Practical synthesis of 4-aryl- and 4-heteroarylazetidin-2-ones: applications in the synthesis of the Taxol® side chain[1]

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Received April 4, 1994

ALLAN W. REY, ROBERT DROGHINI, JAMES L. DOUGLAS, PURUSHOTHAM VEMISHETTI, SUSAN D. BOETTGER, SAIBABA RACHA, and JOHN L. DILLON. Can. J. Chem. **72**, 2131 (1994).

A convenient, high-yielding procedure has been developed for the kilogram-scale synthesis of (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one (**3**), a β-lactam that has been used in the semi-synthesis of Taxol®. The Staudinger reaction between hydrobenzamide (**5**) and acetoxyacetyl chloride in the presence of a base provided the α-benzylideneiminotoluene protected β-lactam **8**. Without isolation of the intermediate β-lactam, the protecting group was removed under various reductive or hydrolytic conditions. The overall yields were about 80%. The synthesis of other (±)-*cis*-4-aryl- and 4-heteroarylazetidin-2-ones by this methodology has also been accomplished. These compounds are of value for the synthesis of 3′-Taxol® side-chain analogs and their preparation demonstrates the generality of this approach.

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On a mis au point une méthode donnant d'excellents rendements et appropriée pour la synthèse de kilogrammes de la (±)-*cis*-3-acétoxy-4-phénylazétidin-2-one (**3**), un β-lactame qui peut être utilisé dans la semi-synthèse du Taxol®. La réaction de Staudinger entre l'hydrobenzamide (**5**) et le chlorure d'acétoxyacétyle, en présence d'une base, conduit au β-lactame **8** protégé par un α-benzylidèneiminotoluène. Sans procéder à l'isolement du β-lactame intermédiaire, on a enlevé le groupe protecteur sous diverses conditions de réduction ou d'hydrolyse. Les rendements globaux sont d'environ 80%. Utilisant cette méthodologie, on a aussi réalisé la synthèse d'autres (±)-*cis*-4-aryl- et 4-hétéroarylazétidin-2-ones. Ces composés sont utiles pour la synthèse d'analogues du 3′-Taxol® portant des chaînes latérales différentes et leur préparation démontre la généralité de cette approche.

[Traduit par la rédaction]

Introduction

Taxol® (paclitaxel, **1**), a potent antineoplastic agent isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), has proven to be very effective for the treatment of various cancers (for recent reviews, see ref. 1). The labour-intensive extraction/purification procedure required and the limited supply of yew trees have motivated extensive research into obtaining paclitaxel from alternative sources. An early solution was supplied by Greene and Guéritte-Voegelein (2) who prepared paclitaxel semi-synthetically by coupling the hydroxyl at the C-13 position of appropriately protected 10-deacetylbaccatin III (**2**) with a derivative of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine. The needles of the ornamental bush *T. baccata* provide a renewable and relatively abundant source (1 g/kg) of the diterpenoid **2**. More recently, Holton (3) patented a method for the semi-synthesis of paclitaxel by acylating protected baccatin III with a derivative of *cis*-3-hydroxy-4-phenylazetidin-2-one. A semi-synthetic route of this type is expected to be the source of most paclitaxel by 1994 (4). A key intermediate in syntheses of the paclitaxel side chain by Holton (3) and others (5) was (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one (**3**). Many other workers have used β-lactams as paclitaxel side-chain synthons (6).

The procedure used by Holton (3) for the preparation of **3** is depicted in Scheme 1. On laboratory scales (i.e., <100 g), this procedure is acceptable. However, for production purposes (i.e., kilogram-scale), the ceric ammonium nitrate (CAN) oxidative removal of the *para*-methoxyphenyl (PMP) group on **4** becomes problematic due to the large quantities of CAN required for the reaction.[3] Other more cost-effective and convenient approaches to **3** were examined. Also, paclitaxel's unique biological profile (8) combined with its unusual chemical architecture make it an important lead for a new series of chemotherapeutic agents. Thus, a route to **3** that could be generalized to allow the synthesis of side-chain analogs of **1** would be desirable.

Results and discussion

The use of hydrobenzamide (**5**) as the imine precursor in the Staudinger reaction (for a recent review, see ref. 9) was reported in 1969 by Wells and Lee (10). Thus, the [2 + 2] cycloaddition reaction between hydrobenzamide and the ketene derived from azidoacetyl chloride furnished, after deprotection, (±)-*cis*-3-azido-4-phenylazetidin-2-one (**7**, Scheme 2). Using a slightly modified Staudinger reaction but identical deprotection conditions, Manhas et al. (11) prepared the same compound in 1981. Both groups employed 10% HCl (aq) for the deprotection and isolated the intermediate hydrochloride salt (**6**).

Applying similar methodology to the preparation of (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one (i.e., using acetoxyacetyl

[1]A subject patent application on this process was filed with the U.S.A. Patent Office, April 23rd, 1993 (*N*-Substituted 2-Azetidinones, USSN No. 08/052,434). An addendum was filed on December 13th, 1993 (USSN No. 08/165,610).

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[3]It is pertinent to note that, for *N*-dearylations of this type (7), the yields are often modest (~60%).

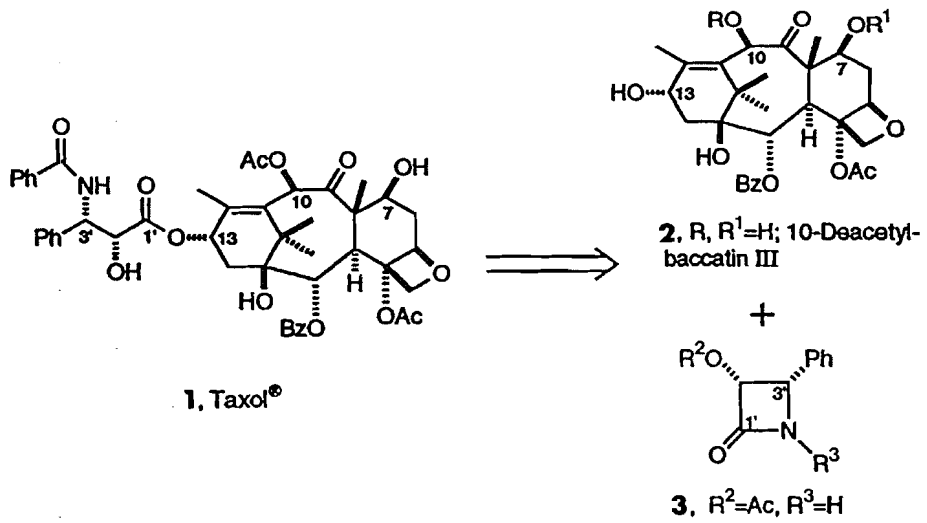
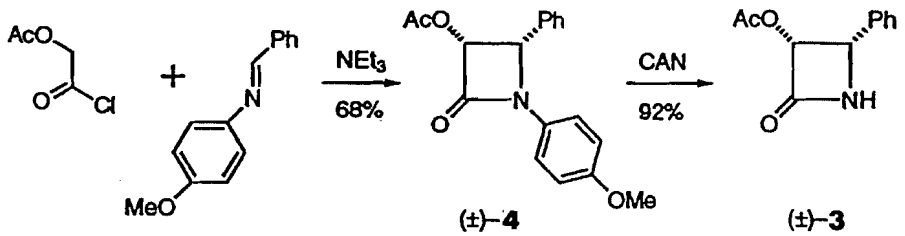
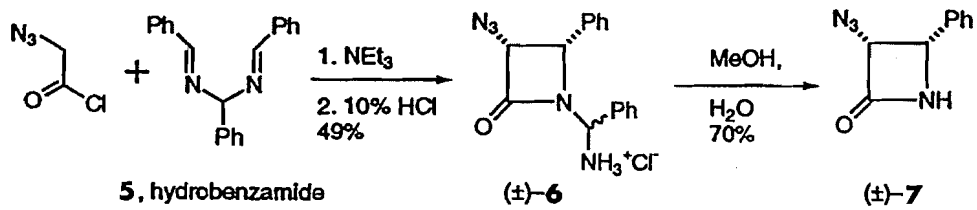


FIG. 1



SCHEME 1



SCHEME 2

chloride instead of azidoacetyl chloride) gave low yields of product (13%), presumably due to the instability of the β-lactam ring and the 3-acetoxy group to aqueous HCl. However, it was noted that the intermediate α-benzylideneiminotoluene-(BIT) protected azetidin-2-one **8** (Scheme 3) could be isolated in acceptable quantities. An investigation was undertaken to find better methods for BIT-group deprotection, relative to the one employed previously (10, 11). Other objectives included the optimization of the Staudinger reaction and the development of a telescoped method that would avoid isolation of the intermediate BIT-lactam.

Synthesis of BIT-lactam 8

The starting material, hydrobenzamide, is commercially available (Lancaster). For this work, it was readily prepared in 250-g batches by condensing benzaldehyde with 30% ammonium hydroxide in 2-propanol (20°C, 3 d, 97%). The product was then collected by filtration. This method is a modification of a preparation described by Nicholson and Portez (12).

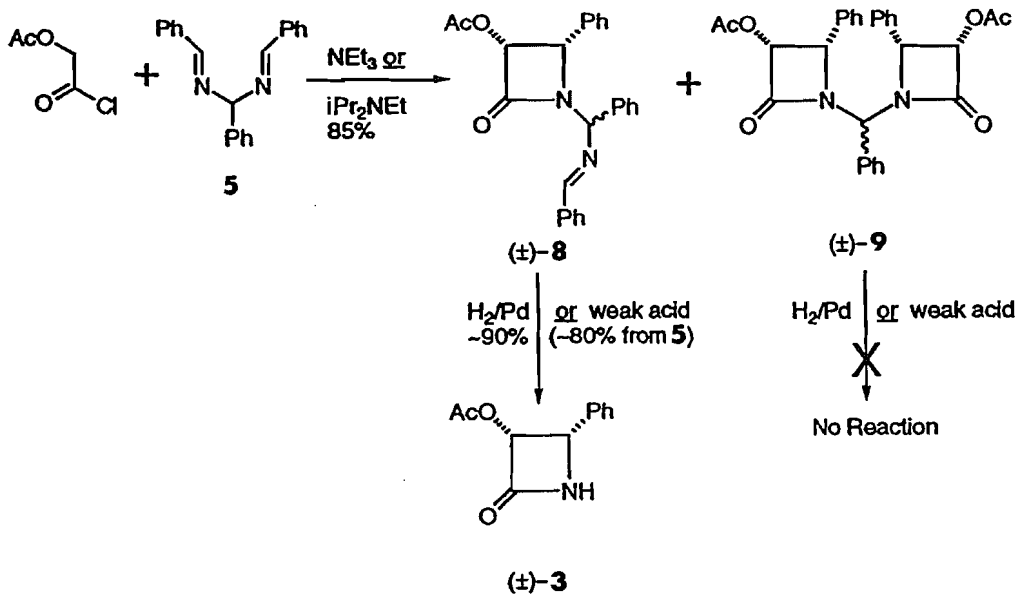
The reaction between hydrobenzamide and acetoxyacetyl chloride in the presence of triethylamine afforded, after an aqueous extractive work-up, predominantly the BIT-protected azetidin-2-one **8** as a mixture of diastereomers (^{1}H nmr; 85% by hplc) (Scheme 3). No (±)-*trans*-3,4-azetidin-2-one was detected by hplc and ^{1}H nmr comparison with the authentic compound (6*c*). The only other clearly identifiable side-products were the *bis*-lactam **9**[4] (~9%, hplc) together with small amounts of free azetidin-2-one **3** and benzaldehyde.

By optimizing the amount of acetoxyacetyl chloride (AAC), the rate of addition of AAC, and the reaction temperature, it was possible to minimize the amount of *bis*-lactam **9** formed to <1.5% (hplc) and to maximize the amount of BIT-lactam (91%) (see experimental section for optimized reaction conditions). Suitable solvents were dichloromethane, toluene, and ethyl acetate. Both triethylamine and *N,N*-diisopropylethylamine (Hünig's base) were acceptable as bases; however, Hünig's base allowed the Staudinger reaction to be accomplished at lower temperatures (−20°C vs. 5°C) and in shorter reaction times (5 h vs. 18 h).

Deprotection of BIT-lactam 8

As mentioned, 10% HCl (aq) has been used (10, 11) for deprotection of the adduct formed between azidoacetyl chloride

[4]The *bis*-lactam **9** was formed by reaction of 2 equivalents of acetoxyacetyl chloride with 1 equivalent of hydrobenzamide. The methods that were used to convert **8** into **3** failed to convert **9** into **3**.



SCHEME 3

and hydrobenzamide. Deprotection of **8** using similar conditions (1% and 10% HCl) provided low yields of product. The ^{1}H nmr spectrum of the crude reaction mixture indicated a mixture of open-chain acids with and without the acetoxy moiety.

Initial attempts to purify the BIT-lactam **8** by silica gel chromatography gave mainly the deprotected azetidin-2-one **3**.[5] The lability of the BIT group to silica gel suggested that other higher yielding methods of deprotection might be available. Indeed, various reagents were found to be significantly more effective than aqueous HCl and are described in the experimental section. The deprotection protocols that were most amenable to scale-up were catalytic hydrogenation (e.g., Pd/C or $Pd(OH)_2$, Method 1), weak-acid hydrolysis (e.g., 75% aqueous acetic acid, Method 2), or 30% aqueous sodium bisulfite (Method 3). Reductive deprotection using sodium cyanoborohydride in methanol (23°C, 1 h) gave equivalent results on smaller scales. The overall isolated yields using the optimized deprotection conditions were in the 70–80% range.

This versatility in terms of deprotection is a valuable feature of the BIT group. It should, for example, be amenable to the synthesis of 3-substituted azetidin-2-ones, which may be sensitive to either acid hydrolysis or catalytic hydrogenation conditions.

Telescoping the sequence

In terms of operational simplicity, a telescoped procedure that would not require isolation of the BIT-lactam **8** was desirable. Thus, after the Staudinger reaction and aqueous extractive processing were complete, the organic layer was submitted to the deprotection conditions described above. For instance, when using the hydrogenation-mediated deprotection method (Method 1), the Staudinger reaction was performed in ethyl acetate. After the aqueous washings, the catalyst was added and the mixture hydrogenated using a Parr apparatus.[6] The catalyst was removed by filtration and the organic layer was washed with 1 *N* HCl to remove the dibenzylamine by-product as its hydrochloride salt. Subsequent concentration of the organic layer precipitated the desired azetidin-2-one **3**.

For the telescoped, weak-acid-mediated hydrolysis, the best option found was to perform the Staudinger reaction in dichloromethane followed by addition of an aqueous mixture of the desired acid (Method 2). Complete BIT-group removal was effected by warming the reaction mixture to ~40°C. The aqueous layer was then neutralized by addition of aqueous NaOH and, after phase separation, the product was precipitated out of the organic layer using heptane.

The Staudinger reaction was accomplished in ethyl acetate for the bisulfite-mediated deprotection (Method 3). After aqueous work-up, the organic layer was treated with aqueous sodium bisulfite at 50°C. Separation and concentration of the organic phase provided **3**.

In all cases, (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one was obtained as a white crystalline product of excellent purity (>99%, hplc). All of these reactions were performed on scales of at least 100 g of starting hydrobenzamide. For the acetic acid mediated hydrolysis, the telescoped sequence was performed on kilogram-scale without having an adverse effect on the yield or purity of **3** obtained.

The separation of the racemic intermediate **3** to give the enantiomeric side-chain precursor of paclitaxel (2′*R*,3′*S*) has been described by Holton (3) using optical resolution of the diastereomeric Mosher's esters of (±)-*cis*-3-hydroxy-4-phenylazetidin-2-one (formed at the 3-position after saponification of the acetoxy moiety). In addition, the kinetic resolution of **3** and derivatives of **3** using highly enantioselective and practical chemoenzymatic methods has been described by Sih et al. (5*a*) and Patel et al. (5*b*).

Analogs of the paclitaxel side chain

To demonstrate the generality of this hydrobenzamide methodology for construction of synthetically useful β-lactams (e.g., refs. 6*g*, 13) and the synthesis of potentially therapeutically useful 3′-paclitaxel side-chain analogs (refs. 6*j*, 6*k*, and 6*l*), a series of analogs of **3** were prepared (Table 1).

The requisite hydroanisamide, hydrofuramide, hydrothien-

[5]BIT-lactam **8** has since been purified by Florisil® chromatography.

[6]Other experiments have demonstrated that these hydrogenations may be performed using a H_2-filled balloon although the deprotection reaction was slower (reaction time ~2 d).

TABLE 1. 4-Analogs of (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one (**3**) prepared by the hydrobenzamide method

Compound	Overall yield (%)	Method of deprotection
(±)-*cis*-3-Acetoxy-4-*p*-methoxyphenylazetidin-2-one, **10**	75	Hydrogenation
(±)-*cis*-3-Acetoxy-4-(2′-furanyl)azetidin-2-one, **11**	61	Hydrogenation
(±)-*cis*-3-Acetoxy-4-(2′-thienyl)azetidin-2-one, **12**	75	Acetic acid
(±)-*cis*-3-Acetoxy-4-*p*-methylphenylazetidin-2-one, **13**	70	Bisulfite

amide, and hydrotoluamide were readily prepared in a manner similar to that described for hydrobenzamide (12). Acetoxyacetyl chloride was used as the ketene equivalent and the reactions were performed with inputs of at least 10 mmol of the starting imine.

Conclusions

A practical procedure that is suitable for the preparation of kilogram quantities of (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one (**3**) was developed. This compound has been used in the semi-synthesis of paclitaxel (3, 5). The key step was the Staudinger reaction between hydrobenzamide and acetoxyacetyl chloride. Subsequent removal of the BIT-protecting group was achieved by hydrogenation, and hydrolytic or reductive protocols.

In terms of many process aspects (processing volumes, cost of reagents, yields, etc.), this methodology is superior to the CAN oxidative removal of the PMP group used previously for the preparation of (±)-*cis*-3-acetoxy-4-phenylazetidin-2-one (3).

The generality of this protocol was demonstrated by the synthesis of several (±)-*cis*-3,4-substituted azetidin-2-ones. These compounds are of use for the synthesis of paclitaxel side-chain analogs. As well, hydrobenzamide methodology may be of general use for the improved synthesis of 4-aryl- or 4-heteroaryl-substituted β-lactams.

Experimental

Melting points were determined on a Büchi 510 melting point apparatus and are not corrected. The ^{1}H nuclear magnetic resonance (^{1}H nmr) spectra were taken on a Bruker AC200SY instrument operating at 200 MHz. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane. The ^{13}C nmr spectra were recorded on a Bruker AMX 400 instrument operating at 100.6 MHz. The carbon chemical shifts are quoted in parts per million (ppm) with reference to $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (39.6 ppm). Mass spectra (ms) were recorded on a Fisons VG Quattro Fast Ion Bombardment mass spectrometer. The infrared spectra (ir) were recorded on a Perkin–Elmer 781 infrared spectrophotometer. Ultraviolet (uv) spectra were recorded on a Hewlett–Packard 8451A diode array spectrophotometer. Elemental analyses were performed by Bristol-Myers Squibb Pharmaceutical Research Institute, Analytical R&D, Syracuse. Solvents and reagents used were reagent grade. High-performance liquid chromatography (hplc) was performed on a Hewlett–Packard 1090 Series 2 system with a diode array detector at 220 nm. A 30 cm × 3.9 mm 10 μ-Bondapack C_{18} column was used. The eluent was 40:60 CH_3CN:0.01M KH_2PO_4 (pH 7.4). Karl-Fischer titrations were performed using a Metrohm 655 Dosimat – Karl-Fischer Automat titrator.

Telescoped preparations of (±)-cis-*3-acetoxy-4-phenylazetidin-2-one (3)*

Method 1. Hydrogenation over Pd/C with isolation of intermediate BIT-lactam 8

A. (±)-cis-*3-Acetoxy-1-[(phenyl)(phenylmethyleneimino)methyl]-4-phenylazetidin-2-one (8).* Triethylamine (16.8 mL, 121 mmol) was added to a solution of hydrobenzamide (**5**) (30.00 g, 101 mmol) in ethyl acetate (150 mL). With stirring and under a blanket of argon, this mixture was cooled to 5°C and a solution of acetoxyacetyl chloride (12.5 mL, 116 mmol) in ethyl acetate (300 mL) was added dropwise over 1.5 h. After 16 h at 5°C, the reaction mixture was allowed to warm to 20°C (1.5 h). The organic layer was washed successively with saturated aqueous NH_4Cl (2 × 120 mL), saturated aqueous $NaHCO_3$ (120 mL), and brine (120 mL). The BIT-lactam **8** was isolated at this stage by drying the organic phase over $MgSO_4$, filtering, and removing the solvent in vacuo. This provided the crude protected β-lactam **8** in quantitative yield as a red glassy solid; hplc purity (area): 87.9% (1:1 mixture of diastereomers). For purposes of characterization, this compound was purified by Florisil® chromatography (ethyl acetate – hexane (1:4)) and recrystallized from ethyl acetate – hexane to yield **8** as a white solid; hplc purity (area): 98.3%; ir ν_{max} (KBr): 1763 (C=O), 1641 (C=N), cm^{-1}; UV λ_{max} (methanol): 216, 252 nm; ^{1}H nmr ($CDCl_3$) δ: 8.45 (s, 1H, N=CH), 7.80–7.85 (m, 1H, Ph), 7.60–7.65 (m, 1H, Ph), 7.26–7.50 (m, 9H, Ph), 7.00–7.10 (m, 4H, Ph), 6.28 (s, 0.5H, NCHN), 6.23 (s, 0.5H, NCHN), 5.81 (d, J = 4.8 Hz, 0.5 H, H-3), 5.76 (d, J = 4.8 Hz, 0.5 H, H-3), 5.30 (d, J = 4.8 Hz, 0.5 H, H-4), 4.75 (d, J = 4.8 Hz, 0.5 H, H-4), 1.63 (s, 3H, CH_3CO); ms (FAB), *m/z*: 399 (M^+ + H, 4%), 294 (M^+ − PhCHN, 17%).

B. (±)-cis-*3-Acetoxy-4-phenylazetidin-2-one (3).* The crude BIT-lactam **8** from above was redissolved in ethyl acetate (500 mL) and carefully transferred, under a stream of argon, to a Parr flask containing 10% palladium on activated carbon[7] (6.00 g). This mixture was treated with hydrogen (4 atm; 1 atm = 101.3 kPa) for 20 h at which point the catalyst was removed by filtration through a pad of Celite®. The filter cake was slurried in ethyl acetate (200 mL), stirred (10 min), filtered, and rinsed with ethyl acetate (100 mL). The filtrates were combined and the organic layer was washed with 10% HCl (300 mL). Both layers were filtered to remove the white precipitate (dibenzylamine·HCl), which was rinsed with ethyl acetate (100 mL). The phases were separated and the organic layer was washed with another portion of 10% HCl (200 mL). The combined 10% HCl washes were re-extracted with ethyl acetate (200 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (300 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of 75 mL. This mixture was cooled to 4°C and the precipitated product isolated by filtration. The filter cake was washed with hexane (200 mL) to provide 16.1 g (78% overall yield from hydrobenzamide) of β-lactam **3** as white needles, mp 150–151°C; hplc purity (area): 99.8%; ir ν_{max} (KBr): 3210 (N-H), 1755, 1720 (C=O) cm^{-1}; UV λ_{max} (methanol): 218, 260 nm; ^{1}H nmr ($CDCl_3$) δ: 7.30–7.38 (m, 5H, Ph), 6.54 (br s, D_2O exchangeable, 1H, NH), 5.87 (dd, J = 2.7, 4.7 Hz, 1H, H-3), 5.04 (d, J = 4.7 Hz, 1H, H-4), 1.67 (s, 3H, CH_3CO); ^{13}C nmr (DMSO-d_6) δ: 168.6, 165.0, 135.9, 128.0, 127.9, 127.3, 78.0, 56.0, 19.7; moisture content (by KF): 0.17%. Anal. calcd. for $C_{11}H_{11}NO_3$: C 64.38, H 5.40, N 6.83; found: C 64.07, H 5.34, N 6.77.

Method 2. Hydrolysis with 75% acetic acid

To hydrobenzamide (100.0 g, 335 mmol) in dichloromethane (335

[7]Wet 10% Pd/C (50% water content) was used as catalyst with identical results.

mL) was added *N,N*-diisopropylethylamine (67.1 mL, 385 mmol). This mixture was cooled to −20°C under N_2 and a solution of acetoxyacetyl chloride (39.6 mL, 368 mmol) in dichloromethane (185 mL) was added dropwise over 5 h. After the reaction was complete (<5% hydrobenzamide by hplc), water (330 mL) was added in one portion and the temperature was increased to 5°C. The phases were separated and the aqueous layer was washed with another 100 mL of dichloromethane. The combined organic layers were treated with acetic acid (150 mL, 2.62 mol) and water (50 mL). The reaction mixture was stirred and warmed to reflux (~40°C). After about 4 h, the hydrolysis was judged complete (<2% **8** by hplc) and the reaction mixture was cooled to 15°C. The pH was adjusted to 6.9 by the addition of 3.75 *N* NaOH (705 mL) over 2 h, keeping the temperature between 10 and 20°C. The mixture was warmed to 25°C to redissolve partially precipitated **3** and the phases separated. The aqueous phase was washed with a portion of dichloromethane (100 mL) and the organic layers combined (~850 mL). The organic layer was then cooled to −5°C–0°C and heptane (850 mL) was added over 1 h with stirring. The resulting slurry was stirred for an additional 1 h at this temperature at which point the solid was collected by filtration. The filter cake was washed with cold 10% dichloromethane in heptane (200 mL). This provided 54.4 g (79% yield from hydrobenzamide) of β-lactam **3** as off-white needles; hplc purity (area): 100%.

Method 3. Hydrolysis with 30% sodium bisulfite

To hydrobenzamide (50.00 g, 167 mmol) in ethyl acetate (500 mL) and under an atmosphere of argon was added triethylamine (26.9 mL, 193 mmol). This mixture was cooled to 5°C and a solution of acetoxyacetyl chloride (18.9 mL, 176 mmol) in ethyl acetate (200 mL) was added dropwise over 1.5 h with stirring. After another 2 h, the stirring was discontinued and the reaction mixture was maintained at 5°C for 17 h. The mixture was diluted with water (250 mL) and the layers separated. The aqueous phase was washed with another portion of ethyl acetate (100 mL) and the organic phases combined and treated with sodium bisulfite (75.0 g) in water (250 mL). The resulting biphasic solution was vigorously stirred (overhead stirrer) at 50 ± 2°C until the hydrolysis was judged complete by tlc (~4 h). The phases were separated and the organic layer was washed with water (150 mL) and then dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of 100 mL. This mixture was cooled to ~4°C and stirred for 2 h. The precipitated product was isolated by filtration. The filter cake was washed with cold ethyl acetate (25 mL) to provide 20.6 g (60% overall yield from hydrobenzamide) of β-lactam **3** as white needles; hplc purity (area): 99.3%.

*(±)-*cis*-3-Acetoxy-4-*p*-methoxyphenylazetidin-2-one (**10**) by Method 1*

The β-lactam **10** was prepared according to Method 1, except that hydroanisamide (14) was used instead of hydrobenzamide. Thus, hydroanisamide (5.00 g, 12.9 mmol), triethylamine (2.15 mL, 15.4 mmol), and acetoxyacetyl chloride (1.59 mL, 14.8 mmol) gave a solution of the protected β-lactam in ethyl acetate (80 mL). This solution was treated with H_2 (4 atm) over 10% palladium on activated carbon (1.00 g). Standard processing and removal of the solvent in vacuo furnished 4.28 g of a crude solid. A portion (300 mg) was purified by preparative tlc (20 cm × 20 cm × 2 mm silica gel; ethyl acetate – hexane (1:1)) and recrystallized from dichloromethane–hexane to provide 160 mg (75% overall yield from hydroanisamide) of the 4-(*p*-methoxyphenyl) β-lactam **10** as white crystals, mp 110–111°C; hplc purity (area): 99.7%; ir ν_{max} (KBr): 3218 (N-H), 1751, 1728 (C═O) cm^{-1}; UV λ_{max} (methanol): 208, 230, 276 nm; ^1H nmr ($CDCl_3$) δ: 7.24 (d, J = 9.0 Hz, 2H, Ar), 6.89 (d, J = 8.7 Hz, 2H, Ar), 6.23 (br s, D_2O exchangeable, 1H, NH), 5.83 (dd, J = 2.7, 4.6 Hz, 1H, H-3), 4.99 (d, J = 4.6 Hz, 1H, H-4), 3.81 (s, 3H, $ArOCH_3$), 1.73 (s, 3H, CH_3CO). Anal. calcd. for $C_{12}H_{13}NO_4$: C 61.27, H 5.57, N 5.95; found: C 61.04, H 5.49, N 5.88.

*(±)-*cis*-3-Acetoxy-4-(2′-furanyl)azetidin-2-one (**11**) by Method 1*

The β-lactam **11** was prepared according to Method 1 except that hydrofuramide (15) was used instead of hydrobenzamide. Thus, hydrofuramide (80.48 g, 300 mmol), triethylamine (50.2 mL, 360 mmol), and acetoxyacetyl chloride (37.0 mL, 344 mmol) gave a solution of the protected β-lactam in ethyl acetate (1.5 L). This solution was treated with H_2 (4 atm) over 10% palladium on activated carbon (12.0 g). The catalyst was removed by filtration through Celite® and the reaction mixture treated with decolourizing charcoal (30 g, Norit®). After the standard aqueous processing, the organic layer was concentrated to a volume of 160 mL. This mixture was cooled to 4°C and the precipitated product was isolated by filtration. The filter cake was rinsed with diethyl ether and hexane (100 mL of each) to provide 36.0 g (61% overall yield from hydrofuramide) of the 4-(2′-furanyl) β-lactam **11** as white needles, mp 118–119°C; hplc purity (area): 99.4%; ir ν_{max} (KBr): 3203 (N-H), 1756, 1726 (C═O) cm^{-1}; UV λ_{max} (methanol): 222 nm; ^1H nmr ($CDCl_3$) δ: 7.44 (t, J = 1.3 Hz, 2H, furyl), 6.39 (d, J = 1.3 Hz, 1H, furyl), 6.21 (br s, D_2O exchangeable, 1H, NH), 5.88 (dd, J = 2.2, 4.6 Hz, 1H, H-3), 5.05 (d, J = 4.6 Hz, 1H, H-4), 1.92 (s, 3H, CH_3CO). Anal. calcd. for $C_9H_9NO_4$: C 55.39, H 4.65, N 7.18; found: C 55.76, H 4.64, N 6.95.

*(±)-*cis*-3-Acetoxy-4-(2′-thienyl)azetidin-2-one (**12**) by Method 2*

The β-lactam **12** was prepared according to Method 2 for the preparation of **3** except that hydrothienamide was used instead of hydrobenzamide. Thus, hydrothienamide (30.0 g, 94.8 mmol), triethylamine (15.9 mL, 114 mmol), and acetoxyacetyl chloride (11.6 mL, 109 mmol) gave a solution of the protected β-lactam in ethyl acetate. In this case, the ethyl acetate was removed in vacuo to provide the crude intermediate protected β-lactam as a viscous oil. A portion of this oil (0.431 g, 1.03 mmol) was redissolved in dichloromethane (2.93 mL) and treated with acetic acid (0.35 mL, 6.1 mmol) and water (0.15 mL). After 2.5 h at reflux, the reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 75 mL) and brine (50 mL). The organic layer was concentrated in vacuo to a brown oil, which was purified by silica gel chromatography (ethyl acetate – hexane (1:10 to 3:2)) to give 0.154 g (75% overall yield from hydrothienamide) of the 4-(2′-thienyl) β-lactam **12** as a white solid, mp 101.4–103.3°C; ir ν_{max} (KBr): 3216 (N-H), 1752, 1724 (C═O) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.32 (dd, J = 1.5, 4.7 Hz, 1H, thienyl), 7.03 (m, 2H, thienyl), 6.75 (br s, D_2O exchangeable, 1H, NH), 5.86 (dd, J = 2.7, 4.6 Hz, 1H, H-3), 5.27 (d, J = 5.3 Hz, 1H, H-4), 1.83 (s, 3H, CH_3CO); ^{13}C nmr ($CDCl_3$) δ: 169.3, 165.5, 138.4, 127.1, 127.07, 126.2, 78.3, 54.0, 20.0. Anal. calcd. for $C_9H_9NO_3S$: C 51.17, H 4.29, N 6.63; found: C 51.17, H 4.31, N 6.48.

*(±)-*cis*-3-Acetoxy-4-*p*-methylphenylazetidin-2-one (**13**) by Method 3*

The β-lactam **13** was prepared according to Method 3 except that hydrotoluamide (15) was used instead of hydrobenzamide. Thus, hydrotoluamide (10.00 g, 29.4 mmol), triethylamine (4.91 mL, 35.2 mmol), and acetoxyacetyl chloride (3.63 mL, 33.8 mmol) gave a solution of the protected β-lactam in ethyl acetate (150 mL). This solution was treated with water (50 mL) and sodium bisulfite (15 g). This biphasic mixture was vigorously stirred at 50°C for 15 h and the organic and aqueous layers were separated. The organic layer was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to 20 mL. The mixture was cooled to 5°C and the precipitated product was isolated by filtration and rinsed with cold ethyl acetate (10 mL) and hexane (20 mL) to provide 2.59 g of **13**. Subsequent evaporation of the filtrate and recrystallization from ethyl acetate yielded another two crops of material (1.27 and 0.65 g) to furnish a total of 4.51 g (70% overall yield from hydrotoluamide) of the β-lactam **13** as white needles, mp 130–131°C; hplc purity (area): 99.8%; ir ν_{max} (KBr): 3192 (N-H), 1778, 1752 (C═O) cm^{-1}; UV λ_{max} (methanol): 222, 266 nm; ^1H nmr ($CDCl_3$) δ: 7.13–7.22 (m, 4H, Ar), 6.29 (br s, D_2O exchangeable, 1H, NH), 5.85 (dd, J = 2.6, 4.7 Hz, 1H, H-3), 5.00 (d, J = 4.7 Hz, 1H, H-4), 2.35 (s, 3H, $ArCH_3$), 1.70 (s, 3H, CH_3CO). Anal. calcd. for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39; found: C 65.85, H 5.91, N 6.40.

Acknowledgements

We would like to thank Mr. J. Lajeunesse, Mr. P. Sirard (Bris-

tol-Myers Squibb, Candiac), and Dr. J.F. Kadow (BMS, Wallingford) for technical assistance and Mr. G. Lacasse (BMS, Candiac) for analytical support. The authors also wish to thank Dr. R.A. Partyka (BMS, New Brunswick) for his interest and encouragement and Drs. E.H. Ruediger and V.S. Rao (BMS, Candiac) for helpful discussion.

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