Stereospecific Glycosylation via Ferrier Rearrangement for Optical Resolution[1]

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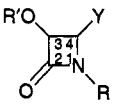
Received May 3, 1994®

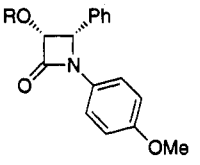
Summary: Diastereospecific glycosylation of racemic alcohols by reaction with suitable glycal derivatives in the presence of iodine provides easy access to both enantiomers as illustrated by the preparation of an optically pure α-hydroxy β-lactam that is an intermediate for the semisynthesis of taxol.

In the course of our continuing studies on β-lactams[1] we have found variously substituted 3-hydroxy-2-azetidinones[2] **1** to be versatile synthons for natural products of different types (including antibiotics,[2] alkaloids,[3] amino acids,[4] amino sugars,[5] etc.). We have noted that (3*R*,4*S*)-



1

R' = H, alkyl, arylalkyl, acyl
Y = aryl, styryl, sugar residue as in **8**



2

R = H or Ac

3-acetoxy-1-(*p*-anisyl)-4-phenyl-2-azetidinone (**2**) has been shown to be a convenient intermediate for the side chain of taxol.[6] For the present investigation, we have selected optically active members of the family of heterocycles **1** with diverse substituents at C-4 and β-lactam nitrogen as our target compounds.

There is a growing perception[7] that enantiomers do not always show the same pharmacological and toxicological profiles. Therefore, the availability of both enantiomeric forms of synthetic compounds is highly desirable for testing purposes. We have explored techniques that could lead conveniently to both enantiomers[8] of our target compounds. Reported here are our preliminary findings about a convenient and general synthetic approach using commercially available reagents.

As an extension of our investigation on glycals[9] we have been interested in an allylic rearrangement described by Ferrier and co-workers.[10] They have reported[10] that treatment with water, phenols, acetic acid, or purines in the presence of an acid catalyst converts substituted glycals with a leaving group at C3 to 2,3-unsaturated pyranosides such as **4** (Scheme 1). A variety of acid catalysts[10] (such as methanolic hydrochloric acid, sulfuric acid, $BF_3{\cdot}Et_2O$, $SnBr_4$, $EtAlCl_2$[11a–e]) and iodonium dicollidinium perchlorate,[11f] a neutral catalyst, have been used in the Ferrier rearrangement. Iodine[11g] has been shown recently to be a catalyst for this type of reaction for glycosylation of cholesterol leading to both α- and β-anomers (90:10 proportion).

In a recent publication Borer and Balogh[12] have described the reaction of tri-*O*-acetyl-D-glucal **3** with the glycolic acid ester **5** (R = CH_2Ph) with $BF_3{\cdot}Et_2O$ as the catalyst. The anomers **6** and **7** were obtained in 70:30 proportion with the α-anomer as the major product.

For studying this reaction, we selected iodine—an inexpensive and environmentally benign reagent—as the catalyst and found it to be ideal for glycosylation *via* the Ferrier rearrangement in THF solution. The ^{13}C NMR spectra of reaction mixtures ($CDCl_3$ was substituted for THF) were found to be a convenient way of monitoring the course of glycosylation since the signals for anomeric carbons appear at a characteristic chemical shift (at about 93 ppm). When we conducted the reaction of tri-*O*-acetyl-D-glucal (**3**) with the glycolic acid ester **5** (R = Et) with iodine as a catalyst (Scheme 1), we obtained essentially a single glycoside **6** (based on a ^{13}C NMR signal at 94.55 ppm) in good yield.[13] This compound was found to be an α-glycoside based on catalytic hydrogenation experiments (see below).

We have applied this glycosylation[14] technique to optically active α-hydroxy β-lactams **8** with three chiral centers. When the reaction was conducted in the presence of iodine in tetrahydrofuran solution, a single

® Abstract published in *Advance ACS Abstracts,* August 1, 1994.

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(7) See, for example: Ariëns, E. J. In *Stereochemistry and Biological Activity of Drugs*, Blackwell Scientific Publishers: Oxford, 1983.

(8) For our recent work on the synthesis of optically active β-lactams see: (a) Bose, A. K.; Manhas, M. S.; Mathur, A.; Wagle, D. R. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, Lukacs, G., Ed.; Springer-Verlag: New York, 1993; Vol. 2, p 551. (b) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R. *Tetrahedron* **1992**, *48*, 4831.

(9) Kaluza, Z.; Manhas, M. S.; Barakat, K. J.; Bose, A. K. *BioMed. Chem. Lett.* **1993**, *3*, 2357.

(10) (a) Ferrier, R. *J. Adv. Carbohydr. Chem. Biochem.* **1969**, 199. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570. (c) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

(11) (a) Herscovici, J.; Muleka, K.; Boumaiza, L.; Antonakis, K. *J. Chem. Soc., Perkin Trans 1* **1990**, 1995. (b) Hadfield, A. F.; Sartorelli, A. C. *Carbohydr. Res.* **1982**, *101*, 240. (c) Grynkiewicz, G.; Priebe, W.; Zamojski, A. *Carbohydr. Res.* **1979**, *68*, 33. (d) Descotes, G.; Martin, J. C. *Carbohydr. Res.* **1977**, *56*, 1680. (e) Lundt, I.; Pederson, C. *Acta Chem. Scand.* **1970**, *24*, 240. (f) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1992**, 94. (g) Houston, T. A.; Klemke, E.; Koreeda, M. 203rd ACS National Meeting, San Francisco, 1992, ORGN 533.

(12) Borer, C. B.; Balogh, D. W. *Tetrahedron Lett.* **1991**, *32*, 1039.

(13) Similar ^{13}C NMR spectral studies showed that the reaction of **3** with ethyl (*R*)-3-hydroxybutyrate produced a single isomer of a glycoside (appearance of the anomeric carbon signal at 92.2 ppm). The same reaction but with the racemic form of the ester produced two ^{13}C signals of equal intensity at 92.2 and 94.9 ppm.

(14) For recent glycosylation reactions see, for example: (a) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, *260*, 1307. (b) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M.; Kinoshita, M. *J. Chem. Soc., Chem. Commun.* **1993**, 704. (c) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (d) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.

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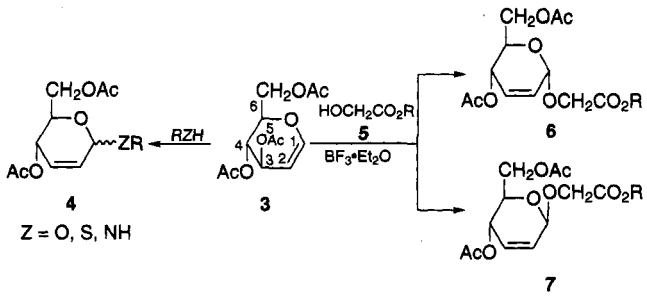
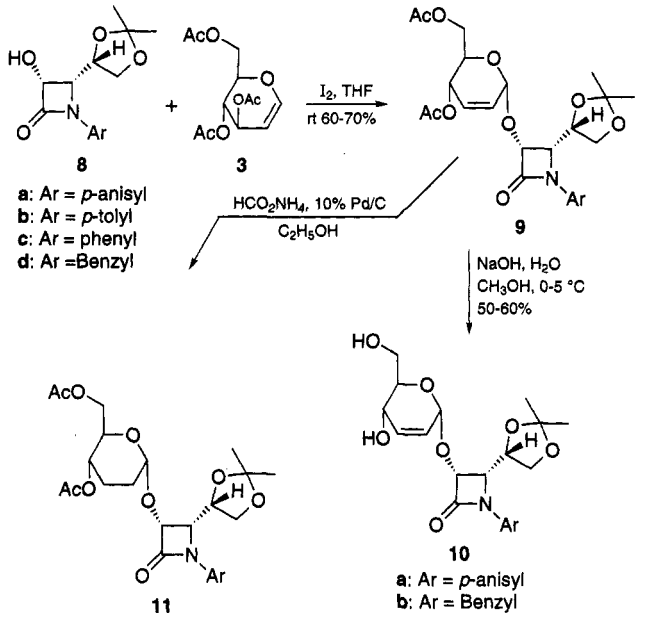
Scheme 1



Scheme 2

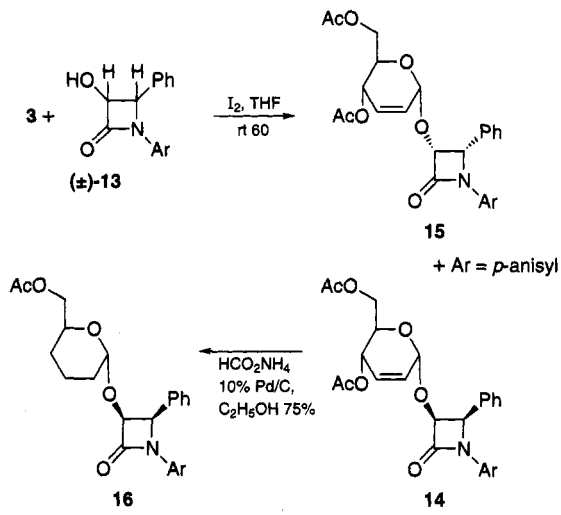


glycoside **9** was obtained in each case in 60−70% yield (unoptimized) after about 30 h at room temperature. On mild alkaline hydrolysis (methanolic sodium hydroxide) of **9**, the dihydroxy compound **10** was obtained in 50−60% yield (Scheme 2).

To establish the steric course of this reaction, the product **9a** was hydrogenated[15] by reaction with ammonium formate in the presence of Pd/C catalyst, when two products **11a** and **12**[16] were isolated. The ^{1}H NMR spectrum of the 2,3-dideoxy sugar derivative **11a** so obtained showed small couplings for the anomeric proton and thus indicated that the glycosidic linkage was in the axial conformation.[17] Therefore, **9**−**11** are represented as D-α-glycopyranosides.

The mechanism of the Ferrier-type rearrangement has not been established. The possibility of allylic isomerization of the glucal **3** to a 2,3-didehydro sugar which then undergoes an S_N1-type reaction (to **6** or **9**) has been suggested. Alternatively, an S_N1'-type reaction cannot be excluded. For obtaining information on the course of this glycosylation reaction NMR monitoring of the reaction mixture was conducted. It was found that the ^{1}H-decoupled ^{13}C-NMR spectrum was superior to the ^{1}H NMR spectrum for this study. The rate of the glycosylation reaction could be increased by using a higher

Scheme 3



concentration of iodine. The reaction failed to take place in the absence of iodine. Quantitative analysis of iodine by titration showed that no consumption of iodine was caused by the glycosylation reaction.

Interestingly, the ^{13}C NMR spectrum of the reaction mixture showed spectral lines characteristic only of the final product and the original glucal and the α-hydroxy β-lactam; no spectral lines corresponding to iodinated intermediates could be discerned. The intermediates involved in this reaction must be transformed into the glycoside very rapidly without allowing the buildup of the concentration of the intermediates to a level that could be easily detected in the reaction mixture. In contrast, it has been reported[14c,d] that the reaction of **3** with alcohols in the presence of *N*-iodosuccinimide[14d] or iodinium dicollidinium perchlorate[14c] leads to 2-deoxy-2β-iodo-3α-glycosides.

The formation of a single glycoside from all the optically active α-hydroxy β−lactams **8** studied raised the possibility of easy access to both enantiomeric forms when starting with racemic β-lactams. Therefore, we studied the glycosylation of racemic *cis*-1-(*p*-anisyl)-3-hydroxy-4-phenyl-2-azetidinone[18] (**13**) which can be synthesized efficiently and rapidly by using microwave-induced reactions.[2a] On treatment with glucal triacetate **3** and iodine in tetrahydrofuran solution, **13** led in 60% yield to a mixture of two diastereomeric compounds **14** and **15** in the ratio of 60:40 (Scheme 3).

Catalytic transfer hydrogenation[15] of **14** produced a 2,3,4-trideoxyglucoside **16**. The small couplings for the anomeric proton indicated that an α-glycosidic linkage had been formed.[17]

Mild acid hydrolysis converted the two glycosidic diastereomers **14** and **15** (separated by chromatography over a silica gel column) into the enantiomeric 1-(*p*-anisyl)-3-hydroxy-2-azetidinones **17** and **19**. To study their optical purity[19] the α-hydroxy β-lactams **17** and **19** were separately converted to their respective α-acetoxy derivatives **18** and **20** by reaction with acetic anhydride and pyridine (Scheme 4). One of these, namely **20**, proved to be the known β-lactam (3*R*,4*S*)-3-acetoxy-1-(*p*-anisyl)-4-phenyl-2-azetidinone (**2**) (R = Ac) which has been used by various groups for the synthesis of the side

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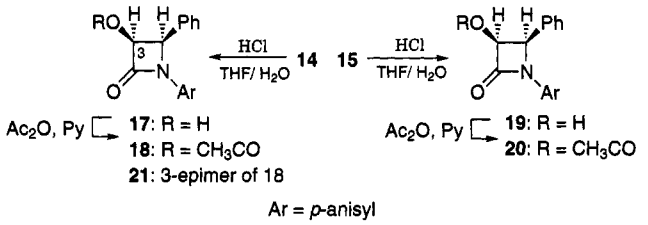
(16) Compound **12** is believed to be a trideoxy compound formed by hydrogenolysis of the allyl acetate group. Structural studies are in progress.

(17) Cf. Lemieux, R. U.; Stevens, J. D. *Can. J. Chem.* **1965**, *43*, 2059.

(18) Amin, S. G.; Glazer, R. D.; Manhas, M. S. *Synthesis* **1979**, 210.

(19) The two β-lactams **18** and **20** were found to be enantiomerically pure as revealed by ^{1}H NMR spectroscopy using an optically active shift reagent. Compound **17**: $[\alpha]^{21}_D$ −179° (*c* = 1.0, $CHCl_3$). Compound **19**: $[\alpha]^{21}_D$ +180° (*c* = 1.0, $CHCl_3$) (for a comparison, see ref 7).

Scheme 4



chain of taxol.[20] Optically active taxol side chain analogs and diastereomers can now be prepared by our method from the racemic forms of 3-hydroxy-2-azetidinones with a variety of substituents at the ring nitrogen and at C-4.

For exploring the scope of this glycosylation reaction for the preparation of enantiomeric α-hydroxy β-lactams, racemic **13** was allowed to react with di-*O*-acetyl-L-rhamnal when two separable diastereomers were produced in nearly equal amounts. Hydrolysis with dilute hydrochloric acid followed by acetylation (Ac_2O, pyridine) provided the same two acetoxy β-lactams **18** and **20** mentioned above.

To obtain a *trans*-β-lactam **21** (which is diastereomeric with **18**), the optically active α-hydroxy β-lactam **17** was tosylated and then reacted with sodium acetate in dimethyl sulfoxide. Using a chiral NMR shift reactant [$Pr(hfc)_3$] it was found that the ee of this acetate **21** was 90% or higher. The racemic form of **21** has been reported recently.[21]

In summary, a room temperature reaction of racemic hydroxy compounds with various 3-acetoxyglucals in presence of iodine as a catalyst has been developed for producing two easily separable, diastereomeric α-glycosides which can be hydrolyzed to the two enantiomers of the starting compound (including α-hydroxy β-lactam synthons for taxol and analogs). This glycosylation reaction conducted with environmentally benign reagents can be used for increasing the hydrophilicity of hydroxy β-lactams (and related compounds) and for providing access to additional functional groups by modification of the sugar moiety. Further studies on the glycosylation of diverse types of hydroxy, amino, and mercapto compounds are in progress.

Acknowledgment. This research was supported by the Stevens Institute of Technology and the Howard Hughes Medical Institute (through a grant to our Chemical Biology Education Enhancement Program). We wish to thank Dr. B. N. Pramanik and Dr. M. S. Puar for optical rotation and NMR data on some key compounds and Dimple Shah[22] and Dorothy Adler[22] for technical assistance.

Supplementary Material Available: Experimental procedures for **9a–d**, **14**, **15**, **10a,b**, **11**, **16**, and **21** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) For some recent publications on the synthesis of the taxol side chain, see: (a) Holton, R. A.; Liu, J. H. *BioMed. Chem. Lett.* **1993**, *3*, 2475 and references cited therein. (b) Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889. (c) Kanazawa, A. M.; Correa, A.; Denis, J. N.; Luche, M. J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255. (d) Hattori, K.; Hiyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151. (e) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985. (f) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mijillano, M. R.; Burke, C. T. *J. Med. Chem.* **1992**, *35*, 4230.

(21) Endo, M.; Droghini, R. *BioMed Chem. Lett.* **1993**, *3*, 2483.

(22) Undergraduate research participants in our UPTAM (Undergraduate Projects in Technology and Medicine) program.