Azetidines and Bisazetidines. Their Synthesis and Use as the Key Intermediates to Enantiomerically Pure Diamines, Amino Alcohols, and Polyamines

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Highly selective reductions of β-lactams (1, 5), direct-tandem bis-β-lactams (6), and tandem bis-β-lactams (7) to the corresponding azetidines (13, 14) and bisazetidines (11, 12) are successfully performed by using diisobutylaluminum hydride (DIBAL-H), monochlorohydroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$) as specific reducing agents: Enantiomerically pure azetidines and bisazetidines are readily synthesized without loss of enantiomeric purity. Possible mechanisms that can accommodate the unique selectivity realized by hydroalanes are discussed. Hydrogenolysis of 2-arylazetidines and 2,2'-diarylbisazetidines on palladium catalyst or Raney-Ni gives the corresponding diamines, amino alcohols, polyamino alcohols, and polyamino ethers in excellent yields, which may serve as useful chiral chelating agents as well as chiral building blocks for organic synthesis and for chiral macrocycles.

Azetidines are an interesting class of four-membered heterocyclic compounds, and it has been shown that a variety of azetidines exhibit various biological activities such as antihypertensive, antiinflammatory, antiarrhythmic, antidepressant, and monoamine oxidase (MAO) inhibitory activities.[3-7] However, the azetidine skeleton has been one of the most difficult amines to synthesize because of its ring strain. Accordingly, developments of effective general methods for the synthesis of azetidines are of significant value. Azetidines can be synthesized by several methods[4,8] including the cyclization of γ-halopropylamines[6,8] or the reduction of β-lactams with $LiAlH_4$[3,7] or B_2H_6.[7,9] However, the former method suffers from associated elimination reaction, i.e., dehydrohalogenation,[6,8] and the applicability of the latter method has been restricted to a couple of *N-unsubstituted* β-lactams, viz., it has been reported that the reductions of *N-substituted* β-lactams with $LiAlH_4$,[7] B_2H_6,[7,10] Raney nickel, $LiAlH_4$–$AlCl_3$ (AlH_3), and $NaBH_4$–$AlCl_3$ all result in cleavage of the 1,2-bond to give the N-substituted 3-aminopropanols. Nevertheless, the latter method seems to be an attractive approach to the general synthesis of azetidines since a variety of β-lactams can be prepared by several established methods.[11] Sammes and Smith[12] developed a two-step synthesis of azetidines from β-lactams consisting of the diborane reduction of a β-lactam to an γ-amino alcohol followed by a modified Mitsunobu reaction, but the yield of the modified Mitsunobu reaction is only moderate. We found that hydroalanes, especially chlorohydroalanes,[13] and diisobutylaluminum hydride (DIBAL-H) in THF served as highly selective reducing agents for the one-step conversion of β-lactams and bis-β-lactams to the corresponding azetidines and bisazetidines, respectively, in high yields.[14,15] We describe here full accounts of our study on the synthesis of a variety of mono- and bisazetidines, including enantiomerically pure azetidines by the one-step selective reduction of mono- and bis-β-lactams with hydroalanes, and the use of mono- and bisazetidines as precursors for diamines, amino alcohols, polyamino alcohols, and polyamino ethers.

Results and Discussion

Reduction of β-Lactams with Metal Hydrides. In general, reduction of a β-lactam may yield an azetidine and/or a γ-amino alcohol. Thus, development of specific reducing agents that can give azetidines with excellent selectivity was crucial for this study. Accordingly, screening of metal hydride reagents was carried out using 3-(benzyloxy)-1,4-diphenylazetidin-2-one (1a) as the substrate. Attempted reduction by BH_3·THF (22 h in refluxing dioxane) and $NaBH_4$–$AlCl_3$ (3.5 h in refluxing ether) resulted in a complete recovery of the starting substrate, and the reduction with $LiAlH_4$, $LiBEt_3H$, or $LiB\text{-}sec\text{-}Bu_3H$ gave 3-(phenylamino)-3-phenyl-2-(benzyl-

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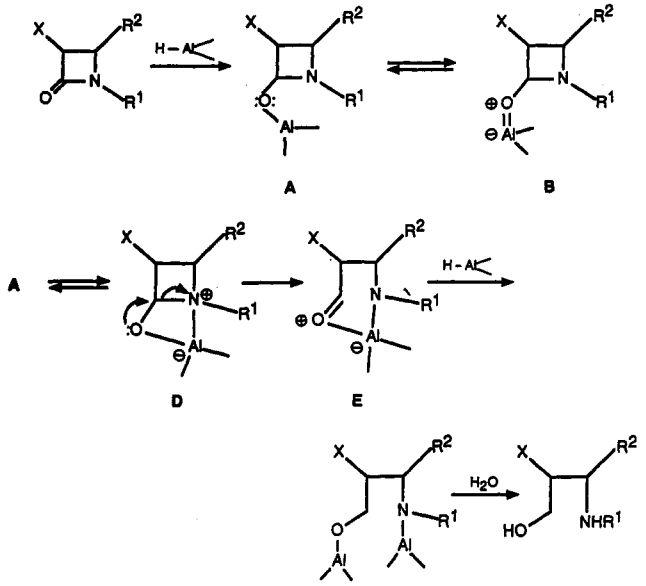
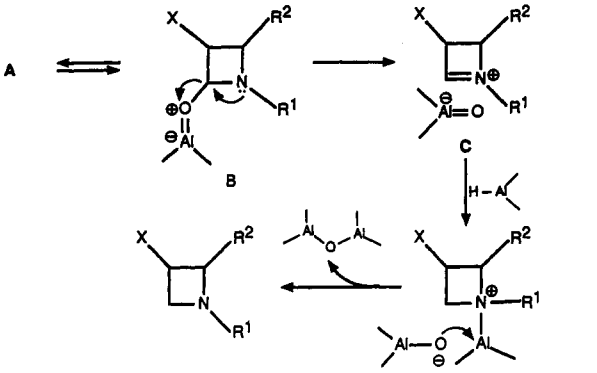
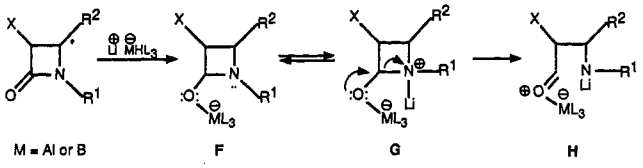
Scheme I



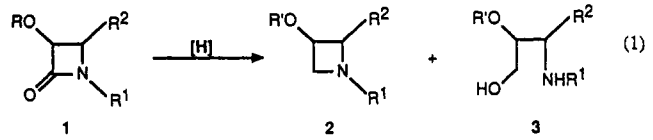
Scheme II



Scheme III



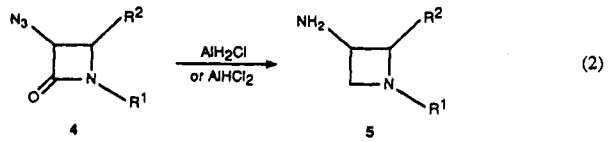
oxy)propanol (**3a**) exclusively through 1,2-bond fission (25 °C in THF). However, it was found that DIBAL-H promoted the desired reduction successfully to give 3-(benzyloxy)-1,2-diphenylazetidine (**2a**) in 73% yield although a small amount (16%) of **3a** was also produced, which was easily separated on a silica gel column. Thus, we carried out the reductions of a variety of 3-(benzyloxy)azetidin-2-ones (**1**) with DIBAL-H in THF and obtained the corresponding azetidines (**2**) in 54–85% yields as shown in Table I (entries 1–7).



(1)

Next, monochloroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$) were examined. We found that AlH_2Cl and $AlHCl_2$ prepared in situ from $LiAlH_4$ and $AlCl_3$ in ether[13] converted **1** into **2** in quite high yields (85–100%) without being accompanied by **3** (entries 8–23). Similarly, 3-azidoazetidin-2-ones (**4**) were converted to 3-aminoazetidines (**5**) in high yields (79–100%) (eq 2). In these cases, the reduction of carbonyl and azide functionality proceeded simultaneously (entries 24–32). The use of alane (AlH_3) itself for the reduction of **1a** resulted in the formation of a mixture of **2a** (29%) and **3a** (59%).

Chiral nonracemic azetidin-2-ones can be transformed to the corresponding azetidines without loss of enantiomeric purity (entries 7, 12–19, 22, 23, 28, 29, 32, 33). When azetidin-2-one *tert*-butyl esters **1k–n**, **1q**, **1r**, and **4h** were employed as substrates for AlH_2Cl reduction, the corresponding azetidine alcohols were obtained, i.e., *tert*-butyl esters were not tolerant to this reduction. Similarly, acetoxy groups in **1q**, **1r** were converted to hydroxy groups in this process (entries 22, 23). Evans' chiral auxiliary, 4-phenyloxazolidinone, was ring opened and the carbonyl group was reduced to a methyl group (entry 33).



(2)

Possible Mechanism for Highly Selective Reduction with Chlorohydroalanes. As to the rationale for the unique results on the selective reduction of azetidin-2-ones by hydroalanes, the contribution of the "oxonium alanate" structure B should be taken into account as a crucial factor. The reaction pathway, which leads to the formation of amino alcohol via 1,2-fission, may involve the "ammonium alanate" intermediate D, which gives the amino aldehyde complex E and the reduction of E finally yields amino alcohol, as shown in Scheme I.

The coordination of the amine moiety to aluminum should be influenced by the Lewis acidity of the aluminum moiety. If this is the case, the selectivity for yielding azetidine should decrease in the order $Cl_2AlH \geq ClAlH_2 > AlH_3 > {}^iBu_2AlH$ simply based on the Lewis acidity. However, the observed results show the order $Cl_2AlH \geq ClAlH_2 > {}^iBu_2AlH > AlH_3$. The results may well be accommodated by taking into account the steric bulkiness of isobutyl group, which weakens the coordination of the amine moiety.

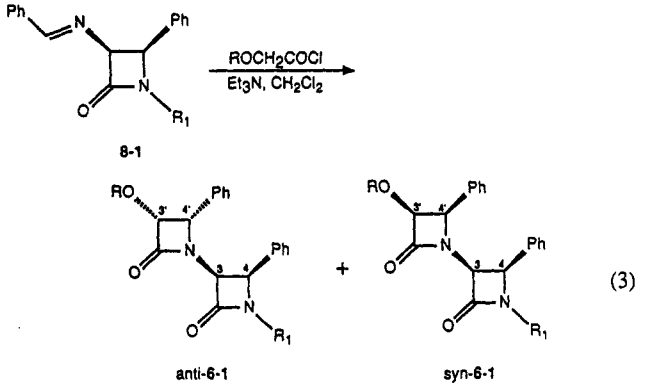
It is quite reasonable to assume the easy cleavage of carbon–oxygen bond because of a strong "oxophilicity" of aluminum to give the iminium salt C, which is readily reduced to azetidine by the action of another molecule of hydroalane (Scheme II). This rationale is strongly supported by the fact that the "oxonium metalate" structure cannot be realized in the reduction with lithium aluminum hydride or lithium borohydride.

Lithium aluminum hydride or lithium borohydride should give the alkoxyalanate or alkoxyborate F, which would be very disadvantageous for the carbon–oxygen bond cleavage. As Scheme III illustrates, lithium cation can coordinate to the amine moiety to give G, and the 1,2-fission would readily proceed to yield H, which is equivalent to E. This could be the reason why lithium aluminum hydride or lithium borohydride did not yield azetidine at all. It should also be noted that there seems to be an inherent difference between hydroboranes and hydroalanes, e.g., Sammes and Smith reported the exclusive 1,2-fission of a penicillin G ester, an N-substituted β-lactam, by diborane to give the corresponding amino alcohol, and proposed a possible mechanism. The observed difference between AlH_3 and BH_3 could be due to the "oxophilicity" of the reagent, which is stronger in AlH_3.

To obtain further supporting evidence for the proposed mechanism, we looked at solvent effects on the selectivity in the reactions using DIBAL-H. Results are summarized

in Table II. As Table II shows, substantial solvent effects on the selectivity of the reaction were observed for the DIBAL-H reductions. When the reaction was carried out in THF, the azetidine (**2a**)/amino alcohol (**3a**) ratio was 90/10 (entry 2), whereas the reaction in toluene gave the **2a**/**3a** ratio of 65/35 (entry 4). The reaction in ether gave a similar result to that in THF (90/10, entry 3). The results clearly indicate the significance of solvent coordination to aluminum metal, viz., THF can strongly coordinate to DIBAL-H, effectively weakening the proposed intramolecular coordination of the azetidine nitrogen to the aluminum which is crucial to push the reaction pathway to the formation of the iminium alanate (C in Scheme II). It is apparent that toluene does not have strong coordination ability compared with THF; thus, two types of reactions take place. Consequently, these results on the solvent effects strongly support our proposed mechanism for the highly selective reduction to azetidines on using chlorohydroalanes as well as DIBAL-H in THF.

Bisazetidines from Bis-β-lactams. (a) Synthesis of Bis-β-lactams. We synthesized two types of bis-β-lactams, viz., direct-tandem bis-β-lactams (**6**) in which two β-lactam rings are directly connected and tandem bis-β-lactams (**7**) in which two β-lactam rings are connected by an amino acid moiety. The direct-tandem bis-β-lactams (**6**) were prepared by the [2 + 2] cycloaddition of an in situ generated ketene to a 3-(benzylideneamino) β-lactam (**8**) followed by chromatographic separation of two diastereomers (eq 3). (Equation 3 exemplifies the reaction only with (3*S*,4*R*)-**8** for simplicity.) In contrast to the azido-

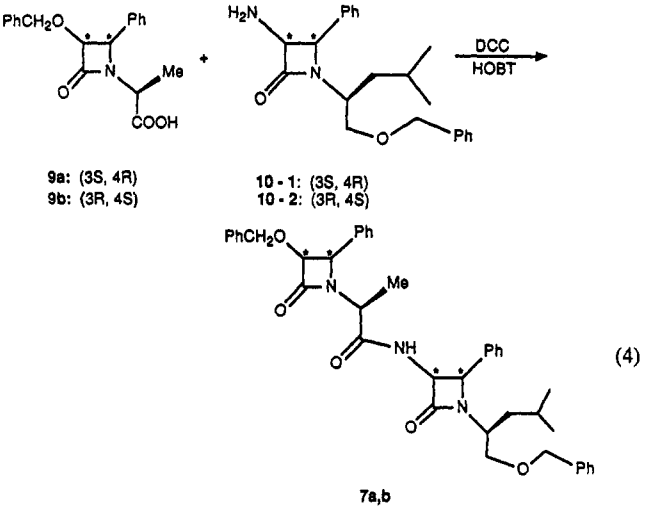


(3)

ketene addition to enantiomerically pure 3-(benzylideneamino) β-lactam (**8**) previously reported from this laboratory,[16] the [2 + 2] cycloaddition of phenoxyketene, (benzyloxy)ketene, and acetoxyketene, which were generated in situ from the corresponding acid chlorides, with **8** did not give high stereoselectivity although they had exclusive cis stereoselectivity on the newly formed β-lactam rings. Results are summarized in Table III.

The assignment of absolute configurations for **6a–d** was made unambiguously based on (i) the comparison of tripeptides obtained through hydrogenolysis of **6c** with an authentically prepared tripeptide, (*S*)-HOCH(CH_2Ph)-CO-(*S*)-Phe-(*S*)-Ala-OBu^t, on HPLC, (ii) the correlation of NMR spectra of **6a,b,d** with those of *anti*- and *syn*-**6c**, viz., anti and syn isomers showed clearly different patterns and the patterns were consistent within the anti and syn isomer series, and (iii) the comparison of optical rotations of **6a,b,d** with those of *anti*- and *syn*-**6c**, viz., each β-lactam moiety has a large specific rotation, thus anti isomers (cancellation) and syn isomers (addition) have very different specific rotations with each other (see the Experimental Section).

The tandem bis-β-lactams (**7a,b**) were prepared by the coupling of a chiral 3-(benzyloxy) β-lactam carboxylic acid (**9**) with a chiral 3-amino β-lactam (**10**) (eq 4). The β-



9a: (3S, 4R)
9b: (3R, 4S)

10 - 1: (3S, 4R)
10 - 2: (3R, 4S)

7a,b

(4)

lactam carboxylic acids (**9a,b**) were prepared by treatment of the corresponding β-lactam *tert*-butyl esters (**1m,n**) with CF_3COOH in anisole: **1m** and **1n** were obtained through the standard [2 + 2] cycloaddition of (benzyloxy)ketene with *N*-benzylidenealanine *tert*-butyl ester followed by separation of the two diastereomers. The absolute configurations of the β-lactams were determined by conversion to phenyllactic acid in two steps. The β-lactam **1n**, which had a smaller R_f value (hexane–EtOAc, 3:1), was subjected to hydrogenolysis cleaving the β-lactam ring and the benzyl group to give the amide **17**, which was then hydrolyzed with 6 N HCl at 120 °C overnight to yield (*S*)-phenyllactic acid. Thus, the configuration of the chiral center at 3-position of the β-lactam ring was determined to be *S*. Since both of the β-lactams are cis based on the coupling constant (4.6 Hz) between the two protons on the β-lactam ring, the configurations of the **1n** are assigned to be 3*S*,4*R* and **1m** 3*R*,4*S*, respectively.

(b) Reduction of Bis-β-lactams with Hydroalanes. The direct-tandem bis-β-lactams **6** thus obtained were submitted to the reduction with chlorohydroalane in refluxing ether to give the corresponding bisazetidines **11** in good yield (eq 5). Results are summarized in Table IV. In the same manner, the tandem bis-β-lactam **7b-1** was converted to the bisazetidine **12** in 33% yield (eq 6).

The novel chiral bisazetidines **11** and **12**, thus obtained, are unique chiral polyamines bearing rigid azetidine rings as stereocontrolling factor and are expected to serve as effective optical resolution reagents, chiral catalysts for asymmetric Michael addition, chiral ligands for metal complexes, and chiral liquid phase or modifier of chiral columns for chromatography. Also, these novel chiral bisazetidines can readily be converted to the corresponding open-chain chiral polyamino alcohols and polyamino ethers by hydrogenolysis on Pd–C, as described below, which will serve as versatile chiral building blocks for the synthesis of biologically active compounds containing polyamines.

Synthesis of Diamines, Amino Alcohols, Polyamino Alcohols, and Polyamino Ethers through Hydrogenolysis of Azetidines and Bisazetidines. Among the azetidines thus obtained, 2-arylazetidines, **2**, **5**, and **Ac-5**, were found to undergo 1,2-bond fission accompanied by removal of benzyl group through hydrogenolysis on Pd–C or Raney nickel to give 3-arylpropylamines **13**, **14**, and **Ac-14**, respectively in high to excellent yields (eq 7).

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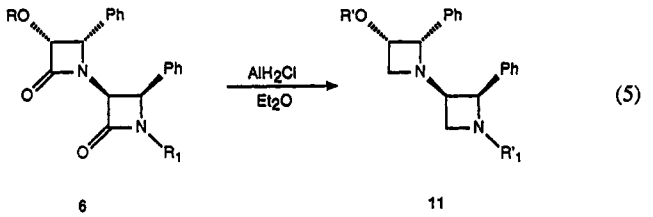
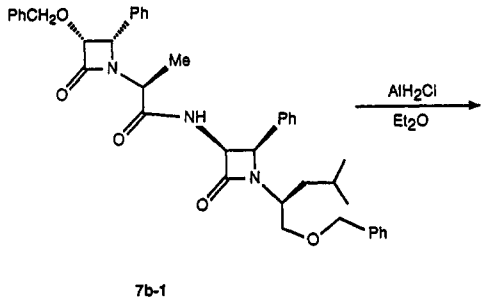
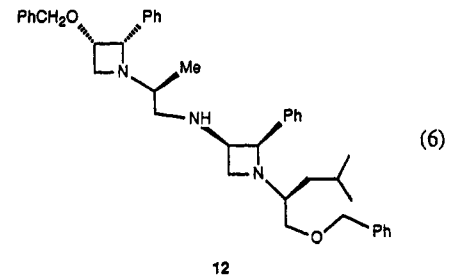


(5)

6 11



7b-1



(6)

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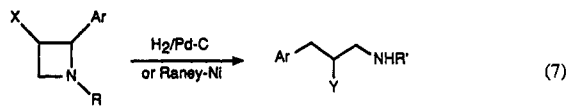
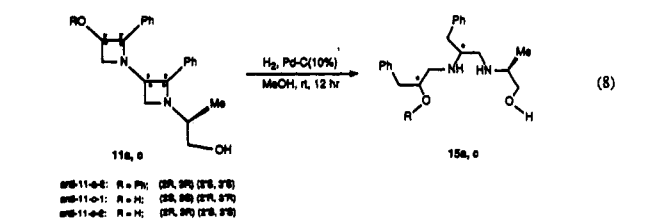


(7)

2: X = $PhCH_2O$
5: X = NH_2
Ac-5: X = AcNH

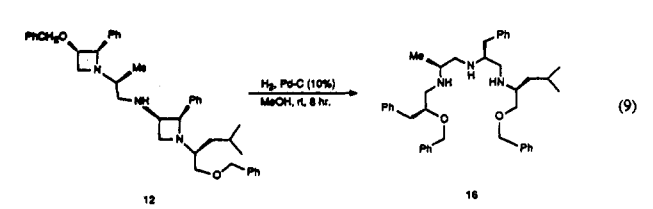
13: Y = OH
14: Y = NH_2
Ac-14: Y = AcNH

When enantiomerically pure azetidines (entries 2, 3, 6, 8, and 9) were submitted to the hydrogenolysis, amino diols and diamino alcohols were obtained without loss of enantiomeric purity. Results are listed in Table V. In a similar manner, bisazetidines **11a, c** and **12** were submitted to hydrogenolysis on Pd–C to give the corresponding polyamines, **15a, c** and **16**, respectively (eqs 8 and 9). It should be noted that the reductive cleavage of azetidine ring is much faster than that of benzyl–oxygen bond, and thus **16** was obtained as dibenzyl ether.



(8)

11a, c 15a, c



(9)

12 16

These amino alcohols, diamines, and polyamino polyols may serve as chiral chelating agents as well as versatile chiral building blocks for organic synthesis and for chiral macrocycles.

Experimental Section

General Methods. Melting points are uncorrected. Microanalyses were performed by M-H-W Laboratories, Phoenix, AZ, and Sagami Chemical Research Center, Japan. ^1H NMR spectra were recorded at 300 MHz with tetramethylsilane as the internal standard. ^{13}C NMR spectra were measured at 75 MHz with the central peak of $CDCl_3$ or methanol-d_4 as the internal standards. IR spectra were recorded using samples as neat liquid or KBr disks. HPLC analyses were carried out using columns packed with a Waters C18 or TOSOH LS 410K (reversed phase) and Waters Resolve 5μ-Spherical Silica or TOSOH LS 310K (normal phase). Mass spectra were obtained at 70 eV, and MS (FAB^+) spectra were acquired by using 3-nitrobenzyl alcohol or glycerol as the matrix solvent.

Materials. All amino acids were the gift of Ajinomoto Co., Inc., and used as obtained. Benzaldehyde and *tert*-butylamine were purchased from Aldrich Chemical Co. Inc., and distilled before use. *tert*-Butyl (*S*)-alaninate[17] and (*S*)-leucinol[18] were prepared from (*S*)-alanine and (*S*)-leucine, respectively, by the literature methods. Azidoacetyl chloride was prepared from azidoacetic acid with thionyl chloride, which was obtained from sodium azide and ethyl bromoacetate followed by saponification.[19] Palladium on carbon (5% and 10%) was purchased from Engelhart Corporation and Aldrich Chemical Co. Inc.

Synthesis of β-Lactams. 3-(Benzyloxy)-4-arylazetidin-2-ones (**1a–n**), 3-phenoxy-4-arylazetidin-2-ones (**1o,p**), 3-acetoxy-4-phenylazetidin-2-ones (**1q,r**), and 3-azido-4-phenylazetidin-2-ones (**4a–h**) were prepared through the standard [2 + 2] cycloadditions of (benzyloxy)ketene, phenoxyketene, acetoxyketene, and azidoketene with aryl imines, respectively, in good to excellent yields.[16] These ketenes were generated in situ by the reaction of (benzyloxy)acetyl chloride, phenoxyacetyl chloride, acetoxyacetyl chloride, and azidoacetyl chloride with triethylamine, respectively.[16] Enantiomerically pure β-lactams (**1g–j,m,n**, and **4d,e,h**) were obtained by chromatographic separation of the corresponding diastereomeric mixtures of cis-β-lactams on silica gel using hexanes/EtOAc as eluant.[16] 1-Methyl-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**4i**) was prepared by the literature method.[20] 1-[(*S*)-1-(*tert*-Butoxycarbonyl)-ethyl]-(3*S*,4*R*)-3-(benzylideneamino)-4-phenylazetidin-2-one (**8a-1**), 1-[(*S*)-1-(*tert*-butoxycarbonyl)ethyl)-(3*R*,4*S*)-3-(benzylideneamino)-4-phenylazetidin-2-one (**8a-2**), (3*S*,4*R*)-1-[(*S*)-1-[(benzyloxy)methyl]-3-methylbutyl]-3-(benzylideneamino)-4-phenylazetidin-2-one (**8b-1**), and (3*R*,4*S*)-1-[(*S*)-1-[(benzyloxy)-methyl]-3-methylbutyl]-3-(benzylideneamino)-4-phenylazetidin-2-one (**8b-2**) were prepared by the literature method.[16] Identification data for the new β-lactams are shown below.

(3*S*,4*R*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-3-(benzyloxy)-4-phenylazetidin-2-one (1g): colorless crystals; mp 72–72.5 °C; $[\alpha]^{20}_D$ −44.61° (*c* 0.777, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (d, *J* = 6 Hz, 3 H), 0.90 (d, *J* = 6 Hz, 3 H), 1.05–1.88 (m, 3 H), 3.27 (m, 2 H), 3.75 (m, 1 H), 4.07 (d, *J* = 11 Hz, 1 H), 4.22 (d, *J* = 11 Hz, 1 H), 4.21 (s, 2 H), 4.68 (d, *J* = 5 Hz, 1 H), 4.77 (d, *J* = 5 Hz, 1 H), 6.75–7.52 (m, 15 H); IR (KBr disk) 1760 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.11; H, 7.70; N, 3.14.

(3*R*,4*S*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-3-(benzyloxy)-4-phenylazetidin-2-one (1h): colorless oil; $[\alpha]^{20}_D$ +51.57° (*c* 0.877, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.66 (d, *J* = 6 Hz, 3 H), 0.83 (d, *J* = 6 Hz, 3 H), 0.75–1.95 (m, 3 H), 3.40–2.50 (m, 2 H), 3.90 (m, 1 H), 4.03 (d, *J* = 11 hz, 1 H), 4.22 (d, *J* = 11 Hz, 1 H), 4.37 (d, *J* = 12 Hz, 1 H), 4.52 (d, *J* = 12 Hz, 1 H), 4.65 (d, *J* = 5 Hz, 1 H), 4.78 (d, *J* = 5 Hz, 1 H), 6.80–7.52 (m, 15 H); IR (neat) 1760 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{29}H_{33}NO_3 \cdot 0.25H_2O$:

(17) Anderson, G. M.; Callahan, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 3359–3363.

(18) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527–3532.

(19) **Caution**: We recommend that the reaction of azidoacetic acid with thionyl chloride should be carried out below 60 °C and the distillation of azidoacetyl chloride should be performed under reduced pressure (8–10 mmHg) and receivers cooled with dry ice under nitrogen flow collecting 30–35 °C fraction. The thionyl chloride reaction could lead to explosion if the reaction is carried out at more than 95–100 °C.

(20) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron Lett.* **1988**, *44*, 5307.

C, 78.52; H, 7.50; N, 3.16. Found: C, 77.65; H, 7.45; N, 3.06.

(3*S*,4*R*)-1-[(*S*)-1-Phenylethyl]-3-(benzyloxy)-4-phenylazetidin-2-one (1i): colorless crystals; mp 156–158 °C; $[\alpha]^{20}_D$ −99.2° (*c* 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.80 (d, *J* = 7.2 Hz, 3 H), 4.13 (d, *J* = 11.2 Hz, 1 H), 4.25 (d, *J* = 11.2 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 1 H), 4.51 (d, *J* = 4.5 Hz, 1 H), 4.77 (d, *J* = 4.5 Hz, 1 H), 6.89–7.40 (m, 15 H); IR (KBr disk) 1737 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.47; H, 6.57; N, 3.89.

(3*R*,4*S*)-1-[(*S*)-1-Phenylethyl]-3-(benzyloxy)-4-phenylazetidin-2-one (1j): colorless crystals; mp 117–120 °C; $[\alpha]^{20}_D$ +59.4° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33 (d, *J* = 7.2 Hz, 3 H), 4.08 (d, *J* = 11.3 Hz, 1 H), 4.19 (d, *J* = 11.3 Hz, 1 H), 4.43 (d, *J* = 4.5 Hz, 1 H), 4.71 (d, *J* = 4.5 Hz, 1 H), 5.09 (q, *J* = 7.2 Hz, 1 H), 6.90–7.50 (m, 15 H); IR (KBr disk) 1747 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.55; H, 6.55; N, 3.95.

(3*R,4*S**)-1-[(*S*)-1-(*tert*-Butoxycarbonyl)-3-methylbutyl]-3-(benzyloxy)-4-(4-fluorophenyl)azetidin-2-one (1k,l)**: mp 87–88 °C; ^1H NMR ($CDCl_3$) (for **1k**) δ 0.58 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.4 Hz, 3 H), 1.15–1.40 (m, 3 H), 1.45 (s, 9 H), 4.17 (d, *J* = 11.4 Hz, 1 H), 4.33 (d, *J* = 11.4 Hz, 1 H), 4.32–4.37 (m, 1 H), 4.91 (d, *J* = 4.7 Hz, 1 H), 5.02 (d, *J* = 4.7 Hz, 1 H), 7.00–7.50 (m, 9 H); (for **1l**) δ 0.79 (d, *J* = 6.4 Hz, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 1.15–1.80 (m, 2 H), 1.38 (s, 9 H), 2.10–2.20 (m, 1 H), 3.75 (dd, *J* = 10.0, 5.5 Hz, 1 Hz), 4.17 (d, *J* = 11.4 Hz, 1 H), 4.33 (d, *J* = 11.4 hz, 1 H), 4.70 (d, *J* = 4.7 Hz, 1 H), 4.85 (d, *J* = 4.7 Hz, 1 H), 7.0–7.4 (m, 9 H); IR (KBr disk) 1762, 1735 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{26}H_{32}FNO_4$: C, 70.73; H, 7.30; N, 3.17; F, 4.30. Found: C, 70.82; H, 7.31; N, 3.20; F, 4.46.

For **1m and 1n**, see the preparation of **9a** and **9c** (vide infra).

(3*S,4*R**)-1-[(*S*)-1-(*tert*-Butoxycarbonyl)-3-methylbutyl]-3-acetoxy-4-phenylazetidin-2-one (1q,r)**: mp 60–61 °C; ^1H NMR ($CDCl_3$) δ [0.63 (d, *J* = 6.6 Hz), 0.86 (d, *J* = 6.5 Hz), 0.99 (d, *J* = 6.5 Hz)] (6 H), [1.40 (s), 1.48 (s)] (9 H), [1.68 (s), 1.73 (s)] (3 H), 1.25–2.26 (m, 3 H), [3.80 (dd, *J* = 9.8, 5.8 Hz), 4.34 (dd, *J* = 9.3, 5.6 Hz)] (1 H), [4.92 (d, *J* = 5.0 Hz), 5.18 (d, *J* = 4.9 Hz)] (1 H), [5.80 (d, *J* = 4.9 Hz, 5.85 (d, *J* = 5.0 Hz)] (1 H), 7.30–7.50 (m, 5 H); IR (KBr disk) 1753, 1729 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.16; H, 7.60; N, 3.76.

Reduction of β-Lactams with DIBAL-H. A typical procedure for the DIBAL-H reduction of **1** is as follows. To a refluxing solution of (3*S**,4*R**)-3-(benzyloxy)-1,4-diphenylazetidin-2-one (**1a**) (207 mg, 0.629 mmol) in 5 mL of THF was added 2.5 mL of 1 M DIBAL-H solution in *n*-hexane (2.5 mmol), and the mixture was refluxed for 2 h with stirring. Then, 50 mL of water was added to the reaction mixture and extracted with CH_2Cl_2 (70 mL). After the extract was dried over anhydrous $MgSO_4$, the solvent was removed and the residue was submitted to a column chromatography on silica gel (EtOAc/hexane, 1/5) to give (2*R**,3*R**)-1,2-diphenyl-3-(benzyloxy)azetidine (**2a**) (144 mg, 73%) and 3-(phenylamino)-3-phenyl-2-(benzyloxy)propanol (**3a**) (34 mg, 16%).

2a: colorless crystals; mp 94–96 °C; ^1H NMR ($CDCl_3$) δ 3.99–4.12 (m, 4 H), 4.55 (ddd, *J* = 6.2, 5.8, 3.4 Hz, 1 H), 5.11 (d, *J* = 6.2 Hz, 1 H), 6.37–7.65 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 57.09, 71.48, 72.13, 72.18, 111.98, 117.63, 127.61, 127.75, 127.86, 128.08, 128.17, 128.26, 128.76; IR (KBr disk) 3100–3010, 2980–2830, 1600, 1500, 1457, 1342, 1120–1060, 753, 742, 698 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 84.04; H, 6.80; N, 4.28.

3a: white solid; mp 105–106 °C; ^1H NMR ($CDCl_3$) δ 1.58 (br, 2 H), 3.69–3.85 (m, 3 H), 4.35 (d, *J* = 11.5 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 4.59 (d, *J* = 3.5 Hz, 1 H), 6.50–7.50 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 58.26, 62.27, 73.14, 83.22, 113.77, 117.59, 127.06, 127.27, 128.02, 128.57, 129.07, 137.64, 141.14, 147.12.

In a similar manner, β-lactams **1b–d** were reduced to the corresponding azetidines **2b–d**, which were isolated through column chromatography on silica gel.

(2*R,3*R**)-1-Phenyl-2-(4-fluorophenyl)-3-(benzyloxy)azetidine (2b)**: white solid; mp 81–83 °C; ^1H NMR ($CDCl_3$) δ 3.83–4.27 (m, 4 H), 4.43 (m, 1 H), 5.03 (d, *J* = 6.0 Hz, 1 H), 6.23–7.67 (m, 14 H); IR (KBr disk) 3080, 3050, 2950, 2870, 1605, 1505, 1350, 1225, 1150, 850, 750, 700 cm^{-1}. Anal. Calcd for $C_{22}H_{20}FNO$: C, 79.26; H, 6.05; N, 4.20. Found: C, 79.11; H, 6.02; N, 4.20.

(2*R,3*R**)-1-Phenyl-2-(2-furyl)-3-(benzyloxy)azetidine (2c)**: colorless oil; ^1H NMR ($CDCl_3$) δ 3.96 (dd, *J* = 8.4, 6.7 Hz, 1 H), 4.02 (dd, *J* = 8.4, 3.2 Hz, 1 H), 4.20 (s, 2 H), 4.49–4.55 (m, 1 H), 5.15 (d, *J* = 6.0 Hz, 1 H), 6.42–6.76 (m, 6 H), 7.17–7.48 (m, 7 H); IR (neat) 3086, 3062, 3030, 2924, 2858, 1600, 1504, 1495, 1455, 1359, 1212, 1178, 1153, 1120, 995, 883, 750, 693, 599, 516 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.51; H, 6.33; N, 4.58.

(2*R,3*R**)-1-Phenyl-2-(2-thienyl)-3-(benzyloxy)azetidine (2d)**: yellow oil; ^1H NMR ($CDCl_3$) δ 3.53 (t, *J* = 5 Hz, 1 H), 4.22 (m, 2 H), 4.43 (d, *J* = 12 Hz, 1 H), 4.61 (d, *J* = 12 Hz, 1 H), 5.02 (d, *J* = 4 Hz, 1 H), 6.47–7.50 (m, 13 H); IR (neat) 3080, 3050, 2950, 2880, 1610, 1510, 1350, 1130, 760, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36; S, 9.97. Found: C, 74.56; H, 5.87; N, 4.23; S, 9.89.

(2*R,3*R**)-1-Phenyl-2-(3,4-dimethoxyphenyl)-3-(benzyloxy)azetidine (2e)**: white solid; mp 129.5–130.5 °C; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 3.87 (s, 3 H), 3.98 (m, 4 H), 4.38 (m, 1 H), 4.93 (d, *J* = 6.0 Hz, 1 H), 6.27–7.50 (m, 13 H); IR (KBr disk) 3050, 2940, 2860, 1600, 1500, 1270, 1130, 750, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.84; H, 6.37; N, 3.61.

Reduction of β-Lactams with Chlorohydroalane. A typical procedure for the AlH_2Cl reduction of **4** is as follows. A mixture of $AlCl_3$ (400 mg, 3.00 mmol) and $LiAlH_4$ (114 mg, 3.00 mmol) in 15 mL of ether was refluxed for 30 min with stirring. To the AlH_2Cl solution thus prepared was added **4e** (379 mg, 1.00 mmol), and the mixture was stirred under refluxing for 4 h. Then 50 mL of water was added to the reaction mixture and extracted with CH_2Cl_2 (90 mL). A centrifugal separation was helpful for this extraction. The extract was dried over anhydrous $MgSO_4$, and the solvent was removed to give (2*R*,3*R*)-1-[(*S*)-1-[(benzyloxy)-methyl]-3-methylbutyl]-2-phenyl-3-aminoazetidin-2-one (**5e**) (217 mg, 64%) as a pale yellow oil.

5e: $[\alpha]^{20}_D$ −96.5° (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 6.5 Hz, 3 H), 1.03–1.18 (m, 2 H), 1.20 (bs, 2 H), 1.54–1.68 (m, 1 H), 2.60–2.68 (m, 1 H), 3.13 (d, *J* = 7.7 Hz, 1 H), 3.41–3.58 (m, 4 H), 4.44 (d, *J* = 6.4 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 7.25–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 22.42, 23.23, 24.92, 39.01, 48.12, 57.40, 61.50, 70.67, 71.65, 73.03, 126.72, 127.29, 127.93, 128.12, 138.47, 139.65; IR (neat) 3374, 3300 (ν_{NH_2}), 1602, 1493, 1466, 1452, 1384, 1365, 1101, 1027, 910, 805, 745, 699 cm^{-1}. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 77.93; H, 8.77; N, 8.14. This compound was converted to its *N*-acetyl derivative (**Ac-5e**) by reaction with acetic anhydride in the presence of pyridine in $CHCl_3$ at ambient temperature overnight in quantitative yield.

(2*R*,3*R*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-2-phenyl-3-(acetylamino)azetidine (Ac-5e): light yellow solid; mp 88–90 °C; $[\alpha]^{20}_D$ −35.2° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.77 (d, *J* = 6.6 Hz, 3 H), 0.79 (d, *J* = 6.4 Hz, 3 H), 0.98–1.17 (m, 2 H), 1.54–1.64 (m, 1 H), 1.65 (s, 3 H), 2.64–2.70 (m, 1 H), 3.23 (dd, *J* = 8.4, 18 Hz, 1 H), 3.46 (d, *J* = 4.3 Hz, 2 H), 3.58 (dd, *J* = 8.4, 7.0 Hz, 1 H), 4.49 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.57–4.64 (m, 1 H), 4.71 (d, *J* = 7.3 Hz, 1 H), 5.61 (bd, *J* = 8.0 Hz, 1 H), 7.25–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 22.39, 22.90, 23.26, 24.96, 38.77, 45.47, 55.93, 61.36, 68.95, 71.48, 73.20, 127.15, 127.27, 127.43, 128.16, 128.26, 128.35, 138.71, 169.74; IR (KBr disk) 3258, 3064, 2954, 2866, 1646, 1552, 1452, 1373, 1293, 1101, 1028, 753, 699, 604 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.71; H, 8.53; N, 7.26.

In a similar manner, other azetidines were synthesized by the reduction of β-lactams with chlorohydroalane.

(2*R,3*R**)-1-Benzyl-2-phenyl-3-(benzyloxy)azetidine (2f)**: colorless oil; ^1H NMR ($CDCl_3$) δ 3.07–3.12 (m, 1 H), 3.40 (d, *J* = 9.0 Hz, 1 H), 3.42 (d, *J* = 13.2 Hz, 1 H), 3.85 (d, *J* = 13.2 Hz, 1 H), 3.96 (d, *J* = 11.5 Hz, 1 H), 4.00 (d, *J* = 11.5 Hz, 1 H), 4.27–4.32 (m, 2 H), 7.00–7.70 (m, 15 H); IR (neat) 3080, 3050, 2940, 2850, 1500, 1453, 1350, 1225, 1152, 1110, 1030, 740, 700 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.83; H, 6.79; N, 4.12. Found: C, 83.85; H, 7.04; N, 4.25.

(2*R*,3*R*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-2-phenyl-3-(benzyloxy)azetidine (2g): yellow oil; $[\alpha]^{20}_D$ −56.62° (*c* 0.773, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.72 (d, *J* = 6.0 Hz, 3 H), 0.78 (d, *J* = 6.0 Hz, 3 H), 0.87–1.90 (m, 3 H), 2.65 (m, 1 H), 3.45

Table I. Reduction of Azetidin-2-ones with Hydroalane Giving Azetidines

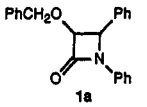
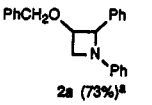
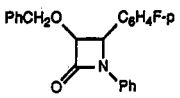
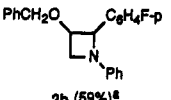
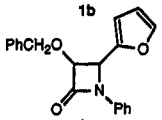
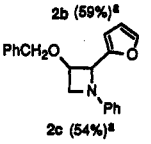
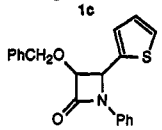
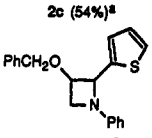
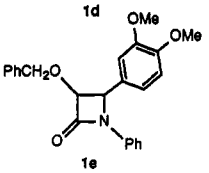
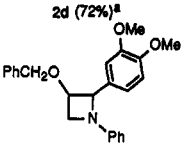
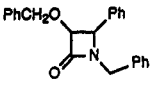
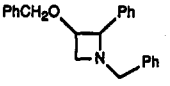
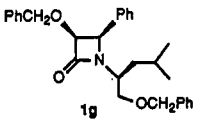
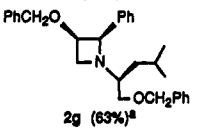
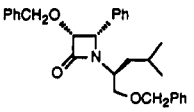
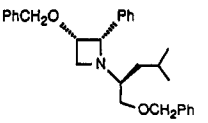
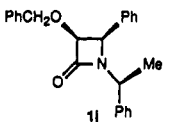
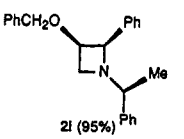
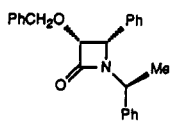
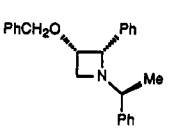
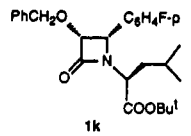
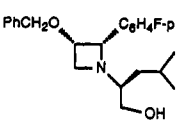
entry	azetidin-2-one	reducing agents	conditions: temp, °C; time, h; solvent	products (isolated yield)
1	 1a	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2a (73%)[a]
2	 1b	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2b (59%)[a]
3	 1c	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2c (54%)[a]
4	 1d	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2d (72%)[a]
5	 1e	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2e (77%)[a]
6	 1f	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2f (85%)[a]
7	 1g	DIBAL-H (3.0)	65; 2; THF *n*-hexane	 2g (63%)[a]
8	1a	AlH_2Cl (2.4)	34; 1.5; Et_2O	2a (94%)
9	1a	$AlHCl_2$ (12.0)	34; 1.5; Et_2O	2a (94%)
10	1b	AlH_2Cl (2.4)	34; 1.5; Et_2O	2b (94%)
11	1f	AlH_2Cl (2.4)	34; 1.5; Et_2O	2f (96%)
12	1g	AlH_2Cl (2.4)	34; 1.5; Et_2O	2g (85%)
13	 1h	AlH_2Cl (2.4)	34; 1.5; Et_2O	 2h (92%)
14	 1i	AlH_2Cl (2.4)	34; 1.5; Et_2O	 2i (95%)
15	 1j	AlH_2Cl (2.4)	34; 1.5; Et_2O	 2j (84%)
16	 1k	AlH_2Cl (4.6)	34; 4; Et_2O	 2k (74%)

Table I (Continued)

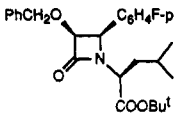
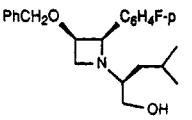
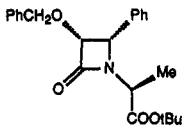
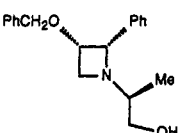
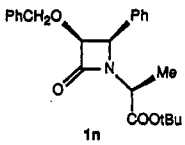
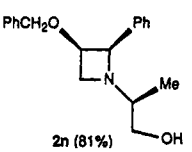
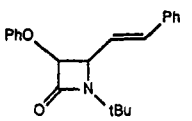
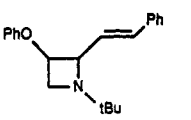
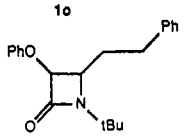
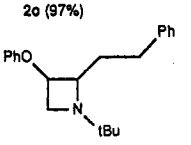
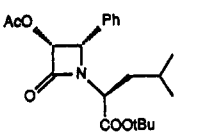
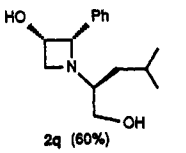
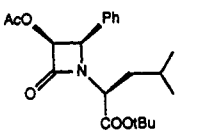
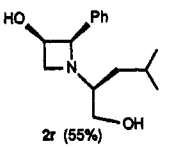
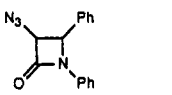
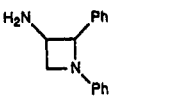
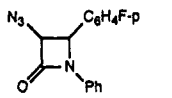
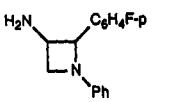
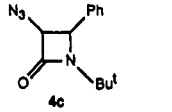
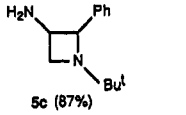
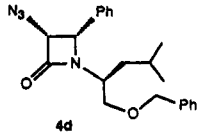
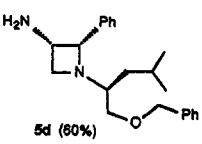
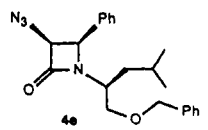
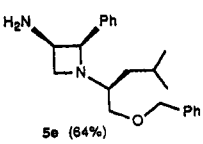
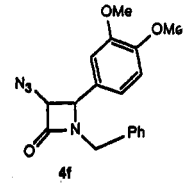
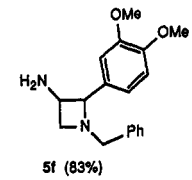
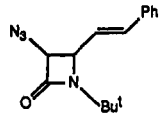
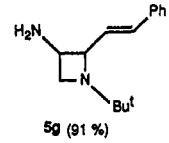
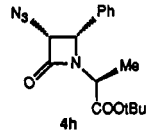
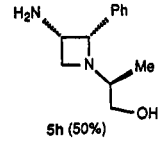
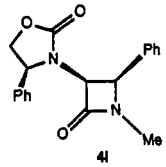
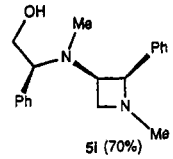
entry	azetidin-2-one	reducing agents	conditions: temp, °C; time, h; solvent	products (isolated yield)
17	 1l	AlH_2Cl (4.6)	34; 4; Et_2O	 2l (89%)
18	 1m	AlH_2Cl (6.0)	34; 4; Et_2O	 2m (89%)
19	 1n	AlH_2Cl (6.0)	34; 4; Et_2O	 2n (81%)
20	 1o	AlH_2Cl (2.4)	34; 1.5; Et_2O	 2o (97%)
21	 1p	AlH_2Cl (2.4)	34; 1.5; Et_2O	 2p (91%)
22	 1q	AlH_2Cl (6.0)	34; 4; Et_2O	 2q (60%)
23	 1r	AlH_2Cl (6.0)	34; 4; Et_2O	 2r (55%)
24	 4a	AlH_2Cl (4.0)	34; 4; Et_2O	 5a (90%)
25	4a	$AlHCl_2$ (16)	34; 2; Et_2O	5a (79%)
26	 4b	AlH_2Cl (3.5)	34; 2; Et_2O	 5b (75%)
27	 4c	AlH_2Cl (4.0)	34; 2; Et_2O	 5c (87%)
28	 4d	AlH_2Cl (6.0)	34; 4; Et_2O	 5d (60%)
29	 4e	AlH_2Cl (6.0)	34; 4; Et_2O	 5e (64%)

Table I (Continued)

entry	azetidin-2-one	reducing agents	conditions: temp, °C; time, h; solvent	products (isolated yield)
30	 4f	AlH_2Cl (3.0)	34; 2; Et_2O	 5f (83%)
31	 4g	AlH_2Cl (10)	34; 2; Et_2O	 5g (91 %)
32	 4h	AlH_2Cl (6.0)	34; 4; Et_2O	 5h (50%)
33	 4l	DIBAL-H (10)	65; 3; THF	 5l (70%)

[a] The reaction gave the ring opened product, amino alcohol **3** as the side product: **3a**, 11%; **3b**, 17%; **3c**, 27%; **3d**, 17%; **3e**, <1%; **3f**, <1%; **3g**, 14%. They were identified by comparison with authentic samples obtained in the $LiAlH_4$ reduction of **1a–g** on ^1H NMR and HPLC.

Table II. Solvent Effects on the Selectivity

entry	reducing agent	solvent	temp (°C)	yield (%)	product ratio (%)[a] 2a	3a
1	AlH_2Cl (2.4)	Ether	34	100	98	2
2	DIBAL-H (3.0)	THF	65	100	90	10
3	DIBAL-H (3.0)	Ether	34	98	90	10
4	DIBAL-H (3.0)	Tolune	50	100	65	35
5	$LiAlH_4$ (2.4)	THF	65	100	<1	>99

[a] Determined by ^1H NMR and HPLC analyses.

(m, 4 H), 3.88 (s, 2 H), 4.20 (m, 1 H), 4.47 (s, 2 H), 4.47 (d, J = 6.0 Hz, 1 H), 6.83–7.73 (m, 15 H); IR (neat) 3070, 3030, 2950, 2860, 1500, 1450, 1460, 1055, 740, 700, 560 cm^{-1}. Anal. Calcd for $C_{29}H_{35}NO_2$: C, 81.08; H, 8.21; N, 3.26. Found: C, 80.67; H, 8.32; N, 3.13.

(2*S*,3*S*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl-2-phenyl-3-(benzyloxy)azetidine (2h): yellow oil; $[\alpha]^{20}_D$ +89.02° (*c* 0.720, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.97 (d, J = 7 Hz, 3 H), 1.10–1.90 (m, 3 H), 2.62 (m, 1 H), 3.28 (m, 3 H), 3.57 (m, 1 H), 4.00 (m, 4 H), 4.23 (m, 1 H), 4.47 (d, J = 6 Hz, 1 H), 6.93–7.77 (m, 15 H); IR (neat) 3080, 3050, 2970, 2880, 1500, 1450, 1120, 740, 700 cm^{-1}. Anal. Calcd for $C_{29}H_{35}NO_2$: C, 81.08; H, 8.21; N, 3.26. Found: C, 81.27; H, 8.40; N, 3.15.

(2*R*,3*R*)-1-(1-Phenylethyl)-2-phenyl-3-(benzyloxy)azetidine (2i): colorless oil; $[\alpha]^{20}_D$ –60.3° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 3 H), 2.93 (dd, J = 9.1, 6.3 Hz, 1 H), 3.25 (d, J = 9.1 Hz, 1 H), 3.44 (q, J = 6.5 Hz, 1 H), 3.85 (d, J = 11.4 Hz, 1 H), 3.90 (d, J = 11.4 Hz, 1 H), 4.18 (m, 1 H), 4.29 (d, J = 5.8 Hz, 1 H), 6.70–7.80 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 22.86, 56.76, 67.98, 71.22, 72.18, 72.32, 126.81, 127.14, 127.17, 127.34, 127.79, 128.01, 128.03, 128.15, 128.51, 137.68; IR (neat) 3100–3000, 2980–2970, 1600, 1490, 1450, 1343, 1215, 1110, 750, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.92; H, 7.22; N, 4.08.

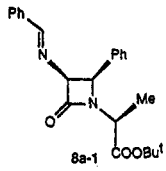
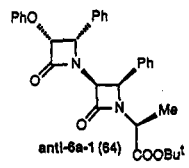
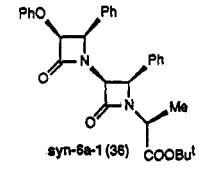
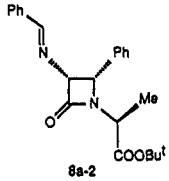
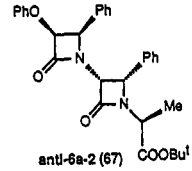
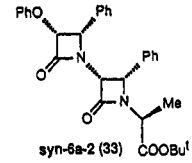
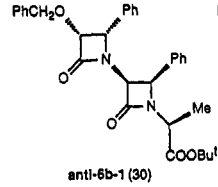
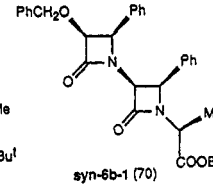
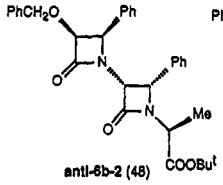
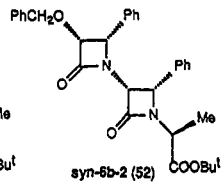
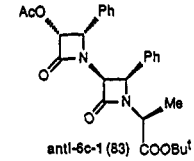
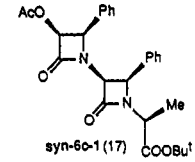
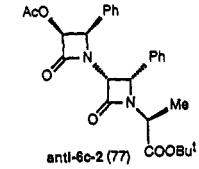
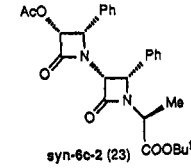
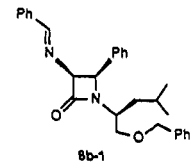
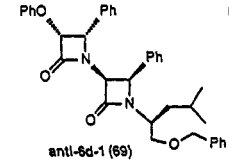
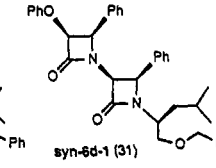
(2*S*,3*S*)-1-(1-Phenylethyl)-2-phenyl-3-(benzyloxy)azetidine (2j): colorless crystals; mp 59–61 °C; $[\alpha]^{20}_D$ +115.1° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3 H), 3.26 (dd, J = 8.7, 6.5 Hz, 1 H), 3.44 (q, J = 6.5 Hz, 1 H), 3.59 (dd, J = 8.7, 1.4 Hz, 1 H), 3.86 (d, J = 11.4 Hz, 1 H), 3.91 (d, J = 11.4 Hz, 1 H), 4.15 (d, J = 5.8 Hz, 1 H), 4.23 (ddd, J = 6.5, 5.8, 1.4 Hz, 1 H), 6.9–7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 20.30, 56.89, 67.04, 71.37, 72.00, 72.59, 126.99, 127.35, 127.51, 127.96, 128.21, 128.34, 128.69, 137.86, 139.70, 144.11; IR (KBr disk) 3100–3000, 2980–2960, 1600, 1490, 1457, 1450, 1347, 1166, 1119, 755, 745, 697 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.02; H, 7.09; N, 4.25.

(2*S*,3*S*)-1-[(*S*)-1-(Hydroxymethyl)-3-methylbutyl]-2-(4-fluorophenyl)-3-(benzyloxy)azetidine (2k): colorless oil; $[\alpha]^{20}_D$ +124.5° (*c* 2.14, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 1.06–1.14 (m, 1 H), 1.35–1.44 (m, 1 H), 1.51–1.65 (m, 1 H), 1.95 (bs, 1 H), 2.37–2.44 (m, 1 H), 3.21 (dd, J = 11.5, 4.3 Hz, 1 H), 3.26 (dd, J = 11.5, 3.1 Hz, 1 H), 3.30 (dd, J = 8.8, 6.1 Hz, 1 H), 3.41 (bd, J = 8.8 Hz, 1 H), 3.90 (d, J = 11.4 Hz, 1 H), 3.99 (d, J = 11.4 Hz, 1 H), 4.24 (td, J = 6.0, 1.6 Hz, 1 H), 4.29 (d, J = 6.0 Hz, 1 H), 7.00–7.60 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 21.91, 23.85, 24.73, 35.63, 54.25, 60.63, 63.94, 70.49, 71.21, 72.35, 114.88, 115.15, 127.40, 127.49, 128.06, 129.85, 129.96, 134.06, 137.41, 162.40 (d, J_{C-F} = 246.3 Hz); IR (neat) 3460, 3063, 3031, 2954, 2928, 2867, 1603, 1508, 1467, 1454, 1346, 1223, 1154, 1112, 1051, 847, 817, 737, 697 cm^{-1}. Anal. Calcd for $C_{22}H_{28}FNO_2$: C, 73.92; H, 7.89; N, 3.92; F, 5.32. Found: C, 73.81; H, 7.77; N, 3.97; F, 5.46.

(2*R*,3*R*)-1-[(*S*)-1-(Hydroxymethyl)-3-methylbutyl]-2-(4-fluorophenyl)-3-(benzyloxy)azetidine (2l): colorless oil; $[\alpha]^{20}_D$ –46.7 (*c* 2.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.77 (d, J = 5.4 Hz, 3 H), 0.79 (d, J = 6.0 Hz, 3 H), 0.78–0.86 (m, 1 H), 1.13–1.26 (m, 1 H), 1.42–1.61 (m, 1 H), 2.33 (bs, 1 H), 2.42–2.48 (m, 1 H), 3.27 (dd, J = 8.9, 6.5 Hz, 1 H), 3.31 (dd, J = 11.4, 3.2 Hz, 1 H), 3.51–3.56 (m, 2 H), 3.88 (d, J = 11.4 Hz, 1 H), 3.97 (d, J = 11.4 Hz, 1 H), 4.25 (bt, J = 6.1 Hz, 1 H), 4.42 (d, J = 5.8 Hz, 1 H), 7.00–7.60 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 21.86, 23.65, 24.86, 36.34, 56.46, 60.49, 64.85, 69.48, 71.24, 72.27, 114.52, 114.79, 127.42, 127.57, 128.06, 129.71, 129.83, 134.56, 137.35, 162.18 (d, J_{C-F} = 246.2 Hz); IR (neat) 3440, 3064, 3031, 2954, 2928, 2867, 1603, 1508, 1222, 1112, 1047, 846, 817, 737, 697 cm^{-1}. Anal. Calcd for $C_{22}H_{28}FNO_2$: C, 73.92; H, 7.89; N, 3.92; F, 5.32. Found: C, 74.14; H, 7.67; N, 3.98; F, 5.51.

(2*S*,3*S*)-1-[(*S*)-2-Hydroxy-1-methylethyl]-2-phenyl-3-(benzyloxy)azetidine (2m): colorless oil; $[\alpha]^{20}_D$ +92.5° (*c* 0.76, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 6.5 Hz, 3 H), 1.95 (bs,

Table III. Synthesis of Direct-Tandem Bis-β-lactams (6)

entry	3-Imino β-lactam (8)	R	isolated yield (%)	bis-β-lactam (6) (diastereomeric %)
1	 8a-1	Ph	71	 antl-6a-1 (64)  syn-6a-1 (36)
2	 8a-2	Ph	80	 antl-6a-2 (67)  syn-6a-2 (33)
3	8a-1	$PhCH_2$	58	 antl-6b-1 (30)  syn-6b-1 (70)
4	8a-2	$PhCH_2$	83	 antl-6b-2 (48)  syn-6b-2 (52)
5	8a-1	Ac	72	 antl-6c-1 (83)  syn-6c-1 (17)
6	8a-2	Ac	77	 antl-6c-2 (77)  syn-6c-2 (23)
7	 8b-1	Ph	87	 antl-6d-1 (69)  syn-6d-1 (31)

1 H), 2.50–2.59 (m, 1 H), 3.15 (dd, J = 11.2, 4.5 Hz, 1 H), 3.25 (dd, J = 11.2, 3.7 Hz, 1 H), 3.31 (dd, J = 8.9, 6.1 Hz, 1 H), 3.43 (bd, J = 8.8 Hz, 1 H), 3.87 (d, J = 11.3 Hz, 1 H), 3.95 (d, J = 11.3 Hz, 1 H), 4.26 (ddd, J = 5.9, 5.9, 1.3 Hz, 1 H), 4.30 (d, J = 5.9 Hz, 1 H), 7.0–7.7 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 13.21, 54.61, 61.74, 63.85, 71.29, 71.75, 72.52, 127.40, 127.74, 128.05, 128.25, 137.48, 138.17; IR (neat) 3418, 3085, 3061, 3028, 2940, 2872, 1494, 1453, 1346, 1163, 1109, 1056, 1026, 734, 699 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.79; H, 7.86; N, 4.55.

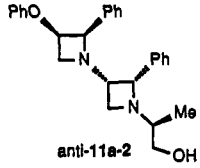
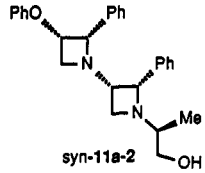
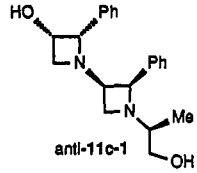
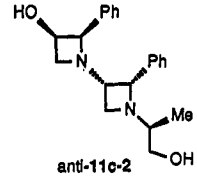
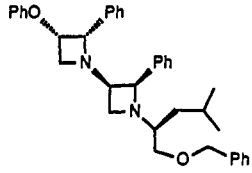
(2*R*,3*R*)-1-[(*S*)-2-Hydroxy-1-methylethyl]-2-phenyl-3-(benzyloxy)azetidine (2n): white solid; mp 57–59 °C; $[\alpha]^{20}_D$ −72.7° (c 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 3 H), 2.41 (bd, J = 6.2 Hz, 1 H), 2.53–2.58 (m, 1 H), 3.22–3.31 (m, 2 H), 3.52–3.58 (m, 2 H), 3.85 (d, J = 11.3 Hz, 1 H), 3.93 (d, J = 11.3 Hz, 1 H), 4.24–4.29 (m, 1 H), 4.40 (d, J = 5.8 Hz, 1 H), 6.9–7.6 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 14.68, 57.06, 62.94, 63.83, 70.88, 71.39, 72.56, 127.41, 127.46, 127.85, 127.94, 128.10, 128.30, 137.47, 138.81; IR (KBr disk) 3406, 3085, 3062, 3028, 2966, 2930, 2861, 1494, 1454, 1345, 1111, 1053, 1028, 734, 698 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.82; H, 7.79; N, 4.72.

(2*R,3*R**)-1-*tert*-Butyl-2-(2-phenylethenyl)-3-phenoxyazetidine (2o)**: white solid; mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 3.34 (d, J = 8.8 Hz, 2 H), 3.51 (dd, J = 8.8, 5.9 Hz, 1 H), 4.27–4.32 (m, 1 H), 4.76 (t, J = 5.9 Hz, 1 H), 6.55 (m, 2 H), 6.80 (d, J = 7.9 Hz, 1 H), 6.88 (d, J = 7.4 Hz, 1 H), 7.15–7.35 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 24.98, 50.47, 52.70, 64.50, 70.68, 115.06, 120.68, 126.43, 127.31, 128.32, 129.13, 129.61, 132.22, 137.09, 157.71; IR (KBr disk) 3085, 3067, 3027, 2980, 2942, 2860, 1599, 1590, 1488, 1357, 1230, 1100, 979, 970, 753, 744, 692 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.26; H, 8.32; N, 4.57.

(2*R,3*R**)-1-*tert*-Butyl-2-(2-phenylethyl)-3-phenoxyazetidine (2p)**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9 H), 1.81–1.90 (m, 1 H), 2.48–2.60 (m, 2 H), 2.67–2.80 (m, 1 H), 3.29 (bd, J = 9.2 Hz, 1 H), 3.45 (dd, J = 9.2, 6.1 Hz, 1 H), 3.64–3.71 (m, 1 H), 4.71 (td, J = 6.4, 2.2 Hz, 1 H), 6.80–7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 25.05, 32.13, 32.88, 50.57, 52.36, 61.26, 68.15, 114.89, 120.64, 125.54, 128.15, 129.28, 142.14, 157.53; IR (neat) 3084, 3061, 3026, 2964, 2863, 1599, 1586, 1494, 1454, 1361, 1242, 751, 692 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.30; H, 8.83; N, 4.46.

(2*S*,3*S*)-1-[(*S*)-1-(Hydroxymethyl)-3-methylbutyl]-2-

Table IV. Synthesis of Bisazetidines (11)

entry	bis-β-lactams	conditions (equiv)	bisazetidines	isolated yield (%)
1	*anti*-**6a**-2	AlH_2Cl (7.2)	 anti-**11a**-2	77
2	*syn*-**6a**-2	AlH_2Cl (7.2)	 syn-**11a**-2	85
3	*anti*-**6c**-1	AlH_2Cl (10)	 anti-**11c**-1	70
4	*anti*-**6c**-2	AlH_2Cl (10)	 anti-**11c**-2	54
5	*anti*-**6d**-2	AlH_2Cl (10)	 anti-**11d**-1	86

phenyl-3-hydroxyazetidine (2q): white solid; mp 94–95 °C; $[\alpha]^{20}_D$ +221.6° (*c* 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.5 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 1.11–1.20 (m, 1 H), 1.36–1.46 (m, 1 H), 1.56–1.70 (m, 1 H), 1.70 (bs, 2 H), 2.43–2.50 (m, 1 H), 3.25 (dd, *J* = 11.5, 4.8 Hz, 1 H), 3.28–3.42 (m, 3 H), 4.38 (d, *J* = 6.1 Hz, 1 H), 4.40–4.47 (m, 1 H), 7.30–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.98, 23.92, 24.85, 35.50, 56.03, 61.10, 63.69, 65.96, 71.48, 127.76, 127.90, 128.53, 137.31; IR (KBr disk) 3410, 3054, 2953, 2865, 2849, 1498, 1470, 1450, 1334, 1164, 1118, 1043, 1017, 756, 718, 697 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.14; H, 9.35; N, 5.58.

(2*R*,3*R*)-1-[(*S*)-1-(Hydroxymethyl)-3-methylbutyl]-2-phenyl-3-(benzyloxy)azetidine (2r): white solid; mp 85–86 °C; $[\alpha]^{20}_D$ −116° (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.775 (d, *J* = 6.6 Hz, 3 H), 0.784 (d, *J* = 6.5 Hz, 3 H), 0.80–0.90 (m, 1 H), 1.23–1.33 (m, 1 H), 1.49–1.61 (m, 1 H), 1.65 (bs, 2 H), 2.43–2.50 (m, 1 H), 3.30 (dd, *J* = 8.8, 5.6 Hz, 1 H), 3.40 (dd, *J* = 11.3, 3.0 Hz, 1 H), 3.46 (bd, *J* = 8.8 Hz, 1 H), 3.59 (dd, *J* = 11.3, 2.6 Hz, 1 H), 4.43–4.48 (m, 1 H), 4.49 (d, *J* = 6.3 Hz, 1 H), 7.30–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.85, 23.75, 24.92, 36.53, 58.73, 60.48, 65.26, 65.72, 70.74, 127.56, 127.67, 128.26, 137.84; IR (KBr disk) 3308, 3064, 3026, 2954, 2928, 2870, 2833, 1560, 1542, 1495, 1466, 1448, 1331, 1177, 1117, 1050, 1031, 719, 689 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.50; H, 9.47; N, 5.69.

(2*R,3*R**)-1,2-Diphenyl-3-aminoazetidine (5a)**: yellow solid; mp 60–64 °C; ^1H NMR ($CDCl_3$) δ 1.31 (s, 2 H), 3.73 (dd, *J* = 7.8, 2.9 Hz, 1 H), 3.94 (td, *J* = 7.1, 2.9 Hz, 1 H), 4.12 (dd, *J* = 7.8, 7.8 Hz, 1 H), 5.08 (d, *J* = 7.1 Hz, 1 H), 6.43 (dd, *J* = 8.6, 1.0 Hz, 2 H), 6.74 (t, *J* = 6.7 Hz, 1 H), 7.30–7.45 (m, 7 H); IR (KBr disk) 3360, 3280, 1600, 1500, 1355, 1340, 750, 695 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.17; H, 7.13; N, 12.35.

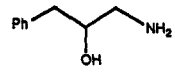
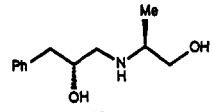
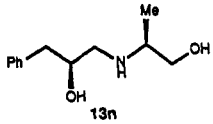
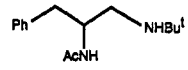
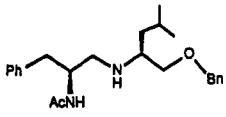
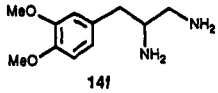
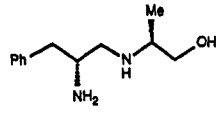
(2*R,3*R**)-1-Phenyl-2-(4-fluorophenyl)-3-aminoazetidine (5b)**: yellow solid; mp 60 °C; ^1H NMR ($CDCl_3$) δ 1.29 (bs, 2 H), 3.70 (dd, *J* = 8.1, 2.9 Hz, 1 H), 3.19 (ddd, *J* = 7.2, 7.2, 2.9 Hz, 1 H), 4.09 (dd, *J* = 7.7, 7.7 Hz, 1 H), 5.04 (d, *J* = 7.0 Hz, 1 H), 6.41 (d, *J* = 8.1 Hz, 2 H), 6.74 (t, *J* = 7.3 Hz, 1 H), 7.10–7.40 (m, 6 H); IR (KBr disk) 3360, 3280, 3080–2850, 1600, 1500, 1347, 1215, 850, 815, 745, 695, 575, 500 cm^{-1}. Anal. Calcd for $C_{15}H_{15}FN_2$: C, 74.36; H, 06.24; N, 11.56; F, 7.84. Found: C, 74.42; H, 6.13; N, 11.40; F, 7.69.

(2*R,3*R**)-1-*tert*-Butyl-2-phenyl-3-aminoazetidine (5c)**: colorless oil; ^1H NMR ($CDCl_3$) δ 0.92 (s, 9 H), 1.35–1.45 (bs, 2 H), 2.88 (bd, *J* = 6.9 Hz, 1 H), 3.48 (dd, *J* = 7.8, 6.4 Hz, 1 H), 3.54 (dd, *J* = 7.8, 6.9 Hz, 1 H), 4.48 (d, *J* = 6.4 Hz, 1 H), 7.20–7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.85, 46.46, 51.67, 52.18, 65.53, 126.53, 127.43, 127.61, 140.38; IR (neat) 3380, 3300, 3070–3030, 2980–2850, 1600, 1395, 1380, 1215, 745, 700 cm^{-1}. This compound was converted to its *N*-acetyl derivative (**Ac-5c**) (vide supra).

(2*R,3*R**)-1-*tert*-Butyl-2-phenyl-3-(acetylamino)azetidine (Ac-5c)**: white solid; mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 0.93 (s, 9 H), 1.66 (s, 3 H), 3.00 (dd, *J* = 8.1, 2.2 Hz, 1 H), 3.62 (dd, *J* = 8.1, 7.4 Hz, 1 H), 4.52 (dddd, *J* = 8.1, 7.6, 7.4, 2.2 Hz, 1 H), 4.72 (d, *J* = 7.6 Hz, 1 H), 5.65 (bs, 1 H), 7.20–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22.77, 24.92, 43.94, 50.44, 52.52, 64.26, 127.18, 127.45, 127.97, 139.62, 169.70; IR (KBr disk) 3276, 3066, 2964, 2855, 1648, 1561, 1236, 752, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.13; H, 8.77; N, 11.42.

(2*S*,3*S*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-2-phenyl-3-aminoazetidin-2-one (5d): pale yellow oil; $[\alpha]^{20}_D$ +150.8° (*c* 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (d, *J* = 6.5 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 1.12–1.21 (m, 1 H), 1.25 (bs, 2 H), 1.37–1.47 (m, 1 H), 1.55–1.68 (m, 1 H), 2.48–2.55 (m, 1 H), 3.17–3.20 (m, 3 H), 3.27 (dd, *J* = 7.8, 6.9 Hz, 1 H), 3.56 (ddd, *J* = 6.9, 6.5, 1.7 Hz, 1 H), 3.92 (d, *J* = 11.9 Hz, 1 H), 4.07 (d, *J* = 11.9 Hz, 1 H), 4.33 (d, *J* = 6.5 Hz, 1 H), 7.1–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 22.43, 23.95, 24.83, 38.08, 47.98, 58.25, 64.59, 70.82, 72.31, 72.72, 126.76, 127.18, 127.36, 127.46, 127.97, 128.02, 138.37, 139.84; IR (neat) 3375, 3316, 3084, 3061, 3028, 2952, 2866, 1950, 1884, 1810, 1603, 1494, 1470, 1454, 1385, 1366 1102, 1028, 912, 748, 699 cm^{-1}. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found:

Table V. Hydrogenolysis of Azetidines

entry	azetidine	catalyst	conditions: temp, °C; time, h; solvent	product	yield (%)
1	**2f**	10% Pd–C	50; 19; MeOH	 **13f**	94
2	**2m**	10% Pd–C	50; 3 days; MeOH	 **13m**	100
3	**2n**	10% Pd–C	50; 3 days; MeOH	 **13n**	98
4	**Ac-5c**	10% Pd–C	50; 16; MeOH	 **Ac-14c**	98
5	**Ac-5c**	Raney-Ni	78; 2; EtOH	**Ac-14c**	88
6	**Ac-5e**	10% Pd–C	25; 20; MeOH	 **Ac-14e**	100
7	**5f**	10% Pd–C	50; 36; MeOH HCl(aq)	 **14f**	81
8	**5h**	10% Pd–C	25; 10; EtOH	 **14h**	95
9	**Ac-5h**	10% Pd–C	25; 16; MeOH	**Ac-14h**	100

C, 78.26; H, 8.74; N, 8.06. This compound was converted to its *N*-acetyl derivative (**Ac-5d**) (vide supra).

(2*S*,3*S*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-2-phenyl-3-(acetylamino)azetidin-2-one (Ac-5d): pale yellow oil; $[\alpha]^{20}_D$ +80.2° (c 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.09–1.18 (m, 1 H), 1.39–1.48 (m, 1 H), 1.53–1.65 (m, 1 H), 1.66 (s, 3 H), 2.50–2.57 (m, 1 H), 3.19 (d, *J* = 3.9 Hz, 2 H), 3.26–3.36 (m, 2 H), 3.92 (d, *J* = 11.8 Hz, 1 H), 4.07 (d, *J* = 11.8 Hz, 1 H), 4.56–4.61 (m, 2 H), 5.7 (bs, 1 H), 7.2–7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 22.30, 22.93, 23.91, 24.77, 37.70, 45.27, 56.70, 64.43, 70.35, 70.42, 72.71, 127.05, 127.25, 127.46, 128.06, 128.11, 138.14, 138.70, 169.80; IR (neat) 3284, 3062, 3028, 2954, 1650, 1548, 1467, 1453, 1371, 1291, 1090, 1028, 735, 698 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.65; H, 8.54; N, 7.24.

(2*R,3*R**)-1-Benzyl-2-(3,4-dimethoxyphenyl)-3-aminoazetidine (5f)**: yellow oil; ^1H NMR ($CDCl_3$) δ 1.34 (bs, 2 H), 3.07 (d, *J* = 7.8 Hz, 1 H), 3.20 (dd, J = 7.2, 7.2 Hz, 1 H), 3.42 (d, *J* = 13.0 Hz, 1 H), 3.61 (ddd, *J* = 6.5, 6.5, 1.4 Hz, 1 H), 3.84 (d, *J* = 13 Hz, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 4.26 (d, *J* = 6.3 Hz, 1 H), 6.86–6.94 (m, 2 H), 7.23–7.31 (m, 5 H); IR (neat) 3380, 3300, 3080–2840, 1610, 1590, 1515, 1470, 1450, 1260, 1030, 880, 810, 760, 720, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.61; H, 7.29; N, 9.19. This compound was converted to its N-acetyl derivative (**Ac-5f**) (vide supra).

(2*R,3*R**)-1-Benzyl-2-(3,4-dimethoxyphenyl)-3-(acetylamino)azetidine (Ac-5f)**: white solid; mp 148.5–150 °C; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3 H), 3.18 (d, *J* = 8.2 Hz, 1 H), 3.31 (d, *J* = 12.9 Hz, 1 H), 3.48 (d, *J* = 12.9 Hz, 1 H), 3.86 (d, *J* = 12.9 Hz, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 4.53 (d, *J* = 7.0 Hz, 1 H), 4.61–4.69 (m, 1 H), 6.93–7.40 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 22.86, 46.21, 56.00, 57.83, 61.24, 70.66, 110.82, 111.86, 119.23, 127.06, 128.25, 128.63, 130.27, 137.92, 148.70, 149.40, 169.69; IR (KBr disk) 3333, 3080–3020, 2998, 2930, 2904, 2838, 1648, 1543, 1515, 1376, 1272, 1233, 1142, 1018, 812, 768, 747, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.64; H, 7.22; N, 8.11.

(2*R,3*R**)-1-*tert*-Butyl-2-(2-phenylethenyl)-3-aminoazetidine (5g)**: yellow oil; ^1H NMR ($CDCl_3$) δ 0.97 (s, 9 H), 2.87 (d, *J* = 6.2 Hz, 1 H), 3.40–3.51 (m, 2 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 6.37 (dd, *J* = 16.0, 7.3 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 7.19–7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.91, 47.03, 52.30, 52.60, 64.16, 126.21, 126.32, 127.27, 128.36, 129.98, 132.13, 136.88; IR (neat) 3380, 3280, 3090–3030, 2980–2860, 1600, 1390, 1365, 1235, 970, 750, 695 cm^{-1}. This compound was converted to its *N*-acetyl derivative (**Ac-5g**) (vide supra).

(2*R,3*R**)-1-*tert*-Butyl-2-(2-phenylethenyl)-3-(acetylamino)azetidine (Ac-5g)**: colorless oil; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.95 (s, 3 H), 2.00–2.40 (b, 2 H), 2.97 (dd, *J* = 7.6, 2.1 Hz, 1 H), 3.53 (dd, *J* = 8.1, 7.6 Hz, 1 H), 4.29 (dd, *J* = 7.2, 6.9 Hz, 1 H), 4.49 (dddd, *J* = 8.1, 7.7, 7.2, 2.1 Hz, 1 H), 6.23 (dd, *J* = 16.0, 6.9 Hz, 1 H), 6.30–6.40 (bd, *J* = 7.7 Hz, 1 H), 6.67 (d, *J* = 16.0 Hz, 1 H), 7.20–7.50 (m, 5 H); IR (neat) 3300, 3080, 2980, 2880, 1650, 1555, 1370, 1240, 970, 750, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.01; H, 8.97; N, 10.10.

(2*S*,3*S*)-1-[(*S*)-2-Hydroxy-1-methylethyl]-2-phenyl-3-aminoazetidine (5h): white solid; mp 95–97 °C; $[\alpha]^{20}_D$ +206.5° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.01 (d, *J* = 6.5 Hz, 3 H), 1.76 (bs, 3 H), 2.54–2.64 (m, 1 H), 3.09 (dd, *J* = 8.6, 1.7 Hz, 1 H), 3.21 (dd, *J* = 11.1, 5.3 Hz, 1 H), 3.27 (dd, *J* = 11.1, 4.4 Hz, 1 H), 3.37 (dd, *J* = 8.6, 6.5 Hz, 1 H), 3.62 (ddd, *J* = 6.5, 6.5, 1.7 Hz, 1 H), 4.35 (d, *J* = 6.5 Hz, 1 H), 7.50–8.00 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.89, 47.94, 55.88, 61.49, 64.44, 71.49, 127.19, 127.55, 128.59, 138.81; IR (neat) 3240, 1603, 1587, 1492, 1462, 1450, 1276, 1204, 1175, 1152, 1065, 1020, 1002, 952, 758, 738, 705 cm^{-1}. This compound was converted to its *N*-acetyl derivative (**Ac-5h**) (vide supra).

(2*S*,3*S*)-1-[(*S*)-2-Hydroxy-1-methylethyl]-2-phenyl-3-(acetylamino)azetidine (Ac-5h): white solid; mp 131.5–132.5 °C; $[\alpha]^{20}_D$ +90.4° (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.04 (d, *J* = 6.4 Hz, 3 H), 1.70 (s, 3 H), 1.84 (bs, 1 H), 2.59–2.69 (m, 1 H), 3.20–3.34 (m, 3 H), 3.48 (dd, *J* = 7.3, 7.3 Hz, 1 H), 4.58–4.68 (m, 2 H), 5.75 (bs, 1 H), 7.30–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.75, 22.80, 45.20, 53.84, 61.25, 64.11, 69.81, 126.92, 127.64, 128.35, 137.88, 169.94; IR (KBr disk) 3296, 3229, 3059, 3027, 2978, 2963, 2828, 1651, 1558, 1449, 1375, 1297, 1228, 1062, 730, 703 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.88; H, 8.27; N, 11.47.

(2*R*,3*R*)-1-Methyl-2-phenyl-3-[*N*-methyl-*N*-[(*S*)-1-phenyl-2-hydroxyethyl]amino]azetidine (5i): pale yellow oil; $[\alpha]^{20}_D$ −142.7° (*c* 1.55, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.35 (s, 3 H), 3.00 (dd, *J* = 8.3, 7.4 Hz, 1 H), 3.36 (dd, *J* = 8.3, 2.8 Hz, 1 H), 3.39 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.61 (dd, *J* = 10.7, 4.9 Hz, 1 H), 3.78 (dd, *J* = 10.7, 10.5 Hz, 1 H), 3.88 (ddd, *J* = 7.7,l 7.4, 2.8 Hz, 1 H), 4.36 (d, *J* = 7.7 Hz, 1 H), 7.0–7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 29.03, 43.93, 55.36, 59.59, 59.71, 67.99, 74.47, 126.80, 127.71, 128.15, 128.31, 138.95; IR (neat) 3433, 3060, 3026, 2932, 2828, 1493, 1451, 1345, 1308, 1250, 1219, 1179, 1059, 1030, 758, 737, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.79; H, 8.27; N, 9.27.

Synthesis of Direct-Tandem Bis-β-lactams (6). The preparation of the bis-β-lactam, **6c-2**, is typically described. To a solution of **8a-2** (1.528 g) and Et_3N (3.35 mL) in dry CH_2Cl_2 (50 mL) was added dropwise acetoxyacetyl chloride (2.758 g) at −15 °C, and the mixture was stirred overnight at 0 °C to ambient temperature. After washing with 5% $NaHCO_3$(aq), water, 10% aqueous citric acid, and brine, drying over anhydrous $MgSO_4$ and removal of solvent, a crude mixture of bis-β-lactams (*anti*-**6c-2** and *syn*-**6c-2**) was obtained, which was submitted to a column chromatography on silica gel (eluant: *n*-hexane/AcOEt, 2/1) to give 1-[(*S*)-1-(*tert*-butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*S*,4′*R*)-3′-acetoxy-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-**6c-2**) (1.158 g) and 1-[(*S*)-1-(*tert*-butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*R*,4′*S*)-3′-acetoxy-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-**6c-2**) (336 mg) as colorless crystals (total yield: 77%).

***anti*-6c-2**: mp 151–152 °C; $[\alpha]^{20}_D$ +57.6° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (d, *J* = 7.5 Hz, 3 H), 1.45 (s, 9 H), 1.57 (s, 3 H), 4.06 (d, *J* = 4.7 Hz, 1 H), 4.54 (d, *J* = 5.0 Hz, 1 H), 4.60 (q, *J* = 7.5 Hz, 1 H), 5.06 (d, *J* = 5.0 Hz, 1 H), 5.13 (d, *J* = 4.7 Hz, 1 H), 7.20–7.60 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.58, 19.56, 27.87, 51.12, 61.19, 61.36, 62.67, 76.95, 82.50, 127.64, 128.17, 128.39, 128.65, 128.87, 129.07, 131.31, 134.77, 163.44, 164.39, 168.87, 169.82; IR (KBr disk) 3036, 2984, 2939, 1773, 1755, 1724, 1496, 1456, 1397, 1368, 1228, 1160, 1069, 705 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85. Found: C, 67.55; H, 6.30; N, 5.74.

***syn*-6c-2**: mp 144.5–145.5 °C; $[\alpha]^{20}_D$ +156.0° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (d, *J* = 7.5 Hz, 1 H), 1.43 (s, 9 H), 1.55 (s, 3 H), 4.24 (d, *J* = 4.8 Hz, 1 H), 4.42 (q, *J* = 7.5 Hz, 1 H), 5.07 (d, *J* = 5.5 Hz, 1 H), 5.22 (d, *J* = 5.5 Hz, 1 H), 5.43 (d, *J* = 4.8 Hz, 1 H), 6.75–7.60 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.33, 19.57, 27.84, 51.30, 61.22, 62.64, 63.91, 76.70, 82.49, 127.55, 127.73, 128.50, 128.57, 128.76, 129.03, 131.75, 135.43, 164.30, 164.91, 168.65, 169.48; IR (KBr disk) 3062, 3034, 2977, 2939, 1789, 1752, 1740, 1497, 1457, 1398, 1366, 1350, 1224, 1158, 1074, 704 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85. Found: C, 67.45; H, 6.31; N, 5.79.

In a similar manner, other direct-tandem bis-β-lactams (**6a–c**) were synthesized.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*R*,4*S*)-2′-oxo-3′-phenoxy-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-6a-1): white solid; mp 197.5–199 °C; $[\alpha]^{20}_D$ −41.3° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.71 (d, *J* = 7 Hz, 3 H), 3.81 (q, *J* = 7 Hz, 1 H), 4.23 (d, *J* = 5 Hz, 1 H), 4.56 (d, *J* = 5 Hz, 1 H), 4.77 (d, *J* = 5 Hz, 1 H), 4.83 (d, *J* = 5 Hz, 1 H), 6.47–7.50 (m, 15 H); IR (KBr disk) 1770, 1730 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{31}H_{32}N_2O_5$ (as a mixture with *syn*-**6a-1**): C, 72.64; H, 6.29; N, 5.46. Found: C, 72.48; H, 6.07; N, 5.41.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*S*,4′*R*)-2′-oxo-3′-phenoxy-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-6a-1): ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.61 (d, *J* = 7 Hz, 3 H), 3.81 (q, *J* = 7 Hz, 1 H), 4.29 (d, *J* = 5 Hz, 1 H), 4.84 (d, *J* = 5 Hz, 1 H), 5.03 (d, *J* = 5 Hz, 1 H), 5.09 (d, *J* = 5 Hz, 1 H), 6.46–7.55 (m, 15 H); IR (KBr disk) 1780, 1770, 1735 ($\nu_{C=O}$) cm^{-1}.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*S*,4′*R*)-2′-oxo-3′-phenoxy-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-6a-2): white solid; mp 197–198 °C; $[\alpha]^{20}_D$ +66.9° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (d, *J* = 7.5, 3 H), 1.44 (s, 9 H), 4.08 (d, *J* = 4.6 Hz, 1 H), 4.57 (d, *J* = 5.0 Hz, 1 H), 4.60 (q, *J* = 7.5 Hz, 1 H), 4.76 (d, *J* = 4.6 Hz, 1 H), 5.08 (d, *J* = 5.0 Hz, 1 H), 6.5–7.5 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 15.62, 27.86, 51.09, 61.13, 62.05, 62.52, 81.81, 82.43, 115.41, 121.83, 127.74, 128.21, 128.59, 128.74, 128.91, 131.64, 135.05, 156.46, 163.55, 165.39, 169.84; IR (KBr disk) 3080–3020, 2978, 1764, 1726, 1495, 1456, 1408, 1368, 1235, 756, 706 cm^{-1}. Anal. Calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.80; H, 6.43; N, 5.50.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*R*,4′*S*)-2′-oxo-3′-phenoxy-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-6a-2): white solid; mp 203–203.5 °C; $[\alpha]^{20}_D$ +162.6° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (d, *J* = 7.5 Hz, 3 H), 1.44 (s, 9 H), 4.35 (d, *J* = 4.8 Hz, 1 H), 4.43 (q, *J* = 7.5 Hz, 1 H), 5.04 (d, *J* = 5.5 Hz, 1 H), 5.09 (d, *J* = 4.8 Hz, 1 H), 5.14 (d, *J* = 5.5 Hz, 1 H), 6.5–7.6 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 15.45, 27.87, 51.29, 61.47, 63.04, 64.53, 81.63, 82.47, 115.54, 121.89, 127.56, 127.67, 128.45, 128.71, 128.89, 128.98, 132.32, 135.56, 156.63, 164.42, 165.89, 169.61; IR (KBr disk) 3062, 3037, 2978, 2940, 1787, 1749, 1736, 1599, 1497, 1458, 1398, 1367, 1350, 1244, 1156, 761, 704 cm^{-1}. Anal. Calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.46. Found: C, 72.67; H, 6.42; N, 5.45.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*R*,4′*S*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-6b-1): white solid; mp 167.5–169 °C; $[\alpha]^{20}_D$ +0.59° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.69 (d, *J* = 7 Hz, 3 H), 3.81 (q, *J* = 7 Hz, 1 H), 4.01 (d, *J* = 11 Hz, 1 H), 4.07 (d, *J* = 5 Hz, 1 H), 4.20 (d, *J* = 11 Hz, 1 H), 4.27 (d, *J* = 5 Hz, 1 H), 4.53 (d, *J* = 5 Hz, 1 H), 4.79 (d, *J* = 5 Hz, 1 H), 6.70–7.45 (m, 15 H); IR (KBr disk) 1765, 1730 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.69; H, 6.49; N, 5.22.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*S*,4′*R*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-6b-1): white solid; mp 175–176 °C; $[\alpha]^{20}_D$ −172.1° (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 1.59 (d, *J* = 7 Hz, 3 H), 3.77 (q, *J* = 7 Hz, 1 H), 3.94 (d, *J* = 11 hz, 1 H), 4.03 (d, *J* = 5 Hz, 1 H), 4.11 (d, *J* = 11 Hz, 1 H), 4.44 (d, *J* = 5 Hz, 1 H), 4.82 (d, *J* = 5 Hz, 1 H), 5.07 (d, *J* = 5 Hz, 1 H), 6.20–7.50 (m, 15 H); IR (KBr disk) 1785, 1745 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.78; H, 6.55; N, 5.23.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*S*,4′*R*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-6b-2): white solid; mp 167.5–168.5 °C; $[\alpha]^{20}_D$ +0.49° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (d, *J* = 7 Hz, 3 H), 1.43 (s, 9 H), 3.92 (d, *J* = 5 Hz, 1 H), 4.03 (d, *J* = 11 Hz, 1 H), 4.24 (d, *J* = 11 Hz, 1 H), 4.27 (d, *J* = 5 Hz, 1 H), 4.51 (d, *J* = 5 Hz, 1 H), 4.53 (q, *J* = 7 Hz, 1 H), 5.01 (d, *J* = 5 Hz, 1 H), 6.74–7.70 (m, 15 H); IR (KBr disk) 1770, 1735 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.65; H, 6.49; N, 5.34.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*R*,4′*S*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-6b-2): white solid; mp 167.5–169 °C; $[\alpha]^{20}_D$ +145.1° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (d, *J* = 7 Hz, 3 H), 1.42 (s, 9 H), 3.95 (d, *J* = 11 Hz, 1 H), 4.09 (d, *J* = 5 Hz, 1 H), 4.12 (d, *J* = 11 Hz, 1 H), 4.38 (q, *J* = 7 Hz, 1 H), 4.48 (d, *J* = 5 Hz, 1 H), 4.97 (d, *J* = 5 Hz, 1 H), 5.08 (d, *J* = 5 Hz, 1 H), 6.70–7.50 (m, 15 H); IR (KBr disk) 1790, 1750, 1735 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.81; H, 6.39; N, 5.21.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*R*,4′*S*)-3′-acetoxy-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-6c-1): white solid; mp 155–155.5 °C; $[\alpha]^{20}_D$ −40.9° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 1.57 (s, 3 H), 1.75 (d, *J* = 7.4 Hz, 3 H), 3.88 (q, *J* = 7.4 Hz, 1 H), 4.18 (d, *J* = 4.7 Hz, 1 H), 4.51 (d, *J* = 5.0 Hz, 1 H), 4.84 (d, *J* = 5.0 Hz, 1 H), 5.15 (d, *J* = 4.7 Hz, 1 H), 7.2–7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.63, 19.56, 27.74, 53.44, 61.39, 61.82,

62.80, 76.84, 82.32, 127.52, 128.16, 128.31, 128.78, 129.00, 131.47, 133.56, 162.57, 168.21, 169.21, 169.21; IR (KBr disk) 1780, 1760, 1730 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_6$ (as a mixture with *syn*-**6c**-1): C, 67.77; H, 6.32; N, 5.85. Found: C, 67.55; H, 6.30; N, 5.74.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*S*,4′*R*)-3′-acetoxy-2′-oxo-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-6c-1): ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.55 (s, 3 H), 1.61 (d, J = 7.4 Hz, 3 H), 3.83 (q, J = 7.4 Hz, 1 H), 4.21 (d, J = 4.8 Hz, 1 H), 4.91 (d, J = 5.4 Hz, 1 H), 5.19 (d, J = 5.4 Hz, 1 H), 5.41 (d, J = 4.8 Hz, 1 H), 6.70–7.60 (m, 10 H); IR (neat) 1790, 1730 ($\nu_{C=O}$) cm^{-1}.

1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-(3*S*,4*R*)-3-[(3′*R*,4′*S*)-2′-oxo-3′-phenoxy-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*anti*-6d-1): white solid; mp 149.5–150 °C; $[\alpha]^{20}_D$ −24.1° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 1.38–1.49 (m, 1 H), 1.64–1.74 (m, 1 H), 1.80–1.92 (m, 1 H), 3.35 (dd, J = 9.6, 4.1 Hz, 1 H), 3.57 (dd, J = 9.6, 7.3 Hz, 1 H), 3.71–3.81 (m, 1 H), 4.10 (d, J = 4.6 Hz, 1 H), 4.25 (d, J = 11.9 Hz, 1 H), 4.28 (d, J = 11.9 Hz, 1 H), 4.45 (d, J = 4.9 Hz, 1 H), 4.79 (d, J = 4.6 Hz, 1 H), 4.83 (d, J = 4.9 Hz, 1 H), 6.50–7.60 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 22.01, 22.85, 24.76, 37.95, 52.31, 61.81, 61.93, 62.36, 71.42, 72.73, 81.89, 115.53, 121.84, 127.33, 127.46, 127.86, 128.20, 128.51, 128.65, 128.74, 128.94, 131.95, 134.69, 137.82, 156.61, 162.86, 165,47; IR (KBr disk) 1765, 1755 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{37}H_{38}N_2O_4$: C, 77.33; H, 6.66; N, 4.87. Found: C, 77.18; H, 6.67; N, 4.79.

1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-(3*S*,4*R*)-3-[(3′*S*,4′*R*)-2′-oxo-3′-phenoxy-4′-phenylazetidin-1′-yl]-4-phenylazetidin-2-one (*syn*-6d-1): white solid; mp 148.5–149 °C; $[\alpha]^{20}_D$ −124.2° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.0 Hz, 3 H), 0.89 (d, J = 5.4 Hz, 3 H), 1.05–1.95 (m, 3 H), 3.33 (dd, J = 9.6, 4.1 Hz, 1 H), 3.51 (dd, J = 9.6, 7.5 Hz, 1 H), 3.69–3.80 (m, 1 H), 4.29 (s, 2 H), 4.36 (d, J = 4.9 Hz, 1 H), 4.87 (d, J = 5.2 Hz, 1 H), 5.01 (d, J = 5.2 Hz, 1 H), 5.05 (d, J = 4.9 Hz, 1 H), 6.45–7.55 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 22.10, 22.88, 24.91, 38.05, 52.32, 62.00, 62.83, 64.62, 71.39, 72.87, 81.72, 104.94, 115.70, 121.98, 127.41, 127.61, 127.72, 127.94, 128.33, 128.70, 128.89, 129.09, 132.54, 135.42, 137.92, 165.94; IR (KBr disk) 1765, 1755 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{37}H_{38}N_2O_4$: C, 77.33; H, 6.66; N, 4.87. Found: C, 77.17; H, 6.63; N, 4.83.

Synthesis of Tandem Bis-β-lactams (7). Synthesis of **7b-2** is typically described. To a solution of **10-2** (325 mg, 0.922 mmol), (3*R*,4*S*)-[(*S*)-1-(hydroxycarbonyl)ethyl]-3-(benzyloxy)-4-phenylazetidin-2-one (**9b**, vide infra) (300 mg, 0.922 mmol) and 1-hydroxybenzotriazole (HOBT) (187 mg, 1.38 mmol) in THF (30 mL) was added DCC (571 mg, 2.77 mmol) at 0 °C with stirring, and the mixture was stirred at ambient temperature overnight. After the removal of solvent, CH_2Cl_2 (20 mL) was added and the resulting white precipitates were filtered out. The filtrate was washed with 10% aqueous citric acid, water, 5% $NaHCO_3$ (aq), water, and brine and dried over anhydrous $MgSO_4$. After the removal of solvent in vacuo, the residue was submitted to chromatographic purification on a short silica gel column (eluant: *n*-hexane/AcOEt, 2/1) to give (3*R*,4*S*)-1-[(*S*)-1-[(benzyloxy)-methyl]-3-methylbutyl]-3-[(*S*)-2-[(3′*R*,4′*S*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]propanoyl]-4-phenylazetidin-2-one (**7b-2**) (494 mg, 81% yield) as a white solid.

7b-2: mp 80 °C; $[\alpha]^{20}_D$ +30.4° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.78 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 7.3 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 1.00–1.09 (m, 1 H), 1.23–1.35 (m, 2 H), 3.52 (dd, J = 10.1, 4.3 Hz, 1 H), 3.61 (dd, J = 10.1, 8.3 Hz, 1 H), 3.88 (q, J = 7.3 Hz, 1 H), 3.92–4.00 (m, 1 H), 4.04 (d, J = 11.0 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.58 (d, J = 11.8 Hz, 1 H), 4.75 (d, J = 4.5 Hz, 1 H), 4.81 (d, J = 4.5 Hz, 1 H), 4.88 (d, J = 5.2 Hz, 1 H), 5.39 (dd, J = 8.4, 5.2 Hz, 1 H), 6.80–7.60 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 15.90, 22.03, 22.62, 24.82, 38.92, 51.56, 51.72, 59.44, 61.30, 62.44, 69.82, 72.11, 72.95, 82.71, 127.78, 127.88, 128.09, 128.32, 128.44, 128.52, 134.71, 135.02, 136.27, 137.69, 167.57, 170.12; IR (neat) 3276, 3062, 3031, 2955, 2868, 1760, 1687, 1544, 1496, 1455, 1396, 1358, 1228, 1171, 1097, 1010, 755, 700 cm^{-1}. Anal. Calcd for $C_{41}H_{45}N_3O_5$: C, 74.63; H, 6.87, N, 6.37. Found: C, 74.60; H, 6.88; N, 6.38.

In a similar manner, other tandem bis-β-lactams were synthesized.

(3*S*,4*R*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-3-[(*S*)-2-[(3′*R*,4′*S*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]propanoyl]-4-phenylazetidin-2-one (7b-1): yield, 91%; white solid; mp 182–184 °C; $[\alpha]^{20}_D$ +13.3° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 7.2 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 1.02–1.18 (m, 1 H), 1.27–1.47 (m, 1 H), 1.58–1.75 (m, 1 H), 3.29 (dd, J = 9.6, 4.1 Hz, 1 H), 3.40 (dd, J = 9.6, 7.5 Hz, 1 H), 3.42–3.55 (m, 1 H), 3.79–3.89 (m, 1 H), 4.04 (d, J = 4.5 Hz, 1 H), 4.10 (s, 2 H), 4.27 (d, J = 12.0 Hz, 1 H), 4.31 (d, J = 12.0 Hz, 1 H), 4.35 (d, J = 4.5 Hz, 1 H), 4.97 (d, J = 5.2 Hz, 1 H), 5.38 (dd, J = 8.3, 5.2 Hz, 1 H), 6.8–7.1 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 15.14, 22.10, 22.85, 24.93, 25.03, 51.66, 51.90, 59.47, 61.60, 61.95, 71.03, 71.91, 72.79, 82.23, 127.48, 127.64, 127.77, 127.99, 128.11, 128.23, 128.28, 128.37, 128.51, 128.57, 128.61, 128.66, 134.30, 135.42, 136.26, 137.82, 166.70, 167.36, 169.41; IR (KBr disk) 3289, 3064, 3031, 2929, 2851, 1766, 1753, 1682, 1657, 1627, 1552, 1456, 737, 700 cm^{-1}. Anal. Calcd for $C_{41}H_{45}N_3O_5$ C, 74.63,; H, 6.87; N, 6.37. Found: C, 74.30; H, 7.02; N, 6.58.

(3*R*,4*S*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-3-[[(*S*)-2-[(3′*S*,4′*R*)-3′-(benzyloxy)-2′-oxo-4′-phenylazetidin-1′-yl]propanoyl]amino]-4-phenylazetidin-2-one (7a-2): yield, 68%; white solid; mp 82–84 °C; $[\alpha]^{20}_D$ +0.2°, $[\alpha]^{20}_{365}$ −4.6° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.02–1.16 (m, 1 H), 1.30–1.41 (m, 1 H), 1.31 (d, J = 7.3 Hz, 3 H), 1.61–1.76 (m, 1 H), 3.43 (q, J = 7.3 Hz, 1 H), 3.53 (dd, J = 10.0, 4.3 Hz, 1 H), 3.63 (dd, J = 10.0, 8.7 Hz, 1 H), 3.88–3.98 (m, 1 H), 4.10 (d, J = 4.6 Hz, 1 H), 4.13 (d, J = 11.5 Hz, 1 H), 4.18 (d, J = 11.5 Hz, 1 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.56 (d, J = 4.6 Hz, 1 H), 4.58 (d, J = 11.8 Hz, 1 H), 4.86 (d, J = 5.2 Hz, 1 H), 5.35 (dd, J = 8.6, 5.2 Hz, 1 H), 6.80–7.50 (m, 20 H); IR (KBr disk) 3235, 3063, 3033, 2955, 2868, 1766, 1734, 1677, 1529, 1496, 1456, 1395, 1359, 1328, 1095, 759, 700 cm^{-1}. Anal. Calcd for $C_{41}H_{45}N_3O_5$: C, 74.63; H, 6.87; N, 6.37. Found: C, 74.44; H, 7.06; N, 6.24.

Preparation of β-Lactam Carboxylic Acids (9a and 9b). The precursors of **9a** and **9b**, 1-[(*S*)-1-(*tert*-butoxycarbonyl)-ethyl]-3-(benzyloxy)-4-phenylazetidin-2-one (**1m** and **1n**), were prepared through [2 + 2] cycloaddition of (benzyloxy)ketene in situ generated from (benzyloxy)acetyl chloride and Et_3N to *tert*-butyl (*S*)-*N*-benzylidenealaninate in the same manner as that reported previously from our laboratory,[16] followed by chromatographic separation of two diastereomers on a silica gel column.

1m [(3*R*,4*S*) isomer]: 50% yield; white solid; mp 130–131 °C; $[\alpha]^{20}_D$ +65.5° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 7.5 Hz, 3 H), 1.46 (s, 9 H), 4.12 (d, J = 11.1 Hz, 1 H), 4.25 (d, J = 11.1 Hz, 1 H), 4.50 (q, J = 7.5 Hz, 1 H), 4.93 (d, J = 4.6 Hz, 1 H), 5.04 (d J = 4.6 Hz, 1 H), 6.8–7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 16.01, 27.96, 50.46, 62.07, 72.23, 82.26, 83.15, 127.77, 128.07, 128.16, 128.44, 128.68, 135.50, 136.56, 169.95; IR (KBr disk) 3064, 3038, 2979, 2928, 2875, 1755, 1736, 1456, 1405, 1368, 1287, 1233, 1162, 752, 702 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.31; H, 6.94; N, 3.66.

1n [(3*S*,4*R*) isomer]: 41% yield; white solid; mp 101–102 °C; $[\alpha]^{20}_D$ −93.7° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 1.64 (d, J = 7.4 Hz, 3 H), 3.82 (q, J = 7.4 Hz, 1 H), 4.15 (d, J = 11.2 Hz, 1 H), 4.28 (d, J = 11.2 Hz, 1 H), 4.82 (d, J = 4.6 Hz, 1 H), 4.87 (d, J = 4.6 Hz, 1 H), 6.8–7.6 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.61, 27.73, 52.58, 62.40, 72.07, 82.05, 83.11, 127.70, 128.00, 128.26, 128.45, 134.07, 136.25, 166.84, 169.32; IR (KBr disk) 3065, 3039, 2984, 2924, 2878, 1750, 1458, 1392, 1368, 1357, 1342, 1240, 1213, 1157, 1050, 1007, 768, 750, 699 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.40; H, 6.94; N, 3.68.

Determination of the Absolute Configurations of β-Lactam 1n: (a) Hydrogenolysis. To a mixture of **1n** (763 mg, 2.00 mmol) and 100 mg of 10% Pd–C was added 15 mL of methanol under hydrogen. Then, the mixture was heated at 50 °C for 48 h with stirring. The progress of the reaction was monitored by TLC and ^{1}H NMR. When the reaction was completed, the catalyst was filtered off and the solvent removed in vacuo to give *tert*-butyl *N*-[(*S*)-2-hydroxy-3-phenylpropanoyl]alaninate (**17**) as a white solid (576 mg, 98% yield): mp 115–118 °C; $[\alpha]^{20}_D$ −58.5° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 7.2 Hz, 3 H), 1.46 (s, 9 H), 2.80 (d, J = 5.0 Hz, 1 H), 2.90 (dd, J = 13.9, 8.2 Hz, 1 H), 3.21 (dd, J = 13.9, 3.8 Hz, 1 H), 4.32 (ddd, J = 8.2, 5.0, 3.8 Hz, 1 H), 4.40 (dq, J = 7.4, 7.2 Hz, 1 H), 7.04 (bd, J = 7.4 Hz,

1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.35, 27.86, 40.61, 48.11, 72.60, 82.03, 126.72, 128.40, 129.56, 136.89, 172,09, 172.42.

(b) Hydrolysis of 17. A mixture of **17** (247 mg, 0.843 mmol) and 5 mL of 6 N HCl was sealed in a 25-mL Pyrex ampule and heated at 110–120 °C overnight with stirring. After cooling with a dry ice–acetone bath, the Pyrex ampule was opened and the content was extracted with ethyl ether (15 mL × 5). The ether extract was dried over anhydrous $MgSO_4$ overnight, and the solvent was removed in vacuo to give a pale yellow solid, which was recrystallized from EtOAc/hexane (1/2) to give (*S*)-2-hydroxy-3-phenylpropanoic acid (84 mg, 60 % yield) as colorless crystals: mp 122–124 °C; $[\alpha]^{20}_D$ −22° (*c* 2.0, H_2O) [lit.[21] mp 124–125 °C; $[\alpha]^{13.5}_D$ +22.8° (*c* 2.56, H_2O) for the *R* enantiomer].

The enantiomerically pure β-lactams, **1n** and **1m**, thus obtained were treated with CF_3COOH in anisole at 0–25 °C for 12 h to give the corresponding β-lactam carboxylic acids, **9a** and **9b**, respectively, in excellent yields (92%).

(3*S*,4*R*)-1-[(*S*)-1-(Hydroxycarbonyl)ethyl]-3-(benzyloxy)-4-phenylazetidin-2-one (9a): white solid; mp 135–137 °C; $[\alpha]^{20}_D$ −114.5° (*c* 0.40, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.68 (d, *J* = 7.4 Hz, 3 H), 2.8–3.1 (bs, 1 H), 3.96 (q, *J* = 7.4 Hz, 1 H), 4.15 (d, *J* = 11.1 Hz, 1 H), 4.29 (d, *J* = 11.1 Hz, 1 H), 4.85 (d, *J* = 4.5 Hz, 1 H), 4.90 (d, *J* = 4.5 Hz, 1 H), 6.9–7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 15.75, 52.95, 64.18, 73.28, 84.33, 128.84, 129.14, 129.36, 129.61, 135.49, 137.92, 169.48, 173.48; IR (KBr disk) 3400–2500 (ν_{OH}), 1772, 1727 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.97; H, 5.91; N, 4.07.

(3*R*,4*S*)-1-[(*S*)-1-(Hydroxycarbonyl)ethyl]-3-(benzyloxy)-4-phenylazetidin-2-one (9b): white solid; mp 131–132.5 °C; $[\alpha]^{20}_D$ +129.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.16 (d, *J* = 7.5 Hz, 3 H), 4.13 (d, *J* = 11.2 Hz, 1 H), 4.26 (d, *J* = 11.2 Hz, 1 H), 4.65 (q, *J* = 7.5 Hz, 1 H), 4.96 (d, *J* = 4.6 Hz, 1 H), 5.04 (d, *J* = 4.6 Hz, 1 H), 6.8–7.6 (m, 10 H), 9.0 (bs, 1 H). ^{13}C NMR ($CDCl_3$) δ 15.66, 49.78, 62.31, 72.32, 82.85, 127.86, 128.08, 128.20, 128.28, 128.64, 134,83, 136.15, 168.43, 174,85; IR (KBr disk) 3400–2500 (ν_{OH}), 1765, 1734, 1720 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.96; H, 5.97; N, 4.31.

Synthesis of Bisazetidines by the Hydroalane Reduction of β-Lactams. A typical procedure is as follows. Direct-tandem bis-β-lactam *anti*-**6c-2** (182 mg, 0.38 mmol) in dry ether (10 mL) was added to the suspension of chlorodihydroalane at ambient temperature, which had been prepared in situ by mixing aluminum trichloride (387 mg, 2.90 mmol) with lithium aluminum hydride (110 mg, 2.90 mmol) in refluxing ether (20 mL) for 30 min. The mixture was heated under reflux for 6 h with stirring. The completion of the reaction was monitored by TLC. Then, water (50 mL) was added to the reaction mixture at ice-cooled temperature, and the reaction mixture was extracted with dichloromethane (90 mL) by using a centrifuge, dried over anhydrous sodium sulfate, and concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel (eluant: hexane/AcOEt = 1) to afford (2*S*,3*S*)-1-[(*S*)-1-methyl-2-hydroxyethyl]-2-phenyl-3-[(2′*R*,3′*R*)-2′-phenyl-3′-hydroxyazetidin-1-yl]azetidine (*anti*-**11c-2**) (92.6 mg, 72% yield) as a colorless viscous oil.

***anti*-11c-2:** $[\alpha]^{20}_D$ +116.7° (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.5 Hz, 3 H), 2.12 (d, *J* = 9.2 Hz, 1 H), 2.45–2.50 (m, 1 H), 2.56 (dd, *J* = 9.2, 5.9 Hz, 1 H), 2.82–2.91 (m, 2 H), 3.06 (dd, *J* = 11.1, 4.8 Hz, 1 H), 3.20 (dd, *J* = 11.1, 3.9 Hz, 1 H), 3.30–3.35 (m, 1 H), 4.14–4.19 (m, 2 H), 4.21–4.26 (m, 1 H), 7.3–7.8 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.80, 50.85, 59.92, 61.39, 61.85, 63.55, 66.51, 70.12, 72.03, 127.42, 127.53, 127.60, 128.02, 138.04, 138.87; IR (KBr disk) 3402 (br), 3060, 3026, 2961, 2838, 1492, 1451, 1248, 1026, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.51; H, 7.88; N, 8.10.

In a similar manner, other direct-tandem bisazetidines **11** and tandem bisazetidines **12** were synthesized.

(2*S*,3*S*)-1-[(*S*)-1-Methyl-2-hydroxyethyl]-2-phenyl-3-[(2′*R*,3′*R*)-2′-phenyl-3′-phenoxyazetidinyl]azetidine (*anti*-11a-2): colorless oil; $[\alpha]^{20}_D$ +121.3° (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, *J* = 6.4 Hz, 3 H), 2.45–2.52 (m, 1 H), 2.53 (bd, *J* = 9.9 Hz, 1 H), 2.78 (dd, *J* = 9.4, 6.3 Hz, 1 H), 2.84 (bd, *J* = 7.5 Hz, 1 H), 2.91 (dd, *J* = 7.0, 7.0 Hz, 1 H), 3.05 (dd, *J* = 11.1, 4.9 Hz, 1 H), 3.20 (dd, *J* = 11.1, 3.6 Hz, 1 H), 3.43 (dd, *J* = 5.5, 5.5 Hz, 1 H), 4.15 (d, *J* = 6.3 Hz, 1 H), 4.30 (d, *J* = 6.5 Hz, 1 H), 4.78 (ddd, *J* = 6.3, 6.3, 2.2 Hz, 1 H), 6.4–7.8 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 12.67, 50.62, 57.54, 61.25, 61.61, 63.65, 70.26, 71.11, 71.73, 115.26, 120.61, 127.78, 127.53, 128.14, 128.44, 128.65, 128.84, 138.01, 138.83; IR (neat) 3422 (br), 3027, 2963, 1600, 1493, 1458, 1242, 753, 696 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.23; H, 7.29; N, 6.76. Found: C, 77.97; H, 7.40; N, 6.50.

(2*S*,3*S*)-1-[(*S*)-1-Methyl-2-hydroxyethyl]-2-phenyl-3-[(2′*S*,3′*S*)-2′-phenyl-3′-phenoxyazetidinyl]azetidine (*syn*-11a-2): pale yellow oil; $[\alpha]^{20}_D$ +130.9° (*c* 1.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.4 Hz, 3 H), 2.58–2.65 (m, 1 H), 3.04 (dd, *J* = 7.5, 7.5 Hz, 1 H), 3.16 (dd, *J* = 8.9, 3.5 Hz, 1 H), 3.23 (dd, *J* = 11.0, 6.1, Hz, 1 H), 3.31 (dd, *J* = 11.0, 4.4, Hz, 1 H), 3.39 (bd, *J* = 8.1 Hz, 1 H), 3.44 (dd, *J* = 7.8, 7.8 Hz 1 H), 3.59 (dd, *J* = 7.1, 7.1 Hz, 1 H), 4.40 (d, *J* = 7.4 Hz, 1 H), 4.66 (d, *J* = 6.6 Hz, 1 H), 4.80–4.86 (m, 1 H), 6.40–7.80 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 12.05, 48.68, 55.33, 57.06, 60,65, 64.36, 69.51, 70.22, 70.92, 115.03, 120.63, 127.13, 127.20, 127.41, 127.98, 128.91, 129.14, 136.10, 139.09, 157.18; IR (neat) 3364 (br), 3061, 2935, 1599, 1494, 1241, 752, 700 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.23; H, 7.29; N, 6.76. Found: C, 78.37; H, 7.32; N, 6.73.

(2*R*,3*R*)-1-[(*S*)-1-Methyl-2-hydroxyethyl]-2-phenyl-3-[(2′*S*,3′*S*)-2′-phenyl-3′-hydroxyazetidinyl]azetidine (*anti*-11c-1): colorless oil; $[\alpha]^{20}_D$ −62.4° (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (d, *J* = 6.5 Hz, 3 H), 2.07 (d, *J* = 9.3 Hz, 1 H), 2.45–2.52 (m, 1 H), 2.58 (dd, *J* = 9.4, 5.8 Hz, 1 H), 2.85 (dd, *J* = 7.8, 6.5 Hz, 1 H), 3.00 (d, *J* = 7.8 Hz, 1 H), 3.19 (dd, *J* = 10.7, 3.1 Hz, 1 H), 3.35 (ddd, *J* = 6.4, 6.4, 1.5 Hz, 1 H), 3.41 (dd, *J* = 10.7, 3.6 Hz, 1 H), 4.17–4.28 (m, 3 H), 7.2–7.7 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 14.54, 53.80, 59.89, 61.70, 63.18, 63.26, 66.55, 69.79, 72.11, 127.25, 127.57, 127.70, 128.22, 137.87, 138.96; IR (neat) 3374 (br), 3026, 2963, 2843, 1492, 1451, 1369, 1340, 1190, 1107, 1028, 754, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.77; H, 7.65; N, 8.39.

(2*R*,3*R*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-2-phenyl-3-[(2′*S*,3′*S*)-2′-phenyl-3′-phenoxyazetidinyl]azetidine (*anti*-11d-1): colorless oil; $[\alpha]^{20}_D$ −62.4° (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.725 (d, *J* = 6.6 Hz, 3 H), 0.734 (d, *J* = 6.6 Hz, 3 H), 0.93–1.00 (m, 2 H), 1.56–1.70 (m, 1 H), 2.44–2.50 (m, 1 H), 2.51–2.60 (m, 1 H), 2.79 (dd, *J* = 9.4, 6.3 Hz, 1 H), 2.91 (d, *J* = 7.5 Hz, 1 H), 2.97–3.06 (m, 1 H), 3.31 (dd, *J* =10.1, 3.7 Hz, 1 H), 3.34–3.46 (m, 2 H), 4.29 (dd, *J* = 5.5, 5.5 Hz, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.74 (ddd, *J* = 6.4, 6.4, 2.2 Hz, 1 H), 6.38–7.65 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 22.74, 23.13, 24.91, 38.66, 52.00, 57.46, 61.51, 62.08, 69.68, 71.19, 71.44, 71.50, 73.14, 115.30, 120.52, 126.96, 127.10, 127.27, 127.43, 127.60, 128.19, 128.73, 128.83, 138.39, 139.81, 157.49; IR (neat) 3084, 3061, 3027, 2952, 2846, 1599, 1587, 1494, 1454, 1242, 1100, 751, 697 cm^{-1}. Anal. Calcd for $C_{37}H_{42}N_2O_2$: C, 81.28; H, 7.74; N, 5.12. Found: C, 81.25; H, 7.76; N, 4.96.

(2*R*,3*R*)-1-[(*S*)-1-[(Benzyloxy)methyl]-3-methylbutyl]-2-phenyl-3-[[(*S*)-2-[(2′*S*,3′*S*)-2′-phenyl-3′-(benzyloxy)azetidin-1-yl]propyl]amino]azetidine (12): pale yellow oil $[\alpha]^{20}_D$ ± 0.1° (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.70 (d, *J* = 6.6 Hz, 3 H), 0.74 (d, *J* = 6.6 Hz, 3 H). 0.79 (d, *J* = 6.3 Hz, 3 H), 0.95–1.05 (m, 3 H), 1.48–1.59 (m, 1 H), 1.59 (dd, *J* = 11.4, 4.9 Hz, 1 H), 1.77 (dd, *J* = 11.4, 6.5 Hz, 1 H), 2.05–2.14 (m, 1 H), 2.52–2.59 (m, 1 H), 2.96–3.08 (m, 3 H), 3.20–3.28 (m, 2 H), 3.36 (dd, *J* = 9.9, 3.9 Hz, 1 H), 3.43 (dd, *J* = 9.9, 5.7 Hz, 1 H), 3.83 (d, *J* = 11.5 Hz, 1 H), 3.91 (s, *J* = 11.5 Hz, 1 H), 3.93 (d, *J* = 5.5 Hz, 1 H), 4.08–4.13 (m, 1 H), 4.31 (d, *J* = 6.6 Hz, 1 H), 4.46 (s, 2 H), 6.92–7.00 (m, 2 H), 7.19–7.41 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 14.66, 22.51, 23.19, 24.95, 38.95, 50.65, 54.04, 54.89, 55.67, 60.68, 61.55, 69.93, 71.01, 71.13, 71.93, 72.31, 73.04, 126.71, 127.11, 127.24, 127.35, 127.63, 127.77, 127.88, 127.96, 128.16, 128.51, 137.81, 138.48, 138.56, 139.56; IR (neat) 3327 (br), 3061, 3027, 2953, 2864, 1493, 1452, 1364, 1111, 1027, 734, 698 cm^{-1}. Anal. Calcd for $C_{41}H_{51}N_3O_2$: C, 79.70; H, 8.32; N, 6.80. Found: C, 79.54; H, 8.25; N, 6.80.

Hydrogenolysis of Azetidines and Bisazetidines. A typical procedure is as follows. Into a 50-mL round-bottomed reaction flask equipped with a standard hydrogenation apparatus is placed a mixture of the substrate (100 mg) and 10% Pd–C (20 mg) in 15 mL of methanol under hydrogen. The mixture is stirred at ambient temperature overnight. The progress of the reaction is

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monitored by TLC and/or ^{1}H NMR. When the reaction is complete, the catalyst is filtered off on a fine-glass filter, and the solvent is removed to give the corresponding ring-opened product in quantitative yield.

1-(Acetylamino)-2-hydroxy-3-phenylpropane (Ac-13f): colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.74 (dd, J = 13.7, 7.9 Hz, 1 H), 2.80 (dd, J = 13.7, 5.3 Hz, 1 H), 3.17 (ddd, J = 14.0, 7.8, 5.0 Hz, 1 H), 3.54 (ddd, J = 14.0, 6.6, 2.9 Hz, 1 H), 3.59 (bs, 1 H), 3.95 (ddd, J = 7.9, 7.8, 5.3, 2.9 Hz, 1 H), 6.00 (bs, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.05, 41.44, 45.13, 71.97, 126.59, 128.58, 129.26, 137.60; IR (neat) 3302 (br), 3086, 3028, 2928, 1651, 1372, 1295, 1091, 748, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.56; H, 8.00; N, 7.33.

(2*R*,5*S*)-1-Phenyl-2-hydroxy-5-methyl-7-oxa-4-azaheptane (13m): pale yellow oil; $[\alpha]^{20}_D$ +18.9° (*c* 1.22, $CHCl_3$); ^{1}H NMR (methanol-d_4) δ 1.28 (d, J = 6.7 Hz, 3 H), 2.77–2.87 (m, 2 H), 2.94 (dd, J = 12.4, 10.3 Hz, 1 H), 3.14 (dd, J = 12.4, 2.7 Hz, 1 H), 3.33–3.41 (m, 1 H), 3.55 (dd, J = 12.0, 6.3 Hz, 1 H), 3.76 (dd, J = 12.0, 3.9 Hz, 1 H), 4.05–4.15 (m, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.92, 40.95, 49.84, 56.47, 61.55, 67.95, 126.43, 128.28, 129.26, 136.78; IR (neat) 3332 (br), 1601, 1496, 1454, 1084, 1052, 750, 702 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.94; H, 8.96; N, 6.57.

(2*S*,5*S*)-1-Phenyl-2-hydroxy-5-(hydroxymethyl)-7-methyl-4-azaheptane (13n): colorless oil; $[\alpha]^{20}_D$ +26.1° (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.5 Hz, 3 H), 2.66–2.80 (m, 4 H), 2.82–2.90 (m, 1 H), 3.34 (dd, J = 11.4, 7.6 Hz, 1 H), 3.54 (dd, J = 11.4, 3.6 Hz, 1 H), 3.94–4.02 (m, 1 H), 4.64 (bs, 3 H), 7.15–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.04, 41.59, 50.75, 54.39, 64.39, 69.61, 126.33, 128.34, 129.26, 137.84; IR (neat) 3332 (br), 1651, 1644, 1634, 1602, 1495, 1454, 1051, 749, 701 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.67; H, 9.21; N, 6.51.

1-(*tert*-Butylamino)-2-(acetylamino)-3-phenylpropane (Ac-14c): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 1.10–1.40 (b, 1 H), 1.95 (s, 3 H), 2.55 (dd, J = 12.0, 4.9 Hz, 1 H), 2.59 (dd, J = 12.0, 4.8 Hz, 1 H), 2.73 (dd, J = 13.7, 7.9 Hz, 1 H), 2.92 (dd, J = 13.7, 6.2 Hz, 1 H), 4.10–4.21 (m, 1 H), 6.10 (bd, J = 7.2 Hz, 1 H), 7.2–7.38 (m, 5 H); ^{13}C NMR ($CHCl_3$) δ 23.38, 28.90, 38.27, 43.76, 50.21, 50.39, 126.27, 128.30, 129.08, 138.09, 169.68; IR (neat) 3279 (br), 3063, 3028, 2964, 2864, 1650, 1556, 1454, 1231, 1112, 1031, 746, 701 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.32; H. 9.77; N, 11.09.

(2*S*,5*S*)-1-Phenyl-2-(acetylamino)-5-(benzyloxymethyl)-7-methyl-4-azaoctane (Ac-14e): colorless oil; $[\alpha]^{20}_D$ +16.2° (*c* 0.45, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 1.26–1.36 (m, 2 H), 1.50–1.63 (m, 1 H), 1.91 (s, 3 H), 2.74 (dd, J = 13.7, 8.3 Hz, 1 H), 2.77 (dd, J = 12.9, 4.3 Hz, 1 H), 2.87 (dd, J = 12.9, 6.9 Hz, 1 H), 2.95 (dd, J = 13.7, 6.1 Hz, 1 H), 3.41 (dd, J = 9.9, 7.1 Hz, 1 H), 3.49 (dd, J = 9.9, 3.7 Hz, 1 H), 4.21–4.32 (m, 1 H), 4.50 (s, 2 H), 6.66 (bs, 1 H), 7.20–7.40 (m, 10 H); ^{13}C NMR (methanol-d_4) δ 22.51, 22.74, 23.54, 25.97, 39.78, 39.87, 50.00, 51.01, 56.36, 71.21, 74.21, 127.64, 128.83, 129.0, 129.50, 130.25, 139.03, 139.23, 173.72; IR (neat) 3260 (br), 3062, 3028, 2955, 2867, 1951, 1879, 1809, 1650, 1556, 1454, 1371, 1296, 1099, 748, 699 cm^{-1}; MS (FAB$^+$) m/z (%) 383 (M + 1, 100), 293 (5.5), 261 (14.9), 202 (4.9), 176 (57.1), 134 (12.7).

14f·2HCl: mp 250 °C (lit.[22] mp 267–268 °C); ^{1}H NMR (DMSO-d_6) δ 2.67–3.37 (m, 6 H), 3.35 (s, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 6.63–7.03 (m, 3 H), 8.72 (s, 4 H); IR (KBr disk) 2950, 1610, 1590, 1520, 1270, 1240, 1140, 1020, 890, 810, 770, 630 cm^{-1}.

(2*R*,5*S*)-1-Phenyl-2-amino-5-methyl-7-oxa-4-azaheptane (14h): pale yellow oil; $[\alpha]^{20}_D$ +21.3° (*c* 0.90, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.4 Hz, 3 H), 2.43 (dd, J = 11.8, 8.7 Hz, 1 H), 2.57 (dd, J = 13.0, 8.4 Hz, 1 H), 2.57–2.67 (m, 4 H), 2.77–2.85 (m, 2 H), 2.89 (dd, J = 11.8, 3.7 Hz, 1 H), 3.08–3.17 (m, 1 H), 3.31 (dd, J = 10.8, 7.4 Hz, 1 H), 3.59 (dd, J = 10.8, 3.7 Hz, 1 H), 7.15–7.40 (m, 5 H); IR (neat) 3334 (br), 3026, 2926, 1601, 1495, 1454, 1379, 1260, 1045, 749, 702 cm^{-1}. This compound was converted to its *N*-acetyl derivative (**Ac-14h**) (vide supra).

(2*R*,5*S*)-1-Phenyl-2-(acetylamino)-5-methyl-7-oxa-4-azaheptane (Ac-14h): white solid; mp 135–137 °C; $[\alpha]^{20}_D$ +38.1° (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.5 Hz, 3 H), 1.96 (s, 3 H), 2.57 (bs, 2 H), 2.72 (dd, J = 12.4, 7.2 Hz, 1 H), 2.80–2.96 (m, 4 H), 3.37 (dd, J = 11.1, 7.1 Hz, 1 H), 3.64 (dd, J = 11.1, 3.8 Hz, 1 H), 4.29–4.36 (m, 1 H), 6.14 (bd, J = 6.8 Hz, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.24, 23.17, 38.76, 49.00, 50.39, 55.30, 64.80, 126.55, 128.46, 129.16, 137.59, 170.99; IR (KBr disk) 3300 (br), 3034, 2981, 2839, 1657, 1546, 1193, 1160, 1050, 992, 747, 704 cm^{-1}; MS m/z (%) 232 (15), 219 (27), 176 (30), 141 (30), 127 (50), 120 (100), 91 (70), 88 (69), 70 (73), 56 (40), 43 (74); MS (FAB$^+$) m/z (%) 251 (M + 1, 100), 233 (1.9), 219 (1.8), 192 (2.0), 176 (19.7), 160 (1.7), 134 (3.2).

(2*S*,5*R*,8*S*)-1-Phenyl-2,5-dibenzyl-8-methyl-1,9-dioxa-4,7-diazadecane (15a-2A): yellow solid; mp 87–89 °C; $[\alpha]^{20}_D$ -7.6° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.4 Hz, 3 H), 2.35 (dd, J = 11.6, 6.7 Hz, 1 H), 2.55–2.95 (m, 11 H), 3.04 (dd, J = 13.8, 5.2 Hz, 1 H), 3.26 (dd, J = 10.7, 7.2 Hz, 1 H), 3.53 (dd, J = 10.7, 4.1 Hz, 1 H), 4.50–4.57 (m, 1 H), 6.80–7.50 (m, 15 H); ^{13}C NMR (methanol-d_4) δ 16.63, 39.16, 40.17, 50.05, 50.83, 56.26, 59.98, 66.24, 79.62, 117.31, 122.14, 127.34, 129.36, 129.51, 130.21, 130.53, 139.20, 139.95; IR (KBr disk) 3275 (br, $\nu_{OH,NH}$), 3024, 2917, 2860, 1598, 1585, 1496, 1451, 1232, 1172, 1085, 1058, 1039, 947, 952, 770, 753, 700 cm^{-1}. Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.48; H, 8.19; N, 6.69. Found: C, 77.38; H, 8.14; N, 6.79.

(2*R*,5*S*,8*S*)-2,5-Dibenzyl-8-methyl-1,9-dioxa-4,7-diazadecane (15c-1A): pale yellow oil; $[\alpha]^{20}_D$ +32.4° (*c* 0.95, $CHCl_3$); ^{1}H NMR (methanol-d_4) δ 1.18 (d, J = 6.7 Hz, 3 H), 2.54 (dd, J = 12.5, 8.5 Hz, 1 H), 2.69–2.83 (m, 3 H), 2.88–3.01 (m, 2 H), 3.05 (dd, J = 12.8, 3.8 Hz, 1 H), 3.16–3.23 (m, 1 H), 3.29–3.35 (m, 1 H), 3.52 (dd, J = 11.8, 6.7 Hz, 1 H), 3.69 (dd, J = 11.8, 4.0 Hz, 1 H), 3.91–3.98 (m, 1 H), 7.15–7.40 (m, 10 H); ^{13}C NMR (methanol-d_4) δ 14.16, 38.46, 42.47, 47.65, 51.92, 56.52, 58.17, 63.37, 72.37, 127.30, 127.96, 129.35, 129.84, 130.26, 130.44, 138.18, 139.34. IR (neat) 3318 (br), 3026, 2938, 1601, 1496, 1454, 1261, 1218, 1053, 750, 701 cm^{-1}; MS (FAB$^+$) m/z (%) 343 (M + 1, 100), 268 (10.7), 192 (12.4).

(2*S*,5*R*,8*S*)-2,5-Dibenzyl-8-methyl-1,9-dioxa-4,7-diazadecane (15c-2A): pale yellow oil; $[\alpha]^{20}_D$ -2.2° (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.7 Hz, 3 H), 2.81 (d, J = 6.5, 2 H), 2.87–3.07 (m, 2 H), 3.13–3.38 (m, 5 H), 3.55 (dd, J = 12.0, 5.9 Hz, 1 H), 3.72 (dd, J = 12.0, 3.8 Hz, 1 H), 3.72–3.80 (m, 1 H), 4.10–4.17 (m, 1 H), 4.91 (bs, 4 H), 7.20–7.40 (m, 10 H); ^{13}C NMR (methanol-d_4) δ 14.17, 37.13, 42.56, 48.17, 51.26, 57.70, 58.47, 62.41, 70.47, 127.58, 128.66, 129.51, 130.20, 130.47, 130.55, 136.66, 138.66; IR (neat) 3360 (br), 3026, 2926, 1602, 1495, 1454, 1055, 746, 701 cm^{-1}; MS (FAB$^+$) m/z (%) 343 (M + 1, 100), 268 (21.5), 254 (13.5), 192 (24.5), 134 (12.8).

(2*R*,5*S*,8*S*,11*S*)-2,8-Dibenzyl-5,13-dimethyl-11-(hydroxymethyl)-1-oxa-4,7,10-triazatetradecane (16): colorless oil; $[\alpha]^{20}_D$ +0.7° (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.2 Hz, 3 H), 0.92 (d, J = 6 Hz, 3 H), 1.19 (d, J = 6.8 Hz, 3 H), 1.55–1.80 (m, 3 H), 2.62–2.88 (m, 6 H), 3.13–3.19 (m, 3 H), 3.30–3.38 (m, 2 H), 3.42–3.50 (m, 1 H), 3.64–3.74 (m, 1 H), 3.73 (dd, J = 11.1, 5.4 Hz, 1 H), 3.87–3.95 (m, 1 H), 4.47 (s, 2 H), 4.50 (d, J = 10.3 Hz, 1 H), 4.59–4.64 (m, 1 H), 4.81 (d, J = 10.3 Hz, 1 H), 6.90–7.50 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 14.07, 21.63, 23.08, 24.93, 36.50, 38.64, 40.00, 47.87, 48.86, 49.95, 55.37, 56.34, 56.94, 668.95, 72.26, 73.30, 76.86, 126.67, 126.94, 127.64, 127.74, 127.78, 128.19, 128.25, 128.38, 128.47, 128.71, 128.82, 129.08, 129.68, 136.48, 137.64, 138.11; IR (neat) 3416 (br), 3028, 2956, 1602, 1584, 1496, 1454, 1368, 1093, 1028, 747, 700 cm^{-1}; MS (FAB$^+$) m/z (%) 622 (M + 1, 100), 401 (2.4), 324 (2.4), 268 (4.5).

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