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HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF β-LACTAMS BY ADDITION OF TITANIUM ENOLATES OF 2-PYRIDYL THIOESTERS TO CHIRAL IMINES

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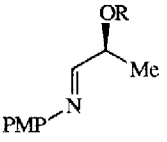
Abstract. *Addition of titanium enolates of 2-pyridyl thioesters to chiral imines derived from alkoxy aldehydes occurs with good diastereofacial control, and opens a simple access to important carbapenem antibiotics.*

We recently described [1] a high yielding , one-pot synthesis of β-lactams by condensation of imines with titanium enolates [2,3] of variously substituted 2-pyridyl thioesters . These were easily generated [2,4] by addition of triethylamine (TEA) to a thioester/$TiCl_4$ adduct .[4] We here report that extension of this β-lactam *synthesis to a series of chiral imines* [5] *derived from alkoxy aldehydes generally occurs with excellent* diastereoselection . Some of the β-lactams obtained have been converted into advanced precursors of important carbapenem antibiotics .

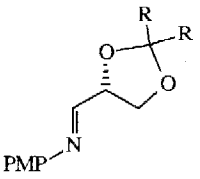
The diastereofacial preference of imines **1-3** , **5** was established by reaction with non-stereogenic titanium enolates derived from thioesters **6** and **7** (Scheme and Table 1) . β-Lactams **11-17** [6] were obtained in fair to good yields . With the only exception of the reaction of **2** with **6** , α-alkoxy substituted imines **1-3** gave very high excess of syn configurated compounds **11s** , **12s** , **14s** , and **15s** over their anti counterparts **a** (see below for stereochemical assignment) .[7] α-Methyl-β-alkoxy imine **5** reacted less stereoselectively to afford a moderate excess of anti products **16a** and **17a** .[8]

The reaction was then extended to stereogenic thioesters **8-10** , that were condensed with imines **1** and **3** to give azetidinones **18-22** (Scheme and Table 2) . In the best conditions a completely diastereofacial selective process was shown to occurr in good yields , affording only syn products . The β-lactam C-3/C-4 trans/cis ratio [9] largely depended on the stereoelectronic nature of the R^1 substituent : a large group (Pr-i) favoured trans products , a coordinating ligand (BnO) led to cis isomers . [1,10] Structural assignment was obtained by correlation of **18t** and **19t** with known compounds , while **20c** (m.p. 91-93°C , lit.[5f] m.p. 92-93°C) has been reported . Lactams **18t** and **19t** were converted into their NH analogues , that were shown to be identical (by 300 MHz ^{1}H NMR) to the compounds recently prepared [5a] and transformed [5a] into carbapenem antibiotics (+)-PS-5 and (+)-PS-6 . The configuration of **22c** ($[\alpha]_D$ +106.3 , c 0.5 in MeOH) was

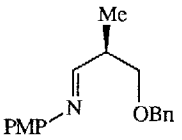
Scheme [a]



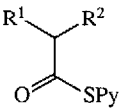
1, 2



3, 4



5

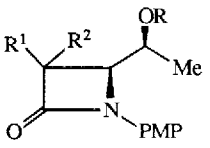


6-10

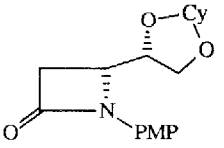
1 R=TBS
2 R= Bn

3 R, R= Cy
4 R= Me

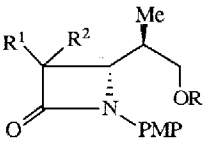
6 $R^1=R^2=H$ **7** $R^1=R^2=Me$
8 $R^1=Et$; $R^2=H$ **9** $R^1=Pr\text{-}i$; $R^2=H$
10 $R^1=BnO$; $R^2=H$



11s-14s



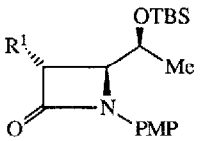
15s



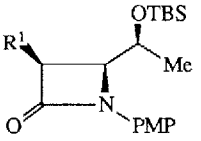
16a, 17a

11 R=TBS; $R^1=R^2=H$
13, 16 R=Bn; $R^1=R^2=H$

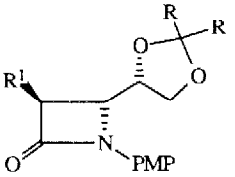
12 R=TBS; $R^1=R^2=Me$
14, 17 R=Bn; $R^1=R^2=Me$



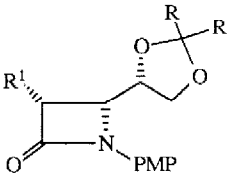
18t-20t



18c-20c



21t-23t



21c-23c

18 $R^1=Et$ **19** $R^1=Pr\text{-}i$ **20** $R^1=BnO$
21 R, R=Cy; $R^1=Et$ **22** R, R=Cy; $R^1=BnO$ **23** R=R=Me; $R^1=BnO$

TBS=$SiMe_2Bu\text{-}t$ Bn=CH_2Ph Cy=-$(CH_2)_5$- PMP=4MeOPh Py=2-pyridyl

[a] For compounds **11-17** only major isomers are shown

inferred from that of known **23c** (m.p. 119-120°C ; $[\alpha]_D$ +107.5 , c 0.4 in MeOH ; lit. [5d] m.p. 120°C ; $[\alpha]_D$ +109.2 , c 0.541 in MeOH), that we prepared (34%) as a single isomer from **4** and **10** , on the basis of the reasonable assumption that the slightly different diol protection should not affect the stereochemical result.[11]

Table 1 . Synthesis of β-lactams **11-17** from imines **1-3** , **5** and thioesters **6** , **7**.

Imine [a]	Ester [b]	Product	Yield % [c]	Diastereoisomeric ratio [d]
				s : **a**
1	**6**	**11s,a**	42	>98: 2
1	**7**	**12s,a**	66	92: 8
2	**6**	**13s,a**	54	65: 35
2	**7**	**14s,a**	80	>98: 2
3	**6**	**15s,a**	52	>98: 2
5	**6**	**16s,a**	71	29: 71
5	**7**	**17s,a**	62	20: 80

[a] Prepared from the corresponding aldehyde and p-anisidine , and used as crude product .

[b] Ester : $TiCl_4$: TEA : imine molar ratio was 2:2:2:1 except for imine **5** (ratio 1:1:1:1) The equimolecular ratio did not affect the stereochemical result and gave slightly lower yield.

[c] Overall isolated yields after flash chromatography . The excess of thioester can be removed by 1M KOH hydrolysis (THF , RT , 3h).

[d] As determined by 300 MHz ^{1}H NMR spectroscopy on the crude and confirmed on the purified products.

Table 2 . Synthesis of β-lactams **18-22** from imines **1**, **3** and thioesters **8-10** .[a]

Imine	Ester	Product	Yield %	Diastereoisomeric ratio
				t : **c**
1	**8**	**18t,c**	50	70: 30
1	**8**	**18t,c**	59	67: 37
1	**9**	**19t,c**	70	>98: 2
1	**10**	**20t,c**	34	10: 90
1	**10**	**20t,c**	64	4: 96
3	**8**	**21t,c**	74	54:46
3	**10**	**21t,c**	82	2:>98

[a] See Table 1 for reaction condition.In the case of imine **3** a 1:1:1:1 reagent ratio was used

Comparison of ^{1}H NMR data for **22c** and **23c** supported this hypothesis . The syn configuration of products **18-20** , **22** , and **23** was therefore extended to the major isomers of **11-15** , and to **21t,c** .[12] The very high diastereofacial preference shown by imines **1-4** can tentatively be rationalized by a chelation controlled [13] addition of the titanium enolates to the imines .[5a] However , the fact that some experimental results do not fit nicely in this picture , [14] and the uncertainity about the nature of the titanium species [2,4] do not allow at this stage the proposal of a consistent model of stereoselection .

References and Notes

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6. All new compounds gave spectral and analytical data in agreement with the proposed structures.
7. Compound **12s** was converted (72% overall yield) into **14s** by oxygen deprotection (aqueous HF , acetonitrile , RT) and benzylation (NaH , cat.Bu_4NI , BnBr , THF , RT) , thus showing that these products have the same configuration .
8. The configuration of the minor isomer **16s** (and thus that of **16a**) was determined by correlation with 4(S)-4-[(1R)-(1-hydroxymethyl)ethyl]azetidin-2-one , a known precursor of 1β-methylthienamycin (Gennari , C. ; Cozzi , P.G. Tetrahedron **1988** , 44 , 5965). The conversion (60% yield) involved CAN oxidation (see ref.5d) and hydrogenolysis (Pd/C , H_2, THF).
9. Attribution of trans and cis stereochemistry was based on the values of the HC-3/HC-4 coupling constants of ca.2.5 Hz and 5.2 Hz for trans and cis isomers , respectively.
10. 2-Pyridylthio(acetoxy)acetate behaved similarly to **10** , affording only a single cis/syn isomer in the reaction with **1**(44% yield).The 3-oxy-derivatives as **20** and **22** open access to biologically important 3-aza-substituted lactams (see ref.5d).These however can also be directly prepared by our method by reaction of 2-pyridylthio -N-BOC-glycinate with fair yields and diastereoselections.
11. Diol protection however seemed to influence the yield , that dropped from 82 to 33% for the reaction of **10** with **3** and **4** , respectively.
12. Chemical shift and coupling constant trends are in agreement with this attribution .The C-3 epimeric structure of **18t** and **18c** was also shown by desilylation and alcohol oxidation to give two diastereoisomeric 4-acetyl lactams.
13. Reetz , M.T. Angew.Chem.,Int.Ed.Engl. **1984** , 23 , 556.
14. For instance the lower syn selectivity generally shown by benzyloxy imine **2** , that should be more prone to chelation than silyloxy imine **1**, does not agree with a chelated model.

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