β-Lactams. 3. Asymmetric Total Synthesis of New Non-Natural 1β-Methylcarbapenems Exhibiting Strong Antimicrobial Activities and Stability against Human Renal Dehydropeptidase-I

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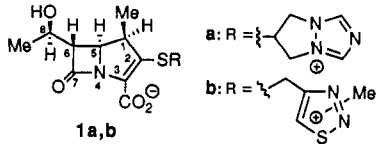
Asymmetric synthesis of **11**, the precursor to chiral (3*R*,4*R*)-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (**3**) was achieved by utilizing a highly diastereoselective aldol-type reaction of acetaldehyde and the chiral tin(II) enolate of **5**. Similar diastereoselective alkylations of chiral and achiral tin(II) enolates **13a–d** with chiral **3** were also performed to obtain the desired alkylated azetidin-2-ones (**17a–d**). Compounds **17a,b** were successfully converted to new, non-natural 1β-methylcarbapenems **1a** and **1b**, which exhibited strong and wide-ranging antimicrobial activities and excellent stability against human renal dehydropeptidase-I.

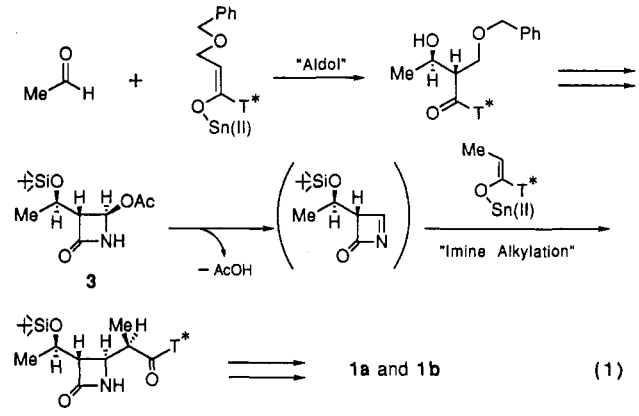
In 1980, a Merck Sharp & Dohme research group published a stereoselective total synthesis of (+)-thienamycin, a fascinating natural β-lactam antibiotic.[2] This synthesis established an excellent synthetic methodology for carbapenems. Since then, there have been numerous reports related to the synthesis of thienamycin and modified thienamycins.[3,4] 1β-Methylcarbapenems in particular attracted attention in the development of new, non-natural carbapenems because they possess strong stability against renal dehydropeptidase-I maintaining the superior antibacterial activity of (+)-thienamycin.[5] The Nagao and Lederle (Japan) groups,[6] the Fuentes group,[7] and other groups[4,8] have each reported a highly diastereoselective alkylation method useful for 1β-methylcarbapenem synthesis.

In the preceding papers, we reported on highly diastereoselective alkylations of 4-acetoxyazetidin-2-one[3a,6] and racemic (3*R**,4*R**)-3-[(1*R**)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one[3b,6] and the utilization of the reaction products for the preparation of chiral key intermediates for the synthesis of carbapenems.[3,6,9] Continuing our series of studies on β-lactam syntheses, we now describe in detail a practical method useful for carbapenem synthesis[3a] and its application to the asymmetric total synthesis of new, non-natural 1β-methylcarbapenems **1a** and **1b**. These particular 1β-methylcarbapenems,



1a,b

bearing a heterocyclic quartenary ammonium as the RS group at C-2, are expected to exhibit excellent antimicrobial activity. Especially, the bicyclic triazolium moiety of **1a** can be regarded as a prochiral σ-symmetric heterocycle by delocalization of the π-electron system. A synthetic strategy for **1a** and **1b** using C-4-chiral thiazolidines was designed as shown in eq 1. In the synthesis of 1β-



(1)

methylcarbapenems, the construction of four consecutive asymmetric carbon atoms (i.e., C1, C5, C6, and C8) is intriguing. We adopted an asymmetric, aldol-type reaction[10] of acetaldehyde with a chiral tin(II) enolate for C6–C8 bond formation, which leads to optically active (3*R*,4*R*)-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (**3**). An efficient, diastereoselective imine alkylation[6,9–11] between another chiral tin(II) enolate and the chiral cyclic acylimine obtained *in situ* from **3** was adopted for C1–C5 bond formation. Utilization of our C-4-chiral thiazolidine reagents for construction of all four asymmetric centers in **1a,b** is the remarkable feature in this 1β-methylcarbapenem synthesis.

3-[3-(Benzyloxy)propionyl]-(4*R*)-isopropyl-1,3-thiazolidine-2-thione (**5**), obtained by the reaction of 3-(benzyloxy)propionic acid (**4**) and (4*R*)-isopropyl-1,3-thiazoli-

(1) (a) The University of Tokushima. (b) Lederle (Japan), Ltd.
(2) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102* exit; 6161.
(3) (a) Nagao, Y.; Kumagai, T.; Nagase, Y. Tamai, S.; Inoue, Y.; Shiro, M. *J. Org. Chem.*, first of three papers in this issue. (b) Nagao, Y.; Nagase, Y.; Kumagai, T.; Kuramoto, Y.; Kobayashi, S.; Inoue, Y.; Taga, T.; Ikeda, H. *J. Org. Chem.*, second of three papers in this issue.
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(10) (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. (b) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211.
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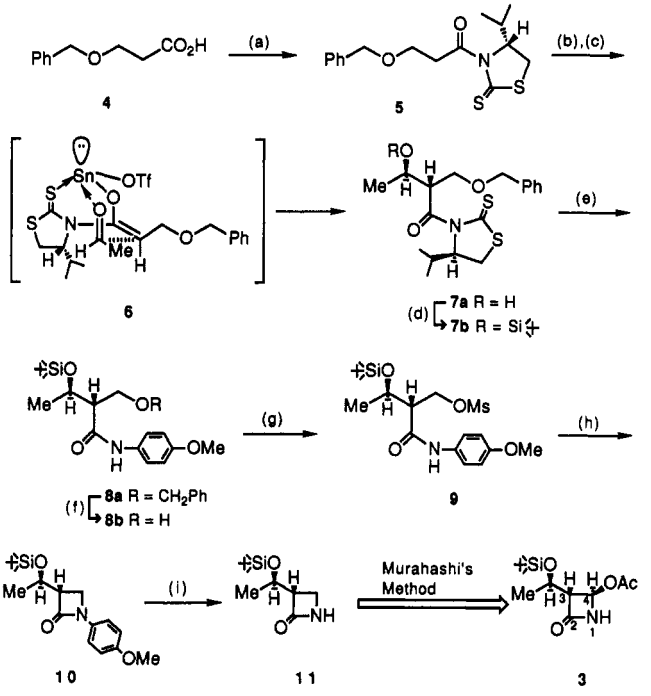
dine-2-thione, was treated with a suspension of tin(II) trifluoromethanesulfonate[12] and *N*-ethylpiperidine[12] in CH_2Cl_2 at −78 °C for 2 h. Excess acetaldehyde was added, and the mixture was stirred at −78 °C for 1 h to afford alcohol **7a** in 84% yield and in 94% diastereomeric excess by HPLC analysis. The stereochemistry of **7a** can be rationalized in terms of transition state **6**, in which acetaldehyde approaches the chiral tin(II) enolate from the less-hindered β-side, opposite the α-isopropyl group of the thiazolidine moiety, to form a chairlike six-membered ring.[10] In the chairlike six-membered ring, the methyl group of acetaldehyde is equatorial. After protection of the hydroxy group of **7a** with the TBDMS group, compound **7b** was submitted to aminolysis with *p*-anisidine to give amide **8a** in 91% yield from **7a**.[13] Hydrogenolysis of the benzyloxy group of **8a** followed by mesylation gave compound **9** in high yield. Cyclization of amide **9** with NaH in 4:1 CH_2Cl_2–DMF proceeded well to give β-lactam **10** quantitatively.[14] Oxidative deprotection of the *p*-methoxyphenyl group of **10** with ceric ammonium nitrate[15] afforded known compound **11**[16] in 67% yield (Scheme I). Efficient conversion of **11** to chiral (3*R*,4*R*)-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (**3**) with $RuCl_3 \cdot nH_2O$ and peracetic acid has already been achieved by the Murahashi group.[17]

We have demonstrated that 3-acetyl-(4*S*)-ethyl-1,3-thiazolidine-2-thione is a matched partner in the alkylation reactions of chiral (3*R*,4*R*)-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (**3**).[3b] Thus, the chiral tin(II) enolates generated *in situ* by enolization of 3-propionyl-(4*S*)-ethyl(and isopropyl)-1,3-thiazolidine-2-thiones (**12a,b**) with tin(II) trifluoromethanesulfonate and *N*-ethylpiperidine were treated with chiral **3** in THF at 0 °C for 1 h. The reaction of **12a** and **3** followed by the usual workup afforded C-4-alkylated azetidin-2-ones **17a** and **18a** in a 90:10 ratio by HPLC analysis (Scheme II and Table I). Alkylation of **3** with **12b** gave a similar mixture of **17b** and **18b** (91:9). The alkylation of chiral **3** with 3-propionyl derivatives **17c,d** of achiral 1,3-thiazolidine-2-thiones has also been carried out.[18] Although the alkylation proceeded smoothly, the diastereoselectivities were poorer than those of the alkylations with C-4-chiral thiazolidines (see Table I).

The absolute configurations of the major products (**17a,b**) were determined by their chemical conversion to known compound **22**,[5a] a key intermediate for 1β-methylcarbapenem synthesis (see Scheme III). Compounds **17a** and **17b**, which both have an active amide structure, were treated with imidazole in MeCN at room temperature to form imidazolide **19**.[3,6,9] Compound **19** was submitted *in situ* to the decarboxylative Claisen-type condensation[2] to afford β-keto PNB ester **21** in 80% yield from **17a** and in 86% yield from **17b**. Elimination of the TBDMS group of **21** was readily done under acidic conditions to give compound **22**.[5a] The stereochemistry of the other major products (**17c,d**) was confirmed by comparison of the HPLC data with that of the compound derived from the dehydrative condensation reaction between 1,3-thiazolidine-2-thione (or 4,4-dimethyl-1,3-thiazolidine-2-thione)

Scheme I[a]



[a] Key: (a) (4*R*)-isopropyl-1,3-thiazolidine-2-thione, EtN=C=N-$(CH_2)_3N(CH_3)_2$·HCl, 4-(dimethylamino)pyridine, CH_2Cl_2, rt (86%); (b) $Sn(CF_3SO_3)_2$, *N*-ethylpiperidine, CH_2Cl_2, −78 °C; (c) MeCHO, CH_2Cl_2, −78 °C (84%); (d) TBDMSCl, imidazole, CH_2Cl_2, 0 °C (91%); (e) *p*-anisidine, CH_2Cl_2, rt (quant); (f) H_2 (4 atm), 10% Pd–C, 4:1 MeOH–AcOH, rt (91%); (g) MsCl, Et_3N, THF, 0 °C → rt (quant); (h) NaH, 4:1 CH_2Cl_2–DMF, rt (quant); (i) CAN, MeCN–H_2O, −15 °C (67%).

and carboxylic acid **20**. (Acid **20** was obtained by acidic hydrolysis of **19**.[13]) The absolute configuration of a minor C-4-alkylated product (**18a**) was determined by its chemical correlation with known compound **25**[5a] as depicted in Scheme IV. Compound **25** was prepared from **23**[3a] in the following manner. Methyl ester **24**, obtained by methanolysis of **23**, was treated with 2 mol equiv of LDA to form the enolate. The enolate was treated with MeI to give methylated product **25**.[5a] Alkaline hydrolysis of **25** and subsequent dehydrative condensation of the resultant carboxylic acid **26** with (4*S*)-ethyl-1,3-thiazolidine-2-thione [(4*S*)-ETT] gave **18a**. The absolute configuration of **18c** was determined by its conversion to **25** under alkaline methanolysis conditions (Scheme IV). The stereochemistry of the other minor alkylation products (**18b,d**) was confirmed by the fact that their HPLC retention times were identical to those of the compounds prepared by dehydrative condensation of carboxylic acid **26** and the corresponding 1,3-thiazolidine-2-thiones.

Because epimerization of the newly formed β-methyl group of the major products **17a–d** has never been observed under the alkylation conditions described above, the stereochemistry of major products **17a–d** and minor products **18a–d** can be explained as follows. Major products **17a–d** could be obtained from the corresponding *Z*-tin(II) enolates **13a–d**[19] *via* six-membered, chelated transition states **15a–d**. To form transition states **15a,b**, the chiral acylimine derived from **3** must approach the

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(13) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Chem. Pharm. Bull.* **1984**, *32*, 2687.
(14) *Kokaltokkyokoho* (Japanese Patent) 1990-108664.
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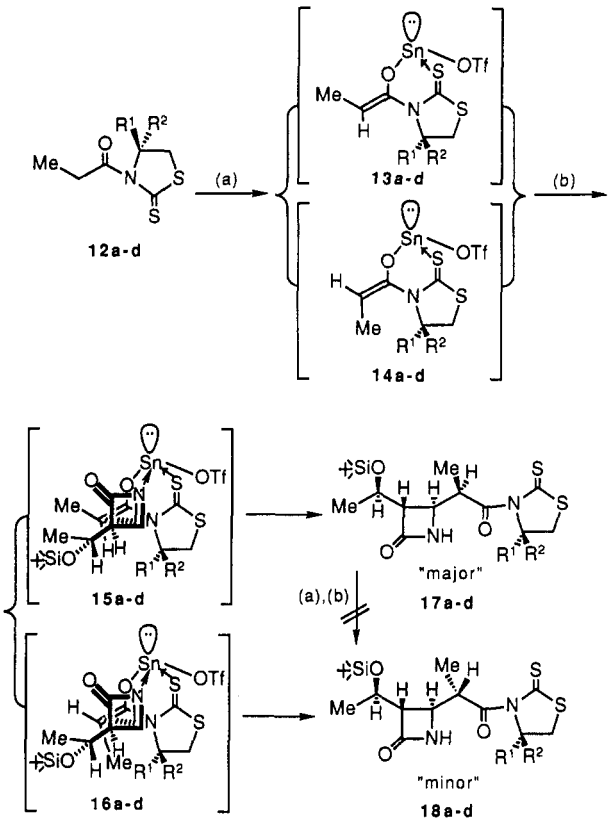
(17) Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820.
(18) After publication of our previous paper (see ref 2a), similar results were published by another group. See ref 8b.

(19) ^1H NMR (400-MHz) analysis of the tin(II) enolates of **12b** in THF-d_8 at 0 °C: δ 1.76 (d, *J* = 6.8 Hz, allylic Me of the *Z*-enolate), 1.62 (d, *J* = 6.8 Hz, allylic Me of the *E*-enolate), 4.49 (q, *J* = 6.8 Hz, olefinic H of the *Z*-enolate), and 5.05 (br q, *J* = 6.8 Hz, olefinic H of the *E*-enolate). Assignment of the signals was confirmed by decoupling experiments.

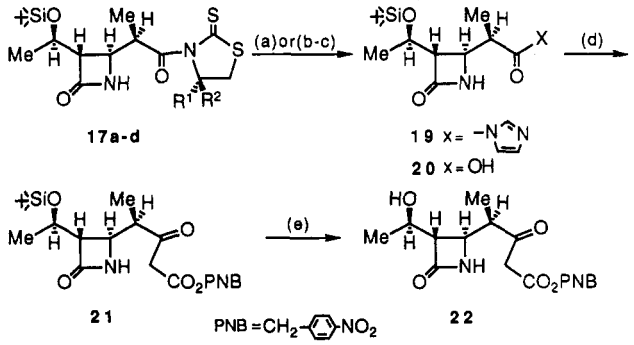
Scheme II[a]



a: R^1=Et,R^2=H; *b*: R^1=*i*-Pr,R^2=H; *c*: R^1=R^2=H; *d*: R^1=R^2=Me

[a] Key: (a) $Sn(CF_3SO_3)_2$, *N*-ethylpiperidine, THF, −40 °C; (b) compound **3**, THF, 0 °C.

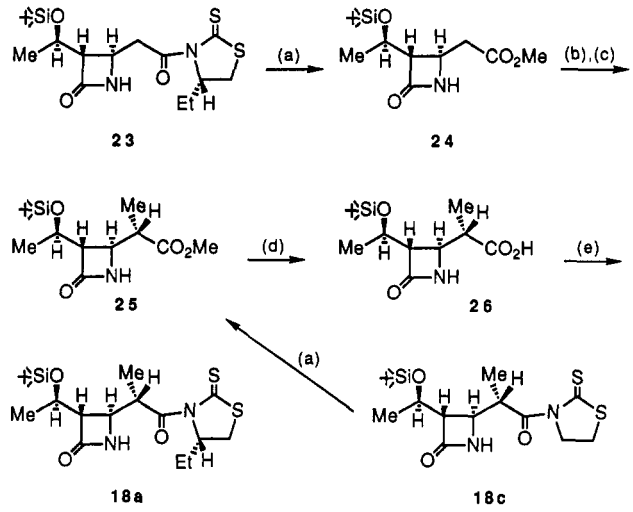
Scheme III[a]



[a] Key: (a) imidazole, MeCN, rt; (b) imidazole, THF, rt; (c) 10% citric acid, rt (**20**: 80%); (d) $Mg(O_2CCH_2CO_2PNB)_2$, MeCN, 60 °C (from **17a** via **19**: 80%), (from **17b** via **19**: 86%); (e) concd HCl, MeOH, rt (95%).

chiral *Z*-tin(II) enolates **13a,b** from the less hindered β-side (α-R^1 = Et, *i*-Pr). To form transition states **15c,d**, the achiral *Z*-tin(II) enolates **13c,d**[20] must approach the chiral acylimine from the less hindered α-side, opposite the β-(silyloxy)ethyl group at C-3 of the β-lactam. In a similar process, minor products (**18a–d**) could be formed *via* transition states **16a–d** involving *E*-tin(II) enolates **14a–d**[19,20] and the acylimine obtained *in situ* from **3**. Further

Scheme IV[a]



[a] Key: (a) K_2CO_3, MeOH, rt (77%: from **23** to **24**) (60%: from **18c** to **25**); (b) LDA, THF–HMPA, −78 °C; (c) MeI, −78 °C (36%); (d) 2.5 N NaOH, aqueous MeOH, rt → 50 °C (63%); (e) (4*S*)-ethyl-1,3-thiazolidine-2-thione, $EtN{=}C{=}N(CH_2)_3N(CH_3)_2{\cdot}HCl$, 4-(dimethylamino)pyridine, CH_2Cl_2, rt (75%).

evidence for these mechanistic speculations was obtained when the substituents of the thiazolidine-2-thione group were changed. The bulkiness of the R^1 and/or R^2 group(s) of the thiazolidine-2-thione moieties affects the product ratios of major compounds **17a–d** and the minor compounds **18a–d** (see Table I). Thus, kinetic enolization giving *Z*-enolates **13a–d** and formation of rigid transition states such as **15a–d** seem to be essential to obtain the desired stereochemical outcome for alkylation of the cyclic acylimines. In our cases, a transition state leading to kinetic *Z*-enolization should be more stable than that leading to kinetic *E*-enolization because the latter bears severe steric repulsion between the methyl group and the R^1 and/or R^2 group(s) (see Figure 1).

Diazotization[2] of **22** with *p*-dodecylbenzenesulfonyl azide in the presence of Et_3N in MeCN gave diazo compound **27** in 90% yield. A solution of **27** in AcOEt was heated at 80 °C in the presence of rhodium(II) octanate[2] to give cyclization product **28**. Compound **28** was treated with diphenyl chlorophosphate and diisopropylethylamine in MeCN to afford a solution of (diphenylphosphono)oxy derivative **29**. Chromatographic purification of the residue obtained by evaporation afforded pure **29** as colorless needles in 80% yield (Scheme V). However, the MeCN solution of **29** could be used directly for the subsequent Michael-type reaction with thiols **30** and **32**. Thus, a solution of **29** was treated with 4-mercapto-*N*,*N*-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (**30**)[21] in the presence of diisopropylethylamine in MeCN to give thioether **31** in 75% yield. After hydrogenolysis of the PNZ and PNB groups of **31**, the resultant pyrazolidine compound was treated with ethyl formimidate hydrochloride in an alkaline solution to produce the desired triazolium carboxylate **1a**, in 44% yield from **31**, as a pale yellow, amorphous powder. *N*-Methyl-1,2,3-thiadiazolium carboxylate **1b** was prepared from **29** according to the following procedure. The 29-containing solution prepared as described above was dissolved in THF and 0.35 *M* phosphate buffer solution (pH 7.0). The mixture was treated with 4-(mercaptomethyl)-*N*-methyl-1,2,3-thiadiazolium trifluoromethanesulfonate (**32**)[22] in alkaline, aqueous methanol to

(20) ^{1}H NMR (400-MHz) analysis of the tin(II) enolates of **12c** in THF-d_8 at −40 °C: δ 1.76 (d, *J* = 6.3 Hz, allylic Me of the *Z*-enolate), 1.68 (d, *J* = 6.3 Hz, allylic Me of the *E*-enolate), 4.88 (br q, olefinic H of the *Z*-enolate, signals overlapped those of the thiazolidine SCH_2–), and 5.07 (br q, *J* = 6.3 Hz, olefinic H of the *E*-enolate). Assignment of the signals was confirmed by the decoupling experiments. Cf. Heathcock, C. *J. Org. Chem.* **1980**, *45*, 1066.

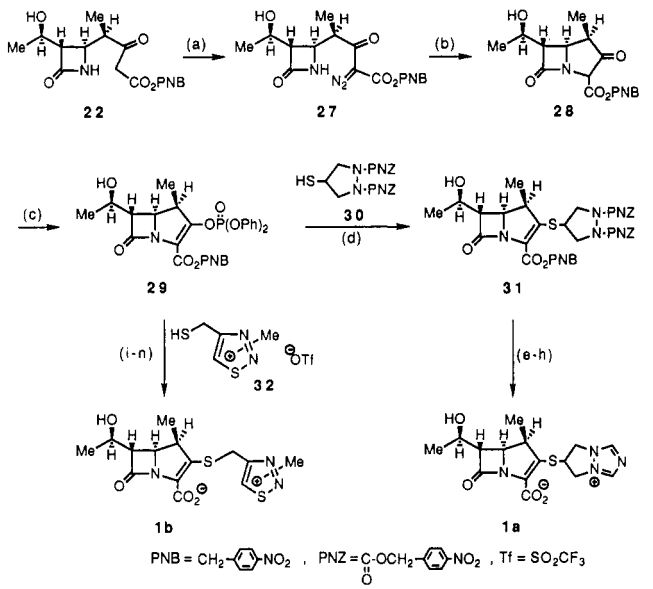
(21) *Kokaitokkyokoho* (Japanese Patent) 1989-25779.
(22) *Kokaitokkyokoho* (Japanese Patent) 1989-25778.

Table I. Diastereoselective Alkylation of Chiral 3-Substituted 4-Acetoxyazetidin-2-one 3 with Chiral and Achiral Tin(II) Enolates 13a–d

chiral tin(II) enolate	C4-alkylated azetidin-2-one	diastereomer excess,[a] %	isolated yield, %	mp, °C	$[\alpha]^{25}_D$ (c in $CHCl_3$)
13a	**17a**	80	80	85.5–86.5[b]	+233.9° (0.77)
13b	**17b**	82	74	131.5–132.5[b]	+295.7° (0.99)
13c	**17c**	60	73	109–109.5[b]	+26.1° (0.50)
13d	**17d**	70	80	165–166[c]	+55.4° (0.73)[d]

[a] Determined by HPLC analysis [column, Partisil-10 ODS 4.6-mm i.d. × 25 cm; eluent, MeCN–water; flow rate, 3.0 mL/min; detection, UV (305 nm)]. [b] Recrystallized from EtOAc–hexane. [c] Recrystallized from $CHCl_3$–hexane. [d] Determined at 26 °C.

Scheme V[a]



[a] Key: (a) *p*-dodecylbenzensulfonyl azide, Et_3N, MeCN, rt (90%); (b) rhodium(II) octanate, AcOEt, 80 °C; (c) diphenyl chlorophosphate, diisopropylethylamine, MeCN, −10 °C, (80% from **27**); (d) MeCN, diisopropylethylamine, −5 °C (75% from **27**); (e) H_2 (4 kg/cm^2), 10% Pd–C, THF–H_2O (1:1), rt; (f) ethyl formimidate hydrochloride, 0.1 M phosphate buffer (pH 7.0), 1 N NaOH, 0 °C; (g) HP-40 column, acetone–H_2O (3:97); (h) lyophylization (44% from **31**); (i) aqueous MeOH solution of **32** and 1 N NaOH; (j) THF–0.35 M phosphate buffer (pH 7.0), 0 °C; (k) 0.35 M phosphate buffer (pH 6.1); (l) Zn powder, 20 °C; (m) DOWEX 50W-X4 type column; (n) lyophylization (54% from **27**).

give the thiol adduct. The thiol adduct was submitted to hydrogenolysis with Zn powder to remove the PNB group to afford the desired product **1b**, in 54% yield from **27**, as a pale yellow, amorphous powder. Both (−)-1β-methylcarbapenems **1a** and **1b** exhibited potent and broad-spectrum antimicrobial activities,. as do thienamycin and imipenem.[23] Excellent stability of **1a** against human renal dehydropeptidase-I was observed.[23]

Experimental Section[24]

(4*R*)-3-[3-(Benzyloxy)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (5). A mixture of benzyl alcohol (9.0 g, 83.2 mmol) and Na (75 mg) was stirred at rt for 30 min under N_2 to give sodium benzyloxide. After addition of methyl acrylate (6.5 g, 75.5 mmol), the mixture was stirred at rt overnight and then treated with aqueous NH_4Cl. The mixture was extracted with AcOEt. The organic portion was washed with brine, dried, and evaporated *in vacuo*. To the residue were added ethanol (150 mL) and 1 N NaOH (91 mL). After being stirred at rt for 1 h, the reaction mixture was neutralized with 1 N HCl and then evaporated *in vacuo* to give an oily residue. A solution of the residue in AcOEt was washed with 1 N HCl, chilled water, and brine, dried, and evaporated *in vacuo* to give 3-(benzyloxy)propionic acid (8.2 g, 60%). To a solution of 3-(benzyloxy)propionic acid (**4**) (2.16 g, 12 mmol) in CH_2Cl_2 (50 mL) were added (4*R*)-isopropyl-1,3-thiazolidine-2-thione (1.93 g, 12 mmol), 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide hydrochloride (2.42 g, 12.6 mmol), and 4-(dimethylamino)pyridine (DMAP) (50 mg, 0.41 mmol). After being stirred at rt overnight, the reaction mixture was washed with water and brine, dried, and evaporated *in vacuo* to give an oily residue. The residue was purified by silica gel column chromatography (elution 5:1 hexane–AcOEt) to give amide **5** (3.32 g, 86%) as a yellow oil: $[\alpha]^{22}_D$ −227.7° (*c* 1.37, $CHCl_3$); IR (neat) 1690, 1370 cm^{-1}; ^{1}H NMR δ 0.97 (d, 3 H, *J* = 6.9 Hz), 1.05 (d, 3 H, *J* = 6.6 Hz), 2.31–2.43 (m, 1 H), 3.01 (dd, 1 H, *J* = 1.0, 11.2 Hz), 3.49 (dd, 1 H, *J* = 7.9, 11.2 Hz), 3.53–3.59 (m, 2 H), 3.76–3.91 (m, 2 H), 4.52, 4.57 (AB, each 1 H, *J* = 11.9 Hz), 5.14 (ddd, 1 H, *J* = 1.0, 7.9, 11.2, Hz); HRMS calcd for $C_{16}H_{21}NO_2S_2$ MW 323.1015, found *m/z* 323.0992 (M$^+$). Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.23; H, 6.67; N, 4.28.

(4*R*)-3-[(2*S*,3*R*)-3-Hydroxy-2-[(benzyloxy)methyl]butanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7a). To a solution of tin(II) trifluoromethanesulfonate[19] (11.61 g, 27.86 mmol) in CH_2Cl_2 (23 mL) at −78 °C was added a solution of *N*-ethylpiperidine (4.2 mL, 30.65 mmol) and compound **5** (3 g, 9.29 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at −78 °C for 30 min under N_2, and a solution of CH_3CHO (1.18 g, 26.86 mmol) in CH_2Cl_2 (3 mL) was added at −78 °C. After being stirred at −78 °C for 30 min, the reaction mixture was treated with 0.1 M phosphate buffer (pH 7.0, 50 mL). The precipitate was filtered through Celite, and the filtrate was washed with brine, dried, and evaporated *in vacuo* to give an oily residue. Chromatographic purification of the residue on a silica gel column with 2:1 hexane–AcOEt afforded compound **7a** (2.88 g, 84%) as a yellow oil: $[\alpha]^{22}_D$ −302.4° (*c* 1.91, $CHCl_3$); IR (neat) 3450, 1690 cm^{-1}; ^{1}H NMR δ 0.98 (d, 3 H, *J* = 6.9 Hz), 1.05 (d, 3 H), 1.26 (d, 3 H, *J* = 6.3 Hz), 2.33–2.40 (m, 1 H), 2.93 (dd, 1 H, *J* = 1.0, 11.6 Hz), 3.05 (d, 1 H, *J* = 3.0 Hz, disappeared upon treatment with D_2O), 3.27 (dd, 1 H, *J* = 7.6, 11.6 Hz), 3.78 (dd, 1 H, *J* = 5.0, 9.2 Hz), 3.91 (dd, 1 H, *J* = 7.9, 9.2 Hz), 4.30 (m, 1 H), 4.45, 4.51 (AB, each 1 H, *J* = 11.9 Hz), 5.01 (ddd, 1 H, *J* = 1.0, 6.6, 7.6 Hz), 5.12 (ddd, 1 H, *J* = 4.0, 5.0, 7.9 Hz); HRMS calcd for $C_{18}H_{25}NO_3S_2$ MW 367.1278, found *m/z* 367.1239 (M$^+$).

(4*R*)-3-[(2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[(benzyloxy)methyl]butanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7b). Imidazole (1.17 g, 17.24 mmol) was added to a solution of TBDMSCl (2.6 g, 17.24 mmol) in CH_2Cl_2 (14 mL),

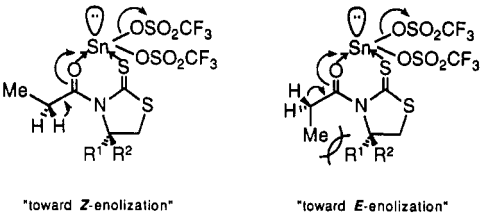


Figure 1. Plausible transition state for enolization of **12a–d**.

(23) (a) Reported by: Hikida, M.; Yoshida, Y.; Nishiki, K.; Furukawa, Y. and Mitsuhashi, S. 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, CA, Oct 24, 1988. (b) Hikida, M.; Nishiki, K.; Furukawa, Y.; Nishizawa, K.; Saito, I.; Kuwao, S. submitted for publication in *Antimicrob. Agents Chemother.*

(24) For general experimental procedures see the preceding articles. Fast atom bombardment mass spectra is abbreviated to FAB-MS; ^{1}H NMR spectra were determined at 270 MHz in $CDCl_3$ unless otherwise noted.

and then the mixture was stirred at 0 °C for 1 h. After addition of a solution of **7a** (2.88 g, 7.83 mmol) in CH_2Cl_2 (8.5 mL), the mixture was stirred overnight at 0 °C under N_2 and then submitted to the usual workup to give compound **7b** (3.42 g, 91%) as yellow needles: mp 68–69 °C (from hexane); $[\alpha]^{22}_D$ −247.1° (*c* 1.1, $CHCl_3$); IR (KBr) 1690 cm^{-1}; ^1H NMR δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H), 0.97 (d, 3 H, *J* = 6.9 Hz), 1.03 (d, 3 H, *J* = 6.6 Hz), 1.27 (d, 3 H, *J* = 6.3 Hz), 2.31–2.38 (m, 1 H), 2.86 (dd, 1 H, *J* = 1.0, 11.2 Hz), 3.15 (dd, 1 H, *J* = 7.6, 11.2 Hz), 3.82–3.88 (m, 2 H), 4.26 (qd, 1 H, *J* = 6.3, 6.9 Hz), 4.45 (s, 2 H), 4.94 (ddd, 1 H, *J* = 1.0, 7.6, 6.9 Hz), 4.99–5.06 m, 1 H); HRMS calcd for $C_{24}H_{39}NO_3S_2Si$ MW 481.2143, found *m/z* 481.2075 (M^+). Anal. Calcd for $C_{24}H_{39}NO_3S_2Si$: C, 59.83; H, 8.16; N, 2.91. Found: C, 59.53; H, 8.33; N, 2.74.

(2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[(benzyloxy)methyl]-*N*-(4-methoxyphenyl)butylamide (8a). *p*-Anisidine (920 mg, 7.47 mmol) was added to a solution of **7b** (3.0 g, 6.24 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at rt overnight. Evaporation of the solvent *in vacuo* followed by purification of the residue on a silica gel column with 5:1 hexane–AcOEt gave amide **8a** (2.76 g, quantitative yield) as colorless needles: mp 71–72 °C (from hexane); $[\alpha]^{22}_D$ +8.7° (*c* 2.16, $CHCl_3$); IR ($CHCl_3$) 3320, 1660, 1510 cm^{-1}; ^1H NMR δ 0.14 (s, 6 H), 0.94 (s, 9 H), 1.20 (d, 3 H, *J* = 6.3 Hz), 2.79 (ddd, 1 H, *J* = 5.3, 6.3, 6.9 Hz), 3.65 (dd, 1 H, *J* = 6.9, 9.6 Hz), 3.78 (s, 3 H), 3.95 (dd, 1 H, *J* = 6.3, 9.6 Hz), 4.21 (qd, 1 H, *J* = 6.3, 5.3 Hz), 4.51, 4.61 (AB, each 1 H, *J* = 11.9 Hz), 6.84 (d, 2 H, *J* = 9.2 Hz), 7.39 (d, 2 H, *J* = 9.2 Hz), 8.48 (br s, 1 H); HRMS calcd for $C_{25}H_{37}NO_4Si$ MW 443.2493, found *m/z* 443.2503 (M^+). Anal. Calcd for $C_{25}H_{37}NO_4Si$: C, 67.68; H, 8.41; N, 3.16. Found: C, 67.51; H, 8.51; N, 3.11.

(2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-(hydroxymethyl)-*N*-(4-methoxyphenyl)butylamide (8b). A solution of amide **8a** (1.0 g, 2.26 mmol) in 4:1 MeOH–AcOH (10 mL) was treated with 10% Pd–C (200 mg) impregnated with water at rt for 2 h under H_2 (4 atm). The catalyst was filtered off through Celite, and the filtrate was evaporated *in vacuo* to give an oily residue. Chromatographic purification of the residue on a silica gel column with 2:1 hexane–AcOEt gave alcohol **8b** (725 mg, 91%) as colorless needles: mp 110–111 °C (from hexane–AcOEt); $[\alpha]^{22}_D$ +11.9° (*c* 1.13, $CHCl_3$); IR (KBr) 3370, 2970, 1660, 1250 cm^{-1}; ^1H NMR δ 0.11 (s, 3 H), 0.13 (s, 3 H), 0.92 (s, 9 H), 1.27 (d, 3 H, *J* = 6.3 Hz), 2.64 (ddd, 1 H, *J* = 3.6, 3.6, 5.9 Hz), 3.49 (dd, 1 H, *J* = 3.6, 8.9 Hz, disappeared upon treatment with D_2O), 3.76 (dd, 1 H, *J* = 5.9, 11.5 Hz), 3.79 (s, 3 H), 4.03 (dd, 1 H, *J* = 3.6, 11.5 Hz), 4.26 (qd, 1 H, *J* = 6.3, 3.6 Hz), 6.86 (d, 2 H, *J* = 9.2 Hz), 7.42 (d, 2 H, *J* = 9.2 Hz), 8.91 (br s, 1 H); HRMS calcd for $C_{18}H_{31}NO_4Si$ MW 353.2023, found *m/z* 353.2006 (M^+). Anal. Calcd for $C_{18}H_{31}NO_4Si$: C, 61.15; H, 8.84; N, 3.96. Found: C, 60.78; H, 9.15; N, 3.72.

(2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[(methanesulfonyl)methyl]-*N*-(4-methoxyphenyl)butylamide (9). Methanesulfonyl chloride (0.4 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol) were added to a solution of alcohol **8b** (900 mg, 2.55 mmol) in THF (12 mL), and the mixture was stirred at 0 °C for 30 min under N_2. The reaction mixture was stirred at rt for an additional 1 h, an aqueous solution saturated with NH_4Cl was added, and the mixture was extracted with AcOEt. The extract was treated as usual to give methanesulfonyl ester **9** (1.1 g, quantitative yield) as a colorless oil: $[\alpha]^{22}_D$ +10.4° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 2960, 1650 cm^{-1}; ^1H NMR δ 0.15 (s, 3 H), 0.16 (s, 3 H), 0.95 (s, 9 H), 1.23 (d, 3 H, *J* = 6.3 Hz), 2.99 (ddd, 1 H, *J* = 4.6, 6.9, 7.3 Hz), 3.05 (s, 3 H), 3.79 (s, 3 H), 4.23 (qd, 1 H, *J* = 6.3, 4.6 Hz), 4.32 (dd, 1 H, *J* = 6.9, 10.6 Hz), 4.63 (dd, 1 H, *J* = 7.3, 10.6 Hz), 6.86 (d, 2 H, *J* = 8.9 Hz), 7.39 (d, 2 H, *J* = 8.9 Hz), 8.30 (br s, 1 H); HRMS calcd for $C_{19}H_{33}NO_6SSi$ MW 431.1799, found *m/z* 431.1800 (M^+).

(3*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-(4-methoxyphenyl)azetidin-2-one (10). A solution of compound **9** (1.0 g, 2.3 mmol) in 4:1 CH_2Cl_2–DMF (20 mL) was added dropwise over 30 min to a suspension of NaH (55% in mineral oil) (120 mg, 2.75 mmol) in 4:1 CH_2Cl_2–DMF (30 mL) at rt under N_2, and then the mixture was stirred for 1.5 h. The reaction mixture was washed with an aqueous solution saturated with NH_4Cl, water, and brine, dried, and evaporated *in vacuo* to give an oily residue. Chromatographic purification of the residue on a silica gel column with 3:1 hexane–AcOEt gave **10** (776 mg, quantitative yield) as colorless needles: mp 50–51 °C (from hexane); $[\alpha]^{22}_D$ −58.2° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.79 (s, 9 H), 1.24 (d, 3 H, *J* = 6.3 Hz), 3.26 (ddd, 1 H, *J* = 2.6, 4.0, 5.3 Hz), 3.56 (dd, 1 H, *J* = 2.6, 5.3 Hz), 3.62 (dd, 1 H, *J* = 5.3, 5.3 Hz), 3.79 (s, 3 H), 4.30 (qd, 1 H, *J* = 6.3, 4.0 Hz), 6.86 (d, 2 H, *J* = 8.9 Hz), 7.29 (d, 2 H, *J* = 8.9 Hz); HRMS calcd for $C_{18}H_{29}NO_3Si$ MW 335.1918, found *m/z* 335.1899 (M^+). Anal. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.09 H, 9.03; N, 3.93.

(3*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]azetidin-2-one (11). A solution of $(NH_4)_2Ce(NO_3)_3$ (1.47 g, 2.7 mmol) in H_2O (9 mL) was added dropwise to a solution of compound **10** (300 mg, 0.9 mmol) in MeCN (5.6 mL) at −15 °C over a period of 2 min with stirring. After being stirred for an additional 20 min, the reaction mixture was extracted with excess AcOEt. The extract was successively washed with water, 10% $NaHSO_3$, 5% $NaHCO_3$, water, and saturated aqueous NH_4Cl. The organic portion was submitted to the usual workup to give **11** (137 mg, 67%) as colorless prisms: mp 67–68 °C (from hexane) (lit.[16] mp 67–68 °C); $[\alpha]^{22}_D$ −74.1° (*c* 1.73, $CHCl_3$) (lit.[16] $[\alpha]^{22}_D$ −74.4° (*c* 1.05, $CHCl_3$)).

Alkylation of (3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (3) with the Tin(II) Enolate of 3-Propionyl-(4*S*)-ethyl(or isopropyl)-1,3-thiazolidine-2-thione (12a or 12b). Tin(II) trifluoromethanesulfonate (1.394 g, 3.34 mmol) was dissolved in anhydrous THF (25 mL) under N_2 at rt. To the solution cooled at −40 ton −50 °C were successively added *N*-ethylpiperidine (0.47 mL, 3.42 mmol) and **12a** (519 mg, 2.55 mmol) in anhydrous THF (3 mL), and the mixture was stirred at −40 °C for 3.5 h to form tin(II) enolate **13a**. To tin(II) enolate **13a** at 0 °C was added a solution of **3** (525 mg, 1.83 mmol) in anhydrous THF (3 mL), and then the mixture was stirred at 0 °C for 1 h. A 0.1 *M* phosphate buffer (pH 7.0, 8 mL) and Et_2O (50 mL) were added to the reaction mixture with vigorous stirring. The precipitate was filtered off through Celite, and the filtrate was extracted three times with Et_2O. The combined organic layer was washed with brine, dried, and evaporated *in vacuo* to give a yellow, viscous oil. The HPLC analysis (column, Partisil-10 ODS 4.6-mm i.d. × 25 cm; eluent, 50:50 MeCN–H_2O; flow rate, 3.0 mL/min; detection UV 305 nm) of the oily residue showed the presence of **17a** and **18a** in a 90:10 ratio. Silica gel column chromatography of the residue (elution with 3:1 hexane–AcOEt) afforded pure **17a** (630 mg, 80%). The HPLC retention time (14 min) of minor product **18a** was identical with that of **18a** obtained from **23** *via* known carboxylic acid **26**. The reaction of **3** (574 mg, 2.0 mmol) with tin(II) enolate **13b**, obtained by the treatment of **12b** (610 mg, 2.8 mmol) an mentioned above, afforded a mixture of **17b** and **18b** in a 91:9 ratio by HPLC analysis. Separation of the mixture by silica gel column chromatography (elution with 5:95 acetone–$CHCl_3$) gave pure **17b** (657 mg, 74%).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (17a): yellow needles; mp 85.5–86.5 °C (from hexane–AcOEt); $[\alpha]^{25}_D$ +233.9° (*c* 0.77, $CHCl_3$); IR (KBr) 1750, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.00 (t, 3 H, *J* = 8.0 Hz), 1.23 (d, 3 H, *J* = 6.0 Hz), 1.26 (d, 3 H, *J* = 6.0 Hz), 1.6–2.03 (m, 2 H), 2.90 (dd, 1 H, *J* = 1.0, 11.0 Hz), 3.07 (m, 1 H), 3.50 (dd, 1 H, *J* = 7.0, 11.0 Hz), 3.95 (m, 1 H), 4.00–4.30 (m, 1 H), 4.90–5.20 (m, 2 H), 6.10 (br s, 1 H); HRMS calcd for $C_{19}H_{34}N_2O_3S_2Si$ MW 430.1779, found *m/z* 430.1749 (M^+).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[((4*S*)-4-isopropyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (17b): yellow needles; mp 131.5–132.5 °C (from hexane–AcOEt); $[\alpha]^{25}_D$ +295.7° (*c* 0.93, $CHCl_3$); IR (KBr) 1750, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (s, 6 H), 0.87 (s, 9 H), 0.97 (d, 3 H, *J* = 7.6 Hz), 1.05 (d, 3 H, *J* = 7.6 Hz), 1.17 (d, 3 H, *J* = 4.1 Hz), 1.24 (d, 3 H, *J* = 3.3 Hz), 2.14–2.53 (m, 1 H), 2.95–3.13 (m, 1 H), 3.49 (dd, 1 H, *J* = 8.2, 12.0 Hz), 3.97 (dd, 1 H, *J* = 2.2, 4.0 Hz), 4.07–4.33 (m, 1 H), 4.98–5.25 (m, 2 H), 6.08 (br s, 1 H); HRMS calcd for $C_{20}H_{36}N_2O_3S_2Si$ MW 444.1936, found *m/z* 444.1940 (M^+).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-methyl-3-(*p*-nitrobenzyloxycarbonyl)-2-

oxopropyl]azetidin-2-one (21). (1) Conversion of 17a to 21. To a solution of **17a** (290 mg, 0.67 mmol) in anhydrous MeCN (7 mL) was added imidazole (115 mg, 1.69 mmol) under N_2. The mixture was stirred at rt for 5.5 h to give imidazolide **19**, and then $Mg(O_2CCH_2CO_2PNB)_2$ (507 mg, 1,01 mmol) was added. The reaction was performed as usual[2] to give **21** (257 mg, 80%) as colorless crystals: mp 77–80 °C (from hexane–AcOEt); ^1H NMR (90 MHz) δ 0.06 (s, 6 H), 0.87 (s, 9 H), 1.16 (d, 3 H, J = 7.0 Hz), 1.20 (d, 3 H, J = 8.0 Hz), 2.90 (m, 2 H), 3.63 (s, 2 H), 3.96 (m, 1 H), 4.17 (m, 1 H), 5.27 (s, 2 H), 5.92 (br s, 1 H); HRMS calcd for $C_{23}H_{34}N_2O_7Si$ MW 478.21345, found m/z 478.2117 (M^+). Anal. Calcd for $C_{23}H_{34}N_2O_7Si$: C, 57.72; H, 7.16; N, 5.85. Found: C, 57.57; H, 7.11; N, 5.90.

(2) Conversion of 17b to 21. Reaction of **17b** and imidazole followed by decarboxylative C–C bond formation[2] with $Mg(O_2CCH_2CO_2PNB)_2$ on a 0.25 mmol scale gave the crude product, which was purified by silica gel column chromatography (elution with 95:5 $CHCl_3$–acetone) to give **21** (102 mg, 86%) as colorless crystals. This product was found to be identical with **21** derived from **17a**.

(3*S*,4*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-carboxyethyl]azetidin-2-one (20). Imidazole (680 mg, 10.00 mmol) was added to a solution of **17a** (860 mg, 2.00 mmol) in anhydrous THF (8 mL), and the mixture was stirred at rt for 5 h. After addition of 10% citric acid (16 mL), the mixture was vigorously stirred at rt for 3 h. The reaction mixture was extracted with AcOEt (3 × 20 mL). The extract was washed with brine, dried, and evaporated *in vacuo* to give an oily residue. Column chromatography of the residue on a silica gel with CH_2Cl_2 and 1:1 CH_2Cl_2–acetone afforded carboxylic acid **20** (470 mg 80%) as colorless crystals: mp 152.5–153 °C (lit.[5a] mp 146–147 °C); $[\alpha]^{20}_D$ –32.3° (*c* 0.30, MeOH) (lit.[5a] $[\alpha]^{20}_D$ –34.6° (*c* 0.26, MeOH)).

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-[(1*R*)-1-methyl-3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (22). To a solution of **21** (478 mg, 1.00 mmol) in MeOH (5 mL) was added concd HCl (0.25 mL, 3.00 mmol). The mixture was stirred at rt for 1 h. The reaction mixture was adjusted to pH 7 with 5% $NaHCO_3$ at 0 °C and then extracted with AcOEt (100 mL). The extract was washed with water and brine, dried, and evaporated *in vacuo* to give **22** (346 mg, 95%) as a colorless solid: mp 95–97 °C (from Et_2O) (lit.[5a] mp 94–96 °C (from Et_2O)); $[\alpha]^{25}_D$ –8.1° (*c* 0.9, CH_2Cl_2) (lit.[5a] $[a]^{21}_D$ –8.0° (*c* 2.5, CH_2Cl_2)).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(methoxycarbonyl)methyl]azetidin-2-one (24). To a solution of **23**[3b] (986 mg, 2.37 mmol) in MeOH (20 mL) was added K_2CO_3 (327 mg, 2.37 mmol). After the reaction mixture stirred at rt for 30 min, 1 N HCl and $CHCl_3$ (30 mL) were added. The organic layer was washed with 5% $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (elution with 3:97 acetone–$CHCl_3$) to give **24** (549 mg 77%) as a colorless solid: mp 97.8–99.0 °C (lit.[5a] mp 96–97.5 °C).

(3*S*,4*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-(methoxycarbonyl)ethyl]azetidin-2-one (25). (1) Conversion of 24 to 25. To THF (2.73 mL) were added diisopropylamine (0.094 mL, 0.67 mmol) and 1.56 *n*-butyllithium in hexane (0.43 mL, 0.67 mmol) under N_2. After being stirred for 5 min at –78 °C, hexamethylphosphoric triamide (HMPA) (0.119 mL, 0.72 mmol) was added, and the mixture was stirred for 10 min. To the mixture at –78 °C was added a solution of **24** (100 mg, 0.33 mmol) in anhydrous THF (0.63 mL). After being stirred for 40 min, the mixture was treated with methyl iodide (0.044 mL, 0.71 mmol) at –78 °C and worked up as usual[5a] to give compound **25** (38 mg, 36%) as a colorless solid: mp 132–133 °C (lit.[5a] mp 133–134 °C); $[\alpha]^{22}_D$ +6.1° (*c* 0.19, CH_2Cl_2) (lit.[5a] $[\alpha]^{22}_D$ +6.0° (*c* 0.20, CH_2Cl_2)).

(2) Conversion of 18c to 25. Anhydrous K_2CO_3 (3.8 mg, 2.7 × 10^{-2} mmol) was added to a solution of **18c** (11 mg, 2.7 × 10^{-2} mmol) in MeOH (1.5 mL). After the mixture was stirred at rt for 1 min, 1 N HCl and $CHCl_3$ (5 mL) were added. The organic layer was washed with 5% $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. Silica gel column chromatography (elution with 3:7 AcOEt–hexane) of the residue gave compound **25** (5.2 mg, 60%). All spectroscopic data for **25** derived from **18c** were identical to those of **25** obtained from **24**.

(3*S*,4*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-carboxyethyl]azetidin-2-one (26). To a solution of **25** (17 mg, 5.4 × 10^{-2} mmol) in MeOH (0.17 mL) was added 2.5 *N* NaOH (0.022 mL). The mixture was treated as usual[5a] to give carboxylic acid **26** (10 mg, 63%) as a colorless solid: mp 189–190 °C (from AcOEt); IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (90 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.23 (d, 3 H, J = 7.0 Hz), 1.26 (d, 3 H, J = 6.0 Hz), 2.50–2.80 (m, 1 H), 2.84 (dd, 1 H, J = 2.0, 5.0 Hz), 3.70 (dd, 1 H, J = 2.0, 10.0 Hz), 4.03–4.26 (m, 1 H).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (18a). To a solution of **26** (4 mg, 1.3 × 10^{-2} mmol) in anhydrous CH_2Cl_2 (0.5 mL) were added (4*S*)-ethyl-1,3-thiazolidine-2-thione [(4*S*)-ETT] (2.3 mg, 1.6 × 10^{-2} mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (3.8 mg, 2.0 × 10^{-2} mmol), and DMAP (0.16 mg, 0.1 × 10^{-2} mmol). The mixture was stirred at rt for 1.5 h. After addition of $CHCl_3$ (3 mL), the organic layer was washed with 1 *N* HCl and brine, dried, and evaporated *in vacuo*. Preparative TLC (95:5 $CHCl_3$–acetone) of the residue afforded **18a** (4.3 mg, 75%) as a pale yellow solid: mp 188–189 °C (from hexane–AcOEt); $[\alpha]^{20}_D$ +30.0° (*c* 0.12, $CHCl_3$); IR (KBr) 1760, 1680 cm^{-1}; ^1H NMR (90 MHz) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.00 (t, 3 H, J = 6.7 Hz), 1.23 (d, 3 H, J = 6.3 Hz), 1.31 (d, 3 H, J = 7.2 Hz), 1.69–1.98 (m, 2 H), 2.80 (dd, 1 H, J = 2.1, 4.7 Hz), 2.94 (dd, 1 H, J = 1.3, 11.3 Hz), 3.57 (dd, 1 H, J = 7.2, 10.9 Hz), 3.93 (dd, 1 H, J = 2.1, 9.2 Hz), 4.12–4.50 (m, 2 H), 5.10–5.33 (m, 1 H), 5.73 (br s, 1 H); HRMS calcd for $C_{139}H_{34}N_2O_3S_2Si$ MW 430.1780, found m/z 430.1793 (M^+). From the HPLC analysis (column, Nucleosil $5C_{18}$; eluent, 6:4 MeCN/H_2O; flow rate, 1.5 mL/min; detection, UV 305 nm), **18a** was identical to a minor product obtained from alkylation of **3** with **14a**.

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*S*)-1-[2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (18c). Dehydrative condensation of **26** (5.0 mg, 1.65 × 10^{-2} mmol) with 1,3-thiazolidine-2-thione (2.6 mg, 2.18 × 10^{-2} mmol) was carried out under the conditions used to convert **26** to **18a** to afford **18c** (5.1 mg, 76%) as a yellow oil: $[\alpha]^{20}_D$ +12.0° (*c* 0.26, $CHCl_3$); IR (neat 1760, 1690 cm^{-1}; ^1H NMR (90 MHz) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.25 (d, 3 H, J = 6.0 Hz), 1.30 (d, 3 H, J = 6.9 Hz), 2.80 (dd, 1 H, J = 2.2, 5.1 Hz), 3.29 (t, 2 H, J = 7.4 Hz), 3.91 (dd, 1 H, J = 2.2, 9.2 Hz), 4.18 (q, 1 H, J = 6.0 Hz), 4.56 (t, 2 H, J = 7.4 Hz), 4.40–4.73 (m, 1 H), 5.83 (br s, 1 H); HRMS calcd for $C_{17}H_{30}N_2O_3S_2Si$ MW 402.1453, found m/z 402.1466 (M^+). From the HPLC analysis (column, Nucleosil $5C_{18}$; eluent, 6:4 MeCN–H_2O; flow rate, 2.0 mL/min; detection UV 305 nm), **18c** was identical to a minor product obtained from alkylation of **3** with **14d**.

Alkylation of (3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (3) with the Tin(II) Enolate of 3-Propionyl-1,3-thiazolidine-2-thione (12c) or 3-Propionyl-4,4-dimethyl-1,3-thiazolidine-2-thione (12d). Alkylation of **3** (392 mg, 1.37 mmol) with the tin(II) enolates obtained by treatment of **12c** (335 mg, 1.91 mmol) as described for the reaction of **12a,b** afforded a mixture of **17c** and **18c** in a 80:20 ratio by HPLC analysis. Separation of the mixture by silica gel column chromatography gave pure **17c** (401 mg, 73%). The HPLC retention time (12.5 min) of the minor product was identical to that of **18c** obtained from the dehydrative condensation of **26** with 1,3-thiazolidine-2-thione. The reaction between **3** (749 mg, 2.61 mmol) and the tin(II) enolates obtained by treatment of **12d** (640 mg, 3.15 mmol) as described above afforded a mixture of **17d** and **18d** in a 85:15 ratio by HPLC analysis. After silica gel column chromatography (elution with 3:1 hexane–AcOEt) of the mixture, pure **17d** (900 mg) was obtained in 80% yield. The minor product was confirmed to be **18d** by a comparison of the HPLC analysis with that of **18c**.

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[(2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidine-2-one (17c): pale yellow needles; mp 109–109.5 °C (from hexane–AcOEt); $[\alpha]^{25}_D$ +26.1° (*c* 0.5, $CHCl_3$); IR (KBr) 1760, 1700 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.21 (d, 3 H, J = 6.0 Hz), 1.26 (d, 3 H, J = 6.0 Hz), 3.30 (dd, 1 H, J = 2.0, 5.0 Hz), 3.28 (t, 2 H, J = 7.5 Hz), 3.94 (dd, 1 H, J = 3.0, 5.0 Hz), 4.18 (m, 1 H), 4.55 (t, 2 H, J = 7.5 Hz), 4.95 (m, 1

H), 6.24 (br s, 1 H); MS m/z 403 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{30}N_2O_3S_2Si$: C, 50.71; H, 7.51; N, 6.96. Found: C, 50.63; H, 7.88; N, 6.70.

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-1-[(2-thioxo-4,4-dimethyl-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (17d): yellow needles; mp 165–166 °C (from $CHCl_3$–hexane); $[\alpha]^{28}_D$ +55.4° (*c* 0.73, $CHCl_3$); IR (KBr) 1760, 1705 cm^{-1}; ^1H NMR (90 MHz) δ 0.06 (s, 6 H), 0.86 (s, 9 H), 1.25 (d, 6 H, J = 7.0 Hz), 1.58 (s, 3 H), 1.63 (s, 3 H), 3.03–3.40 (m, 1 H), 3.20 (d, 2 H, J = 5.0 Hz), 3.96–4.55 (m, 3 H), 5.86 (br s, 1 H); MS m/z 430 (M^+). Anal. Calcd for $C_{19}H_{34}N_2O_3S_2Si$: C, 52.98; H, 7.96; N, 6.50. Found: C, 52.74; H, 8.02; N, 6.60.

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-[(1*R*)-1-methyl-3-diazo-3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (27). To a solution of **22** (470 mg, 1.29 mmol) in MeCN (10 mL) were added dodecylbenzenesulfonyl azide (545 mg, 1.55 mmol) and Et_3N (157 mg, 1.55 mmol) under N_2. The mixture was treated as usual[5a] to give **27** (453 mg, 90%) as a colorless solid: mp 104–107 °C (from hexane–AcOEt); $[\alpha]^{21}_D$ −51.6° (*c* 3.1, CH_2Cl_2) (lit.[5a] $[\alpha]^{21}_D$ −50.4° (*c* 2.5, CH_2Cl_2)).

***p*-Nitrobenzyl (1*R*,5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-2-[(diphenylphosphono)oxy]-1-methylcarbapen-2-em-3-carboxylate (29)**. To a solution of **27** (200 mg, 0.51 mmol) in anhydrous AcOEt (1 mL) at rt was added rhodium(II) octanate (1.2 mg) in anhydrous AcOEt (0.24 mL) under N_2. The usual workup[5a] of the mixture gave 1β-methyl bicyclic keto ester **28**[5a] (186 mg, quantitative) as a white, moisture-sensitive solid. To a solution of **28** (350 mg, 0.97 mmol) in anhydrous MeCN (2 mL) at −10 °C were added diisopropylethylamine (0.19 mL, 1.09 mmol) and diphenyl chlorophosphate (0.22 mL, 1.07 mmol) under N_2. After the mixture was stirred at −10 °C for 0.5 h, the solvent was evaporated *in vacuo*. The residue was treated as usual[5a] to give known product **29**[5a] (459 mg, 80%) as colorless needles: mp 135–136 °C (from AcOEt); ^1H NMR δ 1.22 (d, 3 H, J = 7.3 Hz), 1.33 (d, 3 H, J = 6.3 Hz), 1.80 (d, 1 H, J = 5.0 Hz), 3.33 (dd, 1 H, J = 3.0, 6.6 Hz), 3.49 (m, 1 H), 4.24 (dd, 1 H, J = 3.0, 10.3 Hz), 4.21–4.29 (m, 1 H), 5.22 (d, 1 H, J = 13.7 Hz), 5.36 (d, 1 H, J = 13.7 Hz), 7.15–7.39 (m, 10 H), 7.54 (d, 2 H, J = 8.7 Hz), 8.13 (d, 2 H, J = 8.7 Hz); MS calcd for $C_{29}H_{27}N_2O_{10}P$ MW 594, found m/z 595 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{27}N_2O_{10}P$: C, 58.59; H, 4.58; N, 4.71. Found: C, 58.30; H, 4.30; N, 4.46.

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-2-[[(*N*,*N*-Bis(*p*-nitrobenzyloxycarbonyl)pyrazolidin-4-yl]thio]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (31)**. Conversion of **27** to **31** was carried out one pot as follows. To a solution of **27** (680 mg, 1.74 mmol) in anhydrous AcOEt (4.5 mL) at rt was added rhodium(II) octanate (4 mg) in anhdyrous AcOEt (1 mL) under N_2. After the mixture was stirred at 80 °C for 0.5 h, the solvent was evaporated *in vacuo*. The residue (**28**) was dissolved in anhydrous MeCN (4.5 mL); the solution was cooled to −10 °C, and then diphenyl chlorophosphate (0.40 mL, 1.91 mmol) and diisopropylethylamine (0.27 mL, 1.93 mmol) were added under N_2. The mixture was stirred at −10 °C for 0.5 h to give a solution of **29**. To the solution were added 4-mercapto-*N*,*N*-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (**30**) (883 mg, 1.91 mmol) in MeCN and diisopropylethylamine (0.27 mL, 1.93 mmol). After the mixture was stirred at −5 °C for 40 min, the solvent was evaporated *in vacuo*. The residue was dissolved in AcOEt, and the organic layer was washed with water, 0.1 *M* phosphate buffer (pH 7.0), and brine, dried, and evaporated *in vacuo*. Silica gel column chromatography (elution with 3:1 CH_2Cl_2–acetone) of the residue afforded **31** (1.06 g, 75%) as a pale yellow, amorphous powder: $[\alpha]^{20}_D$ −5.6° (*c* 2.5, CH_2Cl_2); IR (KBr) 1770, 1710, 1620, 1520 cm^{-1}; ^1H NMR (90 MHz) δ 1.24 (d, 3 H, J = 6.0 Hz), 1.35 (d, 3 H, J = 6.0 Hz), 3.20–4.90 (m, 9 H), 5.16 (d, 1 H, J = 15.0 Hz), 5.26 (s, 2 H), 5.47 (d, 1 H, J = 15.0 Hz), 7.30–7.70 m, 6 H), 8.05–8.30 (s, 6 H). Anal. Calcd for $C_{36}H_{34}N_6O_{14}S$: C, 53.60; H, 4.25; N, 10.42. Found: C, 53.85; H, 4.30; N, 10.39.

(1*R*,5*S*,6*S*)-2-[(6,7-Dihydro-5*H*-pyrazolo[1,2-*a*][1,2,4]-triazolium-6-yl)thio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (1a). A solution of **31** (667 mg, 0.83 mmol) in 1:1 THF–water (14 mL) was treated with 10% Pd–C (120 mg) under H_2 (4 atm) at rt for 100 min. After removal of the catalyst, THF was evaporated *in vacuo*. Phosphate buffer (0.1 M, pH 7.0, 15 mL) was added to the resultant aqueous solution, and the pH of the mixture was adjusted to 8.5 with 1 N NaOH. Ethyl formimidate hydrochloride (727 mg, 6.64 mmol) was added to the mixture at 0 °C, and stirring was continued for 5 min. After being adjusted to pH 7.0 with 1 *N* NaOH, the reaction mixture was concentrated *in vacuo* to 10 mL and then charged on a HP-40 column and eluted with 3:97 acetone–water to give **1a** (127 mg, 44%) as a pale yellow, amorphous powder after lyophilization: $[\alpha]^{20}_D$ −32.9° (*c* 0.5, water); IR (KBr) 1750, 1605 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.29 (d, 3 H, J = 7.3 Hz), 1.33 (d, 3 H, J = 6.3 Hz), 3.44 (dq, 1 H, J = 7.3, 9.5 Hz), 3.56 (dd, 1 H, J = 2.9, 6.2 Hz), 4.30 (d, 1 H, J = 6.2 Hz), 4.34 (dd, 1 H, J = 2.9, 9.5 Hz), 4.75–4.84 (m, 2 H), 5.08–5.17 (m, 2 H), 4.98–5.04 (m, 1 H), 9.06 (s, 1 H), 9.07 (s, 1 H); FAB-MS m/z 351 [$(M + H)^+$]. Anal. Calcd for $C_{15}H_{18}N_4O_4S$·0.5H_2O: C, 50.13; H, 5.33; N, 15.59. Found: C, 50.39; H, 5.32; N, 15.72.

(1*R*,5*S*,6*S*)-2-[[(*N*-Methyl-1,2,3-thiadiazolium-4-yl)-methyl]thio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (1b). To a solution of 4-(mercaptomethyl)-*N*-methyl-1,2,3-thiadiazolium trifluoromethanesulfonate (**32**) (676 mg, 2.29 mmol) in 1:4 water–MeOH (5 mL) was added 1 *N* NaOH (2 mL) at −20 °C, and the mixture was stirred at 0 °C for a few minutes. THF (10 mL) and 0.35 M phosphate buffer (pH 7.0, 8 mL) were added to a solution of **29** prepared from **27** (391 mg, 1.00 mmol). The solution of **29** and the solution of **32** were combined at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was treated with 0.35 *M* phosphate buffer (pH 6.1, 20 mL) and then was adjusted to pH 6.1 with phosphoric acid. Zinc powder (1.2 g, 18.83 mmol) was added to the solution, and the mixture was stirred at 20 °C for 2 h. The precipitate was filtered off through Celite. The filtrate was washed with AcOEt and then adjusted to pH 6.4 with 1 *N* NaOH. Column chromatography (Dowex 50Wx4 type, elution with water) of the resultant solution afforded **1b** (192 mg, 54%) as a pale yellow, amorphous powder after lyophilization: $[\alpha]^{20}_D$ −38.5° (*c* 0.5, water); IR (KBr) 1752, 1636, 1598 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.25 (d, 3 H, J = 7.3 Hz), 1.32 (d, 3 H, J = 6.2 Hz), 3.41 (dq, 1 H, J = 7.3, 9.5 Hz), 3.53 (dd, 1 H, J = 2.6, 6.2 Hz), 4.24 (dd, 1 H, J = 2.6, 9.5 Hz), 4.27 (q, 1 H, J = 6.2 Hz), 4.48 (d, 1 H, J = 16.1 Hz), 4.66 (d, 1 H, J = 16.1 Hz), 4.71 (s, 3 H); FAB-MS m/z 356 [$(M + H)^+$]. Anal. Calcd for $C_{14}H_{17}N_3O_4S_2$·H_2O: C, 45.03; H, 5.13; N, 11.25. Found: C, 45.07; H, 5.14; N, 11.32.

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Supplementary Material Available: ^1H NMR spectra for compounds **7a**, **9**, **17a**, **17b**, **18a**, **18c**, **20**, **24**, **25**, **26**, and **28** and physicochemical data of known compounds **11**, **20**, **22**, **24**, **25**, **27**, and **28** (13 pages). Ordering information is given on any current masthead page.