Remarkable Effects of Lone Pair–Lone Pair Interactions on the Extremely Stereoselective [2 + 2] Cycloaddition of Azidoketene to Chiral 3-Imino-β-lactams

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Abstract: The stereoselective [2 + 2] cycloadditions of azidoketene to *cis*-3-imino-β-lactams **1**, **2**, and **3**, *trans*-3-imino-β-lactam **4**, and *cis*-3-iminoazetidine **5** were carried out. It was found that the reactions of **1**, **2**, and **3** proceeded with >99.5% stereoselectivity to give bis-β-lactams **9**, **14**, and **19**, respectively. The reaction of **4** gave a bis-β-lactam **20** with 62% de, and the reaction of **5** gave a β-lactamazetidine **21** with 32% de inducing the asymmetry in the opposite direction. These results clearly indicate that, in addition to the conventional steric effects, the lone pair–lone pair interaction of β-lactam oxygen with the intermediate betaine's oxygen is the crucial factor for the extremely stereoselective [2 + 2] cycloaddition of azidoketene to **1**, **2**, and **3**. Possible mechanisms for these stereoselective [2 + 2] cycloadditions are proposed. The X-ray crystal structure of **3a** and the calculated energy-minimum conformations of **3a**, **4**, and **5** with MODEL–MM2–ROTOCHEM programs are provided.

The [2 + 2] cycloaddition of ketene species to imines serves as one of the most convenient methods for the synthesis of the β-lactam skeleton, and thus the reaction has been used for a variety of β-lactam antibiotic syntheses.[3] In the course of our study on the use of homochiral β-lactams as key intermediates of oligopeptide syntheses,[4] we found that the [2 + 2] cycloaddition of azidoketene to a benzylideneamine bearing a homochiral β-lactam backbone (**1a**, **1b**) proceeded with extremely high stereoselectivity to give an optically pure bis-β-lactam.[5] Although the synthetic importance of the reaction was obvious, we could not rationalize such high stereoselectivity at all based on the usual stereochemical considerations by using Dreiding models and CPK models, viz., the conformation of the imine and the approach of the ketene seemed to have so much freedom that any predictions seemed arbitrary. Accordingly, we planned to clarify the crucial factors which governed the stereochemical course of this unique asymmetric [2 + 2] cycloaddition by using a series of homochiral *cis*-3-imino-β-lactam **3**, *trans*-3-imino-β-lactam **4**, and *cis*-3-iminoazetidine **5** as substrates and found unexpectedly strong lone pair–lone pair interactions (dipole–dipole interaction and/or electrostatic interaction) which controlled the stereochemistry of the reaction. We would like to describe here remarkable effects of β-lactam carbonyl lone pairs as a crucial factor for extremely selective [2 + 2] cycloadditions.

Results and Discussion

Observation of Extremely High Stereoselectivities in the Bis-β-lactam Syntheses via [2 + 2] Cycloaddition.[5] (*S*)-*N*-Benzylidene-1-(*tert*-butoxycarbonyl)ethylamine (**6**), prepared from *tert*-butyl-(*S*)-alaninate and benzaldehyde, was treated with azidoacetyl chloride in the presence of triethylamine in methylene dichloride to give a diastereoisomeric mixture of the cis-β-lactams **7a** and **7b**, which were readily separated by column chromatography on silica gel (80% yield, **7a**/**7b** = 51/49). The azide moiety in **7a** or **7b** was converted into amino group under 1 atm of hydrogen on 5% Pd–C in methanol at 0–5 °C, and the 3-amino-β-lactams produced were condensed with benzaldehyde to give the 1-[(*S*)-1-(*tert*-butoxycarbonyl)ethyl]-3-(benzylideneamino)-4-phenylazetidin-2-ones [**1a**: (3*R*,4*S*)] (96%) and [**1b**: (3*S*,4*R*)] (96%), respectively. Each 3-benzylideneamino-β-lactam was converted into the corresponding bis-β-lactam **9a** or **9b** by cycloaddition with azidoketene generated in situ from azidoacetyl chloride and triethylamine; **9a** was obtained from **1a** in 48% yield[10] and **9b** from **1b** in 74% yield.

In these cycloadditions, only one of the two possible stereoisomers was formed in each case, and none of the other isomer was found in the reaction mixture in spite of the extensive chromatographic workup on silica gel. The relatively low yield of **9b** is mainly due to the low conversion of the reaction.

The newly formed β-lactam ring was proved to have a cis relationship between the 3′-azide and 4′-phenyl groups based on the coupling constants ($J_{3'-4'}$ = 5–5.5 Hz) in the ^{1}H NMR spectra of **9a** and **9b**. However, the absolute configurations of the newly formed β-lactam ringts in **9a** and **9b** remain to be determined. Since we developed a convenient method for the conversion of 4-aryl-β-lactams into the corresponding peptides by reductive cleavage of the β-lactam ring, the absolute configuration of the bis-β-lactams can be unambiguously determined by comparing the peptides derived therefrom with authentic samples. Thus, the azide moiety in **9a** or **9b** was reduced to the amino group and then acetylated to give *N*-acetyl bis-β-lactam **11a** (80%) or **11b** (85%). Reductive cleavage of the *N*-acetyl bis-β-lactam **11a** or **11b** with hydrogen (1 atm) on 5% Pd–C at 50 °C gave the corresponding tripeptides. All four of the possible tripeptides, Ac-(*S*)-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu, Ac-(*R*)-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu, Ac-(*S*)-Phe-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu, and Ac-(*R*)-Phe-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu, were prepared independently by conventional peptide synthesis and compared with the tripeptides from bis-β-lactams by ^{1}H NMR and by HPLC analysis. It was found that Ac-(*S*)-Phe-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu was obtained from **11a** in 92% yield and Ac-(*R*)-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu from

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(3) For example, (a) Sammes, P. G. *Topics in Antibiotic Chemistry*; Ellis Horwood Ltd: Chichester/John Wiley & Sons: New York, 1980; Vol. 4. (b) Elks, J. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; The Chemical Society: London, 1977; references cited therein.
(4) (a) Ojima, I.; Hatanaka, N.; Yoda, N.; Abe, R.; Yatabe, M.; Yamashita, M. *Peptide Chemistry, 1982*; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, 1983; pp 29–34. (b) Yamashita, M.; Abe, R.; Hatanaka, N.; Ojima, I. *Peptide Chemistry, 1982*; Sakakibara, S. Ed.; Protein Research Foundation: Osaka, 1983; pp 85–90. (c) Hatanaka, N.; Abe, R.; Ojima, I. *Chem. Lett.* **1982**, 445–448. (d) Ojima, I. *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1982; Vol. 185, pp 109–138. (d) Hatanaka, N.; Abe, R.; Ojima, I. *Chem. Lett.* **1981**, 1297–1298. (e) Hatanaka, N.; Ojima, I. *Ibid.* **1981**, 231–234. (f) Ojima, I.; Suga, S.; Abe, R. *Tetrahedron Lett.* **1980**, 3907–3910. (g) Ojima, I.; Shimizu, N. *J. Am. Chem. Soc.* **1986**, *108*, 3100–3102.
(5) The preliminary results were reported as a communication: Hatanaka, N.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1981**, 344–346.

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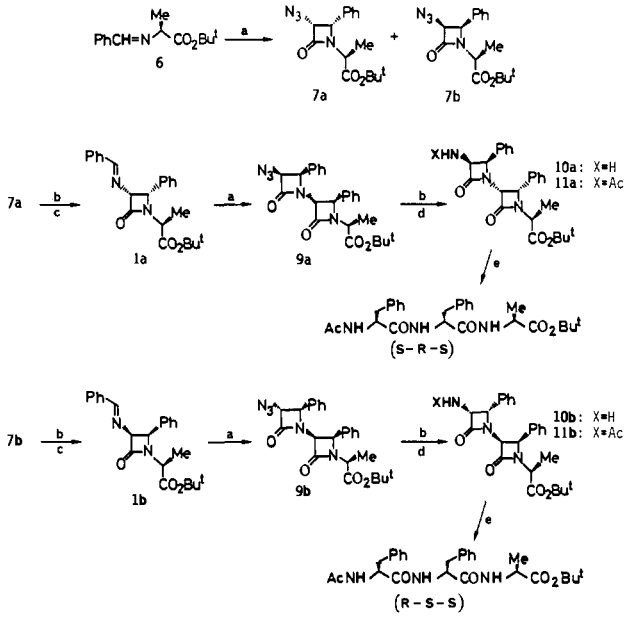
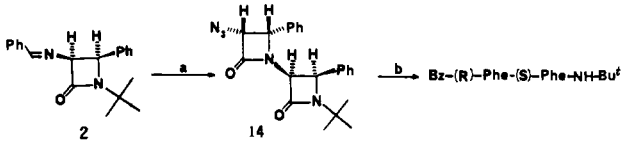
Scheme I. Asymmetric Synthesis of Bis-β-lactams **9a** and **9b**[a]



[a] a: N_3CH_2COCl, Et_3N, CH_2Cl_2, −78 °C–room temperature; b: H_2 (1 atm), 5% Pd–C, MeOH, 0–5 °C; c: PhCHO, Na_2SO_4, benzene; d: Ac_2O, *N*-methylmorpholine, $CHCl_3$; e: H_2 (1 atm), 10% Pd–C, EtOH, 50 °C.

Scheme II. Stereoselective [2 + 2] Cycloaddition of Azidoketene to a 3-Imino-β-lactam **2**[a]



[a] a: H_2 (1 atm), 5% Pd–C, MeOH, 0–5 °C, then PhCHO, Na_2SO_4, benzene; b: N_3CH_2COCl, Et_3N, CH_2Cl_2, −78 °C–room temperature.

11b in 93% yield. Consequently, the stereochemistry of **9a** is (3′*S*,4′*R*, 3*R*,4*S*), and that of **9b** (3′*R*,4′*S*, 3*S*,4*R*). In both cases the newly formed β-lactam ring has the opposite configurations to the parent one (Scheme I).

The results indicate that the chiral ester moiety attached to the β-lactam nitrogen does not have any significant effects on the asymmetric induction although it affects the reactivity to some extent; **1b** is more reactive than **1a** judging from the yields of **9a** and **9b**. For comparison, we employed *N*-(benzylideneamino)-1-*tert*-butylazetidin-2-one (**2**), which is one of the simplest 3-imino-β-lactams bearing no homochiral functional group as substituent, and carried out the [2 + 2] cycloaddition with azidoketene. The reaction gave (3′*R**,4′*S**,3*S**,4*R**)-bis-β-lactam **14** in 45% yield[10] with >99.5% de (^{1}H NMR, HPLC). Thus, it is reconfirmed that the N-substituent does not have any significant effects on the asymmetric induction (Scheme II).

Asymmetric [2 + 2] Cycloaddition of Azidoketene to *cis*- and *trans*-Imino-β-lactams 3 and 4 and *cis*-Iminoazetidine 5. In order to look at the stereochemical course of the asymmetric [2 + 2] cycloaddition of azidoketene to 3-imino-β-lactams in detail, we prepared *cis*-3-imino-β-lactams **3a** and **3b** and *trans*-3-imino-β-lactam **4** as substrates which have the same substituents on N^1, C^3, and C^4 positions. Fortunately, the *cis*-3-imino-β-lactam **3a** gave a good single crystal, and thus the X-ray analysis of the crystal was carried out. The crystal structure of **3a** is depicted in Figure 1, which clearly shows the trans and coplanar structure of benzylidineamino moiety.

The conformational analysis based on MM2 calculations implies that the 4-phenyl moiety in **3** may have a considerable influence on the stereoselection because the phenyl group in the cis position is close to the 3-imino moiety: The minimum energy conformer of **3a** using MODEL–MM2–ROTOCHEM programs[6] is shown in Figure

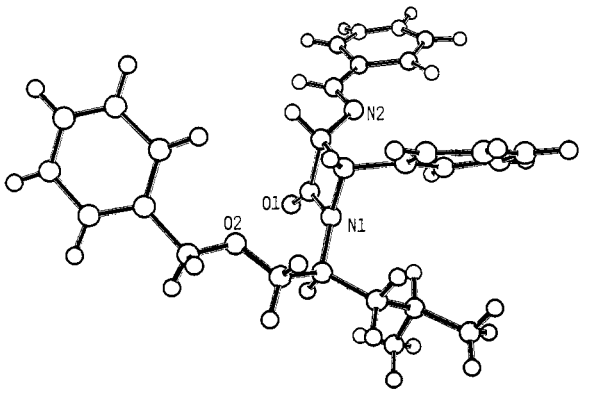


Figure 1. X-ray structure of **3a**.

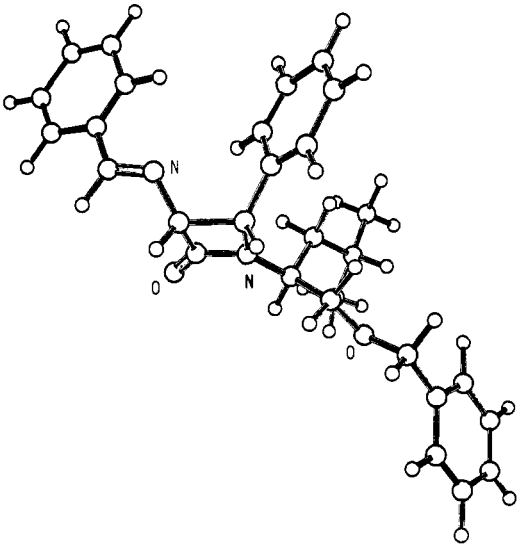
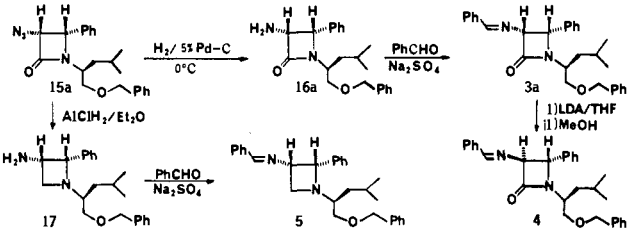


Figure 2. The energy minimum conformation of **3a** obtained by MODEL–MM2–ROTOCHEM programs.

Scheme III. Preparation of Homochiral 3-Imino-β-lactams **3** and **4** and 3-Iminoazetidine **5**



2.[7] However, in the trans isomer **4**, the 4-phenyl group does not seem to have any appreciable influence on the conformation of the imino moiety with regard to the approach of azidoketene: The MM2 calculations for **4** indicate two local minimums, **4A** and **4B** as shown in Figure 3, and **4B** is ca. 0.5 kcal/mol higher than **4A**.[8] Therefore, it was reasonable to assume that the reaction of **3a** would be highly stereoselective while the reaction of **4** would

(6) MODEL: a molecular modeling program developed by Professor Clark Still, Department of Chemistry, Columbia University. ROTOCHEM: a molecular graphics display program developed by Professor Joseph W. Lauher, Department of Chemistry, State University of New York at Stony Brook.

(7) (a) The energy for this conformation was calculated to be 56.98 Kcal/mol. (b) Since the MM2 energy depends on rather arbitrary conformation of the leucinol benzyl ether moiety, which is proved to be noncrucial for stereoselectivity, we performed the MM2 calculations of the N^1–Me derivative focusing on the relative conformation of the 3-benzylideneamino group and the 4-phenyl group. These calculations confirmed the relevance of the energy minimum structure shown in the figure.

(8) The energies for **4A** and **4B** were calculated to be 57.14 Kcal/mol and 57.62 Kcal/mol, respectively. See 7b, too.

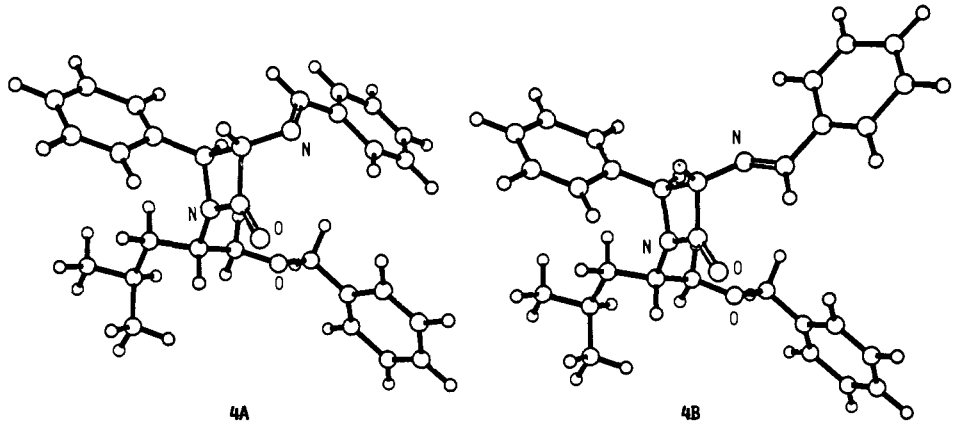


Figure 3. The two local energy minimum conformations of **4**.

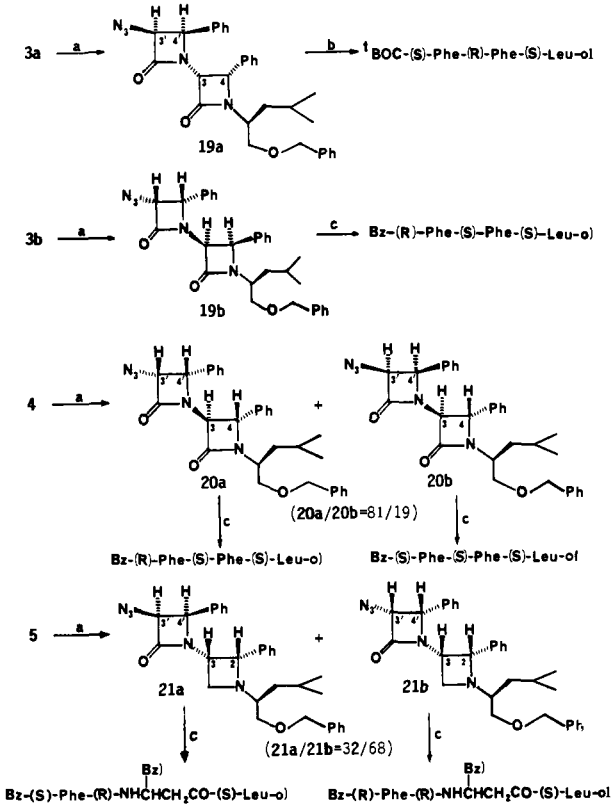
proceed with a low stereoselectively and even the inversion of preferred configuration could be expected.

The *cis*-3-imino-β-lactam **3a** was prepared from (3*R*,4*S*)-3-azido-4-phenyl-β-lactam **15a** by the selective reduction of azide group with 5% Pd-C and H_2 (~100%) followed by the condensation with benzaldehyde (~100%). The homochiral β-lactam **15a** was prepared through the [2 + 2] cycloaddition of azidoketene with *N*-benzylideneleucinol benzyl ether and subsequent separation of diastereomers (**15a**, **15b**) on a silica gel column. The *trans*-3-imino-β-lactam **4** was prepared by the isomerization of **15a** by LDA (1.0 equiv) in THF at −78 °C followed by the purification on a silica gel column (90%). The *cis*-3-iminoazetidine **5** was prepared through the $AlClH_2$ reduction[9] of **15a** (70%) followed by the condensation with benzaldehyde (~100%) (Scheme III).

The [2 + 2] cycloaddition of azidoketene to **3a** was carried out to give the corresponding (3′*S*,4′*R*,3*R*,4*S*)-bis-β-lactam **19a** (46%)[10] with >99.5% de (^{1}H NMR, HPLC) as expected. The absolute configuration was determined by the HPLC analysis of the tripeptide, *t*-BOC–Phe–Phe–Leu-ol, obtained from **19a** via hydrogenolysis on 5% Pd-C. However, contrary to our prediction, the reaction with **4** gave a (3′*R*,4′*S*,3*S*,4*S*)-bis-β-lactam **20** (67%)[10] with a good diastereoselectivity (**20a**/**20b** = 81/19, ^{1}H NMR, HPLC). *This unexpected result indicates that the steric hindrance of 4-phenyl moiety in* **3** *is* ***not*** *the single crucial factor for the observed extremely high stereoselectivity.* In order to exclude the possibility of asymmetric induction caused by the homochiral N-substituent, i.e., (*S*)-leucinol benzyl ether moiety, we also carried out the [2 + 2] cycloaddition of azido ketene to **3b**, (3*S*,4*R*)-isomer. The reaction with **3b** gave (3′*R*,4′*S*,3*S*,4*R*)-bis-β-lactam **19b** with >99.5% de (HPLC) in 60% yield.[10] Thus, it is reconfirmed that the chiral center in the N-substituent does not have any significant effects on the asymmetric induction (vide supra). At this point, we recognized that the only other crucial factor conceivable should be the β-lactam carbonyl moiety, which might have strong directing effects on the approach of azidoketene.

These results prompted us to examine the reaction with the *cis*-3-iminoazetidine **5**, which has the same substituents on C^2 and C^3 positions as **3** and **4** (C^3 and C^4 for β-lactams). *Surprisingly, not only the stereoselectivity was decreased but also the direction of asymmetric induction was reversed by eliminating the β-lactam carbonyl!* Namely, the reaction gave a diastereomeric mixture of azetidin-2-onylazetidine **21** (71%) with 32/68 ratio: The HPLC analysis of Bz–Phe–NH–CH(CH_2Ph)–CH_2–CO–Leu-ol which was obtained via the hydrogenolysis of **21**, disclosed that the major product was (3′*R*,4′*S*,2*S*,3*S*)-isomer **21b** and the minor (3′*S*,4′*R*,2*S*,3*S*)-isomer **21a**. The result is even more surprising

Scheme IV. Asymmetric [2 + 2] Cycloadditions of Azidoketene to Homochiral 3-Imino-β-lactams **3** and **4** and 3-Iminoazetidine **4**[a]



[a] a: N_3CH_2COCl, Et_3N, −78 °C–room temperature; b: (i) H_2 (1 atm), 5% Pd–C, 0–5 °C; (ii) *t*-BOC-S, Et_3N, THF, 25 °C; (iii) H_2 (1 atm), 5% Pd–C, MeOH, 55 °C; c: (i) and (iii), same as b; (ii) PhCOCl, *N*-methylmorpholine, THF, 0–5 °C.

by considering the fact that the most favorable conformation of **5** based on MM2 calculations,[11] which is shown in Figure 4, has almost the same stereochemical arrangements as its β-lactam counterpart **3a** does. (See Scheme IV.)

The remarkable effects of the β-lactam carbonyl are best interpreted by taking into account the interaction between the oxygen lone pair of the β-lactam carbonyl and the oxygen lone pair of the betaine II which is the key intermediate for the reaction (Scheme V). The stereo-model inspections considering such lone pair–lone pair interactions give us clear rationale of the extremely stereoselective reaction.

On the basis of the stereo models, it is very likely that azidoketone approaches the lone pair of the imine–nitrogen perpen-

(9) As for the chlorohydroalane reduction of β-lactams to azetidines, see: Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339–6342.

(10) Although the isolated yields for these bis-β-lactams are only moderate to good, this is mainly due to the relatively low conversion of the reaction, and the reaction itself is clean. Namely, substantial amounts of starting imines were recovered, especially for the cases in which the isolated yields were moderate.

(11) The energy for this conformation was calculated to be 56.54 Kcal/mol. See 7b, too.

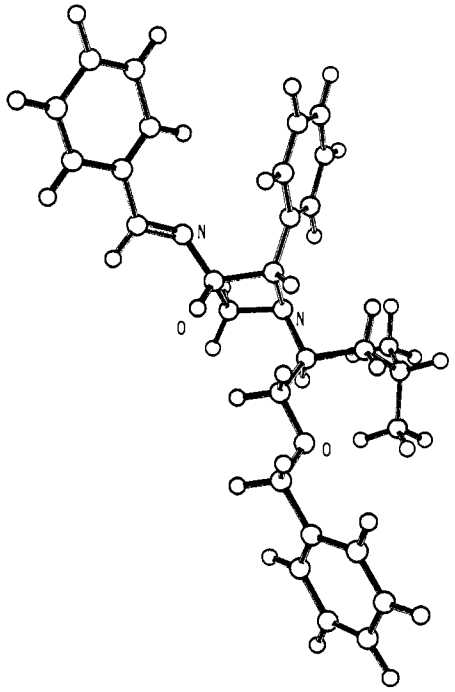
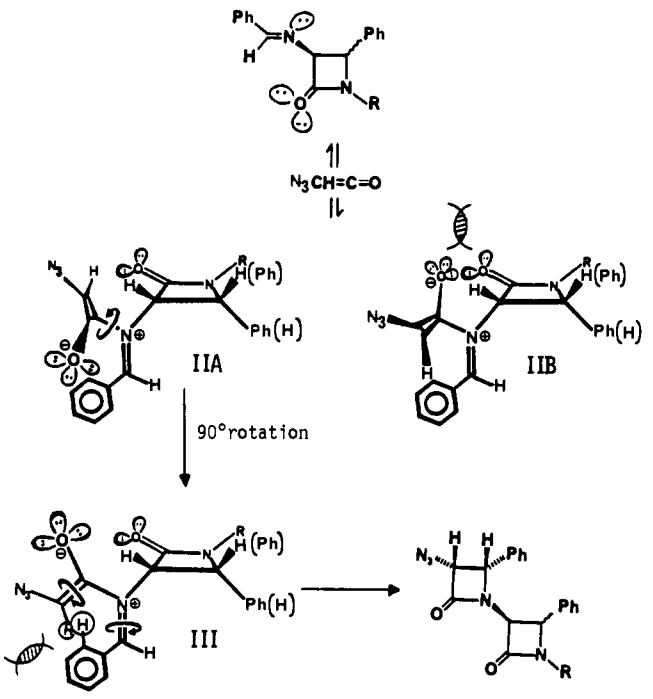


Figure 4. The energy minimum conformation of **5**.

Scheme V. Proposed Mechanism for the Highly Stereoselective [2 + 2] Cycloadditions of Azidoketene to 3-Imino-β-lactams



dicular to the plane of benzylideneamine moiety;[12] there are two directions for the approach and one of them gives IIA and the other IIB. As shown in Scheme V, the betaine IIA is very unfavorable because of the severe repulsion between the oxygen lone pair of the betaine and that of the β-lactam carbonyl whereas the betaine IIB does not have any nonbonded interactions between these lone pairs. Thus, the betaine IIB is much more favorable than IIA. From the initial conformation thus formed, the azido–enolate moiety may rotate ca. 90° along the C–N bond of the betaine following the "principle of least motion"[13] to give a quasi-coplanar transition state for the conrotatory ring closure.[14] In the quasi-coplanar transition state (III), there is steric conflict between two periplanar hydrogens, i.e., the ortho hydrogen of phenyl group and the vinyl hydrogen of the azido–enolate moiety. Because of this coperiplanar repulsion of the two hydrogens, the conrotatory ring closure of IIB proceeds in a direction which releases the repulsion to give the bis-β-lactams **19b** and **20** with the configurations observed.

In conclusion, it is disclosed that the lone pair–lone pair interaction of the β-lactam carbonyl oxygen with the betaine oxygen is the crucial factor for the extremely stereoselective [2 + 2] cycloadditions in the bis-β-lactam synthesis in addition to the conventional steric effects of 4-phenyl group. This finding is very important not only because the nonbonded lone pair–lone pair interaction plays a key role in asymmetric induction but also because the concept of the lone pair–lone pair interaction of this type can be applied to many cycloaddition reactions as a crucial stereocontrolling factor.

Experimental Section

Materials. All amino acids were used as purchased. Benzaldehyde and *tert*-butylamine were purchased and distilled before use. *tert*-Butyl (*S*)-alaninate[15] and (*S*)-leucinol[16] 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 by the literature methods.[17] Palladium on carbon (5% and 10%) was purchased from Engelhart Corporation.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-azido-4-phenylazetidin-2-one (7a) and 1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-azido-4-phenylazetidin-2-one (7b). To a mixture of *tert*-butyl (*S*)-alaninate (3.56 g, 24.5 mmol) and benzaldehyde (2.60 g, 24.5 mmol) in benzene (100 mL) was added anhydrous sodium sulfate (20 g), and the suspension was stirred at room temperature for 14 h. After filtration and the removal of the solvent, *tert*-butyl *N*-benzylidene-(*S*)-alaninate (**6**) was obtained as oil (5.27 g, 92%) [^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 1.50 (d, J = 6.3 Hz, 3 H), 4.02 (q, J = 6.3 Hz, 1 H), 7.34–7.86 (m, 5 H), 8.30 (s, 1 H); IR (neat) 1740 ($\nu_{C=O}$), 1650 ($\nu_{C=N}$) cm^{-1}]. A mixture of **6** (5.07 g, 21.7 mmol) and triethylamine (4.84 g, 47.8 mmol) in dichloromethane (75 mL) was cooled to −78 °C, and a solution of azidoacetyl chloride (5.19 g, 43.5 mmol) in dichloromethane (75 mL) was added dropwise with stirring. The reaction mixture was then allowed to warm up gradually to room temperature for the period of 14 h with stirring. The excess azidoacetyl chloride was quenched with methanol (5 mL), and the solvent was removed in vacuo. The residual solid was treated with *n*-hexane/ethyl acetate (1/1), and insoluble materials were separated by passing through a short silica gel column. The filtrate was concentrated and submitted to the chromatographic separation on a silica gel column (Merck Silica gel 60) by using a medium-pressure LC system or a preparative HPLC (Waters Prep 500). The chromatographic separation with *n*-hexane/ethyl acetate (3/1) as eluant gave **7a** (2.82 g, R_f = 0.29, 41% yield from **6**) and **7b** (2.68 g, R_f = 0.21, 39% yield from **6**) as a colorless solid.

7a: mp 95–96 °C; $[\alpha]_D^{20}$ +125.6° (c 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 7.5 Hz, 3 H), 1.48 (s, 9 H), 4.42 (q, J = 7.5 Hz, 1 H), 4.91 (d, J = 5 Hz, 1 H), 5.12 (d, J = 5 Hz, 1 H), 7.37 (s, 5 H); IR (KBr disk) 2130 (ν_{N_3}), 1770, 1740 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.74; H, 6.34; N, 17.83.

7b: mp 53–54 °C; $[\alpha]_D^{20}$ −122.6° (c 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.67 (d, 3 H, J = 7.5 Hz), 3.78 (q, J = 7.5 Hz, 1 H), 4.83 (d, J = 5.5 Hz, 1 H), 4.92 (d, J = 5.5 Hz, 1 H), 7.27–7.50 (m, 5 H); IR (neat) 2120 (ν_{N_3}), 1770, 1730 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for

(12) The p lobe of azidoketene anti to the azide moiety is expected to react with the imine lone pair exclusively since this lobe is sterically much more favorable for the reaction than the other.

(13) e.g., (a) Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1–61. (b) Rice, F. O.; Teller, E. *J. Chem. Phys.* **1938**, *6*, 489–496. (c) Tee, O. S. *J. Am. Chem. Soc.* **1969**, *91*, 7144–7149. (d) Altmann, J. A.; Tee, O. S.; Yates, K. *Ibid.* **1976**, *98*, 7132–7138.

(14) There are two possible directions for the rotation, viz., ca. 90° rotation and ca. 270° rotation. It is apparent that the 270° rotation is unlikely based on the "principle of least motion".[13]

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

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

(17) **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 with a vacuum pump (0.1–0.3 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.

$C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.72; H, 6.39; N, 17.64.

The absolute configuration of **7a** or **7b** was unambiguously determined by converting **7** to the corresponding dipeptide, Ac-Phe-(*S*)-Ala-O-*t*-Bu, through hydrogenolysis on 10% Pd-C at 50 °C in methanol for 12 h in the presence of an equivalent molar amount of 1 N hydrochloric acid followed by acetylation (Ac_2O, pyridine), and submitting the dipeptide thus obtained by HPLC analysis (TOYO SODA LS 410K, MeOH/H_2O = 7/3) by using authentically prepared Ac-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu and Ac-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu as references. The β-lactams **7a** and **7b** were unambiguously assigned to (3*R*,4*S*)- and (3*S*,4*R*)-diastereomers, respectively, based on the fact that (i) both **7a** and **7b** are cis-β-lactams (J_{3-4} = 5–5.5 Hz; characteristic to cis structure) and (ii) **7a** gave (*R*)-Phe-(*S*)-Ala-O-*t*-Bu·HCl and **7b** gave (*S*)-Phe-(*S*)-Ala-O-*t*-Bu·HCl upon hydrogenolysis.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-(benzylideneamino)-4-phenylazetidin-2-one (1b). A solution of the 3-azido-β-lactam **7b** (500 mg, 1.58 mmol) in methanol (50 mL) was added to freshly purchased 5% Pd-C (50 mg) which was placed in a standard hydrogenation apparatus with a syringe at 0–5 °C (ice-water bath temperature). The mixture was treated with an ambient pressure of hydrogen at 0–5 °C for 6 h with stirring. The progress and the completion of the reaction was monitored by TLC. After filtering the catalyst with a glass filter (fine or medium with Celite) and removing the solvent, the corresponding 3-amino-β-lactam **8b** (442 mg, 96.2%) was obtained as a pale yellow solid.

8b: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.47 (br s, 2 H, exchanged by D_2O), 1.64 (d, *J* = 7.5 Hz), 3.86 (q, *J* = 7.5 Hz, 1 H), 4.39 (d, *J* = 5.5 Hz, 1 H), 4.89 (d, *J* = 5.5 Hz, 1 H), 7.13–7.47 (m, 5 H); IR (neat) 3400 (ν_{NH}), 1750, 1730 ($\nu_{C=O}$) cm^{-1}.

A mixture of the 3-amino-β-lactam **8b** thus obtained (440 mg, 1.52 mmol), benzaldehyde (162 mg, 1.52 mmol) and anhydrous magnesium sulfate (5 g) in benzene (25 mL), was stirred at room temperature for 17 h. After the removal of the drying agent and the solvent, the 3-(benzylideneamino)-β-lactam **1b** was obtained in quantitative yield by NMR. This material was used for the ketene addition without further purification (vide infra).

1b: pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.68 (d, *J* = 7.5 Hz, 3 H), 3.84 (q, *J* = 7.5 Hz, 1 H), 5.06 (s, 2 H), 7.18–7.57 (m, 10 H), 8.40 (s, 1 H); IR (neat) 1760, 1740 ($\nu_{C=O}$), 1640 ($\nu_{C=N}$) cm^{-1}.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-(benzylideneamino)-4-phenylazetidin-2-one (1a). In the same manner as described above, the 3-azide-β-lactam **7a** was reduced to the 3-amino-β-lactam **8a** in 96% yield, and **8a** was converted to the 3-(benzylideneamino)-β-lactam **1a** in quantitative yield.

8a: pale yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, *J* = 7.5 Hz, 3 H), 1.48 (s, 9 H), 1.56 (s, 2 H; exchanged by D_2O), 4.41 (q, *J* = 7.5 Hz, 1 H), 4.46 (d, *J* = 5 Hz, 1 H), 5.03 (d, *J* = 5 Hz, 1 H), 7.16–7.51 (m, 5 H); IR (neat) 3410 (ν_{NH}), 1750 ($\nu_{C=O}$) cm^{-1}.

1a: pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 8 Hz, 3 H), 4.48 (q, J = 8 Hz, 1 H), 5.14 (d, J = 5.5 Hz, 1 H), 5.26 (dd, J = 5.5 Hz, 1 Hz, 1 H), 7.20–7.63 (m, 10 H), 8.42 (d, J = 1 Hz, 1 H); IR (neat) 1760, 1730 ($\nu_{C=O}$), 1640 ($\nu_{C=N}$) cm^{-1}.

1[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*S*,4*R*)-3-[(3′*R*,4′*S*)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (9b). To a solution of **1b** (576 mg, 1.52 mmol) and triethylamine (847 mg, 8.37 mmol) in dichloromethane (30 mL) was added azidoacetyl chloride (910 mg, 7.61 mmol) in dichloromethane (15 mL) dropwise at −78 °C with stirring. The reaction mixture was allowed to warm up to room temperature for the period of 14 h and quenched with methanol (5 mL). After the workup described for the preparation of **7b**, the obtained crude product was submitted to a chromatographic separation on a silica gel column by using *n*-hexane/ethyl acetate (1/1) as eluant, which gave bis-β-lactam **9b** (516 mg, 74% from **1b**) as colorless crystals.

9b: mp 160.5–161.5 °C; $[\alpha]_D^{20}$ +17.7° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.72 (d, *J* = 7.5 Hz, 3 H), 3.84 (q, *J* = 7.5 Hz, 1 H), 4.07 (d, *J* = 5 Hz, 1 H), 4.20 (d, *J* = 5 Hz, 1 H), 4.47 (d, *J* = 5 Hz, 1 H), 4.83 (d, *J* = 5 Hz, 1 H), 7.09–7.53 (m, 10 H); IR (KBr disk) 2120 (ν_{N_3}), 1770, 1760 (sh), 1730 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{25}H_{27}N_5O_4$: C, 65.06; H, 5.90; N, 15.17. Found: C, 65.10; H, 6.02; N, 15.38.

1-[(*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-(3*R*,4*S*)-3-[(3′*S*,4′*R*)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (9a). In the same manner as described above, bis-β-lactam **9a** (320 mg, 48%[10]) was obtained from **1a** (544 mg, 1.44 mmol), triethylamine (799 mg, 7.18 mmol), and azidoacetyl chloride (858 mg, 7.18 mmol).

9a: colorless crystals; mp 183.5–185 °C; $[\alpha]_D^{20}$ +2.7° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.17 (d, *J* = 7.5 Hz, 3 H), 1.45 (s, 9 H), 3.94 (d, *J* = 5.5 Hz, 1 H), 4.19 (d, *J* = 5.5 Hz, 1 H), 4.52 (d, *J* = 5 Hz, 1 H), 4.54 (q, *J* = 7.5 Hz, 1 H), 5.03 (d, *J* = 5 Hz, 1 H), 7.11–7.53 (m, 10 H); IR (KBr disk) 2120 (ν_{N_3}), 1790, 1760, 1720 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{25}H_{27}N_5O_4$: C, 65.06; H, 5.90; N, 15.17. Found: C, 65.07; H, 5.92; N, 15.00.

Determination of the Absolute Configurations of the Newly Formed β-Lactam Rings. The azido-bis-β-lactam **9b** (516 mg, 1.24 mmol) was dissolved in ethyl acetate/ethanol (1/1) (50 mL) and submitted to the hydrogenation at 0–5 °C and ambient pressure over 5% Pd-C (50 mg) for 18 h. After the filtration and the removal of solvent, amino-bis-β-lactam **10b** was obtained in a quantitative yield.

10b: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.45 (s, 2 H, exchanged by D_2O), 1.71 (d, *J* = 7.5 Hz, 3 H), 3.74 (d, *J* = 5 Hz, 1 H), 3.88 (q, *J* = 7.5 Hz, 1 H), 4.11 (d, *J* = 5 Hz, 1 H), 4.50 (d, *J* = 5 Hz, 1 H), 4.83 (d, *J* = 5 Hz, 1 H), 7.06–7.49 (m, 10 H); IR (KBr disk) 3400 (ν_{NH}), 1770, 1740 ($\nu_{C=O}$) cm^{-1}.

A mixture of **10b** (269 mg, 0.62 mmol) and *N*-methylmorpholine (752 mg, 7.44 mmol) in dichloromethane (50 mL) was added acetyl chloride (669 mg, 6.20 mmol) at 0 °C and stirred for 1 h. The reaction mixture was washed with water, 2% hydrochloric acid, water and brine and dried over anhydrous magnesium sulfate. After removal of solvent, the crude product was purified by column chromatography on silica gel (ethyl acetate: eluant) to give (acetylamino)-bis-β-lactam **11b** (252 mg, 85%).

11b: colorless crystals; mp 146.5–147.5 °C; $[\alpha]_D^{20}$ −78.7° (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H). 1.56 (s, 3 H), 1.70 (d, *J* = 7.5 Hz, 3 H), 3.87 (q, *J* = 7.5 Hz, 1 H), 4.14 (d, *J* = 5 Hz, 1 H), 4.52 (d, *J* = 5 Hz, 1 H), 4.74 (dd, *J* = 5 Hz, 8.5 Hz, 1 H), 4.83 (d, *J* = 5 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 7.10–7.48 (m, 10 H); IR (KBr disk) 3300 (ν_{NH}), 1770, 1750 (sh), 1670 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.95; H, 6.59; N, 8.76.

A solution of **11b** (217 mg, 0.46 mmol) in methanol (50 mL) was submitted to hydrogenolysis over 10% Pd-C (200 mg) at 50 °C and ambient pressure for 33 h. The removal of catalyst and solvent gave a tripeptide, Ac-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu in 93% yield (206 mg): mp 203–204 °C, $[\alpha]_D^{20}$ −38.3° (*c* 0.95, MeOH); ^{1}H NMR (CD_3OD) δ 1.35 (d, *J* = 7.5 Hz, 3 H), 1.47 (s, 9 H), 1.84 (s, 3 H), 2.67–3.20 (m, 4 H), 4.25 (q, *J* = 7.5 Hz, 1 H), 4.40–4.73 (m, 2 H), 6.97–7.34 (m, 10 H); IR (KBr disk) 3300 (ν_{NH}), 1740, 1640 ($\nu_{C=O}$) cm^{-1}.

The tripeptide thus obtained was submitted to HPLC analysis by using a column packed with TOYO SODA LS 410K and MeOH/H_2O (7/3) as eluant. All four diastereomers of Ac-Phe-Phe-(*S*)-Ala-O-*t*-Bu, i.e., Ac-(*S*)-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu, Ac-(*R*)-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu, Ac-(*S*)-Phe-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu, and Ac-(*R*)-Phe-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu, were prepared by the standard solution method by using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) as coupling reagents, *N*-(*tert*-butoxycarbonyl)-(*S*)-phenylalanine [*t*-BOC-(*S*)-Phe-OH], *t*-BOC-(*R*)-Phe-OH, and *tert*-Butyl (*S*)-alaninate hydrochloride as amino acids, and *N*-methylmorpholine as base followed by N-deblocking and N-acetylation. The peptide obtained from **11b** was then unambiguously assigned to Ac-(*R*)-Phe-(*S*)-Phe-(*S*)-Ala-O-*t*-Bu.

In the same manner, azido-bis-β-lactam **9a** was converted to (acetylamino)bis-β-lactam **11a** (80% from **9a** via amino-bis-β-lactam **10a**). The hydrogenolysis of **11a** gave a tripeptide, Ac-(*S*)-Phe-(*R*)-Phe-(*S*)-Ala-O-*t*-Bu in 92% yield: colorless solid; mp 134–135 °C; $[\alpha]_D^{20}$ +17.0 (*c* 1.01, MeOH).

10a: ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* = 7.5 Hz, 3 H), 1.46 (s, 9 H), 1.65 (s, 2 H), 3.73 (d, *J* = 5.5 Hz, 1 H), 3.98 (d, *J* = 5.5 Hz, 1 H), 4.54 (d, *J* = 5 Hz, 1 H), 4.55 (q, *J* = 7.5 Hz, 1 H), 5.20 (d, *J* = 5 Hz, 1 H), 7.24–7.57 (m, 10 H); IR (KBr disk) 3400 (ν_{NH}), 1770, 1740 ($\nu_{C=O}$) cm^{-1}.

11a: colorless crystals; mp 92–94 °C; $[\alpha]_D$ +104.9° (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19 (d, *J* = 7.5 Hz, 3 H), 1.47 (s, 9 H), 1.56 (s, 3 H), 4.10 (d, *J* = 5 Hz, 1 H), 4.54 (q, *J* = 7.5 Hz, 1 H), 4.56 (d, *J* = 5 Hz, 1 H), 4.77 (dd, *J* = 5 Hz, 8.5 Hz, 1 H), 5.03 (d, *J* = 5 Hz, 1 H), 6.06 (d, *J* = 8.5 Hz, 1 H), 7.07–7.52 (m, 10 H); IR (KBr disk) 3300 (ν_{NH}), 1780, 1730, 1680 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.60; H, 6.63; N, 8.53.

1-*tert*-Butyl-(3*S,4*R**)-3-[(3′*R**,4′*S**)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (14).** (3*S**,4*R**)-3-Azido-4-phenylazetidin-2-one (**12**) was prepared by azidoketene addition to benzylidene-*tert*-butylamine by using the standard method described above. The 3-azido-β-lactam **12** was then reduced to the corresponding 3-amino-β-lactam **13** by hydrogenation over 5% Pd-C under the standard conditions (vide supra) and allowed to react with benzaldehyde to give 3-(benzylideneamino)-β-lactam **2**. The cycloaddition of azidoketene (3 equiv) generated in situ to **2** was carried out following the standard procedure (vide supra) to give the corresponding azido-bis-β-lactam **14** in 45% yield after purification on a short silica gel column.[10] The HPLC analysis (TOYO SODA LS 310K, *n*-hexane/ethyl acetate = 2/1) of crude product showed the exclusive formation of one isomer. The azido-bis-β-lactam **14** was submitted to our standard hydrogenolysis process at 55

°C (vide supra) to give the corresponding dipeptide, which was converted to its *N*-benzoyl derivative, i.e., Bz–Phe–Phe–NH-*t*-Bu. The HPLC analysis (Waters C18, MeOH/H_2O=3/1), using authentically prepared Bz–(*S*)-Phe–(*S*)-Phe–NH-*t*-Bu and Bz–(*R*)-Phe–(*S*)-Phe–NH-*t*-Bu as references, revealed that the dipeptide obtained from **14** was identical with Bz-(*R*)-Phe–(*S*)-Phe–NH-*t*-Bu. Consequently, it was found that the newly formed β-lactam ring had opposite configurations to the parent one.

2: colorless needles; mp 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 5.04 (dd, *J* = 5.3 Hz, 1.2 Hz, 1 H), 5.10 (d, *J* = 5.3 Hz, 1 H), 7.3–8.0 (m, 10 H), 8.53 (d, *J* = 1.2 Hz, 1 H); IR (KBr disk) 1740 ($\nu_{C=O}$), 1640 ($\nu_{C=N}$) cm^{-1}.

14: colorless needles; mp 137–138 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 3.88 (d, *J* = 5.2 Hz, 1 H), 4.20 (d, *J* = 5.2 Hz, 1 H), 4.35 (d, *J* = 4.9 Hz, 1 H), 4.76 (d, *J* = 4.9 Hz, 1 H), 7.15–7.5 (m, 10 H); IR (KBr) 2120 (ν_{N_3}), 1750 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 68.01; H, 6.03; N, 17.77.

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*R*,4*S*)-3-azido-4-phenylazetidin-2-one (15a) and 1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*S*,4*R*)-3-azido-4-phenylazetidin-2-one (15b). To a suspension of potassium hydride (4.85 g, 0.121 mol) in tetrahydrofuran (THF) (250 mL) was added dropwise a solution of (*S*)-leucinol (12.88 g, 0.110 mol) in THF (50 mL) at room temperature with stirring. After the reaction mixture was stirred for 17.5 h at room temperature, benzyl bromide (18.80 g, 0.110 mol) in THF (50 mL) was added dropwise. Then fine white solid began to precipitate. The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated, and ether (150 mL) and water (50 mL) were added to the residue. The ether layer was separated, washed with water, 20% sodium hydroxide, and brine, and dried over anhydrous sodium sulfate. After the removal of ether, the residue was distilled under reduced pressure to give (*S*)-leucinol benzyl ether (19.4 g 85%) as colorless liquid: bp 103–106 °C/0.6 mmHg; $[\alpha]_D^{20}$ +6.7° (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 1.09 (dd, *J* = 6.6 Hz, 6.5 Hz, 2 H), 1.38 (s, 2 H; exchanged by D_2O), 1.72 (t of heptet, *J* = 6.5 Hz, 6.6 Hz, 1 H), 2.87–3.51 (m, 3 H), 4.49 (s, 2 H), 7.31 (s, 5 H); IR (neat) 3400 (ν_{NH}), 1590 (δ_{NH}) cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.27; H, 10.30; N, 6.84. Found: C, 75.32; H, 10.21; N, 6.76.

In a manner similar to that described for the preparation of **6**, (*S*)-*N*-benzylideneleucinol benzyl ether (**18**) (7.03 g, 98.7%) was obtained by the reaction of (*S*)-leucinol benzyl ether (5.00 g, 24.1 mmol) with benzaldehyde (2.50 g, 24.1 mmol).

18: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, *J* = 6 Hz, 3 H), 0.90 (d, *J* = 6 Hz, 3 H), 1.17–1.80 (m, 3 H), 3.43–3.66 (m, 3 H), 4.47 (s, 2 H), 7.24 (s, 5 H), 7.12–7.83 (m, 5 H), 8.28 (s, 1 H); IR (neat) 1640 ($\nu_{C=N}$) cm^{-1}.

A mixture of **18** (7.03 g, 23.8 mmol), triethylamine (5.30 g, 52.4 mmol) in dichloromethane (75 mL), was allowed to react with azidoacetyl chloride (5.69 g, 47.6 mmol) in a manner similar to that described for the preparation of **7**, and the mixture of **15a** (R_f 0.37, *n*-hexane/ethyl acetate = 4/1) and **15b** (R_f 0.45, *n*-hexane/ethyl acetate = 4/1) was obtained in 86.4% yield (7.78 g). The diastereomer ratio (**15a**/**15b**) was determined to be 44/56 by HPLC analysis (TOYO SODA LS 310K, *n*-hexane/ethyl acetate = 4/1). The two diastereomers **15a** (3.05 g) and **15b** (4.24 g) were separated by HPLC with a Waters Prep 500 system by using *n*-hexane/ethyl acetate (4/1) as eluant.

15a: colorless prisms; mp 63–63.5 °C; $[\alpha]_D^{20}$ +136.4° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.95 (m, 1 H), 1.2 (m, 1 H), 1.6 (m, 1 H), 3.49 (dd, *J* = 10.2 Hz, 4.5 Hz, 1 H), 3.56 (dd, *J* = 10.2 Hz, 8.7 Hz, 1 H), 4.0 (m, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.78 (d, *J* = 5.2 Hz, 1 H), 4.84 (d, *J* = 5.2 Hz, 1 H), 7.2–7.6 (m, 10 H); IR (KBr disk) 2120 (ν_{N_3}), 1765 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.93; N, 14.80. Found: C, 69.85; H, 6.96; N, 14.75.

15b: colorless prisms; mp 77.5–78.5 °C; $[\alpha]_D^{20}$ −124.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.35 (m, 1 H), 1.6 (m, 1 H), 1.75 (m, 1 H), 3.28 (dd, *J* = 9.6 Hz, 1 H), 3.42 (dd, *J* = 9.6 Hz, 7.8 Hz, 1 H), 3.7 (m, 1 H), 4.30 (d, *J* = 12.4 Hz, 1 H), 4.31 (d, *J* = 12.4 Hz, 1 H), 4.83 (d, *J* = 5.2 Hz, 1 H), 4.87 (d, *J* = 5.2 Hz, 1 H), 7.2–7.5 (m, 10 H); IR (KBr disk) 2120 (ν_{N_3}), 1765 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.93; N, 14.80. Found: C, 69.98; H, 7.02; N, 14.79.

The absolute configuration of **15a** or **15b** was determined unambiguously by converting **15** to the corresponding dipeptide, Bz–Phe–(*S*)-Leu-ol, by our standard hydrogenolysis method (vide supra) and HPLC analysis (Waters C18, MeOH/H_2O = 3/1). It was found that **15a** gave (*R*)-Phe–(*S*)-Leu-ol and **15b** gave (*S*)-Phe-(*S*)-Leu-ol.

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*R*,4*S*)-3-(benzylideneamino)-4-phenylazetidin-2-one (3a) and 1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*S*,4*R*)-3-(benzylideneamino)-4-phenylazetidin-2-one (3b). In a manner similar to that described for the preparation of **1**, the azide group of **15** was reduced to amino group to give **16** in quantitative yield through hydrogenation on 5% Pd–C at 0–5 °C for 6 h, and **16** was then allowed to react with 1 equiv of benzaldehyde in the presence of anhydrous sodium sulfate in benzene to give **3** in quantitative yield.

16a: colorless needles; mp 88–88.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 1.02–1.40 (m, 2 H), 1.21 (br s, 2 H, exchanged by D_2O), 1.58–1.75 (m, 1 H), 3.52 (dd, *J* = 9.3 Hz, 4.5 Hz, 1 H), 3.67 (dd, *J* = 9.3 Hz, 9.3 Hz, 1 H), 3.87–3.96 (m, 1 H), 4.38 (d, *J* = 5.4 Hz, 1 H), 4.97 (d, *J* = 11.7 Hz, 1 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.77 (d, *J* = 5.4 Hz, 1 H), 7.24–7.43 (m, 10 H); IR (KBr disk) 3380, 3320 (ν_{NH}), 1725 ($\nu_{C=O}$) cm^{-1}.

16b: colorless needles; mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 1.29 (br s, 2 H, exchanged by D_2O), 1.35–1.77 (m, 3 H), 3.28 (dd, *J* = 9.6 Hz, 4.2 Hz, 1 H), 3.39 (dd, *J* = 9.6 Hz, 7.5 Hz, 1 H), 3.80–3.98 (m, 1 H), 4.30 (s, 2 H), 4.38 (d, *J* = 5.1 Hz, 1 H), 4.85 (d, *J* =5.1 Hz, 1 H), 7.15–7.45 (m, 10 H); IR (KBr disk) 3385, 3320 (ν_{NH}), 1725 ($\nu_{C=O}$) cm^{-1}.

3a: colorless prisms; mp 102–104 °C; $[\alpha]_D^{20}$ +186.1° (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.74 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.9 (m, 1 H), 1.2 (m, 1 H), 1.7 (m, 1 H), 3.52 (dd, *J* = 10.0 Hz, 4.7 Hz, 1 H), 3.62 (dd, *J* = 10.0 Hz, 8.7 Hz, 1 H), 4.05 (m, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 11.7 Hz, 1 H), 4.92 (d, *J* = 5.4 Hz, 1 H), 5.06 (dd, *J* = 5.4 Hz, 1.1 Hz, 1 H), 7.2–7.6 (m, 15 H), 8.46 (d, *J* = 1.1 Hz, 1 H); IR (KBr disk) 1760, 1745 ($\nu_{C=O}$), 1645, 1640 ($\nu_{C=N}$).

3b: pale yellow solid; mp 79–80 °C; $[\alpha]_D^{20}$ +112.9° (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, *J* = 7 Hz, 3 H), 0.94 (d, *J* = 7 Hz, 3 H), 1.05–1.40 (m, 1 H), 1.45–1.95 (m, 2 H), 3.24 (dd, *J* = 6 Hz, 9 Hz, 1 H), 3.45 (dd, *J* = 9 Hz, 9 Hz, 1 H), 4.34 (s, 2 H), 4.98 (d, *J* = 5 Hz, 1 H), 5.06 (dd, *J* = 5 Hz, 2 Hz, 1 H), 7.15–7.60 (m, 15 H), 8.44 (d, *J* = 2 Hz, 1 H); IR (KBr disk) 1750 ($\nu_{C=O}$), 1640 ($\nu_{C=N}$) cm^{-1}.

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*R*,4*S*)-3-[(3′*S*,4′*R*)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (19a) and 1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*S*,4*R*)-3-[(3′*S*,4′*R*)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (19b). In a manner similar to that described for the synthesis of **9**, the imine **3** was allowed to react with azidoketene generated in situ from azidoacetyl chloride (2 equiv) and triethylamine (2.1 equiv) in dichloromethane (15 mL/1 mmol of **3**) at −78 °C. After usual workup and passing the crude product through a short silica gel column, the corresponding azido-bis-β-lactam **19** was obtained pure: **19a**, 46% yield;[10] **19b**, 60% yield.[10]

19a: pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.90–1.10 (m, 1 H), 1.20 (m, 1 H), 1.20–1.40 (m, 1 H), 1.60–1.90 (m, 1 H), 3.51 (d, *J* = 6.4 Hz, 2 H), 3.89 (d, *J* = 5.1 Hz, 1 H), 4.10 (m, 1 H) 4.26 (d, *J* = 5.1 Hz, 1 H), 4.40 (d, *J* = 4.9 Hz, 1 H), 4.42 (d, *J* = 12.1 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.72 (d, *J* = 4.9 Hz, 1 H), 7.1–7.5 (m, 15 H); IR (neat) 2120 (ν_{N_3}), 1760 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{31}H_{33}N_5O_3$: C, 71.11; H, 6.35; N, 13.38. Found: C, 70.95; H, 6.52; N, 13.19.

19b: colorless needles; mp 111–112 °C; $[\alpha]_D^{20}$ +15.2° (*c* 1.04, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.83 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.37–1.52 (m, 1 H), 1.65–1.80 (m, 1 H), 1.80–1.95 (m, 1 H), 3.36 (dd, *J* = 9.6 Hz, 4.1 Hz, 1 H), 3.58 (dd, *J* = 9.6 Hz, 7.4 Hz, 1 H), 3.75 (m, 1 H), 3.93 (d, *J* = 5.2 Hz, 1 H), 4.24 (d, *J* = 5.2 Hz, 1 H), 4.21 (d, *J* = 11.9 Hz, 1 H), 4.28 (d, *J* = 11.9 Hz, 1 H), 4.40 (d, *J* = 4.9 Hz, 1 H), 4.82 (d, *J* = 4.9 Hz, 1 H), 7.1–7.5 (m, 15 H); IR (KBr disk) 2120 (ν_{N_3}), 1770 (sh), 1755 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{31}H_{33}N_5O_3$: C, 71.11; H, 6.35; N, 13.38. Found: C, 71.25; H, 6.31; N, 13.26.

Determination of the Absolute Configurations of the Newly Formed β-Lactam Rings. In a manner similar to the case of the bis-β-lactam **9**, the azido-bis-β-lactams **19a** and **19b** were reduced to the corresponding amino-bis-β-lactams **22a** and **22b**, respectively, through hydrogenation (1 atm) on 5% Pd–C in methanol at 0–5 °C. The amino-bis-β-lactam **22a** was converted to its *tert*-butoxycarbonyl (*t*-BOC) derivative **23a** by using *tert*-butyl *S*-4,6-dimethylpyrimidine-2-thiocarbonate (*t*-BOC-S) and triethylamine in THF and hydrogenolyzed (5% Pd–C, MeOH, 55 °C) to give *t*-BOC–(*S*)-Phe–(*R*)-Phe–(*S*)-Leu-ol. The amino-bis-β-lactam **22b** was converted to its benzoyl derivative **23b** by using benzoyl chloride and *N*-methylmorpholine and submitted to hydrogenolysis on 5% Pd–C in methanol at 55 °C to give Bz–(*R*)-Phe–(*S*)-Phe–(*S*)-Leu-ol. The absolute configurations of the tripeptide were unambiguously determined by HPLC analysis (Waters C18 column, MeOH/H_2O = 7/3) by using authentically prepared diastereomeric tripeptides i.e., *t*-BOC–(*S*)-Phe–(*R*)-Phe–(*S*)-Leu-ol, *t*-BOC-(*R*)-Phe–(*R*)-Phe–(*S*)-Leu-ol, Bz–(*S*)-Phe–(*S*)-Phe–(*S*)-Leu-ol, and Bz–(*R*)-Phe–(*S*)-Phe–(*S*)-Leu-ol, as references.

22a: pale yellow oil; $[\alpha]_D^{20}$ −8.9° (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.81–1.3 (br s,

2 H; disappeared upon D_2O addition), 1.03–1.17 (m, 1 H), 1.32–1.47 (m, 1 H), 1.88 (m, 1 H), 3.61 (d, J = 6.4 Hz, 1 H), 3.90 (d, J = 5.3 Hz, 1 H), 4.03 (d, J = 5.3 Hz, 1 H), 4.17 (m, 1 H), 4.51 (d, J = 5.0 Hz, 1 H), 4.53 (d, J = 11.8 Hz, 1 H), 4.63 (d, J = 11.8 Hz, 1 H), 4.81 (d, J = 5.0 Hz, 1 H), 7.2–7.7 (m, 10 H).

22b: pale yellow oil; $[\alpha]_D^{20}$ +20.3° (c 1.02, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 1.3–1.8 (br s, 2 H, disappeared upon D_2O addition), 1.44 (m, 1 H), 1.73 (m, 1 H), 1.88 (m, 1 H), 3.35 (dd, J = 9.6 Hz, 4.2 Hz, 1 H), 3.58 (dd, J = 9.6 Hz, 7.2 Hz, 1 H), 3.75 (m, 1 H), 3.79 (d, J = 5.4 Hz, 1 H), 3.98 (d, J = 5.4 Hz, 1 H), 4.25 (d, J = 11.8 Hz, 1 H), 4.27 (d, J = 11.8 Hz, 1 H), 4.44 (d, J = 4.8 Hz, 1 H), 4.81 (d, J = 4.8 Hz, 1 H), 7.15–7.85 (m, 15 H); IR (neat) 3380 (ν_{NH}), 1755 ($\nu_{C=O}$) cm^{-1}.

23a: pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.95–1.10 (m, 1 H), 1.17 (s, 9 H), 1.25–1.40 (m, 1 H), 1.78 (m, 1 H), 3.52 (d, J = 6.4 Hz, 2 H), 3.98 (d, J = 4.8 Hz, 1 H), 4.10 (m, 1 H), 4.42 (d, J = 4.9 Hz, 1 H), 4.44 (d, J = 11.8 Hz, 1 H), 4.56 (d, J = 11.8 Hz, 1 H), 4.59 (d, J = 4.8 Hz, 1 H), 4.73 (d, J = 4.9 Hz, 1 H), 5.5–6.1 (br s, 1 H), 7.1–7.5 (m, 15 H).

23b: caramel oil; $[\alpha]_D^{20}$ −48.2° (c 0.83, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 1.45 (m, 1 H), 1.75 (m, 1 H), 1.90 (m, 1 H), 3.37 (dd, J = 9.6 Hz, 4.1 Hz, 1 H), 3.59 (dd, J = 9.6 Hz, 7.2 Hz, 1 H), 3.81 (m, 1 H), 4.22 (d, J = 5.1 Hz, 1 H), 4.25 (d, J = 11.9 Hz, 1 H), 4.29 (d, J = 11.9 Hz, 1 H), 4.87 (d, J = 4.8 Hz, 1 H), 5.03 (dd, J = 5.1 Hz, 8.5 Hz, 1 H), 6.26 (d, J = 8.5 Hz, 1 H), 7.1–7.8 (m, 20 H). Anal. Calcd for $C_{38}H_{39}N_3O_4$: C, 75.85; H, 6.53; N, 6.98. Found: C, 75.79; H, 6.52; N, 6.81.

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*S*,4*S*)-3-(benzylideneamino)-4-phenylazetidin-2-one (4). To a solution of **3a** (648 mg, 1.47 mmol) in THF (5 mL) was added a solution of lithium diisopropylamine (LDA) (1.47 mol) in THF (3 mL) at −95 °C with stirring, the mixture was stirred for 4 h, and the reaction was quenched with methanol (1 mL) at −95 °C. The solvent was evaporated, and the residue was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and evaporated to give a mixture of **4** and **3a** (**4**/**3a** = 96/4 based on HPLC analysis; TOYO SODA LS 310K, n-hexane/ethyl acetate = 4/1). The mixture was submitted to column chromatography on silica gel to give **4** (583 mg, 90% yield) as colorless oil: $[\alpha]_D^{20}$ +3.4° (c 0.58, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 1.03 (m, 1 H), 1.27 (m, 1 H), 1.70 (m, 1 H), 3.58 (dd, J = 10.0 Hz, 4.2 Hz, 1 H), 3.73 (dd, J = 10.0 Hz, 8.4 Hz, 1 H), 3.93 (m, 1 H), 4.51 (d, J = 11.7 Hz, 1 H), 5.62 (d, J = 11.7 Hz, 1 H), 4.66 (dd, J = 1.7 Hz, 0.9 Hz, 1 H), 4.77 (J = 1.7 Hz, 1 H), 7.0–7.8 (m, 15 H), 8.38 (d, J = 0.9 Hz, 1 H).

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(3*S*,4*S*)-3-[(3′*R*,4′*S*)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (20a) and 1-[(*S*)-1-(Benzyloxy)4-methylpent-2-yl]-(3*S*,4*S*)-3-[(3′*S*,4′*R*)-3-azido-4-phenylazetidin-2-on-1-yl]-4-phenylazetidin-2-one (20b). In a similar manner to that described for the reactions of **3**, the imine **4** was allowed to react with azidoketene (5 equiv) in situ generated in dichloromethane at −78 °C. After usual workup and purification on a short silica gel column, the mixture of the corresponding azido-bis-β-lactams **20a** (major) and **20b** (minor) was obtained in 67% yield. The HPLC analysis (TOYO SODA LS 310K, n-hexane/ethyl acetate = 2/1) showed the ratio of 81/19 for the two products. Half of the mixture was submitted to chromatographic separation on silica gel to give **20a** and **20b** in a 4:1 ratio. The other half of the mixture was hydrogenated on 5% Pd–C in methanol at 0–5 °C to give the corresponding amino-bis-β-lactams **24a** and **24b**, which were converted to their benzoyl derivatives **25a** and **25b** with benzoyl chloride and N-methylmorpholine. The overall yield from **17** was 90%. The (benzoylamino)-bis-β-lactam (**24a** and **24b** mixture) was submitted to our standard hydrogenolysis procedure on 5% Pd-C in methanol at 55 °C for 8 h to give the corresponding Bz–Phe–(*S*)-Phe–(*S*)-Leu-ol. The HPLC analysis (Waters C18 column, MeOH/H_2O = 3/2) revealed that the major product was Bz–(*R*)-Phe–(*S*)-Phe–(*S*)-Leu-ol (80%) and minor Bz–(*S*)-Phe–(*S*)-Phe–(*S*)-Leu-ol (20%). Consequently, it was concluded that the major cycloadduct **20a** was the (3*S*,4*R*)-isomer and the minor **20b** was the (3*R*,4*S*)-isomer regarding the newly formed β-lactam rings.

20a: colorless oil; $[\alpha]_D^{20}$ −12.1° (c 1.06, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.63 (d, J = 6.6 Hz, 3 H), 0.67 (d, J = 6.5 Hz, 3 H), 0.95 (m, 1 H), 1.19 (m, 1 H), 1.40 (m, 1 H), 3.25 (dd, J = 8.4 Hz, 3.6 Hz, 1 H), 3.50 (dd, J = 8.4 Hz, 9.3 Hz, 1 H), 3.66 (m, 1 H), 4.27 (d, J = 2.4 Hz, 1 H), 4.30 (d, J = 11.8 Hz, 1 H), 4.34 (d, J = 11.8 Hz, 1 H), 4.89 (d, J = 2.4 Hz, 1 H), 4.98 (d, J = 5.7 Hz, 1 H), 5.00 (d, J = 5.7 Hz, 1 H), 7.10–7.55 (m, 15 H); IR (neat) 2120 (ν_{N_3}), 1765 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{31}H_{33}N_5O_3$: C, 71.11; H, 6.35; N, 13.38. Found: C, 71.28; H, 6.40; N, 13.15.

20b: colorless oil; $[\alpha]_D^{20}$ −136.8° (c 0.19, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.71 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.5 Hz, 3 H), 1.00 (m, 1 H), 1.32 (m, 1 H), 1.60 (m, 3 H), 3.50 (dd, J = 7.7 Hz, 5.7 Hz, 1 H), 3.69 (dd, J = 7.7 Hz, 7.5 Hz, 1 H), 4.20 (d, J = 2.4 Hz, 1 H), 4.46 (d, J = 11.6 Hz, 1 H), 4.54 (d, J = 11.6 Hz, 1 H), 4.84 (d, J = 5.1 Hz, 1 H), 5.01 (d, J = 5.1 Hz, 1 H), 5.16 (d, J = 2.4 Hz, 1 H), 7.15–7.60 (m, 15 H); IR (neat) 2120 (ν_{N_3}), 1765 ($\nu_{C=O}$) cm^{-1}.

24a: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.66 (d, J = 6.6 Hz, 3 H), 0.69 (d, J = 6.6 Hz, 3 H), 0.88 (m, 1 H), 1.16 (m, 1 H), 1.35 (m, 1 H), 2.1 (br s, 2 H, disappeared upon D_2O addition), 3.31 (dd, J = 9.5 Hz, 3.4 Hz, 1 H), 3.51 (dd, J = 9.5 Hz, 8.0 Hz, 1 H), 3.59 (m, 1 H), 4.31 (d, J = 11.8 Hz, 1 H), 4.35 (d, J = 11.8 Hz, 1 H), 4.39 (d, J = 2.4 Hz, 1 H), 4.56 (d, J = 5.4 Hz, 1 H), 4.86 (d, J = 2.4 Hz, 1 H), 4.96 (d, J = 5.4 Hz, 1 H), 7.0–7.6 (m, 15 H).

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(2*S*,3*S*)-2-phenyl-3-(benzylideneamino)azetidine (5). A mixture of aluminum trichloride (267 mg, 2.00 mmol) and lithium aluminum hydride (79 mg, 2.08 mmol) in ether (10 mL) was refluxed for 30 min with stirring. To the chlorodihydroalane thus generated was added **15a** (189 mg, 0.50 mmol), and the mixture was stirred in refluxing ether for 2 h. Aqueous 5% sodium bicarbonate (50 mL) was added to the reaction mixture, which was extracted with dichloromethane and washed with brine. The extract was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo and purified through a short silica gel column to give 3-aminoazetidine **17** (149 mg, 88% yield) as colorless oil: $[\alpha]_D^{20}$ +120.5 (c 0.501, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6 Hz, 3 H), 0.93 (d, J = 6 Hz, 3 H), 1.05–1.93 (m, 3 H), 2.17 (br s, 2 H, disappeared upon D_2O addition), 2.53 (m, 1 H), 3.10–3.30 (m, 4 H), 3.57 (m, 1 H), 3.88 (d, J = 12 Hz, 1 H), 4.07 (d, J = 12 Hz, 1 H), 4.37 (d, J = 6 Hz, 1 H), 6.6–7.5 (m, 10 H).

In a manner similar to the preparation of **1a** and **1b**, the 3-aminoazetidine **17** was allowed to condense with benzaldehyde to give the corresponding 3-(benzylideneamino)azetidine **5** in quantitative yield.

5: colorless oil; $[\alpha]_D^{20}$ +85.6° (c 0.97, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.74 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.0–1.9 (m, 3 H), 3.45 (dd, J = 7.5 Hz, 3 Hz, 1 H), 3.58 (t, J = 7.5 Hz, 1 H), 4.05 (m, 1 H), 4.42 (d, J = 11 Hz, 1 H), 4.63 (d, J = 11 Hz, 1 H), 4.92 (d, J = 5.2 Hz, 1 H), 5.04 (dd, J = 5.2 Hz, 1.2 Hz, 1 H), 7.1–7.7 (m, 15 H), 8.45 (d, J = 1.2 Hz, 1 H); IR (neat) 1640 ($\nu_{C=N}$) cm^{-1}.

1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(2*S*,3*S*)-2-phenyl-3-[(3′*S*,4′*R*)-3-azido-4-phenylazetidin-2-on-1-yl]azetidine (21a) and 1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-(2*S*,3*S*)-2-phenyl-3-[(3′*R*,4′*S*)-3-azido-4-phenylazetidin-2-on-1-yl]azetidine (21b). In a manner similar to those described for the reactions of **3** and **4**, the imine **5** was allowed to react with azidoketene (2 equiv) generated in situ in dichloromethane at −90 °C. After usual workup and purification through a short silica gel column, the diastereomeric mixture of cycloadducts **21a** (minor) and **21b** (major) was obtained in 71% yield. The HPLC analysis (TOYO SODA LS 310K, n-hexane/ethyl acetate = 9/1) showed the ratio of 32/68 for the two products. The diastereomeric mixture was separated by column chromatography on silica gel (n-hexane/ethyl acetate = 9/1) to give pure diastereomers. The absolute configurations of the newly formed β-lactam rings were determined in a manner similar to those described for **19** and **20**. Namely, **21a** and **21b** were converted to their N-benzoyl derivatives by the reduction of the azide group followed by benzoylation and then submitted to our standard hydrogenolysis process in methanol at 55 °C for 8 h to give the corresponding desoxo tripeptides. The authentic desoxo tripeptides, i.e., Bz–(*S*)-Phe–(*R*)-NH–CH(CH_2Ph)CH_2–(*S*)-Leu-ol (**25a**) and Bz–(*R*)-Phe–(*R*)-NH–CH(CH_2Ph)CH_2–(*S*)-Leu-ol (**25b**), were prepared by the coupling of Bz–(*S*)-phenylalanine with **17** by using the DCC-HOBT method in THF. The coupling reaction gave a diastereomeric mixture of the desoxo tripeptides (**25a**/**25b** = 95/5; HPLC analysis, Waters C18, MeOH/H_2O = 4/1) because of partial racemization during the process. The HPLC analysis (Waters C18, MeOH/H_2O = 4/1) disclosed that the desoxo tripeptide derived from **21a** was **25a** and the one derived from **21b** was **25b**. Thus, it was concluded that the minor cycloadduct **21a** was the (3*S*,4*R*)-isomer while the major cycloadduct **21b** was the (3*R*,4*S*)-isomer regarding the newly formed β-lactam rings.

21a: colorless oil; $[\alpha]_D^{20}$ +33.6° (c 0.96, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.4 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 1.15–1.40 (m, 2 H), 1.68 (m, 1 H), 2.60 (m, 1 H), 3.15 (dd, J = 9.7 Hz, 6.4 Hz, 1 H), 3.18 (d, J = 5.0 Hz, 1 H), 3.26 (dd, J = 9.7 Hz, 3.2 Hz, 1 H), 3.31 (t, J = 8.0 Hz, 1 H), 3.72 (ddd, J = 6.7 Hz, 8.0 Hz, 1.7 Hz, 1 H), 3.85 (d, J = 11.9 Hz, 1 H), 3.97 (d, J = 11.9 Hz, 1 H), 4.31 (d, J = 5.0 Hz, 1 H), 4.44 (d, J = 6.7 Hz, 1 H), 4.59, (dd, J = 8.0 Hz, 1.7 Hz, 1 H), 6.9–7.6 (m, 15 H); IR (neat) 2120 (ν_{N_3}), 1765 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{31}H_{35}N_5O_2$: C, 73.05; H, 6.92; N, 13.74. Found: C, 72.86; H, 7.13; N, 13.61.

21b: colorless oil; $[\alpha]_D^{20}$ +174.5° (c 0.99, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 1.02 (m, 1 H), 1.26 (m, 1 H), 1.57 (m, 1 H), 2.54 (m, 1 H), 3.06 (dd, J = 8.7 Hz, 2.4

Hz, 1 H), 3.14 (dd, J = 8.7 Hz, 7.9 Hz, 1 H), 3.25 (d, J = 4.6 Hz, 2 H), 3.99 (d, J = 11.7 Hz, 1 H), 4.05 (d, J = 5.3 Hz, 2 H), 4.10 (d, J = 11.7 Hz, 1 H), 4.64 (d, J = 7.2 Hz, 1 H), 4.74 (dt, J = 7.2 Hz, 2.4 Hz, 1 H), 4.86 (d, J = 5.3 Hz, 1 H), 7.0-7.6 (m, 15 H); IR (neat) 2120 (ν_{N_3}), 1765 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{31}H_{35}N_5O_2$: C, 73.05; H, 6.92; N, 13.74. Found: C, 72.98; H, 7.02; N, 13.50.

X-ray Structure Determination of the *cis*-3-Imino-β-lactam 3a. The structure was solved by using the MULTAN program package and refined by full-matrix least-squares methods and difference fourier syntheses. The positions of the hydrogen atoms were calculated by the program HYDRO.[18]

(18) (a) Okaya, Y. In *Computing in Crystallography*; Schenk, H., Olthof-Hazekamp, R., van Koningsveld, H., Bassi, G. C., Eds.; Delft University Press: 1978; pp 153-165. (b) Frenz, B. A. In *Computing in Crystallography*; Schenk, H.; Olthof-Hazekamp, R., van Koningsveld, H., Bassi, G. C., Eds.; Delft University Press: 1978; pp 64-71.

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Supplementary Material Available: The summary of crystal parameters, data collection, and refinement and tables of positional and thermal parameters, bond lengths, and angles for **3a**, and general experimental methods (38 pages). Ordering information is given on any current masthead page.

Iodide Reduction of Sulfilimines. 2. Evidence for Concurrent Stepwise and Concerted Mechanisms for the Decomposition of Sulfurane Intermediates

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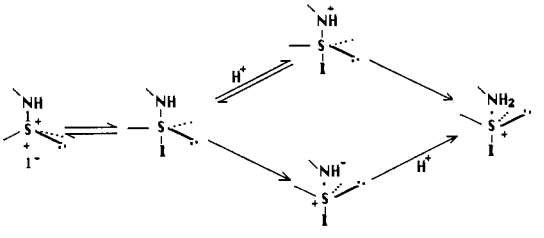
Abstract: The iodide reduction of *N*-(substituted ethyl or phenyl)-*S*,*S*-dimethylsulfilimmonium salts (aqueous solution, 25 °C, μ = 1.0 with KCl) is first order in proton activity and iodide concentration in the pH range 0.5-5. The solvent deuterium isotope effects for the reduction reaction vary in the range k_H/k_D = 0.26-0.48 as the nitrogen substituent is changed from ethyl- to trifluoroethylamine. Electron-withdrawing groups in the leaving group decrease the rate of the reaction and give β_{lg} values of ≈0.7 for cyanoethyl- and trifluoroethylamine leaving groups and ≈0.1 for the more basic ethylamine derivatives; a β_{lg} of 0.58 is observed for aniline derivatives. General acid catalysis is observed in the reduction of the acidic ethylamine and aniline derivatives with Brønsted α values of 0.59 and 0.39 for cyanoethyl- and trifluoroethylamine leaving groups, respectively; for anilines, the Brønsted α values decreased from 0.67 to 0.50 as the leaving group is changed from 4-methyl- to 3-nitroaniline. The value of β_{lg} decreases with decreasing strength of the catalyzing acid and the term $p_{xy} = (\partial\beta_{lg}/\partial pK_a^{HA}) = (\partial\alpha/\partial pK_a^{lg})$ ≈ −0.06 to −0.1. The solvent deuterium isotope effect on the general catalyzed reduction reaction increases with increasing acid strength; for the cyanoethylamine derivative, k_{BH}/k_{BD} = 1.47-2.32 for acetic and chloroacetic acids, respectively. A mechanism is suggested involving concurrent stepwise and concerted mechanisms for the reduction reaction; the mechanism observed seems to depend on the nature of the catalyzing acid.

For complex reaction mechanisms in solution where several possible parallel pathways exist for the conversion of starting materials to products, it is important to understand the factors that dictate which of the possible pathways will be observed for a given class of reactants and under a given set of conditions.[1,2] The iodide reduction of sulfilimine salts[3-7] is an example of a substitution reaction in which an initially formed addition product, a tetracoordinate sulfurane,[7,8] can partition by a variety of mechanisms to give an iodosulfonium ion, which rapidly undergoes a second reduction step to give the final products, the amine, the sulfide, and iodine (Scheme I). In previous work,[7] we have reported that the value of the Brønsted β_{lg} underwent a transition from a small positive value to a larger value (≈0.6) as the leaving group was changed from basic primary amines to less basic anilines. Further, the reaction of basic amine derivative was not subject to general-acid catalysis while a Brønsted α value of about 0.7 was observed for aniline derivatives. These data suggested that a change in the rate-limiting step or in the nature of the mechanism may be occurring as a consequence of the change in leaving group pK_a. In order to define more clearly the nature of

Scheme I



(1) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161-169.
(2) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689-4691.
(3) Tillett, J. G. *Chem. Rev.* **1976**, *76*, 747-772. Gilchrest, T. L.; Moody, C. J. *Ibid.* **1977**, *77*, 409-435. Oae, S.; Furukawa, N. In *Sulfilimines and Related Derivatives*; ACS Monograph 179, American Chemical Society: Washington, D.C., 1983.
(4) Doi, J. T.; Goodrow, M. H.; Musker, W. K. *J. Org. Chem.* **1986**, *51*, 1026-1029.
(5) Dell'Erba, C.; Guanti, G.; Leandir, G.; Corrallo, G. P. *Int. J. Sulfur Chem.* **1973**, *8*, 261-265.
(6) Gensch, K.-H.; Higuchi, T. *J. Pharm. Sci.* **1969**, *56*, 177-184.
(7) Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.* **1985**, *107*, 7572-7577.
(8) Young, P. R.; Hsieh, L.-S. *J. Am. Chem. Soc.* **1978**, *100*, 7121-7122.

0002-7863/87/1509-1805$01.50/0