97. Syntheses of the First Selenium-Containing Bicyclic β-Lactams as Potent Antimicrobial Agents

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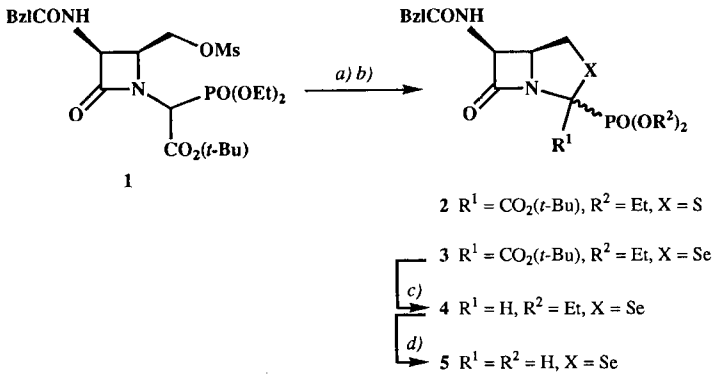
Syntheses of the *cis*-configurated isodethiaselenapenam **5** (*Scheme 1*) as well as the isodethiaselenacephems **29** and **31** (*Scheme 2*) were accomplished, in which the key step involved addition of Se to the corresponding carbanions of **1**, **25**, and **27** followed by internal alkylation. β-Lactams **29** and **31** were found to possess biological activity against several pathogenic microorganisms *in vitro*. The electronic activation of the lactam moiety in the isodethiaselenacephem **31** and the corresponding isocephem **33** remarkably enhanced their biological activity. Isodethiaselenacephem **31** was more toxic than isocephem **33** in experimental animals.

Introduction. – Elemental sulfur reacts with phosphoryl carbanions to give phosphorylmethane thiols, which upon treatment with alkylating agents lead to phosphorylmethyl sulfides [1] [2]. In this connection, we found that the reaction of phosphoryl carbanions of monocyclic β-lactams (*i.e.* **1**) with elemental sulfur gave the corresponding sulfido salts. These salts underwent an internal S_N2 of the mesylate functionality to afford the corresponding bicyclic β-lactams (*e.g.* **2**) [3]. Herein, we report our findings on the exploration of the reaction of the phosphoryl carbanion of **1** and sulfonyl carbanions of **25** and **27** with elemental selenium. These reactions afford the corresponding isodethiaselenapenam **5** (*Scheme 1*) and isodethiaselenacephems **29** and **31** (*Scheme 2*). In addition, we report a new synthesis of biologically active isocephem **33** [4] (*Scheme 2*) by reaction of the sulfonyl carbanion of **27** with elemental sulfur.

Results and Discussion. – We treated the monocyclic β-lactam **1** [5] with *t*-BuOK and Se in THF/DMF 9:1 at 25° for 1.5 h to afford the *cis*-substituted bicyclic β-lactam **3** as a mixture of two diastereoisomers in 75% overall yield (*Scheme 1*). Removal of the *t*-Bu group of **3** with CF_3CO_2H followed by decarboxylation by use of $NaHCO_3$ gave phosphonate **4** (55%) upon acidic workup [5]. Treatment of phosphonate **4** with Me_3SiBr in CH_2Cl_2 produced isodethiaselenapenam **5** in 30% yield [6].

We started our syntheses of the isodethiaselenacephems **29** and **31** and of the isocephem **33** with the sodium salt **6** of the *cis*-epoxysuccinic acid [7] (*Scheme 2*). Reaction of **6** with *tert*-butyl carbamate and Bu_4NCl gave the corresponding (*tert*-butoxy)carbonylamino derivative which, upon treatment with benzyl bromide, produced diester **7** as a racemic mixture in 65% overall yield. Saponification of the less hindered ester group of **7** with 1% aqueous NaOH solution in THF gave acid **10** (90%), which was then methylated with CH_2N_2 in Et_2O to afford ester **11** in 98% yield. Removal of the

Scheme 1



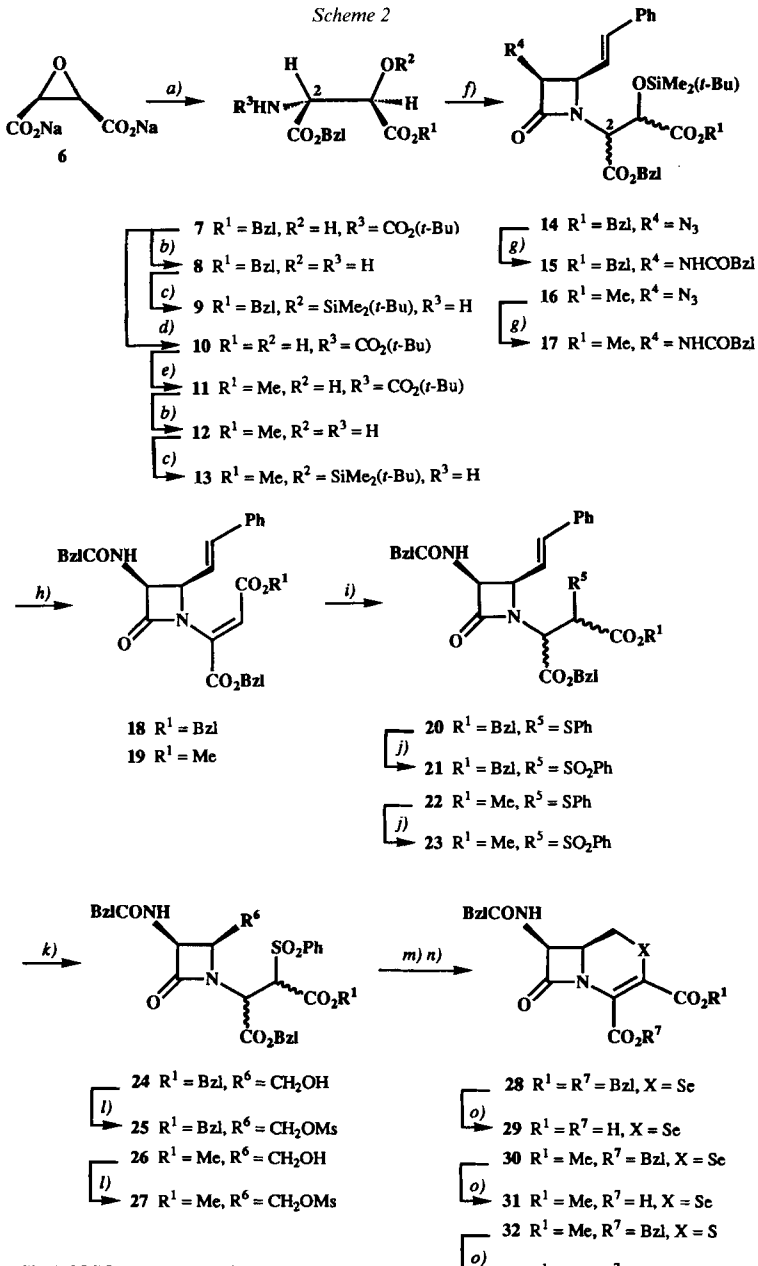
a) 90% for **1**→**2**: S_8, *t*-BuOK, THF. *b*) 75% for **1**→**3**: Se, *t*-BuOK, THF/DMF 9:1. *c*) 55%: 1. CF_3CO_2H; 2. $NaHCO_3$, HCl. *d*) 30%: Me_3SiBr, CH_2Cl_2.

(*tert*-butoxy)carbonyl group from the N-atom of **7** and **11** with CF_3CO_2H gave the corresponding amino esters **8** (95%) and **12** (95%) upon neutralization with $NaHCO_3$ solution. Amino esters **8** and **12** were converted to the (*tert*-butyl)dimethylsilyl derivatives **9** (90%) and **13** (85%), respectively, by use of (*tert*-butyl)dimethylchlorosilane and 1*H*-imidazole. Following the procedure reported by *Doyle et al.* [8], we transformed **9** to the corresponding *N*-cinnamylidene derivative, then to the diastereoisomer mixture **14** of *cis*-3-azido-4-styryl-β-lactams (68%). By the same method, a diastereoisomer mixture **16** was prepared from **13** in 70% yield. We believe that the configuration at C(2) of the succinate moiety in β-lactams **14** and **16**, with respect to C(2) of the corresponding precursors **9** and **13**, was not retained during β-lactam-ring formation. This was observed previously in a similar reaction in which L-serine was used as the starting material [9]. The *cis*-configuration in the β-lactams were determined by ^{1}H-NMR spectrometry (J(H–C(3),H–C(4)) = 5 Hz) of the derivatives, in which the relevant protons did not overlap with other signals [10] [11]. The azide function in **14** and **16** was reduced by H_2S/Et_3N [12], and the resultant amines were further acylated with phenylacetyl chloride to 3-(phenylacetamido)-β-lactams **15** (80%) and **17** (86%), respectively.

Dehydrosiloxylation of **15** and **17** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave fumarates **18** (93%) and **19** (95%), respectively. Their (*Z*)-configuration at the fumarate moiety was established by the chemical shift of their olefinic proton (δ 6.61 and 6.62 (*s*, $CHCO_2R$), resp.); *cf.* olefinic proton of maleates (δ ≈ 5.47–5.68 ppm) *vs.* fumarates (δ ≈ 6.56–6.84 ppm) [13]). Treatment of racemates **18** and **19** with thiophenol in the presence of a catalytic amount of NaH in THF gave (phenylthio)succinates **20** (95%) and **22** (90%) as diastereoisomer mixtures, respectively. Reaction of **20** or **22** with 3-chloroperbenzoic acid (3-$ClC_6H_4CO_3H$) yielded the corresponding sulfones **21** (95%) and **23** (98%). Ozonolysis of the styryl group of **21** and **23**, followed by reductive workup, gave the alcohols **24** (80%) and **26** (90%) which were mesylated to **25** (93%) and **27** (98%), respectively.

Reaction of the monocyclic β-lactams **25** or **27** with Se and *t*-BuOK in THF/DMF 9:1 at 25° for 4 h and subsequent treatment of the corresponding isodethiaselenacepham

Scheme 2



a) 65%: 1. Bu_4NCl, $H_2NCO_2(t\text{-Bu})$; 2. BzlBr, DMF. *b*) 95%: 1. CF_3CO_2H; 2. $NaHCO_3$. *c*) 85–90%: (*t*-Bu)-Me_2SiCl, 1*H*-imidazole, DMF. *d*) 90%: 1% aq. NaOH, THF. *e*) 98%: CH_2N_2, Et_2O. *f*) 68–70%: 1. *trans*-PhCH=CHCHO, benzene; 2. N_3CH_2COCl, Et_3N, CH_2Cl_2. *g*) 80–86%: 1. H_2S, Et_3N; 2. BzlCOCl, pyridine. *h*) 93–95%: DBU, THF. *i*) 90–95%: PhSH, NaH (cat.), THF. *j*) 95–98%: 3-$ClC_6H_4CO_3H$, CH_2Cl_2. *k*) 80–90%: 1. O_3, MeOH; 2. $NaBH_4$. *l*) 93–98%: $MeSO_2Cl$, pyridine. *m*) 65% for **25**→**28**, 70% for **27**→**30**: 1. Se, *t*-BuOK, THF/DMF 9:1; 2. DBU. *n*) 88% for **27**→**32**: 1. S_8, *t*-BuOK, THF; 2. DBU. *o*) 60–75%: H_2, $PdCl_2$, AcOEt, 50 psi.

intermediates with DBU *in situ* at reflux temperature gave racemic bicyclic β-lactams **28** (65%) and **30** (70%), respectively. Sulfonylmesylate **27** was also reacted with S_8 and *t*-BuOK in THF at 25° for 4 h [3] [5]; then the resultant isocepham intermediate was similarly treated with DBU to afford **32** (88%) as a racemic mixture. Hydrogenolysis of **28**, **30**, and **32** in the presence of $PdCl_2$ in AcOEt at 50 psi H_2 gave isodethiaselenacephems **29** (60%) and **31** (75%) and isocephem **33** (60%), respectively.

Biological Activity. – β-Lactams **5**, **29**, **31**, and **33** as well as ampicillin, cloxacillin, and penicillin G were tested *in vitro* against five pathogenic microorganisms up to a level as high as 128 μg/ml [14]. The results are summarized in the *Table*. Isodethiaselenapenam **5**, bearing a phosphonate group in place of the carboxyl function of the naturally occurring penicillins, exhibited low antimicrobial activity. Isodethiaselenacephem **29** showed moderate activity; however, isodethiaselenacephem **31** and isocephem **33** exhibited pronounced antimicrobial activity. The profound antimicrobial effect of **31** and **33**, with respect to **29**, might indicate that the electronic activation of the β-lactam moiety by an electron-withdrawing group (*e.g.* an ester functionality) plays an important role in biological activity of bicyclic β-lactams [4]. It should be noted that our synthetic β-lactams were in racemic form, whereas natural β-lactam antibiotics are single enantiomers [15]. Thus, only one half of the minimal inhibitory concentrations would be necessary for each of the desired single enantiomer of **29**, **31**, and **33**.

Table. *Minimal Inhibitory Concentrations* [μg/ml]

	S. aureus FDA 209P	*E. coli* ATCC 39188	*S. typhi* O-901	*Ps. aeruginosa* 1101-75	*K. pneumoniae* NCTC 418
Isodethiaselenapenam **5**	65.40	[a])	[a])	98.50	[a])
Isodethiaselenacephem **29**	1.20	15.35	38.65	39.45	25.60
Isodethiaselenacephem **31**	0.10	1.25	2.05	8.95	3.54
Isocephem **33**	0.07	0.65	1.50	13.00	2.15
Ampicillin	0.33	2.51	[a])	[a])	[a])
Cloxacillin	0.18	1.70	[a])	[a])	[a])
Penicillin G	0.40	2.30	[a])	[a])	[a])

[a]) Not active up to 128 μg/ml.

Furthermore, we determined the LD_{50} of isodethiaselenacephem **31** in rats: thus, **31** was administered at different doses intravenously (*i.v.*). Compound **31** did not show any detectable toxicity at a concentration level as high as 70 mg/kg. Nevertheless, an LD_{50} (*i.v.*) of *ca.* 180 mg/kg was determined for **31**. For isocephem **33**, an LD_{50} (*i.v.*) of *ca.* 800 mg/kg was reported recently [4]. Compounds **31** and **33** showed similar antimicrobial activity *in vitro*, but exhibited different toxicity in rats.

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Experimental Part

General. Chemicals were purchased from *Fluka Chemical Co.* Reagent-grade solvents were distilled and then stored over molecular sieves (4 Å). Column chromatography (CC): *Merck* silica gel *60* (230–400 mesh), packed in glass column (25 g of silica gel/g of crude material). TLC: *Merck* silica gel *60F 254* anal. sheets. M.p.: *Büchi 510;* uncorrected. IR Spectra: *Beckman-IR-8* spectrophotometer; in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-WH-90* and *Varian-XL-200* spectrometers; δ in ppm rel. to Me_4Si, J in Hz. MS Spectra: *AEI-MS-902* mass spectrometer; *m/z* (rel. intensity in %). Microanalyses: *Perkin-Elmer-240B* microanalyzer.

*(±)-(*tert*-Butyl) (2*RS,*5*SR,*6*SR)- and (2*RS,*5*RS,*6*RS)-2-(Diethoxyphosphoryl)-7-oxo-6-(phenylacetamido)-3-selena-1-azabicyclo[3.2.0]heptane-2-carboxylates* (**3**). To a soln. of **1** (0.56 g, 1.0 mmol) in THF/DMF 9:1 (6 ml) was added Se powder (0.101 g, 1.26 mmol), then *t*-BuOK (0.134 g, 1.20 mmol), at 25° under N_2. The mixture was stirred for 1.5 h, H_2O (20 ml) added, and the aq. soln. extracted with AcOEt. The org. layer was dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, AcOEt/$CHCl_3$ 4:1): 0.40 g (75%) of **3**. Foam. IR (CH_2Cl_2): 3400 (NH), 1780 (β-lactam), 1740 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.15 (*m*, 2 Me, Me_3C); 2.28–2.68 (*m*, CH_2(4)); 3.59 (br. *s*, CH_2CO); 3.90–4.69 (*m*, 2 CH_2, H–C(5)); 5.15, 5.20 (2*dd*, *J* = 5.0, 8.5, H–C(6)); 6.80–7.10 (br., NH); 7.23 (*s*, Ph). Anal. calc. for $C_{22}H_{31}N_2O_7PSe$ (545.42): C 48.45, H 5.73, N 5.13; found: C 48.39, H 5.70, N 5.21.

*(±)-Diethyl (2*RS,*5*SR,*6*SR)- and (2*RS,*5*RS,*6*RS)-7-Oxo-6-(phenylacetamido)-3-selena-1-azabicyclo-[3.2.0]heptane-2-phosphonates* (**4**). CH_2Cl_2/CF_3CO_2H 1:1 (5 ml) was added at 0° to **3** (0.50 g, 0.92 mmol) in CH_2Cl_2 (1 ml). The soln. was stirred at 25° for 10 h and then evaporated. CCl_4 was added and re-evaporated to remove the remaining CF_3CO_2H. A soln. of 5% aq. $NaHCO_3$ soln. (6 ml) was added to the residue in DMF (1 ml) and stirred at 45° for 15 min. The soln. was acidified with HCl to pH 4, and extracted with AcOEt (3 × 20 ml). The org. layer was washed with H_2O (60 ml), dried ($MgSO_4$), filtered, and evaporated. CC (silica gel, $CHCl_3$) gave 0.24 g (55%) of **4**. Oil. IR (CH_2Cl_2): 3400 (NH), 1776 (β-lactam), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.24 (br. *t*, 2 Me); 2.26–2.67 (*m*, CH_2(4)); 3.56 (*s*, CH_2CO); 3.91–4.54 (*m*, 2 CH_2, H–C(5), H–C(2)); 5.18 (*dd*, *J* = 5.0, 9.5, H–C(6)); 6.90 (*d*, *J* = 9.5, NH); 7.28 (*s*, Ph). Anal. calc. for $C_{17}H_{23}N_2O_5PSe$ (445.30): C 45.85, H 5.20, N 6.29; found: C 45.98, H 5.41, N 6.38.

*(±)-(2*RS,*5*SR,*6*SR)- and (2*RS,*5*RS,*6*RS)-7-Oxo-6-(phenylacetamido)-3-selena-1-azabicyclo[3.2.0]heptane-2-phosphonic Acids* (**5**). To a soln. of **4** (0.45 g, 1.0 mmol) in CH_2Cl_2 (13 ml) was added Me_3SiBr (0.46 g, 3.0 mmol). Then the soln. was stirred at 25° for 7 h, MeOH/H_2O 5:1 (20 ml) added, and the mixture evaporated. CC (silica gel, AcOEt) gave 0.13 g (30%) of **5**. M.p. 115–117°. IR (nujol): 3210–3450 (2 OH, NH), 1770 (β-lactam), 1682 (amide). ^{1}H-NMR ((D$_6$)DMSO/D_2O): 2.27–2.69 (*m*, CH_2(4)); 3.60 (*s*, CH_2CO); 4.29 (*m*, H–C(5)); 4.31, 4.39 (2*d*, *J* = 20.0, H–C(2)); 5.21 (*d*, *J* = 4.5, H–C(6)); 7.25 (*s*, Ph). Anal. calc. for $C_{13}H_{15}N_2O_5PSe$ (389.19): C 40.12, H 3.88, N 7.19; found: C 40.27, H 4.08, N 7.23.

*(±)-Dibenzyl (2*RS,*3*RS*)-2-[(*tert*-Butoxy)carbonylamino]-3-hydroxybutanedioate* (**7**). Disodium *cis*-oxirane-1,2-dicarboxylate (**6**; 1.76 g, 0.011 mol) was suspected in MeCN (50 ml) containing Bu_4NCl (2.78 g, 0.011 mol) and *tert*-butyl carbamate (11.7 g, 0.101 mol). The mixture was stirred at reflux temp. for 75 h. After filtration, Et_2O (500 ml) was added to give an oily product. The soln. was decanted and the oil washed with Et_2O (2 × 50 ml) to remove all unreacted *tert*-butyl carbamate. The crude material was dissolved in DMF (30 ml) to which $PhCH_2Br$ (3.42 g, 0.021 mol) was added. The soln. was stirred at 25° for 24 h and then partitioned between Et_2O (100 ml) and H_2O (100 ml). The org. layer was washed with H_2O (4 × 100 ml), dried ($MgSO_4$), filtered, and evaporated, and the residue chromatographed (silica gel, $CHCl_3$): 2.79 g (65%) of **7**. Oil. IR ($CHCl_2$): 3350–3405 (OH, NH), 1748 (esters), 1715 (carbamate). ^{1}H-NMR ($CDCl_3$/D_2O): 1.49 (*s*, Me_3C); 3.96 (*d*, *J* = 2.2, CHN); 4.60 (*d*, *J* = 2.2, CHO); 5.11, 5.13 (2*s*, 2 CH_2); 7.29 (br. *s*, 2 Ph). Anal. calc. for $C_{23}H_{27}NO_7$ (429.46): C 64.32, H 6.33, N 3.26; found: C 64.28, H 6.15, N 3.14.

*(±)-Dibenzyl (2*RS,*3*RS*)-2-Amino-3-hydroxybutanedioate* (**8**). To a soln. of **7** (2.15 g, 5.01 mmol) in CF_3CO_2H (30 ml), a trace amount of $KClO_4$ was added and the soln. stirred at 25° for 1 h. The solvent was evaporated and the residue partitioned between 5% aq. $NaHCO_3$ soln. (50 ml) and Et_2O (100 ml). The org. layer was dried ($MgSO_4$), filtered, and evaporated. CC (silica gel, $CHCl_3$/AcOEt 1:1) afforded **8** (1.57 g, 95%). Foam. IR (CH_2Cl_2): 3340–3420 (OH, NH_2), 1745 (esters). ^{1}H-NMR ($CDCl_3$/D_2O): 3.89 (*d*, *J* = 2.0, CHN); 4.61 (*d*, *J* = 2.0, CHO); 5.12 (*s*, 2 CH_2); 7.25 (br. *s*, 2 Ph). Anal. calc. for $C_{18}H_{19}NO_5$ (329.35): C 65.64, H 5.81, N 4.25; found: C 65.50, H 5.69, N 4.31.

*(±)-Dibenzyl (2*RS,*3*RS*)-2-Amino-3-[(*tert*-butyl)dimethylsilyloxy]butanedioate* (**9**). To **8** (3.30 g, 0.011 mol) in DMF (35 ml) was added 1*H*-imidazole (1.53 g, 0.022 mol) and (*tert*-butyl)chlorodimethylsilane (3.15 g, 0.021 mol). The soln. was stirred at 25° for 15 h, then partitioned between Et_2O (200 ml) and H_2O (250 ml). The Et_2O layer was washed with H_2O (4 × 200 ml), dried ($MgSO_4$), and evaporated and the residue chromatographed

(silica gel, CH_2Cl_2, then $CHCl_3$): 3.73 g (90%) of **9**. Oil. IR (CH_2Cl_2): 3380–3410 (NH_2), 1750 (esters). ^{1}H-NMR ($CDCl_3/D_2O$): 0.12 (2*s*, Me_2Si); 0.91 (*s*, Me_3C); 3.90 (*d*, *J* = 2.0, CHN); 4.69 (*d*, *J* = 2.0, CHO); 5.10, 5.14 (2*s*, 2 CH_2); 7.30 (br. *s*, 2 Ph). Anal. calc. for $C_{24}H_{33}NO_5Si$ (443.62): C 64.98, H 7.50, N 3.16; found: C 64.83, H 7.43, N 3.21.

*(±)-1-Benzyl 4-Hydrogen (2*RS,*3*RS*)-2-[(*tert-*Butoxy)carbonylamino]-3-hydroxybutanedioate* (**10**). To a soln. of **7** (4.29 g, 0.011 mol) in THF (200 ml) was added 1% aq. NaOH soln. (50 ml, 0.0125 mol) within 30 min. The mixture was stirred at 0° for 20 min and then acidified with HCl soln. to pH 3. THF was evaporated, the aq. soln. extracted with AcOEt (50 ml), and the extract dried ($MgSO_4$) and evaporated. CC (silica gel, AcOEt) gave 3.02 g (90%) of **10**. M.p. 93–95°. IR (CH_2Cl_2): 2850–3420 (OH, NH, CO_2H), 1730 (ester), 1710–1726 (acid, carbamate). ^{1}H-NMR ($CDCl_3/D_2O$): 1.48 (*s*, Me_3C); 3.98 (*d*, *J* = 2.1, CHN); 4.58 (*d*, *J* = 2.1, CHO); 5.26 (*s*, CH_2); 7.25 (*s*, Ph). Anal. calc. for $C_{16}H_{21}NO_7$ (339.34): C 56.63, H 6.24, N 4.13; found: C 56.52, H 6.36, N 4.20.

*(±)-1-Benzyl 4-Methyl (2*RS,*3*RS*)-2-[(*tert-*Butoxy)carbonylamino]-3-hydroxybutanedioate* (**11**). Compound **10** (3.40 g, 0.010 mol) was gradually added to a soln. of Et_2O (230 ml) containing CH_2N_2 (27.6 g, 0.660 mol). The soln. was kept at 25° for 30 min and then evaporated. CC (silica gel, $CHCl_3$) gave 3.45 g (98%) of **11**. Foam. IR (CH_2Cl_2): 3350–3410 (OH, NH), 1748 (esters), 1720 (carbamate). ^{1}H-NMR ($CDCl_3/D_2O$): 1.50 (*s*, Me_3C); 3.58 (*s*, Me); 3.95 (*d*, *J* = 2.2, CHN); 4.61 (*d*, *J* = 2.2, CHO); 5.18 (*s*, CH_2); 7.30 (*s*, Ph). Anal. calc. for $C_{17}H_{23}NO_7$ (353.37): C 57,78, H 6.56, N 3.96; found: C 57.82, H 6.48, N 3.85.

*(±)-1-Benzyl 4-Methyl (2*RS,*3*RS*)-2-Amino-3-hydroxybutanedioate* (**12**) was prepared from **11** (3.53 g, 9.99 mmol) in 95% yield (2.41 g) as described for **8**. IR (CH_2Cl_2): 3340–3420 (OH, NH_2), 1745 (esters). ^{1}H-NMR ($CDCl_3/D_2O$): 3.53 (*s*, Me); 3.88 (*d*, *J* = 2.0, CHN); 4.60 (*d*, *J* = 2.0, CHO); 5.12 (*s*, CH_2); 7.27 (*s*, Ph). Anal. calc. for $C_{12}H_{15}NO_5$ (253.25): C 56.91, H 5.97, N 5.53; found: C 56.80, H 6.04, N 5.61.

*(±)-1-Benzyl 4-Methyl (2*RS,*3*RS*)-2-Amino-3-[(*tert-butyl)dimethylsilyloxy]butanedioate* (**13**) was obtained from **12** (2.53 g, 9.99 mmol) in 85% yield (3.12 g) as described for **9**. IR (CH_2Cl_2): 3385–3410 (NH_2), 1750 (esters). ^{1}H-NMR ($CDCl_3/D_2O$): 0.11 (2*s*, Me_2Si); 0.88 (*s*, Me_3C); 3.60 (*s*, Me); 3.92 (*d*, *J* = 2.0, CHN); 4.70 (*d*, *J* = 2.0, CHO); 5.11 (*s*, CH_2); 7.26 (*s*, Ph). MS: 367 (M^+). Anal. calc. for $C_{18}H_{29}NO_5Si$ (367.52): C 58.83, H 7.95, N 3.81; found: C 58.72, H 7.78, N 3.96.

*(±)-Dibenzyl 2-[*cis*-3-Azido-2-oxo-4-(2-phenylethenyl)azetidin-1-yl]-3-[(*tert-*butyl)dimethylsilyloxy]butanedioates* (racemic diastereoisomer mixture; **14**). A soln. of **9** (4.43 g, 0.010 mol) and cinnamaldehyde (5.40 g, 0.040 mol) in benzene (250 ml) was heated at reflux temp. for 18 h using a *Dean-Stark* trap. Evaporation afforded the corresponding *Schiff* base (quant.), which was dissolved in CH_2Cl_2 (100 ml). Et_3N (2.02 g, 0.020 mol) was added, then dropwise a soln. of N_3CH_2COCl (1.20 g, 0.011 mol) in CH_2Cl_2 (5 ml) over 10 min at 25°. After 5 h stirring, the soln. was washed with H_2O (100 ml), dried ($MgSO_4$), and evaporated. The crude product was purified by CC (silica gel, $CHCl_3$): 4.35 g (68%) of **14**. Oil. IR (CH_2Cl_2): 2100 (N_3), 1750–1765 (β-lactam, esters). ^{1}H-NMR ($CDCl_3$): 0.11 (4*s*, Me_2Si); 0.98 (2*s*, Me_3C); 4.46–4.95 (*m*, H–C(3), H–C(4), 2 CH); 5.15, 5.28 (4*s*, 2 CH_2); 6.16–6.92 (*m*, CH=CH); 7.18–7.36 (*m*, 3 Ph). Anal. calc. for $C_{35}H_{40}NO_6Si$ (640.79): C 65.60, H 6.29, N 8.74; found: C 65.73, H 6.38, N 8.85.

*(±)-Dibenzyl 2-[*cis*-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]-3-[(*tert-*butyl)dimethylsilyloxy]butanedioates* (racemic diastereoisomer mixture; **15**). H_2S was bubbled into a soln. of **14** (6.41 g, 0.011 mol) and Et_3N (2.02 g, 0.020 mol) in CH_2Cl_2 (250 ml) added at 0°. After 1.5 h, the soln. was purged with N_2, washed with H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated. To the crude material in CH_2Cl_2 (100 ml) and pyridine (2.40 g, 0.030 mol) was added dropwise $PhCH_2COCl$ (2.37 g, 0.015 mol) in CH_2Cl_2 (10 ml). After stirring for 2 h, the soln. was washed with pH 4.5 buffer soln. (aq. KH_2PO_4 soln., 55 ml) and H_2O (60 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, $CHCl_3$) gave 5.85 g (80%) of **15**. Foam. IR (CH_2Cl_2): 3405–3415 (NH), 1750–1770 (β-lactam, esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 0.10 (2*s*, Me_2Si); 0.92 (*s*, Me_3C); 3.52 (br. *s*, CH_2CO); 4.40 (*d*, *J* = 3.0, $CHCO_2$); 4.64 (*dd*, *J* = 5.0, 9.5, H–C(4)); 4.89 (*d*, *J* = 3.0, CHOSi); 5.17, 5.25 (2 br. *s*, 2 CH_2); 5.49 (*dd*, *J* = 5.0, 8.5, H–C(3)); 6.31 (*dd*, *J* = 9.5, 16.0, PhCH=C*H*); 6.68 (*d*, *J* = 16.0, Ph*CH*=CH); 6.89 (br. *d*, *J* = 8.5, NH); 7.10–7.35 (*m*, 4 Ph). Anal. calc. for $C_{43}H_{48}N_2O_7Si$ (732.94): C 70.46, H 6.60, N 3.82; found: C 70.29, H 6.68, N 3.91.

*(±)-1-Benzyl 4-Methyl 2-[*cis*-3-Azido-2-oxo-4-(2-phenylethenyl)azetidin-1-yl]-3-[(*tert-butyl)dimethylsilyloxy]butanedioates* (racemic diastereoisomer mixture; **16**) were prepared from **13** (1.84 g, 5.01 mmol) in 70% yield (1.97 g) as described for **14**. IR (CH_2Cl_2): 2100 (N_3), 1748–1766 (β-lactam, esters). ^{1}H-NMR ($CDCl_3$): 0.12 (4*s*, Me_2Si); 1.01 (2*s*, Me_3C); 3.53 (2*s*, Me); 4.44–5.01 (*m*, H–C(3), H–C(4), 2CH); 5.19 (2*s*, CH_2); 6.18–6.89 (*m*, CH=CH); 7.15–7.30 (*m*, 2 Ph). Anal. calc. for $C_{29}H_{36}N_4O_6Si$ (564.69): C 61.68, H 6.42, N 9.92; found: C 61.79, H 6.50, N 9.79.

*(±)-1-Benzyl 4-Methyl 2-[*cis*-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]-3-[(*tert-butyl)-dimethylsilyloxy]butanedioates* (racemic diastereoisomer mixture; **17**) were prepared from **16** (5.60 g, 9.92

mmol) in 86% yield (5.60 g) as described for **15**. IR (CH_2Cl_2): 3410 (NH), 1750–1770 (β-lactam, esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 0.12 (2*s*, Me_2Si); 0.98 (*s*, Me_3C); 3.51 (br. *s*, CH_2CO); 3.54 (2*s*, Me); 4.42 (*d*, *J* = 3.0, $CHCO_2$); 4.68 (*dd*, *J* = 5.0, 9.5, H–C(4)); 4.90 (*d*, *J* = 3.0, CHOSi); 5.15 (br. *s*, CH_2); 5.42 (*dd*, *J* = 5.0, 9.0, H–C(3)); 6.28 (*dd*, *J* = 9.5, 16.0, PhCH=C*H*); 6.67 (*d*, *J* = 16.0, PhC*H*=CH); 6.90 (br. *d*, *J* = 9.0, NH); 7.12–7.40 (*m*, 3 Ph). Anal. calc. for $C_{37}H_{44}N_2O_7Si$ (656.85): C 67.66, H 6.75, N 4.26; found: C 67.85, H 6.80, N 4.32.

*(±)-Dibenzyl 2-[(3*RS,*4*RS*)-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]but-2-enedioate* (**18**). To a soln. of **15** (3.66 g, 5.01 mmol) in THF (50 ml) was added DBU (1.53 g, 10.0 mmol). The mixture was heated at reflux temp. for 1 h and then evaporated and the residue chromatographed (silica gel, $CHCl_3$): 2.79 g (93%) of **18**. M.p. 119–121°. IR (CH_2Cl_2): 3410 (NH), 1792 (β-lactam), 1745 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.59 (*s*, CH_2CO); 4.78 (*m*, H–C(4)); 5.26, 5.38 (2*s*, 2 CH_2); 5.50 (*dd*, *J* = 5.0, 10.0, H–C(3)); 6.24–6.70 (*m*, CH=CH); 6.61 (*s*, $CHCO_2$); 7.01 (*d*, *J* = 10.0, NH); 7.19–7.45 (*m*, 4 Ph). Anal. calc. for $C_{37}H_{32}N_2O_6$ (600.67): C 73.99, H 5.37, N 4.66; found: C 73.95, H 5.39, N 4.59.

*(±)-1-Benzyl 4-Methyl 2-[(3*RS,*4*RS*)-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]but-2-enedioate* (**19**) was obtained from **17** (6.57 g, 10.0 mmol) in 95% yield (5.00 g) as described for **18**. M.p. 112–113°. IR (CH_2Cl_2): 3410 (NH), 1792 (β-lactam), 1745 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.58 (*s*, CH_2CO); 3.89 (*s*, Me); 4.80 (*m*, H–C(4)); 5.37 (*s*, CH_2); 5.48 (*dd*, *J* = 5.0, 9.5, H–C(3)); 6.20–6.68 (*m*, CH=CH); 6.62 (*s*, $CHCO_2$); 6.99 (*d*, *J* = 9.5, NH); 7.11–7.38 (*m*, 3 Ph). Anal. calc. for $C_{31}H_{28}N_2O_6$ (524.56): C 70.98, H 5.38, N 5.34; found: C 71.05, H 5.29, N 5.44.

*(±)-Dibenzyl 2-[*cis*-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]-3-(phenylthio)butanedioates* (racemic diastereoisomer mixture **20**). To a soln. of **18** (6.00 g, 0.010 mol) and thiophenol (1.32 g, 0.012 mol) in THF (80 ml), a catalytic amount of NaH was added at 0°. After 1 h of stirring, Et_2O (65 ml) was added and the soln. washed with H_2O (2 × 100 ml). The org. layer was dried ($MgSO_4$), filtered, and evaporated. CC (silica gel, $CH_2Cl_2/CHCl_3$ 1:3) afforded **20** (6.75 g, 95%). Oil. IR (CH_2Cl_2): 3410 (NH), 1762 (β-lactam), 1745 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.56 (br. *s*, CH_2CO); 3.78 (br. *d*, *J* = 3.5, CHS); 4.46 (br. *d*, *J* = 3.5, $CHCO_2$); 4.82 (*dd*, *J* = 4.8, 9.0, H–C(4)); 5.15, 5.27 (2 br. *s*, $2CH_2$); 5.49 (*dd*, *J* = 4.8, 8.0, H–C(3)); 6.25 (*dd*, *J* = 9.0, 16.0, PhCH=C*H*); 6.68 (*d*, *J* = 16.0, PhC*H*=CH); 6.84 (*d*, *J* = 8.0, NH); 6.98–7.39 (*m*, 5 Ph). Anal. calc. for $C_{43}H_{38}N_2O_6S$ (710.83): C 72.66, H 5.39, N 3.94, S 4.51; found: C 72.72, H 5.42, N 4.13, S 4.45.

*(±)-Dibenzyl 2-[*cis*-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]-3-(phenylsulfonyl)butanedioates* (racemic diastereoisomer mixture; **21**). At 25°, 3-$ClC_6H_4CO_3H$ (1.72 g, 0.011 mol) was added to **20** (3.50 g, 4.90 mmol) in CH_2Cl_2 (80 ml). After stirring at 25° for 1.5 h and at reflux temp. for 1 h, 1% aq. $NaHCO_3$ soln. (100 ml) was added and the org. layer dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, AcOEt/CH_2Cl_2 4:1): **21** (3.50 g, 95%). Foam. IR (CH_2Cl_2): 3405 (NH), 1766 (β-lactam), 1750 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.56 (br. *s*, CH_2CO); 4.15–4.50 (*m*, $CHCHSO_2$); 4.95 (*dd*, *J* = 5.0, 8.5, H–C(4)); 5.16, 5.30 (2 br. *s*, 2 CH_2); 5.48 (*dd*, *J* = 5.0, 9.0, H–C(3)); 6.22 (*dd*, *J* = 8.5, 16.0, PhCH=C*H*); 6.67 (*d*, *J* = 16.0, PhC*H*=CH); 6.86 (*d*, *J* = 9.0, NH); 7.20–7.61 (*m*, 5 Ph). Anal. calc. for $C_{43}H_{38}N_2O_8S$ (742.84): C 69.53, H 5.16, N 3.77, S 4.32; found: C 69.60, H 5.29, N 3.91, S 4.39.

*(±)-1-Benzyl 4-Methyl 2-[*cis*-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]-3-(phenylthio)-butanedioates* (racemic diastereoisomer mixture; **22**) were prepared from **19** (2.62 g, 4.99 mmol) in 90% yield (2.85 g) as described for **20**. IR (CH_2Cl_2): 3410 (NH), 1765 (β-lactam), 1746 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.55 (br. *s*, CH_2CO); 3.60 (2*s*, Me); 3.78 (br. *d*, *J* = 3.3, CHS); 4.46 (br. *d*, *J* = 3.3, $CHCO_2$); 4.81 (*dd*, *J* = 5.0, 9.0, H–C(4)); 5.19 (br. *s*, CH_2); 5.47 (*dd*, *J* = 5.0, 8.5, H–C(3)); 6.23 (*dd*, *J* = 9.0, 16.0, PhCH=C*H*); 6.68 (*d*, *J* = 16.0, PhC*H*=CH); 6.90 (*d*, *J* = 8.5, NH); 7.05–7.38 (*m*, 4 Ph). Anal. calc. for $C_{37}H_{34}N_2O_6S$ (634.74): C 70.01, H 5.40, N 4.41, S 5.05; found: C 70.13, H 5.49, N 4.48, S 5.19.

*(±)-1-Benzyl 4-Methyl 2-[*cis*-2-Oxo-3-(phenylacetamido)-4-(2-phenylethenyl)azetidin-1-yl]-3-(phenylsulfonyl)butanedioates* (racemic diastereoisomer mixture; **23**) were obtained from **22** (3.20 g, 5.04 mmol) in 98% yield (3.27 g) as described for **21**. IR (CH_2Cl_2): 3410 (NH), 1767 (β-lactam), 1750 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.56 (br. *s*, CH_2CO); 3.68 (br. *s*, Me); 4.13–4.49 (*m*, $CHCHSO_2$); 4.90 (*dd*, *J* = 5.0, 8.5, H–C(4)); 5.20 (br. *s*, CH_2); 5.47 (*dd*, *J* = 5.0, 9.5, H–C(3)); 6.23 (*dd*, *J* = 8.5, 16.0, PhCH=C*H*); 6.66 (*d*, *J* = 16.0, PhC*H*=CH); 6.90 (*d*, *J* = 9.5, NH); 7.19–7.60 (*m*, 4 Ph). Anal. calc. for $C_{37}H_{34}N_2O_8S$ (666.74): C 66.65, H 5.14, N 4.20, S 4.81; found: C 66.84, H 5.02, N 4.29, S 4.70.

*(±)-Dibenzyl 2-[*cis*-4-(Hydroxymethyl)-2-oxo-3-(phenylacetamido)azetidin-1-yl]-3-(phenylsulfonyl)butanedioates* (racemic diastereoisomer mixture; **24**). A soln. of **21** (0.752 g, 1.02 mmol) in MeOH (60 ml) was saturated with N_2 at −78°. Then a gas mixture O_3/N_2 was bubbled through the soln. until KI/starch paper showed excess O_3. The excess O_3 was removed by a stream of N_2, $NaBH_4$ (0.19 g, 5.0 mmol) added at −45°, and the soln. allowed to warm up to 0° within 1.5 h. Then 5% aq. HCl soln. (5 ml) was added, the mixture concentrated, H_2O (30 ml) added, and the mixture extracted with AcOEt (40 ml). The org. layer was dried ($MgSO_4$), filtered, and evaporated and the

residue chromatographed (silica gel, CH_2Cl_2, then AcOEt/MeOH 18:1): 0.54 g (80%) of **24**. Foam. IR (CH_2Cl_2): 3300–3420 (OH, NH), 1760 (β-lactam), 1740 (ester), 1675 (amide). ^{1}H-NMR ($CDCl_3$): 3.44 (br. *m*, CH_2OH); 3.59 (*s*, CH_2CO); 4.13–4.50 (*m*, $CHCHSO_2$, H–C(4)); 5.13, 5.36 (2 br. *s*, $2\,CH_2$); 5.53, 5.65 (*2dd*, J = 5.0, 10.0, H–C(3)); 6.85 (br., NH); 7.21–7.62 (*m*, 4 Ph). Anal. calc. for $C_{36}H_{34}N_2O_9S$ (670.73): C 64.47, H 5.11, N 4.17, S 4.78; found: C 64.62, H 5.20, N 4.28, S 4.61.

(±)-Dibenzyl 2-{cis-*4-[(Methylsulfonyloxy)methyl]-2-oxo-3-(phenylacetamido)azetidin-1-yl*}*-3-(phenylsulfonyl)butanedioate* (racemic diastereoisomer mixture; **25**). To a soln. of **24** (0.67 g, 1.0 mmol) and pyridine (0.791 g, 10.0 mmol) in CH_2Cl_2 (12 ml) was added $MeSO_2Cl$ (0.260 g, 2.26 mmol) at 0°. After stirring for 5 h, the soln. was diluted with CH_2Cl_2 (30 ml), H_2O (40 ml) added, the org. layer dried ($MgSO_4$) and evaporated, and the residue chromatographed (silica gel, AcOEt): 0.70 g (93%) of **25**. Foam. IR (CH_2Cl_2): 3405 (NH), 1770 (β-lactam), 1740–1750 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 2.84 (br. *s*, $MeSO_3$); 3.57 (*s*, CH_2CO); 3.68 (br., $MsOCH_2$); 4.11–4.51 (*m*, $CHCHSO_2$, H–C(4)); 5.12, 5.32 (2 br. *s*, $2CH_2$); 5.42, 5.55 (*2dd*, J = 5.0, 9.5, H–C(3)); 6.85 (br., NH); 7.25–7.61 (*m*, 4 Ph). Anal. calc. for $C_{37}H_{36}N_2O_{11}S_2$ (748.81): C 59.35, H 4.85, N 3.74, S 8.56; found: C 59.22, H 4.99, N 3.61, S 8.60.

*(±)-1-Benzyl 4-Methyl 2-[*cis-*4-(Hydroxymethyl)-2-oxo-3-(phenylacetamido)azetidin-1-yl]-3-(phenylsulfonyl)butanedioates* (racemic diastereoisomer mixture; **26**) were obtained from **23** (0.700 g, 1.04 mmol) in 90% yield (0.56 g) as described for **24**. IR (CH_2Cl_2): 3300–3420 (OH, NH), 1760 (β-lactam), 1740 (esters), 1675 (amide). ^{1}H-NMR ($CDCl_3$): 3.45 (br., CH_2OH); 3.60 (*s*, CH_2CO): 3.67, 3.69 (2*s*, Me); 4.12–4.53 (*m*, $CHCHSO_2$, H–C(4)); 5.20 (br. *s*, CH_2); 5.53, 5.66 (*2dd*, J = 5.0, 10.0, H–C(3)); 6.95 (br., NH); 7.18, 7.25 (2*s*, 2 Ph); 7.32–7.63 (*m*, $PhSO_2$). Anal. calc. for $C_{30}H_{30}N_2O_9S$ (594.63): C 60.60, H 5.08, N 4.71, S 5.39; found: C 60.78, H 5.19, N 4.88, S 5.41.

(±)-1-Benzyl 4-Methyl 2-{cis-*4-[(methylsulfonyloxy)methyl]-2-oxo-3-(phenylacetamido)azitidin-1-yl*}*-3-(phenylsulfonyl)butanedioates* (racemic diastereoisomer mixture; **27**) were prepared from **26** (5.95 g, 10.0 mmol) in 98% yield (6.59 g) as described for **25**. IR (CH_2Cl_2): 3410 (NH), 1770 (β-lactam), 1745 (esters), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 2.85, 2.87 (2*s*, $MeSO_3$): 3.58 (*s*, CH_2CO); 3.65 (br. *s*, Me); 3.68 (br., $MsOCH_2$); 4.12–4.52 (*m*, $CHCHSO_2$, H–C(4)); 5.17 (br. *s*, CH_2O); 5.48, 5.54 (*2dd*, J = 5.0, 9.5, H–C(3)); 6.90 (br., NH); 7.20, 7.28 (2 br. *s*, 2 Ph); 7.34–7.65 (*m*, $PhSO_2$). Anal. calc. for $C_{31}H_{32}N_2O_{11}S_2$ (672.72): C 55.35, H 4.79, N 4.16, S 9.53; found: C 55.49, H 4.80, N 4.21, S 9.43.

*(±)-Dibenzyl (6*RS,*7*RS*)-8-Oxo-7-(phenylacetamido)-4-selena-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate* (**28**). To a soln. of **25** (0.75 g, 1.0 mmol) in THF/DMF 9:1 (15 ml) was added Se powder (0.101 g, 1.28 mmol), then *t*-BuOK (0.134 g, 1.20 mmol), at 25° under N_2. After stirring for 4 h, DBU (0.360 g, 2.35 mmol) was added and the soln. refluxed for 2 h. After cooling and addition of AcOEt (40 ml), the mixture was washed with H_2O (2 × 50 ml), dried ($MgSO_4$), and evaporated and the residue purified by CC (silica gel, CH_2Cl_2, then $CHCl_3$): 0.38 g (65%) of **28**. Oil. IR (CH_2Cl_2): 3420 (NH), 1794 (β-lactam), 1748 (esters), 1725 (C=C), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 2.31–2.75 (*m*, $CH_2(5)$); 3.52 (*s*, CH_2CO); 4.20 (*m*, H–C(6)); 5.10, 5.12 (2*s*, $2CH_2$); 5.16–5.41 (*dd*, J = 4.5, 9.0, H–C(7)); 6.85 (*d*, J = 9.0, NH); 7.20, 7.38 (2 br. *s*, 3 Ph). Anal. calc. for $C_{30}H_{26}N_2O_6Se$ (589.50): C 61.12, H 4.45, N 4.75; found: C 61.22, H 4.50, N 4.88.

*(±)-(6*RS,*7*RS*)-8-Oxo-7-(phenylacetamido)-4-selena-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylic Acid* (**29**). A mixture of **28** (0.601 g, 1.02 mmol), AcOEt (50 ml), and $PdCl_2$ (200 mg) was hydrogenated at 25° and 50 psi for 7 h. After filtration and evaporation, the crude foam was chromatographed (silica gel, AcOEt/MeOH 9:1): 0.24 g (60%) of **29**. M.p. 180–181°. IR (nujol): 3140–3670 (2 CO_2H, NH), 1780 (β-lactam), 1715, 1700 (2 C=O, C=C), 1675 (amide). ^{1}H-NMR ((D$_6$)DMSO/D_2O): 2.26–2.64 (*m*, $CH_2(5)$); 3.53 (*s*, CH_2CO); 4.33 (*m*, H–C(6)); 5.05 (*d*, J = 5.0, H–C(7)); 7.32 (*s*, Ph). Anal. calc. for $C_{16}H_{14}N_2O_6Se$ (409.25): C 46.96, H 3.45, N 6.84; found: C 47.08, H 3.51, N 6.90.

*(±)-2-Benzyl 3-Methyl (6*RS,*7*RS*)-8-Oxo-7-(phenylacetamido)-4-selena-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate* (**30**) was prepared from **27** (0.680 g, 1.01 mmol) in 70% yield (0.362 g) as described for **28**. IR (CH_2Cl_2): 3418 (NH), 1794 (β-lactam), 1748 (esters), 1725 (C=C), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 2.32–2.78 (*m*, $CH_2(5)$); 3.55 (*s*, CH_2CO); 3.96 (*s*, Me); 4.22 (*m*, H–C(6)); 5.10 (*s*, CH_2); 5.12–5.39 (*dd*, J = 4.5, 9.0, H–C(7)); 6.80 (*d*, J = 9.0, NH); 7.15, 7.32 (2*s*, 2 Ph). Anal. calc. for $C_{24}H_{22}N_2O_6Se$ (513.40): C 56.15, H 4.32, N 5.45; found: C 56.20, H 4.44, N 5.31.

*(±)-3-Methyl 2-Hydrogen (6*RS,*7*RS*)-8-Oxo-7-(phenylacetamido)-4-selena-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate* (**31**) was obtained from **30** (0.50 g, 0.97 mmol) in 75% yield (0.31 g) as described for **29**. M.p. 141–142°. IR (nujol): 3155–3660 (CO_2H, NH), 1790 (β-lactam), 1740 (ester), 1710, 1705 (acid, C=C), 1675 (amide). ^{1}H-NMR ((D$_6$)DMSO/D_2O): 2.29–2.72 (*m*, $CH_2(5)$); 3.53 (*s*, CH_2CO); 3.95 (*s*, Me); 4.34 (*m*, H–C(6)); 5.03 (*d*, J = 5.0, H–C(7)); 7.34 (*s*, Ph). Anal. calc. for $C_{17}H_{16}N_2O_6Se$ (423.27): C 48.24, H 3.81, N 6.61; found: C 48.19, H 3.70, N 6.42.

(±)-2-Benzyl 3-Methyl (6RS,7RS)-8-Oxo-7-(phenylacetamido)-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate (**32**) was prepared from **27** (0.670 g, 0.996 mmol) in 88% yield (0.41 g) as described for **28**, except that S_8 in THF was used instead of Se in THF/DMF 9:1. IR (CH_2Cl_2): 3423 (NH), 1796 (β-lactam), 1750 (esters), 1730 (C=C), 1682 (amide). ^{1}H-NMR ($CDCl_3$): 2.75–3.28 (*m*, CH_2(5)); 3.53 (*s*, CH_2CO); 3.98 (*s*, Me); 4.26 (br., H–C(6)); 5.12 (*s*, CH_2); 5.13–5.42 (*dd*, J = 4.5, 9.0, H–C(7)); 6.82 (*d*, J = 9.0, NH); 7.20, 7.40 (2*s*, 2 Ph). Anal. calc. for $C_{24}H_{22}N_2O_6S$ (466.50): C 61.79, H 4.75, N 6.01, S 6.87; found: C 61.83, H 4.88, N 5.98, S 6.92.

(±)-3-Methyl 2-Hydrogen (6RS,7RS)-8-Oxo-7-(phenylacetamido)-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate (**33**) was obtained from **32** (2.33 g, 4.99 mmol) in 60% yield (1.13 g) as described for **29**. M.p. 150–152° ([4]: m.p. 150–153°). IR (nujol): 3150–3655 (CO_2H, NH), 1790 (β-lactam), 1750 (ester), 1710, 1703 (acid, C=C), 1675 (amide). ^{1}H-NMR ((D_6)DMSO/D_2O): 2.45–3.05 (*m*, CH_2(5)); 3.48 (*s*, CH_2CO); 3.95 (*s*, Me); 4.33 (*m*, H–C(6)); 5.03 (*d*, J = 5.0, H–C(7)); 7.39 (*s*, Ph). CI-MS: 377 ($[M+1]^+$, S-cluster). MS: 201 ($[M - PhCH_2CONHCH{=}C{=}O]^+$, S-cluster). Anal. calc. for $C_{17}H_{16}N_2O_6S$ (376.32): C 54.25, H 4.25, N 7.45, S 8.51; found: C 54.33, H 4.29, N 7.52, S 8.39.

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