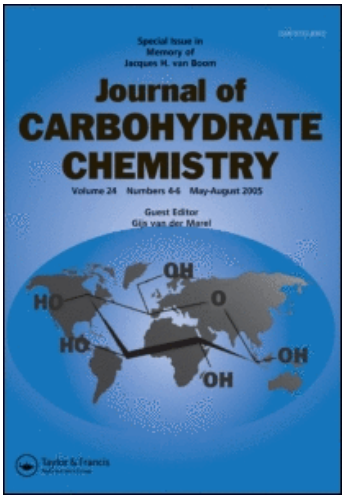

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STEREOSPECIFIC SYNTHESIS OF A DIHYDROXYETHYLENE ISOSTERE OF CYCLOHEXYLALANINE AMIDE, (2S,3R,4S)-4-AMINO-5-CYCLOHEXYL-1-MORPHOLINO-2,3-PENTANEDIOL(ACMP) FROM A PROTECTED SUGAR

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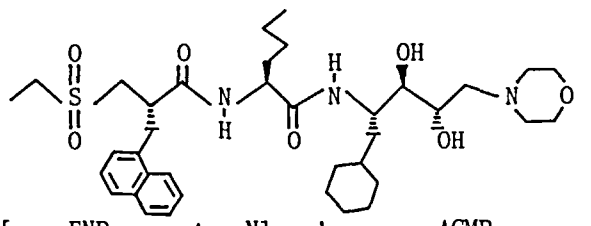
ABSTRACT

A transition-state analogue of a renin inhibitor at the scissile site, a dihydroxyethylene isostere of cyclohexylalanine amide, (2S,3R,4S)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol(ACMP), was synthesized from 1,2:5,6-di-O-isopropylidene-α-D-allofuranose stereospecifically.

INTRODUCTION

In recent years numerous renin inhibitors have been synthesized. Most, however, are substrate-analogous peptides containing an isostere of the scissible bond,[1] and have several drawbacks such as low oral bioavailability, high susceptibility to proteolytic hydrolysis and rapid biliary excretion. The replacement of an amide bond at the scissile site with a dihydroxyethylene isostere, has proven to show a hypotensive activity as the transition-state analogue. We have tried to remove peptide bonds from renin inhibitors in order to improve their oral bioavailability, and have succeeded in producing a nonpeptide, orally active renin inhibitor, BW-175, which incorporates a dihydroxyethylene isostere, ACMP.[2] In this paper we describe the stereospecific



IC_{50}(human plasma renin)[2] 3.3 nM

[----ENP------|---Nle--|--------ACMP---------]

ENP: (2S)-3-ethylsulfonyl-2-(1-naphthylmethyl)propionic acid

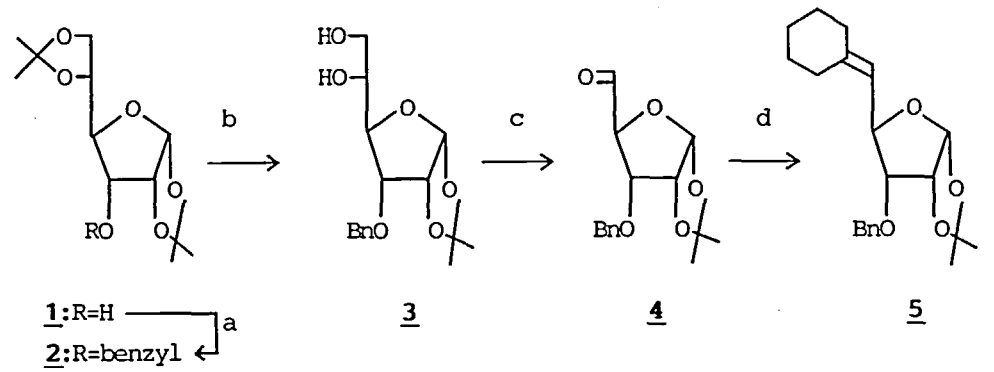
Nle: L-Norleucine

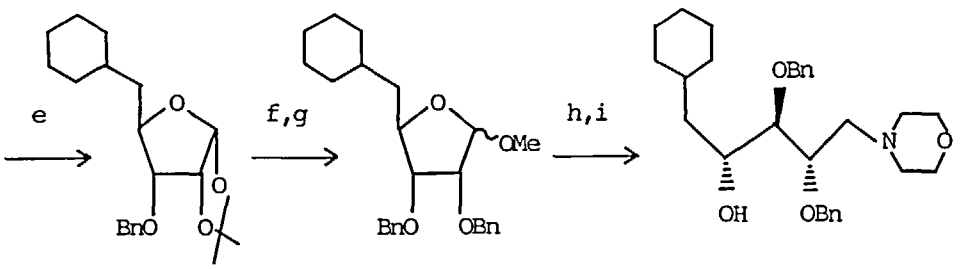
FIG. 1 The structure of BW-175.

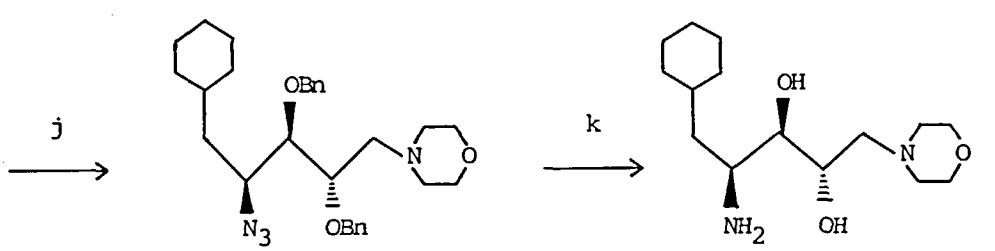
synthesis of a dihydroxyethylene isostere which is (2S,3R,4S)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (ACMP) starting from 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (1).

RESULTS AND DISCUSSION

Renin inhibitors containing ACMP of (2S,3R,4S)-configuration were expected to show the highest potency, based on the study of related diol-containing inhibitors reported by H. D. Kleinert et al.[3] As shown in SCHEME 1, we selected a "chiron approach"[4] for the stereospecific synthesis of ACMP starting from a protected sugar (1)[5] which was efficiently prepared from D-glucose according to a previous method. Recently, Yanagisawa et al. synthesized statine, which is the component of natural aspartic protease inhibitor (pepstatin), and statine analogues starting from 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.[6] The previously reported syntheses of a dihydroxyethylene isostere were stereoselective methods which took advantage of optically pure L-α-(acylamino)aldehydes derived from natural L-α-amino acids via several steps.[7-9] According to the reported results, treatment of the L-α-(acylamino)aldehyde with vinylmagnesium bromide afforded a mixture of anti and syn allylic alcohols which was oxidized and subsequently converted to a diastereomeric mixture of a dihydroxyethylene isostere. Compared with these synthetic methods, our strategy







a. BnBr,NaH,DMF ; b. aq.AcOH ; c. $NaIO_4$; d. Ph_3P^+-⬡ Br^-,BuLi ; e. Ra-Ni ;
f. HCl-MeOH ; g. BnBr,NaH,DMF ; h. aq.AcOH,HCl ; i. morpholine, $NaBH_3CN$
j. $(PhO)_2$-P(=O)-N_3,Ph_3P,EtOOC-N=N-COOEt ; k. Pd,H_2

SCHEME 1 Synthesis of (2S,3R,4S)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol(10, ACMP).

for a stereospecific synthesis of ACMP gave none of unfavorable stereoisomers and thus did not require chromatographic separation of stereoisomeric mixtures.

Treatment of 1 with benzyl bromide and sodium hydride in N,N-dimethylformamide (DMF) produced an O-benzylated compound (2)[10] which was crystallized from the reaction mixture by addition of water. The 5,6-O-isopropylidene protecting group was selectively removed by treatment of 2 with 70% acetic acid to give the diol (3) in 90% yield from 1. Oxidative cleavage of the diol (3) with sodium metaperiodate afforded 3-O-benzyl-1,2-O-isopropylidene-α-D-ribopentodialdo-1,4-furanose (4)[11] as a colorless syrup in excellent yield. The aldehyde (4) was allowed to react with an ylide prepared from cyclohexyltriphenylphosphonium bromide and butyllithium in 1,2-dimethoxyethane, to give an olefin (5) in 61% yield after silica gel column chromatography and subsequent recrystallization. The Wittig reaction in solvents other than 1,2-dimethoxyethane resulted in lower yield because the solubility of cyclohexyltriphenylphosphonium bromide was quite poor. Because of the instability of the cyclohexenyl group in 5, it was necessary to reduce the olefinic double bond before the next step. Reduction of the double bond in 5 without the removal of benzyl group was best performed by catalytic hydrogenation over Raney nickel (W1) to yield 3-O-benzyl-5-cyclohexyl-5-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (6) quantitatively. Treatment of 6 with dry hydrogen chloride in methanol caused removal of the isopropylidene group and gave the anomeric methyl glycosides at the same time. The resulting free hydroxyl group at C-2 was then protected with a benzyl group to produce methyl 2,3-di-O-benzyl-5-cyclohexyl-5-deoxy-D-ribofuranoside (7) in 97% yield (from 5), and the α-anomer and β-anomer forms were separated by silica gel column chromatography. Acid hydrolysis of the methyl glycosides (7) (acetic acid / hydrochloric acid / water 9:1:2), followed by reductive amination with morpholine and sodium cyanoborohydride in methanol gave an alcohol (8) in 90% yield from 7 after silica gel column chromatography. Identification of 8 was performed by ^{1}H NMR spectra, which revealed the signals of N-methylene protons at δ 2.51 (m, 4H), δ 2.39 (dd, 1H, $J_{1a,2}$ = 2.6 Hz,

$J_{1a,1b}$ = 13.1 Hz, H-1a), and δ 3.02 (dd, 1H, $J_{1b,2}$ = 9.0 Hz, $J_{1a,1b}$ = 13.1 Hz, H-1b). The existence of six N-methylene protons and the absence of an anomeric proton, confirmed the linear structure containing a morpholine ring but not a furanose ring. The reaction of the alcohol 8 with diphenylphosphoryl azide in the presence of triphenylphosphine and diethylazodicarboxylate,[12-13] which is the modified Mitsunobu reaction, formed the azide (9) in 43% yield. Hydrogenation of 9 over palladium black under atmospheric pressure of hydrogen produced a hygroscopic material of 10 (ACMP) as a dihydrochloride salt. Thus, we have established the stereospecific synthesis of a dihydroxyethylene isostere starting from 1 for the first time.

EXPERIMENTAL

General Procedures. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined with a HORIBA SEPA-200 HIGH SENSITIVE POLARIMETER. IR spectra were recorded with a HITACHI 270-30 Infrared Spectrophotometer. ^{1}H NMR spectra were recorded with a VARIAN VXR-300 (300 MHz) spectrometer. ^{13}C NMR were recorded with a VARIAN VXR-300 (75 MHz) spectrometer. Mass spectra were recorded with JEOL JMS-DX 300 mass spectrometer. Elemental analyses were measured by a service at Sumika Chemical Analysis Service, Ltd. Thin-layer chromatography was conducted with 0.25 mm glass plates precoated with silica gel 60 F_{254} (E. Merck). For column chromatography, silica gel 60 (70-230 mesh, E. Merck) was used. Concentrations were conducted in vacuo.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose(2).[10] To a stirred and ice-cooled suspension of sodium hydride (3.0 g) in 50 mL of dry N,N-dimethylformamide (DMF) was added 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (30.7 g) in DMF (31 mL). The reaction mixture was warmed to room temperature and then stirred for 1 h. Benzyl bromide (14.5 mL) was added to the mixture with cooling in an ice bath, and the mixture was stirred overnight at room temperature. To the resultant mixture was

added cold water (90 mL) and the product was allowed to crystallize. The crystals were filtered, washed with cold water (50 mL), and dried under reduced pressure to give 39.1 g (95%) of 2 as slightly yellow crystals. This material was used in the next step without any purification. Recrystallization from petroleum ether and hexane gave pure crystals of 2: mp 65-66 °C; $[\alpha]_D^{20}$ +107° (c 1.06, $CHCl_3$). IR (KBr) 2990, 2940, 2890, 1380($-CH_3$), 1270, 1240, 1210, 1170, 1130, 1110, 1090, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H, CMe), 1.39 (s, 3H, CMe), 1.55 (s, 3H, CMe), 1.59 (s, 3H, CMe), 3.89 (dd, 1H, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 3.99 (m, 2H, H-6), 4.14 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 3.2 Hz, H-4), 4.37 (dt, 1H, $J_{4,5}$ = 3.2 Hz, $J_{5,6}$ = 7.1 Hz, H-5), 4.58 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.59 (d, 1H, J = 11.4 Hz, Ph-CH-), 4.78 (d, 1H, J = 11.7 Hz, Ph-CH'-), 5.75 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), and 7.30-7.41 (m, 5H, phenyl).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.28; H, 7.44.

3-O-Benzyl-1,2-O-isopropylidene-α-D-allofuranose (3).[10] Compound 2 (39.1 g) was dissolved in 70% acetic acid (200 mL). The solution was allowed to stand at 37 °C for 7 h and neutralized with aqueous sodium hydrogen carbonate (200 g / 300 mL) with cooling in an ice bath. The product was extracted with ethyl acetate (300 mL and 150 mL) and the extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to afford 3 (34.5 g) as a crude oil: ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H, CMe), 1.60 (s, 3H, CMe), 3.70 (m, 2H, H-6), 3.93 (dd, 1H, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$= 8.7 Hz, H-3), 4.01 (m, 1H, H-5), 4.12 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 3.2 Hz, H-4), 4.56 (d, 1H, J = 11.1 Hz, Ph-CH-), 4.63 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 4.4 Hz, H-2), 4.79 (d, 1H, J = 11.1 Hz, Ph-CH'-), 5.77 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), and 7.3-7.4 (m, 5H, phenyl).

3-O-Benzyl-1,2-O-isopropylidene-α-D-ribopentodialdo-1,4-furanose (4).[11] To a stirred solution of 3 (34.5 g) in a mixture of ethanol / water (7:1,280 mL) was added dropwise aqueous sodium metaperiodate (25 g / 210 mL) over a period of 30 min and the mixture was stirred for 1.5 h at room temperature. The precipitated inorganic salt was filtered off

and washed with a small amount of ethanol. The combined filtrate was concentrated. The residue was dissolved in ethyl acetate (300 mL) and washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated to afford an oil. The residual oil was dissolved in ether and concentrated azeotropically to yield 4 (32.6 g) as a pale yellow oil. This material was used in the next step without any more purification. 4: IR (KBr) 1740 (H-C=O) cm^{-1}.

3-O-Benzyl-5-cyclohexylidene-5-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (5). To a stirred suspension of cyclohexyltriphenylphosphonium bromide (82.7 g) in freshly distilled 1,2-dimethoxyethane (600 mL) in an argon atmosphere, butyllithium (130 mL of 1.5 mol dm^{-3} in hexane) was added dropwise at room temperature. The mixture was stirred for 1 h. The phosphonium salt disappeared and the color of the solution turned red with an ylide. To the reaction mixture, cooled in an ice bath, was added dropwise a solution of 4 in 1,2-dimethoxyethane (36 g / 70 mL). The mixture was warmed to room temperature and stirred for 18 h. The precipitated triphenylphosphine oxide was filtered off and water (100 mL) was added to the filtrate in order to decompose excess ylide. After the solution was concentrated, the residue was dissolved in benzene (300 mL) and washed with water (130 mL) and brine (130 mL), dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (300 g, 8:1 hexane / ethyl acetate) to yield 5 (28.9 g) as a white solid. This material was recrystallized with hexane to afford pure 5 (27.2 g): mp 62-64 °C; $[\alpha]_D^{20}$ -7.2° (c 0.97, $CHCl_3$); IR (KBr) [2930, 2850, and 1460 ($-CH_2-$)], 1680 (), 1500, 1390, 1380 ($-CH_3$), 1250, 1220, 1200, 1170, 1130, 1120, 1090, 1030, and 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H, CMe), 1.58 (m, 6H, $-(CH_2)_3-$), 1.64 (s, 3H, CMe), 2.13 (br, 2H, $=C<^{CH2-}$), 2.29 (br, 2H, $=C<^{CH2-}$), 3.46 (dd, 1H, $J_{2,3}$= 4.4 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 4.53 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 4.4 Hz, H-2), 4.63 (d, 1H, J = 12.4 Hz, Ph-CH-), 4.73 (d, 1H, J = 12.4 Hz, Ph-CH'-), 4.82 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 8.8 Hz, H-4), 5.02 (dd, 1H, J = 1.5 Hz, $J_{4,5}$ = 8.8 Hz, H-5), 5.70 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), and 7.29-7.35 (m, 5H, phenyl).

Anal. Calcd for $C_{21}H_{28}O_4$:C, 73.23; H, 8.19. Found: C, 73.28; H, 8.12.

Methyl 2,3-di-O-benzyl-5-cyclohexyl-5-deoxy-D-ribofuranoside (7). A solution of 5 (27.0 g) in ethanol (230 mL) containing Raney nickel (W1 10 mL vol.) was stirred vigorously under the atmospheric pressure of hydrogen for 4.5 h at room temperature. The catalyst was filtered off and the filtrate was concentrated to afford 6 (28.4 g). Thus obtained 6 was dissolved in 5% dry hydrogen chloride in methanol (130 mL) and allowed to stand at room temperature for 66 h. The mixture was diluted with methanol (100 mL) and neutralized with anion exchange resin (Amberlite IRA-400, OH^-). After the resin was filtered off, the filtrate was concentrated to afford methyl 3-O-benzyl-5-cyclohexyl-5-deoxy-D-ribofuranoside (24.7 g) as a crude oil, which was dissolved in dry DMF (45 mL). The solution was added dropwise to the stirred suspension of sodium hydride (1.9 g) in dry DMF (30 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, then cooled in an ice bath, and treated with benzyl bromide (9.3 mL). The resultant mixture was stirred overnight at room temperature and diluted ethyl acetate (400 mL). The solution was washed with water (300 mL) and brine (300 mL), dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (260 g, 8:1-6:1 hexane / ethyl acetate) to give methyl 2,3-di-O-benzyl-5-cyclohexyl-5-deoxy-α-D-ribofuranoside (3.55 g) and methyl 2,3-di-O-benzyl-5-cyclohexyl-5-deoxy-β-D-ribofuranoside (27.6 g) as pale yellow oil.

7(α-anomer): IR (KBr) 3050 (Ph-H), 2930, 2850, 1510, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.85 (m, 2H), 1.1-1.4 (m, 6H), 1.6-1.8 (m, 5H), 3.45 (s, 3H, OMe), 3.50 (dd, 1H, J_a = 3.6 Hz, J_b = 6.8 Hz), 3.76 (dd, 1H, J_a = 4.0 Hz, J_b = 6.8 Hz), 4.18 (m, 1H, H-4), 4.59 (d, 1H, J = 12.7 Hz), 4.63 (d, 1H, J = 12.2 Hz), 4.68 (d, 1H, J = 12.5 Hz), 4.74 (d, 1H, J = 13.1 Hz), 4.83 (d, 1H, J = 4.5 Hz, H-1), and 7.28-7.40 (m, 10H, phenyl).

7(β-anomer): IR (KBr) 3040 (Ph-H), 2930, 2850, 1500, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (m, 2H), 1.1-1.3 (m, 3H), 1.4-1.6 (m, 3H), 1.6-1.85 (m, 5H), 3.31 (s, 3H, OMe), 3.77 (dd, 1H, J_a = 4.5 Hz, J_b = 7.0 Hz), 3.82 (dd, 1H, J_a = 1.0 Hz, J_b = 4.5 Hz), 4.22 (m, 1H, H-4), 4.41 (d, 1H, J = 12.0 Hz), 4.55 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 4.68 (d, 1H, J = 12.0 Hz), 4.87 (s, 1H, H-1), and 7.27-7.40 (m, 10H, phenyl).

(2S,3R,4R)-5-Cyclohexyl-2,3-dibenzyloxy-1-morpholinopentan-4-ol (8). Compound 7 (α and β mixture, 30.8 g) was dissolved in a mixture of acids (acetic acid / hydrochloric acid / water 9:1:2, 600 mL). The mixture was stayed at 20 °C for 20 h and then diluted with toluene (1 L). The solution was washed with water (2 x 400 mL), 4% aqueous sodium hydrogen carbonate (500 mL), and brine, dried over anhydrous magnesium sulfate, and concentrated to afford 2,3-di-O-benzyl-5-cyclohexyl-5-deoxy-D-ribofuranose as a pale yellow oil. To the methanolic solution (500 mL) of the residue, together with morpholine hydrochloride (41.7 g), was added methanolic sodium cyanoborohydride (8.49 g/ 100 mL). It was stirred at room temperature for 39 h and then concentrated. The residue was dissolved in a mixture of solvents (1 L of benzene / ethyl acetate 4:6), washed with water (2 x 300 mL) and brine (300 mL), dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (260 g, 4:1 chloroform / ethyl acetate) to afford 8 (31.7 g) as a white solid: mp 54-56°C; $[\alpha]_D^{20}$ +31.0° (c 1.09, chloroform); IR (KBr) 3220 (OH), 2930, 2850, 1460, 1120, 1030, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 55 °C) δ 0.85 (m, 2H), 1.1-1.3 (m, 5H), 1.44 (m, 1H), 1.55-1.80 (m, 5H), 2.39 (dd, 1H, $J_{1a,2}$ = 2.6 Hz, $J_{1a,1b}$ = 13.1 Hz, H-1a), 2.51 (m, 4H, $-N<^{CH_2-}_{CH_2-}$), 3.02 (dd, 1H, $J_{1b,2}$ = 9.0 Hz, $J_{1a,1b}$ = 13.1 Hz, H-1b), 3.59 (dd, 1H, J_a = 1.4 Hz, J_b = 5.3 Hz, H-3), 3.66 (m, 4H, $^{-CH_2}_{-CH_2}>O$), 3.77 (m, 2H, H-2 and H-4), 4.56 (d, 1H, J = 12.2 Hz), 4.59 (d, 1H, J = 12.2 Hz), 4.63 (d, 1H, J = 11.7 Hz), 4.76 (d, 1H, J = 11.7 Hz), and 7.2-7.4 (m, 10H, phenyl).

Anal. Calcd for $C_{29}H_{41}NO_4$: C, 74.48; H, 8.84; N, 3.00. Found: C, 74.52; H, 8.87; N, 2.92.

(2S,3R,4S)-4-Azide-5-cyclohexyl-2,3-dibenzyloxy-1-morpholinopentane (9). To a cooled solution (-20°C) of triphenylphosphine (24.9 g) and 8 (27.7 g) in distilled tetrahydrofuran (200 mL) were added diethyl azodicarboxylate (14.9 mL) and diphenylphosphorylazide (20.5 mL). The mixture was stirred at 20°C for 24 h and concentrated. The residue was chromatographed on a column of silica gel (5:1, hexane / ethyl acetate) to afford 9 (12.7 g) as a clear oil: IR (KBr) 2930, 2850, 2110 (N_3), 1750, 1740, 1500, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (m, 2H), 1.1-1.5

(m, 5H), 1.7 (m, 6H), 2.37 (m, 2H, N-CH_2-), 2.59 (m, 2H, N-CH_2-), 2.65 (m, 2H, H-1a, H-1b), 3.56 (ddd, 1H, $J_{3,4}$ = 3.1 Hz, $J_{4,5a}$ = 4.2 Hz, $J_{4,5b}$ = 9.9 Hz, H-4), 3.64 (dd, 1H, $J_{3,4}$ = 3.1 Hz, $J_{2,3}$ = 6.8 Hz, H-3), 3.67 (m, 4H, $^{-CH_2}_{-CH_2}>O$), 3.74 (m, 1H, H-2), 4.58 (d, 1H, J = 11.1 Hz), 4.69 (d, 1H, J = 11.1 Hz), 4.73 (d, 1H, J = 11.5 Hz), 4.79 (d, 1H, J = 11.5 Hz), and 7.28-7.38 (m, 10H, phenyl); FAB MS 493 $(M+1)^+$.

(2S,3R,4S)-4-Amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (ACMP, 10). An ethanolic solution of 9 (12.6 g / 250 mL) containing 10% palladium on carbon (1.0 g) was acidified with 2 mol dm^{-3} hydrochloric acid (32 mL) and it was vigorously stirred under the atmospheric pressure of hydrogen. After 4 h, the catalyst was exchanged with palladium black and the solution was stirred for about 48 h under the same conditions. The catalyst was filtered off and the filtrate was concentrated to give 10 (8.8 g) as a crude solid. This solid was dissolved in water (600 mL) and charged on a column of ion exchange resin (CM-Sephadex C-25, NH^+form, 200 mL). The resin was washed with water (400 mL) and eluted with 0.05 - 0.25 mol dm^{-3} ammonium hydroxide. The eluate was diluted with ethanol and concentrated to give a syrup which was dissolved in ethanol (100 mL). The solution was neutralized with 1 mol dm^{-3} hydrochloric acid and concentrated to afford a white solid, which was recrystallized with a mixture of solvents (ethanol / ether /dichloromethane) to give 10 (6.6 g) as a hygroscopic dihydrochloride salt: ^1H NMR ($CDCl_3$, free base) δ 0.95 (m, 2H), 1.23 (m, 3H), 1.43 (m, 2H), 1.57 (m, 1H), 1.72 (m, 5H), 2.55 (m, 2H), 3.40 (m, 1H), 3.50 (br dd, 1H, J = 1.5 Hz, 7.0 Hz), 3.70 (m, 4H), and 3.88 (m, 1H); ^{13}C NMR ($CDCl_3$-CD_3OD, dihydrochloride salt) δ 25.8 (2 x C), 26.2, 32.6, 33.1, 33.2, 37.2, 48.9, 52.4, 53.5, 60.8, 63.5, 63.6, 65.1, and 69.9; ^{13}C-NMR ($CDCl_3$, free base) δ 26.1, 26.3, 26.4, 32.7, 34.1, 34.2, 40.8, 48.9, 53.9 (2 x C), 63.4, 66.2, 66.7 (2 x C), and 76.3; ^{13}C-NMR (dihydrochloride salt, 20% DCl in D_2O) δ 29.6 (2 x C), 30.0, 36.5 (2 x C), 36.9, 41.0, 53.9, 55.6, 57.7, 63.5, 67.6 (2 x C), 69.6, and 74.1.

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