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Highly Stereoselective Synthesis of β-Lactams by Condensation of the Titanium Enolate of a Chiral 2-Pyridylthioester with Chiral Imines

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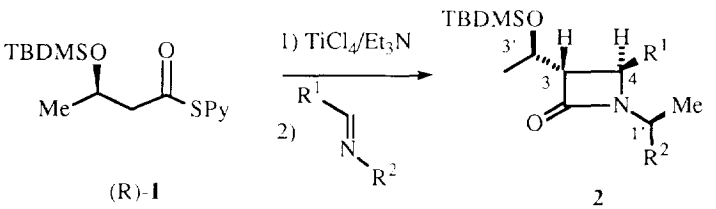
Abstract: The reaction of the titanium enolate of a 2-pyridylthioester derived from (R)-3-hydroxybutyric acid with chiral imines affords 3,3'-anti-3,4-trans configurated β-lactams in a highly selective fashion. The methodology has been applied to the synthesis of a precursor of the carbapenem antibiotic 1β-methylthienamycin.

We recently reported[1] a synthesis of β-lactams by the mild and efficient, one-pot condensation of the titanium enolates[2,3] of 2-pyridylthioesters with imines. Extension of this methodology to the reaction of (R)-(*S*-2-pyridyl)-3-[(t-butyldimethylsilyl)oxy]-thiobutyrate **1** with achiral imines[1b] (Equation 1) afforded with good stereoselectivity β-lactams **2** featuring the 3,3'-*anti*-3,4-*trans* configuration required for their conversion into some of the carbapenem antibiotics of the thienamycin family.[3,4]



Eq. 1

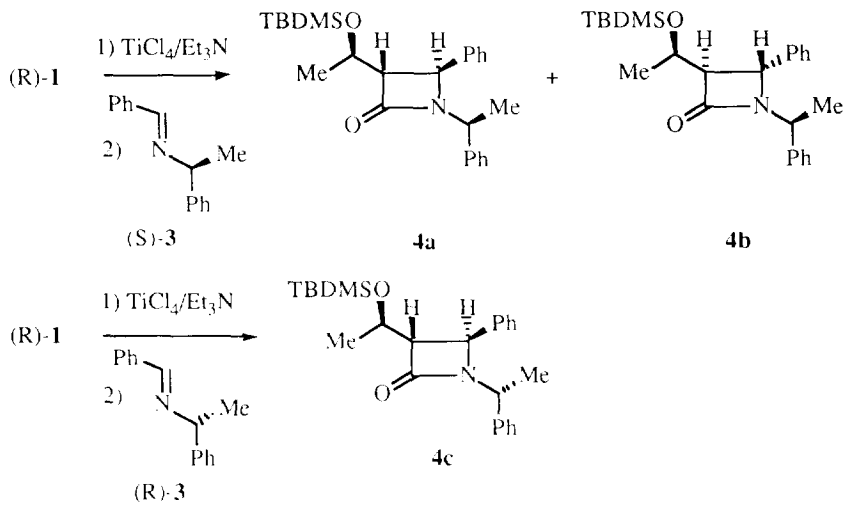
In order to improve the stereoselection of this process we decided to investigate the reaction of the titanium enolate of thioester (R)-**1** with a series of chiral imines derived from (R)- and (S)-1-phenylethanamine, that has already proved to be an efficient chiral auxiliary for the condensation of achiral titanium enolates.[1f] The results of this study are here reported.

The matching[5] combination between the configuration of (R)-**1** and of the chiral residue on the imine was established using benzaldehyde derived imines (S)- and (R)-**3** (Scheme 1). The reaction of (R)-**1** with (S)-**3** afforded a 66 : 34 mixture of the 3,3'-*anti*-3,4-*trans* compound **4a** and of its 3,3'-*syn* -3,4-*trans* isomer **4b** in 30% yield (see Eq. 1 for numbering). On the other hand, the condensation of (R)-**1** with the enantiomeric imine (R)-**3** gave compound **4c** as a single product in 65% yield. The diastereoisomeric ratios (d.r.) were determined by 300 MHz ^{1}H NMR analysis of the crude reaction products. The configuration of these compounds was

determined as follows.

First of all, the 3,4-*trans* stereochemistry was assigned to azetidinones **4a-c** on the basis of the value of the HC-3/HC-4 coupling constant. The configuration at C-4 (and hence at C-3) was determined by ^{1}H NMR following an empirical rule,[6] the reliability of which has been recently confirmed.[1f,7] On these bases, to β-lactams **4a**, **4b**, and **4c** the (1'S, 3'R, 3S, 4S), (1'S, 3'R, 3R, 4R), and (1'R,3'R,3S, 4S) configurations were assigned, respectively.

Scheme 1.



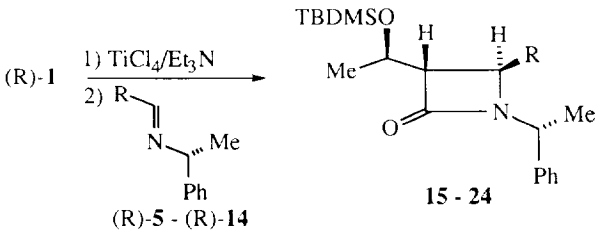
From these results it was concluded that the (R)-**1**/(R)-**3** combination represents the matching pair,[5] while the (R)-**1**/(S)-**3** is the mis-matching[5] one. It is also worth mentioning that the common stereochemistry at C-3 and C-4 featured by the major isomers of **2**, and by **4a** and **4c** clearly suggests that the thioester overrides the imine in determining the sense of the stereoselectivity of the reaction.[8]

Having established the imine chiral auxiliary configuration that secures the best stereocontrol in the condensation with compound (R)-**1**, we extended our reaction to the aromatic, heteroaromatic, unsaturated, and aliphatic imines (R)-**5** - (R)-**14** to give β-lactams **15** - **24** (Scheme1 and Table 1).[9] The diastereoisomeric ratios were determined as described above. The configurational assignments were based as before on NMR evidence[10] in the case of 4-aryl and 4-heteroaryl substituted azetidinones **15** - **21**, and on the reasonable extension of the observed trend of stereoselectivity in the case of compounds **22** - **24**.

As can be seen from the data reported in Table 1, the reaction occurs in low to good yields, and affords virtually a single 3,3'-*anti*-3,4-*trans* product in all cases, with the only exception of the condensation involving the linear aliphatic imine **14** leading to β-lactam **24**. It is interesting to note the marked difference in the 3,3'-*anti* / 3,3'-*syn* ratio observed for the *trans* and the *cis* isomer of **24**: the *trans* product is produced in a highly selective fashion (d.r. 96 : 4), while for the *cis* one shows no stereoselectivity is found (d.r. 50 : 50).

A tentative rationalization of the stereochemical result can be based on a model of stereoselection[11] that combines the model proposed for the reaction of thioester (R)-**1** with achiral imines[1b] with that used for the condensation of achiral thioesters with imines featuring the same chiral auxiliary present in **3**.[1f] In this model

Table 1. Synthesis of β-Lactams **15-24** from Thioester (R)-**1** and Imines (R)-**5** -(R)-**14**.



Imine	R[a]	Product	Yield%[b]	Diastereoisomeric ratio[c]	
				3, 4-*trans/cis*	3, 3'-*anti/syn*
5	2-$MeOC_6H_4$	**15**	83	>98/2	>98/2
6	2-$BnOC_6H_4$	**16**	65	>98/2	95/5
7	2-$AllOC_6H_4$	**17**	64	>98/2	>98/2
8	2-BnO-3$MeOC_6H_3$	**18**	47	>98/2	>98/2
9	4-BnO-3$MeOC_6H_3$	**19**	63	>98/2	>98/2
10	2-Furyl	**20**	61	>98/2	>98/2
11	2-Thienyl	**21**	54	>98/2	>98/2
12	C_6H_{11}-c	**22**	45	>98/2	>98/2
13	(E)-PhCH=CMe	**23**	30	>98/2	>98/2
14	$TBDMSO(CH_2)_2$	**24**	37	76/24	96/4[d]

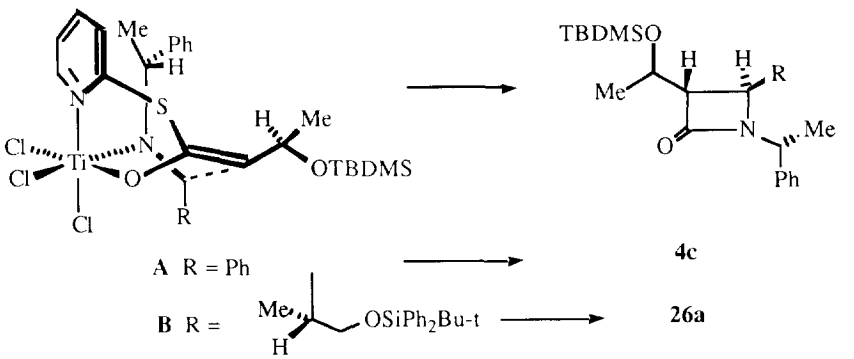
[a]Abbreviations: Bn = $PhCH_2$; All = CH_2=CH-CH_2; TBDMS = t-$BuMe_2Si$. [b] Isolated yields after flash chromatography. [c]As determined by ^1H NMR analysis of the crude products; only the major 3,3'-*anti*--3,4-*trans* isomer of β-lactams **15-24** is shown for simplicity. [d] Of the *trans* isomer; d.r. of the *cis* isomer was 50/50.

(Fig. 1) the (Z)-enolate[1b,12] and the (E)-imine[1e,1f,13] approach each other placing the small H substituent at their stereocenter in the sterically more congested position, *i.e.* inside the core of the transition state. Attack on the opposite face of the enolate (leading to 3,3'-*syn* compounds) appears to be hindered by the methyl group at the thioester stereocenter,[1b] while attack on the opposite face of the imine should suffer from destabilizing interactions between the phenyl group at the imine stereocenter and the pyridine residue.[1f,14,15]

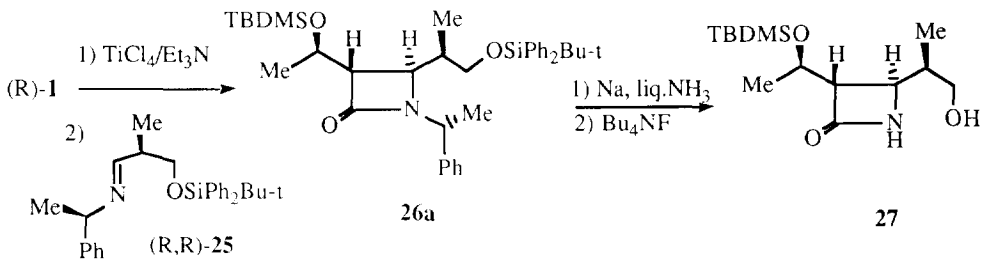
The reaction was then applied to the synthesis of an advanced precursor of 1β-methylthienamycin[16] (Scheme 2). Thus, imine (R,R)-**25** was condensed with the titanium enolate of (R)-**1** to give a single *trans* product **26a** in 23% yield.[17] Scarce stereoselection and an even poorer yield (7%) were obtained in the condensation involving (R,S)-**25**, that gave two *trans* isomers **26b** and **26c** in a 70:30 ratio.[18]

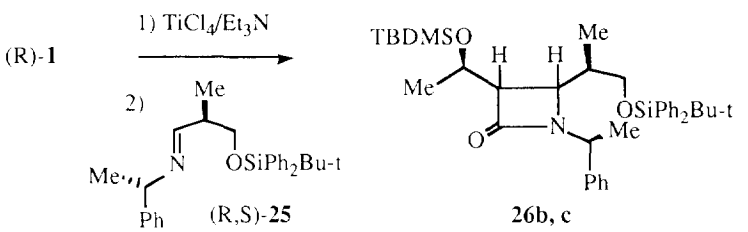
Compound **26a** was converted into the known 1β-methylthienamycin precursor **27** (Scheme 2)[16a,b]by reaction with Na in liq. NH_3 [19] (74% yield), followed by Bu_4NF (1.0 mol. eq., THF, 10 min, RT) promoted partial desilylation.[20] This transformation confirmed the indicated stereochemical assignments to compounds **26a**. In analogy with the above mentioned rationalization, the completely stereoselective synthesis of **26a** can be explained by model **B** of Fig. 1. In this model the (R)-stereocenter at the carbon atom of imine (R,R)-**25** can

Figure 1. Proposed model of stereoselection for the synthesis of **4c** and **26a**.



Scheme 2.





adopt a sterically convenient conformation, placing the small H substituent toward the approaching enolate.

Experimental

General procedure for the synthesis of β-lactams: The synthesis of **3-[1-[[(1,1-dimethylethyl) dimethylsilyl]oxy]ethyl]-4-phenyl-1-[(R)-(1-phenylethyl)]-2-azetidinone 4c** is illustrative of the procedure. To a stirred 0.1M solution of (R)-**1** (311 mg, 1 mmol) in CH_2Cl_2 cooled at -78°C was added a 1.0M solution of $TiCl_4$ in CH_2Cl_2 (1mL, 1 mmol) dropwise. After 5 min of stirring at -78°C, Et_3N (0.140 mL, 1 mmol) was added over a 1 min period. After 30 min of stirring at -78°C, a CH_2Cl_2 (5 mL) solution of crude imine (R)-**3** (prepared from 1 mmol of freshly distilled benzaldehyde and 1 mmol of (R)-1-phenylethanamine in

the presence of anhydrous $MgSO_4$) was added over a 5 min period, and the mixture was stirred while the temperature was allowed to raise to 0°C. After 5h the reaction was quenched by addition of saturated $NaHCO_3$ solution and the mixture was filtered through celite. The organic phase was separated, washed with water, dried, and concentrated. The unreacted thioester was removed by hydrolysis with 1N KOH in THF. This procedure was shown[1] not to alter the diastereoisomeric ratios, and greatly simplified the NMR analysis of the crude product. This was then purified by flash chromatography with a 60 : 40 hexanes : Et_2O mixture as eluant. Compound **4c** was an oil, $[\alpha]_D^{22}$ -22.3 (c 1.67, $CHCl_3$). IR: 1745 cm^{-1}. Selected NMR data are collected in Tables 2 and 3. Anal. Calcd. for $C_{25}H_{35}NO_2Si$: C, 73.30; H, 8.61; N, 3.42. Found: C, 73.18; H, 8.66; N, 3.38. For β-lactams **15-24**, and **26** hexanes : Et_2O eluting mixtures are reported in parentheses after the name of the compound. All products were thick oils or low melting materials. Yields and diastereomeric ratios are reported in Table 1 or in the text. Selected NMR data are collected in Tables 2 and 3.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(2-methoxyphenyl-1-[(R)-(1-phenyl ethyl)]-2-azetidinone 15 (70 : 30) had $[\alpha]_D^{22}$ -8.7 (c 2.24, $CHCl_3$). IR: 1745 cm^{-1}. Anal. Calcd. for $C_{26}H_{37}NO_3Si$: C, 71.03; H, 8.48; N, 3.19. Found: C, 70.94; H, 8.52; N, 3.28.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(2-phenylmethoxy)-phenyl-1-[(R)-(1-phenylethyl)]-2-azetidinone 16 (70 : 30) had $[\alpha]_D^{22}$ -5.8 (c 2.16, $CHCl_3$). IR: 1745 cm^{-1}. Anal. Calcd. for $C_{32}H_{41}NO_3Si$: C, 74.52; H, 8.01; N, 2.72. Found: C, 74.59; H, 7.92; N, 2.77.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-[2-(2-propenyl-1-oxy)-phenyl]-1-[(R)-(1-phenylethyl)]-2-azetidinone 17 (60 : 40) had $[\alpha]_D^{22}$ -7.3 (c 1.00, $CHCl_3$). IR: 1745 cm^{-1}. Anal. Calcd. for $C_{28}H_{39}NO_3Si$: C, 72.21; H, 8.44; N, 3.01. Found: C, 72.09; H, 8.40; N, 2.97.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(3-methoxy-2-phenylmethoxy)-phenyl-1-[(R)-(1-phenylethyl)]-2-azetidinone 18 (70 : 30) had $[\alpha]_D^{22}$ +5.1 (c 1.64, $CHCl_3$). IR: 1745 cm^{-1}. Anal. Calcd. for $C_{33}H_{43}NO_4Si$: C, 72.62; H, 7.94; N, 2.57. Found: C, 72.50; H, 7.99; N, 2.62.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(3-methoxy-4-phenylmethoxy)-phenyl-1-[(R)-(1-phenylethyl)]-2-azetidinone 19 (70 : 30) had $[\alpha]_D^{22}$ -28.0 (c 2.16, $CHCl_3$). IR: 1745 cm^{-1}. Anal. Calcd. for $C_{33}H_{43}NO_4Si$: C, 72.62; H, 7.94; N, 2.57. Found: C, 72.66; H, 7.90; N, 2.67.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(2-furyl)-1-[(R)-(1-phenylethyl)]-2-azetidinone 20 (80 : 20) had $[\alpha]_D^{22}$ +2.2 (c 1.69, $CHCl_3$). IR: 1750 cm^{-1}. Anal. Calcd. for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.50. Found: C, 69.02; H, 8.40; N, 3.47.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(2-thienyl)-1-[(R)-(1-phenylethyl)]-2-azetidinone 21 (80 : 20) had $[\alpha]_D^{22}$ -2.5 (c 1.05, $CHCl_3$). IR: 1750 cm^{-1}. Anal. Calcd. for $C_{23}H_{33}NO_2SSi$: C, 66.46; H, 8.00; N, 3.37. Found: C, 66.55; H, 8.08; N, 3.44.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-cyclohexyl-1-[(R)-(1-phenylethyl)]-2-azetidinone 22 (60 : 40) had $[\alpha]_D^{22}$ -38.7 (c 0.85, $CHCl_3$). IR: 1750 cm^{-1}. Anal. Calcd. for $C_{25}H_{41}NO_2Si$: C, 72.23; H, 9.94; N, 3.37. Found: C, 72.21; H, 10.01; N, 3.43.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-[(E)-(1-methyl-2-phenyl)ethenyl]-1-[(R)-(1-phenylethyl)]-2-azetidinone 23 (80 : 20) had $[\alpha]_D^{22}$ +4.5 (c 0.66, $CHCl_3$). IR: 1750 cm^{-1}. Anal. Calcd. for $C_{28}H_{39}NO_2Si$: C, 74.78; H, 8.74; N, 3.11. Found: C, 74.86; H, 8.86; N, 3.03.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-[2-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl]-1-[(R)-(1-phenylethyl)]-2-azetidinone 24 (60 : 40). The IR spectrum and the elemental analysis were obtained on the diastereoisomeric mixture. IR: 1745 cm^{-1}. Anal. Calcd. for $C_{27}H_{49}NO_3Si_2$: C,

65.93; H, 10.04; N, 2.85. Found: C, 66.06; H, 9.96; N, 2.93.

Table 2. Selected ^{1}H-NMR Data of β–Lactams **4**, **15-24**, and **26**.

Product	HC-3	HC-4	HC-3'	HC-1'	MeC-3'	MeC-1'	$J_{3,4}$	$J_{3,3'}$
4a	2.95	4.48	4.24	4.41	1.14	1.72	2.2	4.0
4b	3.08	4.10	4.11	4.95	1.18	1.33	2.7	4.5
4c	2.96	4.40	4.14	4.90	1.10	1.34	2.7	4.0
15	3.15	4.81	4.16	4.78	1.11	1.33	2.0	4.5
16a[a]	3.11	5.16	4.22	4.85	1.07	1.40	2.3	2.9
16b[b]	3.03	5.08	4.17	4.73	1.06	1.30	2.6	2.6
17	3.12	4.98	4.20	4.81	1.09	1.36	2.2	3.6
18	2.92	5.11	4.23	4.65	1.05	1.40	2.0	4.0
19	2.96	4.36	4.16	4.77	1.12	1.43	2.0	4.5
20	3.30	4.48	4.20	4.90	1.10	1.30	2.2	5.0
21	3.12	4.71	4.16	4.88	1.13	1.42	2.2	6.0
22	2.74	3.34	4.02	4.66	1.17	1.65	2.2	6.0
23	2.92	4.05	4.12	4.83	1.15	1.58	2.3	6.0
24a[a]	2.72	3.65	4.10	4.74	1.16	1.63	2.0	4.6
24b[b]	2.88	3.58	4.10	4.80	1.15	1.60	2.8	4.0
24c[c]	3.07	3.53	4.25	4.79	1.37	1.62	5.5	2.5
24d[c]	3.08	3.75	4.27	4.70	1.33	1.70	6.0	8.0
26a	2.90	3.72	4.11	4.39	1.17	1.56	2.3	5.0
26b[a]	2.95	3.69	4.11	4.50	1.16	1.61	2.5	5.0
26c[b]	2.87	3.63	4.06	4.56	1.20	1.58	2.5	3.0

[a] Of the major *trans* isomer. [b] Of the minor *trans* isomer. [c] Of one of *cis* isomers.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]-oxy]-1-methyethyl]-1-(1-phenylethyl)-2-azetidinone 26. 26a (80 : 20) had $[\alpha]_D^{22}$ -22.5 (c 1.5, $CHCl_3$). IR: 1745 cm^{-1}. Anal. Calcd. for $C_{38}H_{55}NO_3Si_2$: C, 72.44; H, 8.80; N, 2.22. Found: C, 72.29; H, 8.86; N, 2.33; **26b** and **26c** (80 : 20) were obtained as a diastereoisomeric mixture. IR: 1745 cm^{-1}. Found: C, 72.34; H, 8.92; N, 2.18.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(2-hydroxy-1-methylethyl)-2-azetidin-one 27. Na metal (23 mg, 1 mmol) was added in small pieces to a stirred solution of **26a** (100 mg, 0.16 mmol) in THF (5 ml) and liq. NH_3 (4 ml) cooled at -78°C. After 30 min stirring, the reaction was warmed up to room temperature and NH_3 was evaporated. A sat. solution of NH_4Cl was added, the organic phase was separated, dried, concentrated, and the residue was purified by flash chromatography with a 50 : 50 hexanes : Et_2O mixture as eluant to give the product in 74% yield. This was reacted with Bu_4NF hydrate (31 mg, 0.12 mmol) in THF (3 ml) at room temperature for 10 min. After addition of water, extraction with Et_2O, anhydrification, and concentration in vacuum, the residue was purified by flash chromatography with Et_2O as eluant to give **27** in 53% yield. It had m.p. 87-89°C, $[\alpha]_D^{22}$ -21.0 (c 0.3, $CHCl_3$), lit.[16b]: m.p. 86-88°C, $[\alpha]_D^{22}$ -21.4 (c 1.01,

$CHCl_3$). IR: 1755 cm^{-1}.^{1}H NMR: δ 6.35 (bs, 1H); 4.15 (dq, 1H, J=6.2, 8.8Hz); 3.55 (dd, 1H, J=4.6, 11.8Hz); 3.47 (dd, 1H, J=8.4, 11.8Hz); 3.28 (dd, 1H, J=2.0, 8.8Hz); 3.13 (dd, 1H, J=2.0, 8.6Hz); 1.70-1.90 (m, 1H); 1.35 (d, 3H, J=6.2Hz); 0.92 (s, 9H); 0.90 (d, 3H, J=7.0Hz); 0.14 and 0.12 (2s, 3H each).

Table 3. Selected ^{13}C-NMR Data of β-Lactams **4**, **15-24**, and **26**.

Product	C-3	C-4	C-3'	C-1'	MeC-1'	MeC-3'
4a	53.7	55.9	66.7	65.5	19.3	22.5
4b	52.4	56.2	66.7	66.0	18.0	20.6
4c	52.6	56.6	66.7	65.6	19.7	22.6
15	52.8	51.8	65.6	64.9	19.2	22.4
16a[a]	52.8	49.6	65.9	64.9	19.8	22.2
17	52.8	50.7	65.3	65.2	19.6	22.3
18	52.9	49.1	66.9	64.7	20.1	22.1
19	53.2	56.7	66.4	65.6	19.9	22.6
20	51.8	48.8	65.0	63.0	18.5	22.4
21	52.6	51.8	67.5	65.4	19.3	22.4
22	53.7	57.9	65.0	60.3	20.1	23.0
23	52.8	61.1	65.9	61.5	19.0	22.6
24a[a]	52.1	52.8	65.4	59.7	20.5	22.6
24c[b]	53.3	52.6	63.4	58.8	20.0	23.4
24d[b]	52.0	52.8	65.5	59.4	19.0	23.2
26a	54.0	57.0	65.7	58.6	19.2	22.8
26b[a]	54.7	57.0	65.8	59.0	18.8	22.8
26c[c]	53.8	57.2	66.2	56.0	20.1	20.9

[a] Of the major *trans* isomer. [b] Of one of *cis* isomers. [c] Of the minor *trans* isomer.

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(4). For leading references see: (a) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**,*109*, 1129. (b) Cainelli, G.; Panunzio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc. Perkin*

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(5). For leading references to and fundamental definitions of double stereoselection see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.

(6). Rogalska, E.; Belzecki, C. *J. Org. Chem.* **1984**, *49*, 1397. This empirical rule is valid for 4-aryl substituted β-lactams featuring a N-CH(Me)Ph residue as in **4a-c**. It relies on the fact that the aryl group at the C-1' stereocenter lies in the mean plane of the azetidinone ring. The signal of the methine proton at C-1' then resonates at lower field if this proton and the C-4 aryl group are situated on the same side of the ring, and at higher field in the opposite case (compare for instance the HC-1' signals of compounds **4a** *vs* **4b** and **16a** *vs* **16b**). Where comparison is not possible (as in the case of **4c**), the chemical shift value of HC-1' is believed to be diagnostic.

(7). Van der Steen, F.H.; Kleijn, H.; Britovsek, G. J. P.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **1992**, *57*, 3906.

(8). The observation that the reaction between imine (S)-**3** and the titanium enolate of achiral 2-pyridylthioesters (ref. 1f) gave products with the (4R) configuration shown by the minor isomer **4b** led additional support to this hypothesis.

(9). When salicylic aldehyde derived imines featuring *O*-methoxymethyl, *O*-acetyl, and*O*-silyl protecting groups were employed in this reaction, very low yields (5 -10%) were observed.

(10). Diagnostic protons and carbons (see Tables 2 and 3) of homogeneous sets of compounds resonate in a narrow chemical shift range.

(11). For experimental support of the pyridine nitrogen/titanium co-ordination, of the cyclic nature of the transition state, and of the indicated enolate and imine configurations see ref. 1b, 1e, and 1f.

(12). A similar conformation has been proposed to rationalize the $TiCl_4$ promoted addition of the silylketene acetal derived from ethyl (R)-3-t-butyldimethylsilyloxybutyrate to aldehydes: Shirai, F.; Gu, J.-H.; Nakai, T. *Chem. Lett.* **1990**, 1931.

(13). See for instance: (a) Ojima, I.; Inaba, S.*Tetrahedron Lett.* **1980**, *21*, 2077. (b) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3489. (c) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M.*Tetrahedron* **1991**, *47*, 531.

(14). This destabilizing interaction is also present in the mis-matched reaction of (R)-**1** with imines derived from (S)-1-phenylethanamine, leading to 3,3'-*anti* compounds.

(15). The *cis* isomer of **24** can derive from (Z)-enolate attack on the linear aliphatic imine in the (Z) configuration. For a discussion about the influence of the imine C=N configuration on the β-lactam *trans/cis* stereochemistry in this reaction see ref. 1e.

(16). For recent syntheses see: (a) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron* **1988**, *44*, 2149. (b) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549. (c) Gurjar, M. K.; Bhanu, M. N.; Khare, V. B.; Bhandari, A.; Deshmukh, M. N.; Rao, A. V. R.*Tetrahedron* **1991**, *47*, 7117. (d) Murayama, T.; Yoshida, A.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1994**, *35*, 2271. (e) Choi, W.-B.; Churchill, H. R. O.; Lynch, J. E.; Thompson, A. S.; Humphrey, G. R.; Volante, R. P.; Reider, P. J.; Shinkai, I. *Tetrahedron Lett.* **1994**, *35*, 2275. (f) Tsukada, N.; Shimada, T.;Gyoung, Y.S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143. (g) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1096.

(17). The yield did not improve and the diastereoselection did not change when (R)-**1** was reacted with the analogue of (R,R)-**25** featuring the Ph_3C- instead of the t-$BuPh_2Si$- protecting group. On the contrary, the use of the O-benzyl protection increased the yield but depressed the stereoselectivity of the condensation.

(18). Although the low yield of these reaction makes the interpretation of the results an exercise in speculation, we can consider the (R)-**1** and (R,R)-**25** the matching pair. Two ancillary experiments supported this hypothesis. First, the reaction of (R)-**1**with imine **25** prepared from (R)-1-phenylethanamine and racemic 3-(diphenyl-t-butylsilyl)oxy-2-methylpropanal gave exclusively **26a** in 12% yield, thus showing that, when kinetic resolution is possible, thioester (R)-**1** reacts faster with (R,R)- than with (R,S)-**25**. Second when (R)-**1** was condensed with the PMP imine derived from (R)-3-(diphenyl-t-butylsilyl)oxy-2-methylpropanal a 63 : 37 mixture of one *trans* and one *cis* isomer was obtained. The *trans* isomer was converted into compound **27** after PMP group degradation with $Ce(NH_4)(NO_3)_6$ (see ref. 4a), and partial desilylation. This shows the importance of the contribution of the (R)-1-phenylethyl residue at the imine nitrogen in determining the stereoselectivity of the condensation.

(19). Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Tetrahedron* **1991**, *47*, 531. This reaction led to partial reduction of the phenyl groups of the t-$BuPh_2Si$ moiety. The product was not purified, but transformed as such into compound **27**.

(20). For other examples of survival of the t-$BuMe_2Si$ protection at OC-3' under desilylation conditions in related β-lactams see ref. 16c and: Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 113.

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