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A Facile Enantioselective Synthesis of (1*R*, 2*R*, 3*S*)-1-Amino-2,3-bishydroxymethylcyclobutane Derivatives, A Key Synthetic Intermediate of Carbocyclic Oxetanocins

Takao Izawa,[a] Yoshio Ogino,[a] Shigeru Nishiyama,[a] Shosuke Yamamura,[a] Kuniki Kato,[b]* and Tomohisa Takita.[b]

a Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223, Japan

b Research Laboratories, Pharmaceuticals Group, Nippon Kayaku Co. Ltd., 3-31-12 Shimo, Kita-ku, Tokyo 115, Japan

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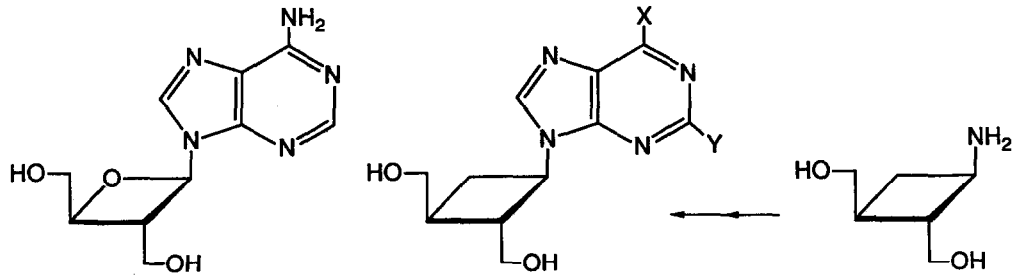
Abstract: (1*R*,2*R*,3*S*)-1-Amino-2,3-bishydroxymethylcyclobutane derivatives (**14, 15**) have been synthesized enantioselectively by [2+3] formation of a cyclopentane ring from (–)-dimenthyl succinate and 3-chloro-2-(chloromethyl)-1-propene and the subsequent ring contraction by the Wolff rearrangement, and the Curtius reaction.

Interest has recently been growing in the synthesis of new nucleoside analogs with potential antiretroviral activity, due to the significant medical problem associated with the treatment of the acquired immunodeficiency syndrome (AIDS). In 1986 a remarkably unusual nucleoside, oxetanocin-A, was isolated from the fermentation broth of ***Baccilus megaterium***, and the structural investigation and X-ray crystallographic analysis revealed that oxetanocin-A was the first natural nucleoside having an oxetane ring as a sugar moiety.[1] Among carbocyclic analogues of purine and pyrimidine nucleoside, carbocyclic oxetanocins, in which a methylene group replaces the oxygen atom of the oxetane ring of natural oxetanocin-A have generated great interest as potential anti-viral agents in recent years. Furthermore, carbocyclic oxetanocin-A (COXT-A) and -G (COXT-G) exhibit broad spectrum activity against herpesviruses and HIV, and are considered as promising agents for the treatment of AIDS.[2]

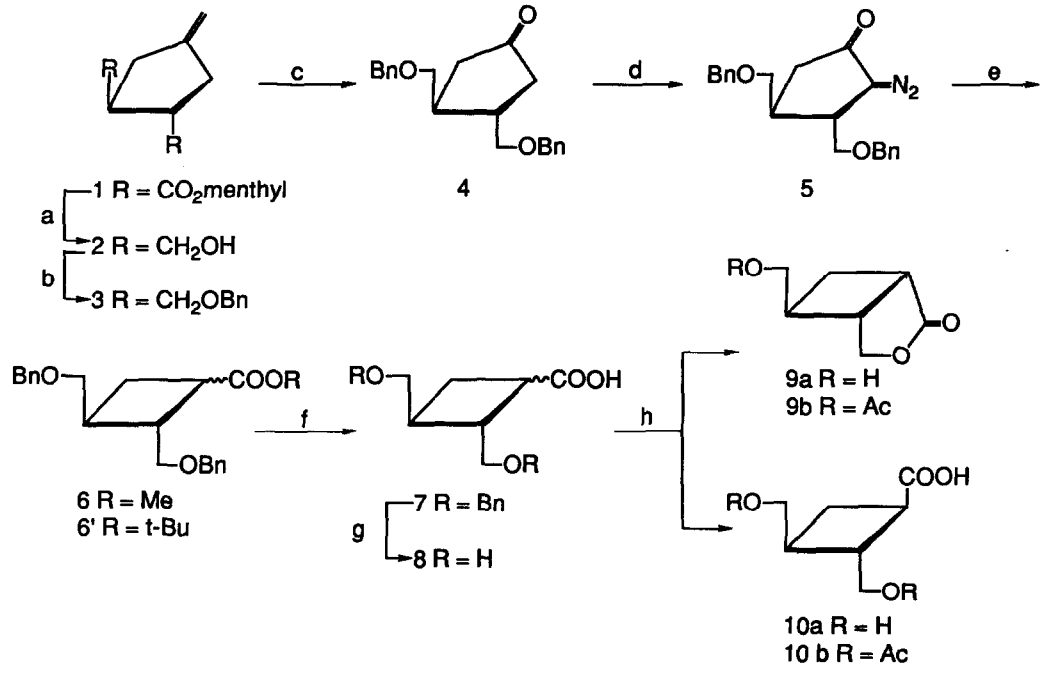


Oxetanocin-A

COXT-A X = NH_2, Y = H
COXT-G X = OH, Y = NH_2

Although the synthesis of protected *r*-1-amino-*t*-2,*c*-3-bishydroxymethylcyclobutanes, which serves as key intermediates for the synthesis of carbocyclic oxetanocin A and G, have been reported as a racemate in non-

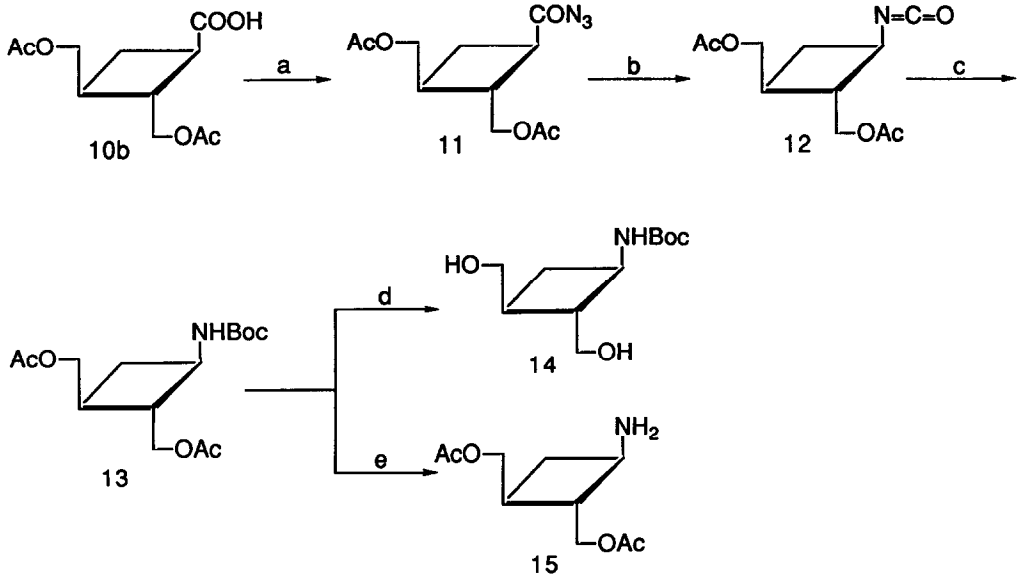
stereoselective[3] and stereoselective[4] reaction approaches, respectively, the chiral synthesis has not been published. In view of the recent findings of Ichikawa[5] and Bisacchi[5] that the "natural" enantiomer of COXT-A and COXT-G can display potent biological activity, a more versatile strategy that could furnish the "natural" enantiomer of *r*-1-amino-*t*-2,*c*-3-bishydroxymethylcyclobutane was required urgently. We disclose herein the facile and enantioselective synthesis of (1*R*,2*R*,3*S*)-1-amino-2,3-bishydroxymethylcyclobutane derivatives. The key feature of our synthetic route is the stereoselective and asymmetric [2+3] formation of a cyclopentane ring and the subsequent ring contraction by the Wolff rearrangement, and the Curtius rearrangement.



Scheme 1 a: $LiAlH_4$ / THF. b: BnBr, NaH / DMF. c: OsO_4 (cat.), $NaIO_4$ / t-BuOH-THF-H_2O. d: NaOEt, HCOOEt / THF, then TsN_3, Et_3N / CH_2Cl_2. e: hυ / MeOH or hυ / t-BuOH. f: KOH / MeOH. g: H_2, 10% Pd-C / MeOH. h: TsOH, MS 4A / DMF, then Ac_2O, Py.

The optically active dimenthylester (**1**) as the first key compound was produced from (–)-dimenthyl succinate and 3-chloro-2-(chloromethyl)-1-propene in 70% yield according to the protocol of Yamamoto.[6] Reduction of (**1**) with $LiAlH_4$ gave the corresponding diol (**2**) in 58% yield.[7] Then, benzylation of the hydroxyl groups of (**2**) followed by Lemieux-Jonson oxidation gave the keto-dibenzylether (**4**) in 71% yield (2 steps). Compound (**4**) was subsequently submitted to the Wolff rearrangement in MeOH *via* the diazo-keto compound (**5**) to produce the desired cyclobutane-methylester (**6**) as *ca.* 1:1 mixture of two stereoisomers in 66% yield (2 steps). In the case of the *tert*-butylalcohol, the cyclobutane-*tert*-butylester (**6'**) was obtained in 57% yield. All attempts made to separate each isomer chromatographically were unsuccessful and therefore, the separation of the isomers (**6**) was achieved by chemical reactions. First, alkaline hydrolysis of (**6**) followed by hydrogenolysis gave the carboxy-diol (**8**) in quantitative yield (2 steps). Then,treatment of (**8**) with *p*-toluenesulphonic acid in dimethylformamide provided a mixture of the lactone (**9a**) and the carboxylic acid (**10a**), which successively were reacted with acetic anhydride-

pyridine in the same reaction vessel to afford a separable mixture of the acetates, (**9b**) and (**10b**) in 32% and 93% yields (2 steps), respectively (Scheme 1). Compound (**10b**) was subjected to the Curtius reaction to afford the isocyanate (**12**) in 95%, which was heated with *tert*-butylalcohol for 2 days to give the desired N-Boc-diacetate (**13**) in 77% yield along with the amino-diacetate (**15**) in 22% yield. Hydrolysis of (**13**) with lithium hydroxide in dioxane-water gave the N-Boc-diol (**14**) as white crystals. The enantiomeric purity of (**14**) was assessed in comparison with $[\alpha]_D$ value of the "natural" enantiomer of (**14**) prepared by an optical resolution method of (±)-(**14**).[8] An enantiomer excess of 68% was found. Finally, deprotection of the Boc group of (**13**) with trifluoroacetic acid gave the key compound (**15**) in 98% yield (Scheme 2). The overall yield was 4.4% in 13 steps.



Scheme 2 a: CbeCl, Et_3N / acetone, then NaN_3. b: toluene, 80°C. c: t-BuOH, 80°C. d: LiOH / dioxane-H_2O. e: CF_3COOH / CH_2Cl_2

Our syntheses provide convenient approaches to useful intermediates such as compounds (**14**) and (**15**), utilizing readily available substrates and reagents. These compounds can be used for the preparation of a wide variety of carbocyclic analogues of oxetanocin-A.

Experimental

^1H N.m.r. spectra were recorded at 400 MHz with JEOL JNM-GX 400 using $CDCl_3$ as a solvent unless otherwise stated. Chemical shifts (δ) are expressed in ppm from Me_4Si as an internal standard. Coupling constants J are in Hz. Mass spectra were recorded in the e. i. mode with HITACHI M-80 Mass Spectrometer. Infra-red spectra were recorded with JASCO A-202 Infrared Spectrophotometer. T.l.c. was performed on precoated plates of Silica Gel 60 F254 (E. Merck, Darmstadt). Silica gel column chromatography was carried out on Katayama K.K. Silica (60-200mesh). Reaction progress was monitored by either u. v. (254nm) or spraying the plates with a solution of 10% phosphomolybdic acid-ethanol, followed in the latter case by heating on an electric plate. Dichloromethane, N,N-dimethylformamide, and toluene were distilled over calcium hydride. THF

and diethyl ether were distilled over sodium benzophenone ketyl prior to use. Reactions were carried out under argon atmosphere unless otherwise stated. Organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, and evaporated under reduced pressure as the usual work-up.

(3*S*,4*S*)-3,4-*Bis*-(–)-*menthyloxycarbonyl*-1-*methylidenecyclopentane* **1**.
To a solution of lithium 2,2,6,6-tetramethylpiperide [prepared from 2,2,6,6-tetramethylpiperidine (78.0ml) in anhydrous tetrahydrofuran (THF, 600ml) and n-butyllithium (306ml, 1.6M hexane solution) at -78°C] was added (–)-dimenthyl succinate (87.0g, 0.218mol) in anhydrous THF (100ml) dropwise at -78°C. The resulting pale yellow solution was stirred for 1 hr. To this reaction mixture was added 3-chloro-2-(chloromethyl)-1-propene (13.6g, 0.109mol) dropwise at -78°C. The mixture was stirred for 2.5 hr at the same temperature and then kept at -20°C overnight. The reaction mixture was quenched with sat. aq.NH_4Cl (50ml), acidified with ice-cold 2N-HCl, and extracted with ether (2x350ml). The combined washed, dried extract was evaporated and the resulting syrup was chromatographed on silica gel (2200g) with hexane-ether (20:1) as eluent to give the dimenthyl ester **1** as a colorless oil (33.9g, 69.7%), $[\alpha]_D^{22}$–41.4° (c 0.82, $CHCl_3$); υ max (film) 2950, 2860, 1725, 1660, and 1180 cm^{-1}; δ_H 0.74, (6H, d, J 7.0), 0.88 (6H, d, J 2.4), 0.91 (6H, d, J 7.0), 0.80-1.15 (4H, complex), 1.38 (2H, bt, J 11.8), 1.47 (2H, complex), 1.67 (4H, complex), 1.85 (2H, complex), 1.99 (2H, complex), 2.52 (2H, complex), 2.76 (2H, complex), 3.15 (2H, complex), 4.68 (2H, dt, J 4.2, 10.8), and 4.90 (2H, ddd, J 2.2, 2.2, 2.3). Anal. Calcd for $C_{28}H_{46}O_2$: C, 75.29; H, 10.38%. Found: C, 75.41; H, 10.47%.

(3*S*,4*S*)-3,4-*Bishydroxymethyl*-1-*methylidenecyclopentane* **2**.
A solution of the dimenthyl ester **1** (67.5g, 0.151mol) in absolute THF (200ml) was added dropwise to a stirred suspension of lithium aluminum hydride (17.4g, 0.458mol) in anhydrous THF (200ml) at 5-10°C. The mixture was stirred for 1hr at room temperature and then cooled to 0°C, when ethanol (22ml) was added, followed by water (200ml). The mixture was filtered through celite pad and concentrated to the volume of ca.200ml, and extracted with ether (3x200ml). The combined washed, dried extract was evaporated and the resultant syrup was chromatographed on silica gel (600g) with hexane-ethyl acetate (1:1—1:6) as eluent to give the diol **2** as a colorless oil (12.41g, 57.6%), $[\alpha]_D^{23}$+60.8° (c 0.28, MeOH); υ max (film) 3300, 2920, 1655, 1035, and 875 cm^{-1}; δ_H 1.97 (2H, bs), 1.99 (2H, complex), 2.48 (2H, complex), 3.75 (2H, complex), 3.3-3.8 (2H, br), 4.41 (2H, complex), and 4.82 (2H, bs). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93%. Found: C, 67.80; H, 9.81%.

(3*S*,4*S*)-3,4-*Bisbenzyloxymethyl*-1-*methylidenecyclopentane* **3**.
A solution of the diol **2** (11.61g, 0.0814mol) in anhydrous DMF (100ml) was added to a stirred suspension of NaH (12.7g, 60% in mineral oil, 0.318mol) in anhydrous DMF (100ml) at room temperature. After the evolution of hydrogen gas ceased, benzyl bromide (48.0g, 0.28mol) in anhydrous DMF (100ml) was added to the reaction mixture at room temperature. The mixture was stirred overnight and diluted with methanol (30ml) and water (500ml), and extracted with ether (4x250ml). The combined washed, dried extract was evaporated and the resultant syrup was chromatographed on silica gel (150g) with hexane-ethyl acetate (20:1) as eluent to afford the dibenzyl ether **3** as a colorless oil (23.8g, 90.7%), $[\alpha]_D^{22}$+22.4 (c 1.42, $CHCl_3$); υ max (film) 2860, 1660, 1500, 1100, 875, 740, and 700 cm^{-1}; δ_H 2.15 (2H, bs), 2.16 (2H, complex), 2.53 (2H, complex), 3.35 (2H, complex), 3.51 (2H, complex), 4.49 (4H, s), 4.82 (2H, complex), and 7.25-7.37 (10H, complex); HRMS:

322.1931 (M^+), $C_{22}H_{26}O_2$ requires 322.1931. Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13%. Found. C, 81.82; H, 8.04%.

(3*S*,4*S*)-3,4-*Bisbenzyloxymethyl*-1-*cyclopentanone* **4**.

To a vigorously stirred solution of the dibenzyl ether **3** (12.6g, 0.039mol) in THF (65ml) and water (100ml) was added OsO_4 (6ml of *tert*-butylalcohol solution prepared from OsO_4 1g and *tert*-butylalcohol 15ml) and sodium metaperiodate (22.5g, 0.105mol). After the mixture was stirred for 6 hr at room temperature, it was diluted with ethyl acetate (200ml), and then the two-phase mixture was stirred vigorously for 15 min. The organic layer was separated, washed, and dried. After evaporation the solvent, the residue was chromatographed on silica gel (460g) with hexane-ethyl acetate (4:1) as eluent to give the keto-ether **4** as a colorless oil (18.6g, 78.3%), $[\alpha]_D^{19}$+31.3° (c 4.05, $CHCl_3$); υ_{max} (film) 2850, 1735, 1495, 1450, 1400, 1362, 1090, 735, and 695 cm^{-1}; δ_H 2.16 (2H, complex), 2.44 (2H, bs), 2.44 (2H, complex), 3.51 (4H, complex), 4.50 (4H, complex), and 7.25-7.35 (10H, complex); HRMS: 324.1740 (M^+), $C_{21}H_{24}O_3$ requires 324.1724. Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46%. Found. C, 77.49; H, 7.54%.

(3*S*,4*S*)-3,4-*Bisbenzyloxymethyl*-2-*diazo*-1-*cyclopentanone* **5**.

To a stirred suspension of sodium ethoxide (1.29g, 0.019mol) in anhydrous THF (100ml) was added the keto-ether **4** (3.56g, 0.011mol) in anhydrous THF (40ml) over 40 min at 0°C, and then ethyl formate (2.1g, 0.022mol) in anhydrous THF (10ml). After the mixture had been stirred for 3hr at room temperature, it was diluted with water (100ml), and extracted with ethyl acetate (200ml). The aqueous layer was neutralized with 1N-HCl under ice-water cooling, and then extracted with ethyl acetate (3x100ml). The combined washed, dried organic extract was evaporated to give an oily compound (3.72g). Triethylamine (3.6ml, 0.025mol) and *p*-toluenesulphonyl azide (2.38g, 0.012mol) were added to a solution of this oily compound in anhydrous dichloromethane (50ml) at room temperature. The mixture was stirred overnight at room temperature, diluted with dichloromethane (100ml), and poured onto ice-water (100ml). The washed, dried organic layer was evaporated to give an oily compound, which was purified by chromatography on silica gel (250g) with hexane-ethyl acetate (3:1) as eluent to give the diazo-ketone **5** (3.07g, 79.6%) as a yellow oil, υ_{max} (film) 2860, 2080, 1667, 1450, 1300, 1097, 735, and 700 cm^{-1}; δ_H 2.23 (1H, dd, J 6.8, 19.5), 2.24 (1H, m), 2.54 (1H, dd, J 10.8, 19.5), 3.44 (2H, complex), 3.51 (2H, complex), 3.80 (1H, m), 4.51 (2H, s), 4.53 (2H, s), and 7.2-7.4 (10H, complex).

Methyl (1*R* and *S*, 2*R*, 3*S*)-2,3-*bisbenzyloxymethylcyclobutane*-1-*carboxylate* **6**.

A solution of the diazo-ketone **5** (6.0g, 17.13mmol) in deoxygenated dry methanol (2000ml) was irradiated with a high pressure mercury lamp (400W, Pyrex filter) at 30-40°C until the evolution of nitrogen gas ceased. After evaporation of the mixture, the residue was purified by chromatography on silica gel (150g) with hexane-ethyl acetate (3:1) as eluent to give the cyclobutyl- methylester **6** as a colorless oil (5.04g, 83%) as 1:1 mixture of two stereoisomers, which was used without separation, υ_{max} (film) 2870, 1730, 1170, 740, and 700 cm^{-1}; δ_H 3.59 (3H, s) and 3.66 (3H, s). Anal. Calcd for $C_{22}H_{26}O_4$: C, 75.38; H, 7.15%. Found: C, 75.62; H, 7.08%.

tert-Butyl (1*R* and *S*, 2*R*, 3*S*)-2,3-*bisbenzyloxymethylcyclobutane*-1-*carboxylate* **6'**.

Using identical condition to those described for the methylester **6**, the *tert*-butylester **6'** was obtained in 71% as 1:1 mixture of two stereoisomers, which was used without separation, υ_{max} (film) 2850, 1720, 1363, 1250, 1210, 1150, 735, and 695 cm^{-1}; δ_H 1.410 (9H, s) and 1.413 (9H, s). Anal. Calcd for $C_{25}H_{32}O_4$: C,75.72; H, 8.13%. Found: C, 75.50; H, 8.29%.

(1*R* and *S*, 2*R*, 3*S*)-2,3-*Bisbenzyloxymethylcyclobutane*-1-*carboxylate* **7**.

A solution of the methylester **6** (5.0g, 14.11mmol) and potassium hydroxide (9.3g, 165.8mmol) in methanol (260ml) was stirred for 22 hr at room temperature and then for 4 hr at 45°C. After evaporation of half the solvent volume, the mixture was diluted with water (300ml) and extracted with ether (200ml). The aqueous layer was acidified with 2N-HCl and extracted with ethyl acetate (2x200ml). The combined washed, dried extract was evaporated to give the carboxy-ether **7** as a colorless oil (4.81g, 100%), which was used without purification, υ_{max} (film) 3300-2500, 1702, 1450, 740, and 700 cm^{-1}.

(1*R* and *S*, 2*R*, 3*S*)-2,3-*Hydroxymethylcyclobutane*-1-*carboxylate* **8**.

The carboxy-ether **7** (4.8g, 14.11mmol) was hydrogenolized in methanol (500ml) over 10% Pd/C (0.9g) as catalyst for 4hr. The mixture was filtered and evaporated to give the carboxy-diol **8** as a colorless oil (2.25g, 99.6%), which was used without purification,υ_{max} (film) 3400, 2950, 1750, 1165, and 1040 cm^{-1}.

Separation of (1*R*, 2*R*, 3*S*)- and (1*S*, 2*R*, 3*S*)-2,3-*Bishydroxymethylcyclobutane* -1-*carboxylate* via their acetates.

A solution of the carboxy-diol **8** (1.5g, 9.35mmol), *p*-toluenesulphonic acid H_2O (190mg), and powdered MS 4A (2.0g) in anhydrous dimethylformamide (28ml) was stirred vigorously for 2 days. To this mixture were added acetic anhydride (7.5ml) and pyridine (12.8ml). The mixture was stirred for 4 hr at room temperature, diluted with water (20ml). After basification with sat. aq. sodium bicarbonate, the mixture was extracted with ethyl acetate (2x100ml). The combined washed, dried extract was evaporated and the resultant residue was chromatographed on silica gel (45g) with hexane-ethyl acetate (2:1) as eluent to give the lactone-acetate **9b** as a colorless oil (277mg, 32.1%), $[\alpha]_D^{21}$+73.5° (c 1.70, $CHCl_3$); υ_{max} (film) 2960, 1770, 1740, and 1240cm^{-1}; δ_H 2.08 (3H, s), 2.29 (1H, m), 2.30 (1H, m), 2.70 (1H, m), 2.99 (1H, m), 3.07 (1H, m), 4.12 (2H, complex), 4.27 (1H, dd, J 0.98, 9.77), and 4.37 (1H, dd, 6.35, 9.77); HRMS: 184.0751, $C_9H_{12}O_4$ requires 184.0735. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57%. Found: C, 58.83; H, 6.62%.

The aqueous layer was acidified with 6N-HCl and extracted with ethyl acetate (2x100ml). The combined washed, dried extracts were evaporated and the residue was purified by chromatography on silica gel (35g) with hexane-ethyl acetate (1:2) as eluent to afford (1*R*, 2*R*, 3*S*)-2,3-*bisacetoxymethylcyclobutane*-1-*carboxylate* **10b** as a colorless oil (1.06g, 93.1%), $[\alpha]_D^{21}$–21.35 (c 0.35, $CHCl_3$); υ_{max} (film) 3200, 2960, 1735, 1712, and 1240 cm^{-1}; δ_H 2.00 (1H, m), 2.08 (3H, s), 2.09 (3H, s), 2.28 (1H, m), 2.40 (1H, m), 2.68 (1H, m), 2.90 (1H, m), and 4.0-4.2 (4H, complex). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60%. Found: C, 53.81; H, 6.69%.

(1*R*, 2*R*, 3*S*)-2,3-*Bisacetoxymethyl*-1-*isocyanatocyclobutane* **12**.

To a solution of the carboxy-diacetate **10b** (0.62g, 2.54mmol) in acetone (40ml) were added triethylamine (0.44ml) and ethyl chloroformate (0.34ml, 3.56mmol). After stirring for 1hr, sodium azide (267mg) in water (3ml) was added under ice-water cooling and stirred for a further 1 hr, the mixture was diluted with cold water (20ml) and extracted with ether (2x20ml). The combined washed, dried extract was evaporated to give the diazo-

ketone **11** (0.62g), which was dissolved in dry toluene (10ml) and heated at 80°C for 30min. Evaporation of the mixture to dryness afforded the isocyanate **12** as a light brown oil (0.58g, 94.7%), which was used without purification, υ max (film) 2965, 2270, 1740, and 1240 cm^{-1}; δ_H 1.77 (1H, m), 2.07 (1H, m), 2.08 (3H, s), 2.09 (3H, s), 2.42 (2H, complex), 3.69 (1H, m), 4.04 (1H, dd, J 6.35, 11.23), 4.10 (1H, dd, J 5.37, 11.23), and 4.12 (2H, d, J 5.86).

N-Boc-(1*R*,2*R*,3*S*)-1-*amino*-2,3-*bisacetoxymethylcyclobutane* **13**.

A solution of the isocyanate **12** (567mg) in *tert*-butylalcohol (30ml) was heated at 80°C for 2 days. Evaporation and chromatography of the residue on silica gel (50g), eluting with $CHCl_3$-MeOH (40:1–10:1) gave the N-Boc-diacetate **13** as a colorless oil (618mg, 77.2%), $[\alpha]_D^{22}$+5.5° (c 2.40, $CHCl_3$); υ max (film) 3400, 3000, 1740, 1715, and 1245 cm^{-1}; δ_H 1.43 (9H, s), 1.54 (1H, q, J 9.0), 2.06 (3H, s), 2.07 (3H, s), 2.07 (1H, m), 2.20 (1H, m), 2.40 (1H, m), 3.85 (1H, m), 4.0-4.1 (3H, complex), 4.19 (1H, dd, J 5.37, 11.23), and 4.66 (1H, bs); HRMS: 242.1011 (M^+-C_4H_9O), $C_{11}H_{16}NO_5$ requires 242.1026. Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.26; H, 8.15; N, 4.29%. (1*R*, 2*R*, 3*S*)-1-*amino*-2,3-*bisacetoxymethylcyclobutane* **15** as a colorless oil (121.4mg, 22.2%), $[\alpha]_D^{21}$–42.1° (c 1.84, $CHCl_3$); υ max (film) 3400, 3350, 2960, 1740, 1640, and 1240 cm^{-1}; δ_H 1.56 (1H, q, J 9.0), 2.07 (3H, s), 2.08 (3H, s), 2.13 (1H, m), 2.20 (1H, m), 2.42 (1H, m), 3.88 (1H, m), 4.03 (1H, dd, J 5.86, 11.23), 4.09 (1H, dd, J 5.86, 11.23), 4.17 (1H, d, J 5.37), and 4.82 (2H, bs); HRMS: 215.1158 (M^+), $C_{10}H_{17}NO_4$ requires 215.1156. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51%. Found: C, 56.02; H, 7.83; N. 6.39%.

Compound **15** was also prepared from **13** by the following procedure; A solution of **13** (200mg) in dichloromethane (5ml) and trifluoroacetic acid (0.5ml) was stirred for 1hr under ice-water cooling. After evaporation to dryness, the residue was basified with 2N-NaOH and extracted with ethyl acetate (2x20ml). The combined washed, dried extracts were evaporated to give a pure **15** (131mg, 98%).

N-Boc-(1*R*,2*R*,3*S*)-1-*amino*-2,3-*bishydroxymethylcyclobutane* **14**.

A solution of the N-Boc-diacetate **13** (430mg) and lithium hydroxide (121mg) in dioxane (8ml) and water (3.5ml) was stirred for 30 min at room temperature. The mixture was diluted with water (20ml) and extracted with chloroform (2x20ml). The combined washed, dried extract was evaporated and the residue was chromatographed on silica gel (9g) with $CHCl_3$-MeOH (13:1) as eluent to give the N-Boc-diol **14** (151mg, 48%) as white crystals, mp 97-98°C, $[\alpha]_D^{24}$+34.7° [c 0.77, $CHCl_3$]; υ max (nujol) 3400, 3300, 2940, and 1690 cm^{-1}; δ_H 1.44 (9H, s), 1.52 (1H, m), 1.90 (1H, m), 2.09 (1H, m), 2.34 (1H, m), 3.13 (2H, bs), 3.45-3.75 (4H, complex), and 4.90 (1H, bs); HRMS: 232.1564 (M+1), $C_{11}H_{22}NO_4$ requires 232.1548. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06%. Found: C, 56.83; H, 9.22; N, 6.19%.

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7. Because of the volatility of **2**, the isolation yield was not optimized.
8. The racemic **14** was prepared according to the procedure of Kaneko et al.[4] We thank Dr. M. Nagai for a generous gift of "natural" enantiomer of **14**.