

**A NOVEL SYNTHESIS OF CYCLOHEXYLNORSTATINE ISOPROPYL ESTER,
THE C-TERMINAL COMPONENT OF A RENIN INHIBITOR¹⁾**

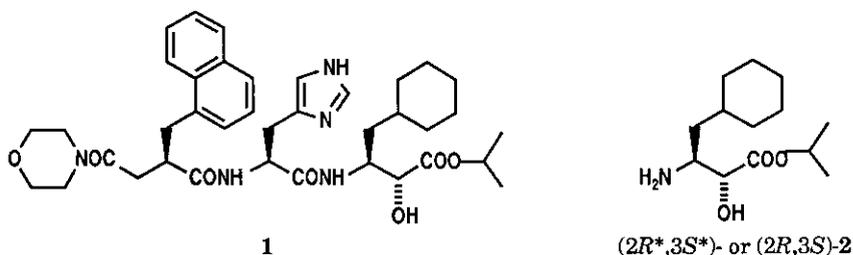
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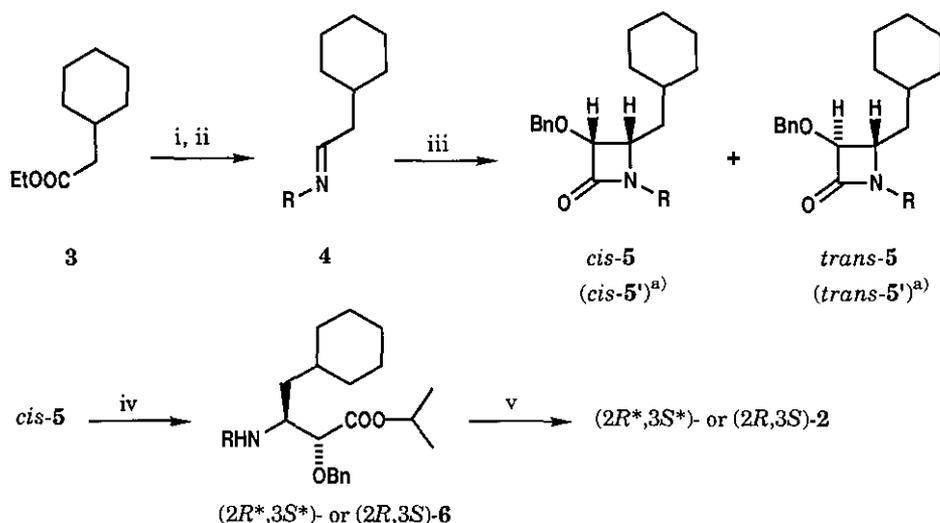
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Abstract - The title compound was produced diastereoselectively in racemic and optically active forms by employing the [2+2] cycloaddition reaction of an imine with benzyloxyketene followed by acidic alcoholysis of the formed 3,4-*cis*-disubstituted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



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 manner⁴⁾ 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*-MeOC₆H₄, b: R=PhCH₂ (Bn), c: R=(*p*-MeOC₆H₄)₂CH, d: R=(*S*)-PhCHMe

i) DIBAL in Et₂O, -78°C, 86% ii) R-NH₂, MgSO₄ in PhMe (for **4a,b,d**) or in PhH (for **4c**), quantitative yields iii) BnOCH₂COCl (1.5 equiv.)-Et₃N (5.0 equiv.) in CH₂Cl₂, 0°C (see **Table**) iv) HCl in *i*-PrOH, 0°C~rt (see **Table**) v) H₂-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* → (*2R**,*3S**)- or (*2R*,*3S*)-**6**], and Hydrogenolysis [(*2R**,*3S**)- or (*2R*,*3S*)-**6** → (*2R**,*3S**)- or (*2R*,*3S*)-**2**]^a

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

a) The reaction products were racemic except 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 (SiO₂). 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 (*2R**,*3S**)-**6c** based on *cis-5c*. g) Yield of (*2R*,*3S*)-**6d** based on the mixture of four diastereomers (*cis-5d*, *cis-5'd*, *trans-5d*, and *trans-5'd*). h) Yield of (*2R*,*3S*)-**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 (*2R**,*3S**)- and (*2R*,*3S*)-**2** in a highly diastereoselective manner. This synthetic scheme was found to undergo in an expected manner, readily yielding desired (*2R**,*3S**)- and (*2R*,*3S*)-**2**.

The explored synthetic scheme starts with reduction of commercially available ethyl cyclohexylacetate (**3**) with diisobutylaluminium hydride (DIBAL) to cyclohexylacetaldehyde. In order to obtain (*2R**,*3S**)-**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 (*2R**,*3S**)-**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 [(*2R**,*3S**)-**6b,c**]. Hydrogenolyses of [(*2R**,*3S**)-**6b,c**] cleanly furnished (*2R**,*3S**)-**2**, mp 73-75°C.⁸⁾

With completion of the synthesis of (*2R**,*3S**)-**2**, the chiral imine (**4d**) prepared from cyclohexylacetaldehyde and (*S*)-1-phenylethylamine was subjected to the same [2+2] cycloaddition reaction to obtain (*2R*,*3S*)-**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 ¹H-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 (SiO₂), the mixture was directly subjected to the next acidic alcoholysis. Separation of the reaction products by column chromatography (SiO₂) gave the β -amino ester [(*2R*,*3S*)-**6d**] as a major product,¹⁰⁾ [α]_D²⁰ -1.5° (c 1.18, CHCl₃), in 49% yield based on **5d** (94% based on *cis*-**5d**). Hydrogenolysis of **6d** gave (*2R*,*3S*)-**2**,¹⁰⁾ mp 86-87°C, [α]_D²⁰ -22.0° (c 1.08, CHCl₃). The HCl salt of (*2R*,*3S*)-**2** prepared by treating with aqueous HCl, was further identified with the authentic sample^{3a-e)} by spectral comparisons, [α]_D²⁰ -9.8° (c 1.24, H₂O) [*lit*]^{3b,e)} [α]_D²³ -7.43° (c 2.40, H₂O)].

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

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- 8) ¹H-Nmr (CDCl₃): δ 0.7~2.0 (16H, m, *c*-C₆H₁₁CH₂, NH₂, OH), 1.29 (6H, d, J=6.4 Hz, Me₂CH), 3.15 (1H, m, NCH), 3.96 (1H, d, J=2.4 Hz, CHOH), 5.13 (1H, quint, J=6.4 Hz, Me₂CH).
- 9) The mixture of β-lactams (**5d**) showed the following ¹H-nmr spectrum. ¹H-Nmr (CDCl₃): δ 0.6~2.0 (16H, m, *c*-C₆H₁₁CH₂ 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 C₃- and C₄-positions of β-lactams, J_{3,4}-*cis*>J_{3,4}-*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**: ¹H-Nmr (CDCl₃): δ 0.4~1.8 (22H, m, *c*-C₆H₁₁CH₂ and Me_{x3}), 2.88 (1H, m, NCH), 3.81 (1H, q, J=6.4 Hz, PhCH), 3.93 (1H, d, J=3.1 Hz, OCH), 4.35, 4.77 (2H, two d, J=each 12.2 Hz, PhCH₂), 5.15 (1H, quint, J=6.2 Hz, Me₂CH), 7.25, 7.30 (10H, two s, Phx₂). (2*R*,3*S*)-**2**: The ¹H-nmr spectrum of this compound was identical with that of (2*R**,3*S**)-**2** (see ref.8).

Received, 15th August, 1989