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Stereospecific Synthesis of a Novel Bicyclic β-Lactam[1]

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Dedicated to Prof. Basanta G. Chatterjee on the occasion of his 70th birthday.

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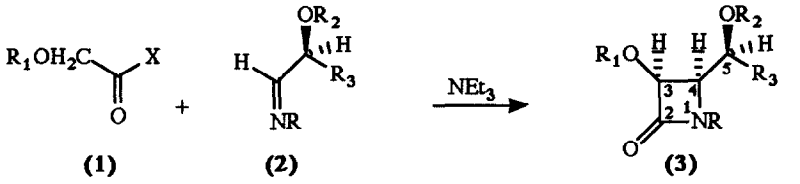
Abstract: *Reductive ozonization in methanol of suitably protected 1,2-glycals of readily available D-sugars led to 4-formates of lower sugars in the aldehyde form. An aza-Wittig type reaction with 2-methoxyethoxymethyl (MEM) azide converted these aldehydes to Schiff bases with multiple chiral centers. Stereospecific cis β-lactam formation was observed on reacting these Schiff bases with benzyloxyacetyl chloride and triethylamine. Mild acid hydrolysis of the formate group in the C-4 side chain led to (1R,2S,3R,7R,8S)-1,2,8-tribenzyloxy-3-benzyloxymethyl-4-oxanonam, a bicyclic β-lactam containing a hexahydro-3-oxazepine ring. The structure and absolute configuration of this β-lactam was determined by X-ray crystallography.*

The synthesis of β-lactams with diverse substituents continues to interest many medicinal chemists and organic chemists. Such compounds serve as intermediates for various β-lactam antibiotics[2] and several types of natural products (for example, amino sugars[3], alkaloids[4] and polyhydroxyamino acids[5]). In recent years we have been engaged in studying the synthesis and transformations of optically active 3-hydroxy-2-azetidinones [6] as versatile synthons and have described synthetic approaches to variously substituted optically active β-lactams.[7,8]

In view of the growing concern about pollution of the environment, we favor those methods that produce a single isomer of a β-lactam in high yield. Such an approach reduces the need for extensive chromatography or fractional crystallization - steps that lead to large quantities of waste solvents.

In previous publications [6] we have reported the enantiospecific synthesis of cis 3-hydroxy-2-azetidinones **3** by the reaction of the α-hydroxyacetic acid derivative **1** and triethylamine with the imino compound **2** derived from an optically active aldehyde and an achiral amino compound. In the examples studied so far, a single optically pure β-lactam **3** was obtained in each case. The absolute configuration at C-4 in **3** could be predicted on the basis of the absolute configuration of the carbon (the future C-5 in **3**) adjacent to the imino group in **2** even if there were additional centers of asymmetry in the starting aldehyde.[9,6]



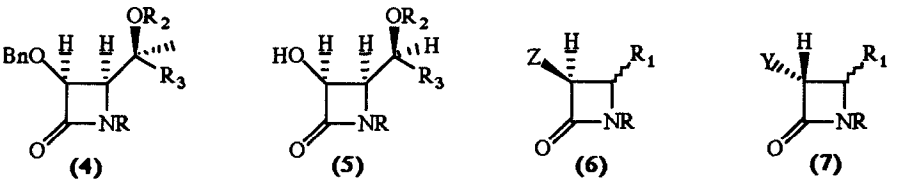
(1) (2) (3)

R_1 = Me, $PhCH_2$, Ph, Ac
X = Halogen or other leaving groups

R_2= Alkyl or hydroxyalkyl as in sugars with R_2 and R_3 together as parts of a 1,2-diol acetonide (for example, see Ref. 7 and 8)

We have shown that the β-lactams **4** derived from benzyloxyacetic acid are converted to the corresponding 3-hydroxy-2-azetidinones **5** in nearly quantitative yield in a few minutes by catalytic transfer hydrogenation using MORE (Microwave-induced Organic Reaction Enhancement) chemistry techniques.[6b]

In case of 6-hydroxy-penams (and other bicyclic β-lactams), the replacement of the hydroxy group by an S_N2 reaction requires the prior formation of a triflate (trifluoromethylsulfonate) derivative.[10] In contrast, the tosylate or mesylate derivative of a monocyclic cis α-hydroxy β-lactam (e.g., **6**) can be readily converted to trans β-lactams **7** by inversion at C-3 with NaOAc or LiN_3.[11,6a]

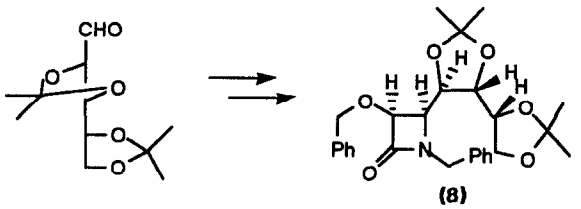


(4) (5) (6) (7)

Z = OMs, OTs Y = OAc, N_3

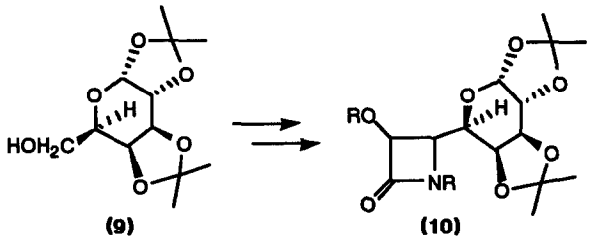
We wish to report here a stereocontrolled approach to α-hydroxy-β-lactams that are part of an uncommon bicyclic system. The key intermediate for this synthesis is an imino compound derived from an achiral amine and an optically active aldehyde with multiple chiral centers.

Readily available carbohydrates are convenient sources for the aldehyde component for preparing imino compound **2** with multiple asymmetric centers. In the past we have used the aldehyde group (C-1) in pentoses and hexoses for preparing Schiff bases, **2**. Thus, the β-lactam **8** was prepared from the diacetonide of D-arabinose.[5]



(8)

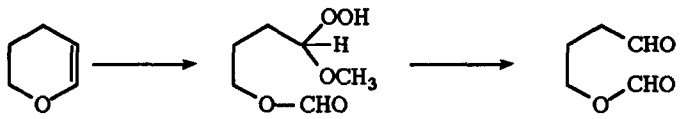
Alternatively, we[12] have converted the primary hydroxyl group of appropriately protected sugars (e.g.,**9**) into an aldehyde group to provide the additional asymmetric centers needed in β-lactams (e.g.,**10**).



(9) (10)

We have now explored the possibility of using the same commonly available sugars for generating different sets of stereocenters in the Schiff bases to be prepared. Thompson[13] has shown that ozonolysis of 3,4-dehydro-2H-pyran **11** in methanol leads to 4-hydroperoxy-4-methoxybutyl formate **12** which can be reduced to an aldehydo formate **13** in high yield (Scheme 1).

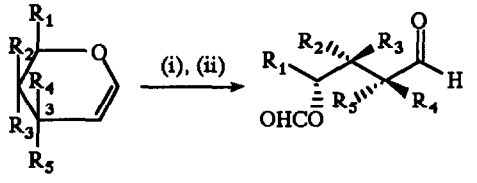
Scheme 1



(11) (12) (13)

Several 1,2-glycals **14** with suitable protective groups are commercially available or are easily prepared from readily available sugars. Ozonolysis and subsequent reduction following Thompson's method were successfully employed to prepare several aldehydes **15** of interest to us in about 90% yield (Scheme 2). Thus, appropriately protected 1,2-D-glucals gave **15a** and **b**, while **15c** was obtained from a protected 1,2-glycal prepared from D-ribose.

Scheme 2



(14) (15)

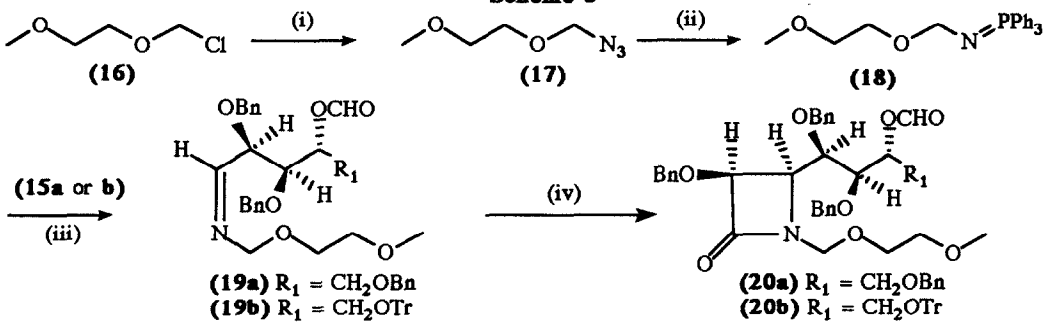
(i) O_3, CH_2Cl_2 / MeOH, - 78°C ; (ii) Me_2S, NH_4Cl / H_2O

(a) R_1 = CH_2OBn, $R_2 = R_5 = H$, $R_3 = R_4 = OBn$
(b) R_1 = CH_2OTr, $R_2 = R_5 = H$, $R_3 = R_4 = OBn$
(c) $R_1 = R_2 = R_4 = H$, $R_3 = R_5 = OBn$

Bn = CH_2Ph, Tr = triphenylmethyl

Various substituents on the β-lactam nitrogen have been used for easy conversion to *N*-unsubstituted β-lactams. We selected the MEM group as an *N*-substituent for our target β-lactams. The aza-Wittig approach [14] seemed to be a promising method for preparing optically active Schiff bases from **15**. 2-Methoxyethoxymethyl (MEM) chloride **16** on treatment with sodium azide gave the azido derivative **17** which was reacted with triphenylphosphine to afford the aza-Wittig reagent **18**.[15] Reaction of **18** with the aldehydes **15** resulted in the formation of the chiral Schiff bases **19a** and **19b** which were used directly for β-lactams synthesis without further purification.

Scheme 3



(i) NaN_3, $(C_4H_9)_4$ $NHSO_4$, $CHCl_3$, Δ, 4h ; (ii) PPh_3, $CHCl_3$, Δ, 1h 75% ; (iii) CH_3CN,-20°- RT, 1h, 70%; (iv) $BnOCH_2COCl$, NEt_3, CH_3 CN, -20°- RT, overnight, 70%

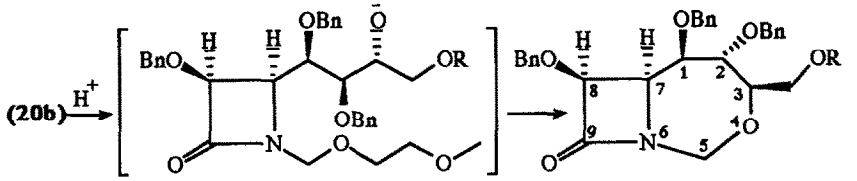
When the Schiff bases **19a** and **b** were allowed to react with benzyloxyacetyl chloride in presence of triethylamine in acetonitrile medium, the substituted cis β-lactams **20a** and **20b** respectively, were formed. The proton NMR of the crude reaction product did not reveal the presence of any diastereomers of **20**.

In an attempt to remove the MEM group to obtain an *N*-unsubstituted β-lactam, the compound **19b** was heated under reflux with *p*-toluenesulfonic acid in chloroform. The product **(22)** was a cis β-lactam that contained a hydroxyl group but lacked the formate and the trityl groups and parts of the MEM group (as indicated by the NMR and IR spectra[16]). The 3,5-dimitrobenzoate **(23)**, mp 191-192°C, of this hydroxy compound, was found to be suitable for x-ray crystallography.

After preliminary single crystal X-ray diffraction studies, Dr. Zofia Urbanczyk-Lipkowska[17] informed us that this compound corresponded to a cis β-lactam fused with a 7-membered oxygen-containing ring as shown by the PLUTO diagram **24**. The absolute configuration of this 4-oxa-nonam[18] derivative could be deduced to be as in the stereostructure **23**. This assignment is based on the reasonable assumption that the configuration of the secondary hydroxyl groups protected by benzylation had not undergone any changes during chemical reactions. The absolute configuration **20b** and **22** can now be assigned to the β-lactams from the Schiff base **19b** (Scheme 4).[19] The ^1H and ^{13}C NMR spectra were found to be consistent with these structures.

It was noted that the absolute configuration (4R) for the β-lactams **20a** and **20b** are as predicted on the basis of the empirical rule (see above) about the chirality induced in the β-lactam by the stereocenter adjacent to the imino group in the Schiff base **19**. This key stereocenter corresponds to C-3 of the starting sugar **14**.

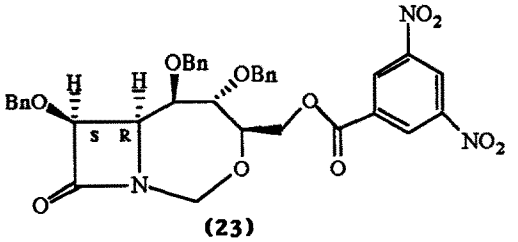
Scheme 4



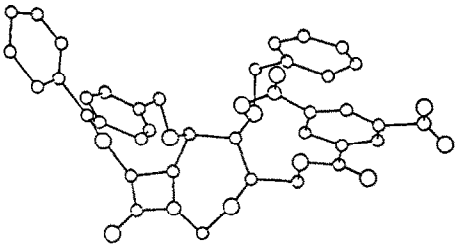
R = Bn or Tr

(21) R = Bn
(22) R = H

Our previous work had involved C-2 and C-5 of hexoses as the key stereocenters for defining the C-4 configuration of β-lactams (e.g., **8** and **10**) formed by the diastereospecific cycloaddition reaction. Studies are in progress on the possibility of forming other types of bicyclic β-lactams by the stereospecific approach described here.



(23)



(24)

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pp 318-323. (b) For the synthesis of optically active α-amino-β-lactam derivatives with complete diastereo control by this approach, see Hubschwerlen, C.; Schmid, G. *Helv. Chem Acta* **1983**, *66*, 2206 and Ref. 7(a): also see, Ikota, N. *Chem. Pharm. Bull.* **1990**, *38*, 1601; Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1991**, *32*, 5187. (c) Using *N,O*-diprotected serinal derived imines in place of **2**, essentially complete diastereoselectivity in the formation of α-hydroxy-β-lactam derivatives has been reported; see Palomo, C; Cossio, F. P.; Cuevas, C. *Tetrahedron Lett.* **1991**, *32* , 3109 and later publications.

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15. β-Methoxyethoxymethyl chloride **16** was refluxed overnight in chloroform with sodium azide in the presence of a catalytic amount of tetrabutyl ammonium hydrogen sulfate. The azido compound so obtained was treated with triphenylphosphine. After the initial exothermic reaction accompanied by nitrogen evolution this reaction mixture was refluxed for 1 hr. The crude oily product, after evaporation of the solvent was further heated on an oil bath for 1 hr and then distilled to get nearly pure **18** in 74% yield which was used for preparing Schiff bases **(19)**.
16. Compound **22** : m.p. 105-106°C IR (Nujol), 3300, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.3 (s, 15 H), 5.4 (d, J=10.9 Hz, 1H), 4.9 (d, J=11.49, 1H), 4.75 (dd, $J_1=J_2=11.6$ Hz, ^1H), 4.65 (d, J=4.5 Hz, 1 H), 4.5 (d, J=11.8 Hz, 1 H), 4.3 (d, 11.6 Hz, 1 H), 4.25 (m, 1 H), 4.2 (m, 1 H), 4.0 (m, 2 H), 3.6 (d, J=2.5 Hz, 1 H), 3.4 (dd, $J_1=2.4$ Hz, $J_2=8.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) ppm: 167.78, 138.47, 137.44, 137.19, 128.54-127.54 (aromatic), 85.34, 81.65, 78.64, 75.59, 74.06, 73.84, 72.42, 64.10, 57.03. CIMS (NH3 reagent gas) m/z 490 (M+1)+. Anal. Calc. for: $C_{29}H_{31}NO_6$; C, 71.14, H, 6.38; N, 2.86; Found: C, 71.52; H, 6.11; N, 3.02.
17. Details of the X-ray analysis will be published elsewhwere by Dr. Z. Urbanczyk-Lipkowska of the Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland.
18. For a convenient nomenclature of fused β-lactams, see Bose, A.K. *J. Heterocyclic Chem.* **1976**, *13*, 93. According to this nomenclature, the stereostructure **22** can be named as (*1R,2S,3R,7R,8S*)-1,2,8-tribenzyloxy-3-benzyloxymethyl-4-oxa-nonam.
19. When **20a** was heated with *p*-toluenesulfonic acid in chloroform an oily compound **21** was obtained which could not be fully purified. On the basis of IR and NMR data[20] and by analogy with **22** this compound was assigned the 4-oxa-nonam structure **21**.
20. Compound **21**: IR (nujol) 1758 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.3 (s, 20 H, aromatic), 5.4 (d, J=10.96 Hz, 1 H), 4.9 (d, J=11.43 Hz, 1 H), 4.75 (d, J=5.93 Hz, 1 H), 4.7 (d, J=11.43 Hz, 1 H), 4.6 (d, J=4.79 Hz, 1 H), 4.5 (d, J=11.78 Hz, 1 H), 4.45 (s, 2 H), 4.3 (d, J=1.54 Hz, 1 H), 4.25 (d, J=9.89 Hz, 1 H), 4.15 (d, J=4.80 Hz, 1 H), 4.0 (d, J=11.54 Hz, 1 H), 3.6 (m, 2 H), 3.4 (m, 4H); ^{13}C NMR ($CDCl_3$) ppm: 168.98, 138.14, 137.88, 136.96, 128.46-127.65 (amomatic), 80.97, 78.64, 76.15, 73.41, 71.49, 68.55, 68.36, 58.85.