Bull. Chem. Soc. Jpn., **68**, 2103—2111(1995) 2103

Headline Articles

Asymmetric Synthesis of a β-Lactam Framework via the Conjugate Addition of Amidocuprates(I) to Chiral Enoates

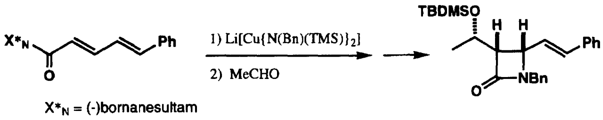
Naoki Asao, Tadao Uyehara,# Naofumi Tsukada, and Yoshinori Yamamoto*

Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980

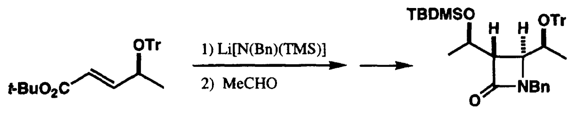
(Received January 27, 1995)

Amidocuprate(I) reagents {Li[Cu(NR_2)$_2$]} and higher order cyanocuprates(I) {Li_2[Cu(CN)(NR_2)$_2$]} have been developed as a new class of nitrogen nucleophiles. These reagents underwent regioselective 1,4-additions to $\alpha,\beta:\gamma,\delta$-dienoates, whereas NHR_2 gave a 1,6-addition product and the lithium reagent $LiNR_2$ afforded a mixture of 1,4- and 1,2-addition products. The amidocuprates(I) were added to chiral $\alpha,\beta:\gamma,\delta$-dienones having a 8-phenyl-*p*-menth-3-yl or a 10,2-bornanesultam chiral auxiliary in order to produce 1,4-adducts in good to high diastereoselectivity. The addition of Li[Cu{N(Bn)(TMS)}$_2$] and Li_2[Cu(CN){N(Bn)(TMS)}$_2$] to 8-phenyl-*p*-menth-3-yl 5-phenyl-2,4-pentadienoate or *N*-(5-phenyl-2,4-pentadienoyl)-10,2-bornanesultam produced an (*R*)-chirality at the β-position. The 1,4-addition of Li_2[Cu(CN){N(Bn)(TMS)}$_2$] to the bornanesultam, followed by trapping with acetaldehyde, gave the α-(1-hydroxyethyl)-β-amino derivative as a single isomer in good yield. This three-component coupling was used in an asymmetric synthesis of a β-lactam.

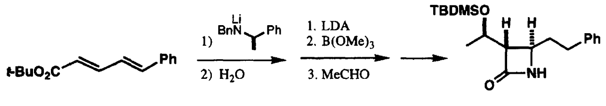
A number of excellent methods for the synthesis of β-lactams including 1β-methylcarbapenems have been developed during the past ten years.[1] We have recently reported on an entirely new approach to the asymmetric synthesis of the β-lactam framework via a three-component coupling (TCC) process using higher order amidocuprates(I);[2] the regioselective conjugate addition of the amidocuprate(I) reagent to certain $\alpha,\beta:\gamma,\delta$-unsaturated esters having chiral auxiliaries, followed by aldol condensation with acetaldehyde and subsequent manipulation, gave the β-lactam with high diastereoisomeric and enantiomeric excess (all in one pot) (Eq. 1). More recently, we have reported on another TCC method using lithium benzyltrimethylsilylamide (LSA);[3] the conjugate addition of LSA to chiral *t*-butyl 4-trityloxy-2-pentenoate, followed by aldol condensation with acetaldehyde and subsequent manipulation, afforded the β-lactam as a single stereoisomer (all in one pot) (Eq. 2). Furthermore, it is demonstrated that a modified TCC procedure using chiral lithium amide reagents is useful for the asymmetric synthesis of certain β-lactams[4] (Eq. 3) and a 1β-methylcarbapenem key intermediate.[5] In these β-lactam syntheses, the chiral center, which induces the asymmetric conjugate addition, is present at the ester part (Eq. 1) at the γ-position (Eq. 2) or at the reagent site (Eq. 3). We now report on a detailed study of previous work related to Eq. 1.



(1)



(2)



(3)

Results and Discussion

Reactions of Metal Amides with Dienoates. The regioselectivities in the reaction of $\alpha,\beta:\gamma,\delta$-unsaturated esters **1** with metal amides are summarized in Table 1. The reactions of **1** with metal amides may provide a mixture of 1,4-(**2**), 1,2-(**3**), 1,2 and 1,4-(**4**), and 1,6-adducts (**5**) (Eq. 4). The reaction using the lithium reagent Li[N(Bn)(TMS)] did not produce a good result; the 1,4-adduct **2a** was obtained in 29% yield along with

---

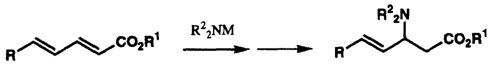
#Present adress: Department of Chemistry, Faculty of Engineering, Utsunomiya University.

Table 1. Reactions of **1** with $\mathrm{MNR^2_2}$[a]

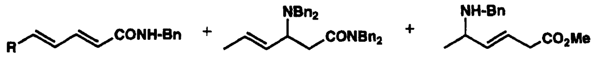
Entry	**1**	$\mathrm{MNR^2_2}$(equiv)	Isolated yield of products/% **2**	**3**	**4**	**5**
1	**1a**	Li[N(Bn)(TMS)] (1.2)	29[b]	18	—	—
2	**1a**	$\mathrm{Li[Cu\{N(Bn)(TMS)\}_2]}$ **6a** (2.0)	54	10	—	—
3	**1a**	Li[N(Bn)(TMS)] (4.0)+cat Cu I (0.2)	60	9	—	—
4	**1a**	$\mathrm{Li_2[Cu(CN)\{N(Bn)(TMS)\}_2]}$ **6b** (2.0)	48	Trace	—	—
5	**1a**	$\mathrm{LiNBn_2}$ (1.2)	—	—	54	—
6	**1a**	$\mathrm{Li[Cu\{NBn_2\}_2]}$ (2.0)	32	—	68	—
7	**1a**	Li[NH(Bn)] (1.2)	—	37[b]	—	—
8	**1a**	$\mathrm{Li[Cu\{NH(Bn)\}_2]}$ (2.0)	—	87	—	—
9[c]	**1a**	$\mathrm{NH_2Bn}$ (2.0)	—	—	—	48
10	**1b**	$\mathrm{Li[Cu\{N(Bn)(TMS)\}_2]}$ (2.0)	68	Trace	—	—
11	**1c**	$\mathrm{Li[Cu\{N(Bn)(TMS)\}_2]}$ (2.0)	60	10	—	—
12	**1d**	$\mathrm{Li[Cu\{N(Bn)(TMS)\}_2]}$ (2.0)	85	—	—	—
13	**1e**	$\mathrm{Li[Cu\{N(Bn)(TMS)\}_2]}$ (2.0)	78	Trace	—	—

a) Reactions were carried out at −78 °C except for Entry 9. b) Several unidentified products were formed in addition to major products. c) The Reaction was carried out at room temperature. Abbreviation: Bn=$\mathrm{CH_2C_6H_5}$, TMS=$\mathrm{SiMe_3}$.

the 1,2-adduct **3a** (Entry 1). The reaction of **1a** with copper reagents gave **2a** with relatively good 1,4-regioselectivity (Entries 2—4); the cuprate-type **6a** (Entry 2) and a higher order cyanocuprate type **6b** (Entry 4) reagent produced a similar regioselectivity. "Higher order" indicates that the stoichiometry of N(Bn)(TMS), Cu, CN, and Li is 2 : 1 : 1 : 2; it does not mean that the copper species possesses the $\mathrm{Li_2[Cu(CN)\{N(Bn)(TMS)\}_2]}$ structure.[6] CuI was used as a source of Cu for the cuprate-type reagent, and CuCN was used for the higher order type reagent. In Entries 1—4, the TMS group of $\mathrm{M[NR^2_2]}$ was removed during the workup process; $\mathrm{NR^2_2}$ of **2** was NH(Bn). Lithium dibenzylamide gave the 1,2- and 1,4-adduct **4** (Entry 5), and the corresponding cuprate reagent afforded a mixture of **2b** and **4** (Entry 6). Lithium benzylamide (Entry 7) and lithium bis(benzylamido)cuprate(I) (Entry 8) produced the 1,2-adduct **3a**. The 1,6-adduct **5** was obtained in the reaction of **1a** with benzylamine (Entry 9). These results suggested that the cuprate reagent **6a** of lithium benzyl(trimethylsilyl)amide might be promising for a regioselective 1,4-addition to $\alpha,\beta:\gamma,\delta$-dienoates. The effect of an ester group upon the regioselectivity of conjugate addition was examined using the cuprate reagent **6a**. The 1,4-adducts **2c**, **2e**, and **2f** were obtained exclusively in the case of a sterically bulky ester group (Entries 10, 12, and 13), whereas the 1,2-adduct **3b** was afforded as a minor product in the case of methyl ester (Entry 11, see also Entry 2). Judging from the results of Entries 12 and 13, the isopropyl ester seemed to give a better yield and regioselectivity than the *t*-butyl ester. Accordingly it is clear that: (1) a dienoate gives the 1,6-adduct **5** with $\mathrm{NH_2Bn}$, the 1,4-adduct **2** with the cuprate reagent **6a** of Li[N(Bn)(TMS)], and a mixture of **2**, **3**, and **4** with the lithium reagents, and that (2) the presence of an *i*-Pr group in $\mathrm{R^1}$ diminishes the formation of the 1,2-adduct.



	R	R′		R	$\mathrm{R^1}$	$\mathrm{R^2}$
1a;	Me	Me	**2a**;	Me	Me	Bn and H
b;	Me	t-Bu	**b**;	Me	Me	Bn and Bn
c;	Ph	Me	**c**;	Me	t-Bu	Bn and H
d;	Ph	i-Pr	**d**;	Ph	Me	Bn and H
e;	Ph	t-Bu	**e**;	Ph	i-Pr	Bn and H
f;	Me	i-Pr	**f**;	Ph	t-Bu	Bn and H



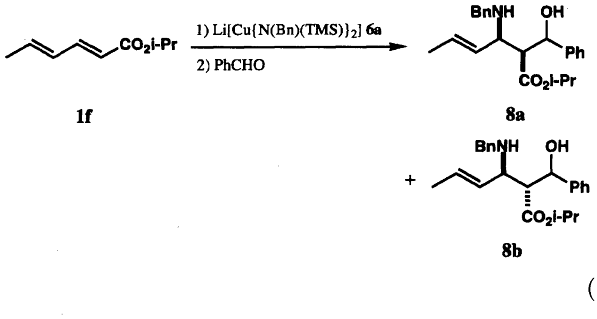
3a; R=Me
b; R=Ph

4

5

(4)

Three-Component Coupling (TCC) Process. Test Case. We next tested whether three-component coupling is effective with **6a**.[7] The conjugate addition of **6a** to **1f**, followed by trapping with PhCHO, gave the desired coupling product **8** in 77% yield as a mixture of two diastreomers **8a** and **8b** (Eq. 5). The ratio of **8a**/**8b** was 48 : 52, although the stereochemistry at –CH(OH)– could not be determined at this stage. A treatment of **8a** and **8b** with KOH/MeOH–$\mathrm{H_2O}$, followed by ring closure with 2-chloro-1-methylpyridinium iodide,[8] gave **9a** and **9b** respectively (Eq. 6).

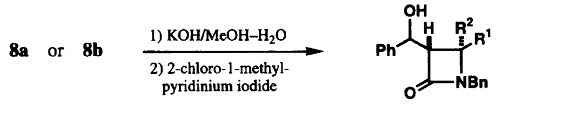


1f

8a

8b

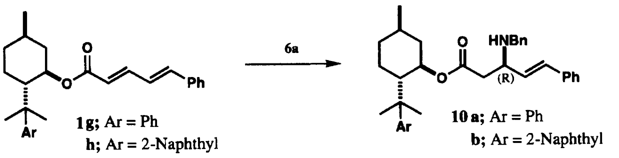
(5)



9a; R^1= CH$_3$CH=CH, R^2= H
9b; R^1= H, R^2= CH$_3$CH=CH

(6)

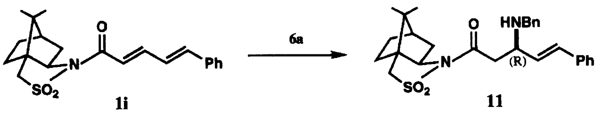
Guided by this result, we examined the asymmetric synthesis with **6a**. The conjugate addition of **6a** to **1g** gave **10a** in 80% yield with 72% de, and **1h** produced **10b** in 95% yield with 74% de (Eq. 7). The addition to **1i** afforded **11** in 78% yield with 90% de (Eq. 8). The diastereomer ratios of **10a**, **10b**, and **11** were determined by their ^{1}H NMR spectra.



1g; Ar = Ph
h; Ar = 2-Naphthyl

10a; Ar = Ph
b; Ar = 2-Naphthyl

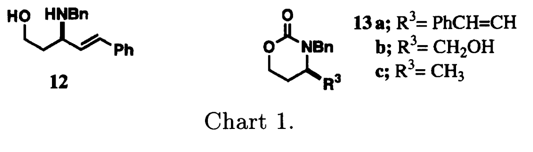
(7)



1i **11**

(8)

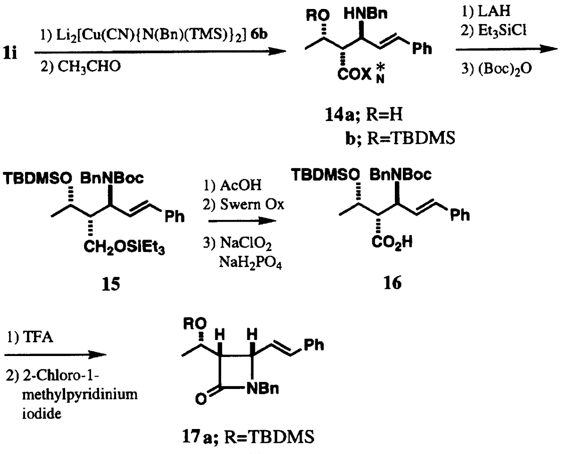
The absolute configuration at the *β*-position of **10a** was determined to be (*R*) by the following procedure. An LAH reduction of **10a** (62%de) gave **12** (62%ee) in 88% yield (Chart 1). The reaction of **12** (62%ee) with trichloromethyl chloroformate afforded **13a** in 97% yield, which was treated with O$_3$/NaBH$_4$ to give **13b** in 65% yield. The treatment of **13b** with CBr$_4$/PPh$_3$, followed by Bu$_3$SnH, gave **13c** (50%ee) in 30% yield. Accordingly, starting from **12** (62%ee, enantiomer ratio=81 : 19), **13c** (50%ee, enantiomer ratio=75 : 25) was obtained, indicating that slight racemization took place during this conversion. At the present time, it is not clear which process is responsible to this racemization. A comparison of **13c** with an authentic material, prepared from (*S*)-3-(benzylamino)-1-butanol,[9] led to the assignment of the (*R*) configuration for **10a**. The absolute configuration of **11** was determined similarly. It is noteworthy that the (*R*) configuration is produced in the amidocuprate(I) addition, whereas the opposite absolute stereochemistry is produced in a high-pressure-induced reaction of NHR$_2$.[10] The "higher order" reagent Li$_2$[Cu(CN){N(Bn)(TMS)}$_2$] **6b** gave similar results. However, the aldehyde trapping reaction proceeded more smoothly and clearly with the higher order reagent **6b** than the trapping reaction using **6a**. During our investigation, it was reported that some chiral lithium amides undergo conjugate addition to enoates with high de.[11] Although we carried out aldehyde trapping with these reagents, a mixture of several products was obtained.



13a; R^3= PhCH=CH
b; R^3= CH$_2$OH
c; R^3= CH$_3$

Chart 1.

Asymmetric Synthesis of a *β*-Lactam via a TCC Process. Finally, three-component coupling was carried out with **1i**. The conjugate addition of the "higher order" reagent to **1i**, followed by trapping with acetaldehyde, and subsequent protection of the hydroxy group with *t*-butyldimethylsilyl chloride (TBDMSCl), gave **14b** as a single isomer in 71% overall yield from **1i**. No other diastereomers were detected! Since the free hydroxy form **14a** was unstable, protection was needed prior to isolation and purification. The reduction of **14b** with LAH gave the corresponding alcohol (deprotection of the bornanesultam X^*_N[12]) in 60% yield. Protection of the alcohol with Et$_3$SiCl and the NH with (Boc)$_2$O produced **15** in 60% yield. Selective deprotection of the Et$_3$Si group followed by Swern oxidation and NaClO$_2$ oxidation afforded **16** in 68% yield. Removal of Boc with TFA followed by a standard cyclization procedure[8] gave **17** in 65% yield. Thus, three contiguous chiral centers can be precisely controlled in good yields by the three-component coupling process. Although the absolute stereochemistry of **17** does not correspond to natural *β*-lactams, a known technology[1d] can convert it into the correct configuration.



14a; R=H
b; R=TBDMS

15 **16**

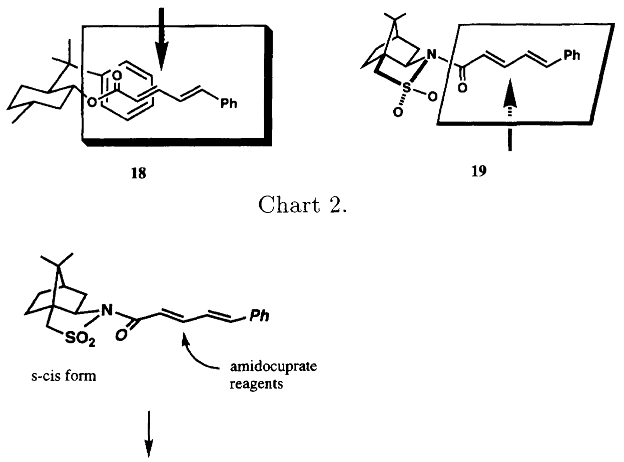
17a; R=TBDMS
b; R=H

(9)

Reaction Course. It is widely accepted that enoate-Lewis acid complexes prefer the *s-trans* conformation not only in the ground state, but also in the transition state of the reactions involving those complexes.[13] On the other hand, the relative populations of the *s-cis* and *s-trans* conformers of uncomplexed methyl cinnamate are almost equal in the isolated molecule at very low temperature and in solution at room and low temperatures.[13] It has been clarified that the conjugate addition of metal amides to uncomplexed enoates proceeds predominantly through the *s-cis* conformation, and that most organocopper conjugate additions in the absence of Lewis acids or related metal salts take place preferentially in the *s-cis* conformation.[13] Since **10a** (*R*-isomer) and **11** (*R*-isomer) are obtained from **1g** and **1i**, respectively, the addition of the amide cuprate reagent takes place via the *s-cis* geometries of the (−)-8-phenyl-*p*-menth-3-yl ester **18** and the *N*-(2,4-pentadienoyl)-10,2-bornanesultam **19**. The reagent attacks the β-carbon of **18** from the direction shown by an arrow, and that of **19** from the bottom side of a plane occupied by the dienoate (see an arrow at Chart 2). The conjugate addition of $Li_2[Cu(CN)\{N(Bn)(TMS)\}_2]$ to the *s-cis* form **19** would give the (*Z*)-type enolate **20**, in which the metal M (either Li or Cu) would chelate the nitrogen and oxygen atoms to form a six-membered ring. It is established that the conjugate addition of a lithium amide to an enoate produces the corresponding (*Z*)-enoate.[14] The reaction of **20** with acetaldehyde would proceed as shown in **21**: A carbonyl oxygen would be chelated to M (and/or M′). This transition-state geometry would lead to the aldol condensation product **22**, which is equivalent to **14a** (Scheme 1).

Experimental

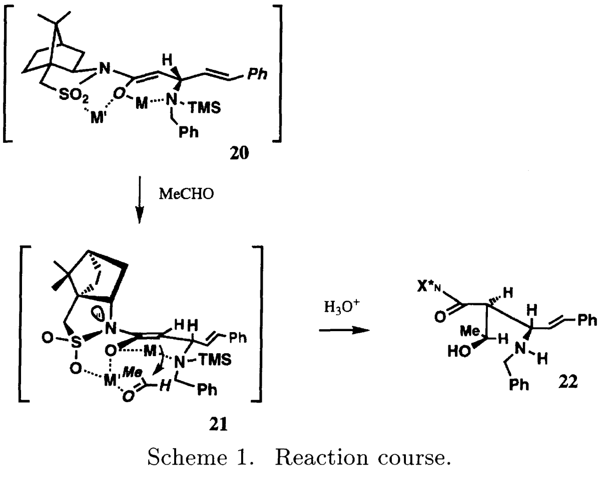
General Remarks. The ^{1}H NMR spectra were recorded using JEOL GSX-270, GX-400 and Bruker AM-600 instruments with tetramethylsilane as an internal standard. The chemical-shift values were recorded as parts per million and the coupling constants as hertz. The IR spectra were recorded with Hitachi 215 and Hitachi 260-10 spectrophotometers. The mass spectra were recorded with Hitachi M-52, JEOL DX-303 and JMS-HX110 spectrometers. The optical rotations were determined at the sodium D line with a JASCO DIP-370 polarimeter. The melting points were determined using a Yamato MP-21 capillary melting-point apparatus, and are uncorrected. All of the solvents were dried before use. Diethyl ether and THF were dried by distillation from sodium and benzophenone. Dichloromethane, toluene, benzene were dried by distillation from phosphorus pentaoxide. Butyllithium in hexane was purchased from Kanto Chemical and standardized by titration. *N*-(Trimethylsilyl)benzylamine and other amines were prepared according to literature procedures.[15]



18

19

Chart 2.



20

21

22

Scheme 1. Reaction course.

Procedure for the Reaction of a Copper Amide Reagent (6a) with $\alpha,\beta:\gamma,\delta$-Unsaturated Esters. The preparation of **2e** is representative. To a solution of *N*-(trimethylsilyl)benzylamine (0.4 mL, 2.0 mmol) in THF (2 mL) at −78 °C was slowly added *n*-BuLi (1.2 mL, 1.62 M in hexane (1 M=1 mol dm^{-3}), 2.0 mmol). After stirring for 30 min, CuI (190 mg, 1.0 mmol) was added and stirred for an additional 30 min at −78 °C. To the mixture was added a solution of **1d** (115 mg, 0.53 mmol) in THF (2 mL) over 10 min. After the mixture had been stirred for 3 h, it was quenched by aqueous saturated NH_4Cl with vigorous stirring, and diluted with Et_2O. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated to leave a crude product, which was purified by chromatography on silica gel using a mixture of hexane and EtOAc (4:1) as an eluent to give **2e** (149 mg, 85% yield) as a colorless oil.

Methyl (*E*)-3-Benzylamino-4-hexenoate (2a): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.71 (dd, *J*=1.5, 6.2 Hz, 3H), 1.80 (br, 1H), 2.48 (dd, *J*=6.0, 12.2 Hz, 1H), 2.52 (dd, *J*=6.9, 12.2 Hz, 1H), 3.46 (ddd, *J*=6.0, 6.9, 8.4 Hz, 1H), 3.65 (d, *J*=13.1 Hz, 1H), 3.66 (s, 3H), 3.82 (d, *J*=13.1 Hz, 1H), 5.33 (ddq, *J*=1.5, 8.4, 15.0 Hz, 1H), 5.62 (dq, *J*=6.2, 15.0 Hz, 1H), 7.40—7.20 (m, 5H); IR (CCl_4) 3030, 2950, 1735, 1170 cm^{-1}. HRMS: Calcd for $C_{14}H_{19}NO_2$: M, 233.1416. Found: *m*/*z* 233.1414.

Methyl (*E*)-3-Dibenzylamino-4-hexenoate (2b): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.76 (dd, *J*=1.3, 5.9 Hz, 3H), 2.41 (dd, *J*=6.7, 13.9 Hz, 1H), 2.71 (dd, *J*=8.9, 13.9 Hz, 1H), 3.34 (d, *J*=13.7 Hz, 2H), 3.57 (ddd, *J*=6.7, 7.7, 8.9 Hz, 1H), 3.60 (s, 3H), 3.74 (d, *J*=13.7 Hz, 2H), 5.46 (ddq, *J*=1.3, 7.7, 15.3 Hz, 1H), 5.57 (dq, *J*=5.9, 15.3 Hz, 1H), 7.17—7.44 (m, 10H); IR (CCl_4) 3030, 2950, 1740, 1450, 725, 695 cm^{-1}. HRMS: Calcd for $C_{21}H_{25}NO_2$: M, 323.1885. Found: *m*/*z* 323.1885.

Methyl (*E*)-3-Benzylamino-5-phenyl-4-pentenoate (2d): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=2.60 (dd, *J*=6.5, 15.0 Hz, 1H), 2.61 (dd, *J*=7.0, 15.0 Hz, 1H), 3.66 (s, 3H), 3.69 (m, 1H), 3.71 (d, *J*=13.0, 1H), 3.87 (d, *J*=13.0, 1H), 6.09 (dd, *J*=8.5, 15.5 Hz, 1H), 6.53 (d, *J*=15.5 Hz, 1H), 7.42—7.20 (m, 10H); IR (KBr) 3310, 3040, 1730, 750, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74%. Found: C, 76.62; H, 6.71; N, 4.77%.

Isopropyl (*E*)-3-Benzylamino-5-phenyl-4-pentenoate (2e): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.19 (d, *J*=6.0 Hz, 3H), 1.21 (d, *J*=6.0 Hz, 3H), 2.56 (m, 2H), 3.68 (m, 1H), 3.71 (d, *J*=13.0 Hz, 1H), 3.87 (d, *J*=13.0

Hz, 1H), 5.01 (sept, J=6.0 Hz, 1H), 6.09 (dd, J=8.0, 15.5 Hz, 1H), 6.53 (d, J=15.5 Hz, 1H), 7.41—7.21 (m, 10H); IR (neat) 2960, 1700, 1645, 1245, 1140, 1000, 765, 700 cm^{-1}.

***t*-Butyl (*E*)-3-Benzylamino-5-phenyl-4-pentenoate (2f):** Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.42 (s, 9H), 2.50 (m, 2H), 2.65 (m, 1H), 3.71 (d, J=13.0 Hz, 1H), 3.86 (d, J=13.0 Hz, 1H), 6.09 (dd, J=8.0, 15.5 Hz, 1H), 6.53 (d, J=15.5 Hz, 1H), 7.41—7.20 (m, 10H); IR (neat) 2980, 1725, 1150, 690 cm^{-1}. HRMS: Calcd for $\mathrm{C_{22}H_{27}NO_2}$: M, 337.2042. Found: m/z 337.2045.

(2*E*,4*E*)-Benzyl-2,4-hexadienamide (3a): White crystals; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.84 (d, J=5.1 Hz, 3H) 4.52 (s, 1H), 4.54 (s, 1H), 5.75 (d, J=14.8, 1H), 6.02—6.23 (m, 2H), 7.19—7.40 (m, 6H); IR (KBr) 3300, 1655, 1630, 1550, 995, 700 cm^{-1}. HRMS: Calcd for $\mathrm{C_{13}H_{15}NO}$: M, 201.154. Found: m/z 201.1157.

(2*E*,4*E*)-*N*-Benzyl-5-phenyl-2,4-pentadienamide (3b): White crystals; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=4.56 (d, J=6.0 Hz, 1H), 5.78 (br, 1H), 5.96 (d, J=14.5, Hz, 1H), 6.85 (m, 2H), 7.23—7.50 (m, 11H); IR (KBr) 3270, 3020, 1645, 1615, 1540, 1280, 990, 690 cm^{-1}. Anal. Calcd for $\mathrm{C_{18}C_{17}NO}$: C, 82.10;.H, 6.51; N, 5.32%. Found: C, 81.56; H, 6.24; N, 5.55%.

(*E*)-*N*,*N*-Dibenzyl-3-(dibenzylamino)-4-hexenamide (4): Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.76 (d, J=4.9 Hz, 3H), 2.62 (dd, J=9.0, 13.9 Hz, 1H), 2.74 (dd, J=4.9, 13.9 Hz, 1H), 3.43 (d, J=13.7, Hz, 2H), 3.68 (d, J=13.7, Hz, 2H), 3.69 (m, 1H), 4.12 (d, J=16.8, Hz, 1H), 4.21 (d, J=16.8, Hz, 1H), 4.36 (d, J=14.6, 1H), 4.67 (d, J=14.6, Hz, 1H), 5.43—5.63 (m, 2H), 7.00—7.38 (m, 20H); IR ($\mathrm{CCl_4}$) 3040, 1650, 1455, 700 cm^{-1}. HRMS: Calcd for $\mathrm{C_{34}H_{36}N_2O}$: M, 488.2828. Found: m/z 488.2863.

Methyl (*E*)-5-Benzylamino-3-hexenoate (5): Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.17 (d, J=6.3 Hz, 3H), 1.37 (br 1H), 3.09 (dd, J=1.1, 6.8 Hz, 2H), 3.24 (dq, J=6.3, 7.6 Hz, 1H), 3.68 (d, J=13.2, Hz, 1H), 3.70 (s, 3H), 3.78 (d, J=13.2, Hz, 1H), 5.46 (ddt, J=1.1, 7.6 15.2 Hz, 1H), 5.67 (dt, J=6.8, 15.2 Hz, 1H), 7.19—7.35 (m, 5H), IR ($\mathrm{CCl_4}$) 3045, 2970, 1750, 975, 735, 702 cm^{-1}. HRMS: Calcd for $\mathrm{C_{14}H_{19}NO_2}$: M, 233.1416. Found: m/z 233.1412.

Procedure for the Conjugate Addition Followed by Aldol Condensation Reactions. To a solution of *N*-(trimethylsilyl)benzylamine (3.14 mL, 16.0 mmol) in THF (10 mL) at −78 °C was slowly added *n*-BuLi (9.88 mL, 1.62 M in hexane, 16.0 mmol). After stirring for 30 min, CuI (1.52 g, 8.0 mmol) was added and stirred for an additional 30 min at −78 °C. To this mixture was added a solution of **1f** (626 mg, 4.0 mmol) in THF (5.0 mL) for over 10 min. After the mixture had been stirred for 2.0 h, benzaldehyde (3.15 mL, 30 mmol) was added. And after stirring for 0.5 h, aqueous saturated $\mathrm{NH_4Cl}$ was added. The organic phase was separated, washed with brine, dried ($\mathrm{Na_2SO_4}$) and concentrated to leave a crude product, which was purified by chromatography on silica gel using a mixture of hexane and EtOAc (6 : 1) as an eluent to give **8a** (541 mg, 37%) as white crystals, and **8b** (590 mg, 40%) as a colorless oil.

Isopropyl (2*R,3*S**,*E*)-3-Benzylamino-2-(α-hydroxybenzyl)-4-hexenoate (8a):** Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.89 (d, J=6.5 Hz, 3H), 1.06 (d, J=6.5, Hz, 3H), 1.72 (dd, J=1.5, 6.5 Hz, 3H), 2.83 (dd, J=4.0, 7.0 Hz, 1H), 3.52 (ddd, J=1.0, 7.0, 8.5 Hz, 1H), 3.63 (d, J=13.0 Hz, 1H), 3.84 (d, J=13.0 Hz, 1H), 4.82 (sept, J=6.5, Hz, 1H), 5.23 (d, J=4.0, Hz, 1H), 5.41 (ddq, J=1.5, 8.5, 15.0 Hz, 1H), 5.60 (ddq, J=1.0, 6.5, 15.0 Hz, 1H), 7.20—7.40 (m, 10H); IR (neat) 3500, 2980, 1720, 1450, 1380, 1170, 1110, 740, 700 cm^{-1}. HRMS: Calcd for $\mathrm{C_{23}H_{29}NO_3}$: M, 367.2148. Found: m/z 367.2145.

Isopropyl (2*R,3*R***E*)-3-Benzylamino-2-(α-hydroxybenzyl)-4-hexenoate (8b):** White crystals; mp 59.5 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.76 (d, J=6.5 Hz, 3H), 1.04 (d, J=6.5, Hz, 3H), 1.74 (dd, J=1.5, 6.5 Hz, 3H), 2.72 (dd, J=3.0, 4.5 Hz, 1H), 3.47 (dd, J=4.5, 8.5 Hz, 1H), 3.63 (d, J=13.0 Hz, 1H), 3.92 (d, J=13.0 Hz, 1H), 4.79 (sept, J=6.5 Hz, 1H), 5.11 (d, J=3.0 Hz, 1H), 5.32 (ddq, J=1.5, 8.5, 15.0 Hz, 1H), 5.65 (ddq, J=1.0, 6.5, 15.0 Hz, 1H), 7.15—7.45 (m, 10H); IR (KBr) 3500, 3300, 3000, 1700, 1380, 1185, 1115, 740, 700 cm^{-1}. HRMS: Calcd for $\mathrm{C_{23}H_{29}NO_3}$: M, 367.2148. Found: m/z 367.2147.

Procedure for the Preparation of β-Lactam 9. The preparation of **9b** is representative. To a solution of **8b** (202 mg, 0.55 mmol) in MeOH (2.5 mL) and $\mathrm{H_2O}$ (0.5 mL) was added KOH (309 mg, 5.5 mmol) at room temperature. After stirring for 4 d, this mixture was neutralized by 1.0 M HCl, then it was evaporated under reduced pressure. To the resulting white solid were added $\mathrm{CH_2Cl_2}$ (30 mL), $\mathrm{Et_3N}$ (0.23 mL, 1.65 mmol), and 2-chloro-1-methylpyridinium iodide (169 mg, 0.66 mmol) succesively. After stirring for 4 d at room temperature, $\mathrm{H_2O}$ was added, then the mixture was extracted by $\mathrm{CH_2Cl_2}$. The organic phase was separated, washed with brine, dried ($\mathrm{MgSO_4}$), and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of $\mathrm{CH_2Cl_2}$ and EtOAc (5 : 1) as an eluent to give **9b** (92 mg, 54% yield) as a colorless oil.

(3*R,4*S**)-1-Benzyl-3-(α-hydroxybenzyl)-4-[(*E*)-1-propenyl]-2-azetidinone (9a):** Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.62 (dd, J=1.5, 6.3 Hz, 3H), 2.80 (brs, 1H), 3.29 (dd, J=2.0, 6.5 Hz, 1H), 3.72 (dd, J=2.0, 8.5 Hz, 1H), 3.88 (d, J=15.0 Hz, 1H), 4.63 (d, J=15.0 Hz, 1H), 5.00 (d, J=6.5 Hz, 1H), 5.29 (ddq, J=1.5, 8.5, 15.0 Hz, 1H), 5.52 (dq, J=6.3, 15.0 Hz, 1H), 6.96—7.02 (m, 2H), 7.20—7.44 (m, 8H); IR ($\mathrm{CCl_4}$) 1750 cm^{-1}. HRMS: Calcd for $\mathrm{C_{20}H_{21}O_2N}$: M, 307.1573. Found: m/z 307.1556.

(3*R,4*R**)-1-Benzyl-3-(α-hydroxybenzyl)-4-[(*E*)-1-propenyl]-2-azetidinone (9b):** Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.69 (dd, J=0.8, 5.0 Hz, 3H), 2.66 (brs, 1H), 3.63 (dd, J=5.5, 6.5 Hz, 1H), 3.96 (dd, J=5.5, 8.0 Hz, 1H), 4.04 (d, J=14.8 Hz, 1H), 4.69 (d, J=14.8 Hz, 1H), 4.90 (brd, J=6.6 Hz, 1H), 5.52 (ddq, J=0.8, 7.0, 15.0 Hz, 1H), 5.60 (dq, J=5.0, 15.0 Hz, 1H), 7.20—7.45 (m, 10H); IR (neat) 1747 cm^{-1}. HRMS: Calcd for $\mathrm{C_{20}H_{21}O_2N}$: M, 307.1573. Found: m/z 307.1558

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menth-3-yl (2*E*,4*E*)-5-Phenyl-2,4-pentadienoate (1g): Colorless oil; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.87 (d, J=6.4 Hz, 3H), 0.90—1.20 (m, 3H), 1.22 (s, 3H), 1.32 (s, 3H), 1.40—2.13 (m, 5H), 4.89 (ddd, J=4.2, 10.5, 10.5 Hz, 1H), 5.42 (d, J=14.9 Hz, 1H), 6.69 (dd, J=9.5, 15.1 Hz, 1H), 6.74 (t, J=14.9 Hz, 1H), 6.92 (ddd, J=0.9, 9.4, 15.2 Hz, 1H), 7.07—7.46 (m, 10H); IR (neat) 2960, 1705, 1625, 1000, 700 cm^{-1}. HRMS: Calcd for $\mathrm{C_{27}H_{32}O_2}$: M, 388.2402. Found: m/z 388.2406.

(1*R*,3*R*,4*S*)-8-(2-Naphthyl)-*p*-menth-3-yl (2*E*,4*E*)-5-Phenyl-2,4-pentadienoate (1h): White crystals; mp 116 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.89 (d, J=6.5 Hz, 3H), 1.00 (m, 1H), 1.20 (m, 1H), 1.29 (s, 3H), 1.42 (s, 3H), 1.48—

1.64 (m, 2H), 1.70 (m, 1H), 1.89 (m, 2H), 2.24 (m, 1H), 4.92 (m, 1H), 4.95 (d, *J*=15.2 Hz, 1H), 6.18 (dd, *J*=10.8 15.2 Hz, 1H), 6.34 (d, *J*=15.2 Hz, 1H), 6.55 (dd, *J*=10.8, 15.2 Hz, 1H), 7.26—7.38 (m, 7H), 7.50—7.82 (m, 5H); IR (KBr) 2955, 1705, 1630, 1240, 745 cm^{-1}. HRMS: Calcd for $C_{31}H_{34}O_2$: M, 438.2559. Found: *m/z* 438.2558.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menth-3-yl (*R*,*E*)-3-Benzylamino-5-phenyl-4-pentenoate [(3*R*)-10a]: Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.82 (d, *J*=6.5 Hz, 3H), 0.84—1.85 (m, 8H), 1.17 (s, 3H), 1.28 (s, 3H), 1.92 (dd, *J*=5.8, 15.2 Hz, 1H), 2.04 (dd, *J*=7.5, 15.2 Hz, 1H), 3.43 (q, *J*=6.5 Hz, 1H), 3.63 (d, *J*=13.0 Hz, 1H), 3.78 (d, *J*=13.0 Hz, 1H), 4.80 (dt, *J*=10.5, 4.0 Hz, 1H), 5.95 (dd, *J*=15.5, 8.0 Hz, 1H), 6.47 (d, *J*=15.5, Hz, 1H), 7.05—7.43 (m, 15H); IR (neat) 2955, 2930, 1720, 1450, 1175, 970, 745, 700 cm^{-1}. HRMS: Calcd for $C_{34}H_{41}NO_2$: M, 495.3137. Found: *m/z* 495.3126. The diastereomer ratio was determined by ^{1}H NMR at the olefin proton; 6.47 ppm in (3*R*)-**10a** and 6.43 ppm in (3*S*)-**10a**.

(1*R*,3*R*,4*S*)-8-(2-Naphtyl)-*p*-menth-3-yl (*R*,*E*)-3-Benzylamino-5-phenyl-4-pentenoate [(3*R*)-10b]: Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.82 (d, *J*=6.5 Hz, 3H), 0.85—1.84 (m, 10H), 1.26 (s, 3H), 1.41 (s, 3H), 3.14 (q, *J*=6.5 Hz, 1H), 3.46 (d, *J*=13.0 Hz, 1H), 3.62 (d, *J*=13.0 Hz, 1H), 4.87 (dt, *J*=4.0, 10.5 Hz, 1H), 5.67 (dd, *J*=8.0, 16.0 Hz, 1H), 6.21 (d, *J*=16.0 Hz, 1H), 7.80—7.20 (m, 17H); IR (neat) 2960, 2930, 1720, 745, 690 cm^{-1}. HRMS: Calcd for $C_{38}H_{43}NO_2$: M, 545.3293. Found: *m/z* 545.3292. The diastereomer ratio was determined by ^{1}H NMR at the olefin proton; 5.67 ppm in (3*R*)-**10b** and 5.72 ppm in (3*S*)-**10b**.

Procedure for the Preparation of 11. To a solution of *N*-(trimethylsilyl)benzylamine (2.4 mL, 12.2 mmol) in THF (24 mL) at −78 °C was slowly added *n*-BuLi (7.3 mL, 1.61 M in hexane, 12.0 mmol). After stirring for 30 min, CuI (1.14 g, 6.0 mmol) was added, and the resulting mixture was stirred for additional 30 min at −78 °C. To this mixture was added a solution of **1i** (743 mg, 2.0 mmol) in THF (10 mL) over a period of 10 min at −100 °C. After the mixture had been allowed to gradually warm to −78 °C over a period of 1 h, it was quenched by a mixture of aqueous saturated NH_4Cl and 28% aqueous NH_3 (1 : 1, 30 mL) with vigorous stirring, and then diluted with Et_2O. The organic phase was separated, and washed with a mixture of aqueous saturated NH_4Cl and 28% aqueous NH_3 (1 : 1, 50 mL) twice. The solution was then treated with 0.5 M HCl (40 mL). After stirring for several minutes, the solution was neutralized by 2 M NaOH. After the addition of aqueous saturated $NaHCO_3$, the organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated to leave a crude product, which was purified by chromatography on silica gel using a mixture of CH_2Cl_2 and EtOAc (7 : 1) as an eluent to give a mixture of (3*R*)-**11** and (3*S*)-**11** (744 mg, 95 : 5, 78% yield) as a viscous oil. The diastereomer ratio was determined by ^{1}H NHR at the olefin proton; 6.11 ppm in (3*R*)-**11** and 6.13 ppm in (3*S*)-**11**.

***N*-[(*R*,*E*)-3-Benzylamino-5-phenyl-4-pentenoyl]-10,2-bornanesultam [(3*R*)-11]** Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.94 (s, 3H), 1.09 (s, 3H), 1.45—1.23 (m, 3H), 2.20—1.65 (m, 5H), 2.90 (dd, *J*=5.0, 15.5 Hz, 1H), 3.08 (dd, *J*=8.0, 15.5 Hz, 1H), 3.42 (d, *J*=13.5 Hz, 1H), 3.48 (d, *J*=13.5 Hz, 1H), 3.70 (d, *J*=13.0 Hz, 1H), 3.77 (m, 2H), 3.84 (d, *J*=13.0 Hz, 1H), 6.11 (dd, *J*=8.0, 15.6 Hz, 1H), 6.52 (d, *J*=15.6 Hz, 1H), 7.40—7.18 (m, 10H); IR (KBr) 3420, 1695, 1330 cm^{-1}. HRMS: Calcd for $C_{28}H_{34}N_2SO_3$: M, 478.2990. Found: *m/z* 478.2287.

***N*-[(*S*,*E*)-3-Benzylamino-5-phenyl-4-pentenoyl]-10,2-bornanesultam [(3S)-11]:** Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.90 (s, 3H), 0.94 (s, 3H), 1.10—1.45 (m, 3H), 1.71—2.05 (m, 5H), 2.92 (dd, *J*=6.9, 15.1 Hz, 1H), 3.09 (dd, *J*=6.2, 15.1 Hz, 1H), 3.41 (d, *J*=13.6 Hz, 1H), 3.45 (d, *J*=13.6 Hz, 1H), 3.70 (d, *J*=13.0 Hz, 1H), 3.74—3.90 (m, 2H), 3.85 (d, *J*=13.0 Hz, 1H), 6.13 (dd, *J*=8.3, 15.6 Hz, 1H), 6.51 (dd, *J*=15.6, Hz, 1H), 7.18—7.40 (m, 10H); IR (CCl_4) 3350, 1695, 1345 cm^{-1}. HRMS: Calcd for $C_{28}H_{34}N_2SO_3$: M, 478.2290. Found: *m/z* 478.2288.

The determination of Stereostructure 10a. Procedure for the Preparation of Authentic Compound. To a solution of 3-(benzylamino)-1-butanol (530 mg, 2.96 mmol, ca. 40% ee) and diisopropylethylamine (2.3 mL, 13.2 mmol) in CH_2Cl_2 (20 mL) was added trichloromethyl chloroformate (0.4 mL, 3.3 mmol) at 0 °C. After stirring overnight at room temperature, ether was added. The reaction mixture was washed with aqueous 5% HCl, saturated $NaHCO_3$, and brine. The solvent was evaporated to leave a residue, which was purified by chromatography on silica gel using EtOAc as an eluent to give **13c** [161 mg, 26% yield, $[\alpha]_D^{20}=-24.9°$ (*c* 0.98, $CHCl_3$)] as a colorless oil.

Procedure for the Preparation of 13c from 10a. To a solution of **10a** (444 mg, 0.87 mmol, 62%ee) in Et_2O (10 mL) at 0 °C was slowly added LAH (45 mg, 0.39 mmol). After stirring for 10 min at this temperature and for 30 min at room temperature, H_2O (0.05 mL), 15% NaOH (0.05 mL), and H_2O (0.15 mL) were successively. After the precipitate had been filtered, the filtrate was evaporated to leave a residue, which was purified by chromatography on silica gel using EtOAc as an eluent to give the desired alcohol **12** [205 mg, 88% yield, $[\alpha]_D^{20}=+56.44°$ (*c* 0.505, $CHCl_3$] as white crystals.

To a solution of **12** (1.0 g, 3.75 mmol) and diisopropylethylamine (1.31 mL, 7.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C was slowly added trichloromethyl chloroformate (0.25 mL, 2.0 mmol). The mixture was stirred overnight at room temperature, and then evaporated under reduced pressure. After the addition of benzene (100 mL) to the residue, the mixture was refluxed for 12 h, and then cooled to room temperature. After removing the solvent, H_2O was added to the resulting oil; the mixture was then extracted repeatedly by Et_2O. The combined organic phase was washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of hexane and EtOAc (2 : 1) as an eluent to give 3-benzyl-3,4,5,6-tetrahydro-4-styryl-2*H*-1,3-oxazin-2-one **13a** (1.08 g, 97% yield) as a colorless oil.

After a solution of **13a** (996 mg, 3.4 mmol) in ethanol (100 mL) was cooled to −50 °C, O_3/O_2 was passed through the solution (15 min) until it sustained the characteristic blue color of ozone. After the disappearance of this color upon passing O_2, the solution was allowed to warm to 0 °C; then, a solution of $NaBH_4$ (1.09 g, 2.72 mmol) in a mixture of H_2O and methanol (1 : 1, 60 mL) was slowly added. The reaction was continued at this temperature for 2 h and then at room temperature overnight. To the mixture was added an aqueous 10% H_2SO_4 to make the solution acidic. After the mixture had been extracted with $CHCl_3$ repeatedly, the combined organic phase was washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was purified by chromatography on silica gel using EtOAc as an eluent to give hydroxymethyl substituted tetrahydrooxazinone **13b** (490 mg, 65% yield) as white crystals.

To a solution of hydroxymethyl substituted tetrahydrooxazinone **13b** (110 mg, 0.5 mmol) in acetonitrile (10 mL) were slowly added carbon tetrabromide (250 mg, 0.75 mmol) and triphenylphosphine (200 mg, 0.75 mmol). The mixture was stirred for 1 h at room temperature, and then evaporated under reduced pressure to leave an oil, which was dissolved in benzene (10 mL) without purification. To the solution were added tributylstannane (0.20 mL, 0.75 mmol) and AIBN (10 mg). After refluxing for 1 h, the solvent was removed under reduced pressure to leave a residue, which was purified by chromatography on silica gel using a mixture of hexane and EtOAc (2 : 1) as an eluent to give methyl-substituted tetrahydrooxazinone **13c** [28 mg, 30% yield in two steps, $[\alpha]_D^{20}=-30.64°$ (c 1.09, $CHCl_3$)] as a colorless oil.

The Determination of Stereostructure 11. The Procedure for the Reduction of 11 for a Comparison with the Same Compound Derived from 10a. To a suspension of LAH (178 mg, 4.7 mmol) in Et_2O (5 mL) was added a solution of **11** (900 mg, 1.88 mmol) in a mixture of THF (5 mL) and Et_2O (15 mL). After stirring for 3 h, aqueous saturated NH_4Cl was added. The mixture was repeatedly extracted with ether. The combined organic phase was evaporated to leave a residue, which was purified by chromatography on silica gel using EtOAc as eluent to give the desired alcohol **12** [322 mg, 64% yield, $[\alpha]_D^{20}=+81.90°$ (c 0.525, $CHCl_3$)] as white crystals.

Procedure for the Preparation of 14b. To a solution of N-(trimethylsilyl)benzylamine (6.08 mL, 31.0 mmol) in THF (40 mL) at −78 °C was slowly added n-BuLi (18.6 mL, 1.61 M in hexane, 30.0 mmol). After stirring for 25 min, CuCN (1.34 g, 15.0 mmol) was added and the mixture was allowed to warm to −45 °C. After stirring for 5 min, the solution was cooled to −78 °C. To the mixture was added a solution of **1i** (1.86 g, 5.0 mmol) in THF (15 mL) over a period of 20 min at −100 °C. After 40 min, acetaldehyde (10 mL, 5M in THF, 50 mmol) was added. After the mixture had been allowed gradually warm to −70 °C over a period of 1 h, it was poured into a mixture of aqueous saturated NH_4Cl and 28% aqueous NH_3 (1 : 1, 50 mL) with vigorous stirring, and then diluted with Et_2O. The organic phase was separated, washed with a mixture of aqueous saturated NH_4Cl and 28% aqueous NH_3 (1 : 1, 50 mL) twice, and brine, dried (K_2CO_3) and concentrated to leave a crude product **14a**, which was dissolved in CH_2Cl_2 (100 mL). To this solution were added imidazole (3.4 g, 49.9 mmol) and t-butyldimethylsilyl chloride (5.7 g, 37.8 mmol) at 0 °C. The mixture was stirred overnight at room temperature, and then quenched with H_2O. The organic phase was separated, washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of hexane and EtOAc (5 : 1) as an eluent to give **14b** (2.26 g, 71% yield) as a viscous oil.

Procedure for the Preparation of β-Lactam 17. To a solution of **14b** (1.7 g, 2.67 mmol) in Et_2O (40 mL) at 0 °C was slowly added LAH (150 mg, 4.0 mmol). After stirring for 1 h, H_2O (0.15 mL), 15% NaOH (0.15 mL), and H_2O (0.45 mL) were added successively. The resulting mixture was stirred vigorously for 30 min and then filtered through a pad of Celite with Et_2O. The filtrate was concentrated in vacuo to leave an oil, which was purified by chromatography on silica gel using a mixture of hexane and EtOAc (3 : 1) as an eluent to give the desired alcohol (686 mg, 60% yield) as a colorless oil.

To a solution of the alcohol derived from **14b** (638 mg, 1.5 mmol)in CH_2Cl_2 (40 mL) at 0 °C were added imidazole (204 mg, 3 mmol) and chlorotriethylsilane (0.504 mL, 3 mmol). This mixture was stirred for 1 h at room temperature and quenched with H_2O. The organic phase was separated, washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of hexane and EtOAc (10 : 1) as an eluent to give the silyl ether derivative (793 mg, 98% yield) as a colorless oil.

A solution of the silyl ether derivative (793 mg, 1.47 mmol), Et_3N (2 mL, 14.4 mmol), and $(Boc)_2O$ (2 g, 9.2 mmol) in DMF (10 mL) was stirred for 4.5 h at 50 °C. To the mixture were added H_2O and Et_2O at 0 °C. The organic phase was separated, washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of hexane and EtOAc (20 : 1) as an eluent to give **15** (574 mg, 61% yield) as a colorless oil.

A solution of **15** (189 mg, 0.3 mmol), H_2O (0.5 mL), and AcOH (0.5 mL) in THF (3 mL) was stirred for 1 d at room temperature. To this mixture was added additional AcOH (0.3 mL). After stirring for 2 d, the mixture was diluted with Et_2O. The mixture was first washed with H_2O (three tines), and then aqueous saturated $NaHCO_3$ and brine. After drying (K_2CO_3), the mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of hexane and EtOAc (7 : 1) as an eluent to give the desired alcohol (152 mg, 98% yield) as a colorless oil.

To a solution of oxalyl chloride (0.22 mL, 2.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added a solution of dimethyl sulfoxide (0.29 mL, 4.2 mmol) in CH_2Cl_2 (2 mL). After stirring for 10 min, the alcohol derived from **15** (439 mg, 0.83 mmol) in CH_2Cl_2 (5 ml) was added dropwise over a period of 10 min. After additional stirring for 30 min, the mixture was allowed to gradually warm to −45 °C. After the mixture had been stirred for 15 min at −45 °C, Et_3N (0.81 mL, 5.8 mmol) was added with vigorous stirring. This mixture was allowed to warm to 0 °C, and was then quenched with saturated aqueous NH_4Cl. The organic phase was separated, washed with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of hexane and EtOAc (10 : 1) as an eluent to give the desired aldehyde (357 mg, 82% yield) as a colorless oil.

To a mixture of aldehyde (357 mg, 0.68 mmol), t-BuOH (5 mL), H_2O (1.5 mL), $NaH_2PO_4\cdot 2H_2O$ (106 mg, 0.68 mmol), and 2-methyl-2-butene (0.53 mL, 5 mmol) was slowly added sodium chlorite (271 mg, 3 mmol) at room temperature. After stirring for 1.5 h at room temperature, aqueous 1 M HCl was added to make the solution acidic. The mixture was extracted with CH_2Cl_2 repeatedly. The combined extracts were dried (Na_2SO_4) and evaporated to leave a residue, which was purified by chromatography on silica gel using a mixture of hexane and EtOAc (5 : 1) as an eluent to give **16** (327 mg, 89% yield) as a colorless oil.

To a solution of **16** (269 mg, 0.5 mmol)in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL). After the mixture had been kept overnight at room temperature, the solvent and excess trifluoroacetic acid were evaporated directly in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL), and treated with Et_3N (0.21 mL, 1.5 mmol) and 2-chloro-1-methylpyridinium iodide (153 mg, 0.6 mmol) at 0 °C. After stirring overnight at room temperature, the mixture was evaporated to leave a residue, which was purified by chromatography on silica gel using a mixture of hexane and EtOAc (1:1) as an eluent to give a mixture of **17a** (100 mg, 47% yield) and **17b** (27 mg, 18% yield) as a colorless oil.

(*R*,*E*)-3-Benzylamino-5-phenyl-4-penten-1-ol (12): White crystals; mp 52.5 °C; ^{1}H NMR ($CDCl_3$) δ=1.80 (m, 2H), 3.48 (m, 1H), 3.74 (d, J=13.0 Hz, 1H), 3.85 (m, 2H), 3.89 (d, J=13.0 Hz, 1H), 6.08 (dd, J=8.0, 15.5 Hz, 1H), 6.48 (d, J=15.5 Hz, 1H), 7.20—7.45 (m, 10H), IR (neat) 3270, 2850, 1495, 1450, 970, 740, 695 cm^{-1}. HRMS: Calcd for $C_{18}H_{21}NO$: M, 267.1623. Found: m/z 267.1615.

(*S*)-3-Benzyl-3,4,5,6-tetrahydro-4-methyl-2*H*-1,3-oxazin-2-one (13c): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.25 (d, J=6.5 Hz, 3H), 1.73 (ddd, J=1.0, 3.0, 13.0 Hz, 1H), 2.10 (ddd, J=4.0, 6.0, 13.0 Hz, 1H), 3.47 (ddq, J=2.0, 4.0, 6.5 Hz, 1H), 4.14 (d, J=15.0 Hz, 1H), 4.24 (ddt, J=1.0, 4.0, 10.5 Hz, 1H), 4.37 (dt, J=3.0, 10.5 Hz, 1H), 5.09 (d, J=15.0 Hz, 1H), 7.20—7.40 (m, 5H); IR (neat) 2980, 1680, 1490, 1450, 1270, 1220, 1145, 700 cm^{-1}. HRMS: Calcd for $C_{12}H_{15}O_2N$: M, 205.1103. Found: m/z 205.1100.

***N*-{(2*S*,3*S*,*E*)-3-Benzylamino-2-[(*S*)-1-(*t*-butyldimethylsiloxy)ethyl]-5-phenyl-4-pentenoyl}-10,2-bornanesultam (14b):** Colorless oil; $[\alpha]^{22}_{D}=-27.02°$ (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.03 (s, 3H), 0.08 (s, 3H), 0.83 (s, 9H), 0.91 (s, 3H), 1.10 (s, 3H), 1.17 (d, J=6.5 Hz, 3H), 1.20—2.10 (m, 7H), 3.22 (m, 1H), 3.51 (m, 2H), 3.60 (d, J=13.0 Hz, 1H), 3.73 (m, 1H), 3.85 (d, J=13.0 Hz, 1H), 4.00 (m, 1H), 4.30 (m, 1H), 6.19 (dd, J=8.5, 15.9 Hz, 1H), 6.46 (d, J=15.9 Hz, 1H), 7.17—7.45 (m, 10H); IR (CCl_4) 2960, 1135, 1115 cm^{-1}. HRMS: Calcd for $C_{36}H_{52}N_2SSiO_4$: M, 636.3417. Found: m/z 636.389.

***t*-Butyl (1*S*,2*R*,3*S*)-*N*-Benzyl-*N*-[3-*t*-butyldimethylsiloxy-1-(*E*)-styryl-2-(triethylsiloxy)methylbutyl]carbamate (15):** Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.06 (s, 3H), 0.11 (s, 3H), 0.50 (q, J=7.5 Hz, 6H), 0.88 (t, J=7.5 Hz, 9H), 0.92 (s, 9H), 1.06 (brd, J=6.0 Hz, 3H), 1.39 (br, 9H), 1.99 (m, 1H), 3.56 (m, 1H), 3.68 (m, 1H), 4.03 (m, 1H), 4.83 (m, 1H), 6.17—6.28 (m, 2H), 7.15—7.30 (m, 10H); IR (neat) 2955, 1695, 1250 cm^{-1}. HRMS: Calcd for $C_{37}H_{61}NO_4Si_2$: M, 639.4139. Found: m/z 639.4155.

(2*R*,3*S*,*E*)-3-(*N*-Benzyl-*N*-*t*-butoxycarbonyl)amino-2-[(*S*)-1-(*t*-butyldimethylsiloxy)ethyl]-5-phenyl-4-pentenoic Acid (16): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.12 (s, 3H), 0.21 (s, 3H), 0.94 (s, 9H), 0.97 (d, J=6.2 Hz, 3H), 1.47 (brs, 9H), 2.85 (m, 1H), 3.92 (m, 1H), 4.20 (d, J=15.9 Hz, 1H), 4.79 (m, 1H), 6.24 (dd, J=8.2, 15.5 Hz, 1H), 6.44 (m, 1H), 7.19—7.33 (m, 10H), 10.50 (br, 1H); IR (CCl_4) 3370, 1690 cm^{-1}. HRMS: Calcd for $C_{31}H_{45}NSiO_5$: M, 539.3067. Found: m/z 539.3073.

(3S,4S)-1-Benzyl-3-[(*S*)-1-(*t*-butyldimethylsiloxy)-ethyl]-4-[(*E*)-styryl]-2-azetidinone (17a): Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.28 (d, J=6.1 Hz, 3H), 3.31 (dd, J=5.2, 5.2 Hz, 1H), 4.11 (d, J=14.5 Hz, 1H) 4.09—4.20 (m, 2H), 4.59 (d, J=14.5 Hz, 1H), 6.23 (dd, J=8.9, 15.7 Hz, 1H), 6.51 (d, J=15.7 Hz, 1H), 7.21—7.36 (m, 10H); IR (neat) 2940, 1758, 835 cm^{-1}. HRMS: Calcd for $C_{26}H_{35}O_2NSi$: M, 421.2437. Found: m/z 421.2401.

References

1) For recent reviews on asymmetric synthesis of β-lactams, see: a) R. D. G. Copper, B. W. Daugherty, and D. B. Boyd, *Pure Appl. Chem.*, **59**, 485 (1987); b) R. C. Thomas, "In Recent Progress in The Chemical Synthesis of Antibiotics," ed by G. Lucas and M. Ohno,. Springer-Verlag, Berlin (1990), p. 533; c) F. H. Van der Steen and G. Van Koten, *Tetrahedron*, **47**, 7503 (1991); d) D. J. Hart and D. C. Ha, *Chem. Rev.*, **89**, 1447 (1989); e) M. J. Brown, *Heterocycles*, **29**, 2225 (1989); f) G. I. Georg, in "Studies in Natural Product Chemistry," ed by A.-ur Rahman, Elsevier, Amsterdam (1989), Vol. 4, p. 431; g) M. J. Miller, *Acc. Chem. Res.*, **19**, 49 (1986); h) L. Ghosez and J. Marchand-Brynaert, in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 5, p. 85; i) G. I. Georg and V. T. Ravikumar, in "The Organic Chemistry of β-Lactams," ed by G. I. Georg, VCH, New York (1992), p. 295. For a general recent review on β-lactams, see: j) J. Backs and Houben-Weyl, "Methoden der Organischen Chemie," ed by E. Muller and O. Bayer, Thieme, Stuttgart (1991), Band E16B, p. 31.

2) Y. Yamamoto, N. Asao, and T. Uyehara, *J. Am. Chem. Soc.*, **114**, 5427 (1992).

3) N. Asao, T. Shimada, N. Tsukada, and Y. Yamamoto, *Tetrahedron Lett.*, **35**, 8425 (1994).

4) N. Asao, N. Tsukada, and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, **1993**, 1660.

5) N. Tsukada, T. Shimada, Y. S. Gyoung, N. Asao, and Y. Yamamoto, *J. Org. Chem.*, **60**, 143 (1995).

6) For discussions on higher order cyano cuprates see: S. H. Bertz, *J. Am. Chem. Soc.*, **112**, 4031 (1990); B. H. Lipshutz, S. Sharma, and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 4032 (1990).

7) The copper (and/or lithum) enolate, produced in organocuprate conjugate additions, is not suitable for further aldol and alkylation reactions. Normally such an enolate is transmetallated to a zinc or tin enolate. Y. Yamamoto, H. Yatagai, and K. Maruyama, *Si, Ge, Sn, and Pb Compds.*, **9**, 25 (1986); M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, **107**, 3348 (1985).

8) H. Huang, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, **1984**, 1465.

9) H. Estermann and D. Seebach, *Helv. Chim. Acta*, **71**, 1824 (1988).

10) The high pressure induced addition of diphenylmethylamine to 8-(2-naphthyl)-p-menth-3-yl crotonate produced (R)-β-amino ester (J. d'Angelo and J. Maddaluno, *J. Am. Chem. Soc.*, **108**, 8112 (1986)).

11) S. G. Davies and O. Ichihara, *Tetrahedron Asym.*, **2**, 183 (1991).

12) W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990).

13) N. Shida, C. Kabuto, T. Niwa, T. Ebata, and Y. Yamamoto, *J. Org. Chem.*, **59**, 4068 (1994).

14) T. Uyehara, N. Asao, and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, **1989**, 753; N. Asao, T. Uyehara, and Y. Yamamoto, *Tetrahedron*, **46**, 4653 (1990).

15) J. Dickmann, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967); S. Narula and N. Kapur, *Irong. Chim. Acta*, **73**, 183 (1983).