A Palladium-Catalyzed, Abnormal Hydrogenolytic Ring-Cleavage Reaction of Fused β-Lactams

Toshiyuki KONOSU* and Sadao OIDA

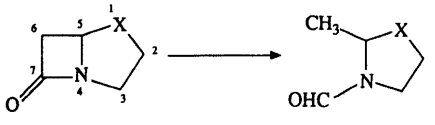
Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., 2–58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140, Japan.
Received September 17, 1991

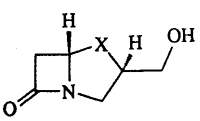
Bicyclic β-lactams, such as 1-oxa- and 1-carba-penams, are reductively cleaved between the lactam carbonyl group and the α-carbon by palladium catalysts to give formamide derivatives.

Keywords ring-opening reaction; β-lactam; palladium catalyst; oxapenam; carbapenam

Palladium catalysts are known to cleave carbon–carbon bonds of strained ring systems.[1] The most common examples of such reactions occur in cyclopropanes.[2] In contrast, simple β-lactams are resistant to hydrogenolysis, with the exception that 4-phenyl-2-azetidinones are known to be cleaved[3] between the N1 and C4 positions because of the benzylic nature of this bond. In the course of a synthetic study of an antifungal 1-oxapenam **1**[4] and its 1-carba analog **2**,[5] however, we discovered that fused β-lactams such as 1-oxa- and 1-carbapenams A undergo novel hydrogenolytic ring-cleavage reaction to give formamide derivatives B. This paper describes the details of this novel reaction.

In a preliminary study aimed at asymmetric synthesis of the antifungal (2*R*,5*S*)-1-oxapenam derivative **1**[4] (penam numbering shown in A will be used in the text), a benzyl ether precursor **3** was planned to be deblocked to give the alcohol **1**. Toward this end, the optically active (2*R*,5*S*) benzyl ether **3** was prepared. Attempted debenzylation of **3** by treatment with 10% palladium/carbon catalyst (Pd/C) in ethanol under an H_2 atmosphere (1 atm) at room temperature for 5 h resulted, however, in an 80% recovery of **3**; no trace of the alcohol **1** was detected in the reaction mixture.[6] In the expectation that a more active catalyst might smoothly cleave the benzyl ether moiety, the benzyl ether **3** was next treated with palladium black[7] in ethanol under an H_2 atmosphere (1 atm) at room temperature for 24 h. However, this condition also failed to produce the desired alcohol **1**. Instead, an unexpected product, whose structure was determined to be **4**, as will be described later, was obtained in 70% yield, along with a 12% recovery of **3**. Similarly, the diastereomeric (2*R*,5*R*) benzyl ether **3'** gave the ring-cleavage product **4'**, a diastereomer of **4**, in 38% yield, along with a 38% recovery of **3'**, on treatment with palladium black [ethanol, H_2 (1 atm), room temperature, 100 h]. No cross product, *i.e.* **4'** from **3**, or **4** from **3'**, was obtained.





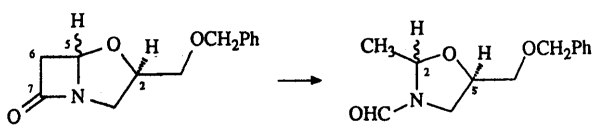


Chart 1

The structures of the products **4** and **4'** were determined as follows. The mass spectra (MS) of these products exhibited molecular ion peaks at $m/z=235$, suggesting that these products were derived from **3** and **3'** by a gain of two hydrogen atoms. Absorption maxima in the infrared (IR) spectrum of both **4** and **4'** were seen at 1660 cm^{-1}, whereas those of the starting oxapenams **3** and **3'** were at 1780 cm^{-1}. This indicated that the β-lactam rings that had been present in **3** and **3'** had been lost in the products **4** and **4'**. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrun, each product **4** and **4'** was observed as a 2 : 1 mixture of two conformers. New signals appeared as singlets at δ 8.25 for **4**, and at δ 8.22 for **4'**. These chemical-shift values and the IR data were indicative of the presence of a formamide moiety in these products. The possibility of two rotamers due to the hindered rotation of the amide bond could then explain why each of these products was observed as a mixture of two conformers in the ^{1}H-NMR spectrum. The resonances that appeared at δ 1.40 and 1.45 (3H combined, relative intensity ≈1 : 2, each doublet, each $J=6$ Hz) for **4**, and at δ 1.46 and 1.54 (3H combined, relative intensity ≈1 : 2, each doublet, each $J=6$ Hz) for **4'**, indicated the presence of CH_3–CH– moieties in these products. The benzyl ether moieties were found to have remained unchanged in these products. Consequently, the plane structure **4** or **4'**, which corresponds to the formula resulting from bond-cleavage between C6 and C7 of **3** or **3'**, was deduced. Assuming that the reaction proceeded with retention of configuration at the chiral centers, the assignment of the configuration of the products **4** and **4'** would be as illustrated, although there is no spectral evidence for this assignment.

The complex nature of the ^{1}H-NMR data for other protons of the products due to the presence of the rotamers, as well as the rarity of this reaction, prompted us to synthesize authentic samples of (±)-**4** and (±)-**4'**. Epibromohydrin was treated with sodium benzyloxide to give the epoxyether (±)-**5**, which was converted into the aminoalcohol (±)-**7** *via* the azidoalcohol (±)-**6**. Treatment

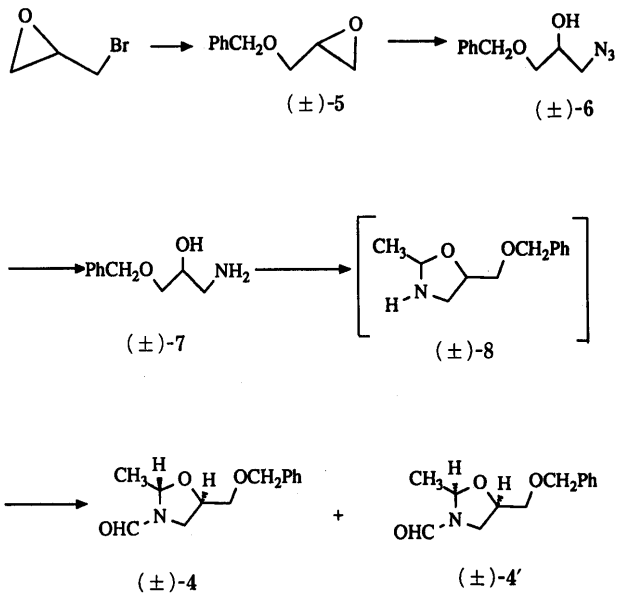


Chart 2

of the aminoalcohol (±)-**7** with acetaldehyde gave the oxazolidine derivative (±)-**8**, which was *N*-formylated to afford (±)-**4** as the less polar isomer and (±)-**4′** as the more polar one in a ratio of *ca.* 3:4 afrer separation by chromatography. The spectral data (IR, ^{1}H-NMR, and MS) of (±)-**4** and (±)-**4′** thus obtained were in accord with those of the products **4** and **4′** that were respectively obtained by hydrogenolysis of **3** and **3′**.

In order to investigate further the features of this ring-opening reaction, we re-examined the use of Pd/C under an activated condition. Treatment of **3** with 10% Pd/C under an H_2 atmosphere (5 atm) in ethanol–methanol in the presence of ammonium formate (26 eq) and formic acid (3 eq) at room temperature for 15 h gave the ring-cleavage product **4** in 5% yield, along with a 5% recovery of **3**. The rest was a polar, insoluble, gummy product. The low recovery here was presumably due to decomposition of **3**, whose 1-oxapenam skeleton was shown to be unstable under acidic conditions.[4] Thus, this ring-cleavage reaction was found to be promoted not only by palladium black, but also by Pd/C.

Next, some other compounds were examined. The benzyl ether moiety in the 1-carbapenam **9** has already been shown to resist debenzylation by treatment with 10% Pd/C in ethanol under an H_2 atmosphere (150 atm) at room temperature for 4 h.[5] Treatment of **9** with palladium black [ethanol, H_2 (1 atm), room temperature, 19 h] gave an inseparable, *ca.* 3:4 mixture of the normal, debenzylated product **2** and the ring-cleavage product **10** in 20% combined yield. The recovery of **9** was 20%. The rest was a polar, insoluble, gummy product, and the low recovery here again was presumed due to decomposition of the 1-carbapenams **2** and **9**.[8] Thus, it was found that palladium black also cleaves the 1-carbapenam skeleton, although in competition with the debenzylation process in the substrate **9**.

Finally, monocyclic β-lactams were subjected to hydrogenolysis. Treatment of the monocyclic β-lactam **11**[9] with palladium black [ethanol, H_2 (1 atm), room temperature, 17 h] resulted only in the quantitative recovery of the subject material. Thus, bicyclic systems, such as 1-oxa- and 1-carba-penam rings, seem to be essential for the ring-cleavage reaction. On the other hand, the benzyl ether **12** underwent hydrogenolysis using 10% Pd/C [methanol, H_2 (1 atm), room temperature, 17 h] to give the debenzylated product **13** in 97% yield as had been described,[5] and prolonged treatment (120 h) did not cleave the β-lactam ring of **13**. The facile debenzylation observed for **13** contrasts with the above-described results that benzyl ethers **3**, **3′**, **4**, **4′**, **9**, and **10**, in which a $PhCH_2OCH_2$– group is attached to the 5-membered ring, are resistant to debenzylation.

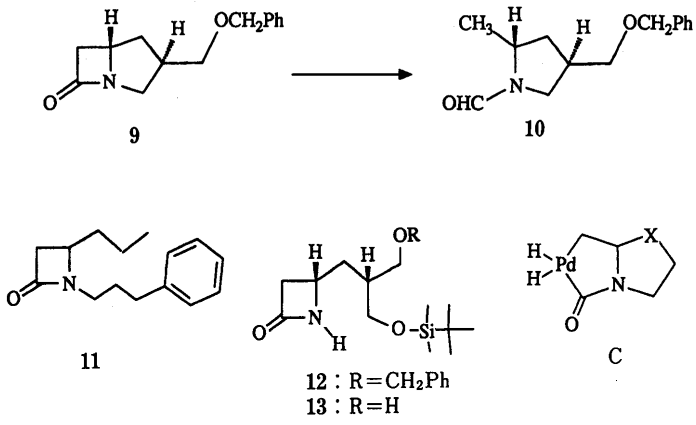


Chart 3

The precise mechanism of the above-described ring-opening reaction is unclear, but a conceivable reaction pathway involves the oxidative insertion of a palladium hydride species into a ring strain-activated β-lactam to form a metalacycle akin to C,[10] which is expected to undergo hydride transfer from palladium to carbon followed by reductive elimination to give the product B.

Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer, ^{1}H-NMR spectra on a Varian EM-360L spectrometer (60 MHz) or a JEOL GX-270 spectrometer (270 MHz) using tetramethylsilane as the internal standard, and MS and high-resolution MS (HRMS) on a JEOL JMS D300 spectrometer. Preparative thin layer chromatography (TLC) was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 2 mm (E. Merck). Chromatography columns were prepared with silica gel (60—110 mesh, Kanto Chemical Co., Inc.), and flash chromatography columns were prepared with silica gel (230—400 mesh, E. Merck). The amount of silica gel used and the developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; q, quartet; m, multiplet; br, broad.

Palladium Black This catalyst was prepared by the following slight modification of the literature procedure.[7] Palladium(II) chloride (500 mg, 2.9 mmol) was dissolved in a hot solution of 2 N HCl (2.7 ml), then boiling water (25 ml) was added. While this solution was boiled by heating with a hot-plate, formic acid (85%, 0.1 ml) was added with vigorous stirring. The solution was adjusted to pH 10 by adding a hot 10% (w/v) KOH solution while being boiled and vigorously stirred. Formic acid (85%) was again added with continued boiling and vigorous stirring, to make the solution pH 3, then heating was continued until the pH became 7. The latter procedure (addition of formic acid and then heating) was repeated two more times, then the precipitates were separated by decantation and washed with a total of 1 l of water. The catalyst thus obtained was used immediately for hydrogenolysis.

Ring-Cleavage Reaction Using Palladium Black. Formation of (2*S*,5*R*)-5-Benzyloxymethyl-3-formyl-2-methyl-1,3-oxazolidine (4) A mixture of (3*R*,5*S*)-3-benzyloxymethyl-1-aza-4-oxabicyclo[3.2.0]heptan-7-one[4] (**3**, 55 mg, 0.24 mmol), freshly prepared palladium black (water suspen-

sion, 1 ml), and ethanol (7 ml) was stirred under H_2 (1 atm) at room temperature for 24 h. Filtration through sanitary cotton and evaporation of the solvent gave an oily residue, which was chromatographed using a preparative TLC plate (AcOEt : hexane = 3 : 2, v/v) to afford **4** (Rf = 0.1, 39 mg, 70%) and recovered **3** (Rf = 0.5, 6.5 mg, 12%) as oils. The spectral data of **4** are as follows. $[\alpha]_D^{25}$ −49.6° (c = 1.49, $CHCl_3$). IR ($CHCl_3$): 3000, 1660, 1190, 1090 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$, observed as a *ca.* 2 : 1 mixture of rotamers) δ: 1.40 and 1.45 (relative intensity ≈ 1 : 2, 3H combined, each d, each J = 6 Hz), 3.4—3.8 (4H, m), 4.2—4.7 (1H, m), 4.55 (2H, s), 5.37 and 5.58 (relative intensity ≈ 2 : 1, 1H combined, each q, each J = 6 Hz), 7.44 (5H, s), 8.25 (1H, s). MS m/z: 235 (M^+), 220, 206, 192, 157, 144, 129, 91 (100%). HRMS Calcd for $C_{13}H_{17}NO_3$: 235.1207. Found: 235.1210.

(2*R*,5*R*)-5-Benzyloxymethyl-3-formyl-2-methyl-1,3-oxazolidine (4′) Following a procedure similar to that described for **4**, (3*R*,5*R*)-3-benzyloxymethyl-1-aza-4-oxabicyclo[3.2.0]heptan-7-one[4] (**3′**, 47 mg, 0.20 mmol) was treated with palladium black in ethanol under H_2 (1 atm) at room temperature for 100 h to give **4′** (18 mg, 38%) and recovered **3′** (18 mg, 38%) as oils after chromatography. The spectral data of **4′** are as follows. $[\alpha]_D^{25}$ +57.3° (c = 1.05, $CHCl_3$). IR ($CHCl_3$): 3000, 1660, 1200, 1090 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$, observed as a *ca.* 2 : 1 mixture of rotamers) δ: 1.46 and 1.54 (relative intensity ≈ 1 : 2, 3H combined, each d, each J = 6 Hz), 3.3—3.9 (4H, m), 4.0—4.5 (1H, m), 4.59 (2H, s), 5.10 and 5.39 (relative intensity ≈ 2 : 1, 1H combined, each q, each J = 6 Hz), 7.43 (5H, s), 8.22 (1H, s). MS m/z: 235 (M^+), 220, 206, 192, 144, 129, 91 (100%). HRMS Calcd for $C_{13}H_{17}NO_3$: 235.1207. Found: 235.1212.

(2*R*,4*R*)-4-Benzyloxymethyl-1-formyl-2-methylpyrrolidine (10) Following a procedure similar to that described for **4**, (3*R*,5*S*)-3-benzyloxymethyl-1-azabicyclo[3.2.0]heptan-7-one (**9**, 72 mg, 0.31 mmol) was treated with palladium black in ethanol under H_2 (1 atm) at room temperature for 19 h to afford an inseparable mixture of a ring-cleavage product **10** and an alcohol **2** (molar ratio ≈ 3 : 4, total 12 mg, yields: 9% and 12%) after preparative TLC (AcOEt). The spectral data of a pure sample of **2** are presented in ref. 5. The IR, ^{1}H-NMR, and HRMS data that were selected for the product **10** from those of the above mixture are as follows. IR ($CHCl_3$): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz, observed as a *ca.* 2 : 1 mixture of rotamers) δ: 1.24 and 1.27 (relative intensity ≈ 1 : 2, 3H combined, each d, each J = 6 Hz), 1.6—1.8 (2H, m), 1.7—2.0 (1H, m), 3.3—3.5 (2H, m), 3.42 (2H, d, J = 6 Hz), 3.97 [*ca.* 2/3H, quintet of doublets, J = 6, 4 Hz], 4.1—4.2 [*ca.* 1/3H, m], 4.51 (2H, s), 7.32 (5H, s), 8.17 and 8.23 (relative intensity ≈ 1 : 2, 1H combined, each s). HRMS Calcd for $C_{14}H_{19}NO_2$: 233.1415. Found: 233.1418.

Hydrogenolysis of 3 Using Pd/C under an Activated Condition A mixture of **3** (70 mg, 0.30 mmol), 10% Pd/C (purchased from Kawaken Fine Chemicals Co., Ltd.), formic acid (41 mg, 0.90 mmol), ammonium formate (0.5 g, 7.9 mmol), ethanol (15 ml), and methanol (5 ml) was shaken under H_2 (5 atm) at room temperature for 15 h. The mixture was diluted with AcOEt, and a phosphate buffer solution (pH 7) was added. The mixture was filtered, and the organic layer was dried over Na_2SO_4 and evaporated to leave an oily residue, which was purified by preparative TLC (AcOEt) to afford **4** (3.5 mg, 5%) and recovered **3** (3.5 mg, 5%) as oils.

Attempted Hydrogenolysis of 11 1-(3-Phenylpropyl)-4-propyl-2-azetidinone (**11**) was prepared as an oil according to the procedure described in ref. 9. IR ($CHCl_3$): 2930, 1725, 1600, 1500, 1458, 1408, 1370, 1095, 910 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.8—2.2 (9H, m), 2.2—3.8 (7H, m), 7.0—7.4 (5H, m). MS m/z: 231 (M^+, 100%), 188, 146, 118, 91, 84. HRMS Calcd for $C_{15}H_{21}NO$: 231.1622. Found: 231.1625.

Following a procedure similar to that described for the palladium black-catalyzed transformation of **3** to **4**, the β-lactam **11** (34 mg, 0.15 mmol) was treated with palladium black (water suspension, 0.2 ml) in ethanol (1.2 ml) under H_2 (1 atm) atmosphere at room temperature for 17 h to give, after filtration and evaporation, a quantitative recovery of **11** (34 mg).

Prolonged Treatment of 12 with 10% Pd/C A mixture of **12**[5] (55 mg, 0.15 mmol), 10% Pd/C (60 mg), and methanol (0.8 ml) was stirred under an H_2 (1 atm) atmosphere at room temperature for 120 h. Filtration of the catalyst and evaporation of the solvent gave essentially pure **13** (39 mg, 95%), whose ^{1}H-NMR and TLC properties were identical with those of an authentic sample of **13**.[5]

2-(Benzyloxymethyl)oxirane [(±)-5] A solution of benzyl alcohol (1.20 g, 11.1 mmol) in *N*,*N*-dimethylformamide (DMF, 4 ml) was added to a suspension of sodium hydride (55% mineral oil suspension, 489 mg, 11.2 mmol, washed with hexane) in DMF (2 ml). When hydrogen gas ceased to evolve, a solution of epibromohydrin (3.0 g, 22 mmol) in DMF (5 ml) was added with stirring and ice-bath cooling, followed by stirring at room temperature for 10 min. The mixture was partitioned between PhH and water. The organic layer was washed with water and brine, successively. The extract was dried over Na_2SO_4, and the solvent was evaporated off to leave an oily residue, which was purified by column chromatography (40 g, PhH) to afford (±)-**5** (1.31 g, 72%) as an oil. *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.33. Found: C, 72.98; H, 7.26. IR ($CHCl_3$): 3010, 2870, 1500, 1454, 1384, 1090 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.58 (1H, dd, J = 5, 3 Hz), 2.76 (1H, t, J = 5 Hz), 3.0—3.4 (1H, m), 3.42 (1H, dd, J = 11, 6 Hz), 3.78 (1H, dd, J = 11, 3 Hz), 4.57 (2H, s), 7.34 (5H, s). MS m/z: 164 (M^+), 107, 105, 91 (100%).

1-Azido-3-benzyloxy-2-propanol [(±)-6] A solution of (±)-**5** (1.31 g, 8.0 mmol), sodium azide (1.03 g, 16 mmol), and ammonium chloride (535 mg, 10 mmol) in DMF (20 ml) was heated at 85 °C for 3.5 h. The solvent was evaporated off *in vacuo*, and the residue was partitioned between PhH and water. The organic layer was washed with water and brine, successively. The extract was dried over Na_2SO_4, and the solvent was evaporated off to leave (±)-**6** (1.68 g, 100%) as a crude oil, which was used for the next step without further purification. IR ($CHCl_3$): 3400, 2100, 1670, 1450, 1090 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.2—3.7 (4H, m), 3.7—4.2 (1H, m), 4.55 (2H, s), 7.34 (5H, s). MS m/z: 208 ($M^+ + 1$), 178, 149, 148, 107, 106, 91 (100%). HRMS Calcd for $C_{10}H_{14}N_3O_2$ ($M^+ + 1$): 208.1085. Found: 208.1083.

1-Amino-3-benzyloxy-2-propanol [(±)-7] A mixture of (±)-**6** (882 mg, 4.3 mmol), 10% Pd/C (150 mg), and ethanol was stirred under an H_2 atmosphere (1 atm) for 1 h. The mixture was filtered through Celite and the solvent was evaporated off to give a solid, which was recrystallized from PhH–hexane to afford (±)-**7** (579 mg, 72%) as a powder, mp 74—78 °C. *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.99; H, 8.05; N, 7.47. IR ($CHCl_3$): 3400, 2870, 1590, 1498, 1454, 1096 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.4—2.9 (2H, m), 3.41 (2H, br d, J = 5 Hz), 3.4—4.0 (1H, br), 4.50 (2H, s), 7.32 (5H, s). MS m/z: 163 ($M^+ - H_2O$), 138, 108, 107, 91 (100%).

***trans*- and *cis*-5-Benzyloxymethyl-3-formyl-2-methyl-1,3-oxazolidine [(±)-4 and (±)-4′]** An aqueous solution of acetaldehyde (16.7%, w/v, 0.33 ml, 1.25 mmol) was added to a solution of (±)-**7** (227 mg, 1.25 mmol) in ethanol (4 ml) at 0 °C. After 15 min, the solvent was evaporated off *in vacuo*. The residue was mixed with benzene, and the volatiles were azeotropically evaporated off with benzene to give (±)-**8** (160 mg, 100%) as a crude oil. A solution of this product in CH_2Cl_2 (1 ml) was treated at room temperature with a solution of 1-formylimidazole that had been obtained by mixing formic acid (106 mg, 2.3 mmol) and 1,1′-carbonyldiimidazole (370 mg, 2.3 mmol) in CH_2Cl_2 (1.8 ml). After 3 h, the mixture was partitioned between AcOEt and water, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified using a preparative TLC plate (AcOEt) and a Lobar® column (AcOEt) to afford the less polar diastereomer (±)-**4** (74 mg, 25%) and the more polar one (±)-**4′** (94 mg, 32%) as oils. The IR, ^{1}H-NMR, and MS data of these products were in accord with those of the afore-mentioned materials obtained by hydrogenolysis of **3** and **3′**, respectively.

References and Notes

1) For a recent review of hydrogenation, see, P. N. Rylander, "Hydrogenation Methods," Academic Press, London, 1985.
2) T. Katsushima, K. Maki, R. Yamaguchi, and M. Kawanishi, *Bull. Chem. Soc. Jpn.*, **53**, 2031 (1980).
3) I. Ojima and N. Shimizu, *J. Am. Chem. Soc.*, **108**, 3100 (1986).
4) T. Konosu and S. Oida, *Chem. Pharm. Bull.*, **39**, 2212 (1991).
5) T. Konosu and S. Oida, *Chem. Pharm. Bull.*, **39**, 2813 (1991).
6) A low-yield but successful debenzylation of (±)-**3** under similar hydrogenolytic conditions has been reported: P. H. Bentley and E. Hunt, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2222.
7) H. Wieland, *Chem. Ber.*, **45**, 484 (1912).
8) These 1-carbapenams were unstable and decomposed even under neutral conditions; see ref. 5.
9) The β-lactam **11** was prepared from 4-allyl-2-azetidinone[a] in the following two steps: i) H_2 (1 atm), 10% Pd/C, MeOH; ii) 1-bromo-3-phenylpropane, powdered KOH, Bu_4NBr,[b] tetrahydrofuran. *a*) K. Fujimoto, Y. Iwano, and K. Hirai, *Bull. Chem. Soc. Jpn.*, **59**, 1363 (1986); *b*) D. Reuschling, H. Pietsch, and A. Linkies, *Tetrahedron Lett.*, **1978**, 615.
10) A similar metalacycle has been proposed for the intermediate of a β-lactam-forming reaction: S. Calet, F. Urso, and H. Alper, *J. Am. Chem. Soc.*, **111**, 931 (1989).