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AN EFFICIENT SYNTHESIS OF METHYL *N*-[2-(*R*)-(1-NAPHTHYLMETHYL)-3-(MORPHOLINOCARBONYL)PROPIONYL]-(*S*)-HISTIDINATE, THE KEY SYNTHETIC INTERMEDIATE OF RENIN INHIBITORS

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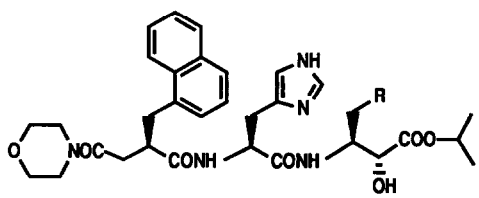
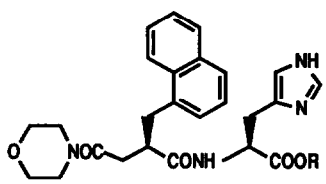
Abstract: Optically pure (*R*)-(1-naphthylmethyl)succinic acid could be efficiently prepared by a combination of optical resolution and racemization of the undesired enantiomer or by catalytic asymmetric reduction of (1-naphthylmethylene)succinic acid over a rhodium (I)-chiral phosphine complex. Highly chemoselective amide formation of di-4-nitrophenyl (*R*)-(1-naphthylmethyl)succinate with morpholine followed by coupling with methyl (*S*)-histidinate readily produced the title key synthetic intermediate.

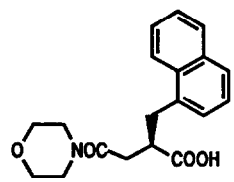
The peptide-like compounds (**1** and **2**) recently explored by Iizuka, *et al.*[1,2] are currently recognized as the promising renin inhibitors which hold promise for treatment of human hypertension. The syntheses of **1** and **2** have been achieved by condensing the following components, *N*-[2-(*R*)-(1-naphthylmethyl)-3-(morpholinocarbonyl)propionyl]-(*S*)-histidine (**3**) produced from the corresponding methyl ester (**4**) by alkaline hydrolysis,[1,2] and (2*R*,3*S*)-norstatine isopropyl ester[1] or (2*R*,3*S*)-cyclohexylnorstatine isopropyl ester.[2,3] The methyl ester (**4**) which constitutes one of the key synthetic intermediates of **1** and **2** was originally prepared by acylation of methyl (*S*)-histidinate [(*S*)-HisOMe] with (*RS*)-2-(1-naphthylmethyl)-3-(morpholinocarbonyl)propionic acid [(*RS*)-**5**] followed by separation of the formed diastereomers.[1] Recentry, it was also disclosed that preparation of **4** could be achieved by condensing (*S*)-HisOMe with (*R*)-**5** obtained by the optical resolution of (*RS*)-**5** with methyl (*S*)-mandelate.[2b-d]



1: R=Me_2CH **2**: R=*c*-C_6H_{11}



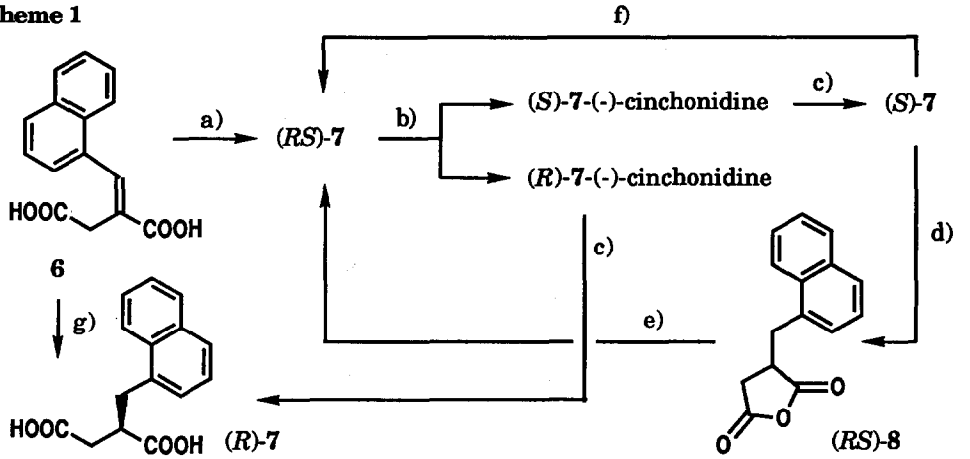
3: R=H **4**: R=Me



(*RS*)- or (*R*)-**5**

With an aim to explore a practical synthetic route to **1** and **2**, a novel preparation method was sought which can afford **4** more effectively than those reported.[1,2] We have now found that optically pure (1-naphthylmethyl)succinic acid [(*R*)-**7**] can be readily synthesized by a combination of optical resolution of (*RS*)-**7** and racemization of undesired (*S*)-**7** or by catalytic asymmetric reduction of (1-naphthylmethylene)succinic acid (**6**) over a rhodium (I) [Rh(I)]-

Scheme 1



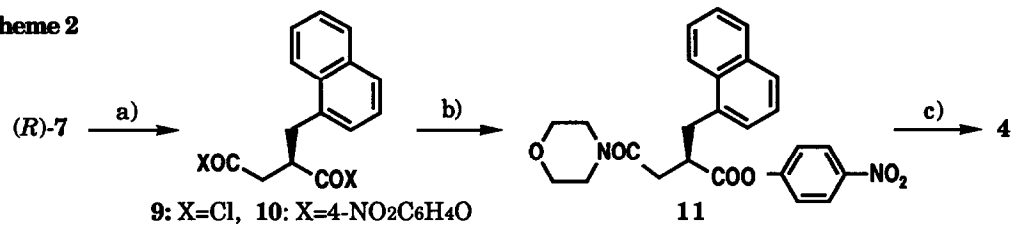
a) H_2-Pd/C in EtOH, 96% b) (-)-cinchonidine (1.0 mol equiv), four repeated recrystallizations from EtOH, 18% [based on (*RS*)-**7**] [(*R*)-**7**-(-)-cinchonidine], concentration of the filtrate obtained from the first recrystallization, 59% [based on (*RS*)-**7**] [(*S*)-**7**-(-)-cinchonidine (47%de)] (see text) c) 1M HCl, 100% d) 250°C in vacuo, 76% e) 1M NaOH, rt, 3h, then 1M HCl 95% or PhMe-H_2O, 90°C, 2d, 98% f) 185°C, 2h, 1M NaOH, 80°C, 1h, then 1M HCl, 97% or 190°C, 2h, then PhMe-H_2O, 100°C, 1d, 92% g) [(+)-BPPM-RhCl] (2.0 mol %)-Et_3N (1.0 mol equiv)-H_2 (1 atm) in MeOH, rt, 20h, 96% [(*R*)-**7**: 85%ee] or [(+)-BPPM-$RhClO_4$] (2.0 mol %)-H_2 (5 atm) in PhH-EtOH (1:3), rt, 20h, 100% [(*R*)-**7**: 87%ee]

chiral phosphine complex. The key synthetic intermediate (**4**) can be effectively elaborated from (*R*)-**7** by highly chemoselective amide formation of di-4-nitrophenyl (*R*)-(1-naphthylmethyl)succinate (**10**) with morpholine followed by coupling with (*S*)-HisOMe.

In view of preparation of a chiral compound bearing single asymmetric center, conventional optical resolution of racemic modification followed by racemization of undesired enantiomer is anticipated to be one of the most practical methods. In order to realize this concept in the synthesis of optically pure (*R*)-**7**, we first examined optical resolution of (*RS*)-**7** followed by racemization of undesired (*S*)-**7**.

As shown in **Scheme 1**, requisite (*RS*)-**7**, mp 184~186°C (*lit.*,[4] mp 183°C), was prepared by catalytic hydrogenation of **6** [(*E*):(*Z*)=14:1][5] obtainable according to the reported procedure.[1a,2] After examinations employing various kinds of chiral amines, we found that a well crystalline salt could be produced by mixing (*RS*)-**7** and (-)-cinchonidine in ethanol. Repeated recrystallizations of the separated salt from the same solvent yielded a pure sample of the (*R*)-**7**-(-)-cinchonidine salt as colorless crystals, mp 198~199°C (decomp.) and $[\alpha]_D^{20}$ -56.6° (c 0.643, MeOH). Concentration of the filtrate obtained from the first recrystallization provided the (*S*)-**7**-(-)-cinchonidine salt as a pale yellow cryatals,[6] 47%de (*vide infra*). Treatments of the (*R*)-**7**- and (*S*)-**7**-(-)-cinchonidine salt with aqueous hydrochloric acid regenerated (*R*)-**7**,[7] mp 162~163°C and $[\alpha]_D^{20}$ +21.8° (c 0.82, MeOH), >98%ee,[8] and partially optically active (*S*)-**7**,[6] 47%ee,[8] respectively. Being different from the previous optical resolution of (*RS*)-**5** in which racemization of undesired (*S*)-**5** had not been attempted,[2b-d] the undesired enantiomer [(*S*)-**7**]

Scheme 2



9: X=Cl, 10: X=4-NO2C6H4O 11

a) $SOCl_2$ (4.0 equiv)-DMF (0.05 equiv), 80 °C, 1h, then 4-$NO_2C_6H_4OH$ (2.1 equiv)-Et_3N (2.5 equiv) in CH_2Cl_2, rt, 8h, 95% b) morpholine (1.0 equiv) in DMF, 0°C, 3h, 97% c) (*S*)-HisOMe-2HCl (1.1 equiv)-Et_3N (2.2 equiv) in DMF, 40°C, 1d, 88%

of low optical purity was found to be readily racemized by way of (*RS*)-(1-naphthylmethyl)succinic anhydride [(*RS*)-**8**]. Thus, heating (*S*)-**7**, 47%ee, at 250°C in vacuo produced completely racemized (*RS*)-**8**, mp 90~91°C. This was treated with water under alkaline or neutral conditions, giving rise to (*RS*)-**7**.[8] Recovery of (*RS*)-**7** from (*S*)-**7** could be achieved more effectively without isolation of intermediate [(*RS*)-**8**] as shown in **Scheme 1**.

As the second method for obtaining (*R*)-**7**, we next examined catalytic asymmetric reduction of **6** over a Rh(I)-chiral phosphine complex.[9] After surveying Rh(I)-complexes modified with various chiral phosphine ligands,[10] we found that [(+)-BPPM-RhCl][11] and [(+)-BPPM-$RhClO_4$][11] complex gave the best results. Thus, catalytic asymmetric hydrogenations of (*E*)-**6**[5] under the conditions shown in **Scheme 1** were found to afford (*R*)-**7**, 85% and 87%ee.[8] In the case where [(+)-BPPM-$RhClO_4$] complex was used, the highest ee value was obtained in the absence of triethylamine under a hydrogen of 5 atmospheric pressure. Since (*RS*)-**7** was prone to crystallize from ethyl acetate faster than (*R*)-**7**, the preparation of (*R*)-**7**, >98%ee,[8] could be readily achieved from (*R*)-**7**, 85%ee, in 66% recovery yield by first removing (*RS*)-**7** by recrystallization from ethyl acetate and then recrystallizing a residual sample from a mixture of ethyl acetate and hexane.

With completion of the synthesis of (*R*)-**7**, we sought an efficient procedure which can convert (*R*)-**7** to **4** by highly chemoselective amide formation of the two carboxyl groups. After experimentations, the preparation of **4** was found to be readily achieved from (*R*)-**7** in 4 steps by way of **10**. Thus, as shown in **Scheme 2**, heating (*R*)-**7** with thionyl chloride ($SOCl_2$) in the presence of *N*,*N*-dimethylformamide (DMF) produced the dichloride (**9**). Without purification, this was treated with 4-nitrophenol in the presence of triethylamine (Et_3N), giving rise to **10**,[12] mp122~123°C and $[\alpha]_D^{20}$ +19.4° (c 1.23, $CHCl_3$). Reaction of **10** with morpholine proceeded in a highly chemoselective manner, resulting in the formation of the monomorpholide (**11**), mp 124~125°C and $[\alpha]_D^{20}$ +81.1° (c 1.90, $CHCl_3$).[13] Coupling of **11** with HisOMe-2HCl could be smoothly effected by mixing the two reactants in the presence of Et_3N to furnish **4** as a colorless caramel, $[\alpha]_D^{20}$ +42.1° (c 1.09, MeOH). Treatment of this caramel with benzene produced the benzene solvate of **4** as colorless crystals, mp 94~96°C and $[\alpha]_D^{20}$ +41.9° (c 1.35, MeOH) [*lit.*,[2d] mp 92-96°C and $[\alpha]_D^{23}$ +35.7° (c 2.2, MeOH)], whose IR and ^{1}H-NMR spectra were identical with those of an authentic sample.[2d,14]

As mentioned above, we have succeeded in exploring an efficient synthetic route to **4**. The developed scheme features not only practical synthesis of (*R*)-**7** by optical resolution or catalytic asymmetric reduction, but also expeditious conversion of (*R*)-**7** to **4** by highly chemoselective amide formation. Taking into account these novel aspects, the overall process may have potential as one of the promising methods applicable to a large scale preparation of **4**.

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References and Notes

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5) The major isomer was tentatively assigned to have (*E*)-configuration based on the ^{1}H-NMR spectra of the dimethyl esters of (*E*)- and (*Z*)-**6** [olefinic proton: (*E*)-dimethyl ester: 8.40 ppm, (*Z*)-dimethyl ester: 7.42 ppm]. Recrystallizations of a mixture of (*E*)-and (*Z*)-**6** (14:1) from MeOH-H2O readily produced a pure sample of the (*E*)-isomer, mp 198~199°C (decomp.).
6) The optical rotation and melting point of this sample were not recorded.
7) The absolute configuration could be determined by the successful synthesis of **4** from this compound.
8) The optical purity of this compound was determined by HPLC (Chiracel OC, Daicel) of the corresponding dimethyl ester provided by treating with trimethylsilyldiazomethane.
9) After completion of our work, Achiwa, *et al.* reported that catalytic asymmetric reductions of methyl 3-carboxy-2-(1-naphthylmethylene)propionate and 2-(1-naphthylmethylene)-3-(morpholinocarbonyl)propionic acid over a Rh(I)-chiral phosphine complex proceeded both with 90%ee. K. Inoguchi, T. Morimoto, and K. Achiwa, *The 35th Symposium on Organometallic Chemistry, Osaka, Japan*, Abstract, p. 334 (1988) and *J. Organomet. Chem.*, **370**, C9 (1989).
10) In addition to (+)-BPPM, we examined (-)-BINAP, (+)-DIOP, (*R,R*)-DIPAMP, (-)-BPPFOH, (-)-BPPFA, (-)-NORPHOS, and (+)-CHIRAPHOS as chiral phosphine ligands. However, attempted catalytic asymmetric reductions using these ligands were found to give rather low optical and/or chemical yields of (*R*)-**7**. For abbreviations of chiral phosphine ligands, see H. B. Kagan, "*Asymmetric Synthesis*", ed. by J. D. Morrison, Academic Press, Vol. 5, p. 1 (1985).
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12) Reaction of **9** with 2,4-dichlorophenol and 2,4,6-trichlorophenol similarly afforded the corresponding diaryl esters. These esters underwent highly chemoselective amide formation the same as **10**.
13) Lower chemoselectivity being at most 3:1 was observed when morpholine was allowed to react with (*RS*)-**8**.
14) The melting point and optical rotation of the benzene solvate of **4** was found to change depending upon the benzene content.

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