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A STEREOSPECIFIC SYNTHESIS OF A RENIN INHIBITOR(BW-175) WHICH INCORPORATES A SULFONEMETHYLENE ISOSTERE AND A DIHYDROXYETHYLENE ISOSTERE.

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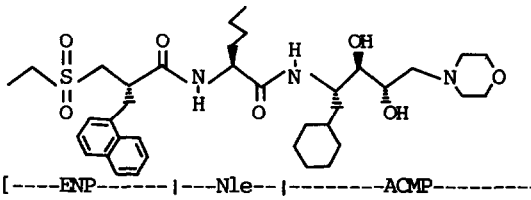
summary: (2S,3R,4S)-4-[L-N-[(2S)-3-ethylsulfonyl-2-(1-naphthylmethyl)-propionyl]norleucyl]amino-5-cyclohexyl-1-morpholino-2,3-pentanediol(BW-175) was synthesized stereospecifically.

In recent years numerous renin inhibitors have been synthesized. Most,however are substrate-analogous peptides containing an isostere of the scissile bond[1] and have several drawbacks such as low oral bioavailability, high susceptibility to proteolytic hydrolysis and rapid biliary excretion. 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, (2S,3R,4S)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol(ACMP) (Fig.1).[2]

Fig. 1 The structure of BW-175



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

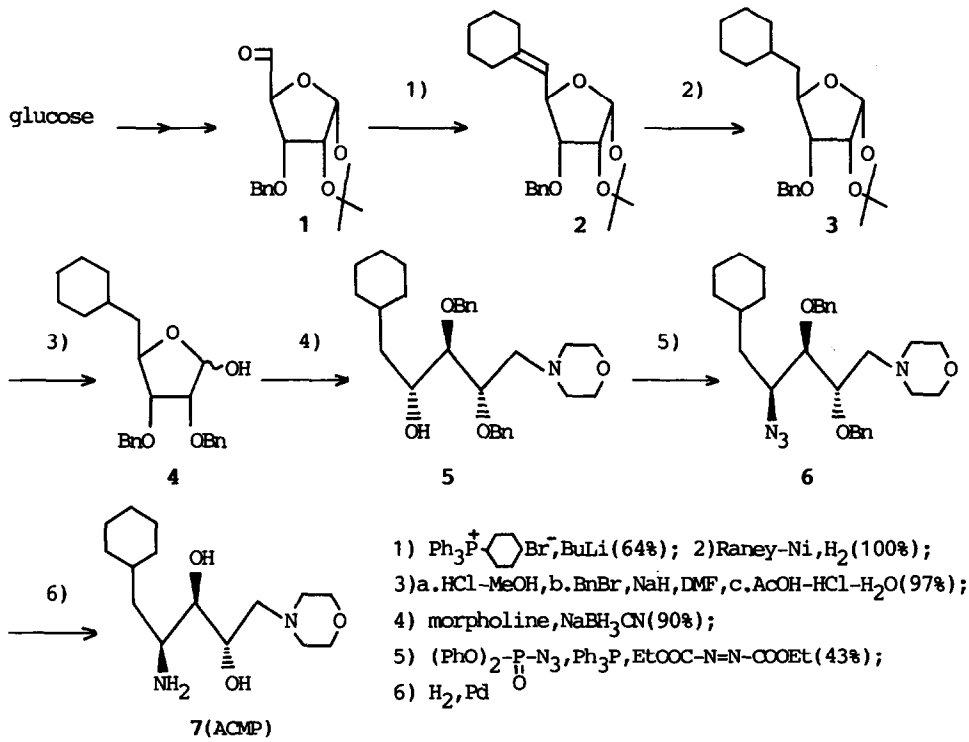
[----ENP------|---Nle--|--------ACMP---------]

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

Nle: L-Norleucine

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 of H.D.Kleinert et al.[3] The C-terminal ACMP of BW-175 was synthesized from 3-O-benzyl-1,2-O-isopropylidene- α -D-ribo-pentodialdo-1,4-furanose(1).[4] The outline was shown in Scheme 1. Compound **1** was readily prepared from D-glucose via 1,2:5,6-di-O-isopropylidene- α -D-allofuranose.[5] The cyclohexyl group was introduced by a Wittig reaction. The aldehyde **1** was treated with the ylide which was prepared from cyclohexyltriphenylphosphonium bromide and n-butyllithium in 1,2-dimethoxyethane.

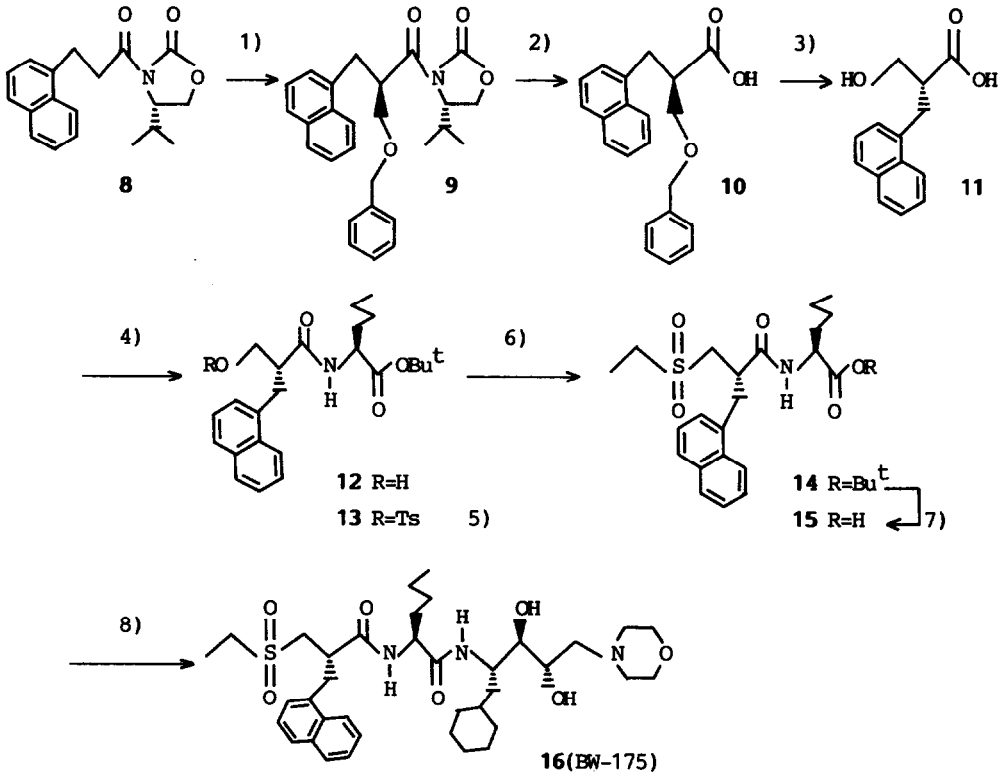
Scheme 1 Stereospecific synthesis of (2S,3R,4S)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol(ACMP).



Selective hydrogenation of the resulted olefine **2** [6] was performed by catalytic hydrogenation over Raney nickel to yield **3**. Treatment of **3** with dry hydrogen chloride in methanol caused the removal of an acetonide protection and methyl glycosidation at the same time. The resulting free hydroxyl group at C-2 was also protected with a benzyl group. Subsequent hydrolysis of the methyl glycoside afforded **4**. The reductive amination of **4** with morpholine hydrochloride and sodium cyanoborohydride afforded the alcohol **5**.[7] The treatment of **5** with diphenylphosphoryl azide in the presence of triphenylphosphine and diethylazodicarboxylate,[8] which is modified conditions of Mitsunobu reaction, formed the azide **6**. Hydrogenation of **6** over palladium black under the atmospheric pressure of hydrogen produced **7**(ACMP).[9]

The N-terminal of BW-175, L-N-[(2S)-3-ethylsulfonyl-2-(1-naphthylmethyl)-propionyl]norleucine(**15**) was synthesized as shown in Scheme 2. 3-(1-Naphthyl)-propionic acid was coupled with Evans's chiral auxiliary [10] to afford **8**.

Scheme 2 Synthesis of the N-terminal sulfonemethylene isostere and BW-175.



1)LDA,  -CH_2-O-CH_2-Br(80%); 2)LiOOH(73%); 3)Pd,cyclohexene,EtOH,reflux(87%); 4)DCC,HOBT(95%); 5)Tos-Cl,pyridine(96%); 6)a.NaSEt,DMF,b.H_2O_2,Na_2WO_4(91%); 7)TFA-CH_2Cl_2(99%); 8)7(ACMP),DPPA,Et_3N(70%)

Asymmetric alkylation was performed by the treatment of **8** with LDA and bromomethyl benzylether which is generated in situ from chloromethyl benzylether.[11] After purification by silica gel column chromatography, the diastereomeric excess value of the purified **9** was determined to be above 99% by HPLC analysis. Crystalline hydroxy acid **11**[12] could be obtained by hydrolysis with lithium hydroperoxide[13] follwed by catalytic transfer hydrogenation using palladium black and cyclohexene as the hydrogen donor.[14] A usual hydrogenation of **10** using palladium black under the atmospheric pressure of hydrogen, afforded a tetralin derivative. Compound **11** was condensed with L-norleucine tert-butyl ester and obtained **12** was p-toluenesulfonylated to give **13**. Compound **13** was treated with sodium thioethoxide in DMF at room temperature and then oxidized with hydrogen peroxide in the presence of sodium tungstate in methanol to yield a sulfone **14**. In

the course of this sequential transformation from **12** to **14**, little racemization took place at the α-position of 3-substituted-2-(1-naphthylmethyl)propionyl moiety. The degree of racemization was determined to be 0.3% by HPLC analysis of **12** and **14**. After treatment of **14** with trifluoroacetic acid, resulted **15** was coupled with **7**(ACMP) by DPPA method[15] to afford **16**(BW-175).[16] Thus, we achieved the stereospecific synthesis of BW-175 which incorporates a dihydroxyethylene isostere at the C-terminal and a sulfonemethylene isostere at the N-terminal.

References and Notes

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6. **2**: ^{1}H-NMR(300MHz,$CDCl_3$) δ 1.35(s,3H),1.58(m,6H),1.64(s,3H),2.13(br,2H),2.29 (br,2H),3.46(dd,1H,J=4.4Hz,8.8Hz),4.53(t,1H,J=4.0Hz),4.63(d,1H,J=12.4Hz),4.73 (d,1H,J=12.4Hz),4.82(t,1H,J=8.9Hz),5.02(dd,1H,J=1.5Hz,8.7Hz),5.70(d,1H,J=3.6Hz), 7.29-7.35(m,5H); mp 62-64°C; $[\alpha]_D^{20}$ -7.2°(c 0.97, $CHCl_3$).
7. **5**: mp 54-56°C; $[\alpha]_D^{20}$ +31.0°(c 1.09, $CHCl_3$).
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16. **16**(BW-175): ^{1}H-NMR(300MHz,$CDCl_3$) δ 0.75-1.05(m,5H),1.05-1.85(m,20H),2.49(m, 2H),2.55-2.95(m,6H),3.01(dd,1H,J=2.0Hz,14.0Hz),3.27-3.76(m,11H),4.25(m,2H),4.63 (br,1H),6.10(d,1H,J=9.3Hz),6.27(d,1H,J=6.1Hz),7.35(dd,1H,J=1.2Hz,7.1Hz),7.42 (t,1H,J=7.6Hz),7.56(m,2H),7.78(d,1H,J=8.1Hz),7.89(dd,1H,J=1.4Hz,7.8Hz),7.99(d, 1H,J=8.7Hz); ^{13}C-NMR(75MHz,$CDCl_3$) δ 6.3,13.8,22.3,26.1,26.2,26.4,27.5,31.9, 32.6,33.6,34.2,35.5,38.3,41.5,47.2,48.2,53.0,54.2(2×C),54.5,63.7,64.1,66.7 (2×C),79.7,122.8,125.3,125.9,126.6,127.3,128.1,129.0,131.3,132.8,133.9,172.4, 172.5; $[\alpha]_D^{20}$ +4.3°(c 0.99, $CHCl_3$); mp 94-97°C.

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