pyridine (0.07 ml, 0.08 mmol) was added. The resultant mixture was poured into saturated sodium hydrogen carbonate, and extracted with dichloromethane. The combined extract was washed with brine, dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=7:1) gave (+)-**8** (932 mg, 78%) as a colorless oil. (+)-**8**: $[\alpha]_D^{23}$ +8.2 (c 1.26, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 4.25 (dt, *J*=8.9 and 6.3 Hz, 1H), 3.95–3.82 (m, 4H), 3.65 (s, 3H), 2.69–2.44 (m, 3H), 2.12 (ddd, *J*=12.5, 7.8 and 6.3 Hz, 1H), 1.948 (dd, A part of AB, *J*=13.4 and 8.6 Hz, 1H), 1.947 (dd, A part of AB, *J*=13.4 and 8.6 Hz, 1H), 1.75 (dd, B part of AB, *J*=13.4 and 3.3 Hz, 1H), 1.66 (dd, B part of AB, *J*=13.4 and 5.3 Hz, 1H), 1.54 (dt, *J*=12.2 and 9.2 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); IR ($CHCl_3$): 2950, 2930, 2890, 2850, 1725, 1470, 1460, 1430 $cm^{-1}$; MS (FAB) m/z 357 ($M^+$+H, 30); HRMS (FAB) calcd for $C_{18}H_{33}O_5Si$ ($M^+$+H) 357.2098, found 357.2076.

### *4.14. (1R,2R,3S,5S)-3-*tert*-Butyldimethylsilyloxy-7,7-ethylenedioxy-2-hydroxymethyl-bicyclo[3.3.0]octane (+)-9*

Diisobutylaluminum hydride (DIBAH, 1.76 M solution in hexane, 5.45 ml, 9.59 mmol) was added dropwise to a solution of (+)-**8** (854 mg, 2.40 mmol) in THF (10 ml) at −65°C under nitrogen atmosphere. After being stirred for 5 min, the reaction mixture was quenched with water. The resultant mixture was concentrated in vacuo to give a residue, which was filtered on silica gel with ethyl acetate. The filtrate was condensed to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=5:1) gave (+)-**9** (729 mg, 93%) as a colorless oil. (+)-**9**: $[\alpha]_D^{20}$ +26.7 (c 1.17, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 3.89 (dd, A part of AB, *J*=9.4 and 4.3 Hz, 2H), 3.86–3.79 (m, 1H), 3.83 (dd,

B part of AB, $J$=9.4 and 4.3 Hz, 2H), 3.64–3.59 (m, 2H), 2.46–2.29 (m, 2H), 2.14–1.83 (m, 5H), 1.66 (dt, $J$=12.7 and 6.0 Hz, 2H), 1.47 (dt, $J$=11.9 and 9.6 Hz, 1H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); IR ($CHCl_3$): 3630–3300, 3010, 2960, 2935, 2895, 2860, 1470, 1460, 1320, 1255, 1100 (br) $cm^{-1}$; MS (FAB) m/z 329 ($M^+$+H, 78); HRMS (FAB) calcd for $C_{17}H_{33}O_4Si$ ($M^+$+H) 329.2148, found 329.2128.

### *4.15. (1R,2S,3S,5S)-3-tert-Butyldimethylsilyloxy-7,7-ethylenedioxy-2-methylbicyclo-[3.3.0]octane (+)-**10***

A solution of (+)-**9** (728 mg, 2.22 mmol) in pyridine (5 ml) was added to a solution of tosyl chloride (847 mg, 4.44 mmol) in pyridine (5 ml) at room temperature under a nitrogen atmosphere. After being stirred for 15 h, the reaction mixture was poured into a cooled saturated sodium hydrogen carbonate solution, then extracted with dichloromethane. The combined extract was washed with brine, dried ($Na_2SO_4$), filtered, and evaporated to give a crude tosylate. The THF (20 ml) solution of crude tosylate was added to a THF (5 ml) suspension of lithium aluminum hydride, and the resultant mixture was stirred at room temperature for 8.5 h. The reaction mixture was poured into ice–water, the resultant salt was filtered off. The filtrate was extracted with ether. The combined ether was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=10:1) gave (+)-**10** (559 mg, 81%, overall 2 steps) as a colorless oil. (+)-**10**: $[\alpha]_D^{22}$ +19.9 (c 0.67, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 3.93–3.82 (m, 4H), 3.53 (dt, $J$=8.9 and 6.3 Hz, 1H), 2.37 (sextet, $J$=8.4 Hz, 1H), 2.09 (ddd, $J$=12.2, 8.4 and 6.2 Hz, 1H), 2.01–1.84 (m, 3H), 1.76–1.55 (m, 3H), 1.39 (ddd, $J$=12.2, 8.9 and 8.4 Hz, 1H), 0.93 (d, $J$=6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); IR ($CHCl_3$): 2960, 2940, 2890, 2860, 1465, 1460, 1325, 1110 (br) $cm^{-1}$; MS (FAB) m/z 313 ($M^+$+H, 46); HRMS (FAB) calcd for $C_{17}H_{33}O_3Si$ ($M^+$+H) 313.2199, found 313.2178.

### *4.16. (1R,2S,3S,5S)-7,7-Ethylenedioxy-3-hydroxy-2-methylbicyclo[3.3.0]octane (−)-**11***

To a THF (3 ml) solution of (+)-**10** (524 mg, 1.68 mmol) was added tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF, 3.36 ml, 3.36 mmol) at 0°C under a nitrogen atmosphere. After being stirred for 19.5 h at room temperature, the reaction mixture was quenched with brine at 0°C, then extracted with ether. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=2:1) gave (−)-**11** (321 mg, 96%) as a colorless oil. (−)-**11**: $[\alpha]_D^{23}$ −6.9 (c 0.59, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) δ: 3.93 (dd, A part of AB, $J$=9.6 and 3.8 Hz, 2H), 3.88 (dd, B part of AB, $J$=9.6 and 3.8 Hz, 2H), 3.59 (dt, $J$=9.0 and 6.3 Hz, 1H), 2.52–2.36 (m, 1H), 2.24 (ddd, $J$=12.3, 8.5 and 6.4 Hz, 1H), 2.06–1.92 (m, 4H), 1.73–1.58 (m, 3H), 1.44 (dt, $J$=12.2 and 8.9 Hz, 1H), 1.02 (d, $J$=6.6 Hz, 3H); IR ($CHCl_3$): 3600 (br), 3560–3300, 3000, 2960, 2940, 1470, 1450, 1430, 1320 $cm^{-1}$; MS (70 eV) m/z 198 ($M^+$, 6.8), 141 (40), 99 (77) 86 (100), 55 (77); HRMS calcd for $C_{11}H_{18}O_3$ ($M^+$) 198.1256, found 198.1274.

### *4.17. (1R,2S,5S)-7,7-Ethylenedioxy-2-methylbicyclo[3.3.0]octan-3-one (+)-**12***

A dichloromethane (1 ml) solution of (−)-**11** (60 mg, 0.31 mmol) was added to a suspension of pyridinium chlorochromate (PCC, 132 mg, 0.61 mmol) in dichloromethane (3 ml) at 0°C under a nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was filtered on silica gel with ethyl acetate to give a crude product. Purification on column chromatography (eluent; hexane:ethyl acetate=3:1) gave (+)-**12** (42 mg, 70%) as a colorless oil. (+)-**12**: $[\alpha]_D^{22}$ +32.5 (c 1.80, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 3.95–3.87 (m, 4H), 2.78 (d quintet,

$J$=8.5 and 2.8 Hz, 1H), 2.46 (dd, A part of AB, $J$=19.1 and 9.0 Hz, 1H), 2.37–2.15 (m, 4H), 2.30 (dd, B part of AB, $J$=9.0 and 4.7 Hz, 1H), 1.91–1.83 (m, 1H), 1.69 (dd, J=13.8 and 8.2 Hz, 1H), 1.08 (d, $J$=6.9 Hz, 3H); IR ($CHCl_3$): 3520 (br), 3460 (br), 2970, 2930, 2890, 1735, 1475, 1450, 1430, 1405, 1375 $cm^{-1}$; MS (70 eV) m/z 196 ($M^+$, 24), 139 (51), 127 (35), 126 (35), 113 (59), 112 (74), 94 (100), 86 (67); HRMS calcd for $C_{11}H_{16}O_3$ ($M^+$) 196.1100, found 196.1091.

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