73. Syntheses of New Isocephems and Isodethiaoxacephems as Antimicrobial Agents

by **Gholam H. Hakimelahi**[a])*, **Shwu-Chen Tsay**[a]), **Zahra Ramezani**[b]), and **Jih Ru Hwu**[a])[c])*

[a]) Organosilicon and Synthesis Laboratory, Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan 11529, Republic of China

[b]) St. Thomas Research Training Laboratory, Dominican International School, Tah Chih, Taipei, Taiwan 104, Republic of China

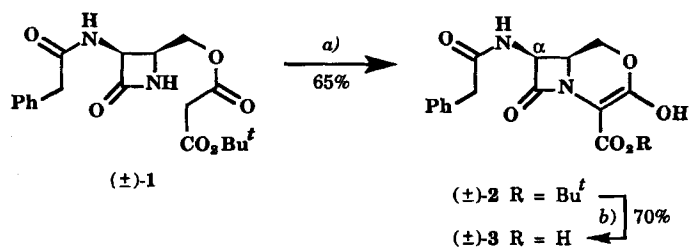
[c]) Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30043, Republic of China

(19.II.96)

The *cis*-configurated isocephem **26** as well as isodethiaoxacephems **21** and **33** were synthesized (*Schemes 4* and *5*). The key step involves chlorination of the corresponding carbanions of **23**, **18**, and **31** with CF_3SO_2Cl followed by internal alkylation. β-Lactams **3**, **21**, **26**, and **33** were found to possess biological activity against several pathogenic microorganisms *in vitro*. Electronic activation of the lactam moiety in isodethiaoxacephem **33** remarkably enhanced its biological activity.

Introduction. – Trifluoromethanesulfonyl chloride (CF_3SO_2Cl) is an effective sulfonating agent for alcohols [1]. It also functions as a chlorinating agent for carbanions. The relative speed is *ca.* 10^5 for chlorination of carbanions *vs.* sulfonation of alcohols [2] [3]. These properties have been utilized in the synthesis of bicyclic β-lactam **2** by treatment of racemic azetidinone **1** with CF_3SO_2Cl in Et_3N and CH_2Cl_2 (*Scheme 1*). Removal of the *tert*-butyl group in **2** with CF_3CO_2H in CH_2Cl_2 gives isodethiaoxacephem **3** [4]. Herein we describe alternative applications of this strategy for constructing a variety of heterocyclic B-rings in β-lactam antibiotics.

Scheme 1

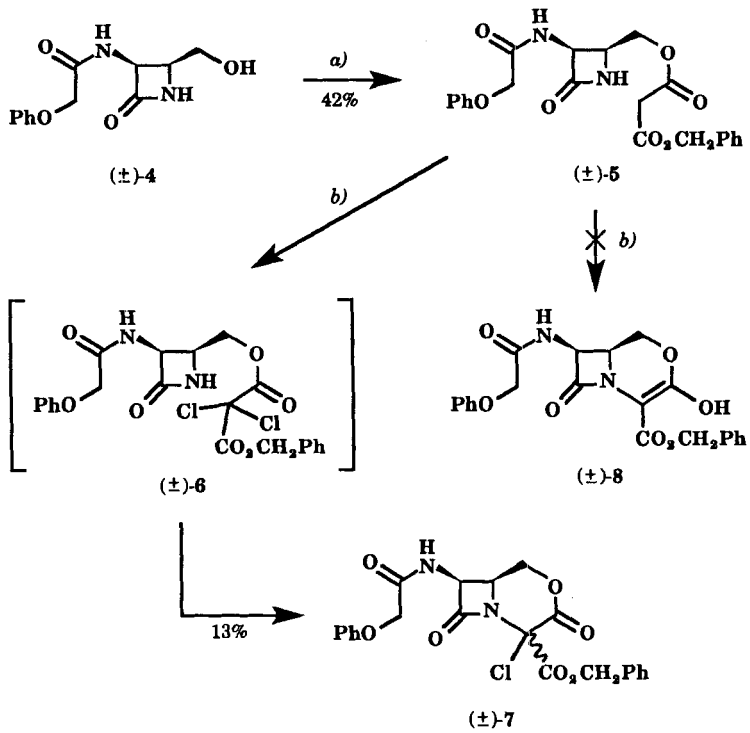


a) CF_3SO_2Cl, Et_3N, CH_2Cl_2. *b*) CF_3CO_2H, CH_2Cl_2, 25°.

Results and Discussion. – The biological activity of β-lactam antibiotics is influenced by their α-side chain [5] [6]. We planned to synthesize isodethiaoxacephem **21**, an analogue of **3**, and to compare their antimicrobial activity. Compounds **3** and **21** bear an α-phenylacetamide or an α-phenoxyacetamide side chain, respectively.

Our strategy for the synthesis of isodethiaoxacephem **21** involves the construction of the morpholin-2-one ring by connection of the (O=C)N–C(=C) single bond as the key step. Thus, we acylated racemic alcohol **4** [7] with benzyl (chloroformyl)acetate to give diester **5** (42%; *Scheme 2*). Treatment of **5** with CF_3SO_2Cl in Et_3N afforded diastereoisomeric isodethiaoxacephems **7**, along with unidentifiable products that did not contain a β-lactam ring. The desired benzyl ester **8**, a precursor of isodethiaoxacephem **21**, was not obtained in the above reaction.

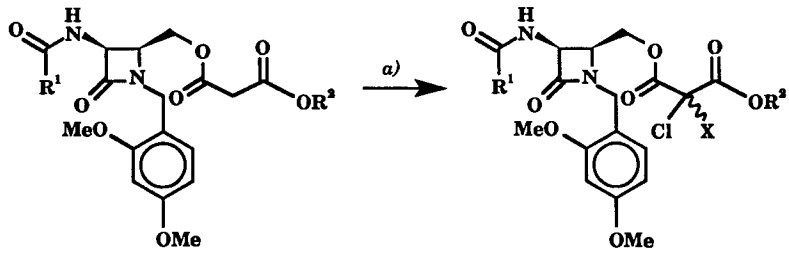
Scheme 2



a) $ClCOCH_2CO_2CH_2Ph$, pyridine, CH_2Cl_2. *b*) CF_3SO_2Cl, Et_3N, CH_2Cl_2.

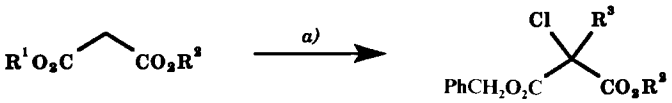
We carried out a model study to indicate that the conversion of **5** to **7** went through the dichloromalonate intermediate **6**. Upon treatment with CF_3SO_2Cl in Et_3N and CH_2Cl_2, benzyl malonate **9** [8] gave dichloromalonate **11** (90%); yet *tert*-butyl malonate **10** [4] afforded monochloromalonate **12** (80%, *Scheme 3*). Under similar conditions, dibenzyl malonate (**13**) and benzyl *tert*-butyl malonate (**14**) were converted to dichloromalonate **16** (95%) and monochloromalonate **17** (75%), respectively (*Scheme 3*); however, di(*tert*-butyl) malonate (**15**) did not react with CF_3SO_2Cl in Et_3N and CH_2Cl_2. Thus, we conclude that significant steric congestion was created by the *t*-Bu group obstructing the chlorination of the methylene unit of malonate.

Scheme 3



(±)-**9** $R^1 = PhCH_2O$, $R^2 = PhCH_2$
(±)-**10** $R^1 = PhCH_2$, $R^2 = Bu^t$

(±)-**11** $R^1 = PhCH_2O$, $R^2 = PhCH_2$, X = Cl
(±)-**12** $R^1 = PhCH_2$, $R^2 = Bu^t$, X = H



13 $R^1 = R^2 = PhCH_2$
14 $R^1 = PhCH_2$, $R^2 = Bu^t$
15 $R^1 = R^2 = Bu^t$

16 $R^2 = PhCH_2$, $R^3 = Cl$
17 $R^2 = Bu^t$, $R^3 = H$

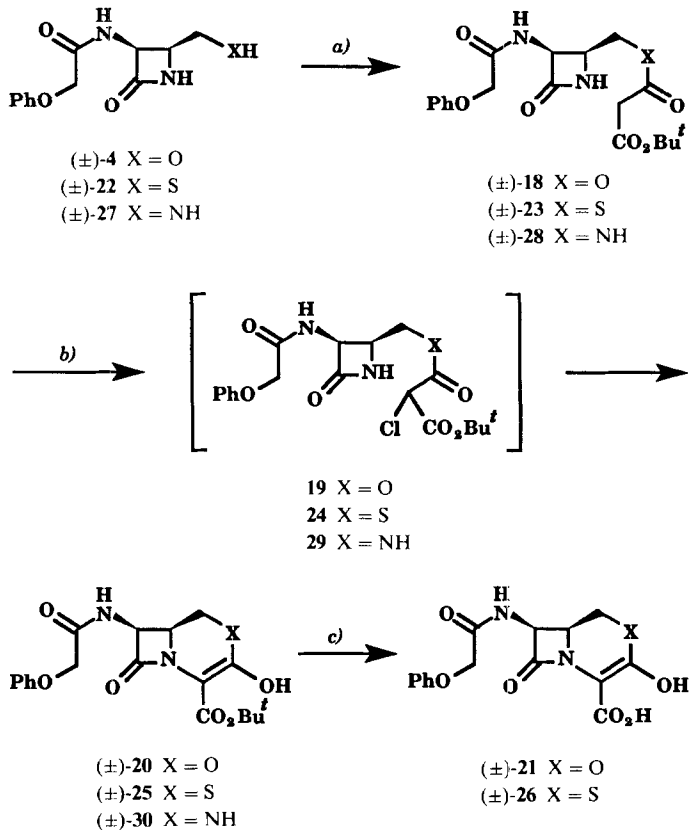
a) CF_3SO_2Cl, Et_3N, CH_2Cl_2; 90% for **9** → **11**; 80% for **10** → **12**; 95% for **13** → **16**; 75% for **14** → **17**; no reaction with **15**.

Consequently, we resumed our synthesis of isodethiaoxacephem **21** by treating *tert*-butyl (chloroformyl)acetate with racemic hydroxyazetidinone **4** in pyridine and CH_2Cl_2 (*Scheme 4*). The resulting ester **18**, obtained in 40% yield, was allowed to react with CF_3SO_2Cl and Et_3N in CH_2Cl_2 to give the desired bicyclic β-lactam **20** (60%). In this process, we believe that CF_3SO_2Cl monochlorinated the carbanion derived from **18** to afford intermediate **19**. Then, the Cl-substituent in **19** was replaced *in situ* by the azetidinyl functionality to give **20**. Finally, removal of the *t*-Bu group from **20** with a catalytic amount of $(Bu_4N)ClO_4$ or $HClO_4$ in CF_3CO_2H and CH_2Cl_2 afforded the target isodethiaoxacephem **21** in 80% yield.

Utilization of the same synthetic strategy enabled us to accomplish the conversions **22** [9] → **23** → **24** → **25** → **26** and **27** [7] → **28** → **29** → **30** (*Scheme 4*). Isodethiaoxacephem **30** did not survive under the aforementioned conditions for removal of the *t*-Bu group.

Cephalosporins may possess different biological activity by activation of the β-lactam moiety with an electron-withdrawing group [10] [11]. Thus, we designed isodethiaoxacephem **33** in which an ester functionality is attached at C(3). For the synthesis of **33**, racemic diastereoisomeric β-lactams **31** [11] were treated with CF_3SO_2Cl in Et_3N and CH_2Cl_2, and then *in situ* with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at reflux temperature to give bicyclic β-lactam **32** in 60% overall yield (*Scheme 5*). Hydrogenolysis of **32** in the presence of $PdCl_2$ in AcOEt at 50 psi afforded isodethiaoxacephem **33** in 70% yield.

Scheme 4



(±)-**4** X = O
(±)-**22** X = S
(±)-**27** X = NH

(±)-**18** X = O
(±)-**23** X = S
(±)-**28** X = NH

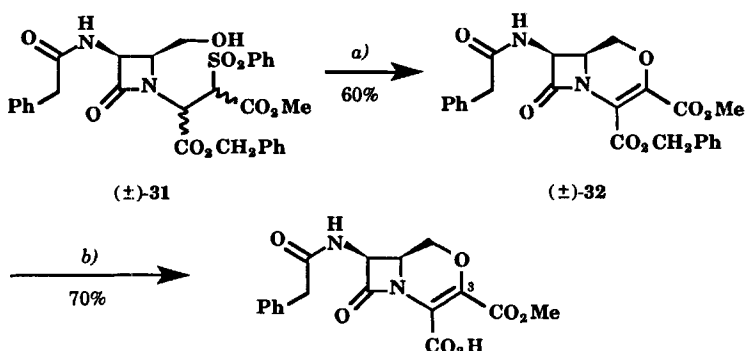
19 X = O
24 X = S
29 X = NH

(±)-**20** X = O
(±)-**25** X = S
(±)-**30** X = NH

(±)-**21** X = O
(±)-**26** X = S

a) $ClCOCH_2CO_2Bu^t$, pyridine, CH_2Cl_2; 40% for **4** → **18**; 58% for **22** → **23**; 70% for **27** → **28**. *b*) CF_3SO_2Cl, Et_3N, CH_2Cl_2; 60% for **18** → **20**; 70% for **23** → **25**; 46% for **28** → **30**. *c*) $(Bu_4N)ClO_4$, CF_3CO_2H, CH_2Cl_2; 80% for **20** → **21**; 85% for **25** → **26**.

Scheme 5



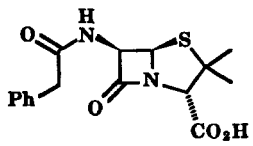
(±)-**31**

(±)-**32**

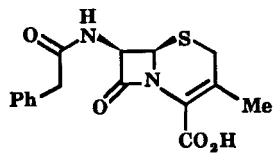
(±)-**33**

a) 1. CF_3SO_2Cl, Et_3N, CH_2Cl_2; 2. DBU.
b) H_2 (50 psi), $PdCl_2$, AcOEt.

Biological Activity of Isodethiaoxacephems 3, 21, and 33, and of Isocephem 26. – We tested the biological activity of the synthesized β-lactams **3**, **21**, **26**, and **33** as well as of naturally occurring penicillin **34** and cephalosporin **35** *in vitro* against five pathogenic microorganisms [12] up to a level as high as 128 μg/ml (*Table*). Our synthetic new β-lactams were in racemic form, whereas natural products **34** and **35** are single enantiomers [13]. Thus, only one half of the minimal inhibitory concentrations would be necessary for the desired single enantiomers of **3**, **21**, **26**, and **33**.



(+)-**34**



(+)-**35**

Table. *Biological Activities of Synthetic β-Lactams (±)-***3**, *(±)-***21**, *(±)-***26**, *and (±)-***33**, *As Well As of Natural Products (+)-***34** *and (+)-***35**

	Minimal inhibitory concentration [μg/ml]				
	S. aureus FDA 209P	*E. coli* ATCC 39188	*S. typhi* O-901	*Ps. aeruginosa* 1101-75	*K. pneumoniae* NCTC 418
(±)-**3**	15.00	70.85	[a])	[a])	98.00
(±)-**21**	12.50	65.60	[a])	[a])	85.50
(±)-**26**	25.49	98.63	[a])	[a])	[a])
(±)-**33**	0.03	0.56	3.94	15.89	0.47
(+)-**34**	0.40	2.30	[a])	[a])	[a])
(+)-**35**	0.64	13.13	24.50	100.0	2.98

[a]) Not active up to 128 μg/ml.

Isodethiaoxacephems **3** and **21** as well as isocephem **26** showed low antimicrobial activity. Isodethiaoxacephem **33**, in contrast, exhibited pronounced antimicrobial activity. Isodethiaoxacephem **33** bears a COOMe group at C(3), whereas an OH group exists in the same position in compounds **3** and **21**. Thus 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 [10] [11].

For financial support, we thank the *National Science Council of Republic of China* (research grants NSC 85-2113-M007-023 and 85-2311-B001-065) and *Academia Sinica*.

Experimental Part

General. See [11]. Column chromatography (CC): *Merck* silica gel *60* (230–400 mesh ASTM) packed in glass column (35 g of silica gel/gram of crude material).

*(±)-Benzyl [*cis*-4-Oxo-3-(2-phenoxyacetamido)azetidin-2-yl]methyl Propanedioate* (**5**). Pyridine (4.80 g, 60.7 mmol) was added to a soln. of *cis*-3-(2-phenoxyacetamido)-4-(hydroxymethyl)azetidin-2-one (**4**; 2.50 g, 9.99 mmol) in CH_2Cl_2 (40 ml) at 25°. Benzyl (chloroformyl)acetate (2.13 g, 9.99 mmol) in CH_2Cl_2 (10 ml) was then added and the soln. stirred at 25° for 1.5 h, washed with 5% aq. $NaHCO_3$ soln. (70 ml) and H_2O (100 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, CH_2Cl_2/AcOEt 1:1): 1.79 g (42%) of **5**. Oil. IR (CH_2Cl_2): 3450–3340 (2 NH), 1776 (β-lactam), 1750–1730 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.87–4.03 (*m*, H–N(1), H–C(2), CH_2–C(2)); 4.05 (*s*, $COCH_2CO$); 4.33 (*s*, OCH_2CO); 5.12 (*s*, $PhCH_2O$); 5.24 (*dd*, J = 5.0, 8.0, H–C(3)); 6.16 (*d*, J = 8.0, NH); 7.31–7.60 (*m*, 2 Ph). Anal. calc. for $C_{22}H_{22}N_2O_7$ (426.22): C 61.97, H 5.20, N 6.57; found: C 61.94, H 5.20, N 6.61.

(±)-Benzyl (2RS,6RS,7RS)- and (2RS,6SR,7SR)-2-Chloro-3,8-dioxo-7-(2-phenoxyacetamido)-4-oxa-1-azabicyclo[4.2.0]octane-2-carboxylates (**7**; diastereoisomer mixture). To a soln. of **5** (4.26 g, 9.99 mmol) in CH_2Cl_2 (60 ml) and Et_3N (2.10 g, 20.8 mmol), CF_3SO_2Cl (1.72 g, 10.2 mmol) in CH_2Cl_2 (8.0 ml) was added dropwise at r.t. After 1.5 h, the soln. was washed with H_2O (100 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, CH_2Cl_2/$CHCl_3$ 1:1): 0.60 g (13%) of **7**. Foam. IR (CH_2Cl_2): 3410 (NH), 1796 (β-lactam), 1750–1730 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.67–4.10 (*m*, CH_2(5)); 4.33 (*s*, OCH_2CO); 4.35–4.53 (*m*, H–C(6)); 5.16 (br. *s*, $PhCH_2O$); 5.30 (*dd*, *J* = 5.0, 9.5, H–C(7)); 6.43 (br., NH); 7.30–7.59 (*m*, 2 Ph). Anal. calc. for $C_{22}H_{19}ClN_2O_7$ (458.57): C 57.59, H 4.17, Cl 7.73, N 6.11; found: C 57.82, H 4.25, Cl 7.92, N 6.17.

(±)-Benzyl [cis-1-(2,4-Dimethoxybenzyl)-4-oxo-3-(2-phenoxyacetamido)azetidin-2-yl]methyl 2,2-Dichloropropanedioate (**11**). To a soln. of **9** (1.92 g, 3.33 mmol) in CH_2Cl_2 (35 ml) and Et_3N (0.67 g, 6.6 mmol), CF_3SO_2Cl (1.11 g, 6.58 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise at r.t. After 1.5 h, the soln. was washed with H_2O (50 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, $CHCl_3$): 1.93 g (90%) of **11**. Oil. IR (CH_2Cl_2): 3410 (NH), 1777 (β-lactam), 1735 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.67 (*s*, 2 Me); 3.90–4.35 (*m*, H–C(2), CH_2–C(2)); 4.31 (*s*, OCH_2CO); 4.66 (*q*, *J* = 6.8, CH_2N); 5.14 (*s*, CH_2O); 5.16 (*dd*, *J* = 5.0, 8.0, H–C(3)); 6.33 (*d*, *J* = 8.0, NH); 6.92–7.65 (*m*, 2 Ph, C_6H_3). Anal. calc. for $C_{31}H_{30}Cl_2N_2O_9$ (645.32): C 57.68, H 4.68, Cl 10.98, N 4.34; found: C 57.62, H 4.59, Cl 11.11, N 4.43.

Dibenzyl 2,2-Dichloropropanedioate (**16**). To a soln. of dibenzyl propanedioate (**13**; 284 mg, 0.999 mmol) in CH_2Cl_2 (20 ml), Et_3N (203 mg, 2.01 mmol) and CF_3SO_2Cl (337 mg, 2.00 mmol) in CH_2Cl_2 (2.0 ml) were added dropwise at r.t. After 1 h, the soln. was washed with H_2O (20 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, CH_2Cl_2): 335 mg (95%) of **16**. Foam. IR (CH_2Cl_2): 1755 (ester). ^{1}H-NMR ($CDCl_3$): 5.20 (*s*, 2 CH_2O); 7.21 (*s*, 2 Ph). Anal. calc. for $C_{17}H_{14}Cl_2O_4$ (353.26): C 57.81, H 4.00, Cl 20.08; found: C 57.78, H 3.99, Cl 20.13.

Benzyl tert-*Butyl 2-Chloropropanedioate* (**17**). As described for **16**, from **14** (250 mg, 0.999 mmol), Et_3N (203 mg, 2.01 mmol), and CF_3SO_2Cl (337 mg, 2.00 mmol): 213 mg (75%) of **17**. Oil. IR (CH_2Cl_2): 1760–1745 (ester). ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, *t*-Bu); 5.09 (*s*, CH_2O); 5.22 (*s*, CH); 7.19 (*s*, Ph). Anal. calc. for $C_{14}H_{17}ClO_4$ (284.56): C 59.06, H 6.02, Cl 12.45; found: C 59.15, H 5.99, Cl 12.50.

*(±)-*tert-*Butyl [*cis*-4-Oxo-3-(2-phenoxyacetamido)azetidin-2-yl]methyl Propanedioate* (**18**). As described for **5**, from **4** (2.50 g, 9.99 mmol), pyridine (4.80 g, 60.7 mmol), and *tert*-butyl (chloroformyl)acetate (1.79 g, 9.99 mmol): 1.57 g (40%) of **18**. Oil. IR (CH_2Cl_2): 3450–3340 (2 NH), 1776 (β-lactam), 1750–1730 (ester), 1681 (amide). ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, *t*-Bu); 3.88–4.06 (*m*, H–N(1), H–C(2), CH_2–C(2)); 4.15 (*s*, $COCH_2CO$); 4.35 (*s*, OCH_2CO); 5.22 (*dd*, *J* = 5.0, 8.0, H–C(3)); 6.15 (br., NH); 7.31–7.59 (*m*, Ph). Anal. calc. for $C_{19}H_{24}N_2O_7$ (392.21): C 58.16, H 6.16, N 7.14; found: C 58.19, H 6.22, N 7.21.

(±) tert-*Butyl 3-{[*cis*-4-Oxo-3-(2-phenoxyacetamido)azetidin-2-yl]methylthio}-3-oxopropanoate* (**23**). As described for **5**, from **22** (2.66 g, 9.99 mmol), pyridine (4.80 g, 60.7 mmol), and *tert*-butyl (chloroformyl)acetate (1.79 g, 9.99 mmol): 2.37 g (58%) of **23**. Foam. IR (CH_2Cl_2): 3450–3300 (2 NH), 1775 (β-lactam), 1745 (ester), 1730 (thioester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, *t*-Bu); 2.78–3.20 (*m*, CH_2S); 3.86 (*s*, $COCH_2CO$); 3.94–4.22 (*m*, H–N(1), H–C(2)); 4.45 (*s*, OCH_2CO); 4.91–5.43 (*dd*, *J* = 5.0, 8.0, H–C(3)); 6.18 (*d*, *J* = 8.0, NH); 7.35–7.60 (*m*, Ph). Anal. calc. for $C_{19}H_{24}N_2O_6S$ (408.38): C 55.87, H 5.92, N 6.86, S 7.85; found: C 55.82, H 5.90, N 6.89, S 7.79.

*(±)-*tert-*Butyl 3-{{[*cis*-4-Oxo-3-(2-phenoxyacetamido)azetidin-2-yl]methyl}amino}-3-oxopropanoate* (**28**). Pyridine (4.80 g, 60.7 mmol) was added to a soln. of **27** (2.49 g, 9.99 mmol) in CH_2Cl_2 (50 ml) at 0°, followed by *tert*-butyl (chloroformyl)acetate (1.79 g, 9.99 mmol) in CH_2Cl_2 (5.0 ml). The soln. was stirred at 0° for 2 h, washed with 5% aq. $NaHCO_3$ soln. (50 ml) and H_2O (100 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, $CHCl_3$/AcOEt 1:1): 2.74 g (70%) of **28**. Foam. IR (CH_2Cl_2): 3460–3220 (3 NH), 1774 (β-lactam), 1740 (ester), 1685–1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, *t*-Bu); 3.38–3.52 (*m*, CH_2N); 3.95–4.12 (*m*, H–N(1), H–C(2)); 3.99 (*s*, $COCH_2CO$); 4.42 (*s*, OCH_2CO); 4.82–5.28 (*dd*, *J* = 5.0, 8.0, H–C(3)); 6.15 (*d*, *J* = 8.0, NH–C(3)); 7.30–7.59 (*m*, Ph, NH). Anal. calc. for $C_{19}H_{25}N_3O_6$ (391.23): C 58.30, H 6.44, N 10.74; found: C 58.22, H 6.40, N 10.85.

*(±)-*tert-*Butyl (6RS,7RS)-3-Hydroxy-8-oxo-7-(2-phenoxyacetamido)-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate* (**20**). As described for **11**, from **18** (3.92 g, 9.99 mmol), Et_3N (2.02 g, 20.0 mmol), and CF_3SO_2Cl (1.69 g, 10.0 mmol): 2.34 g (60%) of **20**. Foam. IR (CH_2Cl_2): 3510–3200 (NH, OH), 1790 (β-lactam), 1755 (ester), 1735 (C=C), 1682 (amide). ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, *t*-Bu); 2.38 (br., OH); 3.60–4.00 (*m*, CH_2(5)); 4.23–4.89 (*m*, H–C(6), H–C(7)); 4.44 (*s*, OCH_2CO); 6.31 (*d*, *J* = 8.0, NH); 7.35–7.62 (*m*, Ph). Anal. calc. for $C_{19}H_{22}N_2O_7$ (390.21): C 58.46, H 5.68, N 7.18; found: C 58.40, H 5.48, N 7.20.

*(±)-*tert-*Butyl (6RS,7RS)-3-Hydroxy-8-oxo-7-(2-phenoxyacetamido)-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate* (**25**). As described for **11**, from **23** (4.08 g, 9.99 mmol), Et_3N (2.02 g, 20.0 mmol), and CF_3SO_2Cl (1.69 g, 10.0 mmol). CC (silica gel, $CHCl_3$/AcOEt 1:2): 2.84 g (70%) of **25**. Foam. IR (CH_2Cl_2): 3400–3200 (NH, OH), 1787 (β-lactam), 1750 (ester), 1715 (C=C), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, *t*-Bu); 2.45 (br., OH); 2.61–3.06 (*m*, CH_2S); 4.20–4.44 (*m*, H–C(6)); 4.45 (*s*, OCH_2CO); 4.58–5.10 (*dd*, *J* = 5.0, 8.0, H–C(7)); 6.40 (*d*,

J = 8.0, NH); 7.35–7.65 (*m*, Ph). Anal. calc. for $C_{19}H_{22}N_2O_6S$ (406.37): C 56.15, H 5.46, N 6.89, S 7.89; found: C 56.21, H 5.45, N 6.93, S 7.77.

*(±)-*tert*-Butyl (6RS,7SR)-3-Hydroxy-8-oxo-7-(2-phenoxyacetamido)-1,4-diazabicyclo[4.2.0]oct-2-ene-2-carboxylate* (**30**). As described for **11**, from **28** (3.91 g, 9.99 mmol), Et_3N (2.02 g, 20.0 mmol), and CF_3SO_2Cl (1.69 g, 10.0 mmol). CC (silica gel, AcOEt): 1.79 g (46%) of **30**. Foam. IR (CH_2Cl_2): 3500–3200 (2 NH, OH), 1788 (β-lactam), 1749 (ester), 1725 (C=C), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, *t*-Bu); 2.68, 2.80 (2 br. *s*, NH, OH); 3.22–3.45 (*m*, CH_2N); 4.18–4.44 (*m*, H–C(6)); 4.43 (*s*, OCH_2CO); 4.60–5.08 (*dd*, J = 4.5, 8.0, H–C(7)); 6.41 (*d*, J = 8.0, NH–C(7)); 7.35–7.60 (*m*, Ph). Anal. calc. for $C_{19}H_{23}N_3O_6$ (389.21): C 58.60, H 5.95, N 10.79; found: C 58.49, H 5.97, N 10.75.

(±)-(6RS,7RS)-3-Hydroxy-8-oxo-7-(2-phenoxyacetamido)-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (**21**). To a soln. of **20** (391 mg, 1.00 mmol) in CH_2Cl_2 (2.0 ml), CF_3CO_2H/CH_2Cl_2 1:2 (10 ml) was added dropwise at 0–5° within 5 min. A trace amount of $(Bu_4N)ClO_4$ was then added and the soln. stirred at r.t. for 1 h and then evaporated. The crude product was crystallized from AcOEt/Et_2O 1:3.3: **21** (268 mg, 80%). M.p. 110–112°. IR (nujol): 3655–3150 (OH, NH, COOH), 1783 (β-lactam), 1725 (C=C), 1680 (amide). ^{1}H-NMR ((D_6)DMSO/$CDCl_3$/D_2O): 3.32–3.61 (*m*, CH_2(5)); 4.21–4.76 (*m*, H–C(6), H–C(7)); 4.42 (*s*, OCH_2CO); 7.34–7.59 (*m*, Ph). Anal. calc. for $C_{15}H_{14}N_2O_7$ (334.19): C 53.90, H 4.22, N 8.38; found: C 53.66, H 4.28, N 8.49.

(±)-(6RS,7RS)-3-Hydroxy-8-oxo-7-(2-phenoxyacetamido)-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (**26**). As described for **21**, from **25** (406 mg, 0.999 mmol), CF_3CO_2H/CH_2Cl_2 1:2 (10 ml), and a trace amount of $(Bu_4N)ClO_4$: 297 mg (85%) of **26**. M.p. 133–135°. IR (nujol): 3645–3155 (OH, NH, COOH), 1781 (β-lactam), 1705 (C=C), 1680 (amide). ^{1}H-NMR ((D_6)DMSO/$CDCl_3$/D_2O): 2.55–2.99 (*m*, CH_2S); 4.17–4.85 (*m*, H–C(6), H–C(7)); 4.44 (*s*, OCH_2CO); 7.36–7.62 (*m*, Ph). Anal. calc. for $C_{15}H_{14}N_2O_6S$ (350.32): C 51.43, H 4.03, N 8.00, S 9.15; found: C 51.45, H 3.81, N 8.12, S 9.25.

(±)-2-Benzyl 3-Methyl (6RS,7RS)-8-Oxo-7-(2-phenoxyacetamido)-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate (**32**). To a soln. of **31** (0.59 g, 1.5 mmol) in CH_2Cl_2 (20 ml) and Et_3N (0.15 g, 1.5 mmol) CF_3SO_2Cl (0.25 g, 1.5 mmol) in CH_2Cl_2 (2.0 ml) was added at 0° within 5 min. The mixture was allowed to warm up to r.t. while being stirred for 1 h. Then DBU (0.36 g, 2.35 mmol) was added and the soln. heated at reflux for 2 h. After cooling and addition of CH_2Cl_2 (40 ml), the mixture was washed with H_2O (50 ml), dried ($MgSO_4$), and evaporated. CC (silica gel, $CHCl_3$): 0.27 g (60%) of **32**. Foam. IR (CH_2Cl_2): 3415 (NH), 1795 (β-lactam), 1750 (esters), 1732 (C=C), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.54 (*s*, CH_2CO); 3.70–4.40 (*m*, CH_2(5)); 3.96 (*s*, MeO); 4.42 (*m*, H–C(6)); 5.12 (*s*, CH_2O); 5.13–5.50 (*dd*, J = 4.8, 9.0, H–C(7)); 6.90 (br., NH); 7.25, 7.35 (2*s*, Ph). Anal. calc. for $C_{24}H_{22}N_2O_7$ (450.32): C 64.00, H 4.89, N 6.22; found: C 64.04, H 4.92, N 6.29.

(±)-3-Methyl 2-Hydrogen (6RS,7RS)-8-Oxo-7-(2-phenylacetamido)-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2,3-dicarboxylate (**33**). Compound **32** (0.45 g, 1.0 mmol) in AcOEt (50 ml) was hydrogenated for 6 h under 50 psi of H_2 in the presence of $PdCl_2$ (0.20 g, 1.1 mmol). After filtration and evaporation, the crude foam was chromatographed (silica gel, AcOEt): 0.25 g (70%) of **33**. M.p. 144–145°. IR (nujol): 3652–3050 (NH, COOH), 1792 (β-lactam), 1738 (ester), 1715 (acid), 1708 (C=C), 1678 (amide). ^{1}H-NMR ((D_6)DMSO/$CDCl_3$/D_2O): 3.50 (*s*, CH_2CO); 3.68–4.41 (*m*, CH_2(5)); 3.99 (*s*, MeO); 4.42 (*m*, H–C(6)); 5.02 (*d*, J = 5.0, H–C(7)); 7.40 (*s*, Ph). Anal. calc. for $C_{17}H_{16}N_2O_7$ (360.33): C 56.67, H 4.48, N 7.77; found: C 56.51, H 4.50, N 7.89.

REFERENCES

[1] G.H. Hakimelahi, A.A. Moosavi-Movahedi, M.M. Sadeghi, S.-C. Tsay, J.H. Hwu, *J. Med. Chem.* **1995,** *38,* 4648.

[2] G.H. Hakimelahi, G. Just, *Tetrahedron Lett.* **1979,** 3643.

[3] G.H. Hakimelahi, G. Just, *Tetrahedron Lett.* **1979,** 3645.

[4] G.H. Hakimelahi, A. Khalafi-Nezhad, *Helv. Chim. Acta* **1984,** *67,* 18.

[5] G.V. Kaiser, S. Kukolja, 'Cephalosporins and Penicillins, Chemistry and Biology', Ed. E.H. Flynn, Academic Press, New York, 1972.

[6] T.W. Doyle, B. Belleau, B.Y. Luh, T.T. Conway, M. Menard, J.L. Douglas, D.T.W. Chu, G. Lim, L.R. Morris, P. Rivest, M. Casey, *Can. J. Chem.* **1977,** *55,* 484.

[7] W.F. Huffman, K.G. Holden, T.F. Buckley III, J.G. Gleason, L. Wu, *J. Am. Chem. Soc.* **1977,** *99,* 2352.

[8] A. Khorshidi, Ph.D. Thesis, Isfahan University, 1984.

[9] D.B. Bryan, R.F. Hall, K.G. Holden, W.F. Huffman, J.G. Gleason, *J. Am. Chem. Soc.* **1977,** *99,* 2353.

[10] G.H. Hakimelahi, M. J. Shiao, J.R. Hwu, H. Davari, *Helv. Chim. Acta* **1992,** *75,* 1840.

[11] J.R. Hwu, L.L. Lai, G.H. Hakimelahi, H. Davari, *Helv. Chim. Acta* **1994,** *77,* 1037.

[12] T.A. Pursiano, M. Misiek, F. Leitner, K.E. Price, *Antimicrob. Agents Chemother.* **1973,** *3,* 33.

[13] J.C. Sheehan, K.R. Henry-Logan, *J. Am. Chem. Soc.* **1959,** *81,* 3089.