Pergamon

Tetrahedron Vol. 51, No. 35, pp. 9657-9670, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00613-3

Studies Toward the Stereocontrolled Synthesis of a Key Azetidinone-Acid Intermediate in the Preparation of a New Carbapenem

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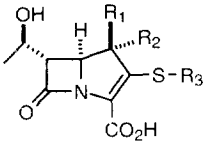
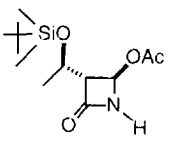
Abstract: An efficient and stereocontrolled preparation of the key azetidinone-acid **5a** is described.

After the discovery of the carbapenem thienamycin **1**,[1] a potent β-lactam antibiotic, a second generation of 1-β-methyl carbapenems **2**[2-4] appeared showing excellent antibacterial activity, chemical stability and resistance to renal dipeptidase-I. In contrast, the isomeric 1-α-methyl carbapenem was shown to have relatively low antibacterial activity.[4]

To evaluate the antibacterial properties of variously substituted 1-β-alkyl carbapenems, it was necessary to identify a stereoselective approach to such derivatives. Based on the work of Menard *et al.*,[5,6] our efforts were directed toward the preparation of 1-β-azidoethyl-acid **5a**, a key intermediate in the synthesis of carbapenems **3a** and **3b**.



1 $R_1 = R_2 = H$, $R_3 = (CH_2)_2\text{-}NH_2$ (thienamycin)
2 $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_2\text{-}C(=NH)N(CH_3)_2$
3a $R_1 = (CH_2)_2\text{-}NH_2$, $R_2 = H$, $R_3 = (CH_2)_2CN$
3b $R_1 = (CH_2)_2\text{-}NH\text{-}C(=NH)NH_2$, $R_2 = H$, $R_3 = (CH_2)_2CN$.



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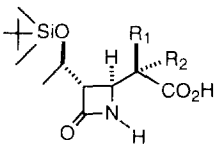
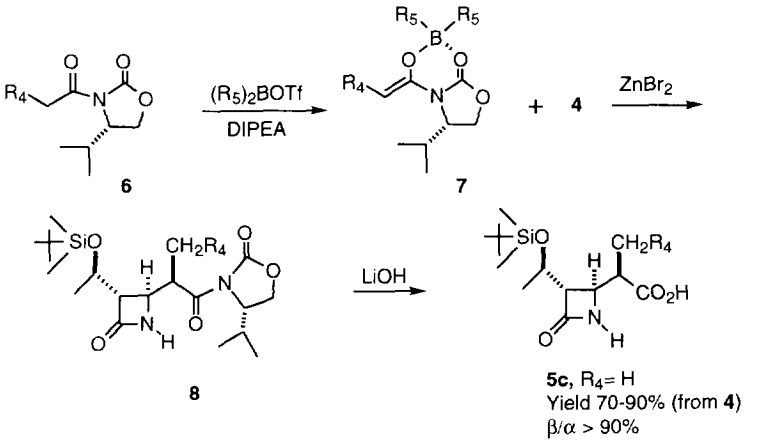


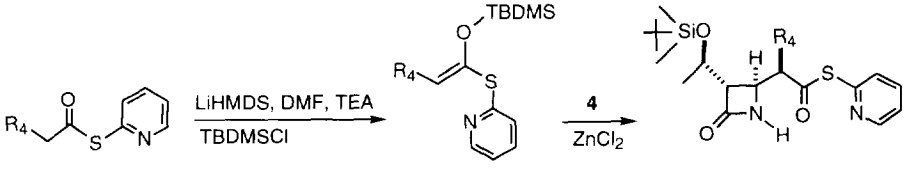
5a $R_1 = (CH_2)_2N_3$, $R_2 = H$
5b $R_1 = H$, $R_2 = (CH_2)_2N_3$

The key steps in the preparation of the 1-β-substituted carbapenem intermediates involves the enolization of amides, esters or thioesters followed by the stereoselective condensation of chiral or achiral metal enolates[7-16] or silylketeneacetals[17-19] with azetidinone **4**[20] under Lewis acid catalysis. One of the most general and successful approaches in the β-methyl carbapenem series was the use of chiral oxazolidinone as **6**, which was described as a powerful inducer of stereoselectivity (Scheme 1).[9-10,21-22]



Scheme 1

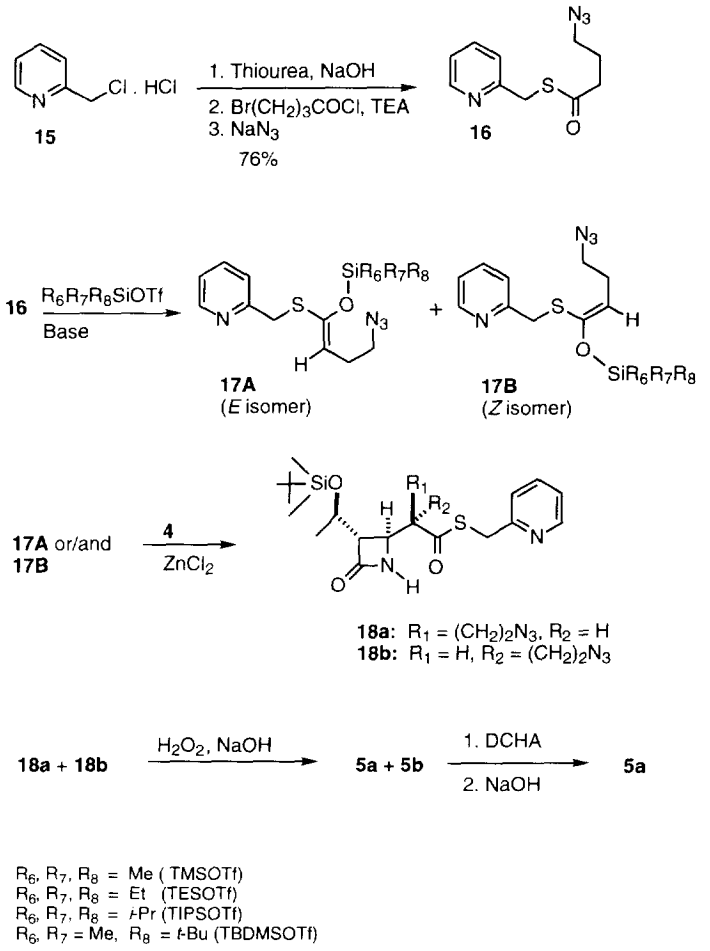
We first attempted to prepare **5a** by using the same methodology with **6** ($R_4 = (CH_2)_2\text{-}N_3$) but with disappointing results. Very poor yields and a tedious work-up were encountered which were not compatible for kilo-scale quantities. We then turned our attention to a different approach for the coupling with **4** by using the 2-thiopyridyl moiety as an auxiliary for the induction of the desired stereoselectivity. Recently,[23] coupling of **4** with **12** was reported, as a versatile method, to give exclusively the β-derivative **14** ($R_4 = CH_3$) in good yield. In these studies, lithium bis(trimethylsilyl)amide (LiHMDS) was used in the presence of 2 equivalents of dimethylformamide (DMF) and triethylamine (TEA) with one equivalent of *t*-butyldimethylsilylchloride (TBDMSCl) before the addition of **10** (Scheme 2).



Scheme 2

Using the same conditions, when we tried to replace the methyl group of **10** by the azidoalkyl side chain of **11**, the corresponding pure *E* enolate **13** was obtained in 78% yield. However, coupling of enolate **13** with **4** gave **14** ($R_4 = (CH_2)_2N_3$) in very poor yield (<20%).

We then focused our attention on the preparation of the silylated enol ester of the 2-picolylthio ester of an appropriately substituted butyric acid, **16**, based on the work of Martel *et al.*[19]



Scheme 3

Thiobutyrate **16** was obtained in 3 steps and a 76 % overall yield from **15**. Typical silylation of thioester **16** was performed by adding an excess of *tert*-butyldimethylsilyltriflate (TBDMSOTf) to a mixture of **16** and TEA in CH_2Cl_2 to give a mixture of geometric isomers **17A** and **17B** in a 60:40 ratio (Scheme 3).

In order to study the influence of the geometry of the silylketeneacetals, we separated **17A** and **17B** by chromatography over silica gel with a purity > 98% for **17A** and > 95% for **17B** (determined by NMR).

Table 1. Influence of the geometry of **17** on the condensation with **4** at 25°C

Isomer[a]	$ZnCl_2$	**4**	Time	Molar composition[b]			Ratio	Yield[d]
				18a+18b/ 16[c] / 4			**18a/18b**	**18a + 18b**
	(equ.)	(equ.)	(h)	(%)			(β/α)	(%)
17A	1	0.95	2	64	20	16	98:2	44.6
17B	1	0.95	2	37	43	20	57:43[e]	28.2
17A+17B[f]	1	0.95	21	54	30	16	84:16	26.7

[a] Typical procedure: 0.5 g pure silylketeneacetal **17** in 6 mL of CH_2Cl_2 followed by $ZnCl_2$ and **4**. [b] Determined by NMR after work-up. [c] In these reactions a large amount of *E* and *Z* isomers were hydrolyzed back to **16**. [d] Isolated yield after crystallization from hexane (after work-up, the crude yields were around 70%). [e] After 20h, the ratio of **18a/18b** was 60:40. [f] Typically with a 58:42 mixture of *E* and *Z* isomers.

We showed that the aldol-type condensation of the pure substrate (*E*)-**17A** with **4** in presence of $ZnCl_2$ gave almost exclusively β-thioester **18a** in 44.6% isolated yield within 2 hours whereas (*Z*)-**17B** gave under the same conditions a mixture of **18a+18b** (60: 40) after 20 hours (Table 1). From these results, the need for a method leading to the selective formation of the *E* ketenethioacetal **17A** was apparent. Therefore, conditions which would allow for the preferential formation of the *E*-isomer were investigated..

Bases such as 2,6-lutidine[24], *N*-methylimidazole, trimethylamine, or *N*-methyl pyrrolidine were tried, but none gave a better *E/Z* ratio or better yields than TEA (Table 2).

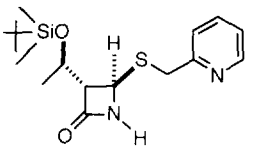
Table 2. Bases influence on silylation of **16** with TBDMSOTf (2 equ.) at 37°C

Entry	Base (2.2 equ.)	Solvent	T (°C)	Ratio **17A/17B**[a]	Isolated yield **17A + 17B** (%)
1	TEA	CH_2Cl_2	37	62:38	71.5[b]
2	TEA	$ClCH_2CH_2Cl$	40	59:41	91.7[b]
3	DBU	$ClCH_2CH_2Cl$	40		no reaction
4	DIPEA	$ClCH_2CH_2Cl$	20		no reaction
5	2,6-lutidine	CH_2Cl_2	25		30[c]
6	*N*-Me-pyrrolidine	CH_2Cl_2	30	55:45	62[c]
7	*N*-Me-pyrrolidine + HMPA	$ClCH_2CH_2Cl$	35	56:44	retrogradation during work-up
8	*N*-Me-imidazole	$ClCH_2CH_2Cl$	35		no reaction
9	*N*-Ethyldimethyl-amine	$ClCH_2CH_2Cl$	35	60:40	retrogradation during work-up

[a] Determined by NMR. [b] After alumina pad purification. [c] After silica gel pad purification.

When **17A** and **17B** were isolated for condensation reactions with **4**, the isolated yields of **18a** and **18b** were only moderate due to the retrograde reaction of the silylketeneacetals to starting material **16**

(from 20 to 40%). The formation of the side-product **19** (5 to 10%), from the condensation of 2-picolylthiol (ester cleavage of **16**) on **4**, was also observed.



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On the other hand, we observed that mixing TBDMSOTf (at least 1.7 equivalents relative to thiobutyrate) with TEA (at least 1.9 eq.) prior to the addition of **16** was beneficial to the enolization reaction, avoiding the formation of insoluble material.[25]

To check the influence of the substituents of the silyl group on the *E/Z* ratio, various silyltriflates were tried as shown in Table 3. With triethylsilyltriflate (TESOTf) we were able to visualize the enol formation only by tlc. The instability of the corresponding enol in the presence of water did not allow us to monitor its formation by HPLC. Only tert-butytldimethylsilyltriflate (TBDMSOTf) and triisopropylsilyltriflate (TIPSOTf) gave reasonable levels of **17A+17B**. With TBDMSOTf, silylation was complete in 3 hours whereas with TIPSOTf, silylation required 20 hours for completion but with the best *E/Z* ratio of the series.

Table 3. Triflate influence on silylation of **16** in presence of TEA

Entry	Triflate	R_1	R_2	R_3	Ratio **17A/17B**[a]
1	TMSOTf	Me	Me	Me	no detectable enol
2	TESOTf	Et	Et	Et	unknown[b]
3	TIPSOTf	*i*-Pr	*i*-Pr	*i*-Pr	70:30[c]
4	TBDMSOTf	Me	Me	*t*-Bu	60:40

[a] Determined by HPLC. [b] 2 close spots observed by tlc (no signal in HPLC). [c] Not isolated.

To avoid the decomposition and loss of **17A+17B** (TBDMS and TIPS routes) during aqueous work-up, silica gel purification, or retrograde reaction when in contact with $ZnCl_2$, both isomers were reacted directly in the basic reaction mixture with **4** in a one-pot fashion to provide a mixture of azetidinones **18a** and **18b** with almost no reversion to **16** and with only a small amount of the side-product **19** (Table 4).

Table 4. Aldol condensation of **4** with **17A+17B** (One-pot reaction from **16**)

Entry	Route	Triflate (equ.)	Ratio **17A/17B**[a]	$ZnCl_2$ (equ.)	**4** (equ.)	Ratio **18a/18b**[a]	Yield **18a+18b**[b] (%)
1	TES	2	unknown	1.5	1.3		<5[a]
2	TBDMS	2	60:40	1.5	1.1	80:20	82[c]
3	TIPS	2	70:30	1.21	1.08	95:5	>100[d]

[a] Estimated by HPLC. [b] yield from **16**. [c] Partially purified over a pad of silica gel. [d] Crude yield.

In the aldol-type coupling reaction, the 60:40 mixture of *t*-butyldimethylsilylketeneacetals **17A+17B** rapidly and predimonantly afforded the β isomer **18a**, the α isomer **18b** being formed only after several hours (Table 4). For triisopropylsilylketeneacetals **17A+17B** (70:30), the β isomer **18a** was obtained exclusively within 2 hours and even after 16 hours only a small amount of **18b** was detectable in the reaction mixture.

Table 5. Preparation of **5a+5b** from **18a+18b**

Entry	Route	Ratio **18a/18b**[a]	Ratio **5a/5b**[a]	Yield **5a+5b**[b] (%)	Yield for purification[c] (%)	Ratio **5a/5b**[a]	Overall yield **5a** (from **15**) (%)
1	TBDMS	80:20	90:10	67	64.4	99:1	27.2
2	TIPS	95:5	99:1	88.7	48	>99.5:<0.5	32.4

[a] Determined by HPLC. [b] Crude yield. [c] DCHA (dicyclohexylamine) salt formation and return to the free acid.

In the TBDMS route the crude mixture of **18a+18b** was rapidly purified over a silica gel pad[26] before the cleavage of thioester with H_2O_2 and NaOH (Table 5). In the TIPS route the crude mixture of **18a+18b** was submitted directly to the same treatment. Finally, crude acid (**5a+5b** mixture) was purified *via* a dicyclohexylamine (DCHA) salt affording after alkaline work-up a pure acid **5a** with less than 1% of the α isomer **5b** in 27-32% overall yield from **15**.

In conclusion, a relatively rugged process avoiding costly chiral auxilaries such as 2-oxazolidinones, 2-thiazolidinethione or 2-oxazolidinethione as well as toxic reagents such as bis(cyclopentadienyl)zirconium dichloride, tin trifluoromethanesulfonate or diethylboron trifluoromethanesulfonate was developed. Moreover, using a telescoped sequence involving silylation with commercially available triflates TBDMSOTf or TIPSOTf, followed by an aldol-type coupling, a highly stereoselective procedure capable of being scaled up to the one kilogram level of preparation of 5a was identified.

EXPERIMENTAL

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Melting points were taken in a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis were performed by the Bristol-Myers Squibb Analytical Department. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Bruker ARX 500 spectrometer at 500 and 50 Mhz respectively. The ^1H chemical shifts are reported in ppm from H_2O as external signal. The ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infra-red spectra were recorded on a Nicolet FT-IR SXC spectrophotometer. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer model 241 polarimeter. HPLC experiments were performed on Varian 9000 series chromatographs.

4-Azidobutyric acid 2-thiopyridin-2-yl ester **11**. To a solution of 22 g (0.14 mole) of ethyl 4-azidobutyrate (from ethyl 4-bromobutyrate and NaN_3) in 240 mL of absolute EtOH, cooled to 0 °C, was added 37.45 mL (0.14 mole) of a 3.74 M aqueous solution of KOH. After 1 h 30 mn at 0 °C, the reaction mixture was allowed to reach room temperature for 1 h 15 mn, and was evaporated under reduced pressure. The residue was taken up in 70 mL of abs. EtOH and was evaporated to dryness.

This process was repeated twice. Finally the white solid was filtered and dried to provide 17.51 g of potassium 4-azidobutyrate (yield 75%); m.p. 261 °C.

To a suspension of 5.2 g (31.1 mmoles) of potassium 4-azidobutyrate in 25 mL of anhydrous Et_2O, cooled at 2 °C, was added two drops of DMF, followed by a solution of 6.04 g (47.6 mmoles) of oxalyl dichloride in 5 mL of anhydrous Et_2O. After 15 mn at 2 °C, the reaction mixture was allowed to reach room temperature for 3 h 30 mn. Insoluble KCl was filtered off under argon and the filtrate was evaporated under reduced pressure to leave 4.59 g of 4-azidobutyryl chloride as an orange oil (yield 97%). This oil was used for the next step without further purification.

To a solution of 6.15 g (55.3 mmoles) of 2-mercaptopyridine in 100 mL of CH_2Cl_2 purged with argon and cooled at 4 °C, was added a solution of 8.6 g (58.3 mmoles) of 4-azidobutyryl chloride. The reaction mixture was allowed to reach room temperature for 1 h 30 mn. The organic layer was washed successively with 40 mL of 0.3N aqueous HCl, 20 mL of 10% aqueous $NaHCO_3$, 10 mL of H_2O, dried ($MgSO_4$) and evaporated under reduced pressure to give 12.3 g of **11** as a brown oil (yield 100%) which was used without further purification for the next step. IR (KBr): 3048, 2932, 2109, 1705, 1569 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.01 (q, 2H, CH_2-$\underline{CH_2}$-CH_2); 2.83 (t, 2H, *J* = 6.4Hz, CO-$\underline{CH_2}$); 3.40 (t, 2H, *J* = 6.4Hz, N_3-$\underline{CH_2}$); 7.31 (m, 1H, H-β, pyr.); 7.62 (m, 1H, H-δ, pyr.); 7.74 (m, 1H, H-γ, pyr.); 8.64 (m, 1H, H-α, pyr.).

(E)-4-Azidobutyric acid 2-thiopyridin-2-yl ester tert-butyldimethylsilyl enol **13**. Under argon was added a solution of 91.9 mL (91.9 mmoles) of LiHMDS in THF to 130 mL of THF cooled at -65 °C. To this solution, still at - 65 °C, was added dropwise 12.9 mL (167.59 mmoles) of dry DMF for 10 mn, 23.39 mL (168.77 mmoles) of TEA, then a solution of 14.13 g (93.77 mmoles) of *tert*-butyldimethylsilyl chloride in 100 mL of THF, followed by a solution of 18.57 g (83.54 mmoles) of thioester **11** in 80 mL of THF while keeping the temperature below - 55 °C. The reaction mixture was maintained at - 65 °C for 20 mn and allowed to reach - 20 °C for 2 h. Finally the reaction mixture was poured over 375 g of ice and extracted with 1.3 L of AcOEt. The organic layer was washed twice with 150 mL of H_2O and 150 mL of a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and evaporated under reduced pressure to give 28 g of a crude oil. Chromatography of this oil over silica gel (AcOEt) provided 25.93 g (78% yield) of pure (*E*)-ketenesilyl acetal **13** as a brown oil. ^{1}H-NMR ($CDCl_3$): δ 0.093 (m, 6H, Me_2Si); 0.89 (m, 9H, *tert*-BuSi); 2.51 (q, 2H, $\underline{CH_2}$-CH_2-N_3); 3.36 (t, 2H, *J*= 7.2 Hz, $\underline{CH_2}$-N_3); 5.39 (t, 1H, *J* = 7.2 Hz, =CH); 7.03 (m, 1H, H-β, pyr.); 7.33 (m, 1H, H-δ, pyr.); 7.56 (m, 1H, H-γ, pyr.); 8.43 (m, 1H, H-α, pyr.).

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl]-4-[(1"R)-1"-(pyridin-2-yl)thiocarbonyl-3"-azido-propyl)]azetidin-2-one **14** (*R4 = CH_2-CH_2-N_3*). Under argon was added 0.826 g (5.94 mmoles) of $ZnCl_2$ to a solution of 0.854 g (2.97 mmoles) of azetidinone **4** in 20 mL of anhydrous CH_2Cl_2 at 22 °C. After 10 mn of stirring of the suspension was added 1g (2.97 mmoles) of silylketeneacetal **13** and 0.42 mL (2.97 mmoles) of TEA. After 20 h at 22 °C, a solution of 7 mL of saturated NH_4Cl was added to the reaction mixture. The aqueous layer was decanted and was extracted twice with 5 mL of CH_2Cl_2. The organic layers were combined, washed with 5 mL of H_2O, 5 mL of saturated $NaHCO_3$,

and 5 mL of brine, dried ($MgSO_4$) and evaporated to leave 1.56 g of a brown oil. Chromatography over silica gel of this oil (AcOEt: heptane 50:50) furnished 0.19 g of pure **14** as a yellow solid (yield 17.4%); m.p. 91 °C. ^{1}H-NMR ($CDCl_3$): δ 0.086 (2s, 6H, Me_2Si); 0.89 (m, 9H, *tert*-BuSi); 1.19 (d, 3H, *J* = 6.3Hz, $\underline{CH_3}$-CH-OSi); 1.82 and 2.13 (2m, 2H, CH-$\underline{CH_2}$-CH_2); 3.08 (m, 1H, $\underline{CH}$-CO-S-pyr.); 3.16 (dd, *J*= 2.2 Hz, 1H, H-3); 3.47-3.53 (2m, 2H, $\underline{CH_2}$-N_3); 3.96 (dd, 1H, *J* = 2.2 Hz, 6.3 Hz, H-4); 4.23 (m, 1H, Me-$\underline{CH}$-OSi); 6.00 (bs, 1H, NH azetid.); 7.34 (m, 1H, H-β, pyr.); 7.62 (m, 1H, H-δ, pyr.); 7.77 (m, 1H, H-γ, pyr.); 8.64 (m, 1H, H-α, pyr.).

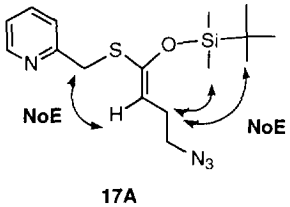
2-Pyridinemethanethiol. To a solution of 1.168 Kg (7.12 moles) of 2-picolyl chloride hydrochloride **15** in 10L of H_2O was added in one portion 583 g (7.66 moles) of thiourea and the reaction mixture was stirred at 85-89 °C for 1h 15. The reaction mixture was cooled at +5 °C and nitrogen was bubbled through the reaction mixture for 2 h. Then keeping the same flow of nitrogen, 853 g of sodium hydroxide (21.32 moles) were added in four portions over 2 h while maintaining the inner temperature below 10 °C. The resulting mixture was stirred for 16 h, under nitrogen, at 22 °C, then washed with two portions of 2 L of *tert*-butylmethyl ether. The aqueous phase was decanted and cooled to 5 °C, the pH carefully adjusted to 7 with *ca* 650 mL of concentrated HCl (d = 1.18), and extracted successively with 2 L, and twice with 1 L of CH_2Cl_2. The combined dichloromethane fractions were washed twice with 500 mL of brine, dried ($MgSO_4$), and evaporated under reduced pressure at 40 °C to provide 843.6 g (96% crude yield) of oily 2-pyridine methanethiol which was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$): δ 2.02 (t, *J*= 7.8 Hz, 1H, SH); 3.65 (d, 2H, *J* = 7.8 Hz, S-$\underline{CH_2}$-pyr); 7.16 (m, 1H, H-β, pyr.); 7.31 (m, 1H, H-δ, pyr.); 7.65 (m, 1H, H-γ, pyr.); 8.54 (m, 1H, H-α, pyr.).

2'-Picolyl-4-bromothiobutyrate. Under nitrogen, a solution of 100 g (0.8 mole) of 2-pyridine-methanethiol in 850 mL dry CH_2Cl_2 was cooled at -5 °C, and 144 mL (1.03 moles) of TEA was added in 10 mn, the temperature being kept below 0 °C. After stirring this solution at 0 °C for 10 mn, a solution of 148 g (0.8 mole) of 4-bromobutyryl chloride (prepared from 4-bromobutyric acid and thionyl chloride) in 160 mL of CH_2Cl_2 was added dropwise over 1h 15 while maintaining the inner temperature below 7 °C. The resulting mixture was stirred for 30 mn under nitrogen at 10 °C, then washed successively with two portions of 250 mL of H_2O, 250 mL of saturated aqueous $NaHCO_3$, 250 mL of 10% aqueous $NaHSO_3$, 250 mL of H_2O and 250 mL of brine. The organic phase was dried ($MgSO_4$), and evaporated under reduced pressure at 40 °C to provide 212.8 g (97% crude yield) of 2'-picolyl-4-bromothiobutyrate as an oil which was used for the next step without further purification. An analytical sample of 2'-picolyl-4-bromothiobutyrate was prepared (SiO_2): Analysis Calcd for $C_{10}H_{12}BrNOS$: C, 43.81; H, 4.41; N, 5.11%; Found C, 43.78; H, 4.58; N, 5.06%. IR (KBr): 3361, 3128, 3050, 3008, 2963, 2935, 1729, 1687 cm^{-1}. Tlc (SiO_2, CH_2Cl_2/AcOEt 50:50) Rf: 0.6. ^{1}H-NMR ($CDCl_3$): δ 2.22 (q, 2H, CH_2-$\underline{CH_2}$-CH_2); 2.79 (t, 2H, *J* = 6.5Hz, CO-$\underline{CH_2}$); 3.44 (t, 2H, *J* = 6.5Hz, $\underline{CH_2}$-Br); 4.27 (s, 2H, S-$\underline{CH_2}$-pyr); 7.18 (m, 1H, H-β, pyr.); 7.31 (m, 1H, H-δ, pyr.); 7.63 (m, 1H, H-γ, pyr.); 8.53 (m, 1H, H-α, pyr.). ^{13}C-NMR ($CDCl_3$): δ 7.72, 28.12, 32.26, 35.16, 41.74, 122.12, 123.08, 136.68, 149.38, 157 ppm.

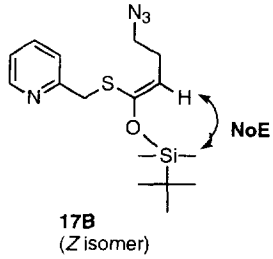
2'-Picolyl-4-azidothiobutyrate **16**. To a solution of 1.2 Kg (4.38 moles) of 2'-picolyl-4-bromothiobutyrate in 3.6 L of dry DMF were added 293 g of NaN_3 (4.51 moles) in one portion and the resulting slurry was stirred for 5 h. The resulting mixture was diluted with 7.2 L of AcOEt and 7.2 L of H_2O. The organic phase was decanted and backwashed with four portions of 2 L of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to provide 959.5 g (93% crude yield) of 2'-picolyl-4-azidothiobutyrate **16** as an oil which was used for the next step without further purification. An analytical sample of **16** was prepared (SiO_2): Analysis Calcd for $C_{10}H_{12}N_4OS$: C, 50.83; H, 5.12; N, 23.71%; Found C, 50.73; H, 5.23; N, 23.40%. IR (KBr): 2933, 2107, 1731, 1688 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.91 (q, 2H, CH_2-$\underline{CH_2}$-CH_2); 2.67 (t, 2H, *J* = 6.5Hz, CO-$\underline{CH_2}$); 3.32 (t, 2H, *J* = 6.5Hz, $\underline{CH_2}$-N_3); 4.25 (s, 2H, S-$\underline{CH_2}$-pyr); 7.13 (m, 1H, H-β, pyr.); 7.31 (m, 1H, H-δ, pyr.); 7.60 (m, 1H, H-γ, pyr.); 8.51 (m, 1H, H-α, pyr.). ^{13}C-NMR ($CDCl_3$): δ 7.71, 24.43, 34.94, 40.16, 50.10, 121.88, 122.84, 136.43, 149.17, 156.84 ppm.

E and Z isomers of t-Butyldimethylsilyl ketenesilyl acetals **17A** *and* **17B** *(R_6 = tert-butyl, R_7 = R_8 = methyl)* To a solution of 7 g (29.6 mmoles) of 2-picolyl-4-azidothiobutyrate **16** in 40 mL of dry CH_2Cl_2 cooled to -10°C were added 7.4 mL (53.1 mmoles) of TEA, followed by the addition of 10.2 mL (44.4 mmoles) of *tert*-butyldimethylsilyltrifluoromethanesulfonate for 15 mn. The reaction mixture was stirred at 25 °C for 4 h . The reaction mixture was evaporated under reduced pressure diluted with 200 mL of hexane (a black insoluble oil was decanted from hexane). The organic phase was washed three times with 100 mL of cold H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to provide 8.89 g of a dark red oil, mixture of silylketene acetals **17A** and **17B**. Flash chromatography over a silica gel pad (AcOEt/hexane 25:75) afforded 7.85g of a mixture of **17A+17B** in 75.6 % yield.

A mixture of 1 g of **17A** and **17B** was chromatographed again (AcOEt/hexane 25:75) in order to separate both isomers as oils. Normal phase HPLC separation, Si diol 10μ-25 cm column, λ = 260 nm, flow rate 1.5 mL/mn, Hexane *t*-BuMe-ether 90: 10, **17B**, rt 6.10 mn; **17A**, rt 7.31 mn. NMR NOESY experiments showed that the compound eluting first from the silica gel column was the *Z* isomer (**17B**) with *E* isomer (**17A**) eluting second.



17A
(*E* isomer)



17B
(*Z* isomer)

An analytical sample of **17A** was prepared: Analysis Calcd for $C_{16}H_{26}N_4OSSi$: C, 54.82; H, 7.48; N, 15.98%; Found C, 54.84; H, 7.50; N, 15.84%; ^{1}H-NMR ($CDCl_3$): δ 0.26 (m, 6H, Me_2Si); 0.98 (m, 9H, *tert*-BuSi); 2.30 (q, 2H, *J*= 7.2 Hz, $\underline{CH_2}$-CH_2-N_3); 3.13 (t, 2H, *J*= 7.2 Hz, $\underline{CH_2}$-N_3); 3.99

(s, 2H, S-$\underline{CH_2}$-pyr); 4.84 (t, 1H, *J* = 7.2 Hz, =CH); 7.14 (m, 1H, H-β, pyr.); 7.28 (m, 1H, H-δ, pyr.); 7.62 (m, 1H, H-γ, pyr.); 8.54 (m, 1H, H-α, pyr.). ^{13}C-NMR ($CDCl_3$): δ -4.18, 25.80, 26.28, 38.75, 50.60, 112.13, 121.85, 123.02, 136.26, 145.36, 149.41, 157.65 ppm.
An analytical sample of **17B** was prepared: ^{1}H-NMR ($CDCl_3$): δ 0.23 (m, 6H, Me_2Si); 0.98 (m, 9H, *tert*-BuSi); 2.29 (dd, 2H, *J*= 7.0 Hz, $\underline{CH_2}$-CH_2-N_3); 3.02 (t, 2H, *J*= 7.0 Hz, $\underline{CH_2}$-N_3); 4.06 (s, 2H, S-$\underline{CH_2}$-pyr); 4.99 (t, 1H, *J* = 7.5 Hz, =CH); 7.14 (m, 1H, H-β, pyr.); 7.27 (m, 1H, H-δ, pyr.); 7.62 (m, 1H, H-γ, pyr.); 8.53 (m, 1H, H-α, pyr.).

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl]-4-[(1"R)- and (1"S)-1"-(pyridin-2-yl)methylthiocarbonyl-3"-azidopropyl)]azetidin-2-one **18a** *and* **18b** (one-pot reaction, TBDMS route). To 4.5 L of dry 1,2-dichloroethane were added 732 mL (5.25 moles) of TEA, followed by the rapid addition of 1.05 L (4.57 moles) of *tert*-butyldimethylsilyltrifluoromethanesulfonate. The reaction mixture was heated at 36 °C and 600 g (2.285 moles) of 2-picolyl-4-azidothiobutyrate **16** in 1.5 L of dry 1,2-dichloroethane were added dropwise for 1.25 h while maintaining the temperature below 40 °C. The formation of intermediate silylketene acetals **17A** and **17B** (mixture of *E* and *Z* isomers, typically a 60:40 ratio) was monitored by HPLC (RP_{18} Merck, acetonitrile/ H_2O 70:30, λ = 264 nm) and was carried out until less than 4% HI of starting material **16** was present (*ca* 3h). The resulting mixture was cooled to 0 °C and 467 g (3.43 moles) of solid $ZnCl_2$ were added portionswise in 0.5 h. The inner temperature reached 9 °C and the reaction mixture was cooled again to 5 °C before adding rapidly 730 g (2.54 moles) of (3*S*,4*R*)-4-acetoxy-3-[(1'*R*)-1'-*tert*-butyldimethylsilyloxyethyl] azetidin-2-one **4**. The reaction mixture was stirred at 5 °C for 2 h then 16 h at 21 °C. The formation of **18a** and **18b** (mixture of α and β isomers, typically a 20:80 ratio) was monitored by HPLC (RP_{18} Merck, acetonitrile/ H_2O 70:30, λ = 264 nm, flow rate 1.5 ml/mn, α-isomer rt 5.68 mn, β-isomer rt 6.25 mn) and was carried out until ketenesilyl acetals **17** were no more detectable (*ca* 18h). The reaction mixture was diluted with 4 L of saturated NH_4Cl. The organic phase was decanted and washed with 4 L of saturated $NaHCO_3$ and 4 L of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to provide 1574.2 g (>100% crude yield) of a black oily mixture of derivatives **18a+18b** which was rapidly purified over 6 Kg of a silica gel pad (CH_2Cl_2/ MeOH 98:2) to give 11 fractions of 2.5 L then 10 fractions of 1 L. The pertinent fractions were collected and evaporated under reduced pressure to yield 870.9 g of **18a+18b** as a pasty brownish solid. Overall yield 82.2%.
An analytical sample of **18a** was prepared: Analysis Calcd for $C_{21}H_{33}N_5O_3SSi$: C, 54.10; H, 7.17; N, 15.05%; Found C, 53.84; H, 7.15; N, 15.07%; m.p. 98 °C. $[\alpha]_D^{25}$ +26.6° (c=1, MeOH). IR (KBr): 3163, 3107, 2928, 2106, 1764, 1716, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.06 (2s, 6H, Me_2Si); 0.87 (m, 9H, *tert*-BuSi); 1.04 (d, 3H, *J* = 6.5Hz, $\underline{CH_3}$-CH-OSi); 1.74 and 2.06 (2m, 2H, CH-$\underline{CH_2}$-CH_2); 2.95 (m, 1H, $\underline{CH}$-CO-S-pic.); 3.06 (d, *J*= 1.7 Hz, 1H, H-3); 3.31-3.42 (2m, 2H, $\underline{CH_2}$-N_3); 3.86 (dd, 1H, *J* = 1.7 Hz, 6.5 Hz, H-4); 4.17 (m, 1H, Me-$\underline{CH}$-OSi); 4.29 (dd, 2H, *J* = 14Hz, 6.5Hz, S-$\underline{CH_2}$-pyr); 5.96 (bs, 1H, NH azetid.); 7.19 (m, 1H, H-β, pyr.); 7.32 (m, 1H, H-δ, pyr.); 7.64 (m, 1H, H-γ, pyr.); 8.54 (m, 1H, H-α, pyr.). ^{13}C-NMR ($CDCl_3$): δ -5.00, -4.29, 9.55, 17.93, 22.22, 25.75, 28.74, 35.66, 48.98, 51.25, 54.63, 62.47, 64.70, 122.35, 123.16, 136.79, 149.59, 156.41, 167.65 ppm.

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl]-4-[(1"R)-1"-(pyridin-2-yl)methylthiocarbonyl-3"-azidopropyl)]azetidin-2-one **18a** (one-pot reaction, TIPS route). In 4 L of dry 1,2-dichloroethane was added 544 mL (3.90 moles) of TEA, followed by a rapid addition at 21 °C of 952 ml (3.54 moles) of triisopropylsilyltrifluoromethanesulfonate. The reaction mixture was cooled to 10 °C and 463.2 g (1.76 moles) of **16** in 4 L of dry 1,2-dichloroethane were added dropwise for 20 mn while maintaining the temperature below 10 °C. The formation of the intermediate silylketene acetals **17A** and **17B** (mixture of *E* and *Z* isomers, typically a 70:30 ratio) was monitored by HPLC (RP_{18} Merck, acetonitrile/ H_2O 80:20, λ = 264 nm) and was carried out until less than 4% HI of **16** was present (*ca* 20h). The resulting mixture was cooled to 0 °C and 364 g (2.67 moles) of solid $ZnCl_2$ was added portionswise in 40 mn. The inner temperature reached 9 °C and the reaction mixture was cooled again to 5 °C before adding rapidly 683 g (2.37 moles) of **4**. Then the reaction mixture was stirred at 20 °C for 3 h. The formation of **18a** and **18b** (mixture of β and α isomers, typically a 95:5 ratio) was monitored by HPLC (RP_{18} Merck, acetonitrile/ H_2O 80:20, λ = 264 nm, flow rate 1.5 ml/mn) and was carried out until material **17A** and **17B** were no more detectable (*ca* 3h). The reaction mixture was diluted with 3 L of saturated NH_4Cl. The organic phase was decanted and washed with 3 L of saturated $NaHCO_3$ then 5 L of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure at 40 °C to provide 1686.8 g (>100% crude yield) of a black oily mixture of derivatives **18a+18b** which was used without any purification for the next step.

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl]-4-[(1"R)- and (1"S-)-1"-carboxy-3"-azidopropyl)] azetidin-2-one **5a** *and* **5b.** To a solution of 1686.5 g (ca. 1.764 moles) of **18a+18b** (TIPS route) in 8 L of tetrahydrofuran cooled to 0 °C, was added 618 ml (7.056 moles) of 35% H_2O_2 for 15 mn, the temperature being kept below 5 °C. The resulting solution was cooled at -4 °C and a solution of 252 g (5.29 moles) of NaOH pellets in 5.2 L of H_2O were added dropwise in 2 h, the temperature being kept below 9 °C. The inner temperature was then allowed to reach 22 °C for 1.5 h. The reaction mixture was washed twice with 2 L of heptane. Then the aqueous layer was decanted and cooled to 0 °C. The pH was carefully brought to 5 with *ca* 450 mL of 6N aqueous HCl and the resulting mixture was stirred overnight at 5 °C, extracted twice with 2 L of AcOEt, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to provide 558 g (88.7 % crude yield) of **5a+5b** as a yellowish solid which was purified by means of DCHA salt.

Tlc (SiO_2, AcOEt:MeOH /98:2) Rf 0.35 (10% phosphomolybdic acid in EtOH). HPLC: RP_{18} Lichrospher 5 μ-12.5 cm; λ = 210 nm; flow rate 1.0 mL/mn; ammonium phosphate buffer pH 7.3: acetonitrile, 73:27, rt β acid **5a**: 4.5 mn, rt α acid **5b**: 9.0 mn.

In the same manner, 1515 g (from 3005 g of chromatographed crude thioester **18**, 80:20 β/α ratio, TBDMS route) were hydrolyzed with H_2O_2 and NaOH in 67 % yield to give 1602 g of **5a+5b** with a 90:10 β/α ratio.

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl] -4-[(1"R)-1"-carboxy-3"-azidopropyl)]azetidin-2-one **5a** *(DCHA salt).* In 5 L of acetone was added 558 g (*ca.* 1.565 moles) of azetidinones **5a** and **5b** (TIPS route) cooled to 7 °C, followed by rapid addition of 283 g (1.56 moles) of dicyclohexylamine, the temperature raised to 12 °C. After 5 mn of stirring at 10 °C a voluminous precipitate

appeared which was stirred overnight at 10 °C, cooled to 0 °C for 30 mn, filtered and washed with 0.5 L of acetone to provide 464 g (yield 55.2%) of **5a** (DCHA salt) as a pale yellow powder.
Analysis Calcd for $C_{27}H_{51}N_5O_4Si$: C, 60.30; H, 9.56; N, 13.02%; Found: C, 59.89; H, 9.53; N, 12.59%. ^1H NMR (acetone-d_6): δ 0.088 (m, 6H, Me_2Si); 0.89 (s, 9H, *t*-BuSi); 1.15-1.45 (m, 13H, $\underline{CH_3}$-CH-O and $\underline{CH_2}$ DCHA); 1.65 (m, 2H, $\underline{CH_2}$ DCHA); 1.74-1.79 (2m, 5H, $\underline{CH_2}$-CH_2-N_3 and $\underline{CH_2}$ DCHA); 1.95 (m, 1H, $\underline{CH_2}$-CH_2-N_3); 2.04 (m, 4H, $\underline{CH_2}$ DCHA); 2.45 (m, 1H, $\underline{CH}$-CO_2H); 2.95 (m, 2H, $\underline{CH}$ DCHA); 3.07 (d, *J*= 2 Hz, 1H, H-3); 3.39-3.47 (2m, 2H, $\underline{CH_2}$-N_3); 3.80 (dd, *J*= 2 Hz, 6.0 Hz, 1H, H-4); 4.19 (m, 1H, CH_3-$\underline{CH}$-O); 7.31 (bs, 1H, NH az.).
HPLC: RP_{18} Lichrospher 5 μ; 12.5 cm; λ = 210 nm; flow rate 1.0 mL/mn; ammonium phosphate buffer pH 7.3: acetonitrile, 73:27; HI 93.16%.
In the same manner from 1515 g of crude **5** (TBDMS route), using the same methodology, a total of 1602 g of **5a** (DCHA salt) was obtained (74% yield, HI 98.3%, 98:2 β/α ratio). Alternatively the potassium salt of crude acid **5** can be prepared in *tert*-butylmethylether with one equivalent of *t*-BuOK (1M solution in THF) followed by precipitation with hexane. From a 85:15 mixture of isomers **5a** and **5b** , the K salt of **5a** could be obtained in 77% yield with a 96:4 β/α ratio.

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl]-4-[(1"R)-1"-carboxy-3"-azidopropyl)] azetidin-2-one **5a** (from DCHA salt). To a solution of 6.7 g (0.0125 mole) of **5a** DCHA salt in 100 mL of H_2O and 50 mL of *tert*-butyldimethylether, cooled to +10 °C, aqueous 2N NaOH was added dropwise until pH 11.6 was attained. The aqueous layer was decanted, washed with 50 mL of *tert*-butyldimethyl ether and acidified to pH 2.5 with aqueous 3N HCl. The precipitate was filtered and washed with H_2O to provide 4.24 g (95.15% yield) of pure acid **5a** as a pale yellow powder; m.p. 170 °C. HPLC: RP_{18} Lichrospher 5 μ, 12.5 cm; λ = 210 nm; flow rate 1.0 mL/mn; ammonium phosphate buffer pH 7.3: acetonitrile 73:27: HI 95.05%.
Analytical samples of acids **5a** and **5b** were prepared (C_{18} chromatography): Acid **5a**, analysis Calcd for $C_{15}H_{28}N_4O_4Si$: C, 50.54; H, 7.92; N, 15.72% ; Found: C, 50.20; H, 7.81; N, 15.46%; m.p. 165°C; $[\alpha]_D^{25}$ -8.5° (c=1, MeOH). IR (KBr): 3261, 2958, 2889, 2858, 2490, 2094, 1705, 1287, 1259 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.088 (2s, 6H, Me_2Si); 0.89 (s, 9H, *t*-BuSi); 1.21 (d, *J*= 6.3 Hz, 3H, $\underline{CH_3}$-CH-O); 1.77-2.02 (2m, 2H, $\underline{CH_2}$-CH_2-N_3); 2.82 (m, 1H, $\underline{CH}$-CO_2H); 3.15 (d, *J*= 2 Hz, 1H, H-3); 3.40-3.48 (2m, 2H, $\underline{CH_2}$-N_3); 3.94 (dd, *J*= 2 Hz, 5.85 Hz, 1H, H-4); 4.23 (m, 1H, CH_3-$\underline{CH}$-O); 6.40 (bs, 1H, NH azetid.). ^{13}C-NMR ($CDCl_3$): δ -5.00, -4.30, 17.93, 22.39, 25.74, 27.80, 45.98, 49.37, 51.50, 61.64, 64.78, 169.88, 176.47 ppm. HPLC: RP_{18} Lichrospher column, $(NH_4)_2HPO_4$ (pH=7.3): CH_3CN/ 73:27, λ= 210nm, rt 7.36 mn, HI 100%.
Acid **5b**, analysis Calcd for $C_{15}H_{28}N_4O_4Si$: C, 50.54; H, 7.92; N, 15.72%; Found: C, 50.55; H, 7.94; N, 15.70%; m.p. 126 °C; $[\alpha]_D^{25}$ -13° (c=1, MeOH). IR (Kr) 3303, 2955, 2890, 2856, 2105, 1705, 1255 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.09 (2s, 6H, Me_2Si); 0.89 (s, 9H, *t*-BuSi); 1.28 (d, *J*= 6.2 Hz, 3H, $\underline{CH_3}$-CH-O); 1.87-1.92 (2m, 2H, $\underline{CH_2}$-CH_2-N_3); 2.63 (m, 1H, $\underline{CH}$-CO_2H); 2.91 (d, *J*= 2 Hz, 5.6 Hz, 1H, H-3); 3.45-3.53 (2m, 2H, $\underline{CH_2}$-N_3); 3.74 (dd, *J*= 2 Hz, 11 Hz, 1H, H-4); 4.18 (m, 1H, CH_3-$\underline{CH}$-O); 7.06 (bs, 1H, NH az.). ^{13}C-NMR ($CDCl_3$): δ -4.72, -4.32, 17.94, 22.84,

25.76, 28.45, 46.73, 49.30, 52.69, 63.35, 65.77, 169.87, 176.12 ppm. HPLC : RP_{18} Lichrospher column, $(NH_4)_2HPO_4$ (pH=7.3): CH_3CN, 73:27, λ= 210nm, rt 10.62 mn, HI 100%.

(3S,4S)-3-[(1'R)-tert-Butyldimethylsilyloxyethyl]-4-[(1"R)-(pyridin-2-yl)methylthio)]-azetidin-2-one **19**. To a solution of 0.68 g (17.1 mmoles) of NaOH pellets in 20 mL of EtOH cooled to 0 °C was added a solution of 2.178 g (17.39 mmoles) of 2-picolylmethanethiol over 2 mn. After stirring 5 mn at 0 °C, 5 g (17.39 mmoles) of azetidinone **4** was added by portions over 1 mn. The reaction mixture was stirred at room temperature for 2 h, concentrated to dryness under reduced pressure. The residue was taken up in 200 mL of CH_2Cl_2 and 30 mL of H_2O, the organic layer was decanted, washed with 40 mL of H_2O, 40 mL of brine, dried ($MgSO_4$) and evaporated to yield 7.96 g of crude **19**. Chromatography over silica gel (Hexane AcOEt 25:75) of this oily material provided 5.33 g of pure **19** as an oil in 87.3% yield. Analysis calcd for $C_{17}H_{27}N_2O_2SSi$: C, 58.08; H, 7.74; N, 7.97%; Found: C, 57.85; H, 7.99; N, 7.90%; $[\alpha]_D^{25}$ +139.5° (c=1, MeOH). IR (KBr) 3217, 2955, 2920, 2855, 1763, 1592, 1254 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.07 (2s, 6H, Me_2Si); 0.89 (s, 9H, *t*-BuSi); 1.19 (d, *J*= 6.3 Hz, 3H, $\underline{CH_3}$-CH-O); 3.05 (d, *J*= 2 Hz, 5.6 Hz, 1H, H-3); 3.96 (s, 2H, $\underline{CH_2}$S-pyr.); 4.22 (d, *J*= 2 Hz, 11 Hz, 1H, H-4); 4.89 (m, 1H, CH_3-$\underline{CH}$-O); 6.41 (bs, 1H, NH az.); 7.19 (m, 1H, H-β, pyr.); 7.32 (m, 1H, H-δ, pyr.); 7.67 (m, 1H, H-γ, pyr.); 8.52 (m, 1H, H-α, pyr.). ^{13}C-NMR ($CDCl_3$) -5.10, -4.34, 17.93, 22.27, 25.70, 37.81, 54.47, 64.65, 65.89, 169.87, 122.24, 123.12, 137.08, 149.31, 158.53, 166.72 ppm.

Acknowledgment. We thank the Lognes Bristol-Myers Squibb Analytical Research and Development Department, for performing elemental analysis, HPLC, and infra-red spectra and especially Dr. T. Shaw for running and interpreting ^1H and ^{13}C NMR spectra.

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25. Reaction of **16** with any silyltriflate at room temperature before adding a base led to the formation of insoluble material which is likely to be a complex of the pyridinyl part of **16** with triflate (30% estimated by HPLC). The use of 1,2-dichloroethane instead of CH_2Cl_2 allowed us to work at higher temperature and to avoid the formation of insoluble material. It was also note worthy that we always observed the formation of the bis silylether [*t*Bu(Me)$_2$Si]$_2$O after work-up in this reaction (up to 40% of the crude mixture).
26. Attempts to hydrolyse the crude mixture of **18a +18b** in the TBDMS route did not allow us to obtain acids **5a+5b** in sufficient purity for the next steps whereas in the TIPS route, the mixture of **5a+5b** crystallized easily as DCHA salts.

(*Received in Belgium* 11 *May* 1995; *accepted* 7 *July* 1995)