  Bull. Chem. Soc. Jpn., 59, 525—533 (1986)

Stereoselective Preparation of Acyclic *syn*-β-Amino Alcohols from β-Hydroxy Ketones via the Corresponding *O*-Benzyl Oximes

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(Received October 2, 1985)

Reduction of β-hydroxy ketone *O*-benzyl oximes with lithium aluminum hydride in the presence of sodium or potassium methoxide afforded the corresponding *syn*-β-amino alcohols in highly stereoselective manner. A lythraceae alkaloid, lasubine II, was synthesized stereoselectively by applying this method.

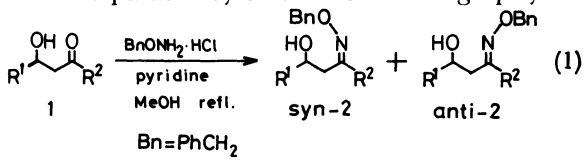
Over the years there have been a large number of efforts directed to control chiral induction in acyclic precursors, and various studies which demonstrate the synthetically useful level of stereocontrol have been published for diastereoselection between adjacent carbon atoms (1,2-relationships).[1] Only a limited number of method, however, have been published to regulate 1,3-chiral induction in acyclic systems,[1b,2,3] leaving this area still in a relatively primitive state of development.

Concerning 1,3-chiral induction of acyclic systems, we have studied and briefly reported the stereoselective preparation of β-amino alcohols from β-hydroxy ketones.[4] In this paper, the results of the stereoselective preparation of *syn*-β-amino alcohols via β-hydroxy ketone *O*-benzyl oximes are reported in detail with the revised mechanism.

Previously one of the authors found that β-hydroxy ketones are stereoselectively reduced with sodium borohydride via boron chelates giving *syn*-1,3-diols.[5] Then we turned our interest to the stereoselective preparation of β-amino alcohols from β-hydroxy imines, hydrazones, or oximes, by stereoselective reduction directed by the hydroxyl group.

Among β-hydroxy imines, hydrazones, and oximes, we chose to use β-hydroxy ketone *O*-benzyl oximes. *O*-Benzyl oximes **2** are readily prepared almost quantitatively from β-hydroxy ketones **1**. They are very stable and easily handled as compared with the corresponding imines. Also it was found that the reactivity of *O*-benzyl oximes toward the reduction with lithium aluminum hydride (LAH) exceeded that of the corresponding dimethylhydrazones.

Various β-hydroxy ketones **1** were prepared by aldol reactions between aldehydes and methyl ketones, and converted to the corresponding *O*-benzyl oximes by the treatment with *O*-benzylhydroxylamine hydrochloride and pyridine in refluxing methanol.[6] The resulting *O*-benzyl oximes **2** were equilibrium mixtures of *syn*- and *anti*-isomers *syn*-**2** and *anti*-**2**,[7] which were separated by column chromatography.



(1)

Then the stereoselectivity of the reduction with LAH was examined based on the following hypothesis. The reaction of **2** with LAH would generate the aluminum alcoholate **3**, and the intramolecular reduction would proceed through cyclic transition states T_1 or T_2 (Fig. 1). The steric interaction between R^1 and R^2 would destabilize the transition state T_2, hence the reduction might be expected to proceed through the transition state T_1 to result in the formation of a *syn*-β-amino alcohol **4**.[8]

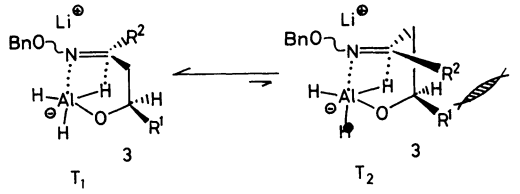
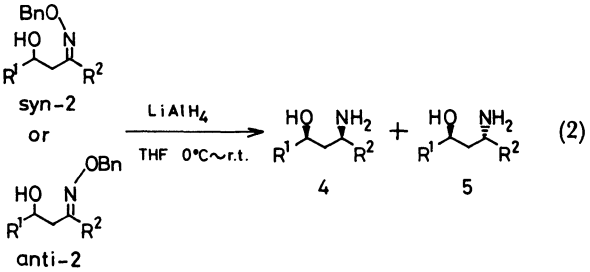


Fig. 1.

Each isomer *syn*-**2** or *anti*-**2** was reduced with an excess amount of LAH in THF between 0 °C and room temperature, and the results are listed in Table 1. From *syn*-*O*-benzyl oximes *syn*-**2**, *syn*-amino alcohols **4** were obtained in high stereoselectivity. In comparison with the high stereoselectivity in the reduction of *syn*-*O*-benzyl oximes *syn*-**2**, the reduction of *anti*-*O*-benzyl oximes *anti*-**2** proceeded only in moderate selectivity. When the reduction of *anti*-*O*-benzyl oxime *anti*-**2a** was tried at lower temperature (ca. −10 °C), the selectivity toward the *syn*-amino alcohol **4a** was found to increase to 89% from 77% but was still not sufficiently high. At the temperature below −10 °C, unfortunately the reduction hardly proceeded.



(2)

During this study, it was found that when sodium methoxide was added to the reaction mixture a significant effect on the stereoselectivity and the acceleration of the LAH reduction was observed. As

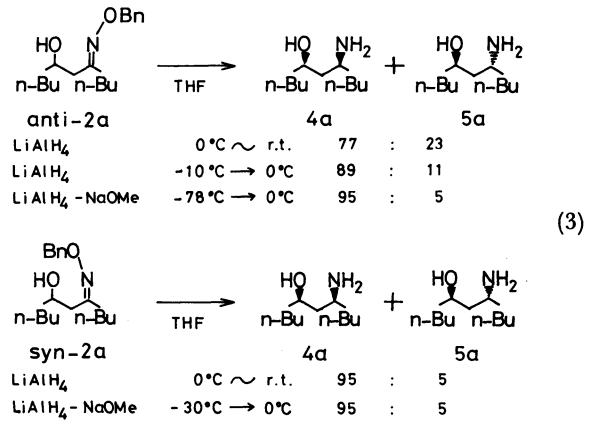
Table 1. Reduction of *O*-Benzyl Oximes **2** with LAH between 0 °C and Room Temperature

	R^1	R^2	Ratio of **4**:**5** from *syn*-**2**	(Total yield/%) from *anti*-**2**
a	*n*-Bu	*n*-Bu	95: 5 (87)[a]	77:23 (96)[a]
b	*i*-Bu	*i*-Bu	95: 5 (77)[a]	77:23 (83)[a]
c	$PhCH_2CH_2$	$PhCH_2CH_2$	91: 9 (85)[b]	79:21 (96)[b]
d	$PhCH_2CH_2$	CH_3	88:12 (78)[c]	78:22 (85)[c]
e	Ph	CH_3	88:12 (74)[c]	85:15 (82)[c]
f	Ph	Ph	85:15 (82)[c]	88:12 (74)[c]

a) Isomeric ratio was determined by GLC (OV-101). b) Isomeric ratio was determined by the isolation of *syn*- and *anti*-amino alcohols. c) Isomeric ratio was determined by the conversion to the corresponding acetates.

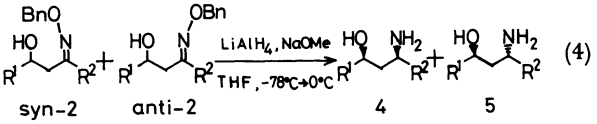
mentioned before, the reduction of *anti*-**2a** with LAH occurred at ca. −10 °C and did not proceed at −78 °C. On the other hand, in the presence of sodium methoxide the LAH reduction of the C=N bond in *anti*-**2a** occurred even at −78 °C. After the reduction of C=N bond in *anti*-**2a** was completed, the reaction temperature was gradually raised to 0 °C to completely convert the resulting half reduced intermediate, *O*-benzylhydroxylamine derivative, to β-amino alcohol and benzyl alcohol. Furthermore, it is important to note that *syn*-amino alcohol **4a** was obtained in excellent stereoselectivity (**4a**:**5a**=95:5) by this procedure (Eq. 3).

The reaction of *syn*-**2a** with LAH was also examined in the presence of sodium methoxide. Although *syn*-*O*-benzyl oxime *syn*-**2a** was scarcely reduced below 0 °C by the treatment with LAH, the presence of sodium methoxide was so effective that the reduction of C=N bond proceeded at −30 °C. And the *syn*-amino alcohol **4a** was also obtained in excellent selectivity (**4a**:**5a**=95:5).



(3)

These results prompted us to examine the prepatation of β-amino alcohol from a mixture of *syn*- and *anti*-*O*-benzyl oxime **2a** by the reduction with LAH–sodium methoxide. A mixture of *syn*- and *anti*-**2a** was treated with 15 molar amounts of LAH in the presence of 10 molar amounts of sodium methoxide at −78 °C. After the consumption of *anti*-**2a** was evidenced by TLC, the reaction temperature was gradually raised to 0 °C and stirred overnight. In excellent stereoselectivity (96%), *syn*-amino alcohol **4a** was obtained. When the reduction was performed employing 7.5 molar amounts of LAH and 5 molar amounts of sodium methoxide, the selectivity was slightly decreased (*syn*-**2a**:*anti*-**2a**=94:6). Further, the reduction did not proceed at −78 °C with 5 molar amount of LAH and 2.5 molar amounts of sodium methoxide. Hence, the reduction of various *O*-benzyl oximes **2** were investigated using 15 molar amounts of LAH and 10 molar amounts of sodium methoxide, and the results are summarized in Table 2. Generally, the selectivity toward *syn*-amino alcohols **4** is quite excellent. Only in the cases that subsituent (R) is (or are) phenyl group(s), the selectivity is decreased but still high.



(4)

The stereochemistry of the products were confirmed by ^{13}C NMR spectra and the conversion of amino alcohols **4** and **5** to cyclic urethanes **8** and **9**. According to the empirical rule of ^{13}C NMR spectra of a β-amino alcohol, the chemical shift of the methine carbon adjacent to the hydroxyl group is observed at the lower field in the case of a *syn*-amino alcohol **4** as compared with an *anti*-isomer **5**.[9]

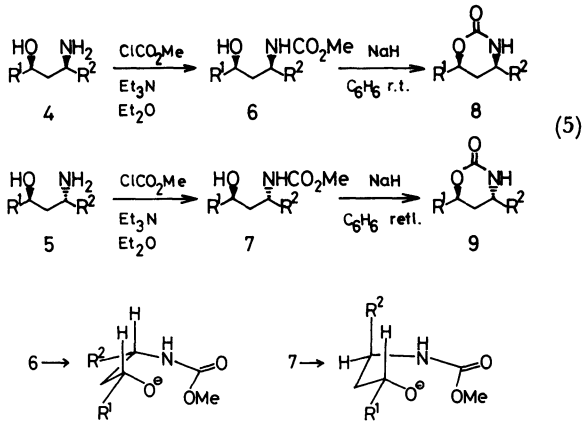
Furthermore, the relative reactivity in the cyclization of urethanes of each isomers **6** and **7** indicated the stereochemistry. Treatment of amino alcohols **4** and **5** with methyl chloroformate and triethylamine gave the corresponding urethanes **6** and **7**, respectively. The *syn*-urethanes **6** were easily converted to the cyclic urethanes **8** at room temperature by treatment with sodium hydride in benzene. On the other hand, the cyclization of *anti*-urethanes **7** did not occurred at room temperature but at the temperature of refluxing benzene. The inferior reactivity of the *anti*-isomers **7** is due to the disfavored transition state of the cyclization in which the R^2 group should orient to the pseudo-axial direction (Fig. 2). The relative stereochemistry of **4e** and **5e** determined by this way was agreed with the stereochemical assignment determined by ^{13}C NMR spectra.[9]

Instead of sodium methoxide, potassium methoxide was also found to be effective for the stereocontrol of

Table 2. Reduction of *O*-Benzyl Oximes **2** with LAH–NaOMe

	R^1	R^2	(*syn*-**2**:*anti*-**2**)	Ratio of **4**:**5** (Total yield/%)
a	*n*-Bu	*n*-Bu	(52:48)	96: 4 (92) 97: 3 (92)[a] 91: 9 (quant.)[b]
b	*i*-Bu	*i*-Bu	(55:45)	95: 5 (92)
c	$PhCH_2CH_2$	$PhCH_2CH_2$	(51:49)	94: 6 (89)
d	$PhCH_2CH_2$	CH_3	(34:66)	97: 3 (94)
e	Ph	CH_3	(28:72)	90:10 (97) 92: 8 (93)[a]
f	Ph	Ph	(82:18)	90:10 (81)

a) Potassium methoxide was used. b) Lithium methoxide was used.

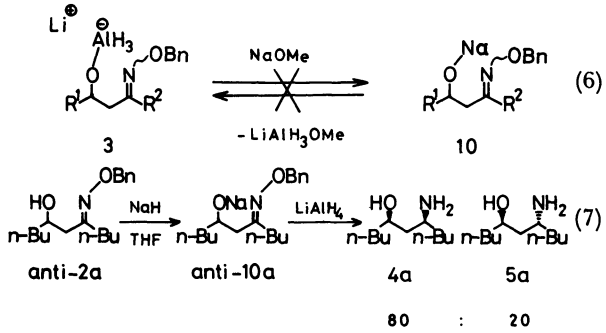


(5)

Fig. 2.

the LAH reduction. However, the slightly inferior selectivity was observed when lithium methoxide was employed (Table 2).

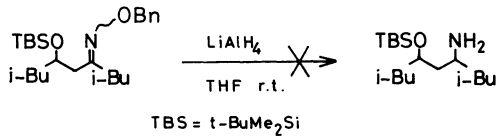
In the previous report,[4b] we supposed that the enhanced selectivity and reactivity by the addition of methoxide may be due to the formation of a sodium alcoholate **10** by an equilibrium between the aluminum alcoholate **3**. In order to ascertain this assumption, the sodium alcoholate *anti*-**10a** generated in situ by treatment of the *anti*-*O*-benzyl oxime *anti*-**2a** with sodium hydride in THF was reduced with LAH. But the reduction did not proceed at −78 °C but −20 to 0 °C, and the products ratio of *syn*- and *anti*-amino alcohols (**4a**:**5a**=80:20) was not so excellent as compared with the result in Table 2. Consequently, it was indicated that the sodium alcoholate **10** is not the actual intermediate in the reduction of *anti*-*O*-benzyl oxime *anti*-**2** in the presence of sodium methoxide.



(6)

(7)

Next, the confirmation of the intramolecular reduction via the intermediate aluminum alcoholate **3** was examined by the reduction of *syn*- and *anti*-*O*-benzyl oximes after the protection of the hydroxyl groups as silyl ethers. The *t*-butyldimethylsilyl ethers of *syn*-**2b** and *anti*-**2b** were treated with LAH, but the reduction did not occur even at room temperature.



(8)

These observations may indicate that the formation of the intermediate aluminum alcoholate **3** is indispensable for the reduction of the C=N bond and the reduction may proceed by the intramolecular fashion as shown in Fig. 1. Coordination of methoxide to the aluminum of this intermediate **3**[10] may increase the nucleophilicity of the hydride, and the reduction proceeds at the lower temperature resulting *syn*-β-amino alcohol **4** in excellent stereoselectivity.

As mentioned, it was noted that the reduction of *O*-benzyl oximes with LAH in the presence of sodium or potassium methoxide provides a highly stereoselective method for the preparation of *syn*-β-amino alcohols starting from β-hydroxy ketones. The present method has a wide applicability to prepare various *syn*-β-amino alcohols because β-hydroxy ketones are readily prepared by directed aldol reactions.[11]

In these years, much efforts have been concentrated in the stereoselective preparation of β-amino alcohols, and several selective methods have been developed by the reduction of isoxazolines[9, 12] and enaminones[3a] the iodocyclocarbamation of a homoallylamine,[3b] the intramolecular Michael addition of *O*-carbamates,[3c] the sulfoxide-mediated intramolecular hydroxylation of a remote olefin,[13] and the Grignard reaction of β-alkoxy imines.[3d] The present method affords the alternative procedure for the preparation of unprotected *syn*-β-amino alcohols.

As an efficient and practical method for the preparation of acyclic *syn*-β-amino alcohols was established, a new synthetic route to a lythraceae alkaloid, lasubine

II,[14] was investigated by applying this method.[15] Lythraceae alkaloids have been generally synthesized by the condensation of isopelletierine with aromatic aldehydes[16] or the [2+3] cycloaddition of tetrahydropyridine *N*-oxide.[17] In our synthetic strategy an acyclic key intermediate, a *syn*-β-amino alcohol **16**, was prepared firstly, and the successive cyclization processes afforded a bicyclic lasubine II (**22**) in a stereoselective manner.

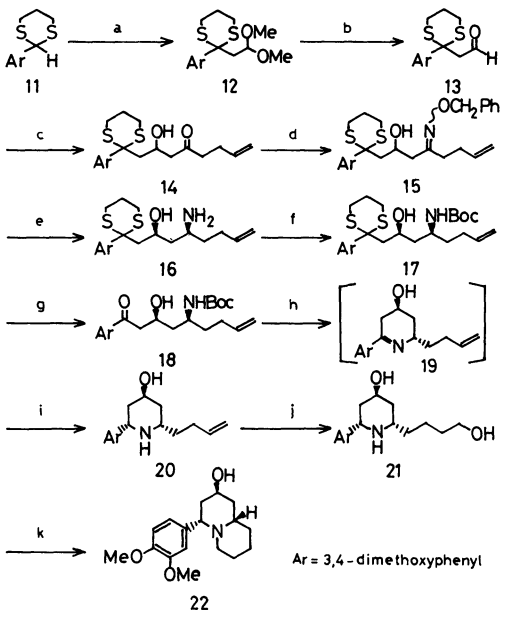
Veratraldehyde was converted to a 1,3-dithiane **11**,[18] which was alkylated with 2-bromo-1,1-dimethoxyethane and the product **12** was hydrolyzed with concd hydrochloric acid to an aldehyde **13**. The aldol reaction between the aldehyde **13** and the kinetic lithium enolate of 5-hexen-2-one afforded a β-hydroxy ketone **14** in 80% yield. At this stage, the whole carbon skeleton required for the synthesis of lasubine II was arranged.

The aldol product **14** was converted to a *O*-benzyl oxime **15** as a mixture of almost equal amount of *syn*- and *anti*-isomers. The *O*-benzyl oxime **15** was reduced with LAH in the presence of potassium methoxide. During this reaction, the reaction temperature should be carefully controlled. After the reduction mixture was stirred at −78 °C overnight, the temperature was gradually raised to −15 °C during 5 h and the mixture was stirred for 12 h at −15 °C. When the reaction temperature was raised above −15 °C, the cleavage of dithioacetal group was observed. After the hydrolysis, the *syn*-β-amino alcohol **16** was isolated in 65% yield.[19]

For the construction of a octahydroquinolizine skeleton, the hydrolysis of dithioacetal group of **16** was investigated but did not afford the fruitful result. Therefore, the amino group of **16** was protected as a *t*-butylcarbamate **17** and then the dithioacetal group was hydrolyzed with *N*-chlorosuccinimide and silver nitrate in aqueous acetonitrile to give a hydroxy ketone **18** in 73% yield. The deprotection of the amino group with trifluoroacetic acid in dichloromethane spontaneously yielded a labile cyclic imine **19**, which was submitted to the successive reduction without isolation. Treatment of **19** with LAH in the presence of sodium methoxide in THF afforded the *cis*-2,6-disubtituted piperidine **20** stereoselectively.[20–22]

Hydroboration of **20** with bis(1,2-dimethylpropyl)-borane and the successive oxidation with alkaline hydrogen peroxide afforded a diol **21**. The regioselective tosylation of the primary hydroxyl group in **21** was carried out employing *p*-toluenesulfonyl chloride and pyridine at −20 °C to give (±)-lasubine II (**22**).

Thus the stereoselective synthesis of lasubine II has been achieved via an acyclic intermediate, demonstrating a new and useful strategy for the preparation of lythraceae alkaloids.



Scheme 1. Total Synthesis of (±)-Lasubine II.
(a): 1) *n*-BuLi, 2) $BrCH_2CH(OMe)_2$; 84%, (b): H_3O^+; 76%, (c): $CH_2=C(OLi)CH_2CH_2CH=CH_2$; 80%, (d) $PhCH_2ONH_2 \cdot HCl$, pyridine; quant., (e): $LiAlH_4$, KOMe; 65%, (f): Boc-S; 77%, (g): NCS, $AgNO_3$, H_2O; 73%, (h): CF_3COOH, (i): $LiAlH_4$, NaOMe; 60% from **18**, (j): 1) bis(1,2-dimethylpropyl)borane; 2) H_2O_2, NaOH; 87%, (k): *p*-TsCl, pyridine; 70%.

Experimental

All the melting points are uncorrected. The IR spectra were determined on a Hitachi Model 260-30 spectrometer. The ^1H NMR spectra were recorded with a Hitachi R-24B, a Varian EM-390, and a JEOL GX-400 spectrometers, and ^{13}C NMR spectra were measured with a JEOL FX-90Q spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. The MS spectra were taken on a JEOL JMS-D300. Benzene was distilled and dried over sodium wire. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl. Pyridine and dichloromethane were distilled from CaH_2 and stored over Molecular Sieve. Purification of products was performed by column chromatography on silica gel (Wakogel C-200 or Merck, Art. 9385 Kieselgel 60, 230—400 mesh), preparative TLC on silica gel (Wakogel B-5F) or on aluminum oxide (Merck, Art. 1103 Aluminiumoxid 60 PF_{254}, Typ E), and Chromatotron on aluminum oxide (Merck, Art. 1092 Aluminiumoxid GF_{254}, Typ E).

β-Hydroxy ketones **1a—f** were prepared by the aldol reaction of kinetic lithium enolates of the corresponding methyl ketones with aldehydes, and purified by column chromatography on silica gel. Further details of the reaction procedure are described in the preparation of **14**.

Preparation of 7-Benzyloxyimino-5-undecanol (2a). A solution of 7-hydroxy-5-undecanone (604 mg, 3.2 mmol) and *O*-benzylhydroxylamine hydrochloride (574 mg, 6.6 mmol) in pyridine (0.5 mL) and methanol (8 mL) was refluxed for 30 min.[6] After the most of methanol was removed in vacuo, water was added to the residue and was extracted with CH_2Cl_2. The separated organic layer was dried over Na_2SO_4 and was

condensed under reduced pressure. Purification by column chromatography on silica gel (hexane:ethyl acetate=15:1, v/v) gave the *syn*-*O*-benzyl oxime *syn*-**2a** (473 mg, 50%) and the *anti*-oxime *anti*-**2a** (431 mg, 46%).[23]

***syn*-7-Benzyloxyimino-5-undecanol (*syn*-2a)**: IR (neat) 3430, 1635 cm^{-1}. ^1H NMR δ=0.60—1.58 (16H, m), 1.93—2.52 (3H, m), 2.30 (1H, d, J=1.6 Hz), 2.42 (1H, d, J=4.0 Hz), 3.48—4.03 (1H, m), 4.93 (2H, s), 7.17 (5H, s).

***anti*-7-Benzyloxyimino-5-undecanol (*anti*-2a)**: IR (neat) 3460, 1635 cm^{-1}. ^1H NMR δ=0.60—1.68 (16H, m), 1.98—2.45 (2H, m), 2.13 (2H, d, J=4.8 Hz), 3.18 (1H, br s), 3.53—4.02 (1H, m), 4.92 (2H, s), 7.17 (5H, s).

Preparation of the other *O*-benzyl oximes **2b—f** was carried out by the same procedure.

***syn*-6-Benzyloxyimino-2,8-dimethyl-4-nonanol (*syn*-2b)**: IR (neat) 3420, 1630 cm^{-1}. ^1H NMR δ=0.80 (12H, d, J=6.2 Hz), 0.95—2.58 (9H, m), 3.57—4.13 (1H, m), 4.92 (2H, s), 7.13 (5H, s).

***anti*-6-Benzyloxyimino-2,8-dimethyl-4-nonanol (*anti*-2b)**: IR (neat) 3440, 1630 cm^{-1}. ^1H NMR δ=0.83 (12H, d, J=6.2 Hz), 0.95—2.02 (4H, m), 2.02—2.32 (4H, m), 3.18 (1H, d, J=3.6 Hz), 3.65—4.18 (1H, m), 4.93 (2H, s), 7.18 (5H, s).

***syn*-5-Benzyloxyimino-1,7-diphenyl-3-heptanol (*syn*-2c)**: IR (neat) 3430, 1630 cm^{-1}. ^1H NMR δ=1.43—1.93 (2H, m), 2.18—2.98 (9H, m), 3.52—4.03 (1H, m), 4.93 (2H, s) 7.02, (10H, s), 7.13 (5H, s).

***anti*-5-Benzyloxyimino-1,7-diphenyl-3-heptanol (*anti*-2c)**: IR (neat) 3430, 1630 cm^{-1}. ^1H NMR δ=1.37—1.88 (2H, m), 2.03 (2H, d, J=6.0 Hz), 2.30—2.92 (6H, m), 3.00—3.30 (1H, m), 3.52—4.12 (1H, m), 4.98 (2H, s), 7.12 (10H, s), 7.24 (5H, s).

***syn*-5-Benzyloxyimino-1-phenyl-3-hexanol (*syn*-2d)**: IR (neat) 3410, 1635 cm^{-1}. ^1H NMR δ=1.35—1.90 (2H, m), 1.77 (3H, s), 2.30—2.85 (5H, m), 3.47—4.02 (1H, m), 4.88 (2H, s), 6.97 (5H, s), 7.07 (5H, s).

***anti*-5-Benzyloxyimino-1-phenyl-3-hexanol (*anti*-2d)**: IR (neat) 3440, 1645 cm^{-1}. ^1H NMR δ=1.37—1.87 (2H, m), 1.70 (3H, s), 2.10 (2H, d, J=6.0 Hz), 2.33—2.82 (2H, m), 2.92—3.15 (1H, m), 3.48—4.03 (1H, m), 4.87 (2H, s), 7.00 (5H, s), 7.09 (5H, s).

***syn*-3-Benzyloxyimino-1-phenyl-1-butanol (*syn*-2e)**: IR (neat) 3400, 1630 cm^{-1}. ^1H NMR δ=1.60 (3H, s), 2.53 (1H, d, J=2.0 Hz), 2.68 (1H, d, J=4.0 Hz), 2.97 (1H, br s), 4.65—5.03 (1H, m), 4.90 (2H, s), 7.12 (5H, s), 7.18 (5H, s).

***anti*-3-Benzyloxyimino-1-phenyl-1-butanol (*anti*-2e)**: IR (neat) 3430, 1640 cm^{-1}. ^1H NMR δ=1.42 (3H, s), 2.43 (2H, d, J=6.4 Hz), 3.40 (1H, d, J=3.0 Hz), 4.83 (1H, dd, J=3.0, 6.4 Hz), 4.95 (2H, s), 7.20 (5H, s), 7.22 (5H, s).

***syn*-3-Benzyloxyimino-1,3-diphenyl-1-propanol (*syn*-2f)**: IR (neat) 3420 cm^{-1}. ^1H NMR δ=2.47 (1H, d, J=6.0 Hz), 3.07 (1H, s), 3.18 (1H, d, J=3.4 Hz), 4.80—5.25 (1H, m), 5.15 (2H, s), 7.00—7.68 (10H, m), 7.28 (5H, s).

***anti*-3-Benzyloxyimino-1,3-diphenyl-1-propanol (*anti*-2f)**: IR (neat) 3430, 1620 cm^{-1}. ^1H NMR δ=2.75 (2H, d, J=6.4 Hz), 3.32—3.50 (1H, m), 4.72—5.07 (1H, m), 4.98 (2H, s), 7.12 (5H, s), 7.15 (5H, s), 7.20 (5H, s).

Stereoselective Reduction of a Mixture of the *O*-Benzyl Oximes *syn*-2a and *anti*-2a. To a THF (135 mL) solution of LAH (30 mmol) and sodium methoxide (1.08 g, 20 mmol) was added a 52:48 mixture of *syn*-**2a** and *anti*-**2a** (total 583 mg, 2 mmol) in THF (6 mL) at −78 °C under an argon atmosphere, and stirred for 6 h at −78 °C. After the complete consumption of *anti*-**2a** was indicated by TLC analysis, the reaction mixture was gradually warmed to 0 °C during 6 h and stirred for 18 h at 0 °C. The mixture was quenched with sat. aqueous sodium sulfate (8.8 mL) and the resulting precipitate was filtered off. The condensed filtrate was purified by preparative TLC on aluminum oxide (CH_2Cl_2: methanol=20:1, v/v) to give *syn*-7-amino-5-undecanol (**4a**) and the *anti*-isomer **5a** (total 343 mg, 92%) in the ratio of 96:4, respectively.

***syn*-7-Amino-5-undecanol (4a)**: IR (neat) 3370, 3300 cm^{-1}. ^1H NMR δ=0.60—1.75 (20H, m), 2.38—3.03 (1H, m), 2.93 (3H, br s), 3.47—3.97 (1H, m). ^{13}C NMR δ=73.00 (>CHOH).

***anti*-7-Amino-5-undecanol (5a)**: IR (neat) 3370, 3300 cm^{-1}. ^1H NMR δ=0.62—1.73 (20H, m), 2.57—3.22 (1H, m), 2.80 (3H, br s), 3.52—4.03 (1H, m). ^{13}C NMR δ=69.13 (>CHOH).

The stereoselective reduction of **2b—f** was carried out by the same procedure, and the elemental analyses were performed after the conversion to the corresponding cyclic urethanes **8** and **9**.

***syn*-6-Amino-2,8-dimethyl-4-nonanol (4b)**: IR (neat) 3370, 3290 cm^{-1}. ^1H NMR δ=0.85 (12H, d, J=6.0 Hz), 0.92—2.02 (8H, m), 2.52—3.02 (1H, m), 3.10 (3H, br s), 3.50—3.98 (1H, m). ^{13}C NMR δ=70.78 (>CHOH).

***anti*-6-Amino-2,8-dimethyl-4-nonanol (5b)**: IR (neat) 3370, 3290 cm^{-1}. ^1H NMR δ=0.83 (12H, d, J=6.2 Hz), 0.92—2.02 (8H, m), 2.85—3.48 (1H, m), 3.10 (3H, br s), 3.48—4.12 (1H, m). ^{13}C NMR δ=66.01 (>CHOH).

***syn*-5-Amino-1,7-diphenyl-3-heptanol (4c)**: IR (neat) 3370, 3290 cm^{-1}. ^1H NMR δ=1.38—2.00 (6H, m), 2.45—3.38 (5H, m), 3.05 (3H, br s), 3.53—4.02 (1H, m), 7.20 (10H, s). ^{13}C NMR δ=72.06 (>CHOH).

***anti*-5-Amino-1,7-diphenyl-3-heptanol (5c)**: IR (neat) 3370, 3300 cm^{-1}. ^1H NMR δ=1.37—1.92 (6H, m), 2.33—2.85 (4H, m), 2.50 (3H, br s), 2.82—3.35 (1H, m), 3.57—4.10 (1H, m), 7.12 (10H, s). ^{13}C NMR δ=68.67 (>CHOH).

***syn*-5-Amino-1-phenyl-3-hexanol (4d) and the *anti*-Isomer 5d**: IR (neat) 3370, 3290 cm^{-1}. ^1H NMR δ=1.03 (3H, d, J=6.0 Hz), 1.17—1.83 (4H, m), 2.43—3.18 (3H, m), 3.05 (3H, br s), 3.43—3.95 (1H, m) 7.08 (5H, s). ^{13}C NMR δ=67.93 (>CHOH, *anti*), 71.29 (>CHOH, *syn*).

The amino alcohol **4d** and **5d** could not be separated by TLC on aluminum oxide. The ratio was determined by the transformation to the corresponding acetates.

General Procedure for Acetylation of Amino Alcohols. To a CH_2Cl_2 (5 mL) solution of a mixture of *syn*- and *anti*-amino alcohols (ca. 100 mg) were added acetic anhydride (0.2 mL), pyridine (0.5 mL) and a catalytic amount of 4-(dimethylamino)pyridine under an argon atmosphere, and the resulting mixture was stirred at room temperature overnight. After evaporation of the excess acetic anhydride, pyridine and CH_2Cl_2 in vacuo, the residue was purified by preparative TLC on silica gel to afford the corresponding acetates.

***syn*-5-Acetamido-3-acetoxy-1-phenylhexane**: IR (neat) 3300, 1735, 1645 cm^{-1}. ^1H NMR δ=1.03 (3H, d, J=6.7 Hz), 1.42—2.12 (4H, m), 1.80 (3H, s), 1.92 (3H, s), 2.30—2.73 (2H, m), 3.50—4.27 (1H, m), 4.53—5.00 (1H, m), 5.80—6.27 (1H, m), 7.08 (5H, s).

***anti*-5-Acetamido-3-acetoxy-1-phenylhexane**: IR (neat) 3290, 1735, 1640 cm^{-1}. ^1H NMR δ=1.05 (3H, d, J=6.8 Hz), 1.45—2.22 (4H, m), 1.88 (3H, s), 1.94 (3H, s), 2.32—2.77 (2H, m), 3.63—4.17 (1H, m), 4.57—5.12 (1H, m), 5.17—5.65 (1H, m), 7.07 (5H, s).

***syn*-3-Amino-1-phenyl-1-butanol (4e) and the *anti*-Isomer 5e**: IR, ^1H NMR, and ^{13}C NMR spectra were identical with

those of lit.[9] IR (neat) 3360, 3280 cm^{-1}. ^{1}H NMR δ=1.13 (3H, d, J=7.2 Hz), 1.50—1.78 (2H, m), 2.67—3.53 (1H, m), 3.17 (3H, br s), 4.91 (1H, dd, J=6.0, 9.6 Hz). ^{13}C NMR δ=71.74 (>CHOH, *anti*), 74.96 (>CHOH, *syn*). The isomer ratio was determined by the conversion to the acetates.

***syn*-3-Acetamido-1-acetoxy-1-phenylbutane**: IR (neat) 3300, 1720, 1645 cm^{-1}. ^{1}H NMR δ=1.08 (3H, d, J=6.6 Hz), 1.58—2.25 (2H, m), 1.85 (3H, s), 2.00 (3H, s), 3.52—3.98 (1H, m), 5.40—5.98 (1H, m), 5.72 (1H, t, J=7.0 Hz), 7.30 (5H, s).

***anti*-3-Acetamido-1-acetoxy-1-phenylbutane**: IR (neat) 3300, 1715, 1640 cm^{-1}. ^{1}H NMR δ=1.08 (3H, d, J=6.8 Hz), 1.70—2.40 (2H, m), 1.82 (3H, s), 2.00 (3H, s), 3.67—4.48 (1H, m), 5.43—5.75 (1H, m), 5.68 (1H, dd, J=8.4, 9.0 Hz), 7.22 (5H, s).

***syn*-3-Amino-1,3-diphenyl-1-propanol (4f) and the *anti*-Isomer 5f**: IR, ^{1}H NMR and ^{13}C NMR spectra were well agreed with those of lit.[9] IR (KBr) 3360, 3280 cm^{-1}. ^{1}H NMR δ=1.65—2.15 (2H, m), 3.12 (3H, br s), 3.82—4.17 (1H, m), 4.62—5.00 (1H, m), 7.12 (5H, s), 7.16 (5H, s). ^{13}C NMR δ=71.78 (>CHOH, *anti*), 74.95 (>CHOH, *syn*). The ratio of *syn* to *anti* was also determined by the transformation to the acetates.

***syn*-3-Acetamido-1-acetoxy-1,3-diphenylpropane**: IR (neat) 3290, 1735, 1645 cm^{-1}. ^{1}H NMR δ=1.62—2.72 (2H, m), 1.80 (3H, s), 1.90 (3H, s), 4.63—5.15 (1H, m), 5.48 (1H, t, J=6.8 Hz), 6.13—6.67 (1H, m), 7.12 (5H, s), 7.17 (5H, s).

***anti*-3-Acetamido-1-acetoxy-1,3-diphenylpropane**: IR (neat) 3320, 1735, 1650 cm^{-1}. ^{1}H NMR δ=1.82 (3H, s), 1.90 (3H, s), 2.03—2.47 (2H, m), 4.73—4.92 (1H, m), 5.55—5.97 (1H, m), 5.62 (1H, dd, J=6.0, 8.4 Hz), 7.17 (10H, s).

Transformation of 4a to *cis*-Cyclic Urethane 8a. To an ether (6 mL) solution of *syn*-amino alcohol **4a** (113 mg, 0.69 mmol) and triethylamine (96 mg, 0.95 mmol) was added dropwise a solution of methyl chloroformate (68 mg, 0.72 mmol) in ether (3 mL) under an argon atmosphere and then stirred for 90 min at room temperature. To the mixture was added ice and the resulting solution was extracted with CH_2Cl_2. The separated organic layer was dried over Na_2SO_4 and condensed under reduced pressure. Purification by preparative TLC on silica gel (hexane: ethyl acetate=1:1, v/v) gave *syn*-7-methoxycarboxylamino-5-undecanol **6a** (113 mg, 76%). Next, a benzene (3 mL) solution of **6a** was added to a suspension of sodium hydride (55% dispersion in mineral oil) (23 mg, 0.52 mmol) in benzene (3 mL) under an argon atmosphere, and the mixture was stirred at room temperature for 3 h. Sat. aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. After being dried over Na_2SO_4, the CH_2Cl_2 solution was condensed in vacuo. The residue was purified by preparative TLC on silica gel (hexane: ethyl acetate=1:1, v/v) to give the cyclic urethane **8a** (90 mg, 70% from **4a**).

***cis*-4,6-Dibutyltetrahydro-2*H*-1,3-oxazin-2-one (8a)**: Mp 73.5—74.5 °C (H_2O–methanol). IR (KBr) 3250, 3130, 1680 cm^{-1}. ^{1}H NMR δ=0.57—2.12 (20H, m), 3.02—3.62 (1H, m), 3.85—4.03 (1H, m), 6.06—6.93 (1H, m). Found: C, 67.85; H, 10.87; N, 6.58%. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57%.

Transformation of 5a to *trans*-Cyclic Urethane 9a. *anti*-Urethane **7a** was obtained by the same procedure for **6a** (quant.). To a suspension of sodium hydride (55% dispersion in mineral oil) (4 mg, 0.08 mmol) in benzene (3 mL) was added a benzene (3 mL) solution of **6a** (18 mg, 0.07 mmol) under an argon atmosphere, and the mixture was refluxed for 30 min. After cooling to room temperature, sat. aqueous NH_4Cl was added and the solution was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and condensed in vacuo. Purification by preparative TLC on silica gel (hexane:ethyl acetate=1:1, v/v) afforded the cyclic urethane **9a** (12 mg, 72% from **5a**).

***trans*-4,6-Dibutyltetrahydro-2*H*-1,3-oxazin-2-one (9a)**: IR (neat) 3260, 3130, 1710 cm^{-1}. ^{1}H NMR δ=0.62—2.27 (20H, m), 3.08—3.60 (1H, m), 3.97—4.47 (1H, m), 5.83—6.17 (1H, m). Found: m/z 213.1689. Calcd for $C_{12}H_{23}NO_2$: M, 213.1727.

Transformation of other amino alcohols **4b—e**, **5b—e** to cyclic urethanes was carried by the same method described above. By the treatment with methyl chloroformate and triethylamine, a mixture of *syn*- and *anti*-β-amino alcohols **4d** and **5d**, **4e**, and **5e** were converted *syn*- and *anti*-urethane **6d** and **7d**, **6e** and **7e**, respectively, which were separated by preparative TLC.

***cis*-4,6-Bis(2-methylpropyl)tetrahydro-2*H*-1,3-oxazin-2-one (8b)**: Mp 94.5—95.0 °C. IR (KBr) 3260, 3130, 1680 cm^{-1}. ^{1}H NMR δ=0.93 (12H, d, J=6.2 Hz), 1.05—2.10 (8H, m), 3.28—3.68 (1H, m), 4.07—4.12 (1H, m), 6.40—6.80 (1H, m). Found: m/z 213.1713. Calcd for $C_{12}H_{23}NO_2$: M, 213.1727.

***trans*-4,6-Bis(2-methylpropyl)tetrahydro-2*H*-1,3-oxazin-2-one (9b)**: IR (neat) 3260, 3135, 1705 cm^{-1}. ^{1}H NMR δ=0.93 (12H, d, J=6.2 Hz), 1.07—2.10 (8H, m), 3.33—3.72 (1H, m), 4.15—4.57 (1H, m), 5.95—6.28 (1H, m). Found: m/z 213.1695. Calcd for $C_{12}H_{23}NO_2$: M, 213.1727.

***cis*-4,6-Diphenethyltetrahydro-2*H*-1,3-oxazin-2-one (8c)**: Mp 112.0—113.0 °C (ether–ethyl acetate). IR (KBr) 3250, 3130, 1705 cm^{-1}. ^{1}H NMR δ=1.65—2.27 (6H, m), 2.50—3.02 (4H, m), 3.18—3.60 (1H, m), 3.93—4.33 (1H, m), 6.85 (1H, br s), 7.22 (10H, s). Found: C, 77.68; H, 7.51; N, 4.52%. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53%.

***trans*-4,6-Diphenethyltetrahydro-2*H*-1,3-oxazin-2-one (9c)**: IR (neat) 3250, 3130, 1705 cm^{-1}. ^{1}H NMR δ=1.55—2.25 (6H, m), 2.48—3.10 (4H, m), 3.28—3.70 (1H, m), 4.10—4.53 (1H, m), 6.48—6.77 (1H, m), 7.19 (5H, s), 7.22 (5H, s). Found: m/z 309.1752. Calcd for $C_{20}H_{23}NO_2$: M, 309.1729.

***cis*-4-Methyl-6-phenethyltetrahydro-2*H*-1,3-oxazin-2-one (8d)**: Mp 121.5—122.5 °C (hexane–toluene). IR (KBr) 3240, 3125, 1700 cm^{-1}. ^{1}H NMR δ=1.22 (3H, d, J=6.0 Hz), 1.28—1.63 (1H, m), 1.73—2.18 (3H, m), 2.67—3.02 (2H, m), 3.28—3.77 (1H, m), 4.02—4.38 (1H, m), 6.97—7.43 (1H, m), 7.23 (5H, s). Found: C, 71.24; H, 7.54; N, 6.29%. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39%.

***trans*-4-Methyl-6-phenethyltetrahydro-2*H*-1,3-oxazin-2-one (9d)**: IR (KBr) 3250, 3140, 1710 cm^{-1}. ^{1}H NMR δ=1.20 (3H, d, J=6.6 Hz), 1.50—2.32 (4H, m), 2.65—2.92 (2H, m), 3.42—3.82 (1H, m), 4.08—4.48 (1H, m), 6.37—6.57 (1H, m), 7.20 (5H, s). Found: m/z 219.1217. Calcd for $C_{13}H_{17}NO_2$: M, 219.1257.

***cis*-4-Methyl-6-phenyltetrahydro-2*H*-1,3-oxazin-2-one (8e)**: Mp 154.0—155.0 °C (benzene), lit, 152—153 °C.[9] IR (KBr) 3240, 3120, 1690 cm^{-1}. ^{1}H NMR δ=1.23 (3H, d, J=6.3 Hz), 1.57—1.92 (1H, m), 1.87—2.33 (1H, m), 3.52—3.93 (1H, m), 5.24 (1H, dd, J=2.1, 11.7 Hz), 6.65 (1H, br s), 7.34 (5H, s).

***trans*-4-Methyl-6-phenyltetrahydro-2*H*-1,3-oxazin-2-one (9e)**: Mp 101.0—102.5 °C. IR (KBr) 3240, 3130, 1725 cm^{-1}. ^{1}H NMR δ=1.27 (3H, d, J=6.3 Hz), 1.73—2.37 (2H, m), 3.32—3.67 (1H, m), 5.46 (1H, dd, J=4.2, 6.8 Hz), 6.61 (1H, br s), 7.33 (5H, s). Found: m/z 191.0940. Calcd for $C_{11}H_{13}NO_2$: M, 191.0945.

Total Synthesis of Lasubine II. 2-(2,2-Dimethoxy-

ethyl)-2-(3,4-dimethoxyphenyl)-1,3-dithiane (12). To a solution of 2-(3,4-dimethoxyphenyl)-1,3-dithiane (**11**)[18] (2.00 g, 7.80 mmol) in THF (40 mL) was added *n*-BuLi (7.15 mmol) in hexane (6.3 mL) at −42 °C under an argon atmosphere was stirred for 2.5 h at −15 °C.[23] At −78 °C a THF (6 mL) solution of 2-bromo-1,1-dimethyoxyethane (1.17 g, 6.50 mmol) was added, and then gradually warmed to 0 °C. After stirred for 24 h at 0 °C, the reaction mixture was quenched with sat. aqueous NH_4Cl and the organic layer was extracted with ether. The separated organic layer was dried over Na_2SO_4 and was condensed under reduced pressure. Purification by column chromatography (hexane:ethyl acetate=5:1, v/v) gave the dimethyl acetal **12** (1.88 g, 84%). ^1H NMR δ=1.69—2.09 (2H, m), 2.12—2.40 (2H, m), 2.50—2.80 (4H, m), 3.13 (6H, s), 3.77 (6H, s), 4.08—4.39 (1H, m), 6.50—6.92 (1H, m), 7.08—7.50 (2H, m).

2-Formylmethyl-2-(3,4-dimethoxyphenyl)-1,3-dithiane (13). To a THF (80 mL) solution of **12** was slowly added concd HCl (20 mL). In a few minutes, the solution was turned to yellow and hydrolysis was completed. The reaction mixture was extracted with ether and the organic layer was washed with 4% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to leave an oily residue. The residue was chromatographed on silica gel with hexane–ethyl acetate (8:1, v/v) as an eluting solvent to yield the aldehyde **13** (1.39 g, 76%). IR (neat) 1720 cm^{-1}. ^1H NMR δ=1.65—2.04 (2H, m), 2.54—2.83 (4H, m), 2.89 (2H, d, *J*=3.6 Hz), 3.76 (6H, s), 6.58—6.80 (1H, m), 7.09—7.40 (2H, m), 9.52 (1H, d, *J*=3.6 Hz). Found: *m/z* 298.0678. Calcd for $C_{14}H_{18}O_3S_2$: M, 298.0695.

2-(2-Hydroxy-4-oxo-7-octenyl)-2-(3,4-dimethoxyphenyl)-1,3-dithiane (14). To a solution of lithium diisopropylamide (5.7 mmol) in THF (50 mL) was added a solution of 5-hexen-2-one (0.50 g, 5.2 mmol) in THF (5 mL) at −78 °C under an argon atmosphere, and the mixture was stirred for 1 min at −78 °C. A THF (5 mL) solution of the aldehyde **13** (1.39 g, 4.5 mmol) was added. Immediately, the reaction mixture was quenched with sat. aqueous NH_4Cl and was extracted with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and condensed under reduced pressure. Purification by column chromatography (hexane : ethyl acetate=3:1—1:1, v/v) gave the β-hydroxy ketone **14** (1.45 g, 80%). IR (neat) 3530, 1710, 1640 cm^{-1}. ^1H NMR δ=1.48—2.83 (15H, m), 3.77 (6H, s), 3.90—4.37 (1H, m), 4.58—5.05 (2H, m), 5.23—5.94 (1H, m), 6.56—6.83 (1H, m), 7.10—7.44 (2H, m). Found: *m/z* 396.1375. Calcd for $C_{20}H_{28}O_4S_2$: M, 396.1427.

***O*-Benzyl Oxime of β-Hydroxy Ketone 14.** A solution of β-hydroxy ketone **14** (1.31 g, 3.3 mmol) and *O*-benzylhydroxylamine hydrochloride (0.63 g, 3.9 mmol) in pyridine (0.6 mL) and methanol (45 mL) was refluxed for 5 h. After removal of the solvents in vacuo, water was added to the residue and was extracted with CH_2Cl_2. The separated organic layer was dried over Na_2SO_4 and was condensed under reduced pressure. Purification by column chromatography on silica gel (hexane: ethyl acetate=2:1, v/v) gave the ca. 1:1 mixture of *syn*- and *anti*-*O*-benzyl oxime **15** (1.66 g, quant.). IR (neat) 3530, 1640 cm^{-1}. ^1H NMR δ=1.57—2.80 (15H, m), 3.70 (6H, s), 3.85—4.25 (1H, m), 4.42—5.00 (2H, m), 4.86 (2H, s), 5.15—5.92 (1H, m), 6.50—6.78 (1H, m), 7.07 (5H, s), 7.10—7.37 (2H, m). Found: *m/z* 501.1961. Calcd for $C_{27}H_{35}NO_4S_2$: M, 501.2006.

***syn*-β-Amino Alcohol 16.** To a suspension of potassium methoxide (5.21 g, 74 mmol) in THF (400 mL) was added a THF (82 mL) solution of LAH (111 mmol) under an argon atmosphere and the mixture was stirred for 15 min at −78 °C. To that solution was added the *O*-benzyl oxime **15** (3.71 g, 7.4 mmol) in THF (100 mL) dropwise and the reaction mixture stirred overnight at −78 °C, then gradually warmed to −15 °C for 5 h, and stirred for 12 h at −15 °C. The reaction was carefully quenched with sat. aqueous Na_2SO_4 (32 mL) and the resulting precipitate was filtered off. The condensed filtrate was purified by Chromatron on aluminum oxide (CH_2Cl_2: methanol=25:1, v/v) to give *syn*-β-amino alcohol **16** (2.94 g, 65%). IR (neat) 3380, 3300, 1640 cm^{-1}. ^1H NMR δ=0.77—1.42 (4H, m), 1.48—2.25 (6H, m), 2.38—2.90 (5H, m), 2.72 (3H, br s), 3.58—4.09 (1H, m), 3.75 (6H, s), 4.57—5.07 (2H, m), 5.29—6.00 (1H, m), 6.60—6.83 (1H, m), 7.12—7.50 (2H, m). ^{13}C NMR δ=24.84, 27.57, 27.74, 29.90, 39.14, 43.53, 51.49, 53.25, 55.80, 55.96, 57.50, 69.15 (>CHOH), 110.81, 112.00, 114.82, 121.27, 134.35, 137.98, 147.87, 148.84. Found: *m/z* 397.1708. Calcd for $C_{20}H_{31}NO_3S_2$: M, 397.1744.

Protection of Amino Alcohol 16 with *t*-Butoxycarbonyl Group. To a CH_2Cl_2 (20 mL) solution of amino alcohol **16** (1.43 g, 3.6 mmol) was added *O*-*t*-butyl *S*-(4,6-dimethyl-2-pyrimidinyl) thiocarbonate (1.74 g, 7.2 mmol) and stirred overnight.[25] The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was chromatographed on silica gel by using hexane–ethyl acetate (1:1, v/v) to give *t*-butoxycarbonylamino alcohol **17** (1.38 g, 77%). IR (neat) 3370, 1700, 1640 cm^{-1}. ^1H NMR δ=1.12—1.73 (4H, m), 1.42 (9H, s), 1.73—2.95 (11H, m), 3.18—4.13 (2H, m), 3.83 (6H, s), 4.40—5.13 (3H, m), 5.37—6.10 (1H, m), 6.68—6.95 (1H, m), 7.28—7.52 (2H, m). Found: *m/z* 497.2244. Calcd for $C_{25}H_{39}NO_5S_2$: M, 497.2269.

Hydroxy Ketone 18. To an acetonitrile (15 mL)–water (1.5 mL) solution of *N*-chlorosuccinimide (178 mg, 1.34 mmol) and silver nitrate (225 mg, 1.50 mmol) was added an acetonitrile (5 mL) solution of **17** (166 mg, 0.33 mmol) at −42 °C and stirred for 1 h at that temperature.[26] To the mixtrure was added sat. aqueous Na_2SO_3 (1 mL) and stirred for 1 min. After addition of sat. aqueous Na_2CO_3 (1 mL), the reaction mixture was stirred for 1 min and brine (1 mL) was added. The resulting precipitate was filtered off and the filtrate was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. Concentration in vacuo and purification by preparative layer chromatography on silica gel (hexane: ethyl acetate=1:1, v/v) gave the hydroxy ketone **18** (99 mg, 73%). IR (neat) 3370, 1690 cm^{-1}. ^1H NMR δ=1.02—2.29 (6H, m), 1.30 (9H, s), 2.85—3.13 (2H, m), 3.57 (1H, br s), 3.77—4.23 (2H, m), 3.76 (6H, s), 4.38—5.04 (3H, m), 5.29—6.00 (1H, m), 6.68 (1H, d, *J*=8.6 Hz), 7.08—7.52 (2H, m). Found: *m/z* 407.2216. Calcd for $C_{22}H_{33}NO_6$: M, 407.2306.

(2S*,4S*,6S*)-6-(3-Butenyl)-2-(3,4-dimethoxyphenyl)-4-piperidinol (20). To a 1:1 mixture of trifluoroacetic acid and CH_2Cl_2 (1 mL) was added the hydroxy ketone **18** (104 mg, 0.23 mmol) at 0 °C. After being stirred for 10 min, the reaction mixture was quenched with 28% aqueous ammonia and extracted with CH_2Cl_2. The extracts were washed with water then brine and immediately condensed in vacuo under 20 °C. The residue, dissolved in THF (5 mL), was added to the suspension of sodium methoxide (175 mg, 3.2 mmol) and LAH (THF soln 1.2 mL, 1.6 mmol) in THF (5 mL) at −78 °C under an argon atmosphere.

The reaction mixture was stirred at −78 °C for 1 h, at −42 °C for 1 h, at −18 °C for 1 h, and at 0 °C overnight.[21] The reaction mixture was quenched with sat. aqueous Na_2SO_4 (0.5 mL) and the resulting precipitate was filtered off. After dried over Na_2SO_4, the filtrate was condensed under reduced pressure and the oily residue was purified by preparative TLC on aluminum oxide (CH_2Cl_2: methanol=40:1 v/v) to furnish *cis*-2,6-disubstituted piperidine **20** (40 mg, 60%). IR (neat) 3400, 1640 cm^{-1}. ^1H NMR δ=1.05—1.90 (6H, m), 1.79 (2H, br s), 1.90—2.34 (2H, m), 2.91—3.42 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 4.01 (1H, dd, J=3.9, 10.2 Hz), 4.18—4.38 (1H, m), 4.75—5.13 (2H, m), 5.52—6.10 (1H, m), 6.71—7.00 (3H, m). ^{13}C NMR δ=30.12, 36.03, 39.03, 41.52, 50.98, 55.55, 55.99, 65.58, 11.57, 111.49, 114.66, 118.91, 137.76, 138.41, 148.25, 149.08. Found: m/z 291.1784. Calcd for $C_{17}H_{25}NO_3$: M, 291.1832.

(2S*,4S*,6S*)-6-(4-Hydroxybutyl)-2-(3,4-dimethoxyphenyl)-4-piperidinol (21). To a THF (0.7 mL) solution of B_2H_6 (1.28 mmol) was added 2-methyl-2-butene (180 mg, 2.56 mmol) in THF (5 mL) at −15 °C and stirred for 2 h at 0 °C under an argon atmosphere.[27] To the mixture was added a THF (6 mL) solution of **20** (93 mg, 0.32 mmol) and stirred for 45 min at that temperature. To the solution were added a few drops of water, then 3 M aqueous NaOH (1 mL (1 M=1 mol dm^{-3})), and 30% hydrogen peroxide (2 mL). After stirred for 1 h the mixture was extracted with chloroform, then washed with 1% aqueous Na_2CO_3, sat. aqueous Na_2SO_3, and brine. The organic layer was dried over Na_2SO_4 and condensed in vacuo. The residue was purified by preparative TLC on aluminum oxide (CH_2Cl_2: methanol=20:1, v/v) to give the diol **21** (86 mg, 87%). IR (neat) 3350 cm^{-1}. ^1H NMR δ=1.03—1.90 (10H, m), 2.18 (3H, br s), 2.68—3.20 (1H, m), 3.26—3.60 (2H, m), 3.70 (3H, s), 3.73 (3H, s), 3.80—4.28 (2H, m), 6.64—6.85 (3H, m). Found: m/z 309.1913. Calcd for $C_{17}H_{27}NO_4$: M, 309.1938.

(±)-Lasubine II (22). To a solution of the diol **21** (86 mg, 0.28 mmol) in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (167 mg, 0.88 mmol) at −20 °C under an argon atmosphere and stirred for 1.5 h at −20 °C. After stirred overnight at 0 °C, the reaction was quenched with ice and extracted with ethyl acetate. The extracts were washed 0.1 M aqueous NaOH, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by preparative TLC on aluminum oxide (CH_2Cl_2 : methanol=20:1) to afford (±)-lasubine II (57 mg, 70%). IR ($CHCl_3$) 3610, 2930 cm^{-1}. ^1H NMR δ=1.26—1.91 (12H, m), 2.39—2.42 (1H, m), 2.69 (1H, d, J=11.60 Hz), 3.31 (1H, dd, J=3.36, 11.60 Hz), 3.86 (3H, s), 3.88 (3H, s), 4.00—4.21 (1H, m), 6.78—6.91 (3H, m). MS, m/z (relative intensity) 291(M^+, 472), 164 (332), 154 (434). Found: m/z 291.1878. Calcd for $C_{17}H_{25}NO_3$: M, 291.1833. ^1H NMR (400 MHz) and IR spectra of the synthetic (±)-lasubine II (**22**) was identical with those of the natural lasubine II. Mass spectrum also completely agreed with those values reported by C. Kibayashi.[17]

The authors are grateful to Professor Teruaki Mukaiyama for valuable discussion during this work. We are indebted to Professor Kaoru Fuji for his kind gift of ^1H NMR (400 MHz) and IR spectra of natural lasubine I and II, and also thank Dr. Tatsushi Murae for performing high-resolution mass spectra.

References

1) a) P. A. Bartlett, *Tetrahedron*, **36**, 2 (1980); b) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); c) "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1984), Vol. 3.

2) P. A. Bartlett and K. K. Jernstedt, *J. Am. Chem. Soc.*, **99**, 4829 (1977); T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, *Tetrahedron Lett.*, **1978**, 2741; D. A. Evans, J. Bartroli, and T. Godel, ibid., **23**, 4577 (1982); M. Hirama and M. Uei, ibid., **23**, 5307 (1982).

3) a) Y. Matsumura, J. Fujiwara, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 6312 (1983); b) Y. F. Wang, T. Izawa, S. Kobayashi, and M. Ohno, ibid., **104**, 6465 (1982); c) M. Hirama, T. Shigemoto, Y. Yamazaki, and S. Ito, ibid., **107**, 1797 (1985); d) Y. Yamamoto, T. Komatsu, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, **1985**, 814.

4) a) K. Narasaka and Y. Ukaji, *Chem. Lett.*, **1984**, 147; b) K. Narasaka, S. Yamazaki, and Y. Ukaji, ibid., **1984**, 2065.

5) K. Narasaka and F. C. Pai, *Chem. Lett.*, **1980**, 1415; *Tetrahedron*, **40**, 2233 (1984).

6) H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969).

7) In this report, the isomer *syn*-**2** whose benzyloxyl group is *syn* to the hydroxyl group is presented as the *syn*-*O*-benzyl oxime, and the other isomer *anti*-**2** is called the *anti*-*O*-benzyl oxime.

8) The relative stereochemistry of β-amino alcohols is presented according to the Masamune's nomenclature using *syn* and *anti* terms; S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, **19**, 557 (1980).

9) V. Jäger and V. Buss, *Justus Leibigs Ann. Chem.*, **1980**, 101.

10) J. W. Akitt and R. H. Duncan, *J. Magn. Reson.*, **15**, 162 (1974).

11) T. Mukaiyama, "Organic Reactions," ed by W. G. Dauben, John Wiley & Sons, Inc., New York (1982), Vol. 28, Chap. 3.

12) A. P. Kozikowski and Y. Y. Chen, *J. Org. Chem.*, **46**, 5248 (1981).

13) F. M. Hauser, S. R. E. Ellenberger, J. C. Clardy, and L. S. Bass, *J. Am. Chem. Soc.*, **106**, 2458 (1984).

14) For the isolation of lasubine II, see: K. Fuji, T. Yamada, E. Fujita, and H. Murata, *Chem. Pharm. Bull.*, **26**, 2515 (1978).

15) Preliminary work of the synthesis of (±)-lasubine II has been briefly reported as a communication: K. Narasaka, S. Yamazaki, and Y. Ukaji, *Chem. Lett.*, **1985**, 1177.

16) W. M. Golebiewski and J. T. Wrobel, "The Alkaloids," ed by R. G. A. Rodrigo, Academic Press, Inc., New York (1981), Vol. 18, Chap. 4.

17) H. Iida, M. Tanaka, and C. Kibayashi, *J. Org. Chem.*, **49**, 1909 (1984) and the references cited therein.

18) H. Raumz, *Arzneim.-Forsch.*, **28**, 2048 (1978).

19) The *anti*-β-amino alcohol was not detectable by ^{13}C NMR spectrum.

20) The *trans*-2,6-disubstituted piperidine was not detectable by ^{13}C NMR spectrum.

21) K. Maruoka, T. Miyazaki, M, Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*,

105, 2831 (1983).

22) Attempt for the preparation of *trans*-2,6-disubsituted piperidine by the reduction of **19** using LAH and trimethylaluminum,[21] however, resulted in affording only *cis*-2,6-disubstituted piperidine **20**.

23) The stereochemical assignment of *syn*- and *anti*-*O*-benzyl oximes was due to the ^{1}H NMR spectra and the transformation to the isoxazolines. In ^{1}H NMR spectra, chemical shifts of methylene protones (-CH(OH)-C$\underline{H_2}$-C=N-) of *syn*-*O*-benzyl oximes *syn*-**2** appears at lower fields than those of *anti*-**2**, see: G. J. Karabatsos and N. Hsi, *Tetrahedron*, **23**, 1079 (1967). The *syn*-isomers *syn*-**2** were transformed to the corresponding isoxazolines by treatment with methanesulfonyl chloride and triethylamine. However, the *anti*-isomers *anti*-**2** were not converted to isoxazolines.

24) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).

25) T. Nagasawa, K. Kuroiwa, K. Narita, and Y. Isowa, *Bull. Chem. Soc. Jpn.*, **46**, 1269 (1973).

26) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).

27) H. C. Brown and A. W. Moerikofer, *J. Am. Chem. Soc.*, **83**, 3417 (1961).