SYNTHETIC STUDIES OF NOVEL 5-AZACARBAPENEMS

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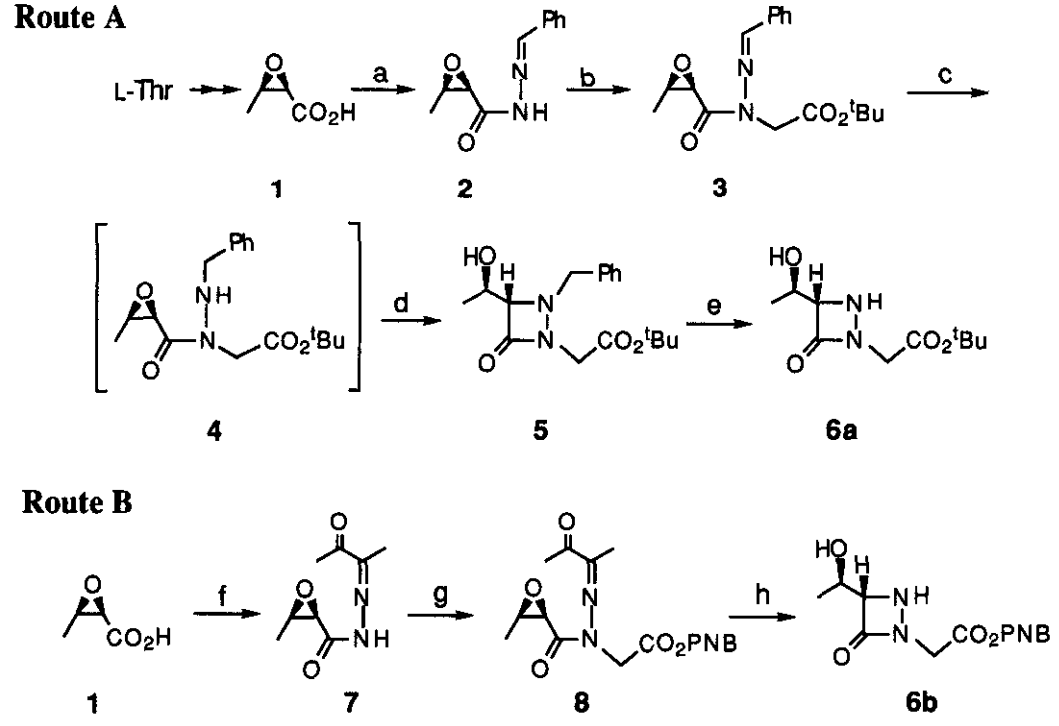
Abstract - 1, 2-Diazetidinones were prepared from (2*R*, 3*R*)-epoxybutanoic acid *via* acidic one-pot deprotection-cyclization reaction and converted to the novel 5-azacarbapenams by an intramolecular Michael cyclization reaction.

The increasing clinical importance of drug-resistant bacterial pathogens has lent additional urgency to microbiological and antibacterial research. Here we report our synthetic approach to the novel structural types of β-lactam antibiotics, 5-azacarbapenems (I, Scheme II).

Over the past decade, the synthetic studies of these types of aza-β(γ)-lactams have been undertaken by only a few research groups.[1] However, no group has succeeded in the synthesis of 5-azacarbapene(a)ms because of some severe side reactions[1] occurred at the cyclization step of 1, 2-diazetidinones to bicyclic aza-β-lactams. To overcome these synthetic problems, we have tried to apply an intramolecular Michael cyclization method, which was developed by Hanessian's group[2] for the total synthesis of (+)-thienamycin. As shown in route A (Scheme I), the first key compound, hydrazide (**4**),[3] was easily prepared in three steps from (2*R*, 3*R*)-epoxybutanoic acid (**1**)[4] under the usual reaction conditions. Cyclization of hydrazide (**4**) proceeded under mild acidic conditions to give 1, 2-diazetidinone (**5**) in a good yield. Subsequent catalytic debenzylation was carried out using palladium hydroxide on charcoal to give 1, 2-diazetidinone (**6a**), an important intermediate for the synthesis of bicyclic aza-β-lactam. In addition, we have developed more convenient and practical synthetic procedure of 1, 2-diazetidinones as shown in route B (Scheme I). Deprotection of hydrazone (**8**) and subsequent cyclization smoothly proceeded in one-pot under the very mild acidic conditions to give 1,2-diazetidinone (**6b**). Michael cyclization of nitro olefins (**9a** and **9b**), converted from the 1, 2-diazetidinones (**6a** and **6b**), gave desired

bicyclic 5-azacarbapenams (**10a**, **10b**, **11a**, and **11b**) in moderate yields, respectively (Scheme II). On the other hand, undesired imidazolidinone (**14**) was obtained from cyano olefin (**9c**) *via* the cleavage of N-N bond and subsequent cyclization (Scheme III). These results suggested that the strong electron withdrawing group such as nitro group was very effective to this type of intramolecular Michael cyclization.

Scheme I [a]



[a](a) $PhCH{=}NNH_2$, DCC, THF, 73%; (b) $BrCH_2CO_2{}^tBu$, NaH, THF, 97%; (c) H_2 / 10% Pd-C, EtOH; (d) *p*-TsOH, $CHCl_3$, 0 °C, 94% in two steps; (e) H_2 / 20% $Pd(OH)_2$-C, MeOH, 92%; (f) $MeCO(Me)C{=}NNH_2$, DCC, DMAP, 74%; (g) *p*-$NO_2C_6H_4CH_2OCOCH_2Br$, NaH, DMF, 0 °C, 83%; (h) *p*-TsOH, MeCN, 0-5 °C, 84%.

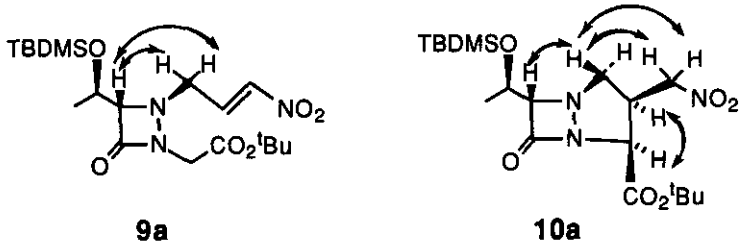
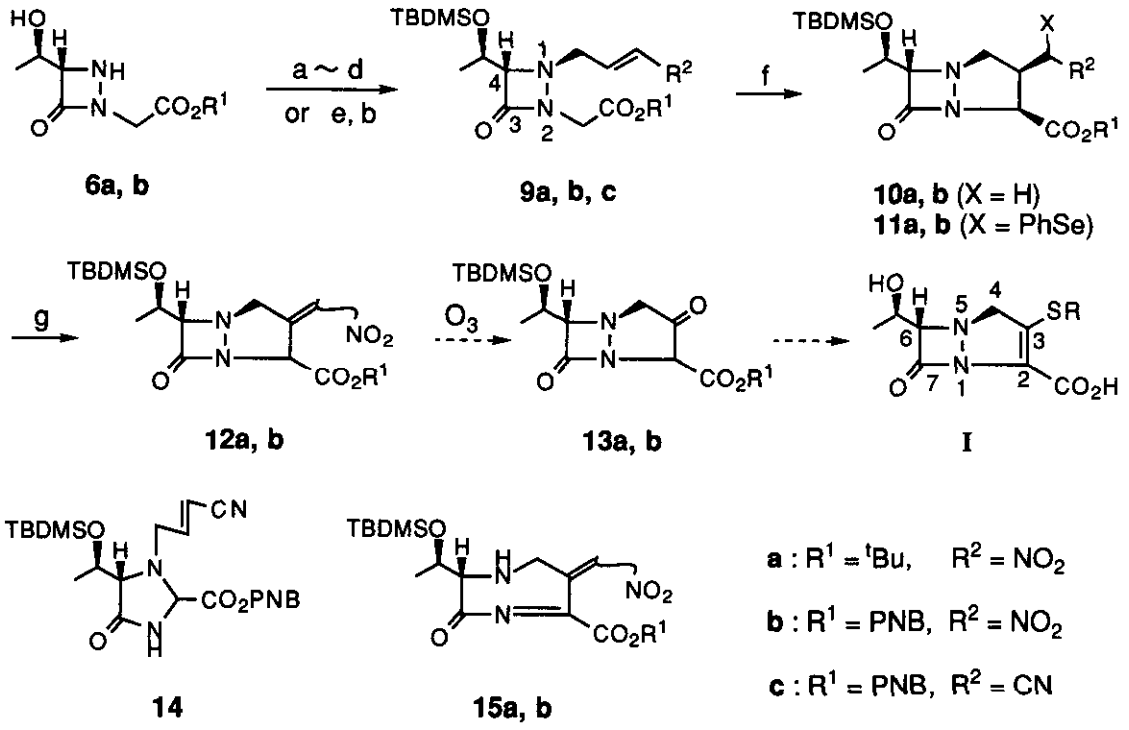


Figure 1. Selected NOEs observed in the 2D NOESY spectra of typical compounds (**9a**) and (**10a**).

Scheme II [a]



6a, b **9a, b, c** **10a, b** (X = H)
11a, b (X = PhSe)

12a, b **13a, b** **I**

14 **15a, b**

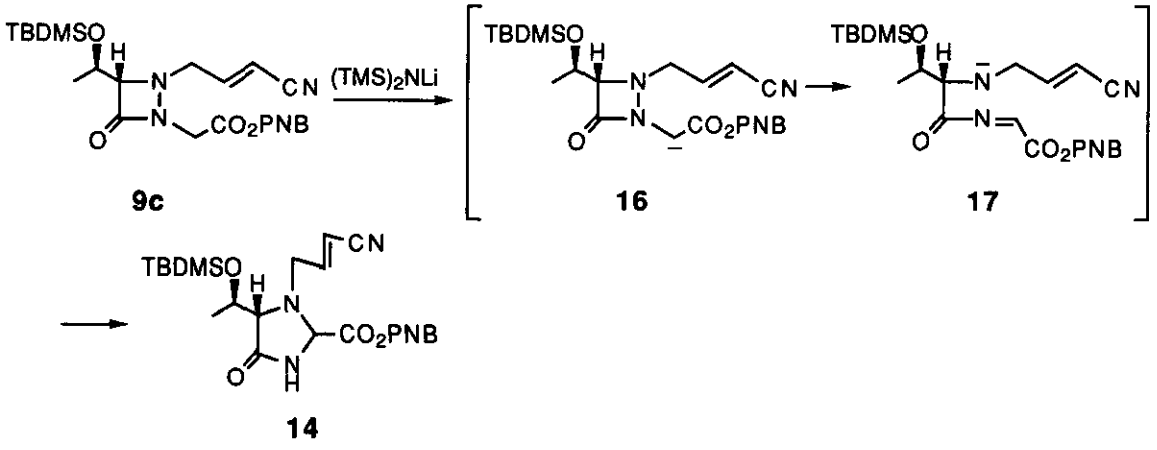
a : R^1 = ^{t}Bu, R^2 = NO_2

b : R^1 = PNB, R^2 = NO_2

c : R^1 = PNB, R^2 = CN

[a](a) allyl bromide, NaI, $NaHCO_3$, DMF, 92-94%; (b) TBDMSO Tf, 2,6-lutidine, CH_2Cl_2, 0 °C, 80-99%; (c) N_2O_4, I_2, ether, 5 °C; (d) NaOAc, ether, 56-57% in two steps; (e) $BrCH_2CH$ =CHCN, NaI, $NaHCO_3$, DMF, 59%; (f) $(TMS)_2NLi$, THF, -78 °C, then AcOH or PhSeCl, 40-79%; (g)AcOOH, THF, 0 °C, 33-49%.

Scheme III



9c **16** **17**

14

The configurarion of 1, 2-diazetidinones (**9a** and **9b**) and 5-azacarbapenams (**10a**, **10b**, **11a**, and **11b**) was determined by the ^{1}H nmr and 2D NOESY spectra (Figure 1). Expectedly, the configuration of these compounds was identical with that of the corresponding azetidinones and carbapenams reported by Hanessian's group.[2] Therefore, it was obviously revealed that the original conformation about the nitrogen atom on 1 position of 1, 2-diazetidinone had been conserved during the cyclization reaction without inversion of the lone pair of the nitrogen atom. Oxidative elimination of selenides (**11a** and **11b**) smoothly proceeded to give desired exocyclic nitro olefins (**12a** and **12b**) in moderate yields. The compounds thus obtained were found to be relatively labile at room temperature and gradually decomposed to give undesired seven-membered lactams (**15a** and **15b**) by the similar mechanism as shown in Schem III. So, the compounds should be handled carefully at low temperature to prevent the unfavorable decomposition.

In this paper, we have shown the first practical synthesis of the novel types of bicyclic β-lactams, 5-azacarbapenams. Our project is now in progress to obtain 5-azacarbapenems (I) as the most promising candidates for the clinical trials.

EXPERIMENTAL SECTION

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H Nmr spectra were obtained on JEOL JNM-FX-200, Varian Gemini-300, and JEOL GSX400 spectrometers. 2D NOESY spectra were obtained on the JEOL GSX400 spectrometer. Optical rotation was measured on a Horiba polarimeter SEPA-200. Mass spectra were obtained on a JEOL JMS-HX100 mass spectrometer. Flash chromatography was performed by using Katayama K230 silica gel.

Benzaldehyde (2*R*,3R)-2,3-epoxybutanohydrazone (2). To a solution of (2*R*,3*R*)-2,3-epoxybutanoic acid (**1**)[4] (1.12 g, 11 mmol) in THF(15 ml) was added 1, 3-dicyclohexylcarbodiimide (DCC, 2.48 g, 12 mmol) at 0 °C. After stirring for 1 h, benzaldehyde hydrazone (1.20 g, 10 mmol) was added by portions. Then, the mixture was stirred at 0 °C for 2.5 h and at room temperature for 1 h. The precipitated *N*, *N'*-dicyclohexylurea (DCU) was removed by filtration. The filtrate was concentrated and the residue was purified by flash column chromatography ($CHCl_3$: AcOEt = 10 : 1) to give hydrazone (**2**) (1.50 g, 73%) as crystals: mp 124.5-125.0 °C (AcOEt-i-Pr_2O); ir (Nujol) 3200, 1690, 1670, 1600, 1070 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.40(d, *J*=5.5 Hz, 3H), 3.2-3.6(m, 1H), 3.64, 4.33(2×d, *J*=4.8 Hz, 1H, 1.6 : 1.0), 7.3-7.5 (m, 3H), 7.6-7.8(m, 2H), 7.96, 8.22(2×s, 1H, 1.0 : 1.6), 9.26, 10.60(2×br s, 1H,

1.6 : 1.0); ms (EI) $^{m}/_{z}$ 204(M^+); Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.51; H, 5.99; N, 13.70.

Benzaldehyde *N*-(*tert*-butoxycarbonylmethyl)-*N*-((2*R*,3*R*)-2,3-epoxybutano)hydrazone (3). To a suspension of sodium hydride (60% dispersion in a mineral oil, 6.00 g, 150 mmol) in THF (100 ml) was added dropwise a solution of hydrazone (**2**) (25.53 g, 125 mmol) in THF (200 ml) at 0 °C under argon. After stirring for 2 h, *tert*-butyl bromoacetate (29.86 g, 150 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h, at room temperature for 2.5 h, and poured into ice water (800 ml). The resulting mixture was extracted (AcOEt, 3×200 ml). The combined extracts were washed (brine, 3×200 ml), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography ($CHCl_3$: MeOH = 40 : 1) to give hydrazone (**3**) (38.64 g, 97%) as an oil : Ir (Neat) 1735; 1690, 1610, 1430, 1150, 970 cm^{-1} ; ^1H nmr (200 MHz, $CDCl_3$) δ 1.35(d, *J*=5.5 Hz, 3H), 1.45(s, 9H), 3.49(dq, *J*=4.8, 5.3Hz, 1H), 4.41(d, *J*=4.8 Hz, 1H), 4.50(d, *J*=16.9 Hz, 1H), 4.94(d, *J*=17.1 Hz, 1H), 7.3-7.5(m, 3H), 7.59(s, 1H), 7.5-7.8(m, 2H); ms (EI), $^{m}/_{z}$ 318(M^+).

***tert*-Butyl (*S*)-1-benzyl-4-((*R*)-1-hydroxyethyl)-3-oxo-1,2-diazetidine-2-acetate (5).** A catalytic hydrogenation of hydrazone (**3**) (38.64 g, 120 mmol) was carried out with 10% Pd-C (2.5g) in EtOH (300 ml) under atmospheric pressure of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated to give crude hydrazide (**4**) (40 g) as an oil. To a solution of crude hydrazide (**4**) (40 g) in $CHCl_3$ (400 ml) was added *p*-toluenesulfonic acid monohydrate (11.87 g, 60 mmol) at 0 °C. After stirring for 5 h, the mixture was neutralized (satd. $NaHCO_3$), concentrated, and extracted (AcOEt, 800 ml). The extract was washed (brine, 3×100 ml), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography ($CHCl_3$: AcOEt = 40 : 1) to give 1, 2-diazetidinone (**5**) (36.26 g, 94%) as an oil : Ir (Neat) 1735, 1690, 1610, 1430, 1150, 970 cm^{-1} ; ^1H nmr (200 MHz, $CDCl_3$) δ 1.35(d, *J*=5.5 Hz, 3H), 1.45(s, 9H), 3.49(dq, *J*=4.8, 5.3 Hz, 1H), 4.41(d, *J*=4.8 Hz, 1H), 4.50(d, *J*=16.9 Hz, 1H), 4.94(d, *J*=17.1 Hz, 1H), 7.3-7.5(m, 3H), 7.59(s, 1H), 7.5-7.8(m, 2H); ms (EI) $^{m}/_{z}$ 318(M^+).

***tert*-Butyl (*S*)-4-((*R*)-1-hydroxyethyl)-3-oxo-1,2-diazetidine-2-acetate (6a).** A catalytic hydrogenolysis of 1, 2-diazetidinone (**5**) (36.26 g, 110 mmol) was carried out with 20% $Pd(OH)_2$-C (2.5 g) in MeOH (300 ml) under atmospheric pressure of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated. The residue was purified by flash column chromatography ($CHCl_3$: MeOH = 40 : 1) to give 1, 2-diazetidinone (**6a**) (23.36 g, 92%) as crystals : mp 75-77 °C (i-Pr_2O); $[\alpha]_D^{24}$ -56.22°

(c = 0.5, $CHCl_3$); ir (Nujol) 3380, 3220, 1740, 1720, 1240, 1160 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 1.31(d, *J*=6.4 Hz, 3H), 1.48(s, 9H), 2.4-3.0(br m, 1H), 4.00(d, *J*=18.1 Hz, 1H), 4.1-4.3(m, 2H), 4.0-5.0(br m, 1H), 4.48(d, *J*=5.4 Hz, 1H); ms (EI) $^m/_z$ 230(M^+); Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.22; H, 7.95; N, 12.02.

2,3-Butanedione (2*R*,3*R*)-2,3-epoxybutanomonohydrazone (7). To a solution of (2*R*, 3*R*)-2, 3-epoxybutanoic acid (**1**) (459 mg, 4.5 mmol), 2, 3-butanedione monohydrazone[5] (300 mg, 3 mmol), and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in THF (10 ml) was added DCC (928 mg, 4.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, at room temperature for 17 h and filtered to remove the precipitated DCU. The filtrate was evaporated and the residue was purified by flash column chromatography ($CHCl_3$) to give hydrazone (**7**) (409 mg, 74%) as crystals: mp 75-76 °C (n-Hex) ; ir (Nujol) 3175, 3120, 1675, 1660, 1600, 1265, 1150 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 1.39(d, *J*=5.5 Hz, 3H), 2.02(s, 3H), 2.42, 2.49(2× br s, 3H, 1 : 1), 3.44 (br dq, *J*=5.1, 5.1 Hz, 1H), 3.70, 4.26 (2× br d, *J*=4.6 Hz, 1H, 1 : 1), 9.07, 9.63(2× br s, 1H, 1 : 1); ms (FAB) $^m/_z$ 185 (MH^+); Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.34; H, 6.55; N, 15.41.

2,3-Butanedione *N*-(4-nitrobenzyloxycarbonylmethyl)-*N*-((2*R*, 3*R*)-2,3-epoxybutano)-monohydrazone (8). To a suspension of sodium hydride (60% dispersion in a mineral oil, 1.30 g, 32.6 mmol) in DMF (50 ml) was added dropwise a solution of hydrazone (**7**) (5 g, 27.1 mmol) in DMF (20 ml) at 0 °C. After stirring for 40 min, 4-nitrobenzyl bromoacetate (8.92 g, 32.6 mmol) was added dropwise. The mixture was stirred at 0 °C for 2.5 h, quenched (AcOH, 1.9 ml), and extracted (AcOEt, 200 ml). The extract was washed (satd. $NaHCO_3$ (100 ml) and brine (3× 100 ml)), dried ($MgSO_4$), and filtered. After evaporation, the residue was purified by flash column chromatography (n-Hex : AcOEt = 2 : 1) to give hydrazone (**8**) (8.45 g, 83%) as crystals; mp 86-87 °C (i-Pr_2O); ir (Nujol) 1740, 1715, 1690, 1685, 1150 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 1.32(d, *J*=4.9 Hz, 3H), 2.11(s, 3H), 2.41(s, 3H), 3.45(dq, *J*=5.4, 5.4 Hz, 1H), 4.19(d, *J*=4.4 Hz, 1H), 4.76(d, *J*=17.6 Hz, 1H), 4.97(d, *J*=18.1 Hz, 1H), 5.29(s, 2H), 7.51(d-like, *J*=8.8 Hz, 2H), 8.24(d-like, *J*=8.8 Hz, 2H); ms (FAB) $^m/_z$ 378(MH^+); Anal. Calcd for $C_{17}H_{19}N_3O_7$: C, 54.11; H, 5.08; N, 11.14. Found: C, 54.10; H, 5.06; N, 10.94.

4-Nitrobenzyl (*S*)-4-((*R*)-1-hydroxyethyl)-3-oxo-1,2-diazetidine-2-acetate (6b).
To a solution of hydrazone (**8**) (27.54 g, 73 mmol) in MeCN (500 ml) was added *p*-toluenesulfonic acid monohydrate (27.77 g, 146 mmol) at 0 °C. After stirring for 9.5 h, the mixture was kept standing for 13 h in a refrigerator (5 °C), evaporated, neutralized (satd. $NaHCO_3$), and extracted (AcOEt, 500 ml).

The extract was washed (brine, 3×100 ml), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography ($CHCl_3$: MeOH = 30 : 1) to give 1, 2-diazetidinone (**6b**) (19.01 g, 84%) as crystals: mp 50-53 °C (i-Pr_2O); ir (Nujol) 3400, 3240, 1730, 1610, 1525, 1220 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 1.29(d, *J*=6.4 Hz, 3H), 2.2-3.2(br m, 2H), 4.15-4.25(m, 1H), 4.21(d, *J*=18.1 Hz, 1H), 4.30 (d, *J*=18.3 Hz, 1H), 4.51(d, *J*=5.4 Hz, 1H), 5.29(s, 2H), 7.53(d-like, *J*=8.7 Hz, 2H), 8.24(d-like, *J*=8.9 Hz, 2H); ms (FAB) $^m/_z$ 310(MH^+).

***tert*-Butyl (*S*)-1-allyl-4-((*R*)-1-hydroxyethyl)-3-oxo-1,2-diazetidine-2-acetate (18a).** To a solution of 1, 2-diazetidinone (**6a**) (24.69 g, 107 mmol) and allyl bromide (15.57 g, 129 mmol) in DMF (400 ml) was added sodium iodide (19.28 g, 129 mmol) and sodium bicarbonate (10.81 g, 129 mmol) at 0 °C. After stirring at room temperature for 15 h, the mixture was diluted with water (400 ml) and extracted (AcOEt, 1 l). The extract was washed (brine, 10×300 ml), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography ($CHCl_3$: AcOEt = 10 : 1) to give 1, 2-diazetidinone (**18a**) (26.51 g, 92%) as an oil : Ir (Neat) 3400, 1770-1710, 1350, 1210, 1140 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 1.28(d, *J*=6.5 Hz, 3H), 1.47 (s, 9H), 2.93(d, *J*=6.2 Hz, 1H), 3.44(dddd, *J*=1.0, 1.3, 6.3, 13.0 Hz, 1H), 3.58(dddd, *J*=1.0, 1.5, 7.1, 13.0 Hz, 1H), 3.83(d, *J*=5.5 Hz, 1H), 3.90(d, *J*=18.1 Hz, 1H), 4.11(d, *J*=17.6 Hz, 1H), 4.15-4.25(m, 1H), 5.27(dddd, *J*=1.0, 1.0, 1.5, 10.2 Hz, 1H), 5.32(dddd, *J*=1.3, 1.5, 1.5, 17.2 Hz, 1H), 5.94(dddd, *J*=6.3, 7.1, 10.2, 17.2 Hz, 1H); ms (FAB) m/z 271(MH^+).

4-Nitrobenzyl (*S*)-1-allyl-4-((*R*)-1-hydroxyethyl)-3-oxo-1,2-diazetidine-2-acetate (18b) : oil (94%); ir (Neat) 3500-3400, 1770, 1750, 1605, 1525, 1350, 1190 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 1.27(d, *J*=6.5 Hz, 3H), 2.57(d, *J*=6.0 Hz, 1H), 3.4-3.6(m, 2H), 3.85(d, *J*=6.0 Hz, 1H), 4.08 (d, *J*=18.3 Hz, 1H), 4.1-4.25(m, 1H), 4.31(d, *J*=18.3 Hz, 1H), 5.2-5.35(m, 2H), 5.28(s, 2H), 5.85-6.0(m, 1H), 7.27(d-like, *J*=8.7 Hz, 2H), 8.24(d-like, *J*=8.7 Hz, 2H); ms (FAB) $^m/_z$ 350(MH^+).

4-Nitrobenzyl (*S*)-1-(3-cyano-2-propenyl)-4-((*R*)-1-hydroxyethyl)-3-oxo-1,2-diazetidine-2-acetate (22). 3-Bromo-1-propenyl cyanide[6] was used instead of allyl bromide to give 1, 2-diazetidinone (**22**) (59%, 6 : 1 mixture of two inseparable diastereomers) as an oil : ^1H Nmr (300 MHz, $CDCl_3$) δ (E-form) 1.30(d, *J*=6.5 Hz, 3H), 2.39(d, *J*=5.0 Hz, 1H), 3.66(ddd, *J*=1.9, 5.7, 15.0 Hz, 1H), 3.74(ddd, *J*=1.5, 7.0, 15.0 Hz, 1H), 3.88(d, *J*=6.4 Hz, 1H), 4.08(d, *J*=18.1 Hz, 1H), 4.2-4.3(m, 1H), 4.25(d, *J*=18.1 Hz, 1H), 5.29(s, 2H), 5.66(ddd, *J*=1.6, 1.7, 16.4 Hz, 1H), 6.77(ddd, *J*=5.7, 6.9, 16.4 Hz, 1H), 7.54(d-like, *J*=8.9 Hz, 2H), 8.26(d-like, *J*=8.9 Hz, 2H); δ (Z-form) 1.30(d, *J*=6.5 Hz,

3H), 2.40(d, *J*=4.5 Hz, 1H), 3.79(ddd, *J*=1.6, 6.4, 14.7 Hz, 1H), 3.92(d, *J*=6.7 Hz, 1H), 3.97(ddd, *J*=1.3, 7.4, 14.6 Hz, 1H), 4.08(d, *J*=18.3 Hz, 1H), 4.2-4.3(m, 1H), 4.31(d, *J*=18.1 Hz, 1H), 5.29(s, 2H), 5.58(ddd, *J*=1.3, 1.6, 11.1 Hz, 1H), 6.67(ddd, *J*=6.4, 7.3, 11.1 Hz, 1H), 7.53(d-like, *J*=8.2 Hz, 2H), 8.24(d-like, *J*=8.9 Hz, 2H); ms (FAB) $^{m}/_{z}$ 375(MH^+).

***tert*-Butyl (*S*)-1-allyl-4-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-3-oxo-1,2-diazetidine-2-acetate (19a).** To a solution of 1, 2-diazetidinone (**18a**) (26.41 g, 98 mmol), 2, 6-lutidine (20.94 g, 195 mmol) in CH_2Cl_2 (100 ml) was added dropwise *tert*-butyldimethylsilyl triflate (33.57 g, 127 mmol) at -8 °C. After stirring at 0 °C for 20 min, the mixture was quenched (ice-cold satd. $NaHCO_3$, 400 ml) and extracted (AcOEt, 2×300 ml). The combined extracts were washed (ice-cold 5% citric acid (300 ml), brine (200 ml), satd. $NaHCO_3$ (200 ml), and brine (400 ml)), dried ($MgSO_4$), and filtered. The filttate was evaporated and the residue was purified by flash column chromatography ($CHCl_3$: AcOEt = 20 : 1) to give 1, 2-diazetidinone (**19a**) (37.07 g, 99%) as an oil : Ir (Neat) 1780, 1740, 1250, 1220, 1150 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.08(s, 3H), 0.10(s, 3H), 0.89(s, 9H), 1.25(d, *J*=6.3 Hz, 3H), 1.47(s, 9H), 3.40(dddd, *J*=1.0, 1.0, 7.8, 13.5 Hz, 1H), 3.54(dddd, *J*=1.6, 1.6, 5.2, 13.5 Hz, 1H), 3.69(d, *J*=8.5 Hz, 1H), 3.88(d, *J*=17.8 Hz, 1H), 4.03(d, *J*=17.9 Hz, 1H), 4.30(dq, *J*=8.5, 6.3 Hz, 1H), 5.15-5.25(m, 1H), 5.28(dddd, *J*=1.1, 1.7, 1.7, 17.3 Hz, 1H), 5.93(dddd, *J*=5.2, 7.8, 10.2, 17.2 Hz, 1H); ms (FAB) $^{m}/_{z}$ 385(MH^+).

4-Nitrobenzyl (*S*)-1-allyl-4-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-3-oxo-1,2-diazetidine-2-acetate (19b) : oil (91%); ir (Neat) 1780, 1750, 1610, 1530, 1350 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.029(s, 3H), 0.034(s, 3H), 0.86(s, 9H), 1.22(d, *J*=6.3 Hz, 3H), 3.38(dd, *J*=8.1, 13.3 Hz, 1H), 3.56(dddd, *J*=1.6, 1.6, 5.1, 13.4 Hz, 1H), 3.73(d, *J*=8.7 Hz, 1H), 4.07(d, *J*=18.0 Hz, 1H), 4.21(dq, *J*=8.6, 6.3 Hz, 1H), 4.24(d, *J*=18.1 Hz, 1H), 5.1-5.3(m, 2H), 5.22(d, *J*=15.3 Hz, 1H), 5.31(d, *J*=13.5 Hz, 1H), 5.91(dddd, *J*=5.1, 8.0, 10.2, 17.2 Hz, 1H), 7.52(d-like, *J*=8.9 Hz, 2H), 8.23(d-like, *J*=8.8 Hz, 2H); ms (FAB) $^{m}/_{z}$ 464(MH^+).

4-Nitrobenzyl (*S*)-4-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-1-((*E*)-3-cyano-2-propenyl)-3-oxo-1,2-diazetidine-2-acetate (9c) : oil (80%) ; ir (Neat) 2225, 1780, 1605, 1525, 1345, 1255 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.03(s, 3H), 0.04(s, 3H), 0.87(s, 9H), 1.23(d, *J*=6.3 Hz, 3H), 3.61(ddd, *J*=1.4, 7.2, 15.2 Hz, 1H), 3.70(ddd, *J*=2.0, 5.0, 15.2 Hz, 1H), 3.79(d, *J*=8.5 Hz, 1H), 4.07 (d, *J*=18.2 Hz, 1H), 4.19(d, *J*=17.9 Hz, 1H), 4.24(dq, *J*=8.7, 6.3 Hz, 1H), 5.23(d, *J*=13.0 Hz, 1H), 5.32(d, *J*=13.2 Hz, 1H), 5.61(ddd, *J*=1.4, 2.0, 16.4 Hz, 1H), 6.75(ddd, *J*=5.0, 7.2, 16.4 Hz, 1H),

7.54(d-like, J=8.9 Hz, 2H), 8.25(d-like, J=8.8 Hz, 2H); ms (FAB) $^{m}/_{z}$ 489(MH^+).

***tert*-Butyl (*S*)-4-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-1-((*E*)-3-nitro-2-propenyl)-3-oxo-1,2-diazetidine-2-acetate (9a).** To a solution of 1, 2-diazetidinone (**19a**) (5 g, 13 mmol) and iodine (3.63 g, 14 mmol) in ether (100 ml) was added dropwise an ice-cold 1 M solution of dinitrogen tetroxide (N_2O_4)[7] in THF (49 ml) at 0 °C. After stirring for 20 min, the mixture was kept standing for 26 h in a refrigerator (5 °C) and quenched with ice-cold satd. $NaHCO_3$ (50 ml) and 10% $Na_2S_2O_3$ (50 ml) at 0 °C. The resulting mixture was extracted (AcOEt, 2×100 ml). The combined extracts were washed (brine, 2×100 ml), dried ($MgSO_4$), and evaporated to give ***tert*-butyl-(*S*)-4-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-1-(2-iodo-3-nitropropyl)-3-oxo-1,2-diazetidine-2-acetate** as a crude oil (6.52 g). To a solution of crude iodide (6.52 g) in ether (60 ml) was added sodium acetate (1.17 g, 14 mmol) at room temperature. After stirring for 21 h, the mixture was diluted with ice-cold brine (80 ml) and neutralized with ice-cold satd. $NaHCO_3$ at 0 °C. The resulting mixture was extracted (AcOEt, 2×100 ml). The combined extracts were washed (ice-cold 10% $Na_2S_2O_3$ (20 ml) and brine (2×50 ml)), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography (n-Hex : AcOEt = 20 : 1→5 :1) to give 1, 2-diazetidinone (**9a**) (3.18 g, 57%) as an oil : Ir (Neat) 1780, 1740, 1525, 1350, 1150 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ 0.08(s, 3H), 0.10(s, 3H), 0.88(s, 9H), 1.26(d, J=6.3 Hz, 3H), 1.46(s, 9H), 3.7-3.8(m, 2H), 3.80(d, J=8.6 Hz, 1H), 3.93(d, J=17.9 Hz, 1H), 4.00(d, J=18.0 Hz, 1H), 4.32(dq, J=8.6, 6.3 Hz, 1H), 7.17(ddd, J=1.5, 1.5, 13.4 Hz, 1H), 7.25-7.35(m, 1H); ms (FAB) $^{m}/_{z}$ 430(MH^+).

4-Nitrobenzyl (*S*)-4-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-1-((*E*)-3-nitro-2-propenyl)-3-oxo-1,2-diazetidine-2-acetate (9b) : oil (56%); ir (Neat) 1780, 1750, 1600, 1525, 1345 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.04(s, 3H), 0.07(s, 3H), 0.87(s, 9H), 1.25(d, J=6.2 Hz, 3H), 3.70(ddd, J=1.0, 7.2, 15.6 Hz, 1H), 3.78(ddd, J=1.7, 5.2, 15.6 Hz, 1H), 3.84(d, J=8.7 Hz, 1H), 4.09(d, J=18.2 Hz, 1H), 4.20(d, J=18.1 Hz, 1H), 4.26(dq, J=8.6, 6.3 Hz, 1H), 5.22(d, J=13.1 Hz, 1H), 5.30(d, J=13.0 Hz, 1H), 7.13(ddd, J=1.1, 1.5, 13.5 Hz, 1H), 7.26(ddd, J=5.2, 7.2, 13.6 Hz, 1H), 7.52(d-like, J=8.9 Hz, 2H), 8.25(d-like, J=8.9 Hz, 2H); ms (FAB) $^{m}/_{z}$ 509(MH^+).

***tert*-Butyl (2*S*, 3*S*, 6*S*)-6-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-3-nitromethyl-7-oxo-1,5-diazabicyclo[3.2.0]heptane-2-carboxylate (10a).** To a solution of 1, 2-diazetidinone (**9a**) (733 mg, 1.71 mmol) in THF (15 ml) was added dropwise a 1.0 M solution of lithium bis(trimethylsilyl) amide in THF (1.9 ml, 1.88 mmol) at -78 °C under argon. After stirring for 5 min, the mixture was

quenched with acetic acid (0.1 ml) in water (10 ml), warmed to room temperature, and extracted with AcOEt (2×15 ml). The combined extracts were washed (brine (2×15 ml), satd. $NaHCO_3$ (10 ml), and brine (2×15 ml)), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography (n-Hex : AcOEt = 10 : 1) to give 5-azacarbapenam (**10a**) (580 mg, 79%) as crystals : mp 72-75 °C (n-Hex); ir (Nujol) 1780, 1760, 1720, 1555, 1165 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ 0.098(s, 3H), 0.103(s, 3H), 0.89(s, 9H), 1.26(d, *J*=6.3 Hz, 3H), 1.50(s, 9H), 2.84(dd, *J*=8.7, 12.1 Hz, 1H), 3.49(dd, *J*=5.5, 8.6 Hz, 1H), 3.75-3.85(m, 1H), 3.86(d, *J*=7.4 Hz, 1H), 4.16(d, *J*=7.9 Hz), 4.16(dq, *J*=7.3, 6.3 Hz, 1H), 4.51(dd, *J*=6.6, 14.5 Hz, 1H), 4.62(dd, *J*=8.6, 14.5 Hz, 1H); ms (FAB) m/z 430(MH^+).

4-Nitrobenzyl (2*S*,3*S*,6*S*)-6-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-3-nitromethyl-7-oxo-1,5-diazabicyclo[3.2.0]heptane-2-carboxylate (10b) : crystals (40%); mp 92-94 °C (n-Hex); ir (Nujol) 1790, 1775, 1720, 1460, 1380, 1350 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.097(s, 3H), 0.10(s, 3H), 0.89(s, 9H), 1.27(d, *J*=6.3 Hz, 3H), 2.81(dd, *J*=8.8, 12.1 Hz, 1H), 3.52(dd, *J*=5.5, 8.7 Hz, 1H), 3.7-3.9(m, 1H), 3.87(d, *J*=7.2 Hz, 1H), 4.17(dq, *J*=7.1, 6.3 Hz, 1H), 4.38(d, *J*=7.8 Hz, 1H), 4.51(dd, *J*=6.4, 14.6 Hz, 1H), 4.57(dd, *J*=8.9, 14.5 Hz, 1H), 5.24(d, *J*=12.9 Hz, 1H), 5.36(d, *J*=12.9 Hz, 1H), 7.56(d-like, *J*=8.9 Hz, 2H), 8.25(d-like, *J*=8.9 Hz, 2H); ms (FAB) m/z 509(MH^+); Anal. Calcd for $C_{22}H_{32}N_4O_8Si$: C, 51.95; H, 6.34; N, 11.02. Found : C, 52.10; H, 6.36; N, 11.01.

The following two compounds were obtained by using phenylselenenyl chloride instead of acetic acid.

***tert*-Butyl (2*S*,3*R*,6*S*)-6-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-3-(nitro(phenylseleno)-methyl)-7-oxo-1,5-diazabicyclo[3.2.0]heptane-2-carboxylate (11a)** : amorphous powder (58%, 5 : 1 mixture of two inseparable diastereomers); ir (Nujol) 1780, 1720, 1550, 1250, 1115 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ (major isomer) 0.10(s, 3H), 0.11(s, 3H), 0.92(s, 9H), 1.25(d, *J*=6.4 Hz, 3H), 1.44(s, 9H), 2.9-3.0(m, 1H), 3.5-3.7(m, 2H), 3.86(d, *J*=7.3 Hz, 1H), 3.99(d, *J*=7.3 Hz, 1H), 4.02(dq, *J*=7.3, 6.4 Hz, 1H), 5.55(d, *J*=11.2 Hz, 1H), 7.4-7.6(m, 5H); δ (minor isomer) 0.05(s, 3H), 0.07(s, 3H), 0.86(s, 9H), 1.22(d, *J*=6.8 Hz, 3H), 1.55(s, 9H), 3.32(dd, *J*=5.4, 8.3 Hz, 1H), 3.6-3.7(m, 2H), 3.79(d, *J*=6.8 Hz, 1H), 4.02(d, *J*=7.8 Hz, 1H), 4.1-4.2(m, 1H), 5.84(d, *J*=11,7 Hz, 1H), 7.4-7.6(m, 5H); ms (FAB) m/z 586 and 584(MH^+).

4-Nitrobenzyl (2*S*,3*R*,6*S*)-6-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-3-(nitro(phenyl-seleno)methyl)-7-oxo-1,5-diazabicyclo[3.2.0]heptane-2-carboxylate (11b) : amorphous powder (45%, 2 : 1 mixture of two inseparable diastereomers); ir (Nujol) 1775, 1730, 1600, 1545, 1520,

1110 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ (major isomer) 0.105(s, 3H), 0.109(s, 3H), 0.92(s, 9H), 1.26 (d, *J*=6.3 Hz, 3H), 2.9-3.0(m, 1H), 3.6-3.8(m, 2H), 3.89(d, *J*=7.4 Hz, 1H) 4.1-4.2(m, 1H), 4.18(d, *J*=7.4 Hz, 1H) 5.09(d, *J*=12.8 Hz, 1H), 5.30(d, *J*=12.9 Hz, 1H), 5.50(d, *J*=11.6 Hz, 1H), 7.3-7.6(m, 5H), 7.45(d-like, *J*=8.9 Hz, 2H), 8.25(d-like, *J*=8.9 Hz, 2H); δ (minor isomer) 0.06(s, 3H), 0.08(s, 3H), 0.87(s, 9H), 1.22(d, *J*=6.4 Hz, 3H), 2.9-3.0(m, 1H), 3.42(dd, *J*=5.4, 8.5 Hz, 1H), 3.6-3.8(m, 1H), 3.81(d, *J*=6.4 Hz, 1H), 4.1-4.2(m, 1H), 4.25(d, *J*=7.9 Hz, 1H), 5.22(d, *J*=12.9 Hz, 1H), 5.37(d, *J*=13.0 Hz, 1H), 5.38(d, *J*=11.8 Hz, 1H), 7.3-7.6(m, 5H), 7.65(d-like, *J*=8.9 Hz, 2H), 8.25(d-like, *J*=8.8 Hz, 2H); ms (FAB) $^m/_z$ 509(M^+-PhSe).

Michael cyclization of 1,2-diazetidinone (9c). An undesired imidazolidinone (**14**) (48%, 2,5-antiform) was obtained as an oil: Ir (Neat) 3200, 2225, 1745, 1710, 1600, 1520, 1340, 1250, 1190 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.004(s, 3H), 0.04(s, 3H), 0.83(s, 9H), 1.25(d, *J*=6.3 Hz, 3H), 3.13(d, *J*=4.2 Hz, 1H), 4.10(dq, *J*=4.2, 6.3 Hz, 1H), 3.65-3.75(m, 2H), 4.54(s, 1H), 5.24(d, *J*=13.1 Hz, 1H), 5.31(d, *J*=13.6 Hz, 1H), 5.66(ddd, *J*=1.7, 1.8, 16.4 Hz, 1H), 6.55(br s, 1H), 6.74(ddd, *J*=5.9, 6.1, 16.4 Hz, 1H), 7.56(d-like, *J*=8.8 Hz, 2H), 8.26(d-like, *J*=8.8 Hz, 2H); ms (FAB) $^m/_z$ 489(MH^+).

Oxidative elimination of selenide (11a). To a solution of selenide (**11a**) (1.03 g, 1.76 mmol) in THF (20 ml) was added dropwise 40% peracetic acid (0.69 ml, 4.12 mmol) at 0 °C. After stirring for 1.5 h, the mixture was quenched with ice-cold $NaHCO_3$ (1.03 mg, 12 mmol) in water (40 ml). The resulting mixture was extracted (AcOEt, 2×80 ml). The combined extracts were washed (brine, 2×50 ml), dried ($MgSO_4$), and filtered. The filtrate was evaporated and the residue was purified by flash columun chromatography (n-Hex : AcOEt = 10 : 1→5 : 1) : Fraction 1, crystals (49%, compound **12a**); mp 108-109 °C (i-Pr_2O); ir (Nujol) 1790, 1725, 1525, 1150 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 0.10(s, 6H), 0.89 (s, 9H), 1.27(d, *J*=6.4 Hz, 3H), 1.54(s, 9H), 3.74(dd, *J*=2.9, 14.2 Hz, 1H), 3.85(d, *J*=7.3 Hz, 1H), 4.19 (dd, *J*=1.0, 14.7 Hz, 1H), 4.25(dq, *J*=7.8, 6.4 Hz, 1H), 5.09(dd, *J*=1.0, 2.0 Hz, 1H), 7.15-7.20(m, 1H); ms (FAB) $^m/_z$ 428(MH^+); Anal. Calcd for $C_{19}H_{33}N_3O_6Si$: C, 53.37; H, 7.78; N, 9.83. Found : C, 53.37; H, 7.82; N, 9.73; Fraction 2, crystals (11%, compound **15a**); mp 51-54 °C (n-Hex); ir (Nujol) 3200, 1740, 1710, 1530, 1250, 1160, 1110 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.03 and 0.09(2×s, 3H, 2.5 : 1.0), 0.05 and 0.11(2×s, 3H, 2.5 : 1.0), 0.84 and 0.89(2×s, 9H, 2.5 : 1.0), 1.25 and 1.39 (2×d, *J*=6.2 and 6.7 Hz, 3H, 2.5 : 1.0), 1.52 and 1.53(2×s, 9H, 2.5 : 1.0), 3.11 and 3.53(2×d, *J*=3.6 and 3.0 Hz, 1H, 2.5 : 1.0), 4.15 and 4.51(2×dq, *J*=3.7, 6.2 and 3.1, 6.8 Hz, 1H, 2.5 : 1.0), 4.20 and 4.70(2×dd, *J*=2.8, 18.1 and 2.5, 17.9 Hz, 1H, 2.5 : 1.0), 4.99 and 5.75(2×dd, *J*=2.5, 18.1 and

2.9, 18.1 Hz, 1H, 2.5 : 1.0), 7.03 and 7.29(2×br s, 1H, 2.5 : 1.0), 7.06 and 7.18(2×dd, *J*=2.5, 2.8 and 2.5, 2.9 Hz, 1H, 2.5 : 1.0); ms (FAB) $^{m}/_{z}$ 428 (MH^+).

Oxidative elimination of selenide (11b) : Fraction 1, amorphous powder (33%, 3 : 1 mixture of compound **12b** and **15b**); ir (Nujol) 1780, 1750, 1605, 1515, 1345, 840 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ (major component **12b**) 0.10(s, 3H), 0.11(s, 3H), 0.89(s, 9H), 1.28(d, *J*=6.3 Hz, 3H), 3.78 (br dd, *J*=2.7, 14.5 Hz, 1H), 3.89(d, *J*=7.1 Hz, 1H), 4.23(dq, *J*=7.2, 6.3 Hz, 1H), 4.27(dd, *J*=1.0, 14.8 Hz, 1H), 5.27(dd, *J*=0.9, 2.0 Hz, 1H), 5.34(d, *J*=13.1 Hz, 1H), 5.39(d, *J*=13.0 Hz, 1H), 7.2-7.3(m, 1H), 7.61(d-like, *J*=8.9 Hz, 2H), 8.24(d-like, *J*=8.9 Hz, 2H); ms (FAB) $^{m}/_{z}$ 507(MH^+); Fraction 2, oil (43%, compound **15b**); ir (Neat) 3100, 1710, 1600, 1520, 1345, 840 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ -0.03(s, 3H), -0.02(s, 3H), 0.76(s, 9H), 1.28(d, *J*=6.2 Hz, 3H), 3.17(d, *J*=2.7 Hz, 1H), 4.23(dq, *J*=2.7, 6.2 Hz, 1H), 4.32(dd, *J*=2.8, 18.0 Hz, 1H), 5.04(dd, *J*=2.4, 17.9 Hz, 1H), 5.27(d, *J*=13.5 Hz, 1H), 5.42(d, *J*=13.5 Hz, 1H), 6.98 (br dd, *J*=2.0, 2.0 Hz, 1H), 7.59(d-like, *J*=8.8 Hz, 2H), 7.5-7.7(m, 1H), 8.25(d-like, *J*=8.8 Hz, 2H); ms (FAB) $^{m}/_{z}$ 507(MH^+).

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