undertaken with fixed isotropic factors and coordinates for H atoms, except for H3 whose coordinates were refined. Most of the calculations were carried out with the X-ray 80 system.[18]

Acknowledgment. A grant (PB 87-0064-CO3-02) from DGICYT of Spain is greatly acknowledged. Professor Odon Arjona kindly recorded the solid ^{13}C CP/MAS spectrum.

Supplementary Material Available: Tables of bond lengths (Å) and angles (deg) and hydrogen bond distances (Å) and angles (deg) of compound **4b**, NMR data of compounds **4a**, **4b**, and **6a**, final atomic parameters, bond distances, and angles (13 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.

(18) Stewart, J. M. The XRAY80 System, Computer Science Center, University of Maryland, College Park, 1985.
(19) Johnson, C. K. ORTEP, Report ORNL-3974, Oak Ridge National Laboratory, TN, 1965.

Stereoselective Synthesis of β-Lactams by Condensation of Titanium Enolates of 2-Pyridyl Thioesters with Imines

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A mild and versatile one-pot synthesis of β-lactams has been performed by condensation of the easily generated titantium enolates of 2-pyridyl thioesters with imines employing chiral reaction partners. Both imines obtained from enantiomerically pure alkoxy aldehydes and the enolate derived from 3-hydroxybutyrate showed high diastereofacial preferences, efficiently transferring the stereochemical information to the stereocenters of the azetidinone ring. Advanced precursors of (+)-PS-5, (+)-PS-6, thienamycin, and 1β-methylthienamycin were prepared to illustrate the potential of this method. A ^1H-NMR study of the enolization process and a tentative rationalization of the stereochemical results are presented.

The well-recognized importance of β-lactams as antibiotics stimulated the pharmaceutical industry to develop new derivatives of this class of compounds possessing broader activity and enhanced resistance to biological degradation.[1] As a consequence, there is growing interest in improved synthetic methods that allow the assembly of a 2-azetidinone ring in a mild and selective fashion. In relation to this, we recently reported[2] a synthesis of β-lactams by the high yielding, one-pot condensation of imines with titanium enolates of 2-pyridyl thioesters.[3,4] The method is very mild and simple, not requiring strong bases or sophisticated reagents, and appears perfectly suitable to be extended to the preparation of nonracemic derivatives. We report here that our procedure can be successfully applied to the synthesis of optically active β-lactams using chiral imines or chiral enolate precursors.

Chart I

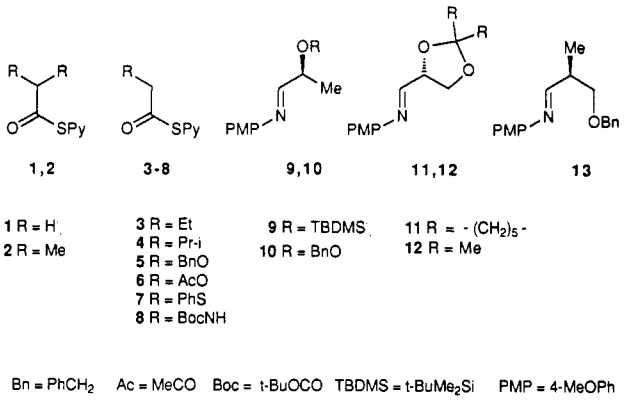


Table I. Synthesis of β-Lactams 14–20 from Thioesters 1 and 2 and Imines 9, 10, 11, and 13

thioester	imine[a]	product	yield[b] (%)	dr[c] s:a
1	9	14	42	>98:2
2	9	15	66	92:8
1	10	16	54	65:35
2	10	17	80	>98:2
1	11	18	52	>98:2
1[d]	13	19	71	29:71
2[d]	13	20	62	20:80

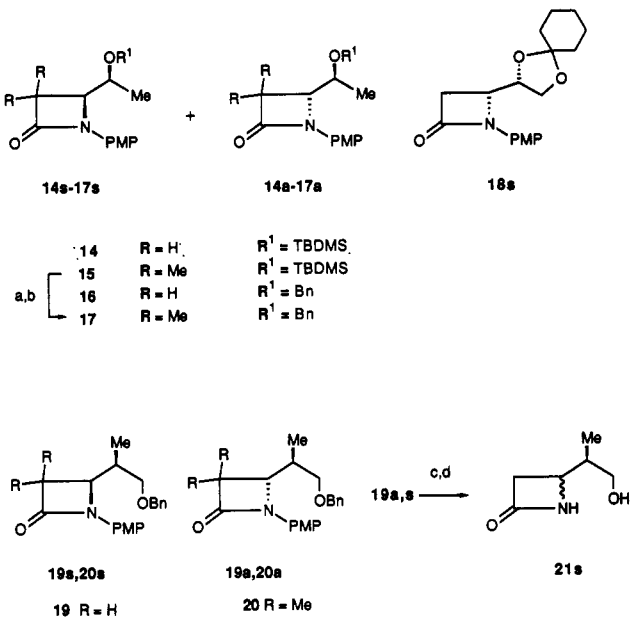
[a] Crude imines were used. [b] Overall isolated yields after flash chromatography. [c] By 300-MHz ^1H-NMR spectroscopy. [d] 1 mol equiv of enolate per mol equiv of imine.

Addition of Achiral Enolates of 2-Pyridyl Thioesters to Chiral Imines.[5,6] 2-Pyridyl thioesters were

(1) (a) Perrone, E.; Franceschi, G. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: New York, 1990, pp 615–703. (b) Palomo, C. *Ibid.* pp 565–612. (c) Georg, G. I. In *Studies in Natural Product Chemistry*, Rahman, A.-U. Ed.; Elsevier: New York, 1989, Vol. 4, p 431. (d) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180. (e) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (f) Cainelli, G.; Panunzio, M. *Farmaco* **1991**, *46*, 177.
(2) Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 8767.
(3) For reviews on the enolate–imine condensation route to β-lactams see: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) Brown, M. J. *Heterocycles* **1989**, *29*, 2225.
(4) For other syntheses of β-lactams involving thioesters see: (a) Otsuka, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. *Tetrahedron Lett.* **1981**, 2109. (b) Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946. (c) Mukaiyama, T.; Suzuki, H.; Yamada, T. *Chem. Lett.* **1986**, 918. (d) Yamasaki, N.; Murakami, T. *Chem. Lett.* **1986**, 1013. (e) Iwasaki, G.; Shibasaki, M. *Tetrahedron Lett.* **1987**, 3257. (f) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Tetrahedron* **1991**, *47*, 531. Only one of these (f) afforded the products in a single-step procedure.

0022-3263/92/1957-4155$03.00/0

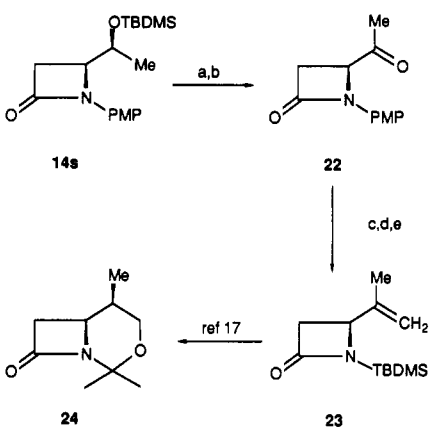
Scheme I[a]



[a] Reagents: (a) HF, CH_3CN, rt, 2 h; (b) BnBr, NaH, Bu_4NI, THF, 50 °C, 2 h; (c) CAN, CH_3CN, -20 °C, 2 h; (d) 10% Pd/C, H_2, THF, rt.

readily prepared in multigram quantities and high yield by reaction of 2-pyridylthiol (PySH) with an acid chloride (as in the case of compounds 1–6) or by condensation of 2-pyridyl disulfide with a carboxylic acid in the presence of triphenylphosphine[7] (compounds 7 and 8). The corresponding titanium enolates were generated by Evans' procedure,[8-10] involving addition of a 1 M solution of $TiCl_4$ to the thioester at -78 °C, followed by triethylamine (TEA).[11]

Scheme II[a]



[a] Reagents: (a) HF, CH_3CN, rt, 2 h; (b) H_2CrO_4, NaH, THF, rt, 1 h; (c) Ph_3PCH_3I, BuLi, THF, -40 °C, 1 h; (d) CAN, CH_3CN, -20 °C, 2 h; (e) TBDMSCl, TEA, CH_2Cl_2, rt, 15 h.

Table II. Synthesis of β-Lactams 25–28 and 31–35 from Thioesters 3–8 and Imines 9, 11, and 12

thioester	imine[a]	product	yield[b] (%)	dr[c] ts	cs	ta	ca
3	9	25	59	67	33		
4	9	26	70	>98	2		
5	9	27	64	4	96		
6	9	28	44	2	>98		
7	9	31	72	81	5	9	5
8	9	32	38	*d*			
3	11	33	74	54	46		
5	11	34	82	2	>98		
5	12	35	34	2	>98		

[a] Crude imines were used. [b] Overall isolated yields after flash chromatography. [c] By 300-MHz ^{1}H-NMR spectroscopy. [d] Undetermined.

Imines (*S*)-**9**, (*S*)-**10**, (*S*)-**11**, (*S*)-**12**, and (*R*)-**13** were prepared from the corresponding aldehydes and 4-methoxyaniline and used as crude products. The *p*-methoxyphenyl (PMP) group was selected because it can be very easily inserted in the imine and readily removed from the β-lactam ring by ceric ammonium nitrate (CAN) degradation.[12]

For a simple evaluation of the intrinsic diastereofacial selectivity of the imines, the reaction of nonstereogenic thioesters **1** and **2** was studied first. The products are shown in Scheme I; yields and diastereoisomeric ratios (dr) are shown in Table I. Generally, 2 mol equiv of enolate was used; this improved the yields while leaving the diastereoselectivity virtually unchanged. The dr were evaluated by 300-MHz ^{1}H-NMR spectroscopy of the crude reaction mixtures and confirmed on the products isolated by flash chromatography (this procedure was used throughout this work). The assignment of the stereochemistry of the products was easily achieved in the case of compounds **14s,a** and **19s,a** by conversion to β-lactams of known configuration (see below). On the basis of chemical shift trends found in the ^{1}H-NMR spectra (for instance, H-4′ always resonates at lower field in the anti (**a**) isomers than in the syn (**s**) ones), these syn and anti structures were extended to the **s** and **a** isomers of azetidinones **15–18**. The conversion of **15s** into **17s** (aqueous HF, acetonitrile, rt, 2 h; NaH, benzyl bromide, Bu_4NI,

(5) For a preliminary account of part of this section, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *Tetrahedron Lett.* **1992**, 1113.

(6) For the recent syntheses of β-lactams involving chiral imines see the following. For enolate condensation: (a) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984. (b) Andreoli, P.; Billi, L.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1991**, *47*, 9061. (c) Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1991**, *56*, 1933. (d) Fujisawa, T.; Ukai, Y.; Noro, T.; Date, K.; Shimizu, M. *Tetrahedron Lett.* **1991**, 7563. For the Staudinger reaction: (e) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, 5065. (f) Palomo, C.; Cossio, F. P.; Cuevas, C. *Tetrahedron Lett.* **1991**, 3109. (g) Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1991**, 3105. (h) Georg, G. I.; Mashava, P. M.; Akgun, E.; Milstead, M. W. *Tetrahedron Lett.* **1991**, 3151. (i) Brown, A. D.; Colvin, E. W. *Tetrahedron Lett.* **1991**, 5187. (j) Frazier, J. W.; Staszak, M. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, 857. (k) Fujioka, H.; Yamanaka, T.; Matsunga, N.; Fuji, M.; Kita, Y. *SynLett* **1992**, 35.

(7) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406.

(8) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (d) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. For earlier references to this procedure for generating Ti enolates, see refs 8b and 8c.

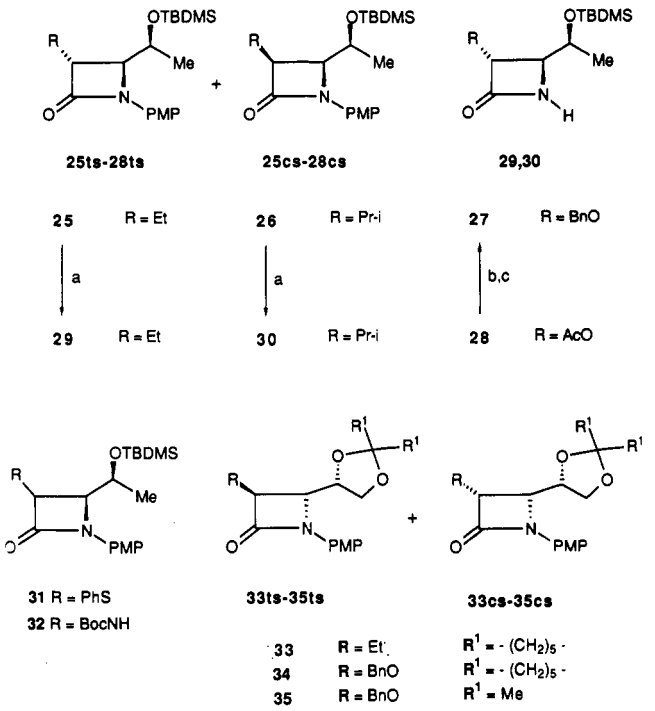
(9) For the extension of this procedure to thioesters and α-thio-substituted esters see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 7897.

(10) Titanium enolates are also prepared by transmetalation. (a) From metal enolates: Duthaler, R. O.; Hafner, A.; Riedeker, M. *Pure Appl. Chem.* **1990**, *62*, 631. Recent reports: Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489. Mikami, K.; Takahashi, O.; Fujimoto, K.; Nakai, T. *Synlett* **1991**, 629. (b) From silyl enol ethers: Nakamura, E.; Shimada, J.; Horiguchi, Y.; Kuwajima, T. *Tetrahedron Lett.* **1983**, 3341. Chan, T. H.; Brook, M. A. *Tetrahedron Lett.* **1985**, 2943. Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009.

(11) The use of diisopropylethylamine instead of TEA (see ref 8) did not improve the stereoselectivity of our reactions.

(12) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129. The experimental conditions for the CAN oxidative degradation described in this paper proved to be the most efficient.

Scheme III[a]



[a] Reagents: (a) CAN, CH_3CN, −20 °C, 2 h; (b) NaOH, THF, MeOH, 0 °C, 2 h; (c) NaH, BnBr, Bu_4NI, THF, 50 °C, 2 h.

THF, 50 °C, 2 h; 72% overall yield) showed that these two products belong to the same steric series and provided additional support to the assignment.

As can be seen from the data reported in Table I, the reaction occurred with good stereocontrol in the case of α-alkoxyimines **9** and **11** to give a large predominance of the syn-configurated β-lactam;[13] on the other hand, α-methyl-β-alkoxy imine **13** reacted less stereoselectively to afford a moderate excess of the anti products **19a** and **20a**.

In view of a possible application of this reaction to the synthesis of biologically active antibiotics, it must be noted that the predominant syn isomers **14s–17s** feature the correct configuration at C-4 of a number of precursors of important β-lactams of the carbapenem class.[1] However, when the **19a,s** mixture was transformed by CAN oxidation and hydrogenolysis (60% overall yield, Scheme I) into **21a,s**, it was the minor component of the mixture, i.e., 4(*S*)-4-[(1*R*)-(1-hydroxymethyl)ethyl]azetidin-2-one (**21s**),[14,15] the precursor of 1β-methylthienamycin.

We therefore decided to investigate the possibility of exploiting the high stereoselectivity observed in the reaction of thioester **1** with imine **9** to obtain an advanced intermediate for 1β-methylthienamycin. With this in mind (Scheme II), compound **14s** was deprotected and oxidized[6a] to 4-acetylazetidinone **22** in 74% overall yield (the unreacted alcohol being recovered almost quantitatively). Wittig reaction (73% yield), followed by CAN oxidation (85% yield), gave the N-unprotected β-lactam that was converted for correlative purpose into the *N*-silyl derivative (−)-(*S*)-**23**, $[\alpha]^{23}_D$ −24.6 (*c* 0.8 in $CHCl_3$). This compound has been transformed into β-lactam **24**, an important precursor in many synthetic routes to 1β-methylthienamycin.[14,17]

The reaction of the stereogenic titanium enolates of thioesters **3–8** with imine **1** was then studied (Scheme III and Table II). Four products can in principle be obtained from each condensation: trans/anti (**ta**), trans/syn (**ts**), cis/anti (**ca**), and cis/syn (**cs**).[18] However, only two isomers were observed by 300-MHz ^{1}H-NMR spectroscopy in the case of β-lactams **25** (R = Et) and **27** (R = BnO), and virtually only a single product in the case of **26** (R = *i*-Pr) and **28** (R = AcO). Chemical correlation established the configuration of the major isomer of **25** and **26** as trans/syn. Nitrogen deprotection gave **29** and **30**, respectively. These were identical by 300-MHz ^{1}H-NMR to the compounds recently prepared and converted by Cainelli and Panunzio into carbapenem antibiotics (+)-PS-5 and (+)-PS-6.[6a] The minor isomer of **25** was a cis[18] β-lactam, to which the **cs** configuration was tentatively assigned on the basis of the high syn selectivity shown by imine **9** in these reactions (see above). The structure of the major isomer of **27** was easily recognized as cis/syn by comparison of its mp (91–93 °C) with that (92–93 °C) of the same compound recently synthesized by Palomo et al.[6f] Following the above reasoning, the **ts** configuration was assigned to the minor isomer of **27** and the **cs** one to the only detected product **28**. Conversion of **28cs** to **27cs** (NaOH, THF, MeOH, 0 °C, 2 h; NaH, BnBr, Bu_4NI, THF, 50 °C, 2 h; 65% overall yield) confirmed this assignment.

The reaction of thioester **7** with imine **9** gave all four possible isomers of β-lactam **31** in a 81:9:5:5 ratio (by NMR). The overall trans/cis ratio was easily determined[18] as 90:10, while the assignment of C-4/C-4′ stereochemistry indicated in Table II is tentatively based on NMR trends (see above). A stereorandom reaction was observed in the condensation of 2-(pyridylthio)-*N*-BOC-glycinate **8** with **9** that gave **32** as a mixture of three isomers with a trans/cis ratio of ca. 50:50. Lower yields or no reaction at all were observed when **9** was reacted with other N-protected glycinates such as *N*-phthalimido-, *N*-acetyl-, and *N*-(carbobenzyloxy)-2-pyridyl thioesters. Thus, our synthesis does not provide a good, direct route to the biologically important 3-aza-substituted azetidinones.[19] However, the 3-oxy-β-lactams **27** and **28**, which are obtained in a highly selective fashion, provide access to these compounds, as reported elsewhere.[20]

Finally, the reactions of α,β-dialkoxyimine **11** with the enolates of esters **3** and **5** were studied (Scheme III and Table II). The former was poorly internally selective, affording an almost equimolecular amount of trans and cis β-lactam **33**, which were both assigned the syn stereochemistry (see below). The condensation of **5** was more satisfactory, since it gave a single product (within the limit of detection of 300-MHz ^{1}H-NMR analysis) featuring the cis configuration. Also, only one β-lactam was obtained from reaction of **5** with imine **12**. The **35cs** structure was

(13) We do not have at present a reasonable explanation for the whimsical behavior of imine **10**.

(14) Gennari, C.; Cozzi, P. G. *Tetrahedron* **1988**, *44*, 5965. The poor selectivity of imine **13** was maintained in the reaction with stereogenic thioesters. For instance, with compound **3** a stereorandom reaction affording four isomers in a 38:30:23:9 ratio was observed.

(15) This transformation established the configuration of **19s** and **19a** and by analogy that of **20s** and **20a**.

(16) Gurjar, M. K.; Bhanu, M. N.; Khare, V. B.; Bhandari, A.; Deshmukh, M. N.; Rao, A. V. R. *Tetrahedron* **1991**, *47*, 7117. The reported rotation was $[\alpha]^{22}_D$ −16.8 (*c* 0.8 in $CHCl_3$). The agreement between observed and reported ^{1}H-NMR data was excellent. The transformation of **14s** into (−)-(*S*)-**23** established the configuration of compounds **14s,a**, and strongly suggested that of **15–17**.

(17) Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563 and references cited therein.

(18) Internal stereochemistry of the β-lactam ring was readily determined on the basis of the H-3/H-4 *J* values of 2.0–2.5 Hz for trans and of 5.0–5.5 Hz for cis products, respectively.

(19) Van Der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

(20) Wagle, D. R.; Garai, c.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227.

Table III. Synthesis of β-Lactams 42–46 from Thioester 36 and Imines 37–41, 48

imine	product	yield[a] (%)	dr[b] ta	ts	ca	cs
37	42	90	89	8	(3)	
38	43	42	84	16		
39	44	28	86	14		
40[c]	45	35	78	12	(10)	
41[c]	46	50			>98	2
48	49	72	88	11	(1)	

[a] Isolated yields after flash chromatography. [b] By 300-MHz ^{1}H-NMR spectroscopy. [c] Crude imines were used.

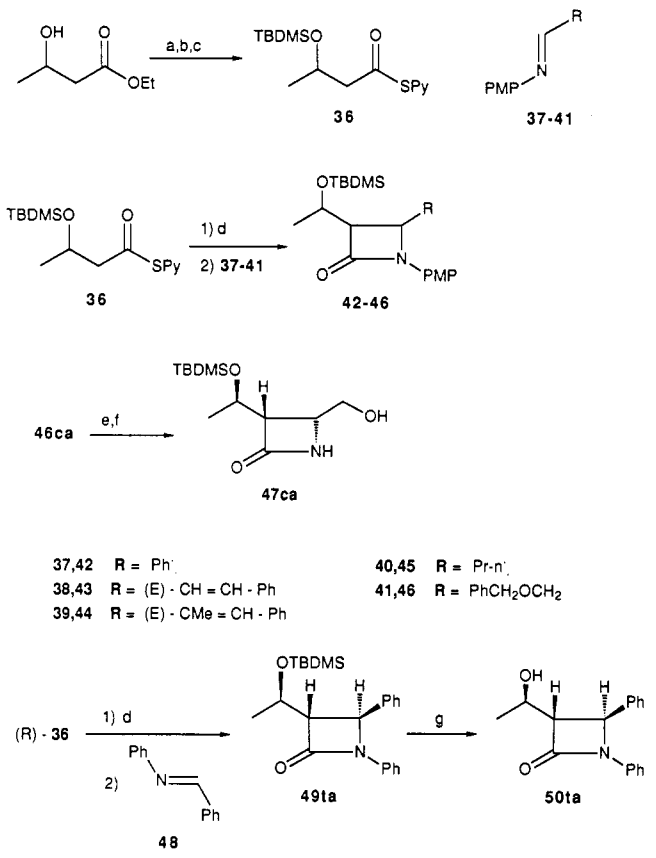
assigned to this compound ($[\alpha]^{23}_D$ +107.5 (*c* 0.4 in MeOH); mp 119–120 °C) by comparison of its optical rotation and mp with those reported by Bose et al.[20] ($[\alpha]^{22}_D$ +109.2 (*c* 0.541 in MeOH); mp 120 °C). β-Lactam **34**, which has a very similar optical rotation ($[\alpha]^{23}_D$ +106.7 (*c* 0.5 in MeOH)) and a closely related NMR spectrum, probably has the same configuration.[21] By analogy, the syn stereochemistry was extended to *cis*- and *trans*-azetidinones **33cs** and **33ts** and to compound **18s** obtained from **1** and **11** (Scheme I).

In concluding this section it is worth pointing out the high diastereofacial selection provided by the α-alkoxy-substituted stereocenter that is the common feature of imines **9–12**. This substitution pattern generally led to a good excess of the syn-configurated product and was found to exert better stereocontrol than the stereocenter of imine **13**.

Addition of the Enolate of *S*-2-Pyridyl 3-[(*tert*-Butyldimethylsilyl)oxy]thiobutyrate to Achiral Imines.[3] The importance of β-lactams possessing an α-hydroxyethyl side chain at C-3 prompted us to investigate the possibility of obtaining these compounds by our convenient procedure. To this end racemic *S*-2-pyridyl 3-[(*tert*-butyldimethylsilyl)oxy]thiobutyrate (**36**) was prepared in three easy steps from ethyl 3-hydroxybutyrate in 70% overall yield (Scheme IV).

The titanium enolate of **36** was reacted under the usual conditions with a series of achiral imines **37–41** to afford β-lactams **42–46** as mixtures of diastereoisomers. Yields and dr (determined as above) are shown in Table III. As before, four isomers could in principle be obtained from the condensation: trans/anti (**ta**), trans/syn (**ts**), cis/anti (**ca**), and cis/syn (**cs**).[18] As can be seen from the reported data the reaction took place in low to good yields and with satisfactory stereoselectivities. The assignment of configuration was firmly established in the case of β-lactam **43**, since all its four possible stereoisomers have been reported by Georg et al.[12] By comparison of NMR data, this product was found to be a 84:16 mixture of **ta** and **ts** isomers. Remarkably, **43ta** has been converted[12] into 4-acetoxy-3-[1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-azetidin-2-one, an important building block for thienamycin. Similar stereoselectivity was observed in the reaction of the related imine **39**, which gave an 86:14 ratio of **44ta** and **44ts** in a disappointing 28% yield. The good anti diastereoface selectivity featured by the enolate of **36** was also observed in the reaction with imine **37** to afford **42ta** and **42ts** in a >10:1 ratio, together with a small amount of a cis β-lactam.

Scheme IV[a]



[a] Reagents: (a) TBDMSCl, imidazole, DMF, rt, 15 h; (b) NaOH, EtOH, rt, 5 h; (c) PySSPy, Ph_3P, CH_2Cl_2, rt, 0.5 h; (d) $TiCl_4$, TEA, CH_2Cl_2, −78 to 0 °C; (e) CAN, CH_3CN, −20 °C, 2 h; (f) Pd/C, H_2, THF, rt; (g) HF, CH_3CN, rt, 2 h.

The condensation of two enolizable imines was also studied. Butanal-derived **40** afforded three products in a 78:12:10 dr. The **ta** and **ts** configurations were tentatively assigned to the two more abundant isomers, respectively. The stereochemical outcome changed markedly in the case of alkoxy-substituted imine **41**. This compound gave a single (by NMR) product **46** with the cis/anti configuration, as determined by conversion to racemic derivative **47** (CAN, CH_3CN, −20 °C, 2 h; Pd/C, H_2, THF, rt; 75% overall yield), that has been reported in optically active form.[12] Finally, we demonstrated that our synthesis does not involve racemization. To this end compound (*R*)-**36** was prepared from (*R*)-ethyl 3-hydroxybutyrate and its titanium enolate condensed with *N*-phenylbenzaldimine **48** to give β-lactam **49** as a 8:1 mixture of **ta** and **ts** diastereoisomers, together with trace amounts of a cis product. The configuration and the stereochemical integrity of **49ta** were established by cleaving the silyl ether to give compound **50ta**, $[\alpha]^{23}_D$ −113.0 (*c* 0.2 in $CHCl_3$) and comparing its optical rotation[12] and NMR spectrum[22] with those reported in the literature.[23] The configuration of the predominant isomer of **49** provided strong evidence for that of **49ts** and of related **42ta** and **42ts**.[24]

As a comment to this section it is important to emphasize the remarkable tendency of the titanium enolate

(21) It seems reasonable that the diol protection should not affect the sense of the diastereofacial selection of the imine. The yields, however, were affected (see Table II), likely because cyclohexylidene glyceraldehyde is more stable that its acetonide counterpart and affords the corresponding imine with a better yield. We did not observed any titanium enolate attack to the acetal moiety of **11** and **12** also in the presence of an excess of enolate (see ref 8b).

(22) Otto, H.-W.; Mayrhoffer, R.; Bergmann, H.-J. *Liebigs Ann. Chem.* **1983**, 152.

(23) The reported (ref 12) optical rotation was $[\alpha]^{22}_D$ −121.1 for a sample of **50ta** containing an undetermined amount (less than 5%) of **50ts**. Our sample was 99% pure by NMR and melted sharply at 192 °C. In ref 12 the mp of **50ta** was not reported.

(24) Some chemical shift trends were observed in the ^{1}H NMR spectrum of **42–46** and **49**: for instance, the HC-3′ proton always resonates at lower field in the anti isomer and at higher field in the syn ones.

Table IV. Chemical Shifts of the Cα-Protons of $PySCOCH_2R$, $TiCl_4$ Adducts, and Enolates in CD_2Cl_2 at −78 °C

			$TiCl_4$ adduct			enolate		
compd	R	thioester	M	m	ratio	M	m	ratio
51[a]	Me	2.75	3.00	3.15	60:40	4.93	5.32	80:20
3[b]	Et	2.70	3.09	2.95	70:30	4.99	5.27	89:11
4[c]	*i*-Pr	2.60	2.69	2.97	60:40	4.86	5.12	95:5
5	BnO	4.33	4.77		>98:2	6.86		>98:2
7	PhS	4.01	4.10	4.34	70:30	5.76		>98:2
36[d]	Me(OTBDMS)CH	2.81	3.14	3.02	67:33	4.96	5.18	65:35

[a] The Me signal resonates at 1.15, 1.01/1.37, 1.81/1.76 for the indicated species, respectively. [b] The CH_2Me signal resonates at 1.67, 1.88/1.81, 2.26/2.13 for the indicated species, respectively. [c] The $CHMe_2$ signal resonates at 2.23, 2.15/2.45, 2.90 for the indicated species, respectively. [d] The *CH*Me signal resonates at 4.37, 4.40/4.40, 4.91/4.56 for the indicated species, respectively.

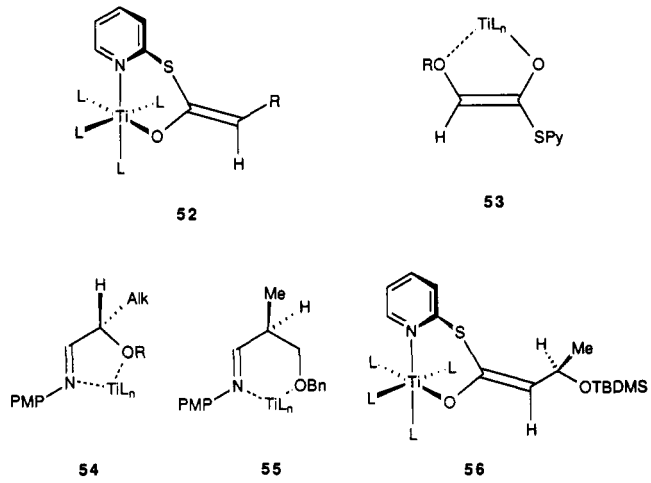
of **36** to undergo anti-selective additions with a variety of imines. However, good control of azetidinone internal stereochemistry is still lacking and largely depends on the imine structure.[25]

^{1}H-NMR Study on the Enolization Process and Rationalization of the Stereochemical Result. To attempt a rationalization of the stereochemical outcome of these reactions some information about the enolate structure was required. Therefore, a ^{1}H-NMR study was undertaken to investigate the complexation between representative thioesters and $TiCl_4$ and the subsequent enolization process. 0.1 Molar solutions of thioesters **3–5, 7,** and **36** were prepared in 5 mL of CD_2Cl_2. These were cooled at −78 °C, and 1 mol equiv of $TiCl_4$ was added. After 5 min at −78 °C, 1-mL samples were withdrawn and transferred under argon to a cooled NMR tube and the spectra recorded at −70 °C. One mol equiv of TEA was then added to the CD_2Cl_2 mother solution, and again 1-mL samples were withdrawn and analyzed by low-temperature NMR. The results, collected in Table IV, were compared to those obtained in a similar study carried out on *S*-2-pyridyl thiopropionate **51**.[9,26]

Upon addition of $TiCl_4$ a shift of relevant signals was observed.[27,28] With the exception of ester **5**, which gave a single adduct, a major (M) and a minor (m) complex were observed in all cases, the ratios ranging from 60:40 to 70:30. These did not change after 2 h at −70 °C. When TEA was added the signals of the adducts disappeared to give rise to those of the enolates. Single species were observed in the case of α-hetero-substituted thioesters **5** and **7**, while alkyl-substituted derivatives **51, 3,** and **4** afforded a mixture of isomers with ratios increasing from 80:20 (R = Me) to 95:5 (R = *i*-Pr) together with the increasing bulkiness of the R residue. The enolates were stable up to −10 °C and showed some tendency to decompose at higher temperature. Warming to −10 °C did not alter the isomeric ratios.

As we have already suggested,[9] the results indicate that there are different binding modes for $TiCl_4$ with these 2-pyridyl thioesters. Although we do not know at present

Chart II



whether we are dealing with mono- or polynuclear Ti complexes, or just with complexes of different geometry,[29] the formation of a 6-membered chelate between the pyridine nitrogen, the carbonyl oxygen, and the titanium atom is likely to account for one of the adducts.[30] However, compound **5** could equally well give a 5-membered chelate involving the carbonyl and the benzyloxy oxygens. Unfortunately, we could not unambigously establish the configuration of the enolates,[31] but the increase of stereoselectivity in the enolate formation with increasing bulkiness of the residue at C-α in the thioester series **51, 3, 4,** and **7** can be tentatively explained with the preferred formation of a *Z* enolate (CIP rules) such as **52**,[32,33] which avoids unfavorable steric interactions between the R group and the ligands at the metal (Chart II).[34] On the other hand, α-alkoxy-substituted thioesters **5** and **6** could give the *E* enolate **53** in which the oxophilic titanium atom prefers oxygen to nitrogen in the coordination.[34,35]

(25) In an attempt to find a shortcut in the synthesis of 1β-methylthienamycin, the reaction of **36** with (*S*)-**10** was found to give a complex mixture of isomers. The PMP imine of (*R,S*)-2-methyl-3-(phenylthio)-propanal, afforded almost exclusively the undesired cis β-lactams.

(26) When the *S*-2-pyridyl thiopropionate/$TiCl_4$ adduct was enolized with diisopropylethylamine (see refs 8b and 11) a 82:18 enolate ratio was observed.

(27) We did not observe any enolate signals until TEA was added. Furthermore, pyridine does not promote enolization of the $TiCl_4$ adduct of phenyl thiopropionate, and the 2-pyridyl thioester/$TiCl_4$ adduct does not react with benzaldehyde.

(28) For leading references on the Lewis acid complexation by neutral Lewis bases, see: (a) Review: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (b) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197 and the papers cited in ref 3 of this article. (c) Faller, J. W.; Ma, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1579. (d) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1991**, *113*, 8973. See also: Turin, E.; Nielson, R. M.; Merbach, A. E. *Inorg. Chem. Acta* **1987**, *134*, 67, 79.

(29) A detailed multinuclear NMR study is currently underway to elucidate the complexation/enolization process.

(30) $TiCl_4$/carbonyl oxygen coordination must occur to activate the esters for proton abstraction (see ref 8). In the absence of $TiCl_4$, TEA was not able to generate a reactive enolate of these esters. Addition of pyridine dramatically changed the complexation mode of thioester **3** with $TiCl_4$.

(31) When we tried to generate the Ti enolate of 2-pyridyl thiopropionate from the *E* or *Z* trimethylsilylketene acetal (see refs 9 and 10b) only extensive decomposition was observed.

(32) Enolates **52** and **53** are meant as a simple working hypotheses. The structure of the Ti enolates is still unknown (see ref 8).

(33) The importance of N–Ti–O chelation for double-bond geometry was suggested by the fact that addition of pyridine to the enolate of ester **3** resulted in the formation of a 50:50 mixture of two enolates as determined by NMR. It is remarkable that when pyridine was added to the $TiCl_4$/**3** complex (see ref 30), also this adduct underwent a stereorandom enolization (50:50 isomer ratio by NMR) and a nonstereoselective reaction with imine **37**.

(34) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986.

Two types of stereoselectivity need to be rationalized: the internal stereochemistry of the β-lactam ring, probably related to enolate geometry, and the diastereofacial selectivity of the chiral reagents; which depends on their conformations in the transition state. The enolate geometry seems to correlate to some extent to the trans/cis ratios observed in the reaction of **3–7** with imines **9** and **11** (Table II): mainly trans compounds from predominantly *Z* enolates of **51**, **3**, **4**, and **7**, mainly cis isomers from the *E* enolates of **5** and **6**. However, thioester **36** which upon enolization gives a 65:35 *Z*/*E* isomer ratio (the configuration being assigned on the basis of chemical shift values reported in Table IV), does not fit this scenario, since with C-aryl or C-alkyl imines **42–45** and **48** it afforded a large excess of trans β-lactams and with α-alkoxy imine **46** only cis products.

The diastereofacial selectivity of imines **9–13** is consistent with enolate addition from the less hindered side of a chelated conformation[36] of the *E* imine as in **54** and **55**.[6a,b] For ester **36** the observed stereoselection can be rationalized by assuming attack on the sterically more accessible face of the double bond in the enolate conformation **55**[37] (Chart II).

Currently, the proposal of transition structures that take into account the above-mentioned features and rationalize all the results is highly speculative. We feel that more information about the enolate structure and the influence of the imine on the titanium coordination is required in order to fully understand these results.

Conclusions

In conclusion we have shown that condensation between the titanium enolates of 2-pyridyl thioesters and imines represents a mild and versatile entry to chiral, nonracemic β-lactams, as demonstrated by the synthesis of advanced precursors of biologically relevant compounds. Work is in progress to find 2-thiopyridyl residues that can act as chiral auxiliaries and to test the possibility of exploiting chiral ligands at titanium to control the stereochemistry of this reaction.

Experimental Section

^{1}H-NMR spectra were obtained on a 80- or a 300-MHz instrument in $CDCl_3$ as solvent. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent. All the reactions employing dry solvent were run under nitrogen. CH_2Cl_2 was distilled from CaH_2, THF from LAH, TEA from KOH. $TiCl_4$ was used as commercially available 1 M solution in CH_2Cl_2.

Thioesters **2**, **3**, **4**, **5**, and **51** were known compounds.[2]

***S*-2-Pyridyl thioacetate (1) and *S*-2-pyridyl acetoxythioacetate (6)** were prepared as described from the corresponding acid chlorides.[2] Compound **1** was a yellow oil isolated in 92% yield by flash chromatography with a 60:40 hexanes/Et_2O mixture as eluant. ^{1}H-NMR: δ 8.65–7.10 (m, 4 H), 2.35 (s, 3 H). IR: 1690 cm^{-1}. Anal. Calcd for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14. Found: C, 54.96; H, 4.70; N, 9.19. Compound **6** was a thick yellow oil isolated in 89% yield with a 30:70 hexanes/Et_2O mixture as eluant. ^{1}H-NMR: δ 8.65–7.10 (m, 4 H), 4.85 (s, 2 H), 2.10 (s, 3 H). IR: 1750, 1700 cm^{-1}. Anal. Calcd for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63. Found: C, 51.26; H, 4.34; N, 6.54.

***S*-2-Pyridyl phenylthioacetate (7) and *S*-2-pyridyl [*N*-(*tert*-butyloxycarbonyl)amino]thioacetate (8)** were prepared by Ohno's method[7] from the corresponding acids. Compound **7** was a yellow solid, mp 48 °C, obtained in 73% yield with a 50:50 hexanes/Et_2O eluant. ^{1}H-NMR: δ 8.65–7.10 (m, 9 H), 3.95 (s, 2 H). IR: 1695 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NOS_2$: C, 59.74; H, 4.24; N, 5.36. Found: C, 59.87; H, 4.18; N, 5.26. Compound **8** was a low-melting yellow solid, obtained in 72% yield with a 10:90 hexanes/Et_2O as eluant. ^{1}H-NMR: δ 8.62–7.28 (m, 4 H), 5.15 (bs, 1 H), 4.20 (s, 2 H), 1.45 (s, 9 H). IR: 1700 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.64; H, 5.97; N, 10.57.

Synthesis of *S*-2-Pyridyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]butanethioate (36). This compound was prepared in three steps from ethyl 3-hydroxybutanoate, without isolation of the intermediates, by standard silylation (1 mol equiv of TBDMSCl, DMF, imidazole, rt, 15 h) and hydrolysis procedure (1 N NaOH, EtOH, rt, 5 h) to afford the crude acid that was subjected to Ohno's reaction. Racemic **36**, a white solid melting at 43–44 °C, was obtained in 70% overall yield with a 65:35 hexane/Et_2O as eluant. ^{1}H-NMR: δ 8.60–7.10 (m, 4 H), 4.37 (m, 1 H), 2.81 (AB part of ABX, 2 H), 1.20 (d, 3 H, *J* = 7.0 Hz), 0.90 (s, 9 H), 0.05 (s, 6 H). IR: 1700 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_2SSi$: C, 57.83; H, 8.09; N, 4.50. Found: C, 57.97; H, 8.16; N, 4.41. (*R*)-**36**, mp 42 °C, had $[\alpha]^{23}_D$ –63.0 (*c* 0.8, $CHCl_3$).

Imines **9–13**, **40**, and **41** were prepared immediately before use by stirring a CH_2Cl_2 solution of the corresponding aldehydes (1.1 mol equiv), 4-methoxyaniline, and anhydrous $MgSO_4$ (2 mol equiv) at rt for 1.5 h. Filtration and evaporation of the solvent at rt gave the crude products that were used as such. Imines **37–39** and **48** were known compounds prepared by standard methods.

General Procedure for the Synthesis of β-Lactams. To a stirred 0.1 M solution of thioester (0.5–10 mmol) in CH_2Cl_2 cooled at –78 °C was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1 mol equiv) dropwise. After 5 min of stirring at –78 °C, TEA

Table V. Relevant ^{1}H-NMR Data of β-Lactams 14–21

lactam	H-3$_a$	H-3$_b$	H-4	H-4′	$J_{4,4'}$ (Hz)
14s	2.74	3.04	3.04	4.12	6.5
15s			3.67	4.02	9.0
15a			3.63	4.30	2.8
16s	2.77	3.04	4.15	3.84	6.2
16a	3.04	3.04	4.07	4.01	1.9
17s			3.77	3.72	9.1
18s	2.71	3.13	4.11	4.02	6.5
19a	2.80	2.94	4.33	2.51	5.5
19s	2.94	3.03	4.23	2.37	5.5
20a			3.90	2.26	6.4
20s			3.84	2.07	9.9
21a	2.61	3.03	3.42	1.76	9.9
21s	2.76	3.01	3.62	1.80	6.5

Table VI. Relevant ^{1}H-NMR Data of β-Lactams 25–31 and 33–35

lactam	H-3	H-4	H-4′	$J_{4,4'}$ (Hz)
25ts	2.93	3.73	4.16	6.0
25cs	3.16	4.02	4.05	8.0
26ts	2.80	3.79	4.16	6.0
27cs	4.69	4.10	4.23	8.8
27ts	4.61	4.04	4.22	5.4
28cs	5.01	4.23	4.17	7.5
29ts	2.70	3.16	3.73	8.0
29cs	3.06	3.42	3.79	9.5
30ts	2.56	3.21	3.80	6.6
31ts	4.13	3.87	4.17	6.0
31cs	4.57	4.25	4.17	8.4
31ca	4.62	4.35	4.41	1.5
31ta	4.46	3.76	4.31	1.5
33ts	2.84	3.79	4.30	7.0
33cs	3.22	4.09	4.36	8.6
34cs	4.72	4.16	4.41	8.6
35cs	4.70	4.17	4.43	9.0

(35) Also α-phenylthio ester **7** could give an enolate similar to **52**. However we showed that sulfur/titanium/oxygen chelation in α-phenyl thioaldehydes is difficult (Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456). We suggest structure **52** for the enolate of **7**, also on the basis of the NMR data of the $TiCl_4$/**7** complex, clearly different from those of $TiCl_4$/**5**. An oxygen/titanium/phenylthio 7-membered chelate has been recently suggested: Harmata, M.; Fletcher, V. R.; Claassen, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9861.

(36) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(37) A similar conformation for the triethylsilylketene acetal of **36** has been recently proposed to rationalize the anti-selective Mukaiyama aldol condensation of this compound with aldehydes mediated by $TiCl_4$: Shirai, F.; Gu, J.-H.; Nakai, T. *Chem. Lett.* **1990**, 1931.

Table VII. Relevant ^{1}H-NMR Data of β-Lactams 42–47, 49, and 50

lactam	H-3	H-3′	H-4	$J_{3,3'}$ (Hz)
42ta	3.06	4.37	5.17	4.2
42ts	3.17	4.31	4.88	4.2
42c	3.07	3.45	5.15	9.0
43ta	3.08	4.36	4.72	4.0
43ts	3.20	4.23	4.53	3.9
44ta	3.06	4.35	4.63	4.0
44ts	3.18	4.30	4.46	3.9
45ta	2.83	4.23	4.08	4.4
45ts	2.98	4.20	3.93	3.9
45c	3.20	4.38	4.16	7.5
46ca	3.32	4.41	4.36	6.0
47ca	3.28	4.38	3.91	6.5
49ta	3.07	4.38	5.11	3.6
49ts	3.17	4.31	4.91	3.8
49c	*a*	3.62	5.19	*a*
50ta	3.13	4.37	5.10	5.2

[a] Undetermined.

(1 mol equiv) was added over a 1-min period. After 30 min of stirring at −78 °C, a CH_2Cl_2 solution of the imine (0.5 mol equiv) was added over a 5-min period and the mixture stirred while the temperature was allowed to raise to 0 °C. After 3 h the reaction was quenched by addition of saturated $NaHCO_3$ and the mixture filtered through Celite. The organic phase was separated, washed with water, dried and concentrated. After NMR analysis, the crude product was purified by flash chromatography. If the unreacted thioester eluted close to the products, it was removed by 1 N KOH hydrolysis in THF at rt for 5–15 h. This procedure was shown not to alter the dr and greatly simplified NMR analysis.[2] Yields and dr are reported in Tables I–III. Relevant ^{1}H-NMR data are collected in Tables V–VII. For each new compound the hexanes/Et_2O eluting mixture is reported in brackets after the name of the compound. β-Lactams **14**,[6g] **21**,[14] **23**,[16] **27**,[6f] **29**,[6a] **30**,[6a] **35**,[20] **43**,[12] **47**,[12] and **50**,[12,22] were known products.

1-(4-Methoxyphenyl)-3,3-dimethyl-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]azetidin-2-one (15) (70:30) was an oil. IR: 1755 cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_3Si$: C, 66.07; H, 9.15; N, 3.85. Found: C, 65.98; H, 9.09; N, 3.91. The 92:8 mixture of **15s**:**15a** had $[\alpha]^{23}_D$ −38.9 (*c* 1, $CHCl_3$).

1-(4-Methoxyphenyl)-4-[1-(phenylmethoxy)ethyl]azetidin-2-one (16) (40:60) was a thick oil. IR: 1750 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.20; H, 6.73; N, 4.55.

1-(4-Methoxyphenyl)-3,3-dimethyl-[1-(phenylmethoxy)ethyl]azetidin-2-one (17) (60:40) was a white solid, mp 70–71 °C. IR: 1750 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.28; H, 7.39; N, 4.20. It had $[\alpha]^{23}_D$ −56.2 (*c* 0.4, $CHCl_3$).

1-(4-Methoxyphenyl)-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one (18) (10:90) was a solid, mp 85–86 °C. IR: 1755 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.20; H, 7.37; N, 4.36. It had $[\alpha]^{23}_D$ +44.8 (*c* 0.4, $CHCl_3$).

1-(4-Methoxyphenyl)-4-[1-methyl-2-(phenylmethoxy)ethyl]azetidin-2-one (19) (40:60) was an oil. IR: 1750 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 78.74; H, 7.06; N, 4.36.

1-(4-Methoxyphenyl)-3,3-dimethyl-4-[1-methyl-2-(phenylmethoxy)ethyl]azetidin-2-one (20) (50:50) was an oil. IR: 1750 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.70; H, 7.77; N, 4.00.

1-(4-Methoxyphenyl)-3-ethyl-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]azetidin-2-one (25) (75:25) was a thick oil. IR: 1750 cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_3Si$: C, 66.07; H, 9.15; N, 3.85. Found: C, 66.00; H, 9.11; N, 3.90.

1-(4-Methoxyphenyl)-3-(1-methylethyl)-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]azetidin-2-one (26) (70:30) was an oil. IR: 1750 cm^{-1}. $[\alpha]^{23}_D$: −33.1 (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71. Found: C, 66.70; H, 9.39; N, 3.77.

1-(4-Methoxyphenyl)-3-acetoxy-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]azetidin-2-one (28) (50:50) was a solid, mp 89–90 °C. IR: 1750 cm^{-1} (broad). $[\alpha]^{23}_D$: −53.2 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{20}H_{31}NO_5Si$: C, 61.04; H, 7.94; N, 3.56. Found: C, 60.97; H, 8.00; N, 3.51.

1-(4-Methoxyphenyl)-3-(phenylthio)-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]azetidin-2-one (31) (75:25) was an oil. IR: 1755 cm^{-1}. Anal. Calcd for $C_{24}H_{33}NO_3SSi$: C, 69.36; H, 8.00; N, 3.37. Found: C, 69.50; H, 8.08; N, 3.30.

1-(4-Methoxyphenyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]azetidin-2-one (32) (0:100) was a solid, mp 88–92 °C. IR: 1750 cm^{-1}. Anal. Calcd for $C_{23}H_{38}N_2O_5Si$: C, 61.30; H, 8.50; N, 6.22. Found: C, 61.22; H, 8.56; N, 6.13.

1-(4-Methoxyphenyl)-3-ethyl-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one (33) (50:50) was a solid, mp 69–72 °C. IR: 1755 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.69; H, 7.80, N, 4.00.

1-(4-Methoxyphenyl)-3-(phenylmethoxy)-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one (34) (50:50) was a solid, mp 100–101 °C. IR: 1750 cm^{-1}. $[\alpha]^{23}_D$: +106.7 (*c* 0.5, MeOH). Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.98; H, 6.83; N, 3.28.

1-(4-Methoxyphenyl)-3-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-4-phenylazetidin-2-one (42) (80:20) was a solid, mp 105–107 °C. IR: 1750 cm^{-1}. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 69.97; H, 8.00; N, 3.43.

1-(4-Methoxyphenyl)-3-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-4-[(1-methyl-2-phenyl)ethenyl]azetidin-2-one (44) (80:20) was a waxeous solid. IR: 1755 cm^{-1}. Anal. Calcd for $C_{27}H_{37}NO_3Si$: C, 71.80; H, 8.26; N, 3.10. Found: C, 71.85; H, 8.29; N, 3.15.

1-(4-Methoxyphenyl)-3-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(1-propyl)azetidin-2-one (45) (75:25) was an oil. IR: 1755 cm^{-1}. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71. Found: C, 66.69; H, 9.40; N, 3.77.

1-(4-Methoxyphenyl)-3-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(phenylmethoxymethyl)azetidin-2-one (46) (60:40) was an oil. IR: 1755 cm^{-1}. Anal. Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.44; H, 8.22; N, 3.00.

1-Phenyl-3-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-4-phenylazetidin-2-one (49) (90:10) was a solid. Isomer **49ta**, mp 70–71 °C, had $[\alpha]^{23}_D$ −99.7 (*c* 0.15, $CHCl_3$). IR: 1755 cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_2Si$: C, 72.39; H, 8.19; N, 3.67. Found: C, 72.47; H, 8.11; N, 3.60.

Synthesis of β-Lactam 17s from 15s. Desilylation.[6a] To a stirred solution of **15s** (144 mg, 0.4 mmol) in acetonitrile (2 mL) were added a few drops of 40% HF at rt. After the solution was stirred for 2 h, solid $NaHCO_3$ was added and the mixture was filtered and concentrated. **Benzylation.** The crude alcohol was dissolved in THF (5 mL) and added to a stirred suspension of oil-free NaH (10 mg, 0.42 mmol) in THF (2 mL) at 0 °C. To the mixture was added a catalytic amount of Bu_4NI followed by benzyl bromide (60 mg, 0.4 mmol); the reaction was stirred at 50 °C for 2 h. Usual workup and purification by flash chromatography gave **17s** (97 mg, 72%).

Synthesis of β-Lactam 21 from 19sa. Compound **19** (97 mg, 0.3 mmol) as a mixture of **s**/**a** isomers in 29:71 ratio was treated with CAN, following precisely Georg's procedure,[12] to give the crude N-unprotected derivative. This was dissolved in THF (10 mL) and hydrogenated over 10% Pd/C (50 mg) for 2 h. The suspension was filtered and the crude mixture analyzed by NMR to reveal the presence of compound **21s**[14] as its minor component. Flash chromatography with a 90:10 mixture of CH_2Cl_2 and MeOH as eluant gave 23 mg (60%) of a a 30:70 mixture of **21a** and **21s**, as a low-melting material. Relevant ^{1}H-NMR data of these compounds are reported in Table V.

Synthesis of 1-[(1,1-Dimethylethyl)dimethylsilyl]-4-(1-methylethenyl)azetidin-2-one (23). Compound **14s** (480 mg, 1.44 mmol) was desylilated as described above to give the corresponding crude alcohol, $[\alpha]^{23}_D$ −67.8 (*c* 1.2, $CHCl_3$), in quantitative yield. This was oxidized[6a] with a 0.6 M solution of H_2CrO_4[6e] in THF (20 mL) at 40 °C for 2 h. The described workup followed by flash chromatography with a 99:1 CH_2Cl_2/MeOH eluant give **1-(4-methoxyphenyl)-4-acetylazetidin-2-one (22)** (233 mg, 74%) as a solid, mp 107–108 °C. $[\alpha]^{23}_D$: −110.5 (*c* 0.3,

$CHCl_3$). IR: 1755, 1725 cm^{-1}. ^1H-NMR: δ 7.20–6.80 (m, 4 H), 4.45 (dd, 1 H, J = 2.5, 5.8 Hz), 3.85 (s, 3 H), 3.40 (dd, 1 H, J = 5.8, 14.1 Hz), 2.90 (dd, 1 H, J = 2.5, 14.1 Hz), 2.12 (s, 3 H). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.75; H, 6.05; N, 6.41.

To a suspension of triphenylmethylphosphonium bromide (536 mg, 1.5 mmol) in THF (10 mL) cooled at 0 °C was added *n*-BuLi (1 mL of a 1.5 M solution in hexane) dropwise. After 20 min of stirring at 0 °C the yellow solution was cooled at −40 °C and the ketone (220 mg, 1 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to warm to rt and stirred overnight. Aqueous NH_4Cl was added and the organic layer separated, dried, and evaporated. The crude product was purified by flash chromatography (40:60 hexanes/Et_2O) to give **1-(4-methoxyphenyl)-4-(1-methylethenyl)azetidin-2-one** as a solid, mp 87–88 °C. $[a]^{23}_D$: −44.1 (*c* 0.3, $CHCl_3$). IR: 1745 cm^{-1}. ^1H-NMR: δ 7.40–6.80 (m, 4 H), 5.15–5.00 (m, 2 H), 4.45 (dd, 1 H, J = 2.4, 6.0 Hz), 3.76 (s, 3 H), 3.24 (dd, 1 H, J = 6.0, 14.5 Hz), 2.83 (dd, 1 H, J = 2.4, 14.5 Hz), 1.70 (bs, 3 H). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.96; H, 7.00; N, 6.50. The alkene (108 mg, 0.5 mmol) was subjected to CAN degradation as described above to give **4-(1-methylethenyl)azetidin-2-one** (47 mg, 85% yield) as a thick oil, $[a]^{23}_D$ −98.0 (*c* 0.5, $CHCl_3$). IR: 3250, 1755 cm^{-1}. ^1H-NMR: δ 6.80 (bs, 1 H), 4.90 (m, 2 H), 4.00 (unresolved dd, 1 H), 3.05 (ddd, 1 H, J = 2.4, 5.8, 14.3 Hz), 2.62 (ddd, 1 H, J = 1.0, 2.8, 14.3 Hz), 1.70 (bs, 3 H). This compound was reacted with TBDMSCl (75 mg, 0.5 mmol) and TEA (0.141 mL, 1 mmol) in CH_2Cl_2 (5 mL) at rt for 15 h. The reaction was diluted with CH_2Cl_2, and the organic phase was washed with phosphate buffer. The dried organic extract was evaporated and purified by flash chromatography (80:20 hexanes/Et_2O) to give **23** as a colorless oil in 80% yield. $[\alpha]^{23}_D$: −24.6 (*c* 0.8, $CHCl_3$). IR: 1755 cm^{-1}. ^1H-NMR: δ 4.90 (m, 2 H), 3.99 (dd, 1 H, J = 2.9, 5.2 Hz), 3.11 (dd, 1 H, J = 5.2, 15.2 Hz), 2.70 (dd, 1 H, J = 2.4, 15.2 Hz), 1.70 (bs, 3 H), 0.88 (s, 9 H), 0.20 (s, 3 H), 0.04 (s, 3 H).

Synthesis of β-Lactams 29 and 30. These compounds were obtained from **25** and **26**, respectively, by CAN degradation in 83 and 87% yield. Compound **29**, an oil, was obtained as a 67:33 mixture of **ts**/**cs** isomers, the major of which was identical to the product reported.[6a] Compound **30ts** had $[\alpha]^{23}_D$ +22.6 (*c* 0.5, $CHCl_3$) (lit.[6a] $[\alpha]^{23}_D$ +22.9 (*c* 1.966)) and ^1H-NMR in agreement with those reported.

Synthesis of β-Lactam 27 from 28. Hydrolysis.[20] To a cooled solution (0 °C) of compound **28** (78 mg, 0.2 mmol) in THF (1 mL) was added NaOH (0.47 mL of a 0.54 M solution in MeOH) dropwise. After 2 h of stirring at 0 °C, the mixture was extracted with CH_2Cl_2, washed with water, dried, and concentrated to give the crude alcohol in 97% yield. This was benzylated (see above) to afford compound **27** in 67% yield after flash chromatography. The product was identical to the same prepared by condensation, $[\alpha]^{23}_D$ −96.2 (*c* 1, $CHCl_3$) and mp 92–93 °C.

Synthesis of β-Lactam 47 from 46. Compound **46** (227 mg, 0.5 mmol) was subjected to CAN oxidation and hydrogenolysis as described above to give **47** (83 mg) in 75% yield after flash chromatography in EtOAc. This compound was identical by ^1H-NMR to that prepared by Georg.[12]

Synthesis of β-Lactam 50ta from 49ta. Standard desylilation procedure of **49ta** gave **50ta** as a white solid in 98% yield, $[\alpha]^{23}_D$ −113.0 (*c* 0.2, $CHCl_3$) and mp 192 °C, and was identical by ^1H-NMR to the compound prepared by Georg.[12]

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Registry No. **1**, 10111-76-9; **2**, 81357-56-4; **3**, 19337-34-9; **4**, 139007-44-6; **5**, 139007-45-7; **6**, 141685-06-5; **7**, 33845-20-4; **8**, 141685-07-6; **9**, 141781-21-7; **10**, 141781-22-8; **11**, 141781-23-9; **12**, 141781-24-0; **13**, 111865-74-8; **14**, 135508-43-9; **14s** alcohol derivative, 141685-08-7; **15s**, 140869-76-7; **15a**, 141685-09-8; **16s**, 140869-77-8; **16a**, 140869-84-7; **17**, 140869-78-9; **18s**, 140869-79-0; **19s**, 140869-80-3; **19a**, 140869-85-8; **20s**, 140869-81-4; **20a**, 140869-86-9; **21s**, 127708-14-9; **21a**, 130609-06-2; **22**, 141781-25-1; **23**, 127626-96-4; **25ts**, 135508-44-0; **25cs**, 140925-32-2; **26**, 140869-82-5; **27cs**, 135508-39-3; **27ts**, 140925-31-1; **28cs**, 135508-35-9; **29ts**, 116078-97-8; **29cs**, 141781-26-2; **30ts**, 135560-65-5; **31ts**, 141685-10-1; **31cs**, 141782-50-5; **31ta**, 141781-27-3; **31ca**, 141781-28-4; **32ts**, 141685-11-2; **33ts**, 140869-83-6; **33cs**, 141318-16-3; **34cs**, 141268-44-2; **35cs**, 115857-84-6; (±)-**36**, 141685-12-3; (*R*)-**36**, 141781-29-5; **37**, 1613-90-7; **38**, 88315-63-3; **39**, 100239-15-4; **40**, 141685-13-4; **41**, 141685-14-5; **42**, 141685-15-6; **42ta**, 141781-30-8; **42ts**, 141781-31-9; **43ta**, 141781-32-0; **43ts**, 106399-98-8; **44ta**, 141685-16-7; **44ts**, 141781-33-1; **45**, 141685-17-8; **45ta**, 141781-34-2; **45ts**, 141781-35-3; **46ca**, 141685-18-9; **47ca**, 141781-36-4; **48**, 1750-36-3; **49**, 141781-37-5; **49ta**, 115869-99-3; **49ts**, 141782-51-6; **50**, 106399-68-2; $OHCCH(OTBDMS)CH_3$, 87727-28-4; $CHOCH(CH_3)OCH_2Ph$, 81445-44-5; $PhCH_2OCH_2CH(CH_3)CHO$, 79027-28-4; ethyl 3-hydroxybutanoate, 5405-41-4; 4-methoxyaniline, 104-94-9; spiro[cyclohexane-1,2′[1,3]dioxolane]-4′-carboxaldehyde, 78008-36-3; 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, 15186-48-8; 1-(4-methoxyphenyl)-4-(1-methylethenyl)azetidin-2-one, 141685-19-0; 4-(1-methylethenyl)azetidin-2-one, 141685-20-3.