Chemoenzymatic Synthesis of Antiviral Carbocyclic Nucleosides: Asymmetric Hydrolysis of *meso*-3,5-Bis(acetoxymethyl)cyclopentenes Using *Rhizopus delemar* Lipase

Masakazu Tanaka,* Yoshihiko Norimine,[1] Toshiaki Fujita, and Hiroshi Suemune

Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-82, Japan

Kiyoshi Sakai*

Kyushu Women's University, 1-1 Jiyugaoka, Yahata-nishi, Kitakyushu 807, Japan

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7-Substituted norbornadienes were stereoselectively converted into the *meso*-3,5-bis(acetoxymethyl)-cyclopentenes by a three-step sequence of ozonolysis, reduction, and acetylation. *Rhizopus delemar* lipase (RDL)-catalyzed asymmetric hydrolysis of *meso*-3,5-bis(acetoxymethyl)cyclopentenes afforded the monoalcohols of high enantiomeric purities (>95% ee) in good yields (64−95%). The obtained monoalcohols **11** and **14** could be applied for the synthesis of antiviral carbocyclic nucleosides (−)-carbovir and (−)-BCA.

Introduction

Recently, the synthesis of nucleoside analogs has been the focus of extensive study in the fields of organic and medicinal chemistry because of the strong biological activities displayed by some of them as antiviral and antitumor drugs. The finding that nucleosides, such as 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxycytidine (ddC), and 2′,3′-dideoxyinosine (ddI), are potentially effective therapeutic agents for the treatment of the acquired immune deficiency syndrome (AIDS) has triggered explosive developments in the modifications of both the heterocyclic base and the sugar moiety of nucleosides.[2] The replacement of the oxygen in the furanose ring by a carbon atom is of particular interest since the resulting carbocyclic nucleosides possess greater chemical stability against acid and metabolic stability against the enzymes that cleave the glycosidic linkage of conventional nucleosides.[3] Much attention is being paid to the unsaturated derivatives such as (−)-carbovir[4] and (1′*R*,4′*S*,5′*S*)-(−)-9-[4′,5′-bis(hydroxymethyl)cyclopent-2′-en-1′-yl]-9*H*-adenine (BCA)[5] for their anti-HIV activity which is comparable to that of AZT. The realization that the biological activity only resides in one nucleoside enantiomer, and the increasing demand for new drug substances to be enantiomerically pure, have made the design and synthesis of optically active carbocyclic nucleosides important targets of study.

We have previously reported the effective synthesis of a carbocyclic nucleoside, (−)-aristeromycin.[6] This success in synthesis of an optically active carbocyclic nucleoside using *Rhizopus delemar* lipase (RDL)[7,8] prompted us to further studies on the generality and ability of RDL for asymmetric hydrolysis of various *meso*-compounds and synthesis of carbocyclic nucleosides. In this paper, we report that *meso*-3,5-bis(acetoxymethyl)cyclopentenes with the bulky substituent at the C4-position could be easily prepared from 7-substituted norbornadiene, and these compounds were further hydrolyzed by RDL to the monoalcohols in an enantioselective manner. The optically active alcohols obtained could be converted into the anti-HIV active carbocyclic nucleosides, (−)-carbovir and (−)-BCA.

Results and Discussion

Preparation of Substrates. 7-*tert*-Butoxynorbornadiene (**1**)[9] is used as a starting material because it is readily accessible. Compound **1** could be readily converted to the diacetates **2a** and **2b** in the ratio of 5.0 (*trans*,*trans*) to 1.0 (*cis*,*cis*), *via* a three-step sequence: [(i) O_3/MeOH−CH_2Cl_2/−78 °C; (ii) $NaBH_4$/0 °C; (iii) Ac_2O/pyridine]. These two products could be easily separated by silica gel column chromatography. It was expected that the less hindered olefin was attacked by ozone to give *trans*,*trans*-diacetate **2a**,[9b] preferentially. Stereochemistry of the products was determined by examination of NOESY ^{1}H NMR spectra of **2a** and **2b**. In the spectrum of **2a**, NOEs were observed between the acetoxymethylene protons [δ: 4.06 (d, J = 6.3 Hz, 4 H)] and the methine proton-H_a [δ: 3.85 (br s, 1 H)]. However, in the NOESY spectrum of **2b**, the NOEs were not observed between the acetoxymethylene protons [δ: 3.97 (dd, J = 7.3, 10.9 Hz, 2 H), 4.27 (dd, J = 5.0, 10.9 Hz, 2 H)] and

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(1) Research Fellow of the Japan Society for the Promotion of Science.

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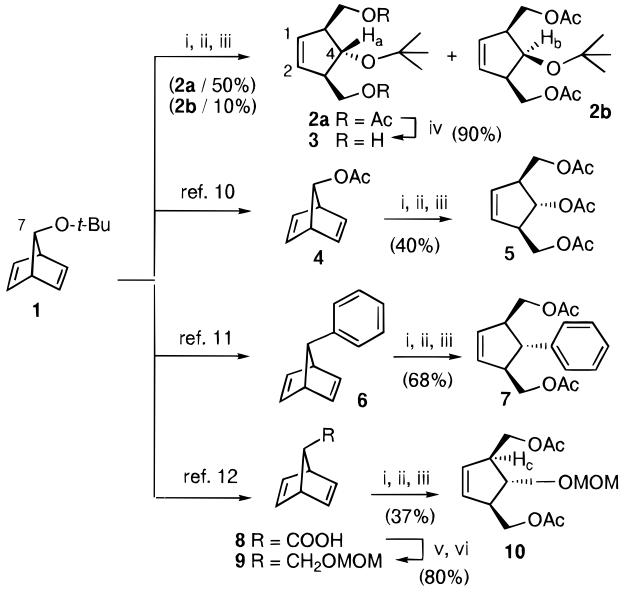
Scheme 1[a]

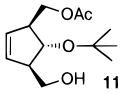
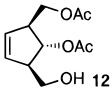
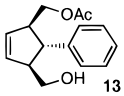
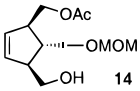


[a] Reagents: (i) O_3; (ii) $NaBH_4$; (iii) Ac_2O/pyridine; (iv) K_2CO_3/MeOH; (v) $LiAlH_4$; (vi) MOMCl.

the methine proton-H_b [δ: 4.48 (t, J = 8.7 Hz, 1 H)]. These observations clearly indicated the stereochemistry of **2a** as *trans,trans* and that of **2b** as *cis,cis*. Solvolysis of **2a** with K_2CO_3 in MeOH gave the diol **3** in 90% yield. 7-Acetoxy- and 7-phenylnorbornadienes (**4** and **6**) were prepared from **1** *via* Story's methods.[10,11] These 7-substituted norbornadienes were stereoselectively converted into the triacetate **5** and the diacetate **7** *via* a similar three-step sequence. In the NOESY ^{1}H NMR spectra, the NOEs were observed between the acetoxymethylene protons [δ: 4.11 (dd, J = 5.6, 11.0 Hz, 2 H), 4.19 (dd, J = 6.6, 11.0 Hz, 2 H)] and the methine proton [δ: 5.00 (t, J = 3.0 Hz, 1 H)] in the case of **5**, and also the NOEs were observed between the acetoxymethylene protons [δ: 4.12 (dd, J = 6.3, 10.9 Hz, 2 H), 4.05 (dd, J = 5.9, 10.9 Hz, 2 H)] and the methine proton [δ: 2.76 (t, J = 7.1 Hz, 1 H)] in the case of **7**. For the synthesis of (−)-BCA, the substrate **10** was also prepared from **1**. Compound **1** was converted to carboxylic acid **8** according to Klumpp's methods,[12] which could be converted to 7-substituted norbornadiene **9** by the reduction of carboxylic acid with $LiAlH_4$ followed by protection of the alcohol with MOMCl. Compound **9** was similarly converted into diacetate **10**. The stereochemistry of **10** was determined as *trans,trans*, because the NOEs were observed between the MOM oxymethylene protons [δ: 3.56 (d, J = 6.6 Hz, 2 H)] and the methine protons-H_c [δ: 2.84 (dd, J = 5.9, 11.2 Hz, 2 H] in the NOESY ^{1}H NMR spectrum.

Enzymatic Hydrolysis. We previously reported the asymmetric hydrolysis of *meso*-1,3-bis(acetoxymethyl)-cyclopentane derivatives using RDL.[7,8] The box-type active site model of RDL has been proposed to explained the enantioselectivities and the absolute configurations of the products. According to this model, it was anticipated that other substrates would be converted to chiral, enantiomerically pure monoalcohols. It was especially interesting whether *meso*-substrates with the bulky substituents at the C4-position of cyclopentene such as *tert*-butoxy and phenyl groups could be hydrolyzed by RDL, or not. It was also interesting to note the position at which the acetate could be hydrolyzed by RDL in the case of triacetate **5**.

Table 1. Enzymatic Hydrolysis of *meso*-Substrates

Entry	Substrate	Enzyme	Reaction time (h)	Product[b]	(% y)	(% ee)	Recovery (%)
1	**2a**	RDL[a]	184	 **11**	95	>99	2
2	**2a**	RDL	40		70	>99	25
3	**2a**	PFL	48		61	>99	39
4	**2a**	PPL	38		60	94	39
5	**5**	RDL	72	 **12**	86	95	7
6	**5**	PFL	64		73	33	27
7	**7**	RDL	116	 **13**	64	95	29
8	**7**	RDL	48		24	95	75
9	**7**	PFL	48		67	74	24
10	**7**	PPL	48		39	87	58
11	**10**	RDL	72	 **14**	95	95	-
12	**10**	PFL	40		60	16	37

[a] In practice, a mixture of *meso*-diacetates **2a** and **2b** (5:1) was used for RDL-catalyzed asymmetric hydrolysis on gram scale. Purification by silica gel column chromatography gave the enantiomerically pure monoalcohol (−)-**11** in 78% yield (>99% ee). [b] The specific rotations of all monoalcohols show minus signs.

The results of enzymatic hydrolyses using three kinds of lipases are summarized in Table 1. The enantiomeric excess (% ee) of the hydrolyzed products was determined by ^{1}H NMR spectra after conversion into the corresponding Mosher's esters [(+)-MTPA esters].[13] Compound **2b** could not be hydrolyzed by these three enzymes because the *cis*-oriented bulky *tert*-butoxy substituent hindered the enzymes from approaching the acetyl functions. However, hydrolysis of the other substrates by these enzymes proceeded satisfactorily. In the cases of *Pseudomonas fluorescens* lipase (PFL)-[14,15] and porcine pancreatic lipase (PPL)-catalyzed hydrolyses, the ee's of the alcohols obtained were low or moderate (16−87% ee), except for that of monoalcohol (**11**, entry 3 and 4). Sicsic *et al.*[16] reported the differentiation of the acetyl groups separated by three carbon atoms in cyclopentene moieties was not easily achieved by the previously known hydrolytic enzymes. On the other hand, RDL-catalyzed hydrolysis of all the substrates afforded monoalcohols of high enantiomeric excess in good yields (64−95%).

It was notable that, in entry 1, the hydrolyzed product **11** was obtained in 95% yield with >99% ee.[17] The ^{1}H NMR spectra of (+)-MTPA[13] ester derived from (±)-**11** showed the methoxy proton signal at δ 3.53 (m, 1.5 H) and 3.55 (m, 1.5 H), while the corresponding signal from (−)-**11** was observed at δ 3.53 (m, 3 H), only. In the case of triacetate **5**, the acetyl function of the secondary alcohol at the C4-position of cyclopentene was not hydrolyzed; however, that of the primary alcohol was

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(15) *Pseudomonas fluorescens* lipase (PFL) has been reclassified as *P. cepacia* lipase (PCL). However, we use the former name for the sake of uniformity with previous results.
(16) Mekrami, M.; Sicsic, S. *Tetrahedron: Asymmetry* **1992**, *3*, 431.
(17) Transesterification of the corresponding diol **3** by PFL in vinyl acetate gave the optically active monoalcohol (+)-**11** in 78% yield (95% ee).

regioselectively hydrolyzed by RDL to afford the alcohol of high enantiomeric purity (**12**, 86% yield, 95% ee). The substrate **7** with an aromatic substituent was also hydrolyzed into the alcohol of high enantiomeric purity (**13**, 64% yield, 95% ee),[18,19] and diacetate **10** was efficiently hydrolyzed into the alcohol of high enantiomeric excess (**14**, 95% yield, 95% ee).

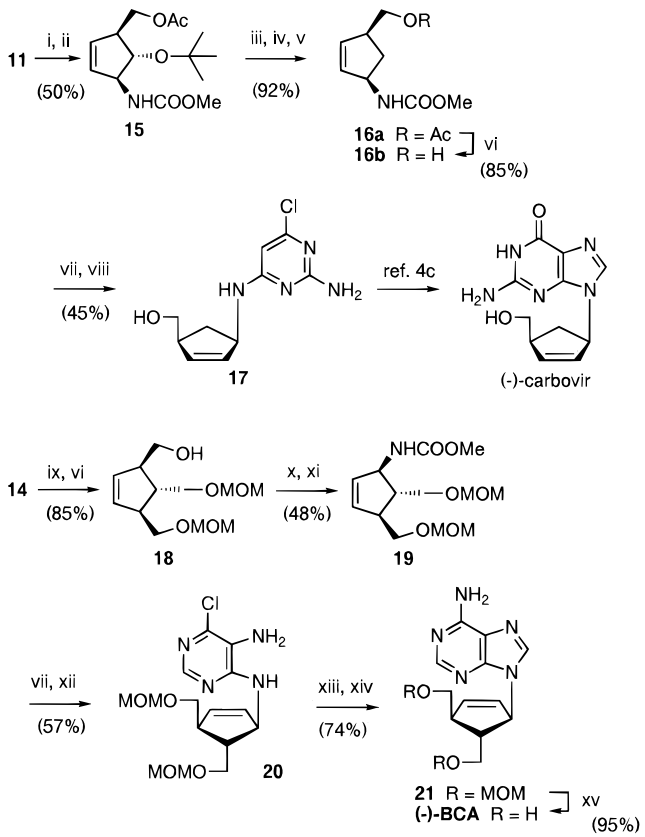
Synthesis of (−)-Carbovir. The obtained optically active alcohol **11** in entry 1 was used for the formal synthesis of (−)-carbovir,[4] which is thought to be a therapeutic candidate for the treatment of AIDS.[2] Oxidation of (−)-**11** with Jones reagent, followed by Curtius rearrangement with diphenyl phosphorazidate (DPPA) afforded the carbamate **15**. The carbamate **15** could be converted to the alcohol **16b** by deprotection of the *tert*-butyl function, reductive removal of the secondary alcohol function, and solvolysis of the acetate. Hydrolysis of carbamate and coupling of the resultant amino alcohol to 2-amino-4,6-dichloropyrimidine furnished the Roberts intermediate **17**.[4c] The absolute configuration of **17** was determined to be 1′*R*,4′*S* by the comparison with the reported specific rotation. This means that the absolute configuration of (−)-**11** is 3*R*,4*R*,5*S*. Thus, the formal synthesis of (−)-carbovir was completed.

Synthesis of (−)-BCA. The absolute configuration of optically active alcohol (−)-**14** was expected to be undesirable for the synthesis of (−)-BCA by our RDL model.[8] Therefore, compound (−)-**14** was converted to alcohol **18** which showed the opposite configuration by protection of the alcohol with MOMCl and subsequent deprotection of the acetyl function. Oxidation of the alcohol function with PCC and then $NaClO_2$, followed by Curtius rearrangement with DPPA, afforded the carbamate **19**. After deprotection of the methoxycarbonyl group by basic hydrolysis, the obtained amine was subjected to reaction with 5-amino-4,6-dichloropyrimidine to give the pyrimidinylamino derivative **20**. Ring closure by treatment with triethyl orthoformate, followed by the substitution of chlorine with ammonia in MeOH, afforded the MOM protected (−)-BCA (**21**). Acidic deprotection of **21** afforded (−)-BCA. The spectroscopic data of the synthetic material were identical with those reported.[5] The success in synthesis of (−)-BCA reveals the stereochemistry of monoalcohol **14** obtained by enzymatic hydrolysis to be (3*S*,4*R*,5*R*)-configuration.

Conclusion

It has become clear that the application of RDL to hydrolysis of *meso*-4-substituted-3,5-bis(acetoxymethyl)-cyclopentenes would be efficient for the preparation of chiral building blocks in the synthesis of carbocyclic nucleoside derivatives. The formal synthesis of (−)-carbovir and the total synthesis of (−)-BCA have been attained. The optically active alcohols obtained in Table 1 might be converted into the carbocyclic nucleoside analogs by similar routes. Further studies on the behavior of RDL, the synthesis of carbocyclic analogs, and anti-HIV activities of these compounds are currently under way.

Scheme 2[a]



[a] Reagents: (i) Jones reagent; (ii) DPPA, Et_3N and then MeOH; (iii) $TiCl_4$; (iv) PhOCSCl; (v) Bu_3SnH, AIBN; (vi) K_2CO_3/MeOH; (vii) KOH; (viii) 2-amino-4,6-dichloropyrimidine; (ix) MOMCl; (x) PCC and then $NaClO_2$; (xi) DPPA and then MeOH; (xii) 5-amino-4,6-dichloropyrimidine; (xiii) $HC(OEt)_3$; (xiv) NH_3; (xv) HCl/MeOH.

Experimental Section

^{1}H NMR spectra were determined at 270 MHz. For O_3 oxidation, an Ishii ozone generator (7800 V, O_2 flow rate; 0.5 mL/min) was used. Chemicals were used as received unless otherwise noted. Et_2O was distilled from Na/benzophenone before use. Benzene and CH_2Cl_2 were distilled from P_2O_5. Vinyl acetate (monomer) was purchased from Tokyo Kasei Corp. PPL (Type II) was purchased from Sigma Corp., RDL (EC 3.1.1.3) was purchased from Seikagaku Kogyo Corp. (Japan), PFL (Amano PS) was given by courtesy of Amano Pharmaceutical Corp. (Japan), and all were used as received. Norbornadiene derivatives **1**, **4**, **6**, and **8** were prepared according to Story's and Klumpp's methods.[9−12]

(3*R*,4*s*,5*S*)-4-*tert*-Butoxy-3,5-bis(acetoxymethyl)cyclopentene (2a) and (3*R*,4*r*,5*S*)-4-*tert*-Butoxy-3,5-bis(acetoxymethyl)cyclopentene (2b). Ozone gas was bubbled into a solution of **1** (5.0 g, 30.5 mmol) in MeOH (70 mL) and CH_2Cl_2 (40 mL) at −78 °C, and the reaction was monitored by TLC. $NaBH_4$ (1.2 g, 30.5 mmol) was added portionwise to the reaction mixture at −78 °C. After 1 h, the reaction mixture was gradually warmed to 0 °C and neutralized with concd HCl aqueous to pH 7.0. The solution was evaporated in vacuo to leave an oily residue, which was dissolved in pyridine (50 mL) and Ac_2O (20 mL), and the whole was stirred overnight. The reaction mixture was diluted with 5% aqueous HCl and extracted with EtOAc. The EtOAc extract was successively washed with 5% aqueous $NaHCO_3$ and brine then dried. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 5% EtOAc in hexane afforded **2a** (4.3 g, 50%) as a colorless oil, and the fraction eluted with 10% EtOAc in hexane afforded **2b** (0.9 g, 10%) as a colorless oil. **2a**: IR (neat) 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.69 (s, 2 H), 4.06 (d, J = 6.3 Hz, 4 H), 3.85 (br s, 1 H), 2.89 (t, J = 6.3 Hz, 2 H), 2.06

(18) (a) Monoalcohol (−)-**13** was converted into 2-phenylcyclopentane-1-methanol by hydrogenation (Pd−C, H_2), oxidation (PCC), decarbonylation [$RhCl(Ph_3)_3$], and solvolysis (K_2CO_3/MeOH). By the comparison of specific rotation of the synthetic sample; $[\alpha]^{33}_D$ −42.1 (*c* 0.45, MeOH) to the reported value;[19] $[\alpha]^{23}_D$ −48.9 (*c* 1.20, MeOH), the absolute configuration of (−)-**13** was determined to be 3*S*,4*R*,5*R*.

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(s, 6 H), 1.23 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.9, 131.3, 75.6, 74.3, 65.3, 55.3, 28.7, 20.8; EIMS *m/z* 284 (M^+, 8), 229 (51), 228 (100), 224 (31), 211 (85); FAB(+)HRMS calcd for $C_{15}H_{25}O_5$ ($M^+ + H$) 285.1702, found 285.1708.

2b: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.79 (s, 2 H), 4.48 (t, J = 8.7 Hz, 1 H), 4.27 (dd, J = 5.0, 10.9 Hz, 2 H), 3.97 (dd, J = 7.3, 10.9 Hz, 2 H), 2.87 (m, 2, H), 2.05 (s, 6 H), 1.19 (s, 9 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.0, 132.2, 73.9, 71.7, 64.9, 47.4, 27.8, 21.1; FAB(+)HRMS calcd for $C_{15}H_{25}O_5$ ($M^+ + H$) 285.1702, found 285.1704.

(3*R*,4*s*,5*S*)-4-*tert*-Butoxy-3,5-bis(hydroxymethyl)cyclopentene (3). A mixture of **2a** (3.5 g, 12.3 mmol) and K_2CO_3 (1.7 g, 12.3 mmol) in MeOH (180 mL) was stirred at 0 °C for 8 h. The mixture was neutralized with 5% aqueous HCl, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 50% EtOAc in hexane afforded **3** (2.4 g, 90%) as colorless crystals: mp 97−99 °C (from hexane); IR (Nujol) 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (s, 2 H), 4.05 (br s, 1 H), 3.82 (dd, J = 3.9, 10.9 Hz, 2 H), 3.77 (dd, J = 4.2, 10.9 Hz, 2 H), 3.25 (br, 2 H), 2.74 (m, 1 H), 1.23 (s, 9 H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 132.0, 76.2, 73.8, 63.5, 58.2, 29.1; EIMS *m/z* 201 ($M^+ + H$, 1), 200 (M^+, 2), 182 (19), 152 (61), 127 (100); FAB(+)HRMS calcd for $C_{11}H_{21}O_3$ ($M^+ + H$) 201.1491, found 201.1487. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.00; H, 10.03.

(3*R*,4*s*,5*S*)-4-Acetoxy-3,5-bis(acetoxymethyl)cyclopentene (5). **5** was prepared from compound **4** in a similar manner to that described for the preparation of **2**. Colorless oil; IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (s, 2 H), 5.00 (t, J = 3.0 Hz, 1 H), 4.19 (dd, J = 6.6, 11.0 Hz, 2 H), 4.11 (dd, J = 5.6, 11.0 Hz, 2 H), 3.01 (m, 2 H), 2.07 (s, 9 H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 170.8, 170.5, 130.9, 78.2, 64.7, 52.5, 21.1, 20.8; EIMS *m/z* 271 ($M^+ + H$, 3), 227 (1), 211 (4), 167 (9), 108 (100); FAB(+)HRMS calcd for $C_{13}H_{19}O_6$ ($M^+ + H$) 271.1182, found 271.1177.

(3*R*,4*r*,5*S*)-4-Phenyl-3,5-bis(acetoxymethyl)cyclopentene (7). Compound **7** was prepared from compound **6** in a similar manner to that described for the preparation of **2**. Colorless oil; IR (neat) 1740, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18−7.34 (m, 5 H), 5.78 (s, 2 H), 4.12 (dd, J = 6.3, 10.9 Hz, 2 H), 4.05 (dd, J = 5.9, 10.9 Hz, 2 H), 3.14 (m, 2 H), 2.76 (t, J = 7.1 Hz, 1 H), 1.95 (s, 6 H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 170.9, 144.3, 131.9, 128.6, 127.6, 126.5, 66.5, 54.4, 51.2, 20.7; EIMS *m/z* 288 (M^+, 3), 228 (2), 168 (100); FAB(+)HRMS calcd for $C_{17}H_{21}O_4$ ($M^+ + H$) 289.1440, found 289.1446.

7-[(Methoxymethoxy)methyl]norbornadiene (9). A solution of carboxylic acid **8** (1.95 g, 14.3 mmol) in Et_2O (15 mL) was added to the stirred suspension of $LiAlH_4$ (550 mg, 14.5 mmol) in Et_2O (150 mL) at 0 °C. After being stirred at room temperature for 5 h, the reaction was quenched with wet Et_2O followed by filtered through Celite. The evaporation of filtrate afforded the crude 7-(hydroxymethyl)norbornadiene as a colorless oil, and this was used to the next step without purification. MOMCl (1.42 mL, 18.6 mmol) was added dropwise to the stirred mixture of above oily residue and diisopropylethylamine (2.40 g, 18.6 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After being stirred overnight at room temperature, the reaction was quenched with H_2O, extracted with Et_2O, and dried over $MgSO_4$. Removal of the solvent afforded 7-substituted norbornadiene **9** (2.00 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 2 H), 6.61 (m, 2 H), 4.54 (s, 2 H), 3.42 (d, J = 7.1 Hz, 2 H), 3.40 (m, 2 H), 3.32 (s, 3 H), 2.78 (t, J = 7.1 Hz, 1 H).

(3*R*,4*r*,5*S*)-4-[(Methoxymethoxy)methyl]-3,5-bis(acetoxymethyl)cyclopentene (10). Compound **10** was prepared from compound **9** in a similar manner to that described for the preparation of **2**. Colorless oil; IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (s, 2 H), 4.63 (s, 2 H), 4.12 (dd, J = 6.3, 10.6 Hz, 2 H), 4.03 (dd, J = 5.9, 10.6 Hz, 2 H), 3.56 (d, J = 6.6 Hz, 2 H), 3.37 (s, 3 H), 2.84 (dd, J = 5.9, 11.2 Hz, 2 H), 2.06 (s, 6 H), 2.02 (m, 1 H); FAB(+)HRMS calcd for $C_{14}H_{23}O_6$ ($M^+ + H$) 287.1495, found 287.1498.

Enzymatic Hydrolysis of *Meso* Compounds. General Methods. A suspension of substrate (100 mg) and enzyme (10 mg) in acetone (0.1 mL) and 0.1 M phosphate buffer (10 mL, pH 7.0) was stirred at 30 °C, and the reaction was monitored by TLC. When a spot of the diol appeared on TLC, hydrolysis was terminated by extracting the mixture with EtOAc. The EtOAc extract was dried over $MgSO_4$ and then concentrated in vacuo to leave an oily residue, which was purified by column chromatography on silica gel.

(3*R*,4*R*,5*S*)-(−)-5-(Acetoxymethyl)-4-*tert*-butoxy-3-(hydroxymethyl)cyclopentene (11): colorless oil; $[\alpha]^{25}_D$ −25.2 (*c* 1.40, $CHCl_3$); IR (neat) 3425, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.71 (br s, 2 H), 4.09 (d, J = 6.6 Hz, 2 H), 3.94 (br s, 1 H), 3.67 (m, 2 H), 2.90 (m, 1 H), 2.80 (m, 1 H), 2.06 (s, 3 H), 1.55 (br 1 H), 1.23 (s, 9 H). EIMS *m/z* 242 (M^+, 0.8), 227 (1), 224 (1), 186 (62), 182 (48), 169 (100); FAB(+)HRMS calcd for $C_{13}H_{23}O_4$ ($M^+ + H$) 243.1596, found 243.1602.

Transesterification of 3. A suspension of diol **3** (500 mg, 2.50 mmol) and PFL (50 mg) in vinyl acetate (10 mL) was stirred at room temperature for 72 h. PFL was removed by the filtration, and the filtrate was concentrated in vacuo to leave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded (+)-**11** (473 mg, 78%) as a colorless oil: $[\alpha]^{22}_D$ +22.0 (*c* 1.21, $CHCl_3$).

MTPA Ester of 11. The 270 MHz ^{1}H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**11** showed the methoxy proton signals at δ 3.53 (m, 1.5 H) and 3.55 (m, 1.5 H), while the corresponding signal from (−)-**11** was observed at δ 3.53 (m, 3 H), and the corresponding signal from (+)-**11** was observed at δ 3.55 (m, 3 H), only.

(3*R*,4*R*,5*S*)-(−)-4-Acetoxy-5-(acetoxymethyl)-3-(hydroxymethyl)cyclopentene (12): colorless oil; $[\alpha]^{23}_D$ −88.14 (*c* 1.62, $CHCl_3$); IR (neat) 3450, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (br s, 2 H) 4.97 (t, J = 3.0 Hz, 1 H), 4.16 (dd, J = 6.3, 11.0 Hz, 1 H), 4.10 (dd, J = 5.6, 11.0 Hz, 1 H), 3.73 (dd, J = 4.3, 11.0 Hz, 1 H), 3.56 (dd, J = 7.6, 11.0 Hz, 1 H), 3.10 (m, 1 H), 2.88 (m, 1 H), 2.70 (br, 1 H), 2.09 (s, 3 H), 2.06 (s, 3 H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 171.8, 170.9, 131.4, 130.4, 79.3, 65.0, 64.1, 56.6, 52.4, 21.2, 20.8; EIMS *m/z* 229 ($M^+ + H$, 2), 211 (1), 169 (5), 155 (3), 138 (100); FAB(+)HRMS calcd for $C_{11}H_{17}O_5$ ($M^+ + H$) 229.1076, found 229.1073.

MTPA Ester of 12. The 270 MHz ^{1}H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**12** showed the methylene signals at δ 4.53 (dd, J = 5.9, 10.9 Hz, 0.5 H), 4.43 (dd, J = 6.3, 10.9 Hz, 0.5 H), 4.36 (dd, J = 6.6, 10.9 Hz, 0.5 H), and 4.29 (dd, J = 6.3, 10.9 Hz, 0.5 H), while the corresponding signals from (−)-**11** were observed at δ 4.43 (dd, J = 6.3, 10.9 Hz, 1 H) and 4.36 (dd, J = 6.6, 10.9 Hz, 1 H), only.

(3*S*,4*R*,5*R*)-(−)-5-(Acetoxymethyl)-3-(hydroxymethyl)-4-phenylcyclopentene (13). colorless oil; $[\alpha]^{29}_D$ −28.25 (*c* 1.04, $CHCl_3$); IR (neat) 3450, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18−7.34 (m, 5 H), 5.82 (m, 2 H), 4.13 (dd, J = 6.3, 10.8 Hz, 1 H), 4.08 (dd, J = 5.9, 10.8 Hz, 1 H), 3.70 (m, 1 H), 3.59 (m, 1 H), 3.15 (m, 1 H), 3.03 (m, 1 H), 2.84 (t, J = 6.9 Hz, 1 H), 1.95 (s, 3 H), 1.34 (br, 1 H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 171.1, 145.1, 132.6, 132.1, 128.6, 127.7, 126.4, 66.9, 65.0, 58.0, 54.5, 50.2, 20.7; EIMS *m/z* 246 (M^+, 2), 228 (1), 216 (3), 187 (15), 186 (100); FAB(+)HRMS calcd for $C_{15}H_{19}O_3$ ($M^+ + H$) 247.1334, found 247.1344.

MTPA Ester of 13. The 270 MHz ^{1}H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**13** showed the acetyl proton signals at δ 1.92 (s, 1.5 H) and 1.90 (s, 1.5 H), while the corresponding signal from (−)-**13** was observed at δ 1.90 (s, 3 H), only.

(3*S*,4*R*,5*R*)-5-(Acetoxymethyl)-3-(hydroxymethyl)-4-[(methoxymethoxy)methyl]cyclopentene (14): colorless oil; $[\alpha]^{24}_D$ −52.11 (*c* 1.04, $CHCl_3$); IR (neat) 3450, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.65 (m, 2 H), 4.67 (br s, 2 H), 4.12 (dd, J = 6.6, 11.0 Hz, 1 H), 4.06 (dd, J = 6.3, 11.0 Hz, 1 H), 3.70 (m, 2 H), 3.45 (m, 2 H), 3.39 (s, 3 H), 2.78 (m, 2 H), 2.62 (m, 1 H), 2.07 (s, 3 H), 2.02 (m, 1 H). FDMS *m/z* 245 ($M^+ + H$, 29), 214 (100); FAB(+)HRMS calcd for $C_{12}H_{21}O_5$ ($M^+ + H$) 245.1389, found 245.1399.

MTPA Ester of 14. 270 MHz ^{1}H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**14** showed the methyl proton signals at δ 3.333 (s, 1.5 H) and 3.328 (s, 1.5 H), while the corresponding signals from (−)-**14** was observed at δ 3.328 (s, 3 H), only.

(3*S*,4*S*,5*S*)-5-(Acetoxymethyl)-4-*tert*-butoxy-3-[(methoxycarbonyl)amino]cyclopentene (15). Jones reagent was added dropwise to the stirred solution of monoacetate **11** (1.60 g, 6.61 mmol) in acetone (20 mL) at 0 °C until the reaction mixture show red-purple color. After being stirred for 1 h, the reaction mixture was diluted with brine, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded the crude carboxylic acid, which was used to the next reaction without purification. Diphenyl phosphorazidate (DPPA, 1.42 mL, 6.61 mmol) and Et_3N (0.92 mL, 6.61 mmol) in benzene (10 mL) were added to the stirred solution of above acid in benzene (10 mL). The reaction mixture was refluxed for 3 h, MeOH (0.50 mL) was added, and the mixture was refluxed for 9 h. After removal of the solvent, the residue was diluted with EtOAc and washed with 5% aqueous HCl, water, 5% aqueous $NaHCO_3$, and brine, successively. Organic layer was dried over $MgSO_4$. Removal of the solvent afforded the oily residue, which was purified by column chromatography on silica gel (20% EtOAc in hexane) to give **15** (941 mg, 50%) as a colorless oil: $[\alpha]^{22}_D$ −34.5 (*c* 2.70, $CHCl_3$); IR (neat) 3340, 1720 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, 2 H), 4.70 (m, 1 H), 4.56 (m, 1 H), 4.12 (dd, J = 5.3, 11.2 Hz, 1 H), 4.08 (dd, J = 5.0, 11.2 Hz, 1 H), 3.78 (br s, 1 H), 3.67 (br s, 3 H), 2.81 (br, 1 H), 2.08 (s, 3 H), 1.23 (s, 9 H); FAB(+)HRMS calcd for $C_{20}H_{28}N_1O_5$ (M^+ + H) 286.1654, found 286.1649.

(3*R*,5*S*)-5-(Acetoxymethyl)-3-[(methoxycarbonyl)amino]cyclopentene (16a). $TiCl_4$ (0.11 mL, 1.0 mmol) was added dropwise to the stirred solution of **15** (273 mg, 0.96 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After being stirred for 30 min at 0 °C, the reaction was quenched with 5% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent afforded the crude alcohol as a colorless oil. Phenyl chlorothionoformate (0.14 mL, 1.0 mmol) was added to the solution of the above crude alcohol and DMAP (3 mg) in pyridine (1 mL) and acetonitrile (2 mL) at 0 °C. After being stirred for 12 h, the reaction was quenched with 5% aqueous HCl and extracted with EtOAc. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of the organic solvent gave crude thiocarbonate ester. *n*-Bu_3SnH (0.40 mL, 1.5 mmol) was added dropwise to the refluxing mixture of AIBN (16 mg, 0.10 mmol) and the above thiocarbonate ester in benzene (17 mL). After being refluxed for 8 h, KF (88 mg, 1.5 mmol) was added, and the mixture was stirred for 30 min at room temperature. The mixture was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (25% EtOAc in hexane) to give **16a** (188 mg, 92%) as a colorless oil; $[\alpha]^{17}_D$ −41.9 (*c* 1.47, $CHCl_3$); IR (neat) 3350, 1720 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.79 (m, 2 H), 4.77 (br s, 2 H), 4.08 (dd, J = 5.9, 10.9 Hz, 1 H), 3.99 (dd, J = 5.6, 10.9 Hz, 1 H), 3.67 (br s, 3 H), 2.94 (m, 1 H), 2.56 (m, 1 H), 2.07 (s, 3 H), 1.30 (m, 1 H); FAB(+)HRMS calcd for $C_{10}H_{16}N_1O_4$ (M^+ + H) 214.1079, found 214.1073.

(3*R*,5*S*)-5-(Hydroxymethyl)-3-[(methoxycarbonyl)amino]cyclopentene (16b). A mixture of **16a** (124 mg, 0.58 mmol) and K_2CO_3 (50 mg, 0.36 mmol) in MeOH (4 mL) was stirred at 0 °C for 5 h. After removal of methanol, the residue was diluted with brine, neutralized with 10% aqueous HCl, and extracted with EtOAc. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded **16b** (85 mg, 85%) as colorless crystals: mp 80−82 °C; $[\alpha]^{22}_D$ −17.2 (*c* 1.04, MeOH); IR (KBr) 3450, 3250, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (m, 2 H), 5.11 (br, 1 H), 4.73 (br, 1 H), 3.66 (br s, 3 H), 3.59 (m, 2 H), 2.83 (m, 1 H), 2.49 (dt, J = 8.5, 13.9 Hz, 1 H), 1.76 (br s, 1 H), 1.43 (dt, J = 4.2, 13.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 134.2, 133.7, 64.7, 56.3, 51.9, 46.8, 34.5; FAB(+)HRMS calcd for $C_8H_{14}N_1O_3$ (M^+ + H) 172.0974, found 172.1004. Anal. Calcd for $C_8H_{13}N_1O_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.13; H, 7.71; N, 7.91.

(1′*R*,4′*S*)-2-Amino-4-[(4′-(hydroxymethyl)cyclopent-2′-en-1′-yl)amino]-6-chloropyrimidine (17). KOH (50 mg, 0.9 mmol) in H_2O (1 mL) was added to a stirred solution of carbamate **16b** (65 mg, 0.38 mmol) in MeOH (0.5 mL), and the solution was refluxed for 24 h. After removal of the solvent, the residue was diluted with H_2O, extracted with EtOAc and dried over $MgSO_4$. After removal of the solvent, the residue, 2-amino-4,6-dichloropyrimidine (125 mg, 0.76 mmol), and diisopropylethylamine (0.6 mL) in *n*-BuOH (3 mL) were refluxed for 14 h. The mixture was diluted with H_2O, extracted with CH_2Cl_2, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to give **17** (42 mg , 45%) as white foam: mp 48−51 °C (lit.[4c] 49−53 °C); $[\alpha]^{22}_D$ −29.2 (*c* 0.50, MeOH), [lit.[4c] $[\alpha]^{24}_D$ −35 (*c* 1, MeOH)]; IR ($CHCl_3$) 3450, 1590, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (s, 2 H), 5.78 (s, 1 H), 5.23 (br, 1 H), 4.93 (br s, 2 H), 4.85 (br, 1 H), 3.69 (dd, J = 3.9, 10.5 Hz, 1 H), 3.61 (dd, J = 4.4, 10.5 Hz, 1 H), 2.90 (m, 1 H), 2.53 (dt, J = 8.5, 13.7 Hz, 1 H), 1.85 (br 1 H), 1.50 (dt, J = 3.9, 13.7 Hz, 1 H); FAB(+)HRMS calcd for $C_{10}H_{14}N_4O_1Cl_1$ (M^+ + H) 241.0856, found 241.0851.

(3*R*,4*S*,5*S*)-3-(Hydroxymethyl)-4,5-bis[(methoxymethoxy)methyl]cyclopentene (18). MOMCl (0.17 mL, 2.2 mmol) was added to a stirred solution of monoacetate **14** (414 mg, 1.70 mmol) and diisopropylethylamine (285 mg, 2.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred overnight. The reaction was quenched with H_2O, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent in vacuo gave an oily residue. A mixture of this residue and K_2CO_3 (225 mg, 1.63 mmol) in MeOH (10 mL) was stirred at room temperature for 2 h. K_2CO_3 was filtered off, and the filtrate was concentrated in vacuo to leave an oily residue, which was purified by column chromatography on silica gel to give **18** (354 mg, 85%) as a colorless oil; $[\alpha]^{22}_D$ + 50.15 (*c* 1.30, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.71 (m, 1 H), 5.61 (m, 1 H), 4.67 (s, 2 H), 4.63 (s, 2 H), 3.75 (m, 2 H), 3.40−3.60 (m, 4 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 2.93 (m, 1 H), 2.78 (m, 1 H), 2.68 (m, 1 H), 2.07 (m, 1 H); FDMS *m*/*z* 247 (M^+ + H, 42), 216 (100); FAB(+)HRMS calcd for $C_{12}H_{23}O_5$ (M^+ + H) 247.1545, found 247.1552.

(3*R*,4*S*,5*S*)-4,5-Bis[(methoxymethoxy)methyl]-3-[(methoxycarbonyl)amino]cyclopentene (19). PCC (400 mg, 2.32 mmol) was added to a stirred solution of **18** (315 mg, 1.28 mmol) in CH_2Cl_2 (10 mL). After being stirred for 5 h, the mixture was diluted with Et_2O, and then black solid was filtered off using a florisil short column. After evaporation of Et_2O, the residue, 2-methyl-2-butene (500 mg), and NaH_2PO_4 (200 mg) were dissolved in H_2O (3 mL) and *t*-BuOH (11 mL). $NaClO_2$ (500 mg, 85%, 4.70 mmol) was added to this stirred solution at 0 °C. After being stirred for 1 h, 1 N aqueous HCl was added to the solution to acidify the reaction mixture to pH 5−7 at 0 °C. The mixture was extracted with CH_2Cl_2 and organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in benzene (7 mL), and a solution of DPPA (400 mg, 1.45 mmol) and Et_3N (160 mg, 1.58 mmol) in benzene (2 mL) was added. The mixture was refluxed for 1 h, MeOH (10 mL) was added, and the solution was refluxed for 3 days. The solvent was removed in vacuo, and the residue was diluted with EtOAc. The organic layer was washed with 5% aqueous HCl, water, 5% aqueous $NaHCO_3$, and brine, successively. Organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (30% EtOAc in hexane) to give **19** (179 mg , 48%) as a colorless oil: $[\alpha]^{22}_D$ +13.59 (*c* 1.30, $CHCl_3$); IR (neat) 3350, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (m, 1 H), 5.72 (m, 1 H), 5.02 (br, 1 H), 4.65 (s, 2 H), 4.63 (s, 2 H), 4.58 (m, 1 H), 3.66 (s, 3 H), 3.50−3.65 (m, 4 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 2.73 (br, 1 H), 2.00 (m, 1 H); FAB(+)HRMS calcd for $C_{13}H_{24}N_1O_6$ (M^+ + H) 290.1603, found 290.1598.

(1′*R*,4′*S*,5′*R*)-5-Amino-4-[[4′,5′-bis[(methoxymethoxy)methyl]cyclopent-2′-en-1′-yl]amino]-6-chloropyrimidine (20). KOH (2.5 g, 44.6 mmol) in H_2O (15 mL) was added to a stirred solution of carbamate **19** (144 mg, 0.50 mmol) in MeOH (10 mL), and the solution was refluxed for 12 h. After removal of the solvent, the residue was diluted with H_2O, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in *n*-BuOH (6 mL). 5-Amino-4,6-dichloropyrimidine (85 mg, 0.52 mmol) and Et_3N (1 mL, 7.2 mmol) were added to this solution. The mixture

was refluxed for 2 days, solvent was evaporated, and the residue was purified by column chromatography on silica gel (70% EtOAc in hexane) to give **20** (102 mg , 57%) as a colorless oil: $[\alpha]^{28}_D$ −84.12 (*c* 0.91, $CHCl_3$); IR (neat) 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (s, 1 H), 5.83 (m, 2 H), 5.49 (br d, J = 8.6 Hz, 1 H), 5.05 (br d, J = 8.6 Hz, 1 H), 4.68 (s, 2 H), 4.65 (s, 2 H), 3.55−3.75 (m, 4 H), 3.42 (br s, 2 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.78 (br, 1 H), 2.17 (m, 1 H); FAB(+)HRMS calcd for $C_{15}H_{24}O_4N_4Cl_1$ (M^+ + H) 359.1486, found 359.1483.

MOM Protected BCA (21). Concentrated HCl (0.5 mL) was added to a solution of amine **20** (30 mg, 0.084 mmol) in triethyl orthoformate (1 mL) at 0 °C. After being stirred at room temperature for 24 h, solid $NaHCO_3$ (50 mg) was added to the reaction mixture. After removal of the solvent, the residue was dissolved in MeOH (freshly distilled, 4 mL) and cooled to −20 °C. This solution in sealed tube was bubbled with NH_3 gas for 10 min, and the whole was warmed to 45 °C in sealed tube. After being stirred at 45−50 °C in sealed tube for 2 days, the reaction mixture was evaporated and the residue was purified by column chromatography on silica gel (from 50% EtOAc in hexane to 10% MeOH in EtOAc) to give the **21** (21.6 mg, 74%) as a colorless oil: $[\alpha]^{25}_D$ −1.85 (*c* 0.70, $CHCl_3$); IR (neat) 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 (s, 1 H), 7.97 (s, 1 H), 6.13 (m, 1 H), 5.98 (br s, 2 H), 5.82 (m, 1 H), 5.64 (m, 1 H), 4.66 (s, 2 H), 4.65 (s, 2 H), 3.78 (d, J = 5.6 Hz, 2 H), 3.73 (dd, J = 4.9, 9.6 Hz, 1 H), 3.63 (dd, J = 5.3, 9.6 Hz, 1 H), 3.38 (s, 3 H), 3.34 (s, 3 H), 2.97 (m, 1 H), 2.41 (dddd, J = 5.6, 5.6, 5.6 and 5.6 Hz, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 155.5, 152.9, 150.0, 139.3, 137.8, 129.2, 119.6, 96.7, 96.6, 69.4, 68.6, 62.3, 55.4, 55.3, 50.2, 48.8; FAB(+)HRMS calcd for $C_{16}H_{24}N_5O_4$ (M^+ + H) 350.1828, found 350.1805.

(−)-BCA. Concentrated HCl (0.25 mL) was added dropwise to the solution of MOM protected (−)-BCA (16 mg, 0.046 mmol) in MeOH (3 mL) at 0 °C. After being stirred overnight at room temperature, the solution was evaporated and the residue was purified by ion-exchange resin (0.1 N NH_3/H_2O) and recrystallized from MeOH to give (−)-BCA (11 mg, 95%) as colorless crystals: mp 207−209 °C dec; $[\alpha]^{28}_D$ −24.0 (*c* 0.20, MeOH), lit.[5a] $[\alpha]^{20}_D$ −29.0 (*c* 0.3, MeOH); IR (KBr) 3450, 3350, 3120 (br), 1680, 1660, 1610, 1570, 1450 (br) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.13 (s, 1 H), 8.06 (s, 1 H), 7.21 (br s, 2 H), 6.06 (m, 1 H), 5.78 (m, 1 H), 5.42 (m, 1 H), 4.84 (br s, 1 H), 3.60 (d, J = 5.9 Hz, 2 H), 3.57 (dd, J = 5.3, 10.7 Hz, 1 H), 3.51 (dd, J = 5.6, 10.7 Hz, 1 H), 2.71 (m, 1 H), 2.22 (dddd, J = 5.6, 5.6, 5.6 and 5.6, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.9, 152.1, 149.3, 139.1, 137.4, 129.0, 119.0, 63.6, 62.31, 62.27, 51.3, 50.8; FAB(+)HRMS calcd for $C_{12}H_{16}N_5O_2$ (M^+ + H) 262.1304, found 262.1309.

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Supporting Information Available: Copies of the ^1H NMR spectra of all new compounds, partial ^1H NMR spectra of MTPA esters for the determination of ee, ^{13}C NMR spectra of compounds **2a**, **2b**, **3**, **5**, **7**, **12**, **13**, **16b**, **21**, and (−)-**BCA**, and a synthetic scheme for the determination of absolute configuration of monoalcohol **13** (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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