(b) With 10% HCl. A suspension of (+)-1 (1.00 g, 4 mmol) in 10% HCl (10 mL) was heated at 90 °C for 2 h. After the suspension was cooled, the resulting precipitates were collected, washed with H_2O, and dried to give racemic 1 (0.97 g, 97%): mp > 280 °C; $[\alpha]^{22}_D$ +0.0° (c 1, DMF).

Racemization of (-)-1. Racemization of (-)-1 (1.00 g, 4 mmol) was carried out according to method b described for the racemization of (+)-1 to give racemic 1 (0.95 g, 95%): mp > 280 °C; $[\alpha]^{22}_D$ -0.1° (c 1, DMF).

Racemization of 6a. Racemization of **6a** (1.00 g, 3.8 mmol) was carried out according to method b described for the racemization of (+)-1 to give racemic **6a** (0.91 g, 91%): mp > 280 °C; $[\alpha]^{22}_D$ +0.1° (c 1, DMF).

Racemization of 6b. Racemization of **6b** (1.00 g, 3.4 mmol) was carried out in 10% HCl (10 mL) at 90 °C for 15 min to give racemic **6b** (0.90 g, 90%): mp 249-250 °C dec; $[\alpha]^{26}_D$ 0.0° (c 1, DMF).

Rate Constants for Racemization of (+)-1, 6a, and 6b. A solution of (+)-1, **6a**, or **6b** (20 mg) in 20% HCl (1.5 mL)-DMF (0.5 mL) was stirred at 90 °C (or 50 °C) in a sealed tube. After the solution was cooled, the optical rotation (α_t) of the resulting compound was measured. These racemizations can be regarded as first-order reactions because linear relationships are found between ln α_0/α_t and time t, as shown in Figure 2. The rate constant of racemization (k_R/h) was calculated by the least-squares method based on eq 1, where α_0 is the initial value of the optical rotation and α_t is a value of the optical rotation at time t h.

$$\ln \alpha_0/\alpha_t = k_R t \quad (1)$$

Crystallography. The diffraction experiment for the complex of (+)-1 with brucine was carried out using a colorless transparent prism with dimensions of 0.70 × 0.30 × 0.10 mm^3 obtained from ethanol-water. The four-circle diffractometer (AFC/5, RIGAKU) was used with graphite-monochromated CuKα radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular setting of 20 reflections (2θ values in the range of 40-60°). The structure was solved by the direct methods using SIR85[14] and difference Fourier method. The refinement of atomic parameters was carried out using full-matrix least-squares methods with anisotropic temperature factors for the non-hydrogen atoms. Of 36 hydrogen atoms, 23 atoms were located on the difference Fourier maps and refined with isotropic temperature factors. The positions of other hydrogen atoms were assumed geometrically and fixed throughout the refinement. The anomalous scattering factors of N and O atoms were included in the refinement. Throughout the refinement, the function $\sum w(|Fo| - |Fc|)^2$ was minimized. During the final refinement stage, the weighting scheme of $\sqrt{w} = 1/\sigma|Fo|$ was used. The final R value was 0.052 (Rw = 0.061). The atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[15]

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Supplementary Material Available: Crystal data parameters, final atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles for the complex of (+)-**3** with brucine (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Formation of 3-[1'-(Dimethylphenylsilyl)ethyl]azetidin-2-ones: Stereocontrolled Formal Approach to (±)-Thienamycin and (±)-β-(Hydroxyalkyl)aspartic Acid Derivatives

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Reaction between (±)-β-(dimethylphenylsilyl)alkanoyl chlorides and imines of glyoxylic esters provided a route to (±)-*cis*-3-[1'-(dimethylphenylsilyl)ethyl]-4-alkoxycarbonyl β-lactams, while addition of the Fleming's silylcuprate reagent to methyl crotonate and further enolate trapping by the above imines furnished the corresponding (±)-*trans*-3-[1'-(dimethylphenylsilyl)ethyl]-4-alkoxycarbonyl β-lactams. These β-lactams, upon appropriate chemical manipulations, provided a stereocontrolled route to (±)-thienamycin precursors and (±)-β-(hydroxyalkyl)aspartic acid derivatives.

Appropriately substituted monocyclic azetidin-2-ones have wide applicability in the synthesis of β-lactam antibiotics[1] and also in the preparation of many natural products including both α- and β-amino acids.[2] One example is the β-lactam 1 derived from aspartic acid,[3] which upon chemical manipulations affords suitable intermediates for natural product synthesis,[4] including a variety of

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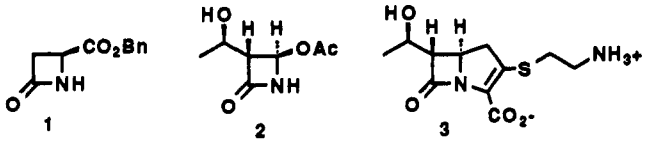
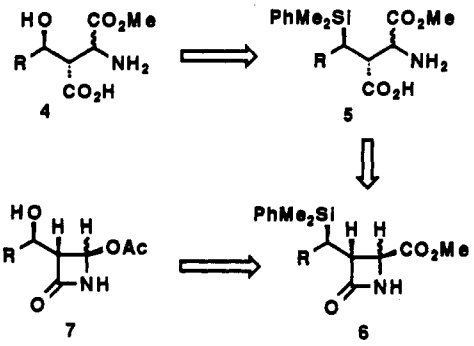
monocyclic β-lactams like **2**, a precursor of the carbapenem antibiotic thienamycin[5] (**3**). Aspartic acid itself can also



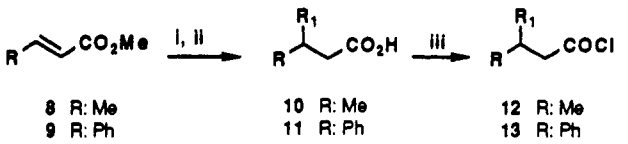
be elaborated through its β-anion derivative[6] to non-proteinogenic amino acids, a class of compounds that represents an important group of natural products because of their varied biological and biochemical properties.[7] For example, β,γ-unsaturated amino acids have been found to be reversible or irreversible enzyme inhibitors[8] and thus a number of methods have been proposed for their synthesis.[7c,6d] One of them involves prior formation of β-(hydroxyalkyl)aspartic acids followed by a carboxy–hydroxy elimination step to furnish the desired β,γ-unsaturated amino acids in good to excellent yields.[6d]

In a recent project directed toward the synthesis of these compounds, we focused our attention on β-lactams **6**, which, upon $N–C_2$ bond cleavage (Scheme I), would render the corresponding aspartic acid derivatives **5** as precursors of β-(hydroxyalkyl)aspartic acids **4**. The synthesis of β-lactams carrying the 1′-(dimethylphenylsilyl)alkyl group at the C_3 position has been previously reported by Fleming and Kilburn, using the hydroxamate methodology,[9] and also by Hart et al.[10] through the lithium ester enolate–imine condensation. However, condensation of lithium ester enolates with imines of glyoxylic esters has proved to be unsuccessful.[11] In general, the metal enolate–glyoxylic ester imine condensation works well with tin(II) enolates, silyl ketene acetals, and boron enolates, to give the corresponding β-substituted aspartic acid derivatives in good to excellent stereoselectivities,[12] which at once could be cyclized by standard procedures.[12,13] Recently, we have described[14] that the organocopper enolate–glyoxylic ester imine condensation could be an efficient alternative to the above approaches leading to trans β-lactams **6** in both excellent chemical yield and stereoselectivity. Alternatively, the β-(dimethylphenylsilyl)butanoyl chloride–glyoxylic ester imine condensation[15] was found to be a good approach for synthesis of the corresponding cis β-lactams **6**.

Scheme I



Scheme II[a]

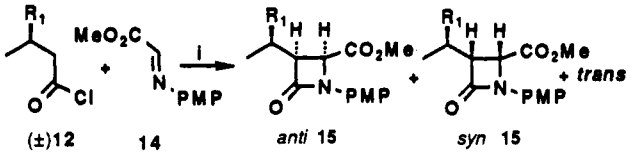


8 R: Me, **9** R: Ph; **10** R: Me, **11** R: Ph; **12** R: Me, **13** R: Ph

a R_1: $PhMe_2Si$, b R_1: Ph_2MeSi, c R_1: Ph_3Si, d R_1: $Ph_2{}^tBuSi$

[a] Reagents and conditions: (i) $(R_1)_2CuCNLi_2$, THF, 0 °C, 20 min; (ii) KOH, MeOH, reflux; (iii) ClCOCOCl, CH_2Cl_2, rt, 1 h.

Scheme III[a]



(±)**12**, **14**, *anti* **15**, *syn* **15**

a R_1: $PhMe_2Si$, b R_1: Ph_2MeSi, c R_1: Ph_3Si, d R_1: $Ph_2{}^tBuSi$

[a] Reagents and conditions: (i) NEt_3, solvent, reflux, 14 h. Abbreviations: PMP, 4-$MeOC_6H_4$.

In this paper we present the details of our methodology for the construction of both cis and trans β-lactams of type **6** as well as their utility in the synthesis of the (±)-thienamycin precursor **7** (R = Me) and (±)-β-(hydroxyalkyl)-aspartic acid derivatives of type **4** with control of the relative stereochemistry at the three chiral centers.

Results and Discussion

Acid Chloride–Methyl Glyoxalate Imine Condensation. The construction of monocyclic β-lactams by the [2 + 2] cycloaddition reaction of ketenes to imines has proved to be particularly successful with acid chlorides bearing electron-withdrawing substituents at the α-position. However, the direct preparation of 3-alkyl β-lactams from monoalkylketenes, generated from their corresponding acid chlorides, is often limited in scope.[16] Even if the formation of 3-(1′-hydroxyethyl) β-lactams has been reported[17] to occur from O-protected 3-hydroxybutyric acid chlorides and phenyl glyoxal imines, such a reaction affords only low yields (3–10%) of β-lactams when carried out

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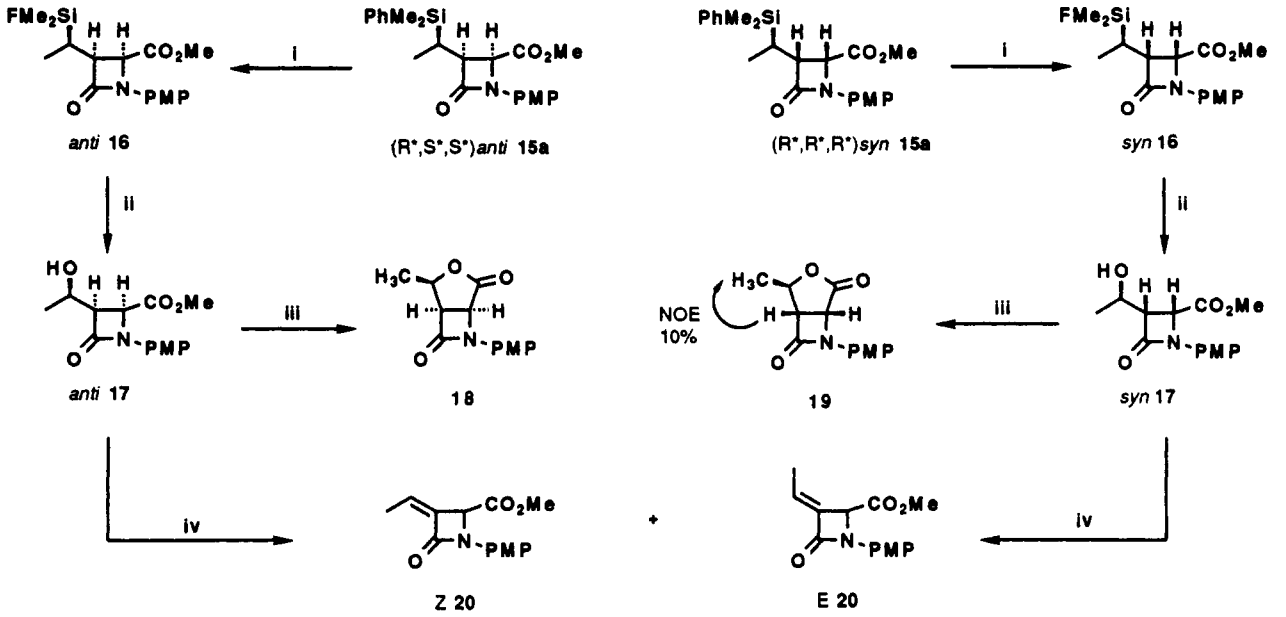
Scheme IV[a]



[a] Reagents and conditions: (i) HBF_4·OEt_2, CH_2Cl_2, 0 °C → rt, 1 h; (ii) $MeCO_3H$, AcOH (32%), NEt_3, 0 °C → rt, 3 h; (iii) BF_3·OEt_2, CH_2Cl_2, rt, 20 min; (iv) $MeSO_2Cl$, pyridine, rt, 30 min, then DBU, benzene, reflux.

from glyoxylic ester imines.[18] In previous papers from our[15,19] and other laboratories,[20] it has been established that the reaction of α-unactivated alkanoyl halides with imines of glyoxylic esters efficiently affords the corresponding 3-alkyl β-lactams in a single synthetic step, thus providing a solution to the aforementioned problem. In our approach, several alkanoyl halides can be used as starting materials, most notably, the β-(dimethylphenylsilyl)butanoyl chloride, which, upon treatment with an imine of glyoxylic methyl ester and further N-deprotection of the resulting β-lactam, provided a route to compounds of type **6**.

The starting acid chlorides **12** (Scheme II) could be easily prepared by saponification of the corresponding methyl esters and further oxalyl chloride activation of the resulting carboxylic acids. In general, β-silylbutanoic esters can be formed from α,β-unsaturated esters in yields ranging from 50 to 67% by addition of the corresponding silylcuprate reagent to methyl crotonate (**8**) following a standard protocol.[21] When the acid chloride **12a** (Scheme III) was allowed to react with the methyl glyoxalate imine **14** in refluxing hexane for 14 h, a mixture of cis and trans β-lactams was produced in 76% isolated yield and in a 66:34 ratio, respectively. The cis isomers were isolated from the corresponding trans isomers by column chromatography and the corresponding cis,anti and cis,syn isomers of the β-lactam **15a** were separated by crystallization from methanol. In a subsequent experiment to achieve a better stereoselective control of the β-lactam formation, following observations on related [2 + 2] cycloadditions,[22] we examined the influence of the solvent. We found that the ratio of cis-anti isomer was increased when the reaction was carried out in a more polar solvent, like acetonitrile. Under these conditions, the ratio of cis isomers increased up to 82% and 18% of the corresponding trans isomers was detected by ^1H NMR from the crude reaction mixture. The relative stereochemistry of diastereomeric β-lactams **15a**, anti and syn, respectively, according to the nomenclature introduced by Masamune,[23] was established on the basis of their respective ^1H NMR spectra and some chemical correlations which will be discussed later.

After studying the influence of the solvent on the stereoselectivity of the reaction, the cycloaddition was examined for different β-silylalkanoyl chlorides carrying diverse silyl groups. Thus, under the same conditions as those used for the formation of **15a**, compounds **15b–d** were obtained in yields varying in the range 50–86%. The results summarized in Table I indicated that an increase in the bulkiness of the silyl moiety has little effect on the cis:trans ratio, but a moderate increase in the anti:syn ratio is observed for cis isomers by using β-(triphenylsilyl)butanoyl chloride (**12c**) or β-(*tert*-butyldiphenylsilyl)butanoyl chloride (**12d**). Furthermore, the cis-anti isomers of compounds **15c** and **15d** were readily isolated from the reaction crudes by crystallization from methanol, affording these compounds in 41% and 60% isolated yields. The stereochemistry of cis and trans isomers was determined on the basis of their ^1H NMR spectral data. Thus, the proton at C_4 in cis isomers shows as a doublet between 4.4 and 4.6 ppm ($J \approx 5$–6 Hz) while the corresponding one in trans isomers appears at 4.0–4.1 ppm ($J \approx 2$ Hz). In general, the C_4-H proton in a trans isomer appears at higher fields than the corresponding C_4-H proton in the respective cis isomer.

The first attempt at determining the ratio of epimers for compounds **15** was (Scheme IV) by the conversion of the silyl moiety into the hydroxyl group and further elimination to the alkenes **20**, according to the Pecquet and d'Angelo protocol used on similar compounds.[24] Conversion of *anti*-**15a** into the β-lactam *anti*-**17** was easily accomplished following Fleming's methodology.[9,21] Ac-

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Table I. Results of Cycloaddition Reaction between β-(Trialkylsilyl)alkanoyl Halides 12 and the Methyl Glyoxalate Imine 14[a]

				ratio isomers 15[c]			
				cis			trans
compd	R_1	solvent	yield, %[b]	anti	mp, °C[d]	syn	
15a	$PhMe_2Si$	hexane	76	38	107–108	28	34
		CH_3CN	47	54	(hexane)	28	18
15b	Ph_2MeSi	hexane	68	37	syrup	32	31
		THF	63	44		34	22
		CH_3CN	50	55		27	18
15c	Ph_3Si	hexane	77	52	224–225	23	25
		CH_3CN	64	65	(MeOH)	18	17
15d	$Ph_2{}^tBuSi$	hexane	78	52	168–169	15	33
		C_6H_6	81	58	(hexane–CH_2Cl_2)	14	28
		CH_3CN	86	70		14	16

[a] Reactions conducted on 5-mmol scale. [b] Yields based on weight of isolated product by column chromatography. [c] All percentages refer to diastereomeric ratios, determined from the crude reaction mixtures. [d] Melting points correspond to *cis,anti*-**15** isomers. Crystallization solvent indicated in parentheses.

cordingly, reaction between *anti*-**15a** and the $HBF_4{\cdot}OEt_2$ complex followed by peracetic acid oxidation of the resulting intermediate fluoride *anti*-**16** afforded the expected hydroxy compound *anti*-**17** in 40% isolated yield together with the cyclized product **18** in 55% yield. Treatment of compound *anti*-**17** with boron trifluoride in methylene chloride as solvent cleanly afforded the lactone **18** in 70% isolated yield. Similarly, when the β-lactam *syn*-**15a** was subjected to the foregoing reaction sequence, the hydroxy compound *syn*-**17** was obtained as single reaction product. This compound upon treatment with boron trifluoride provided the expected lactone **19** in 70% isolated yield. Mesylation of both anti and syn isomers of the β-lactam **17** followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promoted elimination gave a mixture of the corresponding *E* and *Z* alkenes **20**. However, from this method it was not possible to determine the relative stereochemistry at $C_{1'}$ and C_3 positions. Under the above conditions, the hydroxy derivative *anti*-**17** afforded *E* and *Z* alkenes **20** in a ratio of 2:1, respectively, and the syn isomer of **17** furnished an equimolar mixture of both alkenes. These alkenes were separated by crystallization from ethanol and characterized as previously reported from this laboratory.[16]

At this stage, we were able to determine the stereochemistry at $C_{1'}$ and C_3 by means of NOE experiments made on lactones **18** and **19**, respectively. Thus, by presaturation of the methyl group of the lactone **19**, a 10% NOE was observed in the signal corresponding to the C_3-H proton, whereas in the case of lactone **18** no enhancement was detected. Consequently, from this observation, we assigned the relative stereochemistry $1'R^*,3S^*,4S^*$ to compound *anti*-**15a** and $1'R^*,3R^*,4R^*$ to compound *syn*-**15a**. The most relevant ^1H NMR data of β-lactams **15a–d** are compiled in Table II and show that in each case the lower field H_3 and higher field H_4 protons could be assigned to the *cis,syn*-**15** isomers having the larger $J_{3,4}$ values (6.3 Hz) and the smaller $J_{1',3}$ values (2.1–3.6 Hz).[25]

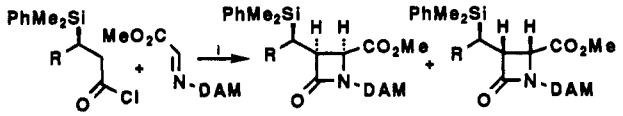
As the best stereoselection in β-lactam formation was observed for azetidinones **15c** and **15d** carrying the triphenylsilyl and *tert*-butyldiphenylsilyl groups, respectively, we tried at this stage to achieve their two-step hydroxylation. However, treatment of the triphenylsilyl β-lactam **15c** with the $HBF_4{\cdot}OEt_2$ complex followed by peracetic acid oxidation under Fleming's protocol did not allow the formation of any detectable amount of the expected 3-(1′-hydroxyethyl) β-lactam. In contrast, the parent *tert*-butyldiphenylsilyl derivative **15d** upon treatment with the $HBF_4{\cdot}OEt_2$ complex in methylene chloride containing acetic acid afforded, after 20 h of reaction at room temperature, the desired fluorosilane. Unfortunately, attempted transformation of such a fluorosilane into the corresponding hydroxy compound by means of peracetic acid was unfruitful and the starting compound was recovered unchanged. The use of other oxidizing reagents, such as *m*-chloroperbenzoic acid–triethylamine[26] or KF/H_2O_2 in *N,N*-dimethylformamide,[27] caused formation of complex mixtures without detection of the desired 3-(1′-hydroxyethyl) β-lactam **17**.

Table II. Significative ^1H NMR Data of Cis Compounds 15a–d[a]

	δ (ppm)		J (Hz)	
compd	H_3	H_4	$J_{3,4}$	$J_{1',3}$
anti-**15a**	3.41	4.54	5.7	12.3
syn-**15a**	3.70	4.43	6.3	3.6
anti-**15b**	3.46	4.54	5.7	11.7
syn-**15b**	3.71	4.42	6.3	3.0
anti-**15c**	3.51	4.57	5.7	11.1
syn-**15c**	4.07	4.45	6.3	2.7
anti-**15d**	3.42	4.65	5.7	9.6
syn-**15d**	3.96	4.42	6.3	2.1

[a] Determined by 300-MHz ^1H NMR spectroscopy in $CDCl_3$ solution.

Scheme V[a]



12a R: Me **13a** R: Ph — **21** — *anti* **22** R: Me, *anti* **23** R: Ph — *syn* **22** R: Me, *syn* **23** R: Ph

[a] Reagents and conditions: (i) NEt_3, solvent, reflux, 14 h. Abbreviations: DAM, $(4\text{-}MeOC_6H_4)_2CH$.

In view of the preceding results, the dimethylphenylsilyl group was considered the most adequate to constitute a precursor of the hydroxy function in β-lactams. Consequently, we next attempted to improve the stereoselectivity of the cycloaddition step by increasing the bulkyness of the imino component of the reaction.[28] To achieve our goal (Scheme V), we examined the method for the imine **21**, derived from methyl glyoxalate and di-*p*-anisylmethylamine (DAM-NH_2).[29] We have found that when a mixture of the methyl glyoxalate imine **21** and triethylamine was treated with β-(dimethylphenylsilyl)butanoyl chloride (**12a**) in refluxing hexane for 14 h, an 88% yield of the corresponding cis isomers of the β-lactam **22** was obtained without traces of the corresponding trans isomers. A similar result was found when the acid chloride

(25) (a) For related observations on similar compounds, see: Burnett, D. A.; Gallucci, J. G.; Hart, D. J. *J. Org. Chem.* **1985**, *50*, 5120. (b) For correlation data on 3-(1′-hydroxyethyl) β-lactams, see: Cainelly, G.; Panuncio, M.; Basile, T.; Bongini, A.; Giacomini, O.; Martelli, G. *J. Chem. Soc., Perkin Trans. I* **1987**, 2637.

(26) Tamao, K.; Kakui, T.; Kumada M. *J. Am. Chem. Soc.* **1978**, *100*, 2268.

(27) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.

(28) (a) Moore, H. W.; Hughes, G.; Srinivasachar, K.; Fernandez, M.; Nguyen, N. V.; Schau, D.; Tranne, A. J. *J. Org. Chem.* **1985**, *50*, 4231. (b) Arrieta, A.; Lecea, B.; Palomo, C. *J. Chem. Soc., Perkin Trans. I* **1987**, 845. (c) Aizpurua, J. M.; Cossio, F. P.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* **1986**, *27*, 4359.

(29) (a) Kobayashi, Y.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3041. (b) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron* **1988**, *44*, 2149. (c) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767.

Table III. Results of Cycloaddition Reaction between β-(Trialkylsilyl)alkanoyl Halides 12a and 13a and Methyl Glyoxalate Imine 21[a]

				isomers ratio[c]		^{1}H NMR			
						anti		syn	
compd	R	solvent	yield, %[b]	anti	syn	$\delta(H_4)$	$J_{1',3}$	$\delta(H_4)$	$J_{1',3}$
22	Me	hexane	88	66	34	4.03	12.3	3.88	3.7
		CH_2Cl_2	76	70	30				
		CH_3CN	70	71	29				
23	Ph	CH_3CN	70	68	32	3.80	12.9	3.74	4.0
		CH_2Cl_2	71	91	9				

[a] Reactions conducted on 5-mmol scale. [b] Yields based on weight of isolated product by column chromatography. [c] All percentages refer to diastereomeric ratios, determined from the crude reaction mixtures.

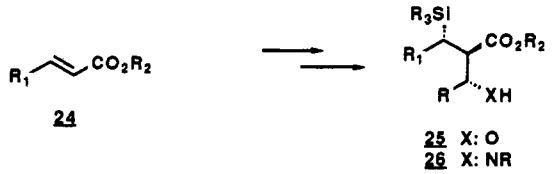
Table IV. Preparation of β-Lactams 29–30 from α,β-Unsaturated Esters 27 and Methyl Glyoxalate Imine 14[a]

			^{1}H NMR			
compd	yield, %[b]	mp, °C	$\delta(H_4)$	$\delta(H_3)$	$J_{3,4}$	$J_{1',3}$
29a	80	80–82	4.16	3.34	2.4	5.1
29b	65	syrup	3.91	2.81	2.4	10.5
30b	11	syrup	4.37	4.10	5.7	13.5
29c	85	89–90	4.19	3.25	2.5	
29d	74	syrup	3.91	3.75	2.4	10.2
30d	64	syrup	4.32	4.06	5.5	13.4

[a] Reactions conducted on 5-mmol scale. [b] Yields based on weight of isolated product by column chromatography.

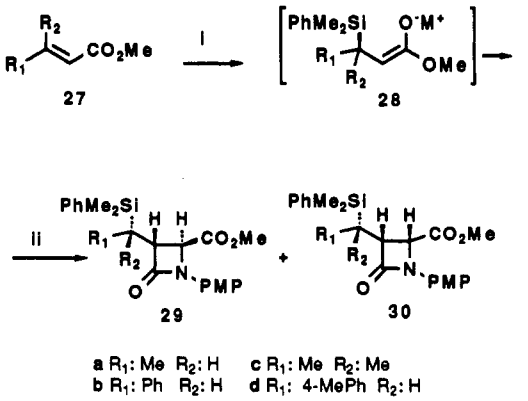
13a was employed in such a cycloaddition reaction to furnish the desired β-lactam **23** in 71% yield exclusively as the cis isomer. Results of some experiments are listed in Table III to illustrate the efficiency of this bulky Schiff base to control the stereoselectivity of the cycloaddition reaction.

Organocopper Enolate–Glyoxylic Ester Imine Condensation. In a previous paper from our laboratory,[16] we showed that addition of Fleming's silylcuprate reagent to α-ethylidene β-lactams provided a route to 3-[1′-(dimethylphenylsilyl)ethyl] β-lactams in good yields but in modest stereoselectivity. The straightforward methodology for the conjugate addition of a silylcuprate reagent to α,β-unsaturated esters **24** followed by enolate trapping by



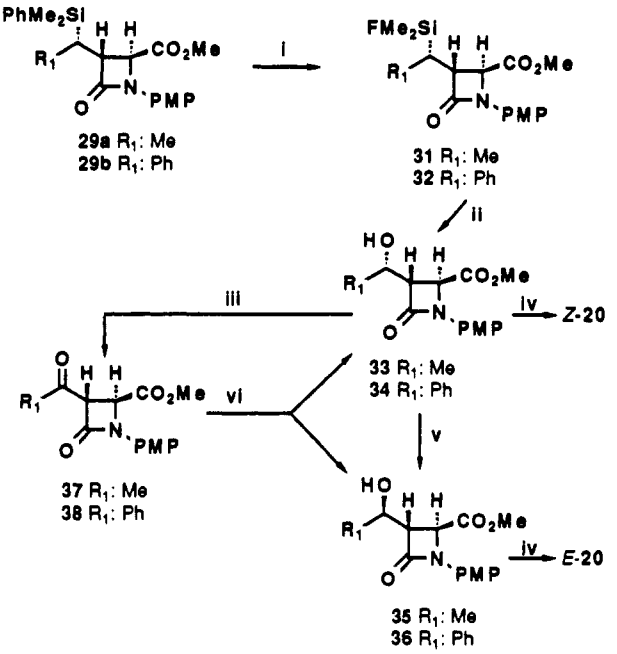
carbonyl compounds constitutes an excellent general procedure for the synthesis of aldol products **25** with concomitant construction of three constiguous chiral centers under very high levels of stereoselectivity.[9,21] Based on this principle, we thought that the use of a methyl glyoxalate imine instead of a carbonyl compound in the last step of the above protocol could give the β-amino ester **26** with an analogous level of stereocontrol. We found that addition of Fleming's silylcuprate reagent to methyl crotonate (**27a**), followed by trapping of the in situ-generated enolate by the methyl glyoxalate imine **14** in THF as solvent, afforded directly the β-lactam **29** in 80% yield as the single diastereomer (Scheme VI). Similarly (see Table IV), when the above two-step procedure was carried out on methyl cinnamates **27b** and **27d**, the corresponding trans β-lactams **29b** and **29d** were produced as major diastereomers together with small amounts of the corresponding cis isomers **30**. In the case of methyl 2-methylbut-2-enoate (**27c**), only the trans β-lactam **29c** was

Scheme VI[a]



[a] Reagents and conditions: (i) $(PhMe_2Si)_2CuCNLi_2$, THF, 0 °C, 20 min; (ii) PMP-N=CHCO$_2$Me (**14**), THF, 0 → 20 °C, 3 h.

Scheme VII[a]



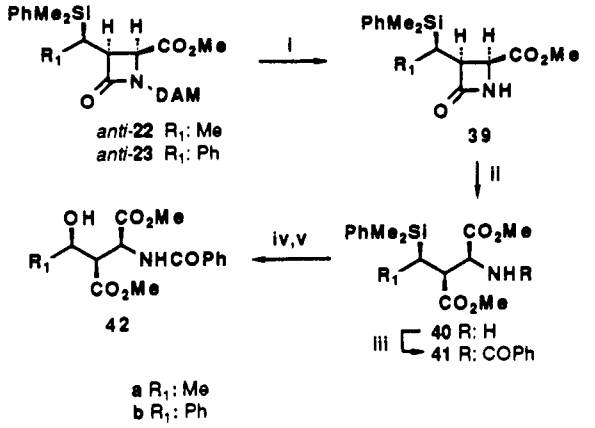
[a] Reagents and conditions: (i) $HBF_4{\cdot}OEt_2$, CH_2Cl_2, 0 °C → 20 h; (ii) $MeCO_3H$, $MeCO_2H$ (32%), NEt_3, 0 °C → rt, 3 h; (iii) NDC, pyridine, C_6H_6, rt 2 h; (iv) $MeSO_2Cl$, pyridine, rt, 30 min, then DBU, C_6H_6, reflux; (v) PPh_3, DEAD, HCO_2H, 0 → 25 °C, 1.5 h, then MeOH, HCl, 25 °C, 1 h; (vi) $NaBH_4$, MeOH–THF (2:1), rt, 30 min.

produced in 85% yield. The assignment of a cis or a trans stereochemistry to these compounds was made by examining the values of the coupling constants $J_{3,4}$, vide supra.

On the other hand, the relative stereochemistry of compound **29a** at $C_{1'}$ and C_3 was determined by two different paths (Scheme VII). First, it was submitted to the fluorination–oxidation sequence described earlier for cis analogues, to give the pure 3-(1′-hydroxyethyl) β-lactam **33** in 81% overall yield. Its conversion into the corresponding methanesulfonate, followed by stereoselective elimination,[24] afforded the alkene[16] (*Z*)-**20**, indicating an anti relationship at $C_{1'}$–C_3 for the parent compound **29a**. As expected, alkene (*E*)-**20** could also be obtained in a similar fashion from the epimer **35**, which, in turn, was derived quantitatively from **33** by the Mitsunobu reaction[30] using

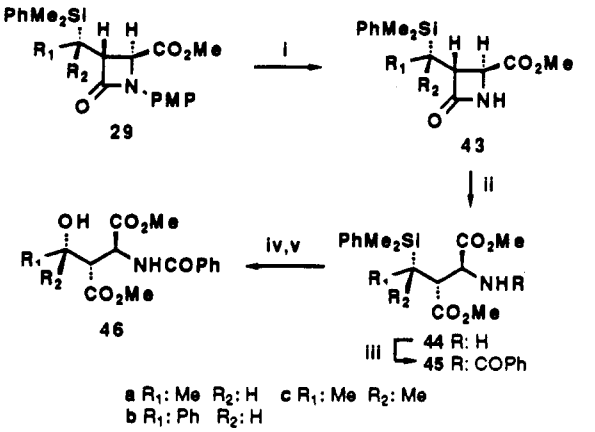
(30) Mitsunobu, O. *Synthesis* **1981**, 1. For application in β-lactam chemistry, see, for example: Corbett, D. F.; Coulton, S.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 3011. Melillo, D. G.; Shinkai, T.; Liu, K.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.

Scheme VIII[a]



[a] Reagents and conditions: (i) $(NH_4)_2Ce(NO_3)_6$, $CH_3CN{\cdot}H_2O$, −10 °C, 3 h; (ii) $ClSiMe_3$ (5 equiv), MeOH, rt, 4 h; (iii) PhCOCl, NEt_3, CH_2Cl_2, rt; (iv) $HBF_4{\cdot}OEt_2$, CH_2Cl_2, 0 °C → rt, 16 h; (v) CH_3CO_3H (32% in AcOH), NEt_3, CH_2Cl_2, 0 °C → rt, 3.5 h.

Scheme IX[a]



[a] Reagents and conditions: (i) $(NH_4)_2Ce(NO_3)_6$, $CH_3CN{\cdot}H_2O$, 0 °C, 45 min; (ii) $ClSiMe_3$ (5 equiv), MeOH, rt, or reflux; (iii) PhCOCl, NEt_3, CH_2Cl_2, rt; (iv) $HBF_4{\cdot}OEt_2$, CH_2Cl_2, 0 °C → rt, 16 h; (v) CH_3CO_3H (32% in AcOH), NEt_3, CH_2Cl_2, 0 °C → rt, 3.5 h.

formic acid as a nucleophile, followed by acid hydrolysis. The second path for confirming the proposed stereochemistry consisted of the borohydride reduction of the 3-acetyl β-lactam **37**, easily obtained by oxidation[31] of **33**. The result of such a reduction was a 60:40 mixture of alcohols **33** and **35** in which the anti epimer predominates, in good agreement with previous observations of Bouffard el at. on related reductions.[32] This last method was choosen to confirm the relative stereochemistry at C_1–C_3 for the β-lactam **29b**. Thus, the same sequence of reactions as above gave the expected 3-benzoyl β-lactam **38** in good yield. Reduction of this compound with sodium borohydride in methanol resulted in an epimeric mixture of alcohols (75:25) in which the major isomer was assigned to the anti epimer **34**.

Since **35** can be stereospecifically obtained from **29a** via Mitsunobu reaction and both N_1 and C_4 groups can be easily elaborated to the β-lactam **2**,[5,11] our procedure constitutes a highly stereoselective formal synthesis of (±)-thienamycin (**3**).

Formation of β-(Hydroxyalkyl)aspartic Acids. Conversion of the β-lactams, prepared as above, into β-(hydroxyalkyl)aspartic acids was accomplished following the sequences illustrated in Schemes VIII and IX. First, the cis β-lactam *anti*-**22** was N-deprotected[33] (Scheme VIII), giving the expected NH azetidin-2-one **39** in 80% yield. The β-lactam ring opening, achieved by means of trimethylchlorosilane in methanol,[34] afforded the expected dimethyl aspartate **40a** in 70% yield, which was isolated as the *N*-benzoyl derivative **41a**. Similarly, the β-lactam *anti*-**23** upon N-deprotection and further β-lactam cleavage of the resulting NH azetidin-2-one **39b** furnished the β-amino ester **40b** in 83% yield, which was also isolated as the *N*-benzoyl derivative **41b**. Conversion of these compounds into their corresponding hydroxy derivatives was performed according to the usual Fleming protocol. For example, when compound **41a** was successively treated with the $HBF_4{\cdot}OEt_2$ complex and peracetic acid, the corresponding dimethyl β-(hydroxyalkyl)aspartate was obtained in 72% yield. Under similar reaction conditions **41b** provided **42b** in 65% isolated yield.

Next, the above sequence of reactions was tested for trans 4-methoxycarbonyl β-lactams **29**, Scheme IX, prepared by the organocopper enolate–imine methodology. Thus, the β-lactam **29a** upon N-dearylation furnished the NH azetidin-2-one **43a** in 92% yield, which was isolated by column chromatography, using hexane–EtOAc (1:1) as eluant. Similarly, compounds **29b** and **29c** gave the corresponding N-unsubstituted derivatives **43** in yields of 70% and 65%, respectively. The opening of the β-lactam ring was achieved as above by treating compounds **43a** and **43b** with trimethylchlorosilane–methanol at room temperature. In the case of compound **43c**, the reaction might be accomplished under reflux conditions to give **44c** in 95% yield. All of these compounds were obtained as syrups and used without further purification in the next step. Protection of the amino group as the benzoyl derivative was carried out under usual conditions by using a slight excess of benzoyl chloride and triethylamine as base and the resulting products were purified by flash column chromatography using hexane–methylene chloride (15:1) as eluant to separate the remaining benzoyl chloride.

Conversion of these β-amino esters into the corresponding β-(hydroxyalkyl)aspartates **46** was achieved under standard conditions by treating them with the $HBF_4{\cdot}OEt_2$ complex in methylene chloride at room temperature. Compound **45a** was completely transformed into its corresponding fluoride with 3 equiv of the above complex, but compounds **45b** and **45c** required 5 equiv of the reagent for completion. The resulting crude fluorides were subjected to treatment with peracetic acid in the presence of triethylamine to furnish the dimethyl β-(hydroxyalkyl)aspartates **46a–c** in excellent yields.

Conclusion

In summary, the use of the dimethylphenylsilyl group as a masked hydroxy function and the choice of the appropriate method for the azetidin-2-one ring formation (acid chloride or organocopper enolate) allows a highly diastereoselective transformation of glyoxylic ester derived imines into either *cis*- or *trans*-3-[1′-(dimethylphenylsilyl)alkyl]-4-methoxycarbonyl β-lactams as intermediates for both β-lactam antibiotics and β-(hydroxyalkyl)aspartic

(31) Cossio, F. P.; Lôpez, M. C.; Palomo, C. *Tetrahedron* **1987**, *43*, 3963. See also: Matikainen, K. T.; Kaltia, S. A. A.; Hase, T. A.; Ssundberg, M. R. *J. Chem. Res., Synop.* **1990**, 150; *J. Chem. Res., Miniprint* **1990**, 1117.

(32) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208.

(33) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(34) Palomo, C.; Arrieta, A.; Cossío, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429. For related methods, see: (a) Hauser, F. M.; Ellenberger, S. R.; Rhee, R. P. *J. Org. Chem.* **1987**, *52*, 5041. (b) For a review on β-lactam cleavage, see: Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.

acid derivatives. The present study establishes the basis for the preparation of the above compounds in a optically active pure form, via enantiomerically pure β-silyl carboxylic acids or derivatives.[35]

Experimental Section

Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. Proton nuclear magnetic resonance spectra and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5930 A spectrometer operated at 70 eV. Microanalytical data were obtained on a Perkin-Elmer 240-C instrument. Commercially available compounds were used in this work without further purification or were prepared by following literature procedures. Acetonitrile and hexane were dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled.

Preparation of β-Silylbutanoic Acids 10a–d and β-Phenyl-β-silylpropanoic Acids 11a–c. General Procedure. A solution of the corresponding silyllithium (1 M, 100 mL, 100 mmol) in tetrahydrofuran was added dropwise over dry CuCN (4.46 g, 50 mmol) kept under nitrogen while being stirred at 0 °C. The dark suspension was stirred for 30 min at the same temperature and then methyl crotonate (5.30 mL, 50 mmol) in tetrahydrofuran (5 mL) or methyl cinnamate (8.10 g, 50 mmol) in the same solvent (5 mL) was added. The solution was stirred for 30 min at 0 °C, poured into methylene chloride (20 mL) and saturated NH_4Cl (100 mL), and stirred for 15 min again. Then, the organic layer was filtered through a pad of Celite, dried, and evaporated to yield the corresponding crude methyl β-silylbutanoate, which was saponified without further purification. Thus, KOH (2.8 g, 50 mmol) was added to a solution of the ester in methanol (50 mL) and water (4 mL), and the solution was refluxed for 3 h. This solution was cooled and poured into 0.5 M KOH (200 mL) and diethyl ether (50 mL). The organic layer was separated, and the aqueous phase was washed with diethyl ether (50 mL). The aqueous phase was acidified with 6 N HCl and extracted with diethyl ether (3 × 50 mL), and the organic layer was dried (Na_2SO_4) and evaporated to yield the corresponding β-silylbutanoic acid, which was purified by reduced pressure distillation or crystallization (hexane/methylene chloride).

Reaction between β-Silylalkanoyl Chlorides and Methyl Glyoxate Imines. General Procedure for the Preparation of β-Lactams 15, 22, and 23. Oxalyl chloride (0.51 mL, 6 mmol) was added dropwise in methylene chloride (5 mL) to a cold (0 °C) solution of pure β-silylbutanoic acid or β-phenyl-β-silylpropanoic acid (3 mmol) in dry methylene chloride (15 mL). After stirring for 1 h at room temperature, the solvent was evaporated in vacuo at 0–5 °C, and the crude acyl chloride was dissolved in the solvent of choice, preferably, methylene chloride (5 mL). This solution was added dropwise to a cooled (0 °C) mixture of the corresponding methyl glyoxalate imine (2 mmol) and triethylamine (0.63 mL, 4.5 mmol) in the same solvent (15 mL) during 10 min. After the ice bath was removed, the reaction mixture was heated at reflux for 20 h and then diluted in methylene chloride (50 mL) and washed successively with H_2O (50 mL), 1 M HCl (50 mL), saturated $NaHCO_3$ (50 mL), and H_2O (50 mL). Drying over $MgSO_4$ and evaporation of solvents yielded the corresponding crude β-lactams as mixtures of anti,cis and syn,cis isomers, which were separated by column chromatography (silica gel; eluent: hexane–methylene chloride 5:1).

Reaction between Copper β-Silyl Ester Enolates and Methyl Glyoxalate Imines. General Procedure for the Preparation of β-Lactams 29 and 30. A solution of (dimethylphenylsilyl)lithium (10 mL, 1 M in THF) was dropped over cold (0 °C) anhydrous copper(I) cyanide (0.45 g, 5 mmol) kept under nitrogen, and the mixture was stirred for 20 min at the same temperature. A solution of the corresponding α,β-unsaturated ester (5 mmol) in THF (10 mL) was dropwise added to the former suspension and the mixture was stirred for 20 min at 0 °C. Then, a solution of *N*-[(methoxycarbonyl)methylene]-*p*-anisidine (0.97 g, 5 mmol) in THF (10 mL) was added and the mixture was stirred at room temperature for 3 h. After this time, the reaction mixture was diluted in methylene chloride (30 mL), washed with saturated ammonium chloride (50 mL) at 0 °C, filtered through a pad of Celite, dried, and evaporated. The crude β-lactams **29** and **30** were purified by column chromatography (silica gel; eluent:hexane–methylene chloride 5:1).

***cis,anti*-3-[1'-(Dimethylphenylsilyl)alkyl]-4-(methoxycarbonyl)azetidin-2-ones (39).** A solution of ammonium cerium(IV) nitrate (12.00 g, 21.9 mmol) in acetonitrile (65.5 mL) and water (7.28 mL) was added dropwise to a cooled (−10 °C) solution of the β-lactam *cis,anti*-**22** (7.3 mmol) in acetonitrile (49 mL) and water (5.4 mL) within 15 min. Then, the reaction mixture was stirred at −10 °C for 3 h. On completion, 2 M sodium hydroxyde (43.5 mL) was added, and stirring was maintained for 30 min at room temperature. The resulting mixture was filtered through Celite, neutralized with 1 M hydrochloric acid, and extracted with methylene chloride (3 × 20 mL). After drying and evaporation of the solvents, the resulting crude was purified by column chromatography (silica gel; eluent:hexane–methylene chloride 1:1), yielding *cis,anti*-3-[1'-(dimethylphenylsilyl)ethyl]-4-(methoxycarbonyl)azetidin-2-one (**39a**) (1.70 g, 80%). Syrup. ^1H NMR ($CDCl_3$): δ 7.57 (m, 2 H, Ar), 7.36 (m, 2 H, Ar), 6.45 (s, 1 H, N*H*), 4.27 (d, 1 H, *J* = 5.4 Hz, C*H*CO_2Me), 3.76 (s, 3 H, OCH_3), 3.40 (dd, 1 H, *J* = 5.4 Hz, *J* = 11.7 Hz, C*H*CO), 1.26 (m, 1 H, C*H*Si), 0.81 (d, 3 H, *J* = 7.2 Hz, CHC*H*$_3$), 0.45 (s, 3 H, $SiCH_3$), 0.39 (s, 3 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 173.3, 170.1, 134.3, 129.0, 127.6, 117.4, 61.2, 53.4, 52.3, 17.8, 14.0, −3.1, −4.2. MS: *m/e* 292 (M^+). Similarly, *cis,anti*-**23** (4.29 g, 7.3 mmol) afforded *cis,anti*-3-[α-(dimethylphenylsilyl)benzyl]-4-(methoxycarbonyl)azetidin-2-one (**39b**) (2.12 g, 82%). Mp: 106–107 °C (hexane/methylene chloride). ^1H NMR ($CDCl_3$): δ 7.31 (m, 4 H, Ar), 7.07 (m, 4 H, Ar), 6.67 (d, 2 H, Ar), 5.98 (s, 1 H, N*H*), 3.95 (d, 1 H, *J* = 4.5 Hz, C*H*CO_2Me), 3.74 (dd, 1 H, *J* = 4.5 Hz, J = 12.0 Hz, C*H*CO), 3.08 (s, 3 H, OCH_3), 2.72 (d, 1 H, *J* = 12 Hz, C*H*Si), 0.48 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 171.2, 168.8, 139.9, 134.9, 129.2, 128.0, 127.5, 125.2, 58.3, 52.1, 51.9, 33.1, −2.9, −3.1. MS: *m/e* 340 (M^+ − 15). Anal. Calcd for $C_{20}H_{23}NO_3Si$: C, 67.95; H, 6.56; N, 3.96. Found: C, 67.53; H, 6.38; N, 3.78.

***trans,anti*-3-[1'-(Dimethylphenylsilyl)alkyl]-4-(methoxycarbonyl)azetidin-2-ones (43).** A solution of ammonium cerium(IV) nitrate (6.56 g, 12.0 mmol) in water (42 mL) was added dropwise to a cooled (0 °C) solution of the β-lactam *trans,anti*-**29a** (1.59 g, 4.0 mmol) in acetonitrile (50 mL) within 15 min. Then, the reaction mixture was stirred at 0 °C for 30 min. On completion, the reaction mixture was taken up over water (160 mL) and extracted with ethyl acetate (3 × 60 mL). The organic layer was washed successively with saturated sodium hydrogen carbonate (140 mL), sodium hydrogen sulfite (4 × 100 mL), sodium hydrogen carbonate (30 mL), and brine (30 mL). After drying and evaporation of the solvents, the resulting crude was purified by column chromatography (silica gel; eluent:hexane–methylene chloride 1:1), yielding *trans,anti*-3-[1'-(dimethylphenylsilyl)alkyl]-4-(methoxycarbonyl)azetidin-2-one (**43a**) (1.34 g, 92%). Mp: 114–116 °C (Et_2O). ^1H NMR ($CDCl_3$): δ 7.53–7.36 (m, 5 H, Ar), 6.21 (s_b, 1 H, N*H*), 3.91 (d, 1 H, *J* = 2.4 Hz, C*H*CO_2Me), 3.74 (s, 3 H, OCH_3), 3.34 (dd, 1 H, *J* = 2.4 Hz, *J* = 4.8 Hz, C*H*CO), 1.58–1.54 (m, 1 H, C*H*Si), 1.05 (d, 3 H, *J* = 7.5 Hz, CHC*H*$_3$), 0.38 (s, 3 H, $SiCH_3$), 0.37 (s, 3 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 171.8, 169.9, 136.8, 133.9, 129.3, 127.3, 60.1, 52.4, 50.8, 18.4, 10.3, −4.7. MS: *m/e* 292 (M^+). Anal. Calcd for $C_{15}H_{20}NO_3Si$: C, 62.01; H, 6.95; N, 4.82. Found: C, 62.10; H, 7.00; N, 4.85. The following compounds were obtained according to a similar procedure: *trans,anti*-3-[α-(dimethylphenylsilyl)benzyl]-4-(methoxycarbonyl)azetidin-2-one (**43b**) (1.15 g, 65%). Mp: 100–102 °C (hexane/methylene chloride). ^1H NMR ($CDCl_3$): δ 7.48–6.91 (m, 10 H, Ar), 6.20 (s_b, 1 H, N*H*), 3.65 (d, 1 H, *J* = 1.0 Hz, C*H*CO_2Me), 3.58 (dd, 1 H, *J* = 1.0 Hz, *J* = 10.6 Hz, C*H*CO), 3.55 (s, 3 H, OCH_3), 2.69 (d, 1 H, *J* = 10.3 Hz, C*H*Ph), 0.41 (s, 3 H, $SiCH_3$), 0.26 (s, 3 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 171.5, 169.0, 140.3, 136.0, 129.3,

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128.2, 127.6, 125.6, 59.9, 53.7, 52.2, 36.5, -2.9, -3.6. MS: m/e 340 ($M^+ - 15$). Anal. Calcd for $C_{20}H_{23}NO_3Si$: C, 67.95; H, 6.56; N, 3.96. Found: C, 68.12; H, 6.59; N, 3.99. *trans,anti*-3-[1′-(Dimethylphenylsilyl)-2′-propyl]-4-(methoxycarbonyl)azetidin-2-one (**43c**) (1.07 g, 70%). Syrup. ^1H NMR ($CDCl_3$): δ 7.55–7.52 (m, 2 H, Ar), 7.38–7.33 (m, 3 H, Ar), 6.24 (s_b, 1 H, NH), 3.90 (d, 1 H, J = 2.7 Hz, $CHCO_2Me$), 3.73 (s, 3 H, OCH_3), 3.24 (t, 1 H, J = 2.7 Hz, J = 2.7 Hz, CHCO), 1.11 (s, 3 H, CCH_3), 1.01 (s, 3 H, CCH_3), 0.42 (s, 3 H, $SiCH_3$), 0.38 (s, 3 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 172.1, 169.2, 136.2, 134.7, 129.2, 127.6, 65.8, 52.4, 49.5, 22.7, 20.9, 20.5, -5.3, -5.4. MS: m/e 290 (M^+).

Preparation of Dimethyl *N*-Benzoyl-β-[(dimethylphenylsilyl)alkyl]aspartates 41 and 45 from 39 and 43. General Procedure. Chlorotrimethylsilane (2.50 mL, 20 mmol) was added to a solution of 3-[1′-(dimethylphenylsilyl)alkyl]-4-(methoxycarbonyl)azetidin-2-one **39** or **43** (4.0 mmol) in methanol (10.0 mL) and the mixture was stirred for 4–10 h at room temperature (for **43c** the reaction was refluxed for 4 h). On completion, the reaction mixture was evaporated, diluted with methylene chloride (30 mL), and washed with saturated sodium hydrogen carbonate (20 mL). Drying and evaporation of the solvents yielded crude dimethyl β-[(dimethylphenylsilyl)alkyl]-aspartates **40** and **44**, which were directly dissolved in methylene chloride (30 mL) and triethylamine (1.10 mL, 8 mmol). Benzoyl chloride (0.51 mL, 4.4 mmol) in methylene chloride (11 mL) was dropped over the preceding solution cooled to 0 °C within 10 min, and the resulting solution was stirred at room temperature for 4 h and then washed successively with water (10 mL), 1 M hydrochloric acid (10 mL), and saturated sodium hydrogen carbonate (10 mL). Drying and evaporation of the solvents yielded crude dimethyl *N*-benzoyl-β-[(dimethylphenylsilyl)alkyl]aspartates **41** and **45**, which were purified by column chromatography (silica gel; eluent:methylene chloride–hexane (1:15).

Preparation of 3-(1′-Hydroxyalkyl)-4-(methoxycarbonyl) β-Lactams 17, 33, and 34 and Dimethyl *N*-Benzoyl-β-(hydroxyalkyl)aspartates 42 and 46. General Procedure. HBF_4·OEt_2 (1.06 mL, 10 mmol) was added to a cooled (0 °C) solution of 3-(1′-dimethylphenylsilylalkyl)-4-(methoxycarbonyl)azetidin-2-one (5 mmol) or dimethyl *N*-benzoyl β-[(dimethylphenylsilyl)alkyl]aspartate (5 mmol) in methylene chloride (20 mL) and the mixture was stirred at room temperature for 1 h. After this time, the reaction mixture was washed with cold water (10 mL) and brine (20 mL). The organic solvent was dried and evaporated to yield the corresponding dimethylfluorosilane. The crude product was dissolved in cold (0 °C) 32% peracetic acid in acetic acid (25 mL, 25 mmol), and triethylamine (1.25 mL, 11 mmol) was added dropwise within 5 min at the same temperature. The mixture was stirred at room temperature for 3 h, then methylene chloride (30 mL) was added, and the resulting solution was successively washed with 1 M HCl (30 mL), 40% $NaHSO_3$ (30 mL), $NaHCO_3$ (30 mL), and water (30 mL). Drying and evaporation afforded the hydroxy derivatives **33** and **34** or **42** and **46**. The crude products were purified by column chromatography (silica gel, eluent:methylene chloride:hexane 1:3). *anti,trans*-3-(1′-Hydroxyethyl)-4-(methoxycarbonyl)-1-(*p*-methoxyphenyl)azetidin-2-one (**33**) (1.32 g, 95%). Mp: 91–92 °C (hexane/methylene chloride). ^1H NMR ($CDCl_3$): δ 7.25 (d, 2 H, Ar), 6.86 (d, 2 H, Ar), 4.42 (d, 1 H, J = 2.4 Hz, $CHCO_2Me$), 4.24–4.20 (m, 1 H, CHOH), 3.80 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.38 (dd, 1 H, J = 2.4 Hz, J = 5.4 Hz, CHCO), 1.43 (d, 3 H, J = 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.3, 163.7, 156.5, 129.3, 117.9, 114.4, 65.7, 61.2, 55.5, 53.6, 52.8, 21.2. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.19; H, 6.15; N, 5.01. Found: C, 60.20; H, 6.15; N, 5.03. *anti,trans*-3-(α-Hydroxybenzyl)-4-(methoxycarbonyl)-1-(*p*-methoxyphenyl)azetidin-2-one (**34**) (1.02 g, 60%). Syrup. ^1H NMR ($CDCl_3$): δ 7.52–7.18 (m, 5 H, Ar), 7.21 (d, 2 H, Ar), 6.84 (d, 2 H, Ar), 5.13 (d, 1 H, J = 5.24 Hz, CHOH), 4.40 (d, 1 H, J = 2.6 Hz, $CHCO_2Me$), 3.76 (s, 3 H, OCH_3), 3.74 (dd, 1 H, J = 2.6 Hz, J = 5.4 Hz, CHCO), 3.72 (s, 3 H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 170.1, 163.1, 156.5, 140.0, 130.6, 128.9, 128.7, 128.2, 126.6, 118.0, 114.4, 71.9, 61.1, 55.4, 54.0, 52.8. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.91; H, 5.62; N, 4.14. Methyl 2(*S**)-(benzoylamino)-4(*R**)-hydroxy-3-(*S**)-(methoxycarbonyl)pentanoate (**42a**) (1.11 g, 72%). Syrup. ^1H NMR ($CDCl_3$): δ 7.80 (d, 2 H, Ar), 7.52 (m, 3 H, Ar), 5.28 (dd, 1 H, J = 5.4 Hz, J = 8.6 Hz, CHNH), 4.09 (m, 1 H, CHOH), 3.80 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.04 (dd, 1 H, J = 2.7 Hz, J = 5.4 Hz, CHCO), 1.37 (d, 3 H, J = 6.6 Hz, CH_3CH). ^{13}C NMR ($CDCl_3$): δ 171.9, 171.0, 167.4, 132.3, 132.0, 128.6, 127.5, 66.7, 53.6, 53.0, 52.3, 52.2, 22.0. MS: m/e 279 ($M^+ - 30$). Methyl 2(*S**)-(benzoylamino)-4(*R**)-hydroxy-3(S*)-(methoxycarbonyl)-4-phenylbutanoate (**42b**) (1.21 g, 65%). Syrup. ^1H NMR ($CDCl_3$): δ 7.80 (d, 2 H, Ar), 7.53 (m, 2 H, Ar), 7.47 (d, 2 H, Ar), 7.38 (d, 4 H, Ar), 5.18 (dd, 1 H, J = 5.1 Hz, J = 8.1 Hz, CHNH), 5.09 (d, 1 H, J = 5.1 Hz, CHOH), 3.79 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.53 (t, 1 H, J = 5.1 Hz, CHCO). ^{13}C NMR ($CDCl_3$): δ 172.5, 171.2, 167.8, 141.1, 132.6, 129.2, 129.0, 128.5, 127.7, 126.4, 72.7, 53.8, 53.6, 53.3, 52.9. MS: m/e 237 ($M^+ - 144$). Methyl 2(*S**)-(benzoylamino)-4(*S**)-hydroxy-3(*R**)-(methoxycarbonyl)pentanoate (**46a**) (1.08 g, 70%). Mp: 200–202 °C (methanol). ^1H NMR ($CDCl_3$): δ 7.92–7.90 (m, 2 H, Ar), 7.55–7.41 (m, 3 H, Ar), 5.08 (qd, 1 H, J = 6.7 Hz, J = 8.9 Hz, CHOH), 4.93 (dd, 1 H, J = 8.9 Hz, J = 7.5 Hz, CHNH), 4.02 (t, 1 H, J = 8.9 Hz, $CHCO_2Me$), 3.76 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 1.34 (d, 3 H, J = 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 172.4, 169.6, 166.8, 132.6, 131.5, 127.9, 127.2, 74.5, 72.9, 52.1, 50.7, 47.9, 17.0. Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.20; N, 4.53. Found: C, 59.02; H, 6.25; N, 4.56. Methyl 2(*S**)-(benzoylamino)-4(*S**)-hydroxy-3(*R**)-(methoxycarbonyl)-4-phenylbutanoate (**46b**) (1.67 g, 90%). Syrup. ^1H NMR ($CDCl_3$): δ 7.8–7.24 (m, 2 H, Ar), 5.01 (d, 1 H, J = 8.6 Hz, CHOH), 4.69 (dd, 1 H, J = 3.1 Hz, J = 8.6 Hz, CHNH), 3.77 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.50 (dd, 1 H, J = 3.1 Hz, J = 8.6 Hz, $CHCO_2Me$). MS: m/e 265 ($M^+ - 106$). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.74; H, 5.71; N, 3.81. Methyl 2(*S**)-(benzoylamino)-4-hydroxy-3(*R**)-(methoxycarbonyl)-4-methylpentanoate (**46c**) (1.45 g, 90%). Syrup. ^1H NMR ($CDCl_3$): δ 8.13–7.61 (m, 5 H, Ar), 5.20 (dd, 1 H, J = 2.2 Hz, J = 8.2 Hz, CHNH), 4.06 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 3.46 (d, 1 H, J = 2.2 Hz, $CHCO_2Me$), 1.18 (s, 3 H, CH_3). MS: m/e 265 ($M^+ - 44$). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.22; H, 6.50; N, 4.29.

When the *anti*-3-[1′-(dimethylphenylsilyl)ethyl]-4-(methoxycarbonyl)-1-(*p*-methoxyphenyl)azetidin-2-one (**15a**) (1.98 g, 5 mmol) was subjected to the above protocol, a mixture of compounds *anti*-**17** and **18** was obtained, which was separated by column chromatography (silica gel, eluent:methylene chloride: hexane 1:8), yielding compound *anti*-**17** (0.56 g, 40%) [Mp: 165–167 °C (hexane–methylene chloride). ^1H NMR ($CDCl_3$): δ 7.27 (d, 2 H, Ar), 6.86 (d, 2 H, Ar), 4.59 (d, 1 H, J = 6.3 Hz, $CHCO_2Me$), 4.18 (q, 1 H, J = 6.3 Hz, CHOH), 3.78 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.60 (t, 1 H, J = 6.3 Hz, CHCO), 1.38 (d, 3 H, J = 6.3 Hz, CH_3CH). ^{13}C NMR ($CDCl_3$): δ 170.3, 163.7, 156.5, 130.7, 117.9, 114.4, 65.7, 61.2, 55.5, 53.6, 52.8. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.19; H, 6.15; N, 5.01. Found: C, 60.29; H, 6.31; N, 5.22.] and the lactone **18** (0.37 g, 30%) [Mp: 162 °C (hexane–methylene chloride). ^1H NMR ($CDCl_3$): δ 7.51 (d, 2 H, Ar), 6.89 (d, 2 H, Ar), 4.84 (dq, 1 H, J = 6.6 Hz, J = 7.8 Hz, CHOCO), 4.62 (d, 1 H, J = 4.8 Hz, CHN), 4.05 (dd, 1 H, J = 4.8 Hz, J = 7.8 Hz, CHCO), 3.79 (s, 3 H, OCH_3), 1.65 (d, 3 H, J = 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.4, 160.7, 156.7, 130.5, 118.3, 114.4, 75.1, 55.5, 54.5, 53.7, 17.9. MS: m/e 247 (M^+). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.31; N, 5.66. Found: C, 63.17; H, 5.10; N, 5.48.].

6-(*p*-Methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]-heptane-4,7-dione (19). A solution of the alcohol *syn*-**17** (0.56 g, 2 mmol) and boron trifluoride etherate (0.05 mL, cat.) in methylene chloride (10 mL) was stirred at room temperature for 20 min. The reaction mixture was washed with water (20 mL) and brine (20 mL), dried, and evaporated, affording the lactone **19** (0.39 g, 80%). Mp: 163–165 °C (hexane–methylene chloride). ^1H NMR ($CDCl_3$): δ 7.49 (d, 2 H, Ar), 6.90 (d, 2 H, Ar), 5.08 (dq, 1 H, J = 6.6 Hz, J = 1.8 Hz, CHOCO), 4.67 (d, 1 H, J = 4.5 Hz, CHN), 3.79 (s, 3 H, OCH_3), 3.73 (dd, 1 H, J = 1.8 Hz, J = 4.5 Hz, CHCO), 1.50 (d, 3 H, J = 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.4, 162.9, 157.3, 130.9, 118.3, 114.5, 75.2, 55.8, 55.5, 53.5, 22.8. MS: m/e 247 (M^+). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.31; N, 5.66. Found: C, 63.11; H, 5.12; N, 5.44.

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Supplementary Material Available: Characterization data for **10a**, **10b**, **10d**, **11a**, **11b**, **11c**, *anti*-**15a**, *syn*-**15a**, *anti*-**15b**, *syn*-**15b**, *anti*-**15c**, *syn*-**15c**, *anti*-**15d**, *syn*-**15d**, *anti*-**22**, *syn*-**22**, **23**, **29a**, **29b**, **29c**, **29d**, **37**, **38**, **41a**, **41b**, **45a**, **45b**, and **45c** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Reaction of Nucleic Acid Bases with α-Acetylenic Esters. 5.[1] Synthesis and Properties of Adenosine and Cytidine Derivatives

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α-Acetylenic esters are able to react under mild experimental conditions with the base moiety of adenosine and cytidine, while guanosine is unreactive. A double reaction of the triple bond and the ester group of the reagent with the NH_2 group and the adjacent ring nitrogen of the base yields derivatives in which an additional pyrimidone ring is fused to the original base. These derivatives can exist in two isomeric forms. In alkaline solution, or by prolonged heating in water, the medium pyrimidine ring of adenosine derivatives opens by loss of carbon 5. If the derivatization is performed with chlorotetrolic (4-chloro-2-butynoic) acid esters, the modified nucleobases contain a chloromethyl side chain. Tests of the alkylating abilities of the latter in the two isomeric adenosine derivatives show that the chlorine can be easily substituted by a thiol in the presence of alkali; a partial Dimroth rearrangement of one of the reaction products is observed. The reaction with amines is accompanied by ring opening. Nucleic acids containing these alkylating base derivatives can be cross-linked to other macromolecules such as solid supports or contact proteins.

Introduction

Nucleic acid bases having an exocyclic NH_2 and an adjacent ring nitrogen are able to react with certain types of electrophilic bifunctional reagents, yielding derivatives in which an additional five- or six-membered heterocycle is fused to the original purine or pyrimidine. Many of these reagents contain a halogen atom and/or an unsaturated group including C=O,[3-8] C=C,[9-12] C≡N,[13-16] and N=C=O.[17-19] The long known chlorotetrolic (4-chloro-2-butynoic) acid esters, $ClCH_2C{\equiv}CCOOR$,[20-22] have such functions and therefore, like other bifunctional nucleobase reagents, should be able to react with the amidine -N=C(NH_2)- system of adenine or cytosine or the guanidine -N=C(NH_2)NH- system of guanine. This expectation was strengthened by our earlier works which have shown that methyl chlorotetrolate can be used as a bifunctional protein modifier, reacting through its chloromethyl group and the triple bond with protein nucleophiles such as amine, thiol, or imidazole.[23] A similar behavior toward

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