Tetrahedron Letters, Vol.31, No.46, pp 6707-6710, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ENANTIOSPECIFIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF β-LACTAM INTERMEDIATES FROM 2-AMINO-1-PHENYL-1,3-PROPANEDIOLS

Tamas E. Gunda,*[¶] Siegfried Vieth,[○] Katalin E. Kövér[○] and Ferenc Sztaricskai[¶]

[¶]Research Group of Antibiotics, Hungarian Academy of Sciences, H-4010 Debrecen and [○]BIOGAL Pharmaceutical Works, H-4042 Debrecen, Hungary; [○]Zentral Institut fur Organische Chemie, Akademie der Wissenschaften der DDR, 1199-Berlin, DDR

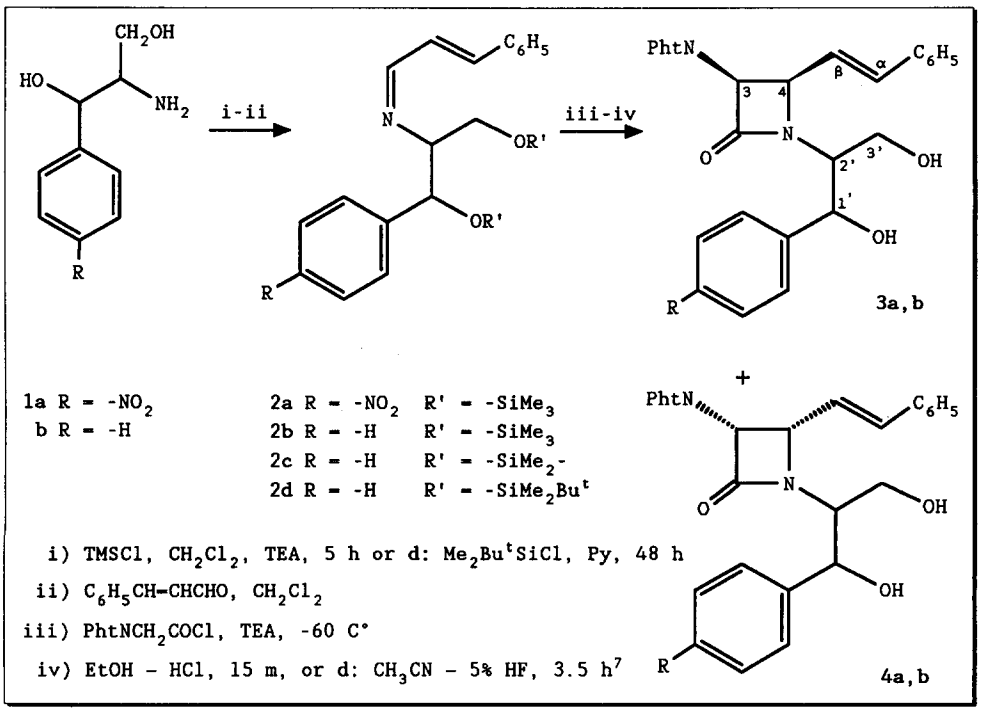
Summary: The aldimines derived from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediols as chiral starting materials were used to prepare *cis*-β-lactams (**3**, **4**) *via* the Staudinger-reaction. High diastereoselectivity was reached only with large silyl protecting groups. The **6** oxazine derivative was obtained when using butyryl chloride as ketene precursor.

The enantiospecific construction of β-lactams continues to be an area of high interest. Beyond carbapenems, monobactams and other β-lactam antibiotics, 2-azetidinones serve as efficient intermediates for a variety of other products[1a,b]. One of the possible approaches to 2-azetidinones is the *Staudinger*-reaction, a formal cycloaddition between an acyclic imine and a ketene. Considerable effort has been devoted to find appropriate ways for inducing chirality into this reaction.[1c] Approaches include the use of chiral ketene precursors and different substitution patterns of Schiff-bases' aldimine carbon.[2,3] However, relatively little is known about the influence on diastereoselectivity of chiral amines used in the Schiff-base component. Although the chiral carbons attached to the N-atom of a Schiff-base are not in the proximity of the reactive aldimine carbon, asymmetric addition was observed in the case of L-threonine derivatives,[4] especially if bulky protective groups were used.[2]

We have been interested in examining chiral Schiff-bases for the induction of asymmetry and we used as our starting material the readily available 1*S*,2*S*-2-amino-1-phenyl-1,3-propanediols **1a** and **b** (the enantiomer of the former known as the base moiety of chloramphenicol).

After conventional silylation with trimethylsilyl chloride **1a** and **1b** were converted to the aldimines **2** by reacting with cinnamic aldehyde (CH_2Cl_2, r.t., overnight). Without isolation, **2** upon reaction with phthalimidoacetyl chloride and excess triethylamine (-60 °C to r.t., 12 hr) followed by the removal of silyl groups (EtOH - 2N HCl) gave

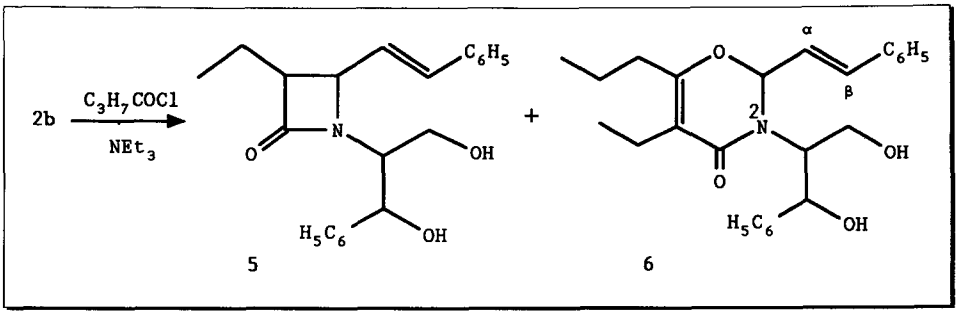
β-lactams **3a** (m.p. 110-1 °C, ν 1728, 1395 cm^{-1})[8] and **4a** (m.p. 207-11 °C, ν 1725, 1390 cm^{-1}) in a ratio of 2.5:1. Similarly **3b** (m.p. 170-2 °C, ν 1720, 1390 cm^{-1}, MS (EI) 468 (M^+, 0.2%), 281) and **4b** (m.p. 184-6 °C, ν 1728, 1395 cm^{-1}) were also obtained, the separation of the latter diastereomers was easier (SiO_2, toluene - ethyl acetate 5:1, Σ 50.6 %).



If butyryl chloride was used in place of phthalimidoacetyl chloride, the reaction yielded only a small amount of the desired **5** (~5%, MS: 351 (M^+, 0.3%), 281; ν 1740 cm^{-1}), and about 15% of oily **6** could be isolated from the complex mixture. The latter showed no characteristic ^{1}H-NMR pattern of coupled β-lactam protons, instead the simultaneous presence of an ethyl and propyl groups was observed. It is obviously a diadduct.[5,6] The 2-H proton of the oxazine ring is coupled only with the cinnamyl β proton (6.03, d, 2-H, J= 5.6 Hz; 6.28, dd, β-H, J=5.6 and 15.9 Hz; 6.76, d, α-H, J=15.9 Hz), thus, excluding the possibility of diadducts of other types.[9] The mass spectrum (MS: 421 (M^+, 0.8%), 371, 350, 314, 281, 131) exhibits a stepwise cleavage under electron impact to regenerate **2b**, R'=H.

As the conformation of the acyclic chiral propanediol moiety is not fixed, a more rigid cyclic intermediate **2c** was prepared by using the dimethylsilyl protecting group. However, there was little influence on the steric course of the cycloaddition, the ratio of **3b** to **4b** was 3:1.

The use of the bulky dimethyl-*tert*-butyl protecting group has a more



pronounced effect as **3b** formed in a ninefold excess (isolated as its oily bis-$Me_2{}^tBuSi$-ether in 62 % yield and converted to the free **3b** with CH_3CN - 5% HF (r.t., 3 h) in near quantitative yield).

In the ^1H-NMR spectra ($CDCl_3$) of **3** and **4** there is a characteristic, well resolved pattern of 3-H, 4-H, vinyl-α-H and vinyl-β-H protons, e.g.:

	3-H	4-H	vinyl-β	vinyl-α
3b	5.58 (d, 5.2 Hz)	4.79 (dd, 5.2, 9.1 Hz)	5.92 (dd, 9.1, 15.9 Hz)	6.58 (d, 15.9 Hz)
4b	5.48 (d, 5.0 Hz)	~4.1 (overlayed dd)	6.04 (dd, 9.0, 15.8 Hz)	6.21 (d, 15.8 Hz)

According to the coupling constants the 3 and 4 protons are *cis* in both compounds and the configuration of $C_6H_5CH{=}CH{-}$ is E. Worthy of note is the considerable upfield shift of 4-H in **4b** suggesting the spatial proximity of the C-1′ phenyl group.

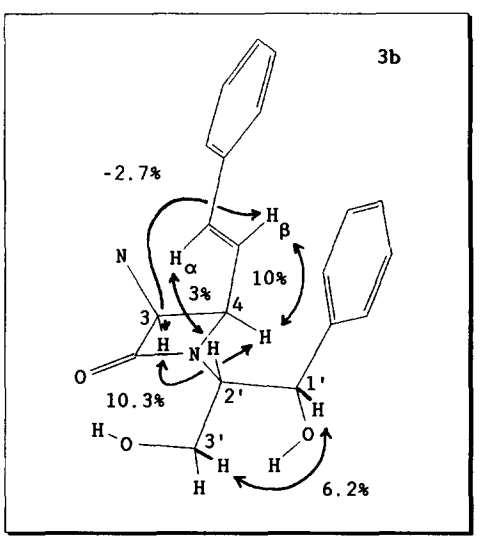


Fig. 1.

For visual clarity, the phthalyl moiety is omitted, as well as some minor NOE data.

A NOE experiment on **3b** showed that 3-H, 4-H and β-H are on the same side of the molecule; the negative NOE between 3-H and β-H indicates a nearly collinear arrangement of these protons (see fig 1. for an MM2 re-

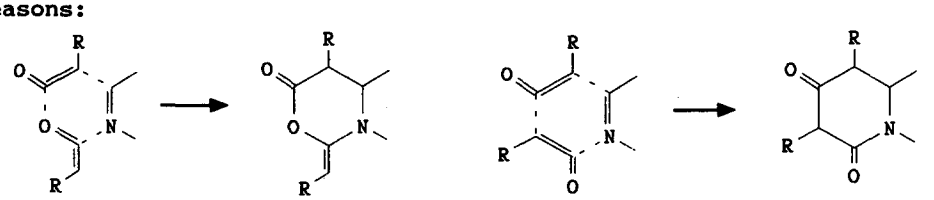
fined plot of **3b**), i.e. the 3→β direct NOE interaction is negligible compared to the 3→4→β indirect path. The spatial arrangement of the propandiol moiety is supported by the observed 3 % enhancement between α-H and 2'-H, and, in turn, by the stabilizing effect of a possible H-bond interaction between the β-lactam carbonyl and 3'-OH. In this conformation the 1'-phenyl group is above the β-lactam plane without affecting the 4-H and β-H protons. However, in the case of **4b** these protons are close enough to the 1'-phenyl ring to experience the upfield shift mentioned above due to the diamagnetic shielding of the aromatic ring. The NOE signals of **4b** for 3-H, 4-H and β-H are practically the same as those in **3b**, but lack a 2'-H - α-H interaction.

Acknowledgement

This work was supported by a grant from the Hungarian Academy of Sciences (OTKA 298).

References and footnotes

1. For recent reviews see: a) Labia, R. and Morin, C.: *J. Antibiotics*, **37**, 1104 (1984); b) Manhas, M. S., Wagle, D.R., Chiang, J. and Bose, A. K.: *Heterocycles*, **27**, 1755 (1988); c) Cooper, R. D. G., Daugherty, B. W. and Boyd, D.B.: *Pure & Appl. Chem.*, **59**, 485 (1987)
2. Wagle, Dilip R., Garai, C., Chiang, J., Montelone, M. G., Kurys, B. E., Strohmeyer, T. W., Hegde, V. R., Manhas, S. M. and Bose, A. K.: *J. Org. Chem.*, **53**, 4227 (1988) and ref. cit. therein
3. Hubschwerlen, C., and Schmid, G.: *Helv. Chim. Acta*, **66**, 2206 (1983)
4. a) Tenneson, S. M. and Belleau, B.: *Can. J. Chem.*, **58**, 1605 (1980); b) Bose, A., Manhas, M. S., Vincent, J. E., Gala, K. and Fernandez, I. F.: *J. Org. Chem.*, **47**, 4075 (1982)
5. a) Szmuszkovicz, J., Chidester, C. G., Duchamp, D. J., MacKellar, F. A. and Slomp, G.: *Tetrahedron Lett.*, 3665 (1971)
   b) Similar oxazino derivatives were obtained from diazepame and medazepame on reacting with (di)chloroacetyl chloride in the presence of TEA (T. E. G., unpublished results, cf. T. E. Gunda and C. Enebäck, *Acta Chem. Scand. B*, **37**, 75 (1983))
6. Johnson, P. Y. and Caldwell, J. W.: *J. Org. Chem.* **40**, 2408 (1975)
7. Newton, R. F., D. P. Reynolds, Finch, R. A. W., Kelly, D. R., and Roberts, S. M.: *Tetrahedron Lett.*, 3981 (1979)
8. All of the ^{1}H NMR spectra were recorded in $CDCl_3$ and the IR spectra in KBr.
9. The following known[10] formal double additions can be excluded on NMR reasons:



10. a) Martin, J. C., Hoyle, V. A., Jr. and Brannock, K. C.: *Tetrahedron Lett.*, 3589 (1965); b) Medici, A., Fantini, G., Fogagnolo, M., Pedrini, P., Dondoni, A., Andreotti, G. D.: *J. Org. Chem.*, **49**, 590 (1984)

(Received in UK 18 September 1990)