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# A Facile Synthesis of (*2S,3R,4S*)-4-Amino-5-Cyclohexyl-1-Morpholino-2,3-Pentanediol, the C-Terminal Compound of Renin Inhibitor BW-175

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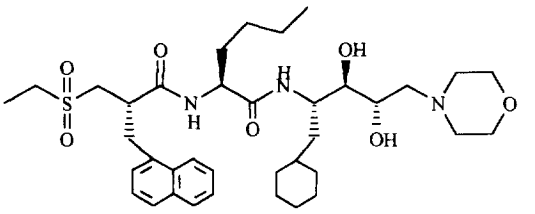
***Abstract***: A facile synthesis of (*2S, 3R, 4S*)-4-amino-5-cyclohexyl-1-morpholino-2,pentanediol (ACMP), the C-terminal compounds of renin inhibitor BW-175 is described.

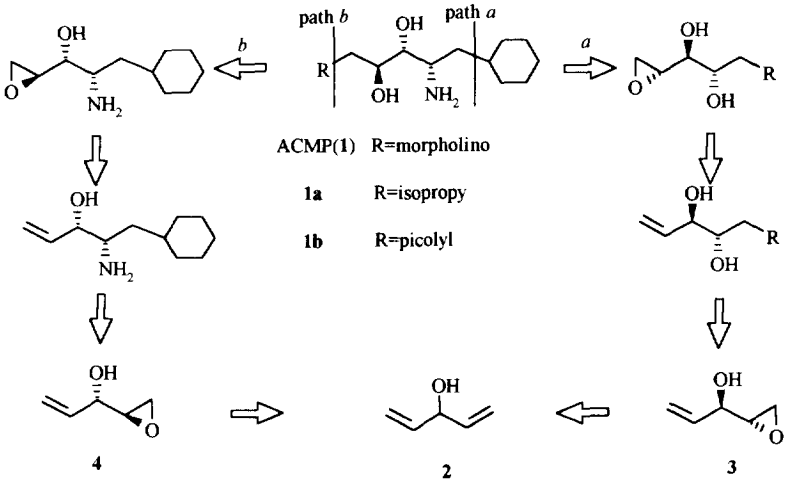
The renin-angiotensin system plays a central role in the regulation of blood pressure.[1] Renin is a highly specific aspartic acid protease which cleaves a decapeptide fragment from angiotensinogen to generate angiotesin I. While no biological activity is observed for angiotesin I, the octapeptide angiotesin II formed from angiotesin I by angiotesin-converting enzyme shows a potent vasoconstricting activity and stimulates the release of aldosterone. Thus, renin inhibitors are currently the object of intensive research aimed at development of novel antihypertensive drugs.[2] A large number of renin inhibitors have the structures which incorporate a dihydroxyethylene dipeptide (DHED) isostere into the inhibitor molecules.[3a] The 1,2-diol moiety of the dihydroxyethylenedipeptide isostere binds to the enzyme by forming tight hydrogen bonds to the aspartic acid residues which are present in the active site.[3]BW-175, a novel renin inhibitor, is a nonpeptidic, orally active, low-molecular-weight inhibitor, bearing the dihydroxyethylene isostere, (*2S,3R,4S*)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (ACMP, **1**) as C-terminal moiety.[4] A-77003,[5] bearing (*2S,3R,4S*)-4-amino-5-cyclohexyl-1-isopropyl-2,3-pentanediol (**1a**) and another improved renin inhibitor[6] bearing (*2S,3R,4S*)-4-amino-5-cyclohexyl-1-picolyl-2,3-pentanediol (**1b**) also show high potency. So the synthesis of



BW-175

C-terminal of renin inhibitors is important in exploration of the potential antihypertensive drugs.

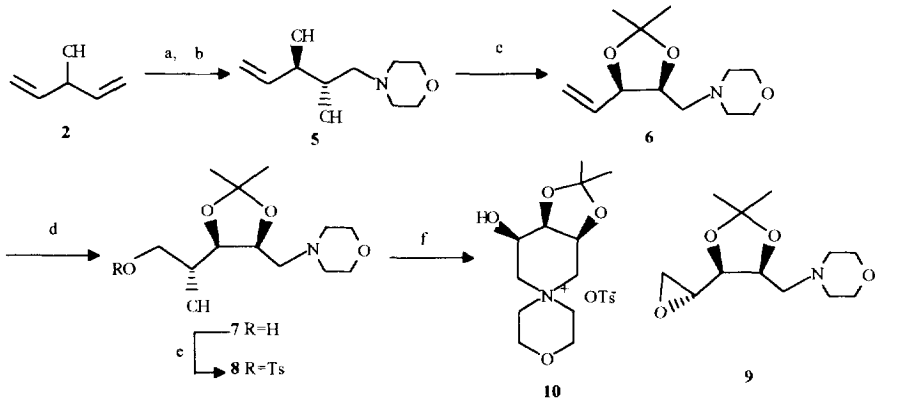
The ACMP was synthesized from 1,2;5,6-di-O-isopropylidene-D-allofuranose[7] and 4-O-benzyl-2,3-isopropylidene-D-threose.[8] Here, we describe a new and efficient chiral synthesis of ACMP from the divinylcarbinol *via* the Sharpless asymmetric epoxidation and it is a suitable approach to some other C-terminal of rennin inhibitors, such as C-terminal of A-72517, A-77003 (**1a**)[5] , (*2S,3R,4S*)-4-amino-5-cyclohexyl-1-picolyl-2,3-pentanediol (**1b**) etc.. The retrosynthetic route is outlined in Scheme 1.




Scheme 1

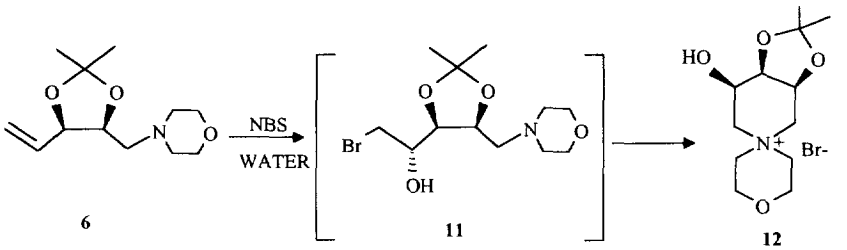
The molecule of ACMP is conceptually considered to possess pseudo-symmetry, based on the resemblance of cyclohexyl group with the morpholino group. Thus, ACMP could be derived from **3** or **4** by ring opening with cyclohexylmagnesium chloride (path a) or morpholine (path b). The epoxide alcohol **3**,**4** can be easily obtained by Sharpless asymmetric epoxidation using L-(+)- or D-(-)-DIPT as chiral ligand from **2** respectively. Since we have reported the one-pot aminolysis of 1,2-epoxy-4-penten-3-ol,[9]as a continuation of our work, we tried to synthesize ACMP *via* path *a* first. (see Scheme 2).

Compound **5** was readily generated by one-pot aminolysis of (*2R,3S*)-1,2-epoxy-4-pentene-3-ol (**3**) using morpholine as nucleophile in 89% yield from **2**. Protection of diol in **5** easily provided the isopropylidene derivative **6** in 91% yield. The direct epoxidation of double bond in **6** was unsuccessful under various conditions. Finally dihydroxylation of **6** with osmium tetraoxide afforded dihydroxyl compound **7**(85% yield, d.r=7:1). Tosylation of the primary hydroxy group of **7** followed by the treatment with potassium carbonate failed to afford the desired oxirane **9**. Instead, an ammonium salt **10** was obtained. The formation of **10** was rationalized by the stronger nucleophilicity of the nitrogen atom of the morpholino group than the oxygen atom of the hydroxyl group, so nitrogen atom predominantly attacked the carbon atom containing a leaving group (OTs). It is also confirmed by the treatment of **6** with NBS and water resulting in the formation of an ammonium salt **12**. Obviously, it is due to the intramolecular nucleophilic cyclization of **11** with Br as leaving group (Scheme 3).



**Scheme 2**

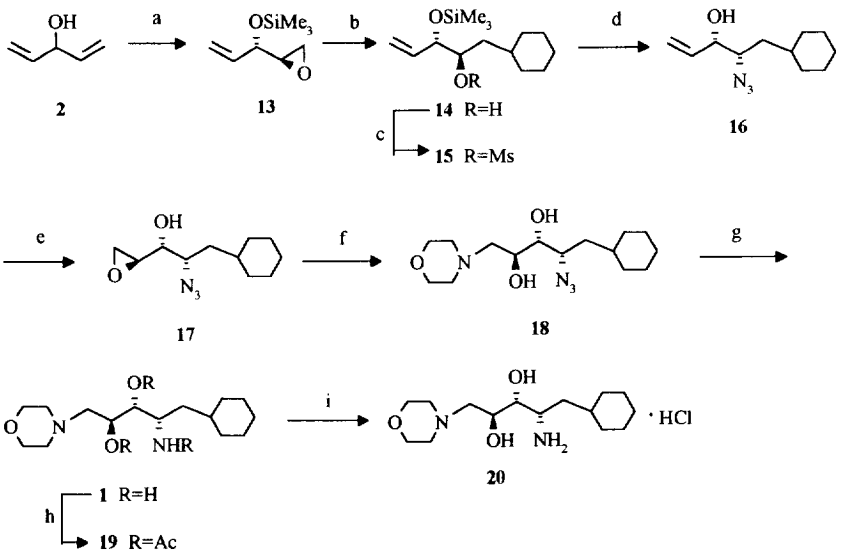
Reaction conditions: a): D-(-)-DIPT, TBHP, $Ti(OPr^i)_4$, 4Å molecule sieves, -20°C, 10 days. b): morpholine, $CH_2Cl_2$, r.t., 1 day, 89% yield from **2**. c): 2,2-dimethoxypropane, PTS(10% mol), $CH_2Cl_2$, 91% yield. d): $OsO_4$(cat), $K_3Fe(CN)_6$, $K_2CO_3$, t-BuOH : $H_2O$ =1 : 1, r.t., overnight, 85% yield, d.r =7:1. e): *p*-TsCl, $NEt_3$, 0°C, $CH_2Cl_2$, 86.5% yield. f): $K_2CO_3$, MeOH, r.t., 81% yield.



**Scheme 3**

Therefore our effort was turned to the introduction of the cyclohexyl group at the early stage instead of the morpholino group according to path *b*.(see Scheme 4)

The epoxide **13** was readily obtained in 65% yield with high diastereomeric (98%) and enantiomeric excess (97%). Regioselective opening of **13** with cyclohexylmagnesium chloride in the presence of CuI followed by mesylation gave **15** in 61% yield from **13**. Treatment of **15** with sodium azide completed the replacement of the mesyloxy group by azide group. Then, removal of the silyl group by hydrolysis with 2N HCl produced **16** (87% yield). The epoxide **17** is easily generated by the stereoselective epoxidation of double bond of **16** with TBHP as oxidant in the presence of $VO(acac)_2$ in 68% yield, the stereochemistry of new formed stereocenter was assigned as the desired *S* by comparing the data of our synthesized ACMP with literature. Reaction of **17** with morpholine at room. temp. easily gave **18** in quantitative yield. Hydrogenation of **18** with 10% Pd/C in methanol at atmospheric pressure afforded ACMP in 92% yield. The spectroscopic data of the synthesized ACMP is compatible with the authentic compound prepared from 1,2;5.6-di-O-isopropylidene-D-allofuranose in all respects,[7] and the data of the hydrochloride of ACMP, triacetate of ACMP are also consistent with literature.[8a]




**Scheme 4**

Reaction conditions: a): (1), L-(+)-DIPT, TBHP, $Ti(OPr^i)_4$, 4Å molecule sieves, $CH_2Cl_2$, -20°C. (2), $Et_3N$, $ClSiMe_3$, -10°C, 65% yield from **2**. b): cyclohexyl magnesium bromide, CuI(10% mol), THF, -10°C, 81% yield. c): methanesulfonyl chloride, pyridine, $CH_2Cl_2$, r.t., 75% yield. d): sodium azide, DMF, 90°C, 12hr, then 5% HCl aq., 87% yield. e): TBHP, $VO(acac)_2$, $CH_2Cl_2$, r.t., 68% yield. f): morpholine, MeOH, r.t, 100% yield. g): 10% Pd/C, MeOH, 92% yield. h): $Ac_2O$, pyridine, r.t., 85% yield. i): HCl(gas), 89% yield.

Thus, we have provided a facile stereoselective synthesis of ACMP from divinylcarbinol by Sharpless asymmetric epoxidation. This approach will be useful to the synthesis of similar compounds.

## Experimental:

Melting points were measured on a Büchi 535 spectrometer and are uncorrected. Infrared spectra were recorded on a Shimadzu IR-440 spectrometer and only the strongest / structurally most important peaks are listed in $cm^{-1}$. $^1H$ NMR spectra were obtained at Bruker AM 300 (300 MHz) spectrometer using TMS as internal standard. Routine mass spectra were run on a Finnigan 4021 apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line and 25°C. Flash column chromatography were carried out using silica gel (200-300 mesh, made in Shanghai, China).

***(3R,4S)*-5-morpholino-3,4-dihydroxy-1-pentene(5).** To a mixture of 3g of 4Å molecule sieves and 75 ml of dried $CH_2Cl_2$, were added 1.0 ml of D-(-)-DIPT (4.75 mmol), 7.5 ml of TBHP (7.4 M in $CH_2Cl_2$) and 1.5 ml of $Ti(OPr^i)_4$ (5.0 mmol) at -20°C under positive $N_2$ pressure. After stirring for 0.5 hr, 3 ml of **2** (31.0 mmol) was added *via* syringe. The mixture was kept in a refrigerator at -20°C for 10 days until completion of the reaction was shown by the disappearance of **2** on TLC. 3 ml of $P(OEt)_3$ (25.5 mmol) was then added at -20°C. The stirring was continued for 0.5 hr followed by the addition of 12 ml of $Ti(OPr^i)_4$ together with 20 ml of morpholine (0.23 mol). The mixture was stirred overnight at r.t., then 150 ml of $CH_3Cl$ and 40 ml of

10% NaOH in brine were added. The mixture was stirred for 5 hr. The organic layer was separated and dried over anhydrous $Na_2SO_4$. The mixture was subjected to flash column chromatography to yield 5.14 g of **5** (89%). $[\alpha]_D^{25}$ -0.87 (c, 1.56, $CHCl_3$). $\nu_{max}$: 3520; 1490; 1280 $cm^{-1}$. $\delta_H$ ($CDCl_3$) 2.50-2.60 (4H, m, -$N(CH_2)_2$); 2.95 (2H, m, 5-$CH_2$); 3.75 (4H, t, J=4.2 Hz, -$O(CH_2)_2$); 4.41 (2H, br, 2 x OH); 4.31 (1H, dd, J=6.8, 7.0 Hz, 4-CH); 4.55 (1H, m, 3-CH); 5.23 (1H, dd, J=10.4, 1.8 Hz, H1); 5.37 (1H, dd, J=17.2, 1.8 Hz, H1'); 5.90 (1H, m, H2) ppm. $\delta_C$ 136.8; 116.3; 75.1; 67.6; 66.8; 60.1; 53.8; 51.8 46.0 ppm. m/z (%): 188 ($M^+$+1, 60); 86 (morpholino, base). HRms: calcd for M-1 ($C_9H_{16}NO_3$) 186.1130; Found: 186.1199.

**(*3R,4S*)-5-morpholino-*O*-3,4-isopropylidene-1-pentene (6):** To a solution of 1.91 g of **5** (10.2 mmol) in 50 ml of $CH_2Cl_2$, was added 1.9 g of PTS (10.0 mmol) followed by addition of 5 ml of 2,2-dimethoxypropane (30.2 mmol). The reaction mixture was stirred at ambient temperature until the completion of reaction monitored by TLC. 2 g of $NaHCO_3$ (23.8 mmol) in 10 ml of water was poured into the flask, the mixture was extracted with $CH_2Cl_2$ 3 times. The combined organic layer was dried over anhydrous $Na_2SO_4$, then subjected to flash column chromatography to produce 2.11 g of **6** as a pale viscous oil in 91% yield. $[\alpha]_D^{25}$ + 7.5 (c, 0.55, $CHCl_3$). $\upsilon_{max}$: 3010; 1460; 1380 $cm^{-1}$. $\delta_H$ ($CDCl_3$) 1.37 (3H, s, $CH_3$); 1.50 (3H, s, $CH_3$); 2.40-2.60 (6H, m, -$N(CH_2)_3$); 3.72 (4H, t, J=4.3 Hz, -$O(CH_2)_2$); 4.38 (1H, m, 4-CH); 4.55 (1H, m, 3-CH); 5.23 (1H, d, J=11.0 Hz, H1); 5.35 (1H, d, J=17.2 Hz, H1'); 5.80 (1H, m, 2-CH) ppm. $\delta_C$: 134.3; 118.0; 108.7; 79.3; 76.7; 75.8; 66.8; 59.2; 54.3; 29.7; 28.1; 25.5 ppm. m/z(%): 228 ($M^+$+1, 25); 212 ($M^+$-$CH_3$, 65); 100 ($CH_2$-$N(CH_2)_4O$, base). HRms: calcd for M-$CH_3$ ($C_{11}H_{18}NO_3$) 212.1287. Found: 212.1303.

**(*2R, 3R, 4S*)-5-morpholino-1,2-dihydroxy-*O*-3,4-isopropylidene-pentane (7):** 466 mg of **6** (2.05 mmol) was dissolved in mixture of 30 ml of t-BuOH and 30 ml of water, 2.8 g of $K_3Fe(CN)_6$ (8.5 mmol) and 1.0 g of $K_2CO_3$ (7.2 mmol) were then added, followed by dropwise addition of 1 ml of (0.05 mmol) solution of 0.5 g of $OsO_4$ in 40 ml of t-BuOH to the reaction mixture. The resulting mixture was stirred at r.t. for 24 hr. Sodium sulfite (2.7 g, 21.4 mmol) was added to quench the reaction. The reaction mixture was concentrated to remove the t-BuOH, then extracted with ethyl acetate 3 times and the combined extracts were washed with sat. aq. NaCl. and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent left an oil which was chromatographed on silica gel, eluting with petroleum ether and ethyl acetate to give 455 mg of 7 as a white solid ( 85 % yield). mp 102.5-103.4°C. $[\alpha]_D^{25}$ +25.3 (c, 0.95, $CH_2Cl_2$). $\upsilon_{max}$: 3350; 2950; 1450; 1380 $cm^{-1}$. $\delta_H$ ($CDCl_3$) 1.33 (3H, s, $CH_3$); 1.40 (3H, s, $CH_3$); 2.45-2.80 (6H, m, -$N(CH_2)_3$); 3.70 (6H, m, -$O(CH_2)_2$ and $HOCH_2$-); 3.85 (1H, ddd, J=2.4, 3.1, 3.1 Hz, 2-CH); 4.19 (1H, dd, J=9.1 and 5.8 Hz, 4-CH); 4.45 (1H, m, 3-CH) ppm. $\delta_C$: 108.9; 78.0; 76.7; 73.1; 69.3; 66.5; 64.7; 58.3; 54.2; 53.9; 27.9; 25.2 ppm. m/z(%): 262 ($M^+$+1, 21); 230 ( $M^+$-$CH_2OH$, 56); 101 ($CH_2$-$N(CH_2)_4O$+1,87); 86 (morpholino, base). HRms: calcd for M-$CH_2OH$ ($C_{11}H_{20}NO_4$) 230.1393. Found: 230.1378.

**(*2R, 3R, 4S*)-5-morpholino-1-*p*-toluenesulfonyloxy-2-dihydroxy-*O*-3.4-isopropylidene-pentane (8):** 400 mg of 7 ( 1.53 mmol) was dissolved in 10 ml of $CH_2Cl_2$ in a pre-dried flask, and 4 ml of triethylamine (28.8 mmol) and 1.0 g of *p*-tolunesulfonyl chloride (5.25 mmol) were then added at 0°C. The resulting mixture was stirred at 0°C until completion of reaction as monitored by TLC, then 200 ml of $CH_2Cl_2$ was added to dilute the reaction mixture. The organic layer was subsequently washed with 50 ml of 1.5% aq. HCl, 50 ml of sat. aq. $NaHCO_3$ and 80 ml of sat. aq. NaCl, then dried over anhydrous $Na_2SO_4$. Removal of the solvent left an oil which was subjected to flash column chromatography to produce 613 mg of monotosylate **8** as a white powder in 96.4% yield. $[\alpha]_D^{25}$ + 9.0 (c, 0.9, acetone). $\upsilon_{max}$: 3300(br); 2990; 1640; 1600; 1380 $cm^{-1}$. $\delta_H$ ($CDCl_3$): 1.33 (3H, s, $CH_3$); 1.52 (3H, s, $CH_3$); 2.34 (3H, s, $CH_3$); 3.45 (2H, m); 3.65-3.90 (6H, m); 4.10 (4H, m); 4.60

(3H, m) ppm. m/z(%): 313($M^+$- $CH_2$-N($CH_2$)$_4$O-1, 12); 172 (OTs, 9.8); 100($CH_2$-N($CH_2$)$_4$O, 79.4); 86 ( -N($CH_2$)$_4$O, base).

**Ammonium salt (10):** To a solution of 474 mg of **8** (1.14 mmol) in 10 ml of methanol, 315 mg of $K_2CO_3$ (2.28 mmol) was added . The mixture was stirred at r.t. for 5 min. Removal of the methanol gave an oil which was purified by flash column chromatography with dichloromethane and methanol as eluent to produce 385 mg of pure ammonium salt **10** (81 % yield). $[\alpha]_D^{25}$ + 41.0 (c, 1.0, $H_2O$). $\upsilon_{max}$: 3350; 2950; 1380; 1240 $cm^{-1}$. $\delta_H$ ($D_2O$): 0.82 (3H, s, $CH_3$); 0.95 (3H, s, $CH_3$); 3.36 (3H, s, $CH_3$); 3.25-3.70 (8H, m, -N($CH_2$)$_4$); 4.20 (4H, t, J=5.9 Hz, -O($CH_2$)$_2$); 4.55 (1H, m, HOC<u>H</u>-); 5.68 (1H, m, -OCH); 5.62 (1H, m, -OCH); 7.01 (4H, m, -$C_6H_4$-) ppm. m/z(%): 397 ($M^+$, 2.1); 379 ($M^+$-$H_2O$, 12); 226 ($M^+$-OTs, 45).

**Ammonium salt (12):** To a solution of 164 mg of **6** (0.63 mmol) in 10 ml of $Et_2O$, 130 mg of NBS (0.73 mmol) and 1 ml of water were added. The mixture was stirred at r.t. and the reaction was monitored by the TLC. Removal of the water of water layer gave a viscous oil, which was purified by flash column chromatography eluting with dichloromethane and methanol (200 : 15) to produce 156 mg of **12** as a pale syrup in 66.7 % yield. $[\alpha]_D^{25}$ +18.4 (C, 1.25, $H_2O$). $\upsilon_{max}$: 3350; 2950; 1380 $cm^{-1}$. $\delta_H$ ($D_2O$): 0.80 (3H, s, $CH_3$); 0.91 (3H, s, $CH_3$); 3.36 (3H, s, $CH_3$); 3.25-3.60 (8H, m, -N($CH_2$)$_4$); 4.15 (4H, t, J=5.4 Hz, -O($CH_2$)$_2$); 4.51(1H, m, HOC<u>H</u>-); 5.40 (1H, m, -OCH); 5.62 (1H, m, -OCH) ppm. m/z(%): 308, 306 ($M^+$-$H_2O$, 11); 226 ($M^+$-Br, base).

***(2R,3S)*-1,2-epoxy-3-trimethylsilyloxy-4-pentene (13):** To a mixture of 6g of 4Å molecule sieves and 150 ml of dried $CH_2Cl_2$, were added subsequently 2.0 ml of L-(+)-DIPT ( 9.5 mmol), 15 ml of TBHP (7.4 M in $CH_2Cl_2$) and 3.0 ml of Ti(OPr$^i$)$_4$ (10.0 mmol) at -20°C under positive $N_2$ pressure. After stirring for 0.5 hr, 6 ml of divinylcarbinol (62.0mmol) was added *via* syringe. The mixture was kept in a refrigerator at -20°C for 10 days. 1.2 g of citric acid (6.2 mmol) and 120 ml of 10% acetone-$Et_2O$ were added. The mixture was stirred at r.t. for 1 hr then was filtered through a pad of celite. Removal of solvent gave a yellow oil, which was then dissolved in 250 ml of $CH_2Cl_2$. Triethylamine (25 ml, 179.4 mmol), 1.5 g of DMAP (12.3 mmol), 19 ml of trimethylsilyl chloride (90.0 mmol) were then added to the mixture at 0°C. The mixture was stored in a refrigerator at -10°C for 24 hr , then was filtered through a pad of celite, washed with sat. aq. NaCl and dried over anhydrous $Na_2SO_4$. Removal of the solvent and purification by flash column chromatography gave 10.3 g of pure **13** as a colorless oil with 65% yield. $[\alpha]_D^{25}$ +36.6 (c, 0.68, $CH_2Cl_2$). $\upsilon_{max}$: 3500; 2980; 1450; 1260 $cm^{-1}$. $\delta_H$ ($CDCl_3$) 0.68 (9H, s, -SiMe$_3$); 0.85-1.68 (13H, m, $CH_2C_6H_{11}$); 2.01 (1H, br, -OH); 3.55 (1H, m, 4-CH); 3.85 (1H, dd, J=5.3, 3.7 Hz, 3-CH); 5.02 (1H, d, J=11.2 Hz, H1); 5.10 (1H, dd, J=9.6, 1.5 Hz, H1'); 5.71 (1H, m, 2-CH) ppm. m/z(%): 256 ($M^+$, 1.5); 183 ($M^+$-SiMe$_3$, 15).

***(3S,4R)*-3-trimethylsilyloxy-4-hydroxy-5-cyclohexyl-1-pentene (14):** To a solution of 3 g of **13** ( 11.7 mmol) in 12 ml of dry THF, was added 300 mg of CuI ( 1.58 mmol). Cyclohexyl magnesium chloride (0.7 g of Mg, 4 ml of cyclohexyl chloride in 10 ml of THF) was added dropwise at -10°C. The mixture was stirred and gradually warmed to r.t.. After the completion of the reaction as monitored by TLC, 20 ml of sat. aq. $NH_4Cl$ was added to quench the reaction. Removal of THF under reduced pressure gave a mixture, which was extracted with $Et_2O$, washed with sat. aq. NaCl and dried over anhydrous $Na_2SO_4$. Removal of solvent and purification by flash column chromatography gave 3.19 g of pure **14** as a pale viscous oil with 81% yield. $[\alpha]_D^{25}$ +10.9 (c, 0.66, $CH_2Cl_2$). $\upsilon_{max}$: 3005; 2980; 1750; 1450; 1360 $cm^{-1}$. $\delta_H$ ($CDCl_3$): 0.13 (9H, s, -SiMe$_3$); 0.90-1.65 (13H, m, -$CH_2C_6H_{11}$); 3.06 (3H, s, $CH_3$); 4.19 (1H, ddd, J=5.1, 2.6, 1.3 Hz, 3-CH); 4.73

(1H, ddd, J=9.6, 3.5, 2.7 Hz, 4-CH); 5.23 and 5.26 (2H, m, 1-$CH_2$); 5.82 (1H, m, 2-CH) ppm. m/z(%): 336 ($M^+$, 12); 195; 183.

**(*3S,4S*)-3-hydroxy-4-azide-5-cyclohexyl-1-pentene (16):** 520 mg of pure **14** (1.46 mmol) was dissolved in 5 ml of $CH_2Cl_2$, 1.2 ml of pyridine(14.8 mmol) and 0.45 ml of methanesulfonyl chloride (5.9 mmol) were added dropwise under $N_2$ pressure. The mixture was stirred at r.t. and the reaction was monitored by TLC. After the completion of the reaction, 100 ml of $CH_2Cl_2$ was added to dilute the mixture, which was then washed with sat. aq. $CuSO_4$ to remove pyridine and finally dried over anhydrous $Na_2SO_4$. Removal of solvent gave a pale viscous oil which was then dissolved in 10 ml of DMF without purification, 1.5 g of $NaN_3$ (23.1 mmol) was added under $N_2$. The mixture was stirred at 90°C for 12 hr, and 1.5 ml of 5% aq. HCl was added to the mixture and the stirring was continued for 15 min. The mixture was extracted 3 times with 120 ml of $Et_2O$. The ethereal layers were combined, washed with sat. aq. NaCl and dried. Removal of $Et_2O$ gave a residue which was subjected to flash column chromatography to produce 199.2 mg of pure **16** as a colorless oil in 65.3% yield. $[\alpha]_D^{25}$ -28.8 (c, 0.11, $CH_2Cl_2$). $\upsilon_{max}$: 3400; 2900; 2090(-$N_3$); 1440; 1260 $cm^{-1}$. $\delta_H$ ($CDCl_3$): 0.85-1.85 (13H, m, $CH_2C_6H_{11}$); 3.32 (1H, m, 4-CH); 4.02 (1H, m, 3-CH); 5.24 (1H, dd, J=12.8, 1.3 Hz, 1-H); 5.31 (1H, ddd, J=17.0, 1.5, 1.1 Hz, 1'-H); 5.89 (1H, m, 2-CH) ppm. m/z(%): 209 ($M^+$, 8.8); 167 ($M^+$-$N_3$, 15.4); 181 ($M^+$-$N_2$, 18.5)

**(*2S,3S,4R*)-1,2-epoxy-3-hydroxy-4-azide-5-cyclohexyl-pentane (17):** To a solution of 300 mg of **1** (1.44 mmol) in 10 ml of dry $CH_2Cl_2$, was added 90 mg of $VO(acac)_2$ (0.26 mmol) and 1.8 ml of TBHP (6.8 M in $CH_2Cl_2$) under $N_2$ pressure. The mixture was stirred at r.t. . After the completion of the reaction, the mixture was diluted with 150 ml of $CH_2Cl_2$, washed with 100 ml of sat. aq. NaCl 2 times and dried over anhydrous $Na_2SO_4$. Finally the rude product was subjected to flash column chromatography to give 219.6 mg of pure **17** as a colorless oil in 68% yield. $[\alpha]_D^{25}$ -10.0 (c, 0.91, $CH_2Cl_2$). $\upsilon_{max}$: 3400; 2950; 2100; 1450; 1260 $cm^{-1}$. $\delta_H$ ($CDCl_3$): 0.88-1.68 (13H, m, -$CH_2C_6H_{11}$); 2.88 (2H, m, 1-$CH_2$); 3.08 (1H, m, 4-CH); 3.52 (1H, m, 2-CH); 3.78 (1H, m, 3-CH) ppm. m/z (%): 242 ($M^+$+$H_2O$-1, 12.3); 225 ($M^+$, 1.3); 224 ($M^+$-1, 5.1)

**(*2S,3S,4R*)-1-morpholino-2,3-dihydroxy-4-azide-5-cyclohexylpentane (18):** 80 mg of pure **17** (0.36 mmol) was dissolved in 8 ml of methanol, 0.2 ml of morpholine (2.3 mmol) was then added. The mixture was stirred at r.t.. After 15 min, the methanol was removed *in vacuo* and the residue was subjected to flash column chromatography to obtain 110.9 mg of pure **16** as a pale viscous oil in quantitative yield. $[\alpha]_D^{25}$ +7.5 (c, 0.74, $CH_2Cl_2$). $\upsilon_{max}$: 3360; 2090; 1450; 1265 $cm^{-1}$. $\delta_H$ ($CDCl_3$): 0.80-1.69 (13H, m, -$CH_2C_6H_{11}$); 2.65 (6H, m, -$N(CH_2)_3$); 2.95 (1H, br, -OH); 3.55 (1H, dd, J=7.9, 2.1 Hz, 3-CH); 3.68 (1H, m, 4-CH); 3.75 (4H, t, J=4.5 Hz, -$O(CH_2)_2$); 3.89 (1H, m, 2-CH) ppm. m/z (%): 312 ($M^+$, 8.1); 311 ($M^+$-1, 21.5); 270 ($M^+$-$N_3$+1, 32.1); 100 (-$CH_2N(CH_2)_4O$, base). HRms: calcd for $C_{15}H_{28}N_4O_3$ 312.2148; Found: 312.2155.

**ACMP(1):** 50 mg of **18** ( 0.16mmol) in 5 ml of methanol was hydrogenated in the presence of 40 mg of 10% Pd/C at 1 atm for 4 hr. The catalyst was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography ($CHCl_3$: MeOH=1:1) to obtain 42.2 mg of ACMP as a syrup in 92% yield. $[\alpha]_D^{25}$ -3.9 (c, 0.35, $CH_3OH$). $\upsilon_{max}$: 3350; 1570; 1460; 1120 $cm^{-1}$. $\delta_H$($CDCl_3$): 0.80-1.78 (13H, m, $CH_2C_6H_{11}$); 2.55-2.68 (6H, m, -$N(CH_2)_3$); 3.25 (1H, m, 3-CH); 3.49 (1H, m, 4-CH); 3.80 (1H, m, 2-CH); 3.70 (7H, m,-$O(CH_2)_2$ , -OH and -$NH_2$) ppm. m/z (%): 287 ($M^+$+1, 32); 186 ($M^+$-$CH_2N(CH_2)_4O$, 45.2); 100 (-$CH_2N(CH_2)_4O$, base)

**Triacetate of ACMP(19):** 20 mg of **1** (0.07 mmol) was dissolved in 1.1 ml of pyridine, and 0.15 ml of acetic anhydride (2.6 mmol) was then added. The mixture was stirred for 24 hr. Removal of solvent gave a residue

which was purified by column chromatography to produce 24.5 mg of triacetate of ACMP in 85% yield. $[\alpha]_D^{25}$ -44.2 (c, 0.72, $CHCl_3$). $\delta_H$ ($CDCl_3$): 0.8-1.8 (13H, m, $CH_2C_6H_{11}$); 1.96, 2.05, 2.10 (9H, 3 s, 3-$COCH_3$); 2.49 (5H, m, -$N(CH_2)_2$ and 1H of $NCH_2$); 2.60 (1H, dd, J=14.5, 5.5 Hz, 1H of -$NCH_2$); 3.65 (4H, t, J=4.6 Hz, -$O(CH_2)_2$); 4.50 (1H, m, -CHNHAc); 5.11 (1H, dd, J=6.5, 3.3 Hz,3-CHOAc); 5.25 (1H, m, 2-CHOAc); 5.42 (1H, d, J=10.3 Hz, -NH) ppm. m/z(%): 413 ($M^+$+1, 1.5); 369; 184; 100.

**Dihydrochloride of ACMP(20):** Hydrogen chloride gas was passed through a solution of 30 mg of **1** (0.10 mmol) in 10 ml of $CHCl_3$ for 10 min. Removal of $CHCl_3$ gave a crude product which was recrystallized from ethanol to obtain 33.5 mg of dihydrochloride of ACMP as white solid with 89% yield. $[\alpha]_D^{25}$ -16.6 (c, 0.7, MeOH) . $\upsilon_{max}$: 3350; 1620; 1450 $cm^{-1}$. $\delta_H$ ($D_2O$): 0.90-1.80 (13H, m, $CH_2C_6H_{11}$); 3.25-3.70 (8H, m, 3-CH, 4-CH and -$N(CH_2)_3$); 3.90-4.28 (5H, m, 2-CH and -$O(CH_2)_2$) ppm. m/z(%): 287 ($M^+$-2HCl, 65.3).

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