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A FACILE IODINE-CATALYZED GLYCOSYLATION: ENANTIOMERICALLY PURE β-LACTAMS WITH THE THIENAMYCIN SIDE CHAIN

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Abstract - A facile iodine-catalyzed glycosylation of the hydroxyethyl side chain as present in thienamycin side chain has been achieved with tri-*O*-acetyl-D-glucal. This method has produced two separable diasteromeric α-glycosides in excellent yields which on acid-induced cleavage have provided two optically pure alcohols. The absolute stereochemistry of the products has been determined from physiochemical data.

INTRODUCTION

The glycosylation of alcohols is an interesting and challenging area of research because of the biological activities of *O*-glycosides.[1] Although discovered many years ago, the Ferrier rearrangement[2,3] is still considered to be one of the most attractive methods for the preparation of glycosides. Many Lewis acids[4] and acidic-supports[5] have been used to accomplish this transformation. The shortcomings of these processes are the non-stereoselectivity of the reactions in most of the cases. As a result, mixtures of α- and β-glysosides are generally formed in this reaction. Attempts have been made to improve stereoselectivity; a few successful preparations of α- or β-isomer have been achieved.[6]

Our exploration on indium metal-induced reactions has culminated in a convenient method for the stereoselective synthesis of β-glycosides in good yield by the reaction of an alcohol and acetobromoglucose.[7] In addition, a stereospecific glycosylation of alcohol *via* bismuth nitrate-catalyzed Ferrier rearrangement has also been reported from our laboratory.[8a] We present herein an iodine-

catalyzed convenient and facile strategy involving reaction with glycal derivatives for obtaining both enantiomeric forms of racemic β-lactams with the 1-hydroxyethyl side chain of thienamycin types of antibiotics.

RESULTS AND DISCUSSION

We have reported the use of iodine in organic synthesis.[9] In the course of our continuing studies on antibiotics and anticancer agents, we have synthesized and studied medicinal activities of several β-lactams.[10] In an extension of iodine-catalyzed glycosylation of alcohol,[6] we have studied chiral resolution of a racemic alcohol that is present in thienamycin side chain for obtaining both enanatiomers of this important antibiotic.[9a-b] The strategy is to prepare two separable diastereomeric *O*-glycosides by the Ferrier rearrangement[2] as one of the important steps.

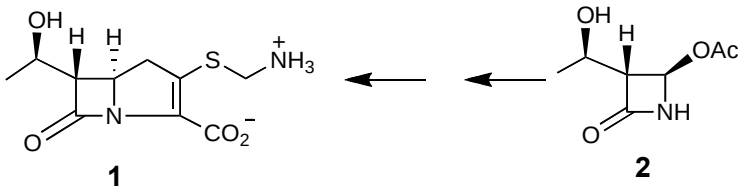
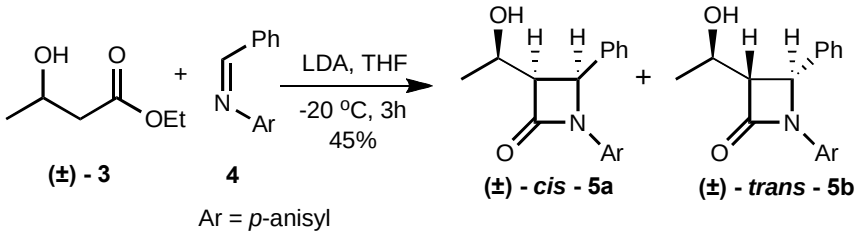


Figure 1

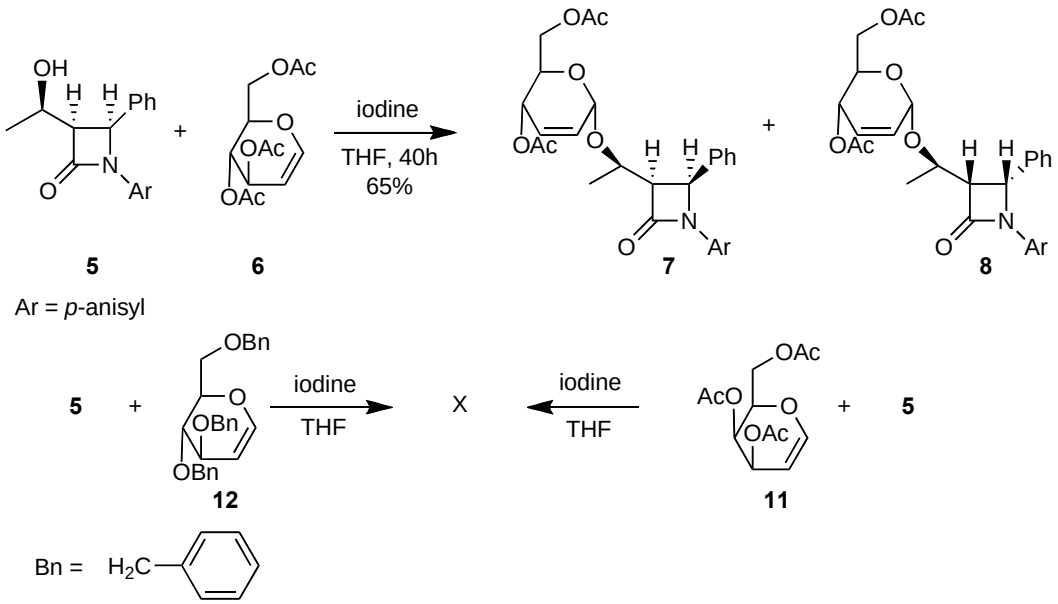
In 1979, the clinical use of the β-lactam antibiotic thienamycin (**1**, Figure 1) has been initiated.[11] PS-5 and carpetimycin also belong to this family of antibiotics.[12] Various synthetic methods are appeared for the preparation of thienamycin.[13] Most of these methods require optically pure 3-(1-hydroxyethyl)-4-acetoxy-2-azetidinone (**2**) as one of the starting materials.[14] Since enantiomers differ in their biological properties, availability of both enantiomeric forms of this compound is highly desirable.[15] One way to obtain both enantiomers is to perform an easy chrial resolution of a readily available racemic alcohol. Toward this objective, the starting racemic *cis*-3-(1-hydroxyethyl)-4-phenyl-*N*-*p*-anisyl-2-azetidinone (**5**) was prepared in satisfactory yield.[16] The reaction of the dianion of (±)-ethyl 3-hydroxy-butyrate (**3**) and *N*-*p*-anisyl-benzylideneamine (**4**) in dry THF at -20 °C-room temperature afforded β-lactams as a mixture of *cis*- and *trans*-isomer in 45% yield (9:1). The *cis*-isomer **5** was separated from this mixture by crystallization (Scheme 1).



Scheme 1

Next, our glycosylation method was conducted to this racemic β-lactam alcohol **5** with iodine in dry tetrahydrofuran at room temperature. The reaction was conducted for 40 h by mixing a solution of the β-lactam **5** and tri-*O*-acetyl-D-glucal (**6**) in anhydrous tetrahydrofuran solution in the presence of iodine (5-10 mol%) as catalyst. Thin layer chromatography of the crude reaction mixture using ethyl acetate-hexane (20:80) showed the presence of two major spots along with minor amounts of the starting unreacted material **5**. After work-up and column chromatography of the crude reaction mixture, two products were obtained in 65% yield (Scheme 2). These compounds were characterized as the unsaturated glycosides **7** and **8**. Conducting the reaction for 90 h did not improve the yield of these glycosides **7** and **8,** while a shorter reaction time (approximately 10 h) decreased the yield of the products. Increasing the percentage of iodine (40 mol%) led to the consumption of glycal **6** in about 10 h, but the yield of the resulting glycosides **7** and **8** was not improved. The yield of **7** and **8** had decreased significantly when a higher proportion of iodine was used.

To establish the stereochemistry of the glycosidic bond, both **7** and **8** were reduced by catalytic transfer hydrogenation method with ammonium formate in the presence of 10% Pd-C catalyst in ethanol at high temperature.[17] A few laboratories employed catalytic transfer hydrogenation as a safe and simple operation.[17] Many other hydrogen donors such as cyclohexene, hydrazine, formic acid, cyclohexadiene and sodium hypophosphite gave poor results.

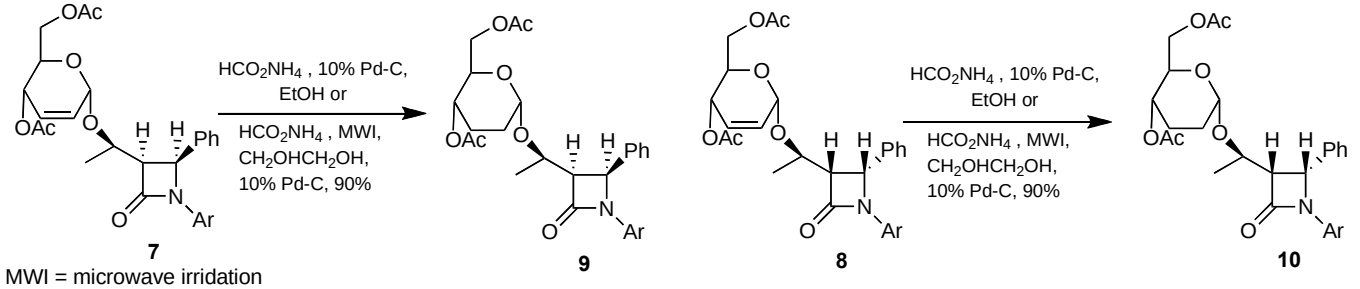


Scheme 2

Microwave-induced hydrogenation using ethylene glycol as the reaction medium and ammonium formate as the hydrogen donor in the presence of 10% Pd-C was helpful for obtaining the saturated products **9** and **10** very easily. The reaction was complete within 1 min (Scheme 3).[18,19] Similar hydrogenation of the β-lactam containing a reducible group and an aromatic ring at C_4 afforded a propionamide derivative as a

result of the N_1-C_4 bond fission.[20] It appeared that the sugar moiety in the glycosides **7** and **8** posed steric hindrance to the hydrogenolysis of the N_1-C_4 bond. However, conducting the hydrogenation reaction longer afforded many other uncharacterized materials. In the complex reaction mixtures several compounds could be detected, but they were not identified thoroughly; these compounds were formed due to the cleavage of the N_1-C_4 bond, reduction of the olefinic group and allylic deacetoxylation of the carbohydrate group. The ^{1}H NMR spectra of the 2, 3-dideoxy carbohydrate derivatives **9** and **10** showed only small couplings (1-2 Hz) for the anomeric proton indicating axial stereochemistry of the glycoside bonds.[9a-b,21] A higher coupling constant (8-10 Hz) was expected with a β-glycoside product.

To test the scope and application of this method, other glycals were also examined. Surprisingly, a similar reaction with commercially available 3,4,5-tri-*O*-acetyl D-galactal (**11**) with the alcohol **5** did not produce any detectable amounts of the glycosides. In addition, 3,4,5-tri-*O*-benzyl D-glucose (**12**) also failed to yield the desired products. This indicates that the nature of the glycal was crucial for the success of this reaction (Scheme 2). The protecting group and stereochemistry of the glycals seemed to play a major role in the iodine-catalyzed glycosylation reaction of the racemic β-lactam alcohol **5**. In order to confirm the role of iodine in the Ferrier rearrangement, a few other reagents were examined. Ferric nitrate, copper nitrate and zinc nitrate-mediated reactions proceeded very slowly and the products were formed in very low yield (not isolated). Copper sulfate, sodium nitrate and potassium nitrate proved to be ineffective. In the past, a variety of other acidic catalysts such as methanolic hydrochloric acid, sulfuric acid



Scheme 3

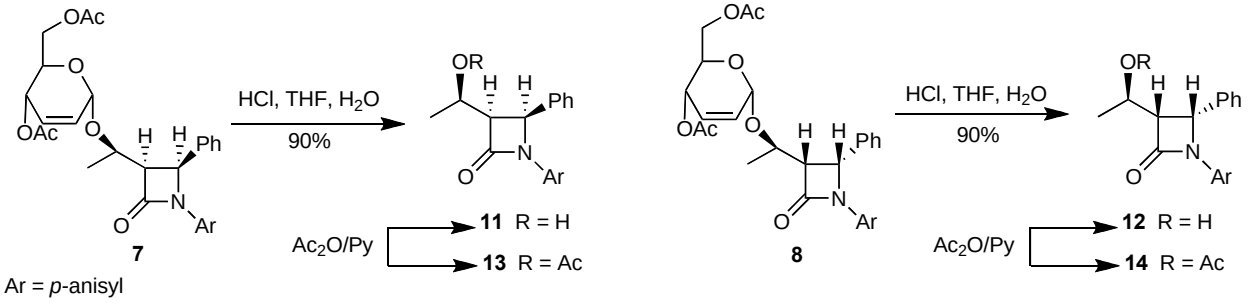
borontrifluoride etherate and stannic chloride were used in the Ferrier rearrangement of several different types alcohols with varying success.[22] Ferrier rearrangement with the neutral catalysts *N*-iodosuccinimide, *N*-bromosuccinimide and iodonium dicollidinium perchlorate was also used for this purpose.[23] In some cases, the products were not unsaturated *O*-glycosides; instead, halogenated *O*-glycosides were obtained. Most importantly, these acid- and neutral catalysts were not tested for the glycosylation of alcohol that is a part of a β-lactam (e.g. **5**) prior to our present study. However, these reagents produced mixtures of products in very low yield with **5**. In contrast to these protocols, our iodine-catalyzed method is stereoselective and produced products in good yield.

The mechanism of the Ferrier rearrangement was investigated earlier. The exclusive formation of α-glycosides in the present study deserved attention. The reaction between **5** and **6** was conducted with catalytic amounts of hydroiodic acid. However, desired products **7** and **8** could not be isolated. An aqueous solution of iodine also failed to produce the expected glycosides **7** and **8** in good yields. This raised the possibility that there might be a complexation role of iodine with the unsaturated bond of the glycal **6**. The proton NMR spectra of a mixture containing glycal **6** and iodine (10 mol%) in $CDCl_3$ showed continuous change, particularly at the olefinic region of the glycal at room temperature. But, there was no change of the proton NMR spectra of the reaction mixture when glycal **6** was mixed with iodine (10 mol%) in the presence of potassium carbonate (20 mol%). These observations suggest an allylic isomerization of glycal **6** to an intermediate 2,3-dehydro sugar and a subsequent S_{N1} reaction is involved.[2,3] This is supported by the fact that only glycal **6** produced stereoselective diastereromeric products in good yield. The glycals **11** and **12** derived from D-galactose and D-glucose were not effective indicating the critical role of the protective groups and their strereochemistries (acetoxy and benzyl ether) in this type of reaction. The stereochemistry of compounds **6** and **12** is identical, only the protective groups are different. This result indicated that the presence of an acetoxy functionality at C_4 of the sugar moiety as a suitably oriented leaving group is necessary for effective glycosylation. The glycal **11** derived from D-galactose has a differently oriented acetoxy functionality at C_4 of the sugar unit; it failed to produce the desired diastereomeric products. Therefore, the stereochemistry of the substituent at C_4 of the sugar moiety is crucial for the success of this reaction.[2,3] An anchimeric assistance by the acetoxy group in C_4 of **6** favored the departure of the C_3 acetoxy group of the glycal and thereby facilitated the reaction. The possibility of anchimeric assistance by the 4-acetoxy group in glucose derivatives was first suggested by Ferrier. This assistance could be prevented using nonparticipating protecting groups at C_4.[3d] According to the previous literature, galactal derivatives can also undergo Ferrier rearrangement under special conditions; anomalous behavior is observed under standard conditions.[22c] In conformity with this hypothesis, the importance of leaving group properties are also observed in the present study. The glycal that has a benzyl protecting group **12** proved to be ineffective; this supports earlier observations.

The two diasteromeric glycosides **7** and **8** were separated by column chromatography over silica gel. Then the sugar group of **7** and **8** was removed by mild aqueous hydrochloric acid treatment to afford the enantiomeric β-lactams **11** and **12**. β-Lactams **11** and **12** were converted to their respective acetates **13** and **14** following usual method. β-Lactam **13** was found to be enantiomerically pure as revealed by ^1H NMR spectroscopy using an optically active shift reagent.[24] This NMR study further confirmed that the compounds **13** and **14** are mirror images of each other (Scheme 4).

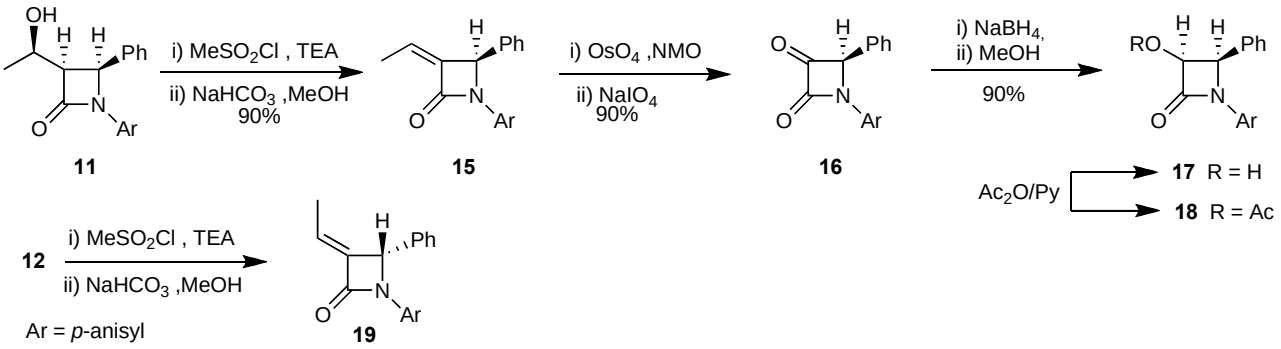
While this method provided two enantiomeric forms of β-lactams (**11** and **12**; **13** and **14**), determination of their absolute stereochemistry was not straight forward. To determine the absolute stereochemistry of the β-lactams **13** and **14**, a highly efficient method was adopted. The hydroxy-β-lactam **11** was converted

to the olefin **15** in good yield by a two-step sequence of mesylation and elimination. The formation of



Scheme 4

olefin as depicted in structure **15** established the stereochemistry of the hydroxy group at the side chain and the hydrogen at the C_3 of the β-lactam ring.[25] The olefin **15** on osmium-catalyzed dihydoxylation and subsequent oxidative cleavage of the intermediate diol (with sodium periodate) produced the 3-keto-β-lactam **16** in 80% yield. The keto β-lactam **16** was then reduced to the *cis*-hydroxy-β-lactam **17**. The optical rotation of this *cis* hydroxy β-lactam **17** was compared with the known authentic sample and the absolute stereochemistry was deduced.[9a-b] The hydroxy β-lactam **17** was converted to the acetate **18** by a standard method. The absolute stereochemistry was further confirmed using the acetate **18**. Proton NMR studies of **18** using a chiral shift reagent[24] and comparing literature data established the stereostructure of **11** as shown. A similar reaction using **13** afforded **19** (Scheme 5). Furthermore, this sequence of reactions established the absolute stereochemistry of all the compounds **11**, **12**, **13** and **14**.



Scheme 5

CONCLUSION

In conclusion, a room temperature reaction of (±)-3-hydroxyethyl-4-*p*-methoxyphenyl-2-azetidinone (**5**) with glycal **6** in the presence of iodine has been developed for producing separable α-glycosides **7** and **8** which can be cleaved to **11** and **12** by acid-induced reactions. The condition of the experiment is very mild. The absolute stereochemistry of the products **11** and **12** has been confirmed by physicochemical

correlation studies with known authentic compound described earlier. Aromatic substituent at the 4-position of such β-lactams can be oxidized to generate a carboxyl group. The β-lactams **11** and **12** can therefore, serve as chiral intermediates for thienamycin (**1**) antibiotic and related compounds. The glycosylation reaction of alcohol conducted with environmentally benign and simple iodine-catalyzed reactions can be used for increasing the hydrophilicity of these types of β-lactam molecules and for providing an easy access to additional functional groups by modification of the carbohydrate component.

EXPERIMENTAL PROCEDURE

General Methods. All of the solvents and reagents were obtained from commercial sources and used without purification. Reactions were monitored by TLC using pre-coated silica gel aluminum plates containing a fluorescence indicator. Chemical shifts of ^{1}H NMR spectra were given in parts per million with respect to TMS, and the coupling constant J was measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). ^{1}H NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra were expressed as wave numbers (cm^{-1}). For the preparation of the racemic **5**, see reference 16.

Glycosylation of racemic alcohol 5:

To a solution of the β-lactam (**5**) (3 g, 10.1 mmol) and tri-*O*-acetyl- D-glycal (**6**) (4.1 g, 15.1 mmol) in dry THF (40 mL) was added iodine (1.5 mmol). The reaction mixture was stirred at rt for 40 h. The aqueous mixture was then extracted with EtOAc (3 x 20 mL), washed with aqueous sodium thiosulfate solution, saturated aqueous $NaHCO_3$ solution (10 mL), brine (2 x 20 mL) and dried over Na_2SO_4. After evaporation of the solvent, crude product was chromatographed over silica gel using EtOAc-hexane (20:80) as the eluant. The pure product **7** was obtained by crystallization from EtOAc-hexane (35%), mp 137-138 °C; IR (CH_2Cl_2): 1740 cm^{-1}; ^{1}H NMR: 7.5-6.7 (m, 9H), 5.75 (s, 1H), 5.65 (m, 1H), 5.55 (d, *J* = 5.79 Hz, 1H), 4.55 (s, 1H), 4.10 (m, 4H), 3.75 (m, 1H), 3.74 (s, 3H), 3.60 (m, 1H), 2.05 (s, 3H), 2.0 (s, 3H), 1.10 (d, *J* = 6.16 Hz, 3H); Anal. Calcd for $C_{28}H_{31}NO_8$: C, 65.99; H, 6.13; N, 2.74. Found: C, 66.21; H, 6.18; N, 2.80. The other diastereomer (**8**) was isolated as an oil (30%), IR (CH_2Cl_2): 1740 cm^{-1}; ^{1}H NMR: 7.39-7.21 (m, 7H), 6.84-6.77 (m, 2H), 5.98-5.72 (m, 2H), 5.57-5.51 (m, 1H), 5.2 (d, *J* = 5.80 Hz, 1H), 5.14 (s, 1H), 4.58-3.99 (m, 3H), 3.76 (s, 3H), 3.65-3.61 (m, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 0.86 (d, *J* = 6.15 Hz, 3H); Anal. Calcd for $C_{28}H_{31}NO_8$: C, 65.99; H, 6.13; N, 2.74. Found: C, 66.30; H, 6.38; N, 2.92.

Hydrogenation of Diastereomeric Glycosides 7 and 8.

β-Lactam **7** (200 mg, 0.39 mmol) was dissolved in absolute EtOH (5 mL). Ammonium formate (200 mg) and 10% Pd-C (50 mg) were added to this solution and the mixture was refluxed for 15 min. The catalyst was then filtered and the EtOH was evaporated. The oily residue was purified by column

chromatography using EtOAc-hexane (1:2) as the eluent to afford **9**, 180 mg; IR (CH_2Cl_2): 1735, 1700 cm^{-1}; ^1H NMR: 7.34-7.23 (m, 7H), 6 80 (d, *J* = 8.98 Hz, 2H), 5.15 (d. *J* = 5.74 Hz, 1H), 4.65 (m, 1H), 4.40 (brs, 1H), 4.10 (m, 1H), 4.00 (m, 1H), 3.90 (m, 1H), 3.75 (s, 3H), 3.70 (m, 1H), 3.60 (dd, J_1 = 6.43 Hz and J_2 = 13.44 Hz, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 1.90-1.88 (m, 2H), 1.7-1.62 (m, 2H), 1.10 (d, *J* = 6.19 Hz, 3H); Anal. Calcd for $C_{28}H_{33}NO_8$: C, 65.73; H, 6.50; N, 2.73. Found: C, 65.62; H, 6.43; N, 2.83.

The above reaction was repeated in a similar way as described for **8** to obtain **10**; IR (CH_2Cl_2): 1740, 1710 cm^{-1}; ^1H NMR: 7.36-7.22 (m, 7H), 6.80 (d, *J* = 8.l1 Hz, 2H), 5.10 (d, *J* = 5.90 Hz, 1H), 4.85 (s, 1H), 4.65 (m, 1H), 4.30 (m, 1H), 3.95 (m, 2H), 3.80 (m, 4H), 3.78 (s, 3H), 3.65 (dd, J_1 = 5.89 Hz and J_2 = 9.16 Hz, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 2.00-1.95 (m, 2H), 1.85-1.80 (m, 2H), 0.85 (d, *J* = 5.94 Hz, 3H); Anal. Calcd for $C_{28}H_{33}NO_8$: C, 65.73; H, 6.50; N, 2.73. Found: C, 65.90; H, 6.23; N, 2.71.

General Procedure for Catalytic Transfer Hydrogenation Reaction.

We found the following protocol to be safe for conducting catalytic transfer hydrogenation. Caution was exercised, however, since some of the catalysts are pyrophoric; also mixtures of hydrogen and air can cause an explosion. An unmodified domestic microwave oven (600-100 W) was placed in a hood. The reaction vessel was a beaker or an Erlenmeyer flask of fairly large size. A beaker of water was placed near this reaction vessel to serve as a "heat sink" to provide a finer control on the amount of microwave energy input into the hydrogenation mixture. The purpose of keeping water was to use microwave energy very efficiently and thereby reduce the amount of energy absorbed by the reaction mixture. The approximate amount of water to be used was determined by a trial run involving only the solvent but without the catalyst.

The temperature of the reaction mixture was raised to 110–120 ^oC in about 3 min. The catalyst was quickly introduced into the reaction vessel and covered with the solvent ethylene glycol (bp 198 ^oC) and made into a slurry by gentle swirling motion of the beaker or the conical flask. The compound to be reduced was mixed with the solvent and then added to the reaction vessel. The hydrogen donor ammonium formate was added next. Microwave irradiation for the predetermined period of time to reach a temperature of 110–130 ^oC was applied. The microwave oven door was opened, and the temperature of the reaction mixture checked to be in the desired range.

The oven door was then closed and irradiation resumed for another 3–4 min. The reaction vessel was removed from the oven after the microwave oven was switched off. Careful decantation of the reaction mixture after cooling followed by the addition of glycol to the reaction vessel would preserve the catalyst for the next experiment.

It is customary in our laboratory to place a filter funnel on top of the reaction vessel to prevent any accidental spillage. After the hydrogenation, the reaction mixture was cooled and then filtered. The

filtrate was diluted with water and extracted with ethyl acetate, and the organic layer was washed with water. Evaporation of the solvent from the organic layer (dried over anhydrous Na_2SO_4) followed by crystallization gave the pure product in 90% yield. We observed that the optimal ratio of the catalyst (10% Pd/C) to substrate is 0.3:1 by weight for each reducible group. Five equivalents of ammonium formate for each reducible group gave good results.

Hydrochloric Acid-Induced Cleavage of the Diastereomeric Glycosides 7 and 8:

To a solution of the glycosides **7** (1.5 g. 2.94 mmol) in THF (20 mL) was added aqueous HCl (1:1, 6 mL). The mixture was stirred for 8 h at rt, the acid was then neutralized with saturated aqueous $NaHCO_3$ solution and most of the THF was evaporated under reduced pressure. The residue was extracted with EtOAc (3 x 20 mL), washed with brine (2 x 10 mL), dried with Na_2SO_4 and evaporated to give crude **13** as a semi solid mass. This was crystallized from EtOAc-hexane, 90% yield, mp 150-151 °C, IR (CH_2Cl_2): 3650, 1735 cm^{-1}; ^1H NMR: 7.75-7.19 (m, 7H), 6.81-6.71 (m, 2H), 5.18 (d, J = 5.82 Hz, 1H), 3.70-3.68 (m, 1H), 3.65 (s, 3H), 3.50 (dd, J_1 = 5.84 Hz and J_2 = 8.4 Hz, 1H), 2.90 (d, J = 1.85 Hz, 1H), 0.95 (d, J = 6.10 Hz, 3H); Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.90; H, 6.34; N, 4.83.

The above reaction was repeated with the glycoside **8** (1.5 g). The pure product **14** was isolated through extraction and crystallization, 90% yield, mp 149-150 ° C; IR (CH_2Cl_2): 1735 cm^{-1}; ^1H NMR: 7.70-7.20 (m, 7H), 6.82-6.73 (m, 2H), 5.15 (d, J = 81 Hz, 1H), 3.80, -3.78 (m, 1H), 3.75 (s, 3H), 3.50 (dd, J_1 = 5.87 Hz and J_2 = 8.38 Hz, 1H), 2.40 (s, 1 H), 0.90 (d, J = 6.07 Hz, 3H); Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.86; H, 6.34; N, 4.92.

Acetylation of the Hydroxy β-lactams 13 and 14.

To a solution of the β-lactam **13** (100 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.2 mL), followed by acetic anhydride (0.2 mL) at rt and the mixture was stirred for 3 h. After evaporation of the solvent and reagent, the crude product was passed through a wide column of florisil (4g) using EtOAc-hexanes (20:80) as eluent to afford **15**, 102 mg, 91%; mp 143°C; IR (CH_2Cl_2): 1730, 1700 cm^{-1}; ^1H NMR: 7.35-7.19 (m, 7H), 6.78 (d, J = 9.00 Hz, 2H), 5.20 (d, J = 5.99 Hz, 1H), 4.85 (m, 1H), 3.75 (s, 3H), 3.65 (m, 1H), 1.90 (s, 3H), 1.20 (d, J = 6.39 Hz, 3H).

The above reaction was repeated in a similar way with **14**. After passing through a column of florisil, pure product **(16)** was isolated as a solid, mp 131 °C ; IR (CH_2Cl_2): 1730, 1700 cm^{-1}; ^1H NMR: 7.33-7.21 (m, 7H), 6.77 (d, J = 9.00 Hz, 2H), 5.15 (d, J = 5.99 Hz, 1H), 4.80 (m, 1H), 3.75 (s, 3H), 3.60 (m, 1H), 1.80 (s, 3H), 1.15 (d, J = 6.4 Hz, 3H).

Synthesis of 3-Keto-4-phenyl-*N*-*p*-anisyl-2-azetidinone (16)

To a solution of alcohol **11** (2 mmol) in dry CH_2Cl_2 (40 mL) was added methanesulfonyl chloride (2.3 mmol) and triethylamine (5 mmol) at rt. The reaction mixture was kept at rt overnight. The reaction

mixture was then washed with HC1 (5%, 2 x 10 mL), aqueous $NaHCO_3$ solution (5%, 2 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4) and the solvent evaporated. To the crude mesylate thus obtained were added dry CH_3OH (10 mL) and anhydrous $NaHCO_3$ (500 mg) and the reaction mixture was refluxed for 2 h. The reaction mixture was filtered and MeOH was evaporated. To the residue, EtOAc (30 mL) was added and the solution washed thoroughly with H_2O (3 x 10 mL), dried (Na_2SO_4) and evaporated.

A solution of the 3-alky1idene-β-lactam **15** (1.5 mmol) in *t*-BuOH/H_2O (7:1, 80 mL), *N*-methyl-morpholine-*N*-oxide (1.5 mmol) and OsO_4 (0.08 mmol) was stirred at rt for 16 h. Aqueous $NaHSO_3$ solution (50%, 5 mL) was then added and the mixture was stirred for 30 min. The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (2 x 10 mL), dried (Na_2SO_4) and the solvent evaporated. The crude product was dissolved in MeOH-H_2O (4:1, 15 mL) and $NaIO_4$ (2.0 mmol) was added. The reaction mixture was stirred at rt for 2 h and filtered. Most of the MeOH was evaporated and the residue extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried and solvent evaporated. The crude product on crystallization afforded the 3-keto β-lactam **16** (70%), mp 131 °C.

Synthesis of α-Hydroxy-4-phenyl-*N*-*p*-anisyl-2-azetidinone (17):

To a solution of the keto β-lactam **16** (50 mg) in dry MeOH (10 mL) was added $NaBH_4$ (50 mg) at 0-5 °C and the mixture was stirred for 1h. Water (5mL) was added to it and most of the MeOH evaporated under reduced pressure. The residue was extracted with EtOAc (2 x 15 mL), dried, and evaporated. The crude product on crystallization afforded pure **17**, mp 214 °C; $[\alpha]_D^{23}$ -179° (c 1.0, MeOH). A portion of this compound was acetylated with acetic anhydride in the presence of pyridine to give **18**. ^{1}H NMR study in the presence of chiral shift reagent established the absolute stereochemistry and found to be identical with the compound synthesized ear1ier; mp 134 °C, IR (Nujol): 3400, 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 7.39 (m, 5H), 7.21 (d, 2H), 6.77 (d, 2 H), 5.10 (d, *J* = 2.36 Hz, 1H), 4.35 (brs, 1H), 3.73 (s, 3H) 3.12 (dd, *J* = 2.39, 4.83 Hz, 1H), 1.35 (d, *J* = 6.37 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 165.2, 155.9, 138.0, 131.0, 129.1, 128.2, 126.0, 118.4, 114.2, 67.0, 64.9, 56.8, 55.3, 21.5; CIMS (CH_4 gas) m/z 298 $(M+H)^+$; Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.61; H, 6.49; N, 4.87.

E-1-*p*-Anisyl-3-ethylidene-4-phenylazetidin-2-one-(15) and Z-1-*p*-Anisyl-3-ethylidene-4-phenyl-azetidin-2-one (19): To a solution containing the alcohols **11** and **12** (1.68 mmol) and TEA (5 mmol) in CH_2Cl_2 (50 mL) was added methanesulfonyl chloride (2.2 m mol) at rt. The reactants were kept overnight and filtered. The filtrate was washed with dilute HCl (5%, 2 x 10 mL), aqueous $NaHCO_3$ (5%, 2 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4) and solvent evaporated. To the crude mesylates, thus obtained, were added dry MeOH (10 mL) and anhydrous $NaHCO_3$ (500 mg) and the reaction mixture was refluxed for 2 h. The title compounds were isolated after flash chromatography followed by crystallization from Et_2O. **15:** yield 90%, mp 157 °C; IR (CH_2Cl_2): 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.5-6.80 (m, 9H), 6.33 (q, d, *J* = 7.2, 1.42 Hz), 5.44 (s, 1H), 3.77 (s, 3H), 1.62 (d, *J* = 7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 161.0,

155.9, 142.8, 136.8; 131.45, 129.0, 128.6, 127.1, 122.8, 118.1, 114.3, 62.9, 55.4; 13.26; CIMS (CH_4 gas) m/z: 280 $(M+H)^+$; Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.36; H, 6.00; N, 4.93.

19: yield 15%, mp 128 °C; IR (CH_2Cl_2): 1740 cm^{-1}; ^1H NMR ($CDCl_3$): 7.35-7.23 (7H, m), 6.77 (d, 2H), 5.59 (v, d, J = 7.23, 1.20 Hz),3.74 (s, 3H), 2.07 d, 7.35 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 162.0; 156.6, 142.1, 138.7; 132.0, 128.9, 128.4, 126.5, 126.2, 118.1, 114.3, 62.7, 55.4, 14.6; CIMS (CH_4, reagent gas) m/z: 280 (M+H); Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.39, H, 6.13; N, 5.01 Found: C, 77.16; 11, 6.01; N, 4.83.

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