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Galactose-Imines in the Staudinger Reaction

Gunda I. Georg,* Eyüp Akgün,[1a] Peter M. Mashava,[1b] Mark Milstead,[1c] He Ping, Zhi-jun Wu, and David Vander Velde

Department of Medicinal Chemistry
University of Kansas, Lawrence, KS 66045

Fusao Takusagawa[1d]

Department of Chemistry
University of Kansas, Lawrence, KS 66045

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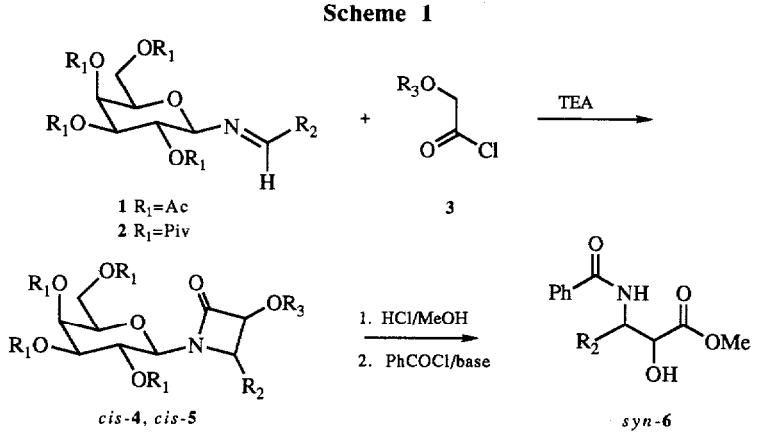
Abstract: *Staudinger reaction of imines **1** and **2** derived from galactose with a variety of acid chlorides resulted in the formation of two β-lactams with cis configuration, typically in a 60:40 ratio and in good yields. The β-lactams were separated and the absolute stereochemistry of the diastereoisomers was determined by single crystal X-ray analysis and correlation of their ^{1}H-NMR data.*

We recently reported[2] on preliminary results concerning the asymmetric Staudinger reaction[3] utilizing the benzaldehyde-imine **1** (**Scheme 1**) derived from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosylamine[4,5] as the chiral auxiliary.[6] The resulting cis-β-lactams (**4, 5**) can be hydrolyzed and subsequently benzoylated[2] to yield *N*-benzoyl-3-phenylisoserines[7] of type **6** (R_2 = Ph), which are important building blocks for the semi-synthesis of the antitumor agent taxol[8] and its analogues.

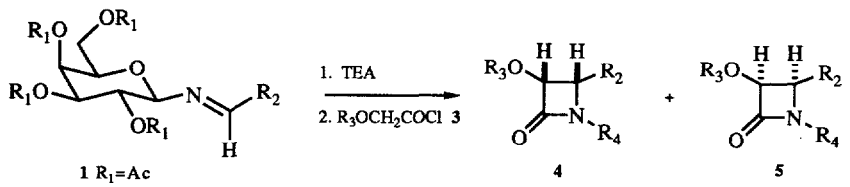
Scheme 1



Because our preliminary studies appeared[2] to be very promising, we decided to investigate the potential of this reaction for the asymmetric synthesis of β-lactams and α-hydroxy-β-amino acids with a variety of substrates. The results of our studies are detailed in the **Table**. The reactions were carried out[9] with different acid chlorides **3** (R_3 = Ph, Ac, and *p*-MeOPh) and imines **1** (R_1 = acetyl) or **2** (R_1 = pivaloyl) in dichloromethane (solvent A), dichloroethane (solvent B), or a dichloromethane-dichloroethane mixture (1:1) (solvent C), in the presence of triethylamine, and at room temperature. As evident from the **Table**, the reactions resulted in the formation of the two *cis*-isomers **4** and **5**, typically in a 60 to 40 ratio with a preference for the formation of the cis-isomer carrying both β-lactam substituents R_2 and OR_3 in the α–orientation. As determined by their NMR-data, all of the products **4a-4j** and **5a-5j** possess β–configuration at the anomeric center.

In most experiments we utilized the β–anomers of imines **1** or **2**. However, when an α– and β–mixture (1:3) of imine **1** (R_2 = *p*-MeOPh) was subjected to the Staudinger reaction with phenoxyacetyl chloride **3** (R_3 = Ph), we found that the α-anomer did not react with the ketene.[10] Thus, the reaction of the β-anomer of this mixture produced similar yields and isomeric ratios (55:45) for the formation of β-lactams **4g** and **5g** as observed in the reaction with the pure β-anomer. No α–anomeric reaction products were observed.

Table



1 R_1=Ac
2 R_1=Piv

4 **5**

R_4 = 2,3,4,6-tetra-*O*-acyl-β-D-galactopyranosyl

Com-pound	Imine	R_2	R_3	(%) of **4**	(%) of **5**	Solvent	Yield (%)
a	1	Ph	Ph	45-75	55-25	A	90
b	1	Ph	Ac	50	50	A	72
c	2	Ph	Ac	57	43	C	32
d	1	Ph	*p*-MeOPh	60	40	A	75
e	1	*p*-ClPh	Ph	60	40	A	85
f	1	*p*-NO_2Ph	Ph	66	33	A	85
g	1	*p*-MeOPh	Ph	55	45	A	86
h	1	*p*-MePh	Ph	60	40	A	93
i	1	PhCH=CH-	Ac	54	46	C	87
j	1	PhCH=CH-	Ph	40	60	B	85

The isomers **4a**, **4b**, **4d-4i** and **5a**, **5b**, **5d-5i** were separated by gravity column chromatography or medium pressure column chromatography and fully characterized by ^{1}H-NMR, IR, optical rotation, and elemental analysis or HRMS. In all instances isomer **5** eluted from the column before isomer **4**. Due to the highly crystalline character of β-lactams **4** and **5**, isomers **4a**, **5i**, and **5j** could also be isolated in pure form through fractional recrystallization.

Since it was initially not obvious how the absolute stereochemistry at the β–lactam moiety of products **4** and **5** could be assigned, single crystal X-ray analyses of **4a** (R_2 = Ph, R_3 = Ph), **4e** (R_2 = *p*-ClPh, R_3 = Ph) (**Figure**) and **5i** (R_2 = PhCH=CH-, R_3 = Ac) were performed. The assignment of the other isomers was made by comparison of their ^{1}H-NMR data[11] and optical properties[12] with derivatives **4a**, **4e**, and **5i**.

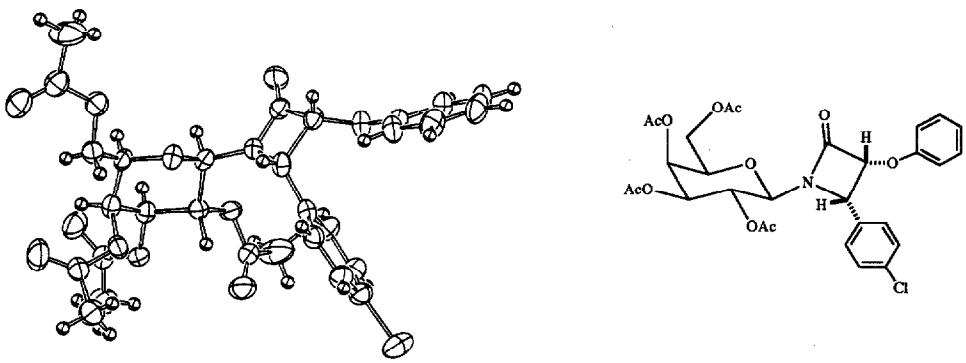


Figure: ORTEP-drawing and structure of β-lactam **4e**.

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REFERENCES AND NOTES

(1) (a) Recipient of an award from the Wesley Foundation Scholar Program in Cancer Research (Wichita, KS). (b) African-American Institute (New York) Post-Graduate Award recipient. Visiting Scientist on leave from the University of Zimbabwe, Department of Science and Mathematics Education, Harare, Zimbabwe, Africa. (c) National Institutes of Health predoctoral trainee (GM 07775). (d) X-Ray crystallography.

(2) Georg, G. I.; Mashava, P. M.; Akgün, E.; Milstead, M. W. *Tetrahedron Lett.* **1991**, *32*, 3151. The formation of a single isomer was reported. For a correction of these results see the **Table** (compounds **4d** and **5d**) in this letter. Please also note the Corrigendum in *Tetrahedron Lett.* **1992**, *33*, 1524

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(8) For a recent review on taxol chemistry see: Kingston, D. G. I.; Samaranayake, G.; Ivey, C. A. *J. Nat. Prod.* **1990**, *53*, 1. For a recent review on preclinical and clinical studies see: Rowinsky, E., K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.

(9) General procedure for the formation of β-lactams **4** and **5**: Imine **1a** (1mmol) and triethylamine (0.63 mL, 4.5 mmol) were dissolved in the given (**Table**) solvent (15 mL) under anhydrous conditions and cooled to 0 °C. Then a solution of the acid chloride (3.5 mmol) in dichloromethane (5 mL) was added dropwise over a time period of 30 minutes to the reaction mixture. The ice bath was removed and the solution was stirred at room temperature overnight. After quenching the reaction mixture with ice water, the organic layer was washed with saturated $NaHCO_3$ solution (2x10 mL), water (3x15 mL), and brine (10 mL). After evaporation of the solvent, the crude reaction product was subjected to column chromatography on silica gel utilizing ethyl acetate/hexanes (2:3) as the eluent.

(10) For a review on the use of galactose imines in asymmetric synthesis, and on similar results with respect to the reactivity of α-anomers see: Kunz, H. In *Selectivities in Lewis Acid Promoted Reactions;* Schinzer, D., Ed.; Kluver Academic: Dordrecht, 1989; pp 189-202.

(11) The resonance frequency (^{1}H-NMR) for H-2 (galactose) of β-lactams **4a-4h** (~4.9 ppm) was consistently found at higher field than for the corresponding isomers **5a-5h** (~5.4 ppm).
^{1}H-NMR data (300 MHz in $CDCl_3$) for β-lactam **4g**: δ 1.89(s, 3H); 1.91(s, 3H); 2.06(s, 3H); 2.08(s, 3H); 3.77(s, 3H, -OCH_3); 3.97(t, J=6.9Hz, 1H, H_5); 4.12(d, J=6.6Hz, 2H, H_{6a}, H_{6b}); 4.89(dd, $J_{1,2}$=$J_{2,3}$=9.9Hz, 1H, H_2); 4.95(dd, $J_{2,3}$=9.3Hz, $J_{3,4}$=3.0Hz, 1H, H_3); 5.11(d, J=8.7Hz, 1H, H_1); 5.15(d, J=5.1Hz, 1H, $H_{4'}$); 5.33(d, J=2.7Hz, 1H, H_4); 5.43(d, J=4.8Hz, 1H, $H_{3'}$); 6.73(d, J=7.8Hz, 2H); 6.81(d, J=8.7Hz, 2H); 6.89(t, J=7.4Hz, 1H); 7.13(t, J=8.0Hz, 2H); 7.32(d, J=8.7Hz, 2H).
^{1}H-NMR data (300 MHz in $CDCl_3$) for β-lactam **5g**: δ 1.96(s, 3H); 1.98(s, 3H); 2.02(s, 3H); 2.14(s, 3H); 3.76(s, 3H, -OCH_3); 3.80-3.92(m, 3H, H_5, H_{6a}, H_{6b}); 5.00(dd, $J_{2,3}$=10.3Hz, $J_{3,4}$=3.4Hz, 1H, H_3); 5.04(d, J=9.4Hz, 1H, H_1); 5.15(d, J=4.8Hz, 1H, $H_{4'}$); 5.29(d, J=3.4Hz, 1H, H_4); 5.35(d, J=4.6Hz, 1H, $H_{3'}$); 5.37(dd, $J_{1,2}$=$J_{2,3}$=10.0Hz, 1H, H_2); 6.74(d, J=8.3Hz, 2H); 6.79(d, J=8.7Hz, 2H); 6.90(t, J=7.3Hz, 1H); 7.14(t, J=7.9Hz, 2H); 7.36(d, J=8.61Hz, 2H).

(12) All diastereoisomers **4** displayed (+) optical rotations and all isomers **5** showed (-) optical rotations. β-Lactam **4g**: $[\alpha]_D$+50.7°(c, 1.085, $CHCl_3$). β-Lactam **5g**: $[\alpha]_D$-21.8°(c, 1.030, $CHCl_3$). The CD spectra of isomer **4g** and isomer **5g** displayed mirror image-like curves.

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