A NOVEL SYNTHESIS OF CYCLOHEXYLNORSTATINE ISOPROPYL ESTER, THE C-TERMINAL COMPONENT OF A RENIN INHIBITOR[1)]

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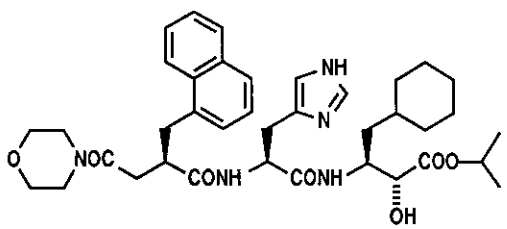
Abstract - The title compound was produced diastereoselectively in racemic and optically active forms by employing the [2+2] cycloaddition reaction of an imine with benzyloxyketene followed by acidic alcoholysis of the formed 3,4-*cis*-disubstituted β-lactam with isopropanol.

Renin is a highly specific aspartic protease which produces angiotensin I from angiotensinogen, and studies on renin inhibitors have been a current area of intense researches aiming at development of a novel antihypertensive agent.[2)] Recently, it was found by Iizuka *et al.* that the peptide-like compound (**1**) shows a strong inhibitory activity against human renin along with chemical and metabolic stability.[3a~e)] The synthesis of **1** could be achieved by sequential condensations of the following three components, (*R*)-2-(1-naphthylmethyl)-3-(morpholin-4-ylcarbonyl)propionic acid,[3)] (*S*)-histidine, and (2*R*,3*S*)-cyclohexylnorstatine isopropyl ester [(2*R*, 3*S*)-**2**].[3a~e)] While (2*R*, 3*S*)-**2** used as the C-terminal component of **1**, had been originally synthesized from (*S*)-phenylalanine by diastereoselective cyanohydrin formation followed by acidic hydrolysis, another preparation method of racemic and/or optically active **2** [(2*R**,3*S**)- and/or (2*R*,3*S*)-**2**] was sought based on a novel synthetic strategy. In this communication we wish to report a diastereoselective synthesis of (2*R**,3*S**)- and (2*R*,3*S*)-**2** in which the [2+2] cycloaddition of an imine with benzyloxyketene constitutes the key diastereoselective reaction.



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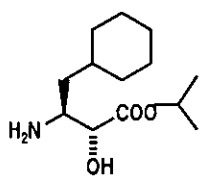
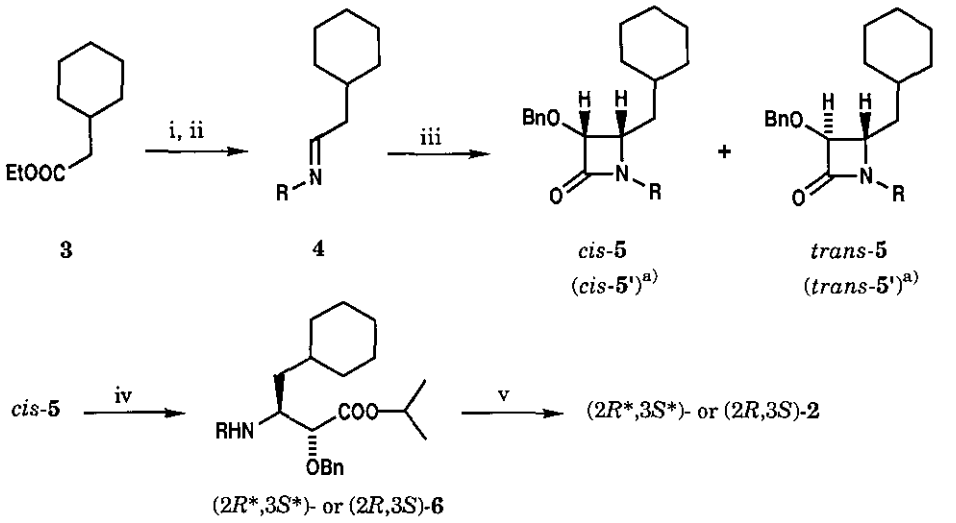


(2*R**,3*S**)- or (2*R*,3*S*)-**2**

It is well recognized that the [2+2] cycloaddition of an imine with a ketene can produce 3,4-*cis*-disubstituted β-lactam in a highly stereoselective manner[4)] and β-lactam is readily susceptible to nucleophilic ring opening due to its enhanced chemical reactivity.[5,6)] Accordingly, we examined the [2+2]



a: R=*p*-MeOC$_6$H$_4$, **b**: R=PhCH$_2$ (Bn), **c**: R=(*p*-MeOC$_6$H$_4$)$_2$CH, **d**: R=(*S*)-PhCHMe

i) DIBAL in Et$_2$O, -78°C, 86% ii) R-NH$_2$, MgSO$_4$ in PhMe (for **4a,b,d**) or in PhH (for **4c**), quantitative yields iii) BnOCH$_2$COCl (1.5 equiv.)-Et$_3$N (5.0 equiv.) in CH$_2$Cl$_2$, 0°C (see **Table**) iv) HCl in *i*-PrOH, 0°C~rt (see **Table**) v) H$_2$-Pd/C (see **Table**)

a) *Cis*-**5'** and *trans*-**5'** represent the other 3,4-*cis*- and 3,4-*trans*-disubstituted β-lactams obtained from **4d** [see text and ref 9)].

Table. Chemical Yields of the [2+2] Cycloaddition Reaction (**4** → **5**), Acidic Alcoholysis [*cis*-**5** → (2*R**,3*S**)- or (2*R*,3*S*)-**6**], and Hydrogenolysis [(2*R**,3*S**)- or (2*R*,3*S*)-**6** → (2*R**,3*S**)- or (2*R*,3*S*)-**2**]a)

Run	R	Yield (%)		
		4 → **5** (cis:trans)	*cis*-**5** → (2*R**,3*S**)- or (2*R*,3*S*)-**6**	(2*R**,3*S**)- or (2*R*,3*S*)-**6** → (2*R**,3*S**)- or (2*R*,3*S*)-**2**
1	*p*-MeOC$_6$H$_4$	30 (1:0)b)	-e)	-e)
2	Bn	41 (1:0)b)	94	95
3	(*p*-MeOC$_6$H$_4$)$_2$CH	94 (11:1)c)	96f)	67i)
4	(*S*)-PhCHMe	84 [(52:32):(10:6)]d)	49g) (94)h)	99

a) The reaction products were racemic expect for run 4. b) Formation of *trans*-**5a,b** could not be detected. c) Determined by weighing the amounts of *cis*-**5c** and *trans*-**5c** separated by column chromatography (SiO$_2$). d) This sample consisted of the four diastereomers [*cis*-**5d**, *cis*-**5'd**, *trans*-**5d** (or *trans*-**5'd**), and *trans*-**5'd** (or *trans*-**5d**)] in a ratio of 52:32:10:6. See text and ref.9). e) The reaction was not examined. f) Yield of (2*R**,3*S**)-**6c** based on *cis*-**5c**. g) Yield of (2*R*, 3*S*)-**6d** based on the mixture of four diastereomers (*cis*-**5d**, *cis*-**5'd**, *trans*-**5d**, and *trans*-**5'd**). h) Yield of (2*R*,3*S*)-**6d** based on *cis*-**5d** involved in **5d**. i) A catalytic amount of hydrogen chloride was added to the reaction mixture to accelerate the hydrogenolysis.

cycloaddition reaction of the imines (**4**) obtainable from cyclohexylacetaldehyde with benzyloxyketene and the subsequent acidic alcoholysis of the produced 3,4-*cis*-disubstituted β-lactams (*cis*-**5**) to prepare (2*R**,3*S**)- and (2*R*,3*S*)-**2** in a highly diastereoselective manner. This synthetic scheme was found to undergo in an expected manner, readily yielding desired (2*R**,3*S**)- and (2*R*,3*S*)-**2**.

The explored synthetic scheme starts with reduction of commercially available ethyl cyclohexylacetate (**3**) with diisobutylaluminium hydride (DIBAL) to cyclohexylacetaldehyde. In order to obtain (2*R**,3*S**)-**2**, cyclohexylacetaldehyde was condensed with achiral primary amines such as *p*-anisidine, benzylamine, and bis(*p*-methoxyphenyl)methylamine in the presence of magnesium sulfate to afford the imines (**4a~c**) in quantitative yields. The [2+2] cycloaddition reactions of **4a~c** with benzyloxyketene *in situ* produced from benzyloxyacetyl chloride in the presence of triethylamine proceeded smoothly, yielding desired *cis*-**5a~c** as major products (**Table**, runs 1~3). Interestingly, the yields and diastereoselectivities were found to largely depend upon the structures of **4a~c**. Thus, *cis*-**5a,b** were obtained from **4a,b** as sole products in rather low yields and formations of the undesired 3,4-*trans*-disubstituted β-lactams (*trans*-**5a,b**) could not be detected. On the other hand, the [2+2] cycloaddition reaction of **4c** gave an excellent yield of the β-lactam mixture where desired *cis*-**5c** was highly predominant (*cis*-**5c**:*trans*-**5c**=11:1). The latter result is quite similar to those observed for the [2+2] cycloaddition reaction of imines with diketene.[7] Conversion of *cis*-**5b,c** into (2*R**,3*S**)-**2** could be readily achieved in 2 steps. Thus, treatments of *cis*-**5b,c** in isopropanol in the presence of hydrogen chloride effected alcoholyses of the β-lactam moieties, producing the racemic β-amino esters [(2*R**,3*S**)-**6b,c**]. Hydrogenolyses of [(2*R**,3*S**)-**6b,c**] cleanly furnished (2*R**,3*S**)-**2**, mp 73~75°C.[8]

With completion of the synthesis of (2*R**,3*S**)-**2**, the chiral imine (**4d**) prepared from cyclohexylacetaldehyde and (*S*)-1-phenylethylamine was subjected to the same [2+2] cycloaddition reaction to obtain (2*R*,3*S*)-**2** (**Table**, run 4). The reaction proceeded smoothly in a similar manner to that for **4c**, to give a mixture of the β-lactams (**5d**) in a high combined yield. The 400 MHz ^{1}H-nmr spectrum of this sample clearly disclosed that it consists of the four diastereomers [*cis*-**5d**, *cis*-**5'd**, *trans*-**5d** (or *trans*-**5'd**), and *trans*-**5'd** (or *trans*-**5d**)] in a ratio of 52:32:10:6.[9] Since these four diastereomers could not be separated by column chromatography (SiO_2), the mixture was directly subjected to the next acidic alcoholysis. Separation of the reaction products by column chromatography (SiO_2) gave the β-amino ester [(2*R*,3*S*)-**6d**] as a major product,[10] $[\alpha]_D^{20}$ -1.5° (c 1.18, $CHCl_3$), in 49% yield based on **5d** (94% based on *cis*-**5d**). Hydrogenolysis of **6d** gave (2*R*,3*S*)-**2**,[10] mp 86~87°C, $[\alpha]_D^{20}$ -22.0° (c 1.08, $CHCl_3$). The HCl salt of (2*R*,3*S*)-**2** prepared by treating with aqueous HCl, was further identified with the authentic sample[3a~e] by spectral comparisons, $[\alpha]_D^{20}$ -9.8° (c 1.24, H_2O) [*lit*,[3b,e] $[\alpha]_D^{23}$ -7.43° (c 2.40, H_2O)].

As mentioned above, we have succeeded in establishing a combination of the [2+2] cycloaddition reaction of an imine with benzyloxyketene and acidic alcoholysis of the formed 3,4-*cis*-disubstituted β-lactam as

one of the promising routes to (2*R**,3*S**)- and (2*R*,3*S*)-**2**. Further studies for improving enantioselectivity of the [2+2] cycloaddition reaction are in progress and will be the subject of forthcoming communication.

References

1) This paper is dedicated to the memory of the late Professor Tetsuji Kametani.

2) J. Boger, *Annual Reports in Medicinal Chemistry*, 1985, **20**, 257.

3) a) K. Iizuka, T. Kamijo, T. Kubota, K. Akahane, H. Harada, I. Shimaoka, H. Umeyama, and Y. Kiso, *"Peptide Chemistry 1987"*, 1988, p. 649. b) T. Kamijo, H. Harada, A. Tsubaki, T. Yamaguchi, A. Iyobe, K. Iizuka, and Y. Kiso, *Japan Kokai Tokkyo Koho,* 1989, *JP* 1-172365. c) K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama, and Y. Kiso, *J. Pharmacobio-Dyn.*, 1989, **12**, s-132. d) K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, H. Umeyama, and Y. Kiso, *J. Chem. Soc. Chem. Commun.*, in press. e) H. Harada, A. Tsubaki, T. Kamijo, K. Iizuka, and Y. Kiso, *Chem. Pharm. Bull.*, in press. f) K. Iizuka, T. Kamijo, T. Kubota, K. Akahane, H. Umeyama, and Y. Kiso, *J. Med. Chem.*, 1988, **31**, 701.

4) W. Dürckheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 180. K. Hirai, *Yuki Gosei Kagaku Kyokai Shi*, 1980, **38**, 97.

5) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1981, **46**, 227.

6) M. S. Manhas, D. R. Wagle, J. Chiang, and A. K. Bose, *Heterocycles*, 1988, **27**, 1755.

7) Y. Ito, T. Kawabata, and S. Terashima, *Tetrahedron Lett.*, 1986, **27**, 5751. T. Kawabata, Y. Kimura, Y. Ito, S. Terashima, A. Sasaki, and M. Sunagawa, *ibid.*, 1986, **27**, 6241.

8) ^{1}H-Nmr ($CDCl_3$): δ 0.7~2.0 (16H, m, *c*-$C_6H_{11}CH_2$, NH_2, OH), 1.29 (6H, d, J=6.4 Hz, $\underline{Me}_2CH$), 3.15 (1H, m, NCH), 3.96 (1H, d, J=2.4 Hz, $\underline{CH}OH$), 5.13 (1H, quint, J=6.4 Hz, $Me_2\underline{CH}$).

9) The mixture of β-lactams (**5d**) showed the following ^{1}H-nmr spectrum. ^{1}H-Nmr ($CDCl_3$): δ 0.6~2.0 (16H, m, *c*-$C_6H_{11}CH_2$ and Me), 3.42 (1Hx0.06, ddd, J=1.6, 4.2, 10.4 Hz, NCH), 3.47 (1Hx0.10, ddd, J=1.6, 4.0, 10.0 Hz, NCH), 3.56 (1Hx0.52, dt, J=4.6, 9.0 Hz, NCH), 3.63 (1Hx0.32, dt, J=4.8, 8.3 Hz, NCH), 4.0~4.9 (4H, m, other protons), 7.2~7.4 (10H, m, Phx2). Based on coupling constants of the C_3- and C_4-positions of β-lactams, $J_{3,4\text{-cis}} > J_{3,4\text{-trans}}$, the major and the minor two products could be assigned to have 3,4-*cis*- and 3,4-*trans*-configurations (*cis*-**5d**+*cis*-**5'd** and *trans*-**5d**+*trans*-**5'd**), respectively. While successful preparation of (2*R*,3*S*)-**6d** from **5d** in 49% yield clearly established that the predominantly produced *cis*-isomer was *cis*-**5d** (*cis*-**5d**:*cis*-**5'd**=52:32), the ratio of *trans*-**5d** to *trans*-**5'd** could not be determined.

10) (2*R*,3*S*)-**6d**: ^{1}H-Nmr ($CDCl_3$): δ 0.4~1.8 (22H, m, *c*-$C_6H_{11}CH_2$ and Mex3), 2.88 (1H, m, NCH), 3.81 (1H, q, J=6.4 Hz, Ph$\underline{CH}$), 3.93 (1H, d, J=3.1 Hz, OCH), 4.35, 4.77 (2H, two d, J=each 12.2 Hz, $PhCH_2$), 5.15 (1H, quint, J=6.2 Hz, $Me_2\underline{CH}$), 7.25, 7.30 (10H, two s, Phx2). (2*R*,3*S*)-**2**: The ^{1}H-nmr spectrum of this compound was identical with that of (2*R**,3*S**)-**2** (see ref.8).

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