Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3849–3857

TETRAHEDRON: *ASYMMETRY*

Preparation of a synthetic equivalent of chiral methyl 2,5-dihydroxycyclohexane-1,4-dienecarboxylate

Naoyuki Yoshida, Hiroyuki Konno, Takashi Kamikubo, Michiyasu Takahashi and Kunio Ogasawara *

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Received 23 August 1999; accepted 13 September 1999

Abstract

A chiral tricyclic diol, serving as a synthetic equivalent of chiral methyl 2,5-dihydroxycyclohexane-1,4-dienecarboxylate, has been prepared in both enantiomeric forms by employing a lipase-mediated kinetic resolution in vinyl acetate. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Owing to its inherent convex-face selectivity, a chiral tricyclic α,β-unsaturated ketone **2**, obtained from the *meso* tricyclic 1,4-enediol **1** precursor, is shown to be versatilely useful for the diastereo- and enantiocontrolled construction of a variety of natural products as a synthetic equivalent of chiral cyclohexadienone.[1,2] This compound, however, requires a somewhat tedious operation to modify the tertiary center next to the ketone functionality. As noted in the synthesis[3] of (−)-carvone **8**, it required blocking of the other side so as to install the methyl functionality at the necessary position, and the blocking epoxide functionality had to be removed at a later stage (Scheme 1). In order to obviate the need for such extra steps, we investigated the preparation of a new chiral building block carrying a flexible functionality on the appropriate position of the tricyclic framework. We wish to report here the preparation of a compound having an appropriately positioned carbomethoxy functionality, by employing a lipase-mediated kinetic transesterification,[4] which is expected to serve as a synthetic equivalent of chiral methyl 2,5-dihydroxycyclohexane-1,4-dienecarboxylate.

* Corresponding author. Fax: +81-22-217-6845; e-mail: konol@mail.cc.tohoku.ac.jp

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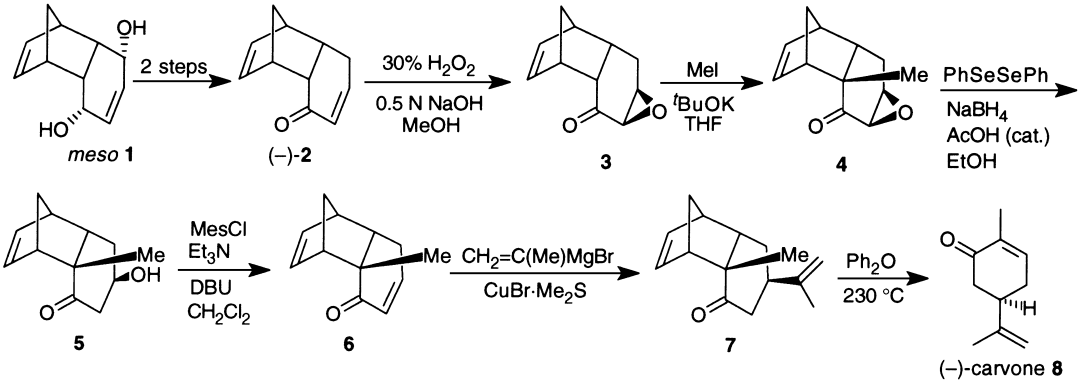
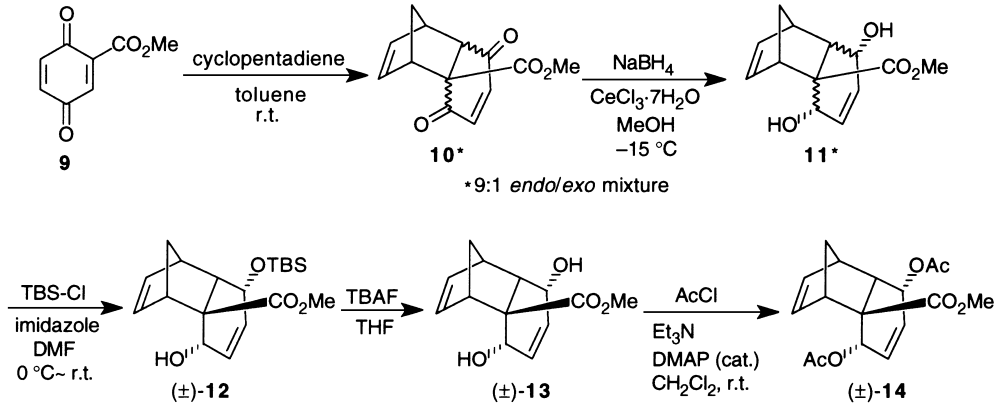
PII: S0957-4166(99)00414-0



Scheme 1.

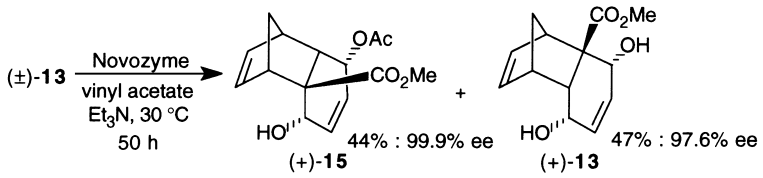
2. Results and discussion

In order to install a chemically flexible functionality at the requisite position regioselectively, we employed the Diels–Alder reaction between cyclopentadiene and 2-carbomethoxybenzoquinone **9** (Scheme 2). Thus, treatment of the benzoquinone **9**, prepared in situ from methyl 2,5-dihydroxybenzoate (methyl gentisate) with silver(I) oxide in toluene,[5] with a slight excess (1.1 equiv.) of cyclopentadiene at room temperature gave the adduct **10**, regioselectively, in 86% yield as an inseparable *endo* and *exo* mixture in a ratio of 9:1 which was determined by the ^{1}H NMR spectrum. The mixture without separation was then reduced with sodium borohydride in methanol in the presence of cerium(III) chloride heptahydrate[6] to give a mixture of the diols **11** which was silylated to separate the *exo* isomer to give rise to the diastereomerically pure *endo* isomer as the monosilyl ether (±)-**12** in 79% yield. After removal of the silyl group by treating (±)-**12** with tetrabutylammonium fluoride (TBAF), the resulting diol (±)-**13** obtained in 87% yield was used as the substrate for the lipase-mediated kinetic transesterification (Scheme 3). The racemic diol (±)-**13** was further transformed into the racemic diacetate (±)-**14** used as the substrate for the lipase-mediated kinetic hydrolysis reaction. The stereochemistry of the diastereomerically pure diol (±)-**13** was determined by NOE experiments after transformation into the silyl ether **12** which revealed a significant interaction between hydrogens Ha and Hb as well as Hb and Hc supporting the *endo* stereochemistry (Fig. 1).



Scheme 2.

Among the five immobilized enzymes, lipase MY (*Candida cylindracea*, Meito), lipase AK (*Pseudomonas* sp., Amano), lipase PS (*Pseudomonas* sp., Amano), lipase LIP (*Pseudomonas* sp., Toyobo)



Scheme 3.

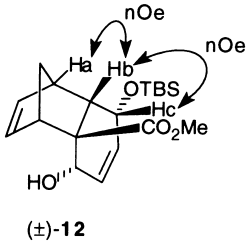


Figure 1.

Table 1
Transesterification of the diol (±)-**13**

Entry	Enzyme	Solvent	Additive	Temp (°C) : Time (h)	(+)-**15** (%[a]:% ee[b])	(+)-**13** (%[a]:% ee[b])	*E*
1	Lipase PS[c]	vinyl acetate	–	40 144	36.0 : n.d.	50.0 : 55.3	–
2	Lipase MY[c]	vinyl acetate	–	40 144	0 : –	95.0 : ~ 0	–
3	Lipase LIP[c]	vinyl acetate	–	30 144	11.0 : –	58.0 : 37.4	–
4	Lipase AK[c]	vinyl acetate	Et_3N	30 50	20.6 : 99.9	79.2 : 31.0	2576
5	Novozyme[c]	THF[e]	–	40 144	39.0 : 85.1	54.0 : 61.3	21
7	Novozyme[c]	CH_2Cl_2[e]	–	40 144	22.7 : 98.0	38.1 : 73.1	131
8	Novozyme[c]	toluene[e]	–	40 60	29.1 : 90.3	29.2 : 77.1	28
8	Novozyme[c]	Bu^{t}OMe[e]	–	40 60	37.9 : 96.0	36.6 : 77.2	89
9	Novozyme[c]	vinyl acetate	–	40 48	39.4 : 97.8	50.1 : 73.9	174
10	Novozyme[c]	vinyl acetate	Et_3N	40 16	37.4 : 99.9	56.5 : 82.3	3681
11	Novozyme[c]	vinyl acetate	Et_3N	30 50	44.1 : 99.9	46.9 : 97.6	4836

a: isolated yield after SiO_2 column chromatography. *b*: determined by HPLC equipped with a column with a chiral stationary phase (CHIRALCEL OD, hexane-Pr^{i}OH, 200:1) after transformation into the dibenzoate. *c*: immobilized on Celite [Lipase AK (*Pseudomonas* sp., Amano), Lipase PS (*Pseudomonas* sp., Amano), Lipase MY (*Candida cylindracea*, Meito), Lipase LIP (*Pseudomonas* sp., Toyobo), Novozyme (*Candida antarctica*, Novo)]. *d*: ~2% of the solvent was used. *e*: a large excess

and Novozyme (*Candida antarctica*, Novo) examined, Novozyme exhibited the best results when it was used with triethylamine in vinyl acetate (Table 1). Thus, when the diol (±)-**13** was stirred with Novozyme in vinyl acetate containing 2% of triethylamine at 30°C for 50 h, the monoester (+)-**15** and the diol (+)-**13** were obtained in good yields with high enantiomeric excesses (Entry 11). Without addition of triethylamine the reaction proceeded very slowly, leaving the diol (+)-**13** in low enantiomeric excess. Although the effect of triethylamine is uncertain,[7] we have observed its acceleration effect in the transesterification of some instances,[8,9] in particular with the use of lipase LIP in an organic solvent. The kinetic hydrolysis of the racemic diacetate (±)-**14**, on the other hand, proceeded too slowly with all five lipases shown to give the resolution products in practical yields.

Having obtained the resolution products in satisfactory enantiomeric excess and chemical yields under the transesterification conditions, we next examined the determination of the absolute configuration of the resolution products. Since we have our own empirical rule[10,11] for the determination of the configuration of a stereogenic center carrying a secondary hydroxy functionality by extension of Mosher's rule,[12] we transformed the diol (−)-**13** obtained from the acetate (+)-**15** into the bis-MTPA esters **16** by using both

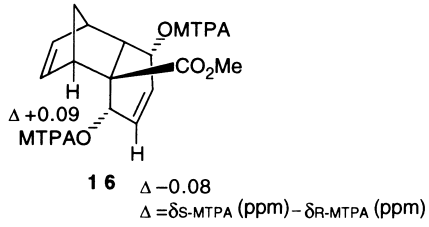
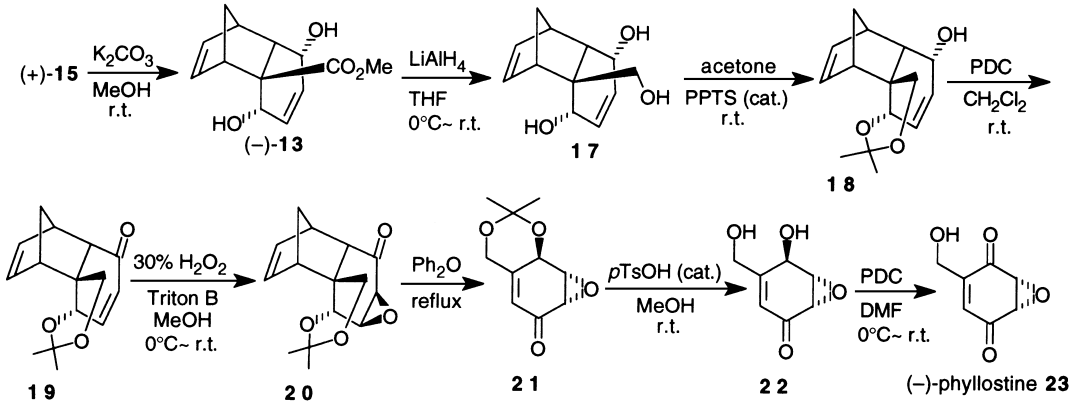


Figure 2.

of the enantiomeric Mosher reagents. The ^{1}H NMR spectra of **16** showed significant differences at the C1 and C3 centers between two diastereomeric esters **16** which indicated that the diol (−)-**13** should have the structure as shown and, consequently, (+)-**13** as shown in the light of our empirical rule (Fig. 2).

In order to ascertain the absolute configuration of the resolution products unambiguously, the diol (−)-**13** obtained from the acetate (+)-**15** by alkaline methanolysis was transformed into (−)-phyllostine **23**, a phytotoxic compound isolated from culture broth of *Phyllosticta* sp.[13] and determined by enantiocontrolled synthesis.[14]

Thus, reduction of (−)-**13** with lithium aluminum hydride afforded the triol **17** which furnished the acetonide **18** in 50% overall yield. Although it seems a little curious to see the formation of such an acetonide **18**, no significant steric compression was found to exist in this molecule by examination of models. Oxidation of **18** gave the enone **19** which diastereoselectively afforded the *exo* epoxide **20** on oxidation with alkaline hydrogen peroxide. Retro-Diels–Alder reaction of **20** proceeded without difficulty on heating in refluxing diphenyl ether to give the cyclohexenone **21** in 40% overall yield from **18**. Removal of the acetonide functionality of **21**, followed by chemospecific oxidation of the secondary allylic hydroxyl of the diol **22**, generated by using pyridinium dichromate (PDC) in DMF,[14] afforded (−)-phyllostine **23** in 37% overall yield. Thus, the absolute configuration of the starting diol (−)-**13** was confirmed unambiguously and, consequently, that of the enantiomeric diol (+)-**13** was confirmed as shown (Scheme 4).



Scheme 4.

In conclusion, we have obtained a tricyclic diol intended to serve as a synthetic equivalent of chiral methyl 2,5-dihydroxycyclohexane-1,4-dienecarboxylate in both enantiomeric forms from the adduct generated from methyl benzoquinonecarboxylate and cyclopentadiene by employing a lipase-mediated enantiospecific transesterification reaction. Utilization of enantiopure compounds for the enantiocontrolled construction of natural products is currently under investigation.

3. Experimental

Melting points were determined on a Yanagimoto hotstage and are uncorrected. IR spectra were recorded on a JASCO-IR 700 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz) spectrometer. Optical resolutions were measured with a JASCO-DIP-370 digital polarimeter. Enantiomeric purities were determined on a Gilson Model-307 instrument equipped with a column with a chiral stationary phase.

3.1. *Methyl tricyclo[6.2.1.0^{2,7}]undec-4,9-diene-3,6-dione-2-carboxylate* ***10***

To a stirred solution of methyl 2,5-dihydroxybenzoate (0.73 g, 4.3 mmol) in toluene (5 ml) was added Ag_2O (2.0 g, 8.6 mmol) and cyclopentadiene (0.43 ml, 5.2 mmol) at room temperature and the mixture was stirred at the same temperature for 12 h. Concurrent oxidation to methyl 1,4-benzoquinonecarboxylate **9** and Diels–Alder reaction occurred to give rise to a mixture of two adducts (9:1). The mixture was filtered through a Celite pad, evaporated, and chromatographed (SiO_2, 20 g, elution with AcOEt:hexane, 1:2, v/v) to give a mixture of *endo*-**10** and *exo*-**10** (9:1): 0.86 g (86%).

Compound *endo*-**10**: IR (film): ν=1745, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (1H, d, *J*=7.7 Hz), 1.66 (1H, d, *J*=7.7 Hz), 3.38 (1H, d, *J*=3.8 Hz), 3.48 (1H, m), 3.73 (3H, s), 3.79 (1H, m), 6.08 (1H, dd, *J*=5.5, 2.7 Hz), 6.13 (1H, dd, *J*=5.5, 2.7 Hz), 6.62 (2H, m).

Compound *exo*-**10**: IR (film): ν=1745, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (1H, d, *J*=8.0 Hz), 1.47 (1H, d, *J*=8.0 Hz), 2.90 (1H, d, *J*=3.8 Hz), 3.28 (1H, m), 3.66 (3H, s), 3.84 (1H, m), 6.29 (1H, dd, *J*=5.5, 2.7 Hz), 6.42 (1H, dd, *J*=5.5, 2.7 Hz), 6.81 (2H, s).

3.2. *Methyl 6-*tert*-butyldimethylsilyloxy-3-hydroxytricyclo[6.2.1.0^{2,7}]undec-4,9-diene-2-carboxylate (±)-**12**

To a stirred solution of the mixture of **10** (5.0 g, 22 mmol) and $CeCl_3 \cdot 7H_2O$ (8.1 g, 22 mmol) in MeOH (100 ml) was added $NaBH_4$ (1.6 g, 43 mmol) at −15°C. After 30 min at the same temperature, acetone (5 ml) was added to the mixture and, after stirring for 30 min at room temperature, was evaporated under reduced pressure. The residue was diluted with AcOEt and the solution was washed successively with 3% HCl, brine, 5% $NaHCO_3$, and brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, 100 g, elution with AcOEt:hexane, 1:1, v/v) to give the diol mixture **11** (9:1) (4.4 g, 86%) as colorless crystals.

To a stirred solution of **11** in DMF (50 ml) was added imidazole (1.9 g, 28 mmol) and *tert*-butyldimethylsilyl chloride (3.4 g, 22 mmol) at 0°C and the mixture was stirred at room temperature for 2 h. The mixture was diluted with ether and washed with water, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed (SiO_2, 100 g, elution with AcOEt:hexane, 1:4, v/v) to give the siloxy-alcohol (±)-**12** (5.2 g, 79%) as a colorless oil.

IR (film): ν=3486, 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (3H, s), 0.10 (3H, s), 0.93 (9H, s), 1.26 (1H, d, *J*=8.5 Hz), 1.35 (1H, d, *J*=8.5 Hz), 2.76 (1H, d, *J*=3.3 Hz), 3.07 (1H, br s), 3.26 (1H, br s), 3.30 (1H, dd, *J*=8.2, 3.6 Hz), 3.82 (3H, s), 4.33 (1H, br s), 4.43 (1H, d, *J*=8.2 Hz), 5.25 (1H, d, *J*=10.4 Hz), 5.30 (1H, ddd, *J*=10.4, 2.7, 1.6 Hz), 5.82 (1H, dd, *J*=5.2, 3.0 Hz), 5.92 (1H, dd, *J*=5.2, 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.0, −4.96, 18.0, 25.8, 45.3, 46.2, 46.8, 50.4, 52.6, 58.1, 66.9, 69.1, 128.9, 131.0, 134.4, 139.2, 178.7; MS: *m/z*=293 (M^+-Bu^t), 75 (100%). HRMS calcd $C_{19}H_{30}O_4Si$ (M^+-Bu^t): 293.1208. Found: 293.1222.

3.3. Methyl 3,6-dihydroxytricyclo[6.2.1.0^{2,7}]undec-4,9-diene-2-carboxylate (±)-**13**

To a stirred solution of (±)-**12** (5.2 g, 15 mmol) in THF (50 ml) was added dropwise tetrabutylammonium fluoride (TBAF) in THF (1 M, 30 ml, 30 mmol) at room temperature and the stirring was continued at the same temperature for 10 h. The solution was diluted with AcOEt and was washed successively with 3% HCl, 5% $NaHCO_3$, and brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, 100 g, elution with AcOEt:hexane, 1:1, v/v) to give the *endo*-diol (±)-**13** (3.0 g, 87%) as colorless crystals: mp 124–126°C; IR (film): ν=3484, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (1H, d, *J*=8.5 Hz), 1.41 (1H, d, *J*=8.5 Hz), 1.70 (1H, d, *J*=5.5 Hz), 2.77 (1H, d, *J*=3.3 Hz), 3.10 (1H, br s), 3.29 (1H, br s), 3.42 (1H, dd, *J*=8.0, 3.3 Hz), 3.82 (3H, s), 4.35 (1H, m), 4.52 (1H, m), 5.37 (2H, m), 5.87 (1H, dd, *J*=5.5, 3.0 Hz), 5.95 (1H, dd, *J*=5.5, 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.8, 46.0, 47.2, 50.4, 52.8, 58.2, 66.8, 69.2, 129.5, 130.0, 135.1, 138.5, 178.6; MS: *m/z*=236 (M^+), 66 (100%). HRMS calcd $C_{13}H_{16}O_4$ (M^+): 236.1048. Found: 236.1016.

3.4. Methyl 3,6-diacetoxytricyclo[6.2.1.0^{2,7}]undec-4,9-diene-2-carboxylate (±)-**14**

To a stirred solution of the diol (±)-**13** (1.18 g, 5 mmol), Et_3N (1.52 g, 15 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (1.0 g, 8.2 mmol) in dichloromethane (30 ml) was added dropwise acetyl chloride (942 mg, 12 mmol) in dichloromethane (5 ml) at 0°C and the stirring was continued overnight at room temperature. After the mixture was diluted with dichloromethane, the solution was washed successively with 5% $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, 50 g, elution with AcOEt:hexane, 1:2, v/v) to give the diacetate (±)-**14** (1.54 g, 96%) as colorless crystals: mp 92–95°C; IR (film): ν=1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.41 (2H, br s), 2.11 (3H, s), 2.13 (3H, s), 2.84 (1H, br s), 3.24 (1H, dd, *J*=8.5, 3.5 Hz), 3.29 (1H, br s), 3.76 (3H, s), 5.37 (2H, m), 5.54 (1H, d, *J*=1.7 Hz), 5.64 (1H, br s), 5.87 (1H, dd, *J*=5.5, 3.1 Hz), 5.95 (1H, dd, *J*=5.5, 3.1 Hz); MS: *m/z*=320 (M^+), 66 (100%). HRMS calcd $C_{17}H_{20}O_6$ (M^+): 320.1259. Found: 320.1262.

3.5. Kinetic transesterification of the racemic diol (±)-**13**: methyl (1S,2S,3S,6R,7S,8R)-6-acetoxy-3-hydroxytricyclo[6.2.1.0^{2,7}]undec-4,9-diene-2-carboxylate (+)-**15** and (+)-(1R,2R,3R,6S,7R,8S)-(+)-**13**

A suspension of the diol (±)-**13** (200 mg, 0.85 mmol) and Novozyme (*Candida antarctica*, Roche, 200 mg) in vinyl acetate (2.0 ml) containing Et_3N (0.04 ml) was stirred at 30°C for 50 h. After filtration through a Celite pad, the mixture was evaporated under reduced pressure and the residue was chromatographed (SiO_2, 5 g, elution with AcOEt:hexane, 1:2→1:1) to give the acetate (+)-**15**, $[\alpha]_D^{27}$ +20.1 (*c* 0.8, $CHCl_3$), as a colorless oil (104 mg, 44%) and the diol (+)-**13**, mp 124–126°C, $[\alpha]_D^{29}$ +13.4 (*c* 1.0, $CHCl_3$), as colorless crystals (93.8 mg, 47%).

3.6. Methyl (1S,2S,3S,6R,7S,8R)-6-acetoxy-3-hydroxytricyclo[6.2.1.0^{2,7}]undec-4,9-diene-2-carboxylate (+)-**15**

IR (film): ν=3400, 1745, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (1H, d, *J*=8.8 Hz), 1.39 (1H, d, *J*=8.8 Hz), 2.12 (3H, s), 2.87 (1H, m), 3.29 (1H, br s), 3.55 (1H, dd, *J*=8.2, 3.6 Hz), 3.81 (3H, s), 4.37 (1H, br s), 5.25 (1H, m), 5.44 (2H, m), 5.90 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 42.2, 45.5, 46.8, 50.5, 52.7, 57.6, 68.8, 69.4, 125.7, 131.0, 135.3, 138.1, 170.6, 178.2; MS: *m/z*=278 (M^+), 66 (100%). HRMS calcd $C_{15}H_{18}O_5$ (M^+): 278.1153. Found: 278.1144. The enantiomeric excess of (+)-**13**

was determined as 97.6% by HPLC using a column with a chiral stationary phase (Chiralcel OD, elution with hexane:Pr^{i}OH, 200:1) after transformation into the dibenzoate.

*3.7. (1S,2S,3S,6R,7S,8R)-Methyl 3,6-dihydroxytricyclo[6.2.1.0^{2,7}]undec-4,9-diene-2-carboxylate (−)-**13***

A solution of the acetate (+)-**15** (270 mg, 1.0 mmol) in MeOH (5 ml) was stirred with K_2CO_3 (200 mg, 1.45 mmol) at room temperature overnight. After evaporation of the solvent under reduced pressure, the residue was dissolved in dichloromethane and the solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to leave the diol (−)-**13**, mp 124–126°C, $[\alpha]_D^{28}$ −13.6 (*c* 1.0, $CHCl_3$), as colorless crystals (221 mg, 94%). Spectroscopic data were identical with those of (+)-**13**. The enantiomeric excess of (−)-**13**, thus (+)-**15**, was determined as 99.9% by HPLC using a column with a chiral stationary phase (Chiralcel OD, elution with hexane:Pr^{i}OH, 200:1) after transformation into the dibenzoate.

*3.8. (1R,2S,3S,6S,11R,12S)-3-Hydroxy-8,8-dimethyl-7,9-dioxatetracyclo[10.2.1.0^{2,11}.0^{6,11}]pentadec-4,13-diene **18***

To a stirred solution of (−)-**13** (500 mg, 1.8 mmol) in THF (5 ml) was added $LiAlH_4$ (37 mg, 1.0 mmol) at 0°C and the stirring was continued for 1 h at the same temperature and 2 h at room temperature. The reaction was quenched by addition of 3% NaOH and filtered through a Celite pad. After evaporation of the solvent under reduced pressure, the residue was stirred in acetone (10 ml) containing pyridinium *p*-toluenesulfonate (2 mg) and the stirring was continued for 12 h at room temperature. After dilution with AcOEt, the mixture was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with AcOEt:hexane, 1:2, v/v) to give the acetonide **18** (230 mg, 51% from (−)-**13**) as a colorless oil: $[\alpha]_D^{29}$ +26.2 (*c* 0.6, $CHCl_3$); IR (film): ν=3426 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (1H, d, *J*=9.1 Hz), 1.49 (6H, s), 1.51 (1H, d, *J*=9.1 Hz), 1.74 (1H, br s), 2.23 (1H, dd, *J*=8.0, 3.8 Hz), 2.98 (1H, br s), 3.36 (1H, br s), 3.86 (1H, d, *J*=11.0 Hz), 4.10 (1H, d, *J*=11.0 Hz), 4.47 (2H, m), 5.29 (2H, s), 5.80 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 29.7, 44.4, 45.6, 46.1, 47.2, 47.8, 68.9, 73.2, 73.3, 100.4, 127.1, 131.5, 136.2, 137.1; MS: *m/z*=233 (M^+−Me), 66 (100%). HRMS calcd $C_{15}H_{20}O_3$ (M^+−Me): 233.1177. Found: 233.1165.

*3.9. (1R,2S,6S,11S,12R)-8,8-Dimethyl-3-oxo-7,9-dioxatetracyclo[10.2.1.0^{2,11}.0^{6,11}]pentadec-4,13-diene **19***

To a stirred solution of **18** (200 mg, 0.81 mmol) in dichloromethane (5 ml) was added pyridinium dichromate (610 mg, 1.6 mmol) at 0°C and the stirring was continued for 2 h at room temperature. After filtration through a Celite pad, the mixture was evaporated under reduced pressure and chromatographed (SiO_2, 5 g, elution with AcOEt:hexane, 1:4, v/v) to give the enone **19** (180 mg, 90%) as a colorless oil: $[\alpha]_D^{27}$ +267.5 (*c* 1.0, $CHCl_3$); IR (film): ν=1654 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (1H, d, *J*=9.1 Hz), 1.49 (3H, s), 1.52 (3H, s), 1.60 (1H, d, *J*=9.1 Hz), 2.60 (1H, d, *J*=4.4 Hz), 3.26 (1H, br s), 3.52 (1H, br s), 3.86 (1H, d, *J*=10.7 Hz), 4.08 (1H, d, *J*=10.7 Hz), 4.87 (1H, m), 5.75 (2H, m), 6.15 (1H, dd, *J*=5.2, 3.0 Hz), 6.46 (1H, dd, *J*=10.2, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 29.4, 44.2, 47.5, 47.7, 51.5, 52.3, 72.1, 73.5, 101.1, 131.4, 136.5, 137.1, 146.6, 200.8; MS: *m/z*=246 (M^+), 66 (100%). HRMS calcd $C_{15}H_{18}O_3$ (M^+): 246.1255. Found: 246.1275.

3.10. (1R,2S,6R,11S,12S)-4,5-Epoxy-8,8-dimethyl-3-oxo-7,9-dioxatetracyclo[10.2.1.$0^{2,11}$.$0^{6,11}$]pentadec-13-ene **20**

To a stirred solution of the enone **19** (81 mg, 0.33 mmol) in THF (1 ml) was added 30% H_2O_2 (0.17 ml, 1.5 mmol), Triton B (40% in MeOH, 0.08 ml, 0.18 mmol) at 0°C and the stirring was continued at the same temperature for 1 h and at room temperature for 2 h. After dilution with dichloromethane, the mixture was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give the epoxide **20** which was immediately used for the next reaction. IR (film): ν=1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (3H, s), 1.53 (3H, s), 1.64 (2H, m), 2.40 (1H, d, *J*=4.1 Hz), 2.96 (2H, m), 3.10 (1H, br s), 3.59 (1H, br s), 3.68 (1H, d, *J*=11.3 Hz), 3.84 (1H, m), 4.00 (1H, d, *J*=11.3 Hz), 6.18 (1H, dd, *J*=5.8, 2.7 Hz), 6.43 (1H, dd, *J*=5.8, 2.7 Hz); MS: *m/z*=262 (M^+), 66 (100%). HRMS calcd $C_{15}H_{18}O_4$ (M^+): 262.1204. Found: 262.1222.

3.11. (1R,9S,10S)-9,10-Epoxy-3,3-dimethyl-2,4-dioxabicyclo[4.4.0]dec-6-en-8-one **21**

A solution of the above epoxide **20** in diphenyl ether (2 ml) was refluxed for 5 min. After cooling, the mixture was chromatographed (SiO_2, 2 g, elution with AcOEt:hexane, 1:4, v/v) to give the cyclohexenone **21** (30 mg, 46%) as a colorless oil: $[\alpha]_D^{27}$ −174.2 (*c* 0.1, $CHCl_3$); IR (film): ν=1679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (3H, s), 1.61 (3H, s), 3.45 (1H, m), 3.69 (1H, d, *J*=3.3 Hz), 4.27 (1H, d, *J*=14.6 Hz), 4.60 (1H, dt, *J*=14.6, 1.4 Hz), 4.83 (1H, s), 5.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 27.2, 52.4, 57.3, 63.9, 64.1, 101.4, 120.4, 154.2, 191.3; MS: *m/z*=196 (M^+), 43 (100%). HRMS calcd $C_{10}H_{12}O_4$ (M^+): 196.0735. Found: 196.0753.

3.12. (4R,5R,6R)-5,6-Epoxy-4-hydroxy-3-hydroxymethylcyclohex-2-en-1-one **22**

A solution of the acetonide **21** (8 mg, 0.041 mmol) was stirred in MeOH (1 ml) containing *p*-toluenesulfonic acid (1 mg) at room temperature for 30 min. The mixture was diluted with AcOEt and the solution was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 1 g, elution with $CHCl_3$:MeOH, 9:1, v/v) to give the diol **22** (6 mg, 95%) as a colorless oil: $[\alpha]_D^{26}$ −107.0 (*c* 0.2, EtOH); IR (film): ν=3416, 1679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (1H, br s), 3.49 (1H, s), 3.82 (1H, br s), 3.83 (1H, s), 4.37 (1H, d, *J*=15.4 Hz), 4.56 (1H, d, *J*=15.4 Hz), 4.75 (1H, s), 6.02 (1H, s); MS: *m/z*=156 (M^+), 82 (100%). HRMS calcd $C_7H_8O_4$ (M^+): 156.0422. Found: 156.0439.

3.13. (−)-Phyllostine **23** [(5S,6R)-5,6-epoxy-2-hydroxymethylcyclohex-2-ene-1,4-dione]

To a stirred solution of the diol **22** (5 mg, 0.032 mmol) in DMF (1 ml) was added pyridinium chlorochromate (25 mg, 0.064 mmol) at 0°C and the stirring was continued at the same temperature for 3 h, then at room temperature for 3 h. After filtration through a Celite pad, the mixture was evaporated under reduced pressure and the residue was chromatographed (SiO_2, 1 g, elution with AcOEt:hexane, 1:2, v/v) to give phyllostine **23** (2 mg, 41%): mp 53–54°C; $[\alpha]_D^{26}$ −118.7 (*c* 0.05, EtOH) [lit.:[14] mp 54.5–55°C; $[\alpha]_D^{31}$ −100.4 (*c* 0.62, EtOH)]; IR (film): ν=3442, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90–2.20 (1H, br s), 3.81–3.87 (2H, m), 4.40 (1H, dd, *J*=17.6, 1.9 Hz), 4.58 (1H, dd, *J*=17.6, 1.9 Hz), 6.69 (1H, dd, *J*=4.1, 1.9 Hz); MS: *m/z*=154 (M^+), 126 (100%). HRMS calcd $C_7H_6O_4$ (M^+): 154.0266. Found: 154.0266. Spectroscopic data were all identical with those of an authentic material.

Acknowledgements

Financial support provided by the Ministry of Education, Science, Sports and Culture, Japan, is gratefully acknowledged. Thanks are also due for a scholarship from the Japan Society for the Promotion of Science for Junior Scientists (to H.K. and T.K.).

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