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Enantiopure α-Hydroxy-β-Lactams *via* Stereoselective Glycosylation[1]

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Dedicated to Prof. Usha R. Ghatak

Abstract: *Stereospecific glycosylation via the Ferrier rearrangement catalyzed by iodine has been used to obtain both enantiomers of a trans 4-aryl-3-hydroxy-2-azetidinone. Unexpectedly, a rhamnal derivative had to be employed for this reaction since a glucal derivative failed to work. This synthesis complements our previously described preparation of the corresponding cis isomers by the same methodology. Thus, convenient access has become available to all four homochiral stereoisomers of α-hydroxy-β-lactams some of which are synthons for Taxol® and analogs.* © 1997 Elsevier Science Ltd.

Recently α-hydroxy-β-lactams have attracted much attention because they are convenient intermediates for the semi-synthesis of the anti-tumor drugs Taxol[R] (paclitaxel), Taxotere[R] (docletaxel) and their analogs[2]. We[3] have shown that variously substituted 3-hydroxy-2-azetidinones are versatile synthons for amino acids, alkaloids, antibiotics and many other types of natural products.

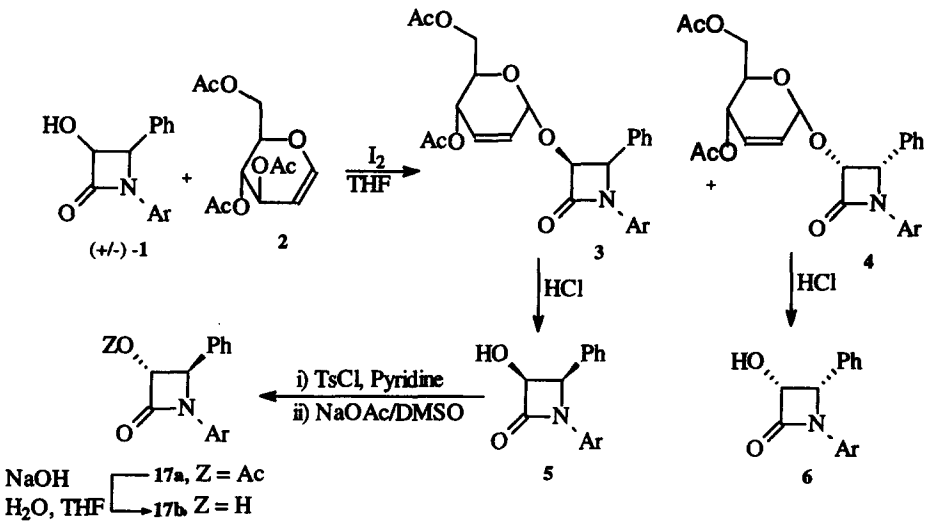
To obtain these end products in optically active forms, we have synthesized enantiopure α-hydroxy-β-lactams by cycloaddition to optically active Schiff bases. Alternatively, we have described a simple method[4] for stereospecific glycosylation *via* the Ferrier rearrangement leading to both enantiomers of hydroxy compounds. In particular, we prepared the enantiomeric forms **5** and **6** of *cis* 1-(*p*-anisyl)-3-hydroxy-4-phenyl-2-azetidinone (**1**) by a two step process (Scheme **1**):

(1) the stereospecific formation of two diastereomeric α-glycosides (**3,4**) which were separated by chromatography;
(2) the hydrolysis of **3** and **4** to optically pure **5** and **6**, respectively. These α-hydroxy-β-lactams are an enantiomeric pair.

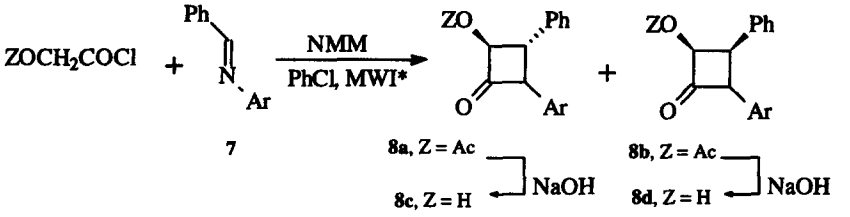
We[5] have reported recently that easy access to certain *trans* β-lactams can be obtained by conducting the β-lactam ring forming reaction at a high temperature under microwave irradiation[6] (Scheme **2**). Thus, the reaction of the Schiff base **7** with acetoxyacetyl chloride and N-methylmorpholine under high power (~800 watts) microwave irradiation produced the *trans* and the *cis* β-lactams **8a** and **8b** in the ratio of 95:5. In contrast, the same annelation reaction under traditional reaction conditions at 0-5°C provided essentially a single isomer - the *cis* α-acetoxy-β-lactam **8b.**

Following our earlier work[4], we attempted glycosylation of the *trans* β-lactam (**8c, Z=H**) with glucal triacetate **2** in presence of iodine[7]. To our surprise, this attempt was unsuccessful even after prolonging the reaction time to 30h at room temperature. With increased concentration of iodine, there was considerable decomposition of the glucal but no formation of glycosides was observed on monitoring by ^{1}H NMR spectroscopy and TLC analysis.

Scheme 1



Scheme 2



NMM = N - methylmorpholine; MWI* = microwave irradiation; Ar = p - anisyl

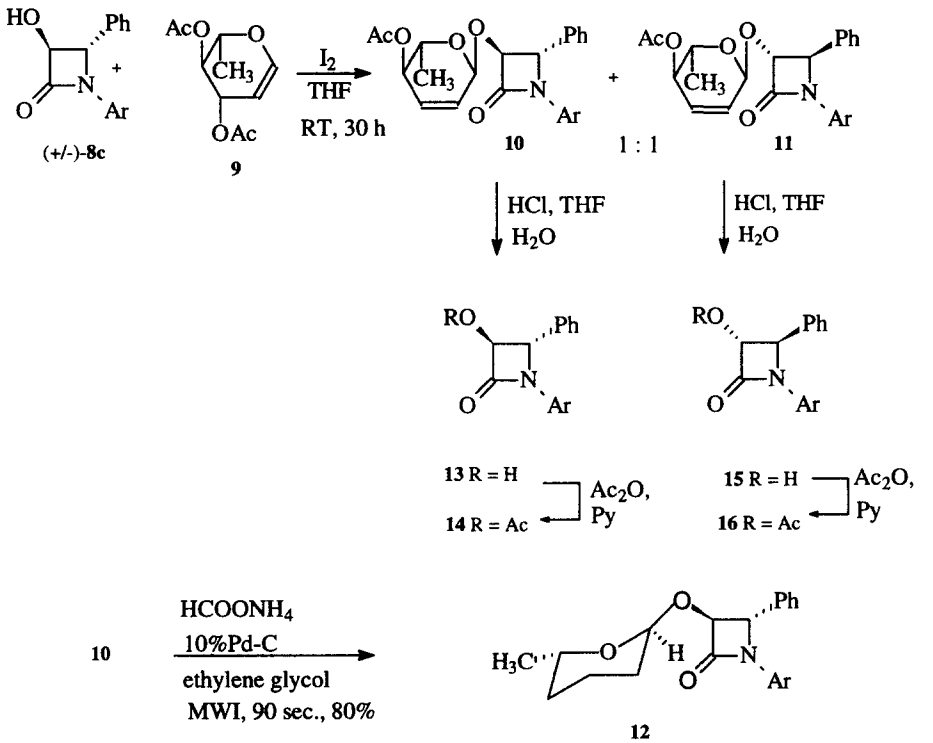
In our previous study we had successfully employed several glycals besides glucal **2**. We selected rhamnal diacetate **9** to replace D-glucal triacetate (**2**). Now the glycosylation of **8c** with **9** in the presence of Iodine (0.3 eq) proceeded readily and a mixture of two products **10** and **11** in the ratio of 1:1 was obtained in about 50% yield (Scheme **3**). These diastereomers (**10** and **11**) could be separated by column chromatography.

The ^{1}H NMR spectra of **10** and **11** showed the tell-tale coupling pattern of α-glycosides[8], no β-glycosides were observed. For obtaining corroborative evidence, **10** was subjected to catalytic reduction[9] under microwave irradiation as in our earlier studies[4]. The expected reduction product **12**[13] was obtained in which the anomeric proton showed the small couplings characteristic of Jee and Jae and thus supported the α-glycoside structure assigned to **10**. It is known that the corresponding β-glycoside would have displayed one small (Jae) and one large (Jaa) coupling[10].

Mild hydrolysis under acidic conditions (HCl/THF/H_2O) of **10** and **11** led to the desired enantiomeric pair **13** and **15** which were converted to their acetates (**14** and **16**) by room temperature reaction with acetic

anhydride in pyridine solution. Both **14** and **16** were shown to be optically pure and enantiomeric to each other by ^{1}H NMR studies using an optically active shift reagent as in our earlier work.[4, 11]

Scheme 3



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In our previous study[4] (**Scheme 1**) we had shown **5** to have the absolute configuration indicated by its stereostructure by comparison with the known compounds which has been used in other laboratories for the partial synthesis of Taxol^R and Taxotere^R. Tosylation of **5** followed by reaction with sodium acetate had led with S_N2 inversion to a *trans* 3-acetoxy-β-lactam **17a**. The corresponding 3-hydroxy-β-lactam which was readily obtained by the mild hydrolysis of **17a** must therefore have the absolute configuration shown by **17b**.

We observed that **16** was identical with **17a** and thus the absolute configuration for **16**, **11**, and **10** could be assigned with confidence.

With the limited data at hand it is difficult to explain the lack of reaction between glucal triacetate and the *trans* α-hydroxy-β-lactam **8c**. The difference in steric bulk at C-6 between the D-glucal triacetate and L-rhamnal diacetates could be one of the contributing factors.

It is obvious that further work is necessary to obtain a clearer understanding of the iodine catalyzed Ferrier rearrangement and to account for the difference in reactivity of *cis* and *trans* β-lactams. Nonetheless, practical methods are available now, based on the present study, for the preparation of all four stereoisomers of α-hydroxy-β-lactams[12] in the optically pure form. Such synthons, in turn, can lead to diastereomeric forms of Taxol^R and various other natural products.

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References and Notes

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10. The ^{1}H NMR spectrum of the hydrogenated product **12** obtained from **10** indicated the α-glycosidic linkage. See: Lemieux, R. U.; Stevens, J. D. *Can. J. Chem.* **1965**, *43*, 2059.
11. Compound **13**: mp 152°C; $[\alpha]_D^{23}$ + 110° (c 1.0, CH_3OH). Compound **15**: mp 152°C; $[\alpha]_D^{23}$ -108° (c 1.0, CH_3OH). ^{1}H NMR of **14** and **16** in the presence of a chiral shift reagent confirmed the absolute configuration of these β-lactams and their mirror image relationship.
12. All new compounds described here gave satisfactory spectral and elemental analyses.
13. Data for **12**: IR (CH_2Cl_2): 1740, 1610 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ: 7.35(s, 5H), 7.25(d, *J*=6.90Hz, 2H), 5.13 (brs, 1H), 4.89(d, *J*=1.51Hz, 1H), 4.65(d, *J*=1.55Hz, 1H), 4.13-3.94(m, 1H), 3.73(s, 3H), 2.05-1.26(m, 6H), 1.07(d, *J*=6.29Hz, 3H); ^{13}C NMR: 164.09, 156.35, 148.22, 136.52, 130.88, 129.01, 128.50, 126.15, 116.90, 114.36, 110.49, 99.26, 88.17, 84.62, 65.92, 64.48, 55.37, 32.75, 29.07, 21.59, 21.03, 17.22, 9.13. Anal. Calcd for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.85; N, 3.81. Found: C, 71.80; H, 6.73; N, 3.64.

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