55.45; H, 5.37; N, 10.57; S, 8.07.

When the reaction was repeated with methanol substituted for ethanol or by conducting the reaction at room temperature for 1 h in the presence of 1 mol equiv of silver tetrafluoroborate comparable yields of thiazole **10a** were realized.

Method B. To a stirred dimethylformamide (10 mL) solution of thioamide **9** (1.04 g, 3.53 mM) was added ethyl bromopyruvate (600 μL, 40% excess). The reaction mixture rapidly became yellow and TLC at 40 min showed that all starting material was consumed. The mixture was diluted with ethyl acetate (150 mL) and washed with 1% sodium bicarbonate (100 mL) and water (3 × 100 mL). The organic phase was dried, solvent evaporated, and the residue crystallized from ethyl acetate–ether to afford 1.19 g of thiazole **10a**, mp 155–156 °C.

***N*-Acetyl-DL-(gln)Thz Ethyl Ester (10b).** Thiazole **10a** (103 mg) was treated with 0.7 mL of 27% hydrogen bromide in acetic acid at 0 °C. A clear solution was obtained within 5 min and allowed to warm to room temperature. After 1 h at room temperature a considerable quantity of yellow gummy material had precipitated and TLC did not detect any starting material. Solvent was evaporated (in vacuo) and the residue treated with pyridine (0.5 mL)–acetic anhydride (0.5 mL). Acylation was complete (by TLC) in 1 h and crystalline material separated from solution. The solvent was removed in vacuo and the residue dissolved in chloroform (100 mL) was washed with 5% sodium bicarbonate (10 mL). The organic phase was dried and solvent evaporated to a white solid (84 mg) which crystallized from ethanol–ether to yield *N*-acetyl-(gln)Thz ethyl ester **10b** melting at 226–227 °C. Anal. Calcd for $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.73; N, 14.03; S, 10.71. Found: C, 48.37; H, 5.59; N, 14.15; S, 10.53.

***N*-Z-DL-(gln)Thz (10d).** A solution prepared from thiazole ester **10a** (3.5 g, 9.33 mM), dioxane (60 mL), water (60 mL) and 1.0 N sodium hydroxide (10 mL) was allowed to react at room temperature. After 2 h, TLC showed complete saponification and the mixture was extracted with ether (200 mL). The aqueous phase was acidified with 3 N hydrochloric acid and the precipitate collected by filtration. Crystallization from ethanol–hexane yielded pure ***N*-Z-DL-(gln)Thz (10d**, 2.8 g, 86%): mp 185–186 °C; ν_{max} 3475, 3352, 3132, 1720, 1660, 1634, 1586, 1543, and 1338 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.89–2.33 (m, 4 H, CH_2CH_2), 4.90 (m, 1 H, C*H*NH), 5.07 (s, 2 H, PhCH_2O), 6.86 (br, 1 H) and 7.35 (br, 1 H) (CONH_2), 8.30 (d, J = 7 Hz, N*H*CH), 8.46 (s, 1 H, thiazole CH); ^{13}C NMR (Me_2SO-d_6) δ 29.9 (t), 31.1 (t), 53.0 (d), 65.6 (t), 127.5 (d, 2×), 127.7 (d, 2×), 128.3 (d), 128.7 (d), 136.8 (s), 147.0 (s), 155.9 (s), 162.0 (s), 173.3 (s), 174.4 (s); MS(SP-SIMS) (sodium iodide–glycerol matrix),[21] m/e 386 $[M + Na]^+$ and 364 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}N_3O_5S$: C, 52.88; H, 4.71; N, 11.56; S, 8.82. Found: C, 52.67; H, 4.50; N, 11.52; S, 8.55.

DL-(gln)Thz (1e) and *N*-(*tert*-Butyloxycarbonyl)-DL-(gln)Thz (10e). To *N*-Z-DL-(gln)Thz ethyl ester (**10a**) (1.96 g, 0.5 mM) suspended in dry methylene chloride (20 mL) at 0 °C was added 20 mL of 32% hydrogen bromide in acetic acid and the mixture was stirred at 0 °C for 4 h. A clear light yellow solution was obtained. Ether (60 mL) was added slowly and the precipitated hydrobromide (1.77 g) was collected and dried in vacuo. Without further purification the hydrobromide was dissolved in a mixture of dioxane (20 mL) and water (10 mL). The solution was neutralized with dilute sodium hydroxide solution and an additional 5 mL of 1 N sodium hydroxide was added. The solution was stirred at room temperature until hydrolysis of the ester was complete (4 h by TLC). The **DL-(gln)Thz (1e)** sodium salt was characterized by direct conversion to the Boc derivative **10f** as follows. The aqueous solution of thiazole **10e** sodium salt was cooled to 0 °C and di-*tert*-butyl pyrocarbonate (1.4 g) in dioxane (3 mL) was added. The reaction mixture was stirred at 0 °C for 24 h and acidified (to pH 2) with 3 N hydrochloric acid. The precipitate (1.64 g) was collected, dried, and crystallized from methanol–ether to give a pure specimen of ***N*-Boc-DL-(gln)Thz (10e**, 1.36 g, 83%); mp 124–126 °C; ^1H NMR (Me_2SO-d_6) δ 1.52 (s, 9 H, $(CH_3)_3C$), 4.77 (m, 1 H, C*H*NH), 8.25 (d, J = 7.5 Hz, CHN*H*), 8.49 (s, H, thiazole CH); MS (SP-SIMS) (glycerol matrix),[21] m/e 330 $[M + H]^+$. Anal. Calcd for $C_{13}H_{19}N_3O_5S$: C, 47.41; H, 5.81; N, 12.76; S, 9.73. Found: C, 47.60; H, 5.75; N, 12.70; S, 10.08.

Partial Resolution of *N*-Z-(gln)Thz (10d). The DL-thiazole carboxylic acid (**10d**, 1.08 g, 3 mM) was treated with brucine (1.18 g, 3 mM) in hot 1:1 methanol–water. The crystals which slowly separated in cooling were collected and recrystallized (three times) from 1:1 methanol–water. The crystaline salt (198 mg, mp 233–235 °C) was treated with dilute hydrochloric acid. The *N*-Z-Thz(gln) was separated and purified by crystallization from ethanol–hexane to afford 62 mg melting at 182–183 °C; $[\alpha]^{25}_D$ –6.2° (*c* 1.5, DMF). Because of the negative rotations shown by the preceding L-Glu derivatives this isomer may also have the L configuration. The product with $[\alpha]_D$ –6.2° (36 mg, 0.1 mM) was heated in a refluxing solution of hydrogen bromide (0.1 mM) in ethanol (3 mL) for 30 min. The recovered starting material (22 mg) displayed $[\alpha]^{25}_D$ –5.6° (*c* 0.5, DMF).

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Registry No. **1e**, 96307-11-8; **2**, 1155-62-0; **3**, 4124-76-9; **4**, 6398-06-7; **5**, 51163-40-7; **6**, 31883-92-8; **7**, 31883-94-0; **8**, 96307-06-1; **9**, 96307-07-2; **10a**, 96307-08-3; **10b**, 96307-09-4; **10d**, 96391-81-0; **10e**, 96307-10-7; H-DL-(gln)Thz ethyl ester hydrobromide, 96307-12-9; *N*-Z-(gln)Thz brucine salt, 96307-13-0; *N*-Z-(gln)Thz, 95716-10-2; ethyl bromopyruvate, 70-23-5; di-*tert*-butyl pyrocarbonate, 24424-99-5; brucine, 357-57-3; dolastatin 3, 80387-90-2.

Chiral Synthesis of the Key Intermediates of (+)- and (–)-Thienamycin

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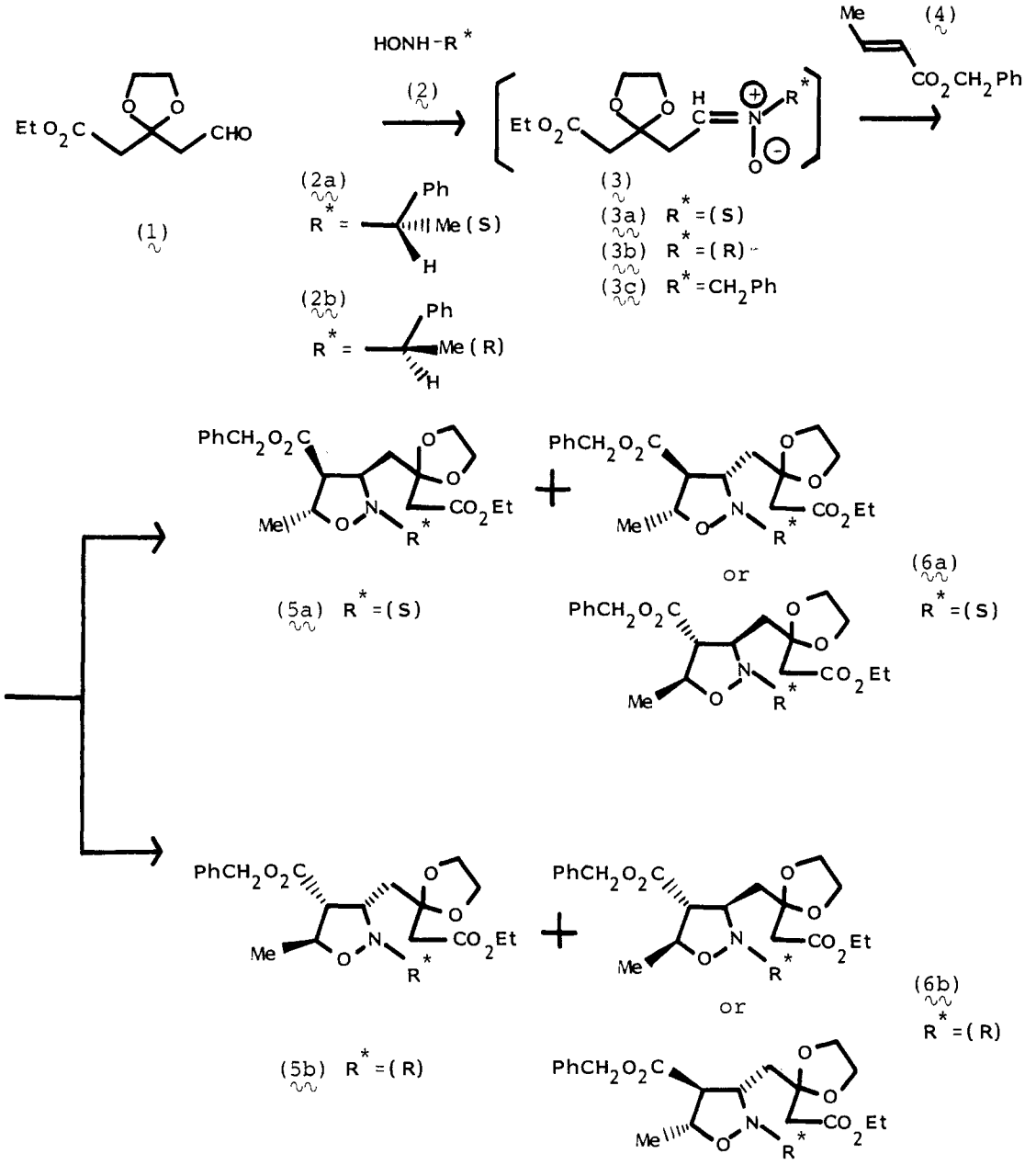
Synthesis of the optically active β-keto ester **11a**, the key intermediate in the preparation of (+)-thienamycin, has been achieved. An enantioselective [3 + 2] cycloaddition of the chiral nitrone with benzyl crotonate was employed as a key reaction.

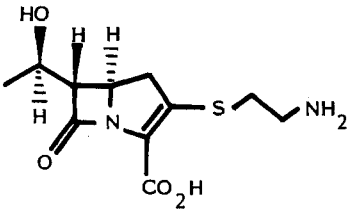
The recent discoveries of the potent antibiotics thienamycin[1] and its relatives[2] provided impetus to the design of general strategies for the synthesis of these naturally occurring carbapenem antibiotics, members of nonclassical

0022-3263/85/1950-2327$01.50/0

Scheme I



β-lactams, due to the significant biological activity in addition to the structural diversity exhibited by this class of antibiotics. Consequently, a number of enantiospecific syntheses of the natural enantiomer of thienamycin have appeared by elaboration of a chiral starting substrate such as L-aspartic acid,[3] D-glucose,[4] D-glucosamine,[5] 6-aminopenicillanic acid,[6] and D-allo-[7] and L-threonine[7] and by an enzymatic selection process.[8]



Previous investigations[9] of the 1,3-dipolar cycloaddition

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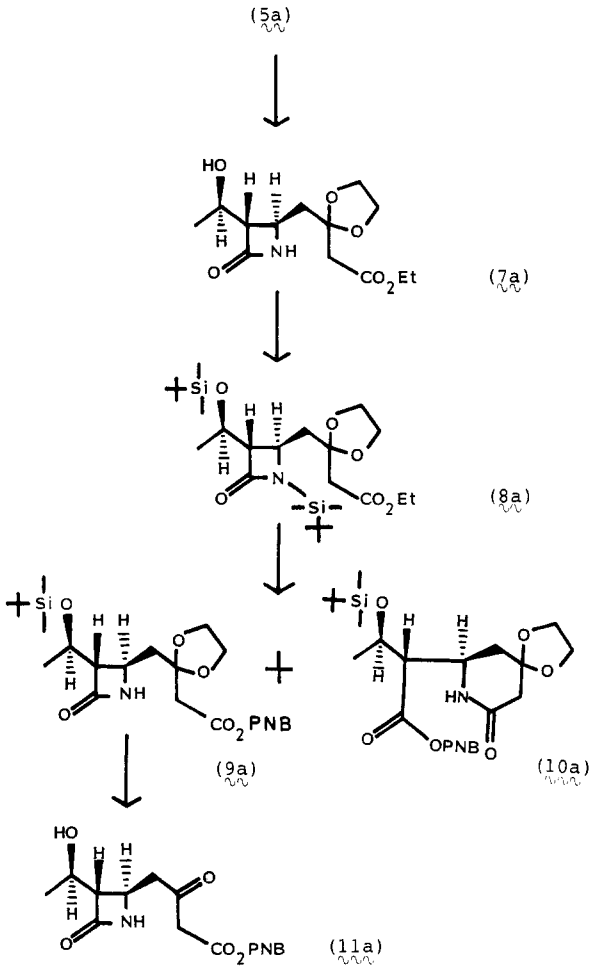
of the nitrone **3c** with benzyl crotonate have indicated the utility of such processes in the synthesis of the thienamycin analogue bearing the hydroxyethyl function at the 6-position with the desired stereochemistry. As a continuation of our work on the synthesis of carbapenem antibiotics, we have further studied the synthesis of the key intermediate for thienamycin in an optically active form. The enantioselective [3 + 2] cycloaddition[10] of a chiral nitrone would be expected to afford the cycloadduct with three contiguous chiral centers of proper relative configuration to thienamycin on the basis of our previous work.[9a]

Results and Discussion

The requisite chiral nitrones (**3a** and **3b**) were prepared in the following manner. Heating of the aldehyde[9a] **1** with (*S*)-(−)-*N*-(α-phenylethyl)hydroxylamine (**2a**) in benzene at 50 °C for 1 h afforded the nitrone **3a**. On the other hand, (*R*)-(+)-*N*-(α-phenylethyl)hydroxylamine was prepared from (*R*)-(+)-(α-phenylethyl)amine according to Chimiak's procedure[11] and was treated with aldehyde **1** to generate nitrone **3b**. 1,3-Dipolar cycloaddition of nitrone **3a** with benzyl crotonate (**4**) in refluxing benzene for 16 h furnished the desired adduct **5a**, which is homogeneous on TLC and HPLC, in 22.7% yield together with its stereoisomer **6a** (Scheme I). Since the diastereomer of **5a** could not be isolated in this reaction, the enantioselectivity of the cycloaddition would be considered to be significantly high. The stereochemistry of the products **5a** and **6a** was determined on the basis of their NMR spectral data. As this result disappointed us in terms of the lack of stereoselectivity,[12] the 1,3-dipolar cycloaddition reaction of nitrone **3a** with benzyl crotonate was further attempted under various reaction conditions, e.g., in chloroform, ethanol, ether, and toluene at 0–100 °C to improve the selectivity. However, none of the improved stereoselectivity was observed under such reaction conditions. This is in contrast with the observed complete stereoselectivity in the case of the racemate.[9] Thus, the isoxazolidine (**5a**) obtained was subjected to the catalytic hydrogenation over palladium–carbon in acetic acid under medium pressure (4.5 atm) of hydrogen to give rise to an amino acid, whose cyclization with *N*,*N*′-dicyclohexylcarbodiimide (DCC) in acetonitrile furnished the azetidinone **7a** in 24.5% yield [$[\alpha]^{25}_D$ +14.2° (*c* 1.5, EtOH)]. The spectral data of the azetidinone **7a** were identical with those of the racemate.[9]

In order to accomplish the chiral synthesis of (+)-thienamycin, we next focused our attention to the conversion of the ethyl ester of azetidinone **7a** into its *p*-nitrobenzyl ester. The protection[13] of the hydroxyl function and lactam nitrogen of **7a** with *tert*-butyldimethylsilyl chloride in dimethylformamide in the presence of triethylamine afforded the bis-silylated azetidinone **8a** [$[\alpha]^{25}_D$ −27.0° (*c* 1.6, MeCN)] in 57.8% yield, whose treatment with 0.25 N sodium hydroxide solution followed by *p*-nitrobenzyl bromide yielded the desired azetidinone **9a** in 56.9% yield together with the δ-lactam **10a** in 20.9% yield. Deprotection of the silyl and ketal groups of **9a** on treatment with hydrochloric acid and subsequently with perchloric acid afforded the expected azetidinone **11a** [mp 123–124 °C, $[\alpha]^{25}_D$ +21.0° (*c* 0.189, $CHCl_3$) [lit.[6b] mp 121 °C, $[\alpha]^{25}_D$ +21.3° (*c* 0.31, $CHCl_3$)]] in 89.9% yield, whose spectral data were identical with those reported (Scheme II).[14]

Scheme II



Since compound **11a** was already transformed into (+)-thienamycin (**12**) by the Merck group,[3] this synthesis constitutes a formal total synthesis of naturally occurring thienamycin.

Moreover, the key intermediate (**11b**) of (−)-thienamycin was also synthesized from the isoxazolidine **5b**, prepared from the reaction of D-(+)-*N*-(α-phenylethyl)hydroxylamine (**2b**) with benzyl crotonate, by adopting the same procedure as described above.

Thus, the chiral synthesis of thienamycin was achieved by employing an enantioselective [3 + 2] cycloaddition[15] as a key reaction.

Experimental Section

Melting points were measured on a Yanagimoto micro hot plate apparatus and are not corrected. Optical rotations were measured with JASCO DIP-181 and Perkin-Elmer Model 141 instruments.

(9) The achiral route was published by us and by Stevens independently, see: (a) Kametani, T.; Huang, S.-P.; Nakayama, A.; Honda, T. *J. Org. Chem.* **1982**, *47*, 2328. (b) Stevens, R. V.; Albizati, K. *J. Chem. Soc., Chem. Commun.* **1982**, 104.

(10) Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212.

(11) Polonski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, 2453.

(12) Since this cycloaddition afforded the mixture of stereoisomers at the C_3 position of the isoxazolidine, this result would be rationalized by assuming that this reaction would proceed via both the *endo*-crotonate–(*E*)-nitrone and *exo*-crotonate–(*E*)-nitrone transition states. Though the absolute stereochemistry was not determined, compound **6a** seemed to be a single compound and any other diastereomer of **6a** was not detected.

(13) When the hydrolysis of **7a** was carried out without this protection, none of the desired β-lactam was obtained. The formation of δ-lactam was only observed.

(14) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.

(15) On the basis of the results obtained, the enantioselectivity of the 1,3-dipolar cycloaddition reaction of the nitrone with benzyl crotonate was deduced to be higher than 98%, since none of the diastereomers of the desired products were detected in each step of the conversion of **5a** into **11a**, whose $[\alpha]_D$ value is almost the same as that reported.

IR spectra were run on a Hitachi 215 spectrophotometer in $CHCl_3$ solution. NMR spectra were determined with JEOL-PMX-60 and JEOL FX90Q spectrometers in $CDCl_3$ solution, and chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained with JEOL-JMS-OISG2 and JEOL-JMS-D300 spectrometers.

Benzyl (−)-(3,4-*cis*,4,5-*trans*)-3-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-5-methyl-2-((1*S*)-1-phenylethyl)isoxazolidine-4-carboxylate (5a) and Benzyl (−)-(3,4-*trans*,4,5-*trans*)-3-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-5-methyl-2-((1*S*)-1-phenylethyl)isoxazolidine-4-carboxylate (6a). A mixture of aldehyde **1** (5.23 g, 27.3 mmol) and (*S*)-(−)-(α-phenylethyl)hydroxylamine (**2a**) (3.74 g, 27.3 mmol) in 60 mL of dry benzene was heated at 50 °C for 1 h under nitrogen. The solvent was evaporated to give nitrone **3a** as a pale yellowish liquid: NMR ($CDCl_3$) δ 1.20 (t, 3 H, *J* = 7.0 Hz, CO_2CH_2Me), 1.76 (d, 3 H, *J* = 7.0 Hz, NCH(Ph)*Me*), 2.61 (s, 2 H, CH_2CO_2Et), 3.03 (d, 2 H, *J* = 6.0 Hz, N=CHC*H*$_2$), 3.57 (s, 4 H, OCH_2CH_2O), 4.10 (q, 2 H, *J* = 7.0 Hz, CO_2CH_2Me), 5.00 (q, 1 H, *J* = 7.0 Hz, NC*H*(Ph)Me), 6.76 (t, 1 H, *J* = 6.0 Hz, N=C*H*CH$_2$), 7.30 (s, 5 H, 5 × Ar H).

A solution of the above nitrone (**3a**) and benzyl crotonate (**4**) (11.36 g, 64.5 mmol) in 60 mL of dry benzene was refluxed for 16 h under nitrogen. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with benzene–ether (19:1 v/v) afforded the isoxazolidine **5a** (3.09 g, 22.7%) as a yellowish oil: exact mass for M^+ peak, calcd *m/e* 497.2412, found 497.2412; $[\alpha]^{25}_D$ −45.6° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.22 (d, 3 H, *J* = 7.3 Hz, NCH(Ph)*Me*), 1.28 (t, 3 H, *J* = 7.2 Hz, CO_2CH_2Me), 1.48 (d, 3 H, *J* = 6.5 Hz, 5-Me), 2.04 (dd, 1 H, *J* = 14.4, 6.1 Hz, 3-CH*H*), 2.24 (dd, 1 H, *J* = 14.4, 6.3 Hz, 3-CH*H*), 2.78 (s, 2 H, CH_2CO_2Et), 2.80 (dd, 1 H, *J* = 9.0, 8.5 Hz, 4-H), 4.14 (q, 2 H, *J* = 7.2 Hz, CO_2CH_2Me), 5.03 (d, 1 H, *J* = 6.1 Hz, CO_2CHHAr), 5.18 (d, 1 H, *J* = 6.1 Hz, CO_2CHHAr), 7.34 (s, 10 H, 10 × Ar H).

Further elution with the same solvent afforded the isoxazolidine **6a** (3.73 g, 27.4%) as a pale yellowish oil: exact mass for M^+ peak, calcd *m/e* 497.2412, found 497.2410; $[\alpha]^{25}_D$ 37.7° (*c* 1.40, $CHCl_3$); IR 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.19 (t, 3 H, *J* = 7.2 Hz, CO_2CH_2Me), 1.40 (d, 3 H, *J* = 6.8 Hz, NCH(Ph)*Me*), 1.41 (d, 3 H, *J* = 6.3 Hz, 5-Me), 2.04 (dd, 1 H, *J* = 16.6, 7.0 Hz, 3-CH*H*), 2.22 (dd, 1 H, *J* = 16.6, 7.0 Hz, 3-CH*H*), 2.26 (dd, 1 H, *J* = 12.4, 1.5 Hz, CH*H*CO_2Et), 2.42 (dd, 1 H, *J* = 12.4, 1.5 Hz, CH*H*CO_2Et), 3.08 (dd, 1 H, *J* = 9.0, 3.6 Hz, 4-H), 4.04 (q, 2 H, *J* = 7.2 Hz, CO_2CH_2Me), 4.50 (dq, 1 H, *J* = 8.5, 3.6 Hz, 5-H), 5.16 (s, 2 H, CO_2CH_2Ph), 7.26 (s, 5 H, 5 × Ar H), 7.34 (s, 5 H, 5 × Ar H).

(+)-4β-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-3α-((1*R*)-1-hydroxyethyl)azetidin-2-one (7a). A mixture of the isoxazolidine **5a** (2.27 g, 4.57 mmol) and 10% palladium–carbon (1.80 g) in 50 mL of acetic acid was shaken at room temperature under a current of hydrogen (4.5 atm) for 38 h. After filtration of the catalyst, followed by evaporation of the filtrate, the residue was dissolved in 100 mL of acetonitrile. After addition of *N,N'*-dicyclohexylcarbodiimide (1.24 g, 6.02 mmol), the resulting mixture was stirred for 3 h at 60 °C. After filtration, the solvent was evaporated to give a syrup, which was subjected to column chromatography on silica gel. Elution with chloroform–methanol (99:1 v/v) afforded the azetidinone **7a** (320 mg, 24.5%) as a colorless syrup, $[\alpha]^{25}_D$ +14.2° (*c* 1.50, EtOH), which had identical IR and NMR spectra and TLC behavior with those of the racemate.[9]

(−)-1-(*tert*-Butyldimethylsilyl)-3α-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4β-[3-(ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]azetidin-2-one (8a). A mixture of the azetidinone **7a** (250 mg, 0.874 mmol), *tert*-butyldimethylchlorosilane (395 mg, 2.62 mmol), and triethylamine (265 mg, 2.62 mmol) in 10 mL of dry dimethylformamide was stirred at room temperature for 18 h. The mixture was diluted with benzene and washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give a syrup, which was subjected to column chromatography on silica gel. Elution with benzene–acetone (99:1, v/v) afforded the N,O-bis-silylated azetidinone **8a** as a syrup: mass spectrum, *m/e* 516 (M^+ + 1); $[\alpha]^{25}_D$ −27.0° (*c* 1.60, MeCN); IR ($CHCl_3$) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.07 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), 0.22 (s, 3 H, SiMe), 0.25 (s, 3 H, SiMe), 0.82 (s, 9 H, $SiCMe_3$), 0.97 (s, 9 H, $SiCMe_3$), 1.22 (d, 3 H, *J* = 6.5 Hz, CH*Me*), 1.26 (t, 3 H, *J* = 7.2 Hz, CO_2CH_2Me), 2.04 (dd, 1 H, *J* = 12.4, 10.8 Hz, 4-CH*H*), 2.28 (dd, 1 H, *J* = 12.4, 2.5 Hz, 4-CH*H*), 2.63 (d, 1 H, *J* = 14.4 Hz, CH*H*CO_2Et), 2.78 (d, 1 H, *J* = 14.4 Hz, CH*H*CO_2Et), 3.04 (dd, 1 H, *J* = 4.5, 2.5 Hz, 3-H), 3.71 (ddd, 1 H, *J* = 10.8, 2.5, 2.5 Hz, 4-H), 3.97 (s, 4 H, OCH_2CH_2O), 4.16 (q, 2 H, *J* = 7.2 Hz, CO_2CH_2Me).

(+)-3α-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4β-[3-[[(*p*-nitrobenzyl)oxy]carbonyl]-2,2-(ethylenedioxy)propyl]azetidin-2-one (9a) and 6β-[(2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-(1*S*)-1-[[(*p*-nitrobenzyl)oxy]carbonyl]propyl]-4,4-(ethylenedioxy)piperidin-2-one (10a). To a stirred solution of the N,O-bis-silylated azetidinone **8a** (49 mg, 0.095 mmol) in tetrahydrofuran (3 mL)–water (1 mL) was added 0.25 N NaOH (0.38 mL) at room temperature and the resulting mixture was stirred for 2 h. After evaporation of the solvent, the residue and *p*-nitrobenzyl bromide (21 mg, 0.097 mmol) were dissolved in 3 mL of dry dimethylformamide and stirred at room temperature for 2 h. The reaction mixture was partitioned between benzene and water. The organic layer was dried (Na_2SO_4) and evaporated to give a residue. Purification of the residue by preparative TLC (benzene/acetone 100:13 v/v, 3× developed) gave the azetidinone **9a** and the piperidinone **10a**. **9a** (27.5 mg, 56.9%): semisolid; mass spectrum, *m/e* 509 (M^+ + 1); $[\alpha]^{25}_D$ +14.2° (*c* 0.043, MeCN); IR ($CHCl_3$), 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.06 (s, 6 H, $SiMe_2$), 0.84 (s, 9 H, $SiCMe_3$), 1.20 (d, 3 H, *J* = 6.5 Hz, CH*Me*), 2.04 (dd, 1 H, *J* = 14.4, 10.0 Hz, 4-CH*H*), 2.38 (dd, 1 H, *J* = 14.4, 2.5 Hz, 4-CH*H*), 2.68–2.84 (m, 3 H, 3-H and CH_2CO_2PNB), 3.78 (ddd, 1 H, *J* = 10.0, 2.5, 2.5 Hz, 4-H), 4.00 (s, 4 H, OCH_2CH_2O), 4.15 (dq, 1 H, *J* = 6.5, 6.5 Hz, C*H*Me), 5.22 (s, 2 H, CH_2Ar), 6.08 (br s, 1 H, NH), 7.50 (d, 2 H, *J* = 9.4 Hz, 2× Ar H), 8.22 (d, 2 H, *J* = 9.4 Hz, 2× Ar H). **10a** (10.1 mg, 20.9%): semisolid; mass spectrum, *m/e* 509 (M^+ + 1); IR ($CHCl_3$), 1730, 1660 cm^{-1} (C=O); NMR ($CDCl_3$), 0.06 (s, 3 H, SiMe), 0.09 (s, 3 H, SiMe), 0.84 (s, 9 H, $SiCMe_3$), 1.21 (d, 3 H, *J* = 6.5 Hz, CH*Me*), 2.44 (s, 2 H, CH_2CONH), 2.54 (dd, 1 H, *J* = 5.1, 4.2 Hz, C*H*CO_2PNB), 3.76–4.20 (m, 5 H, 5-H and OCH_2CH_2O), 4.34 (1 H, dq, *J* = 6.5, 5.1 Hz, C*H*Me), 5.24 (s, 2 H, CH_2Ar), 6.33 (br s, 1 H, NH), 7.51 (d, 2 H, *J* = 9.4 Hz, 2× Ar H), 8.23 (d, 2 H, *J* = 9.4 Hz).

(+)-3α-((1*R*)-1-Hydroxyethyl)-4β-[3-[[(*p*-nitrobenzyl)oxy]carbonyl]-2-oxopropyl]azetidin-2-one (11a). To a stirred solution of the azetidinone **9a** (21.0 mg, 0.041 mmol) in 3 mL of methanol was added concentrated hydrochloric acid (6 drops) at 5 °C. After it was stirred for 2 h at 5 °C, the mixture was partitioned between phosphate buffer (0.2 M, pH 6.81) and chloroform. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a residue. To the solution of the above residue in 3 mL of dichloromethane was added 60% perchloric acid (4 drops) at 5 °C. The resulting mixture was stirred for 0.5 h at 5 °C and then was partitioned between phosphate buffer (0.2 M, pH 6.81) and chloroform. The organic layer was washed with brine, dried, and evaporated to give a residue. Purification of the residue by preparative TLC (chloroform/methanol 10:1 v/v) gave azetidinone **11a** (13.0 mg, 89.9%) as a solid: mass spectrum, *m/e* 351 (M^+ + 1); mp 123–124 °C; $[\alpha]^{25}_D$ +21.0° (*c* 0.189, $CHCl_3$); IR ($CHCl_3$) 1760, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 3 H, *J* = 6.5 Hz, CH*Me*), 2.82 (dd, 1 H, *J* = 6.5, 2.3 Hz, 3 H), 2.86 (dd, 1 H, *J* = 18.0, 8.0 Hz, 4-CH*H*), 3.10 (dd, 1 H, *J* = 18.0, 5.7 Hz 4-CH*H*), 3.59 (s, 2 H, $COCH_2CO_2PNB$), 3.95 (ddd, 1 H, *J* = 8.0, 5.7, 2.2 Hz, 4-H), 4.17 (dq, 1 H, *J* = 6.5, 6.5 Hz, C*H*Me), 5.28 (s, 2 H, CH_2Ar), 6.16 (br s, 1 H, NH), 7.57 (d, 2 H, *J* = 9.4 Hz, 2× Ar H), 8.24 (d, 2 H, *J* = 9.4 Hz, 2× Ar H).

Benzyl (+)-(3,4-*cis*,4,5-*trans*)-3-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-5-methyl-2-((1*R*)-1-phenylethyl)isoxazolidine-4-carboxylate (5b) and Benzyl (+)-(3,4-*trans*,4,5-*trans*)-3-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-5-methyl-2-((1*R*)-1-phenylethyl)isoxazolidine-4-carboxylate (6b). A mixture of the aldehyde (**1**) (4.86 g, 2.41 mmol) and (*R*)-(+)-*N*-(α-phenylethyl)hydroxylamine (**2b**) (3.30 g, 2.41 mmol) in 60 mL of dry benzene was heated at 50 °C for 1 h under nitrogen. The solvent was evaporated to give the nitrone **3b**, whose NMR spectrum was identical with that of nitrone **3a**.

A solution of the above nitrone (**3b**) and benzyl crotonate (**4**) (10.0 g, 5.68 mmol) in 60 mL of dry benzene was refluxed for 16

h under nitrogen. The same workup described as for the isoxazolidines **5a** and **6a** afforded the isoxazolidines **5b** and **6b**. **5b** (2.70 g, 22.5%): yellowish oil; exact mass for M^+ peak, calcd m/e 497.2412, found 497.2404; $[\alpha]^{25}_D$ +43.9° (c 1.96, $CHCl_3$); IR and NMR spectra of the isoxazolidine (**5b**) were identical with those of the isoxazolidine **5a**. **6b** (3.70 g, 30.9%): yellowish oil; exact mass for M^+ peak, calcd m/e 497.2412, found 497.2412; $[\alpha]^{25}_D$ +41.3° (c 1.36, $CHCl_3$); IR and NMR spectra of the isoxazolidine **6b** were identical with those of the isoxazolidine **6a**.

(−)-4α-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-3β-((1*S*)-1-hydroxyethyl)azetidin-2-one (7b). This compound (**7b**) was prepared from **5b** by using the procedure described for **7a** in 20.1% yield, $[\alpha]^{25}_D$ −14.1° (c 2.23, EtOH).

(+)-1-(*tert*-Butyldimethylsilyl)-3β-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4α-[3-(ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]azetidin-2-one (8b). This compound (**8b**) was prepared from **7b** by using the procedure described for the preparation of **8a** in 52.0% yield, $[\alpha]^{25}_D$ +28.0° (c 1.95, MeCN).

(−)-3β-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4α-[3-[[(*p*-nitrobenzyl)oxy]carbonyl]-2,2-(ethylenedioxy)-propyl]azetidin-2-one (9b) and 6α-[(2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-(1*R*)-1-[[(*p*-nitrobenzyl)oxy]carbonyl]-propyl]-4,4-(ethylenedioxy)piperidin-2-one (10b). The azetidinone **8b** was converted into **9b** and **10b** in 66.7% and 24.0% yields, respectively, by using the procedure described for the preparation of **9a** and **10a**. **9b**: semisolid; $[\alpha]^{25}_D$ −12.7° (c 0.40, MeCN).

(−)-3β-((1*S*)-1-Hydroxyethyl)-4α-[3-[[(*p*-nitrobenzyl)-oxy]carbonyl]-2-oxopropyl]azetidin-2-one (11b). This compound (**11b**) was prepared from **10b** by using the procedure described for **11a**, in 79.8% yield, $[\alpha]^{25}_D$ −19.9° (c 0.156, $CHCl_3$).

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Registry No. 1, 32296-85-8; **2a**, 53933-47-4; **2b**, 67377-55-3; **3a**, 96326-21-5; **3b**, 96326-22-6; **4**, 65416-24-2; **5a**, 96347-28-3; **5b**, 96326-23-7; **6**, 96326-24-8; **7a**, 96392-33-5; **7b**, 96392-34-6; **8a**, 96326-25-9; **8b**, 96392-35-7; **9a**, 96326-26-0; **9b**, 96392-36-8; **10a**, 96326-27-1; **10b**, 96392-37-9; **11a**, 75321-07-2; **11b**, 96392-38-0; (+)-thienamycin, 59995-64-1; (−)-thienamycin, 78339-91-0; 4-nitrobenzyl bromide, 100-11-8.

3-(Acylamido)-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranones. Synthesis of Novel Amino Acid Analogues

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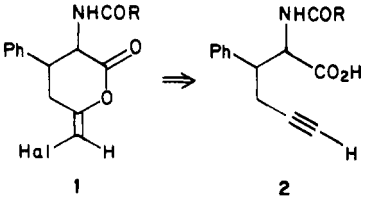
We have synthesized the 3*R**,4*R** and 3*R**,4*S** diastereomers of two 3-(acylamino)-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranones (**13A,B** and **14A,B**) by iodolactonization of substituted 5-hexynoic acid precursors (**11A,B** and **12A,B**). Halolactonization of the 2*R**,3*R** diastereomers (**11A** and **12A**) is considerably more rapid and efficient than that of the 2*R**,3*S** diastereomers (**11B** and **12B**), presumably because of higher torsional strain in the transition states for cyclization of the latter diastereomers. The same 3*R**,4*R** precursor acids (**11A** and **12A**) can also be cyclized under mercuric ion catalysis to the protiolactones **15** or **16**, but the other diastereomers **11B** and **12B** fail to cyclize. These precursor acids are synthesized from a substituted malonic acid (**3**), either by an amination–decarboxylation sequence or by a modified Curtius rearrangement. The lack of stereoselectivity in the Curtius rearrangements of the malonate half ester is accounted for by equilibration of the readily enolizable species under the conditions of the reaction. With each sequence, a mixture of 2*R**,3*R** and 2*R**,3*S** diastereomers were obtained. The assignment of relative configuration of all the intermediates is made by correlation with the corresponding lactones and is based on the magnitude of the ^1H NMR coupling constants. These synthetic methods have permitted the preparation of several α-acylamido-β-phenyl-substituted enol and halo enol lactone systems that are close analogues of the amino acid phenylalanine. These compounds are of interest as potential mechanism-based irreversible inactivators of the serine protease α-chymotrypsin.

We have been interested in the development and synthesis of halo enol lactones as novel enzyme-activated irreversible inhibitors of serine proteases.[1] In connection with our recent investigations extending the synthesis of these halo enol lactones to α-acylamino-substituted systems that mimic the structure of α-amino acids,[1d] we have become particularly interested in the preparation of the α-acylamino-β-phenyl system **1**, as this system bears a close structural resemblance to phenylalanine derivatives which are often very good substrates for α-chymotrypsin. In previous publications, we have demonstrated that halo enol lactones can be prepared efficiently by stereoselective halolactonization of acetylenic acid precursors with electrophilic halogenating agents.[1bd] In this report we describe the use of this halolactonization methodology for the preparation of the desired α-acylamino-β-phenyl systems **1** from the requisite acetylenic amino acid precursors **2**.



1 **2**

Results

Synthesis of the (3*R**,4*R**)- and (3*R**,4*S**)-3-Acetamido- and 3-Benzamido-4-phenyl-6(*E*)-(iodomethylidene)tetrahydropyranones (13A,B and 14A,B).

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