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SYNTHESIS OF OPTICALLY PURE 4-HYDROXYMETHYL-3-PHENOXY-2-AZETIDINONE FROM D-GLUCAL

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Abstract –A convenient approach to enantiomerically pure 4-hydroxymethyl-3-phenoxy-2-azetidinone has been carried out using the easily available aldehyde **5** as chiral starting material.

The use of carbohydrate derivatives as chiral auxiliaries in β-lactam synthesis using the Staudinger reaction is well documented in the literature.[1] Regarding the asymmetric induction obtained from imines derived from sugar aldehydes, compounds such as **1**,[2] **2**[2] or **3**[3] (Figure 1) have been used although with different levels of diastereoselectivity depending on the chiral auxiliary employed.[4]

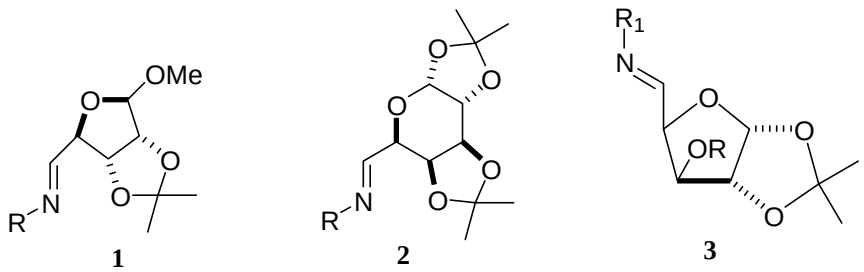
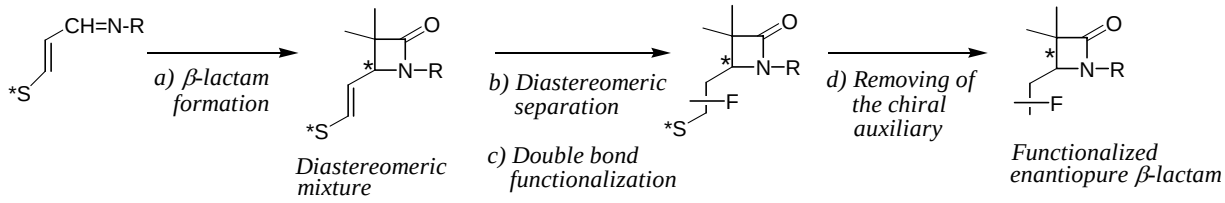


Figure 1. Imines derived from sugar aldehydes

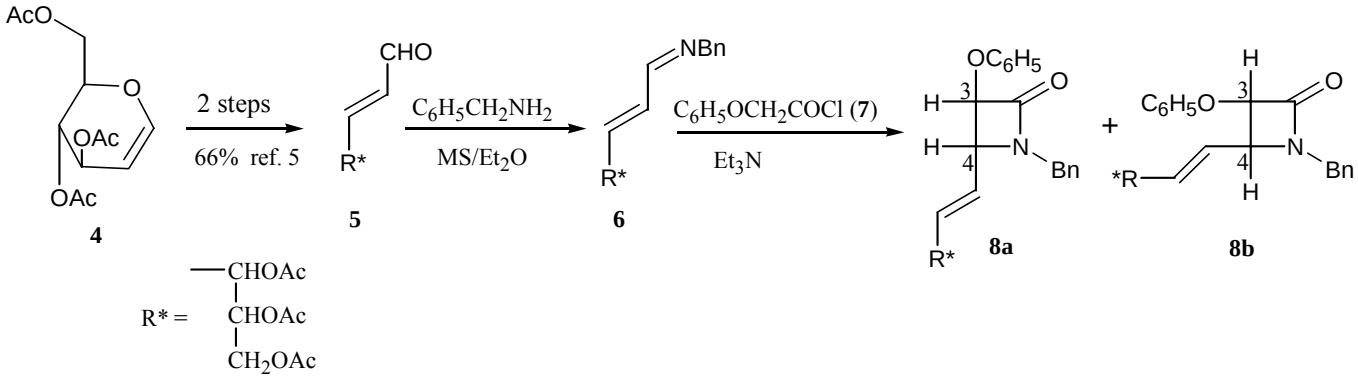
A major problem associated with this methodology is the elimination of the chiral auxiliary because, in some cases, the experimental conditions necessary to achieve this process are incompatible with the β-lactam moiety. In this way, the introduction of an appropriate, synthetically versatile functionality between the imino group and the sugar moiety in the imino derivative partner may be a convenient

solution to this problem. In this case, the chiral auxiliary, not directly attached to the β-lactam ring, could be removed or transformed under smooth conditions, which would be compatible with the β-lactam ring. Within this general approach a double bond constitutes an appealing possibility. Considering the distance between the chiral auxiliary and the imino group, low levels of diastereoselectivity should be hoped and the method will be useful providing a convenient separation of the diastereomeric mixture. (Scheme 1)



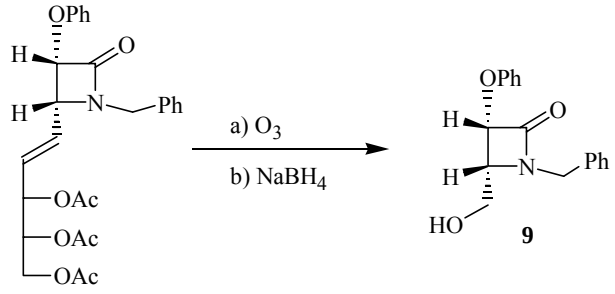
Scheme 1

We have tested this approach in the following way (Scheme 2): aldehyde **5**, easily accessible from tri-O-acetyl-D-glucal (**4**) in two steps and 66% overall yield,[5] was transformed into imine **6** under standard conditions ($C_6H_5CH_2NH_2$, molecular sieves, Et_2O, 97% isolated yield). Reaction of **6** with phenoxyacetyl chloride **7** in the presence of Et_3N gave a diastereomeric mixture (1.3:1) of β-lactams **8a** and **8b** in 70% isolated yield after purification by column chromatography of the reaction crude (silica gel, ethyl acetate-hexane 1:3). The *cis* relationship at the β-lactam nucleus was deduced from the $J_{H3/H4}$ value (4.8 Hz). Diastereomerically pure β-lactams were isolated by HPLC (ethyl acetate-hexane 1:1 as eluent, flow 5 ml/min, λ_{opt} = 280 nm).



Scheme 2

Having achieved the steps a) and b) of our methodology (Scheme 1) we decided to check the procedure fusing the steps c) and d) in only one. In this way, ozonolysis of the β-lactam **8a** followed by treatment with $NaBH_4$ allowed us for the synthesis of enantiomerically pure 4-hydroxymethyl β-lactam **9** in 66% isolated yield (Scheme 3).



8a **9**

Scheme 3

The relative configuration of **9** (and hence **8**) was determined by X-ray crystallography as 3*S*, 4*R* (Figure 2).

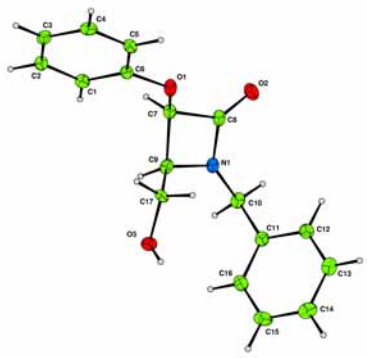


Figure 2

In summary, in this communication we have described a convenient procedure for the synthesis of optically pure β-lactams having a tethered chiral auxiliary able to be appropriately functionalized.

EXPERIMENTAL

General Methods

Chemicals and solvents were obtained from commercial sources and distilled or dried according to standard methods. Progress of the reaction was monitored by thin layer chromatography, which was performed on Aldrich precoated plated (silica gel, POLIGRAM®SIL G/UV_{254} Machery-Nagel) with thinckness of 0.22 mm, by staining with Hanessian´s stain. Chromatographic purification was performed on silica gel columns (Keselgel 60, 230-400 mesh, Merck) with an indicated eluent. Melting points were determined on a Barnstead Electrotermal 9100 apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter. IR spectra were obtained on a Thermo IR-300 spectrometer (Electron Corporation), as a thin film on NaCl plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 espectrometer at room temperature and 400 MHz and 100 MHz respectively, in $CDCl_3$ as solvent, with TMS as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectra were recorded using a Micromass AutoSpec under CI (at 3000 dalton resolution) or Bruker Microtof ESI-TOF under ESI-TOF. Separation of isomers was performed by an HPLC Agilent 1100 Series apparatus (Agilent Technologies)

with a semipreparative Zorbax RX-Sil USHL001118 column (9.4 x 250 mm, 5-micron). Crystal data were collected on a diffractometer having a *Nonius Kappa CCD* area detector.

(3*S*,4*R*)-4-[(1'*E*)-3',4',5'-Tri-*O*-acetyl-1',2'-dideoxy-D-*erythro*-penten-1-yl]-*N*-benzyl-3-phenox-2-azetidinone (8a) and (3*R*,4*S*)-4-[(1'*E*)-3',4',5'-tri-*O*-acetyl-1',2'-dideoxy-D-*erythro*-penten-1--yl]-N-benzyl-3-phenoxy-2-azetidinone (8b).

To a solution of the imine **6** (1.52 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (4.56 mmol) under N_2 at 0ºC, and a solution of phenoxyacetyl chloride **7** (2.28 mmol) in CH_2Cl_2 (4 ml) was introduced dropwise. Then, the reaction was warmed to rt and stirred for 6.5 h. After the reaction was completed, the reaction mixture was poured into water (10 mL), stirred for 15 min, and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 5% $NaHCO_3$ (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, EtOAc/hexane 1:3) to afford a mixture (1.3:1) of the two diastereomers (colourless oil, 70%), which were separated by HPLC (hexane/EtOAc 1:1).

Isomer 8a: $[\alpha]_D^{21}$ +18º (*c* 0.25, CH_2Cl_2); IR: υ_{max} (film): 1747 s (N-C=O), 1747 s (C=O, ester), 1227 s (C-O-C), 1049 (=C-O) cm^{-1}. HRMS (CI, M+H) calcd for $C_{27}H_{30}NO_8$ 496.1971, found 496.1985; m/z (%) 496 (M+1, 10), 436 (M+1-AcOH, 63), 376 (M+1-2AcOH, 72), 302 (53), 172 (65), 107 (60), 91 (CH_2Ph, 100); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ (ppm) 7.38-7.32 (m, 3H, Ph), 7.27-7.23 (m, 4H, Ph), 6.97 (t, *J* = 7.2 Hz, 1H, Ph), 6.91 (d, *J* = 8.0 Hz, 2H, Ph), 6.99 (t, *J* = 2 Hz, 1H, Ph), 6.90 (2H, Ph), 5.73-5.72 (m, H-1', H-2'), 5.45-5.42 (m, H-3'), 5.29 (d, $J_{3,4}$ = 4.8 Hz, H-3), 5.06 (quintet, $J_{4',3'}$ = 3.8 Hz, $J_{4',5'b}$ = 3.6 Hz, $J_{4',5'a}$ = 7.6 Hz, H-4'), 4.67 (d, $J_{1'',1''b}$ = 14.8 Hz, H-1''$_a$), 4.29-4.26 (m, H-4), 4.10 (d, $J_{1'',1''b}$ = 14.8 Hz, H-1''$_b$), 3.98 (dd, $J_{4',5'a}$ = 8.0 Hz, $J_{5'a,5'b}$ = 12.4 Hz, H-5'$_a$), 3.87 (dd, $J_{4',5'b}$ = 3.6 Hz, $J_{5'a,5'b}$ = 12.4 Hz, H-5'$_b$), 2.03 (s, 6H, CH_3OAc), 1.96 (s, 3H, CH_3OAc); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ(ppm) 170.4, 170.1, 169.2 (CO, 3AcO), 164.8 (CO, lactam), 156.9 and 134.8 (2C-1''') 130.8 (C-1'), 129.5, 128.9 and 128.1 (C-2'''/C-6''', 2C-3'''/C-5''') 128.6 and 128.5 (2C-4'''), 122.1 (C-2'), 115.3 (C-2'''/C-6''', PhO), 81.5 (C-3), 71.2 (C-4'), 71.6 (C-3'), 61.3 (C-5'), 59.3 (C-4), 44.6 (C-1'') 20.8, 20.7, 20.6 (CH_3).

Isomer 8b: $[\alpha]_D^{23}$ +26.5º (*c* 0.66, CH_2Cl_2); IR: υ_{max} (film): 1747 s (N-C=O), 1747 s (C=O, ester), 1227 s (C-O-C), 1047 (=C-O) cm^{-1}; HRMS (CI, M+H) calcd for $C_{27}H_{30}NO_8$ 496.1971, found 496.1982; m/z (%) 496 (M+1, 15), 436 (M+1-AcOH, 100), 376 (M+1-2AcOH, 85); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.31 (m, 3H, Ph), 7.26-7.22 (m, 4H, Ph), 6.97 (t, *J* = 7.6 Hz, 1H, Ph), 6.90 (d, *J* = 3.2 Hz, 2H, Ph), 5.80 (dd, $J_{1',2'}$ = 16.0 Hz, $J_{1',4}$ = 8.8 Hz, H-1'), 5.68 (dd, $J_{2',3'}$ = 6.0 Hz, $J_{1',2'}$ = 15.2 Hz, H-2'), 5.38-5.35 (m, $J_{4',3'}$ = 4.4 Hz, $J_{2',3'}$ = 6.0 Hz, H-3'), 5.28 (d, $J_{3,4}$ = 4.4 Hz, H-3), 5.08 (q, $J_{4',3'}$ = 4.8 Hz, $J_{4',5'a}$ = 5.0 Hz, $J_{4',5'b}$ = 5.2 Hz, H-4'), 4.74 (d, $J_{1'',1''b}$ = 14.4 Hz, H-1''$_a$), 4.24 (dd, $J_{3,4}$ = 4.4 Hz, $J_{4,1'}$ = 8.8 Hz, H-4), 4.06 (d, $J_{1'',1''b}$ = 14.8 Hz, H-1''$_b$), 3.97 (d, $J_{4',5'}$ = 5.2 Hz, 2H, H-5'), 2.03 (s, 3H, CH_3OAc), 2.01 (s, 3H, CH_3OAc), 1.99 (s, 3H, CH_3OAc); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ (ppm) 170.4, 170.0, 169.2 (CO,

3AcO), 164.8, (CO, lactam), 131.3 (C-1'), 156.9 and 134.8 (2C-1"'), 131.3 (C-1'), 129.6 and 128.0 (2C-4"') 128.9, 128.8 and 128.5 (C-2"'/C-6"', 2C-3"'/C-5"'), 122.3 (C-2') 115.3 (C-2"'/C-6"', PhO), 81.5 (C-3), 71.3 (C-3'), 71.3 (C-4'), 61.4 (C-5'), 58.9 (C-4), 44.4 (C-1''), 20.8, 20.1 ($3CH_3$).

(3*S*, 4*R*)-4-hydroxymethyl-*N*-benzyl-3-phenoxy-2-azetidinone (9).

Through a stirred solution of β-lactam **8a** (0.169 mmol) in a mixture of CH_2Cl_2 (3.5 mL) and MeOH (4 mL) at -78 ºC, O_2 was bubbled for 2 min and then ozone for 35 min. After that, the solution was purged, first with O_2 (10 min) and afterwards with argon, and treated portionwise with $NaBH_4$ (1.18 mmol). The reaction mixture was stirred for 10 min and then 2 h at rt. The mixture was diluted with NH_4Cl solution (3.2 ml), and extracted with CH_2Cl_2. The organic phase was then washed with water and dried ($MgSO_4$). After evaporation, reaction crude was purified by column chromatography (silica gel, EtOAc/hexane 1:2) to give the enantiomerically pure alcohol **9** (31.6 mg, 66%), as a white solid which was recrystalized from hexane/CH_2Cl_2. mp 69-72ºC; $[\alpha]_D^{19}$ +11.9º, (*c* 1.3, CH_2Cl_2); IR: υ_{max} (film): 3441 s (OH), 2927 s (CH_2), 1746 s (N-C=O), 1236 s (C-O-C), 1048 m (=C-O) cm^{-1}; HRMS (ESI-TOF, M+H) calcd for $C_{17}H_{18}NO_3$ 284.1272, found 284.1281; m/z (%) 284 (M+1, 100), 253 (M+1-CH_2OH, 82), 150 (96); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ (ppm) 7.40-7.29 (m, 5H, PhO), 7.11-7.05 (m, 5H, Ph), 5.3 (d, $J_{3,4}$ = 3.5 Hz, H-3), 4.74 (d, $J_{1''a,1''b}$ = 11.9 Hz, H-1"$_a$), 4.34 (t, $J_{1"b,1"a}$ = 11.9 Hz, H-1"$_b$), 3.9-3.8 (m, 3H, H-1'$_a$, H-1'$_b$, H-4) 1.95 (OH) cm^{-1}. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ(ppm) 166.0 (CO, lactam), 157.6, 137.9, 135.6, 130.1, 129.4, 128.8, 128.4, 123.1 (C-2"'/C-6"', 2C-3"'/C-5"', 2C-4"'), 116.1 (C-2"'/C-6"', PhO), 81.2 (C-3), 60.6 (C-1'), 58.3 (C-4), 45.4 (C-1''). Crystal structure analysis: $C_{17}H_{17}NO_3$, M_r = 283.32 g mol^{-1}, monoclinic, space group *Pbca*, a = 23.4831 (9), b = 5.7989 (2), c = 23.9343 (9) Å, β = 118.879 (2) º, V = 2853.96 (18) $Å^3$, Z = 8, ρ = 1.319 g cm^{-3}, μ = 0.091 mm^{-1}, F(000) = 1200, crystal size: 0.16 x 0.07 x 0.06 mm^3. Crystal data were collected on a diffractometer having a *Nonius KappaCCD* area detector. A total of 14110 reflections ($3.65 < \theta < 27.47$º) were collected of which 3265 were unique R(*int*) = 0.0931. Crystallographic data (excluding structure factors) for compound **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-614962.

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