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Synthesis of Renin Inhibitors Containing a Sulfonemethylene Isostere at Their N-Terminals

Masato NAKANO,* Shugo ATSUUMI, Yutaka KOIKE, Seiichi TANAKA, Hiroshi FUNABASHI, Junko HASHIMOTO, Mitsuru OHKUBO, and Hajime MORISHIMA
Chemistry of Natural Products, Exploratory Research Laboratories, Banyu Pharamaceutical Co., LTD. Shimomeguro, Meguro-ku, Tokyo 153

We describe an efficient synthesis of highly active renin inhibitors containing a sulfonemethylene isostere at their N-terminals and a hydroxyethylene isostere at their C-terminals. The stereospecific synthesis of N-terminal key intermediate, L-N-[(2R)-2-benzyl(or 1-naphthylmethyl)-3-hydroxypropionyl]-norleucine t-butyl ester is described.

In the course of our studies of renin inhibitors,[1] we found that some structures which have a sulfonemethylene isostere at the amino terminal showed remarkable activities. Their characteristic amino terminals are L-N-[(2S)-3-alkylsulfonyl(or heteroarylsulfonyl)-2-benzyl(or 1-naphthylmethyl)propionyl]norleucine. A homostatine derivative,[2,3] a hydroxyethylene isostere is located at the C-terminal.[4] These inhibitors are illustrated in Fig.1.[5] In this manuscript we describe the total syntheses of inhibitors(**1a-d**), and the efficient stereospecific syntheses of their N-terminal elements. Initially, L-N-[(2R)-2-benzyl-3-hydroxypropionyl]norleucine t-butyl ester (**7a**) and its diastereomer **6a** were prepared from diethyl malonate(**2**) (Scheme 1, Route A). Half ester **4a** was coupled with L-norleucine t-butyl ester to give a mixture of diastereomers **5a**. Reduction of **5a** with sodium borohydride in ethanol for 6 hours afforded **6a**(36%) and **7a**(32%) which were separated by silica gel chromatography.[6] In the same manner, L-N-[(2R)-3-hydroxy-2-(1-naphthylmethyl)propionyl]norleucine t-butyl ester(**7b**,33%) and its diastereomer (**6b**,44%) were prepared.[7] With respect to the

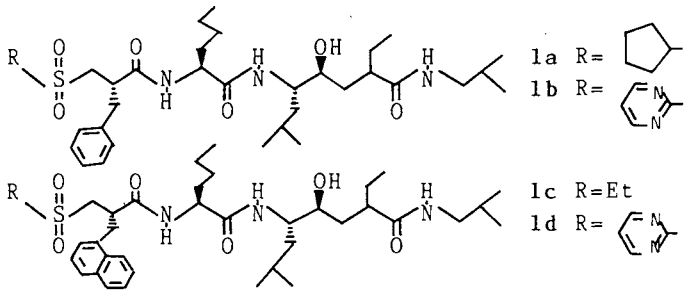
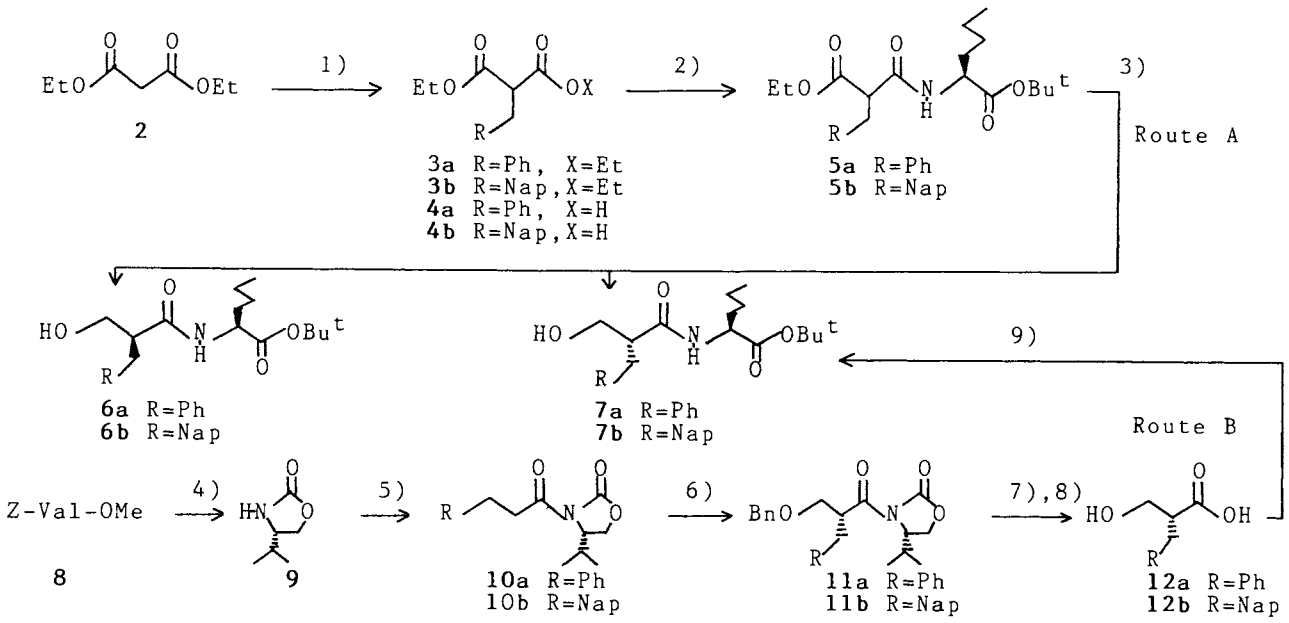


Fig. 1. Renin inhibitors containing a sulfonemethylene isostere.

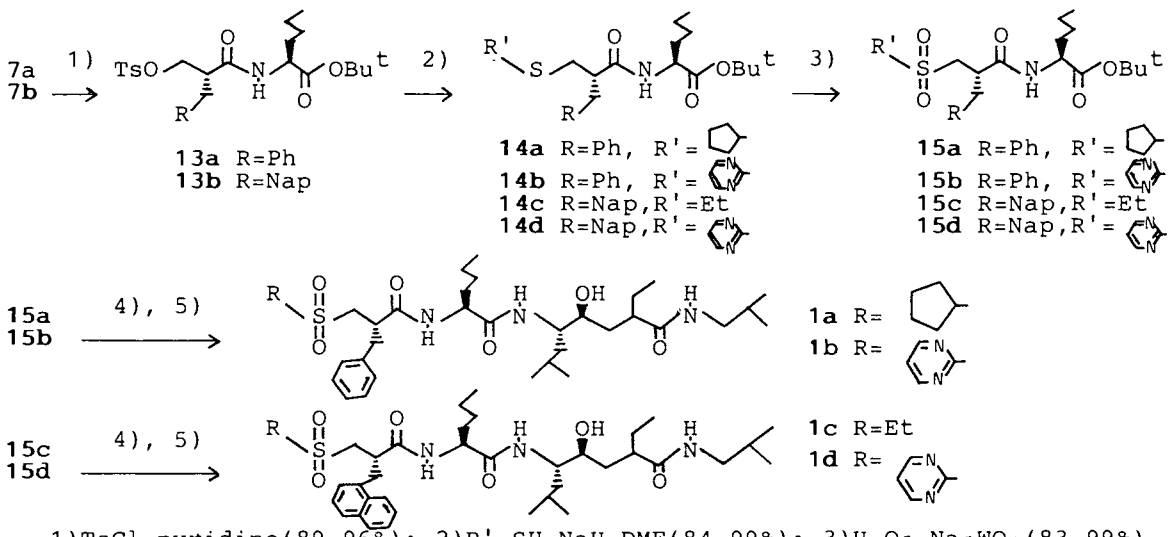


1)NaH,R-CH_2-Br(64%); 2)a.KOH(77%),b.L-Nle-OBu^t,HOBT,DCC or DPPA,Et_3N(88-95%); 3)$NaBH_4$,EtOH; 4)a.$NaBH_4$,b.NaOH(70%); 5)n-BuLi,3-phenylpropionyl chloride(90%); 6)LDA,$BnOCH_2Br$ (90%); 7)LiOOH(98%); 8)H_2/Pd-black(98%), or Pd-black,cyclohexene,EtOH,reflux (87%); 9)HOBT,DCC(86-90%)

Bu^t:tert-butyl, Z-Val-OMe:L-N-benzyloxycarbonylvaline methylester
Bn:benzyl, Ph:phenyl, Nap:1-Naphthyl, DPPA:diphenylphosphorylazide

Scheme 1.

configuration of 2-benzyl(or 1-naphthylmethyl)-3-hydroxypropionic acid, **7a,b** and **6a,b** were determined to be R and S respectively by the stereospecific syntheses shown in Route B. The well-known chiral auxiliary (4S)-4-(1-methylethyl)-2-oxazolidinone(**9**)[8] was readily prepared from **8** by a new method.[9] The resulting phenylpropionyl amide **10a** was treated with LDA and benzyl bromomethyl ether to afford **11a**. This asymmetric alkylation was first reported by Evans et al.,[8,10] and utilized in the synthesis of homostatine by Rich et al.[11] By HPLC analysis, the diastereomeric purity of **11a** was calculated to be 95% after the reaction and 99% after purification by silica gel chromatography. Crystalline hydroxy acid **12a**[12] could be obtained by hydrolysis of **11a** with lithium hydroperoxide,[13] followed by hydrogenation over palladium black at atmospheric pressure. (2R)-Enantiomer **12a** was coupled with L-norleucine t-butyl ester to afford a single diastereomer **7a** without any detectable amount of **6a**. (2R)-3-Hydroxy-2-(1-naphthylmethyl)propionic acid (**12b**) was similarly prepared from **10b**. However, in this case the benzyl ether was cleaved by hydrogenolysis under catalytic transfer hydrogenation, using palladium black and cyclohexene as the hydrogen donor.[14] The naphthyl group in **11b** was expected to suffer reduction to a tetralin compound under the hydrogenation conditions to prepare **12a** from **11a**. After tosylation of **7a,b** using standard conditions, the products **13a,b** were treated with sodium thioalkoxides in DMF at



1)TsCl,pyridine(89-96%); 2)R'-SH,NaH,DMF(84-99%); 3)H_2O_2,Na_2WO_4(83-99%)
4)TFA-CH_2Cl_2(quantitative); 5)homostatine isobutylamide,DPPA,Et_3N(50-70%)

Scheme 2.

room temperature to give sulfides such as **14a-d.** Oxidation of **14a-d** by hydrogen peroxide in the presence of sodium tungstate in methanol, gave sulfones **15a-d** in good yield. During the conversion of **7a,b** to **15a-d,** little racemization took place at the α-position of 2-benzyl(or 1-naphthylmethyl)-3-substituted-propionic acid. For example, the ratio of racemization was calculated to be 0.3% by HPLC analysis of **15a** and **7a.** This racemization appears to occur during the sulfide formation, because the elimination product formed from **13a** can react with thioalkoxide through the Michael addition. After treatment of **15a-d** with trifluoroacetic acid to remove the t-butyl ester, the resulting free acids were coupled with homostatine derivative:[3] (2RS,4S,5S)-5-amino-2-ethyl-4-hydroxy-7-methyloctanoic acid isobutylamide using DPPA.[15] Renin inhibitors **1a-d** are obtained as a mixture of stereoisomers at the 2-position of homostatine. However, these can be separated by HPLC. Thus we established stereospecific syntheses of potent renin inhibitors containing a sulfonemethylene isostere at their N-terminals.

References

1) W. J. Greenlee, Pharmaceutical Research, 4, 364 (1987).
2) P.Herold, R.Duthaler, G.Rihs, and C.Angst, J.Org.Chem., 54, 1178 (1989); P.K. Chakravarty, S.E.de Laszlo, C.S.Sarnella, J.P.Springer, and P.F.Schuda, Tetrahedron Lett., 30, 415 (1989); M.Shinozaki, T.Hata, and Y.Furukawa, ibid., 30, 3669 (1989); R.H.Bradbury, J.M.Revill, J.E.Rivett, and D.Waterson, ibid., 30, 3845 (1989); H.Yanagisawa, T.Kanazaki, and T.Nishi, Chem.Lett., 1989, 687.
3) We synthesized a homostatine derivative starting from natural statine as a mixture of 2R- and 2S-stereoisomers. M.Nakano, S.Atsuumi, Y.Koike, S.Tanaka, H.Funabashi, J.Hashimoto, M.Ohkubo, and H.Morishima, submitted for publication.
4) We have synthesized a sulfonemethylene-containing renin inhibitor, BW-175 which incorporates a dihydroxyethylene isostere at the scissile site.

M. Nakano, S. Atsuumi, Y. Koike, S. Tanaka, H. Funabashi, J. Hashimoto, and H. Morishima, submitted for publication.

5) Recently, a related renin inhibitor which is L-N-[(2S-2-benzyl-3-(t-butylsulfonyl)propionyl]-His-HOMOSTATINE was reported. P. Buhlmayer, et al. J. Med. Chem., 31, 1839 (1988).

6) **6a:** ^{1}H-NMR(300 MHz,$CDCl_3$) δ 0.87(3H,t,J=7.2 Hz),1.08(2H, m),1.25(2H,m),1.44(9H,s) 1.53(1H,m),1.65(1H,m),2.61(1H,m),2.77(1H,dd,J=6.5 Hz,13.7 Hz),3.01(1H,dd,J=9.2 Hz,13.7 Hz),3.20(1H,t,6.5 Hz),3.75(2H,m),4.40(1H,ddd,J=5.4 Hz,7.7 Hz,13.0 Hz), 5.89(br d,1H,J=7.8 Hz),7.18-7.33(5H,m). Mp 117-119 °C. $[\alpha]_D^{20}$ -35.5°(c 1.0, $CHCl_3$). **7a:** ^{1}H-NMR(300 MHz,$CDCl_3$) δ 0.88(3H,t,J=7.1 Hz),1.14-1.38(4H,m),1.45(9H,s),1.63(1H,m),1.79(1H,m),2.59(1H,m),2.75(1H,m),2.88(1H,dd,J=7.8 Hz,14.1 Hz), 3.00(1H,dd,J=7.7 Hz),3.67-3.83(2H,m),4.41(1H,ddd,J=5.9 Hz,7.4 Hz,13.4 Hz),6.15 (1H,br d,J=7.8 Hz),7.18-7.33(5H,m). Mp 108-109 °C. $[\alpha]_D^{20}$ +34.6°(c 1.0,$CHCl_3$).

7) **6b:** ^{1}H-NMR(300 MHz,$CDCl_3$) δ 0.84(3H,t,J=7.4 Hz),0.92(2H,m),1.17(2H,m),1.35-1.55 (2H,m),1.43(9H,s),2.79(1H,m),3.26(2H,m),3.48(1H,dd,J=9.0 Hz,14.1 Hz),3.86(2H,t, J=6.5 Hz),4.36(1H,m),5.74(1H,br d,J=7.8 Hz),7.36(2H,m),7.51(2H,m),7.73(1H,m), 7.86(1H,dd,J=1.5 Hz,8.1 Hz),8.02(1H,dd,J=1.0 Hz,7.8 Hz). Mp 92-94 °C. $[\alpha]_D^{20}$ -72.6°(c 1.0,$CHCl_3$). **7b:** ^{1}H-NMR(300 MHz,$CDCl_3$) δ 0.86(3H,t,J=7.1 Hz),1.13-1.35(4H,m),1.43(s,9H),1.62(1H,m),1.77(1H,m),2.77(2H,m),3.33(1H,dd,J=7.7 Hz, 13.9 Hz),3.49(1H,dd,J=7.5 Hz,13.8 Hz),3.82(1H,m),4.37(1H,ddd,J=5.6 Hz,7.1 Hz, 12.9 Hz),6.12(1H,br d,J=7.2 Hz),7.38(2H,d,J=5.1 Hz),7.52(2H,m),7.74(1H,m),7.86 (1H,dd,J=1.5 Hz,8.1 Hz),8.05(1H,dd,J=0.9 Hz,8.4 Hz). Mp 94-95 °C. $[\alpha]_D^{20}$ +50.5°(c 1.0, $CHCl_3$).

8) D. A. Evans, M. D. Ennis, and D. J. Mathre, J. Am. Chem. Soc., 104, 1737(1982).

9) (4S)-4-(1-methylethyl)-2-oxazolidinone(**9**)
Z-Val-OMe (125 g, 0.47 mol) was reduced with sodium borohydride(107 g, 2.8 mol) in stirring 900 ml ethanol at r.t. for 14 h. After concentration of the solution in vacuo, the residual paste was dissolved in methanol(900 ml) and stirred for 2 h. To the reaction mixture, 400 ml of 3 mol dm^{-3} NaOH(2.5 equiv.) was added and the mixture was stirred for 2.5 h. The solution was adjusted to pH 3 with 6 mol dm^{-3} HCl and then concentrated to a suspension, which was then dissolved in 0.4 L of water. The solution was neutralized with sodium hydrogen carbonate and extracted with dichloromethane successively(4 × 600 ml). After concentration of the organic layer, the residual oil was dissolved in 0.5 mol dm^{-3} sulfuric acid(700 ml) and washed with a mixture of hexane-benzene(100:1, 6 × 700 ml) to remove benzyl alcohol. The aqueous layer was neutralized with sodium hydrogen carbonate and extracted with dichloromethane. The extract was concentrated to a syrup which was allowed to crystallize overnight in a cold room. The resulting crystals were filtered, washed with pentane, and dried yielding 44.5 g(70%) of white crystals. Mp 68-70 °C (lit.[10] mp 69-70 °C). $[\alpha]_D^{20}$ -16.8°(c 5.4, ethanol), lit. $[\alpha]_D^{20}$ -16.6°(c 5.81, ethanol).

10) D. A. Evans, D. J. Mathre, and W. L. Scott, J. Org. Chem., 50, 1830 (1985).

11) M. W. Holladay, F. G. Salituro, and D. H. Rich, J. Med. Chem., 30, 374 (1987).

12) 12a:$[\alpha]_D^{20}$ +14.9°(c 1.11, $CHCL_3$), mp 69 °C. 12b:$[\alpha]_D^{20}$ +34.8°(c 1.16, $CHCl_3$), mp 96-99 °C.

13) D. A. Evans, T. C. Britton, and J.A. Ellman, Tetrahedron Lett., 28,6141(1987).

14) G. Brieger and T. J. Nestrick, Chem. Rev., 74, 567 (1974); S. Hanessian, T. J. Liak, and B. Vanasse, Synthesis, 1981, 396.

15) T. Shioiri, K. Ninomiya, and S. Yamada, J. Am. Chem. Soc., 94, 6203 (1972).

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