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 rearrangement2,3 is still considered to be one of the most attractive methods for the preparation of glycosides. Many Lewis acids4 and acidic-supports5 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-glycosides 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. In the course of our continuing studies on antibiotics and anticancer agents, we have synthesized and studied medicinal activities of several β-lactams. In an extension of iodine-catalyzed glycosylation of alcohol, we have studied chiral resolution of a racemic alcohol that is present in thienamycin side chain for obtaining both enanatiomers of this important antibiotic. The strategy is to prepare two separable diastereomeric O-glycosides by the Ferrier rearrangement 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. PS-5 and carpetimycin also belong to this family of antibiotics. Various synthetic methods are appeared for the preparation of thienamycin. Most of these methods require optically pure 3-(1-hydroxyethyl)-4-acetoxy-2-azetidinone (2) as one of the starting materials. Since enantiomers differ in their biological properties, availability of both enantiomeric forms of this compound is highly desirable. One way to obtain both enantiomers is to perform an easy chiral 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. The reaction of the dianion of (±)-ethyl 3-hydroxy-butyrte (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.

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 C₄ afforded a propionamide derivative as a

![Scheme 2](image-url)
result of the $N_1$-$C_4$ bond fission.\textsuperscript{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.\textsuperscript{9a-b,21} A higher coupling constant (8-10 Hz) was expected with a $\beta$-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 $\beta$-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 borontrifluoride etherate and stannic chloride were used in the Ferrier rearrangement of several different types alcohols with varying success.\textsuperscript{22} Ferrier rearrangement with the neutral catalysts $N$-iodosuccinimide, $N$-bromosuccinimide and iodonium dicollidinium perchlorate was also used for this purpose.\textsuperscript{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 $\beta$-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.

Scheme 3
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 CDCl3 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. This is supported by the fact that only glycal 6 produced stereoselective diasteromeric 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 stereochemistries (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 C4 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 C4 of the sugar unit; it failed to produce the desired diastereomeric products. Therefore, the stereochemistry of the substituent at C4 of the sugar moiety is crucial for the success of this reaction. An anchimeric assistance by the acetoxy group in C4 of 6 favored the departure of the C3 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 C4. According to the previous literature, galactal derivatives can also undergo Ferrier rearrangement under special conditions; anomalous behavior is observed under standard conditions. 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. 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 straightforward. 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 olefin as depicted in structure 15 established the stereochemistry of the hydroxy group at the side chain and the hydrogen at the C3 of the β-lactam ring. The olefin 15 on osmium-catalyzed dihydroxylation 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. 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 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 4**

**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$_2$SO$_4$. 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$_2$Cl$_2$): 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$_2$Cl$_2$): 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 (CH₂Cl₂): 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, J₁ = 6.43 Hz and J₂ = 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 C₂₈H₃₃NO₈: 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 (CH₂Cl₂): 1740, 1710 cm⁻¹; ¹H NMR: 7.36-7.22 (m, 7H), 6.80 (d, J = 8.11 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, J₁ = 5.89 Hz and J₂ = 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 C₂₈H₃₃NO₈: 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 °C in about 3 min. The catalyst was quickly introduced into the reaction vessel and covered with the solvent ethylene glycol (bp 198 °C) 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 °C 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$_2$SO$_4$) 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$_2$SO$_4$ 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$_2$Cl$_2$): 3650, 1735 cm$^{-1}$; $^1$H 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$_2$Cl$_2$): 1735 cm$^{-1}$; $^1$H 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, 4.92.

**Acetylation of the Hydroxy β-lactams 13 and 14.**

To a solution of the β-lactam 13 (100 mg, 0.33 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$): 1730, 1700 cm$^{-1}$; $^1$H 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$_2$Cl$_2$): 1730, 1700 cm$^{-1}$; $^1$H NMR: 7.33-7.19 (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$_2$Cl$_2$ (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 HCl (5%, 2 x 10 mL), aqueous NaHCO₃ solution (5%, 2 x 10 mL), brine (2 x 10 mL), dried (Na₂SO₄) and the solvent evaporated. To the crude mesylate thus obtained were added dry CH₃OH (10 mL) and anhydrous NaHCO₃ (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 H₂O (3 x 10 mL), dried (Na₂SO₄) and evaporated.

A solution of the 3-alkylidene-β-lactam 15 (1.5 mmol) in t-BuOH/H₂O (7:1, 80 mL), N-methylmorpholine-N-oxide (1.5 mmol) and OsO₄ (0.08 mmol) was stirred at rt for 16 h. Aqueous NaHSO₃ 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 (Na₂SO₄) and evaporated. The crude product was dissolved in MeOH-H₂O (4:1, 15 mL) and NaIO₄ (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 NaBH₄ (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; [α]D₂⁰ -179° (c 1.0, MeOH). A portion of this compound was acetylated with acetic anhydride in the presence of pyridine to give 18. ¹H NMR study in the presence of chiral shift reagent established the absolute stereochemistry and found to be identical with the compound synthesized earlier; mp 134 °C, IR (Nujol): 3400, 1735 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): 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); ³¹C NMR (CDCl₃) 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 (CH₄ gas) m/z 298 (M+H)+;


E-1-p-Anisyl-3-ethylidene-4-phenylazetidin-2-one-(15) and Z-1-p-Anisyl-3-ethylidene-4-phenylazetidin-2-one (19): To a solution containing the alcohols 11 and 12 (1.68 mmol) and TEA (5 mmol) in CH₂Cl₂ (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 NaHCO₃ (5%, 2 x 10 mL), brine (2 x 10 mL), dried (Na₂SO₄) and solvent evaporated. To the crude mesylates, thus obtained, were added dry MeOH (10 mL) and anhydrous NaHCO₃ (500 mg) and the reaction mixture was refluxed for 2 h. The title compounds were isolated after flash chromatography followed by crystallization from Et₂O. 15: yield 90%, mp 157 °C; IR (CH₂Cl₂): 1740 cm⁻¹; ¹H NMR (CDCl₃): 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); ³¹C NMR (CDCl₃) 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; CIMS (CH₄ gas) m/z: 280 (M+H)⁺; Anal. Calcd for C₁₈H₁₇O₂N: 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 (CH₂Cl₂): 1740 cm⁻¹; ¹H NMR (CDCl₃): 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); ¹³C NMR (CDCl₃) 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 (CH₄, reagent gas) m/z: 280 (M+H); Anal. Calcd for C₁₈H₁₇O₂N: C, 77.39, H, 6.13; N, 5.01. Found: C, 77.16; H, 6.01; N, 4.83.

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REFERENCES AND NOTES


24. Chiral praseodymium trans-3-(heptafluoropropylhydroxymethylene)camphorate was used as shift reagent in the NMR study.