Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2021–2029

Approaches to the synthesis of enantiopure α-hydroxy-β-lactams with functionalized side chains

Yan Yang,[†] Jianmei Wang and Margaret Kayser[*]

Department of Physical Sciences, University of New Brunswick, Saint John, NB, Canada E2L 4L5

Received 7 February 2007; accepted 2 August 2007

Abstract—We report a synthesis of pharmaceutically important α-hydroxy (or *t*-butyldimethylsilyl protected α-hydroxy)-β-lactams with functionalized chains in position 4 of the azetidinone ring. A convenient and high-yielding route to these compounds was developed and optimized. Preparation and characterization of several new enantiopure title compounds with various functional groups are discussed.

1. Introduction

3-Hydroxy-β-lactams and their derivatives, β-amino-α-hydroxy acids, are key fragments of pharmaceutically important compounds such as phenylisoserine analogues used in the synthesis of new taxane anticancer drugs,[1,2] or inhibitors of enzymes renin[3] and HIV-1 protease.[4] Although the biological importance and synthetic applications of hydroxy-β-lactams led to the development of numerous syntheses, the wide variety of functionality and substitution patterns in the target compounds continues to drive the search for new and practical stereoselective methods for their preparation.[5,6] We have been interested in the synthesis of enantiopure 3-hydroxy-β-lactams substituted in position 4 with side chains that carry both gem dimethyl and a polar group such as OH, CHO, and morpholine (**1a**–**e**, Fig. 1). Our goal was to develop an efficient and relatively easy synthesis of racemic *cis*-3-acetoxy precursors **2a**,**b** and to access the corresponding enantiopure 3-hydroxy or *t*-butyldimethylsilyl (TBS) protected 3-hydroxy compounds **1a**–**e** via lipase PS resolution.[7,8] We also intended to convert **1a** to derivative **16** (vide infra), which is directly attachable to baccatin III, to obtain access to new paclitaxel analogues.

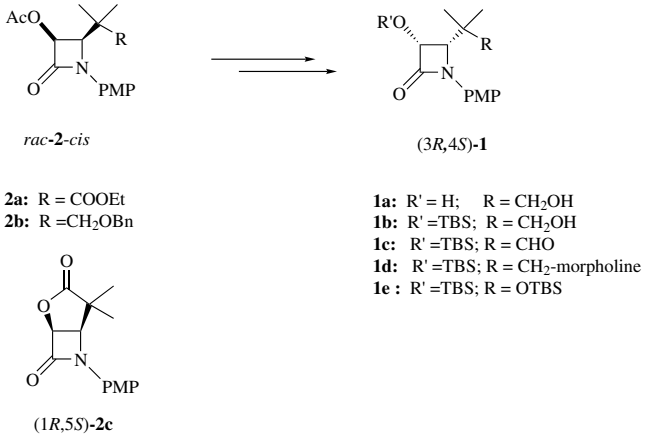
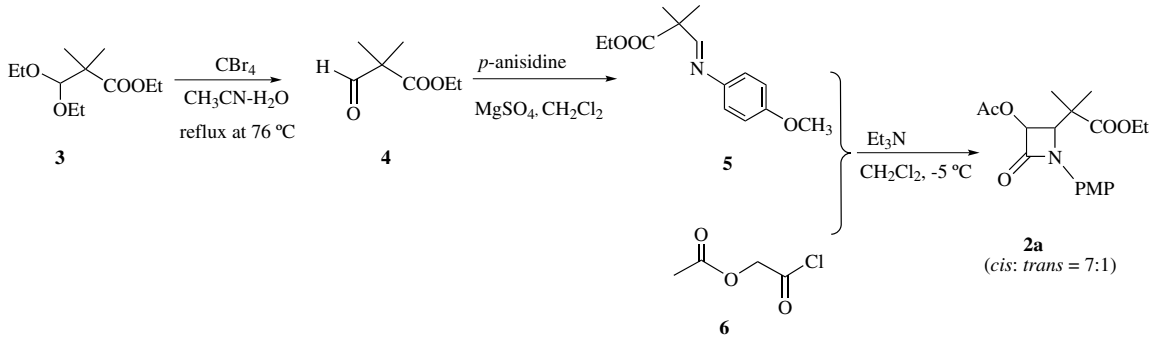


Figure 1. Structure of product **1** and **2**.

In an earlier paper we reported the synthesis of racemic **2a** as a mixture of *cis* and *trans* diastereomers in a 1:2 ratio.[9] Since selective formation of *cis* β-lactam **2a** is required for the lipase PS resolution (the lipase does not accept *trans* β-lactams), *cis*-selectivity needed to be improved. In this communication we describe a modified protocol for the preparation of racemic **2a** as a *cis*:*trans* (7:1) mixture (Scheme 1). However, even with an improved access to *rac*-**2a**-*cis*, the synthesis of **1a** was found to be inefficient due to the formation of by-product **2c** (Fig. 1) during lipase resolution step.[6] To circumvent this problem we developed an alternative route to enantiopure compound **1a** and its derivatives **1b**–**e**.

* Corresponding author. Tel.: +1 506 648 5576; fax: +1 506 648 5948; e-mail: kayser@unbsj.ca
† Present address: Department of Chemistry, Southern Methodist University, Dallas, TX 75275, USA.

0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2007.08.012



Scheme 1. Synthesis of 3-acetoxy β-lactam **2a**.

2. Results and discussion

To obtain *cis*-**2a** as a principal product we focused on the generation of *E* imine, since the structure of an imine plays a crucial role in the stereochemical course of a Staudinger cycloaddition reaction.[10] In the original experiments imine **5** was prepared in a one-pot reaction by deprotection of diethyl acetal **3** with TsOH at 145 °C, followed by condensation with *p*-anisidine. ^{1}H NMR spectrum of the crude product showed it to be a mixture of *Z* and *E* imines in the ratio of 1.6:1, respectively. We thought that the elevated temperature in the one-pot protocol may be responsible for the high proportion of the *Z* imine and the consequent increase in the formation of the *trans* β-lactam during the condensation with the aldehyde.[‡] To obtain imine **5** at lower temperature we decided to prepare aldehyde **4** prior to the condensation with *p*-anisidine. Among several deprotection methods[11–13] refluxing of acetal **3** with CBr_4/H_2O–CH_3CN at 76 °C[14] turned out to be the most effective and gave complete conversion after 6 h. The resulting aldehyde **4** was used without purification in the preparation of imine **5** at room temperature in the presence of anhydrous $MgSO_4$. In view of its low stability, imine **5** was used without purification in the following Staudinger reaction. The condensation of **5** with acetoxyacetyl chloride **6** was performed at −5 °C in the presence of excess triethylamine and produced β-lactam **2a** in the ratio *cis*:*trans* = 7:1 (Scheme 1). Unfortunately, the improved access to *rac*-*cis*-**2a** did not save this synthesis since the following lipase resolution of *rac*-*cis*-**2a** gave a poor yield of enantiopure **1a** because of a spontaneous formation of cyclic lactone **2c** under the work-up conditions.[9]

To improve the synthesis of compound **1a**, we switched to a different strategy that employs benzyloxyaldehyde **11**[15] as a key intermediate (Scheme 2). Selective monobenzylation of glycols is an important protecting step in organic synthesis. It can be achieved via direct monoalkylation with benzyl chloride or via reductive cleavage of benzylidene acetals.[16] Benzylidenation of neopentyl glycol **7** with benzaldehyde dimethylacetal **8** in the presence of camphorsulfonic acid (CSA), performed according to a protocol reported in the literature,[17] gave benzylidene acetal **9** in essentially quantitative yield. In the following ring-opening reaction, the reduction with $LiAlH_4/AlCl_3$[18] cleaved acetal **9** to benzyl ether alcohol **10** in excellent yield (93%). Subsequent Swern oxidation[19] with oxalyl chloride yielded benzyloxyaldehyde **11** in 92% yield (Scheme 2). In this case, the condensation of aldehyde **11** with *p*-anisidine gave exclusively *E* imine **12** as shown by ^{1}H NMR of the crude product. The Staudinger reaction of imine **12** and acetoxyacetyl chloride **6** gave *rac*-*cis*-**2b** β-lactam in 75% yield. The cycloaddition was fast (3 h) and free of the *trans* isomer.

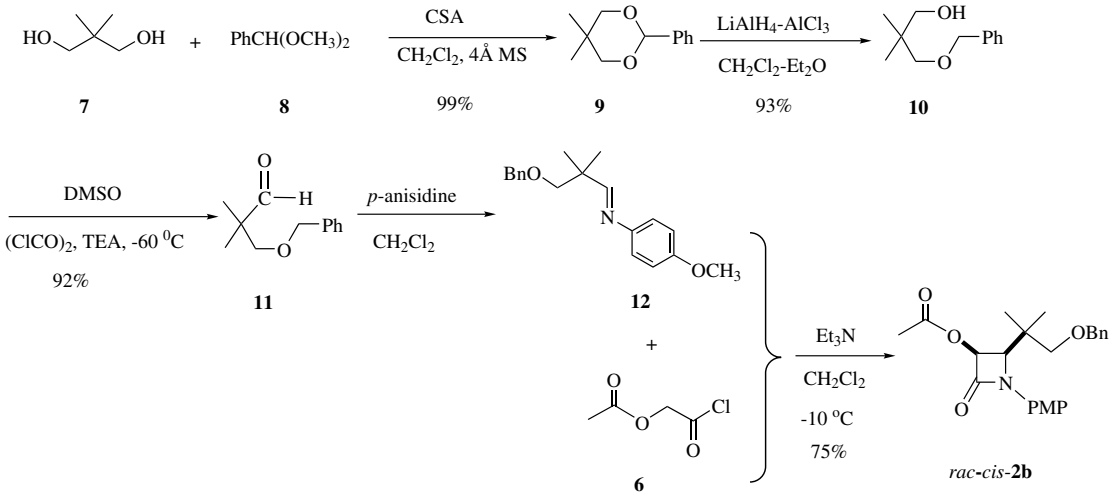
With all reactions optimized, lipase PS-catalyzed kinetic resolution provided a route to the enantiopure targets. Thus, (3*S*,4*R*)-**13** (>99% ee) was prepared via kinetic resolution of *rac*-*cis*-**2b**, and its antipode (3*R*,4*S*)-**13** was accessed by 2 M KOH hydrolysis of the unreacted (3*R*,4*S*)-**2b** (>99% ee). Alcohol (3*S*,4*R*)-**13** was oxidized to the corresponding ketone (4*R*)-**14**. Baker's yeast reduction of (4*R*)-**14** gave (3*R*,4*R*)-**13** in 90% yield, as shown in Scheme 3. A parallel synthesis of the (3*S*,4*S*)-**13** enantiomer was not attempted at this time since our earlier studies have shown that neither whole cell baker's yeast, nor any of the available isolated yeast reductases, screened against several racemic 3-keto β-lactams, was successful in producing a significant proportion of 3*S*,4*S* isomer.[20,21]

The absolute configuration of (3*S*,4*R*)-**13** was assigned by analogy to the related (3*S*,4*R*)-3-hydroxy-4-aryl-β-lactams from lipase resolution, whose absolute configurations have been confirmed by X-ray crystallographic analyses[9,20,22] and proton NMR data.[23] Furthermore, the three compounds (3*R*,4*S*)-**13**, (3*S*,4*R*)-**13**, and (3*R*,4*R*)-**13** are clearly resolved on chiral HPLC (*S*,*S*)-Whelk-O 1 column and each individual compound shows a single peak, indicating >99% enantiomeric excess for each compound.[§]

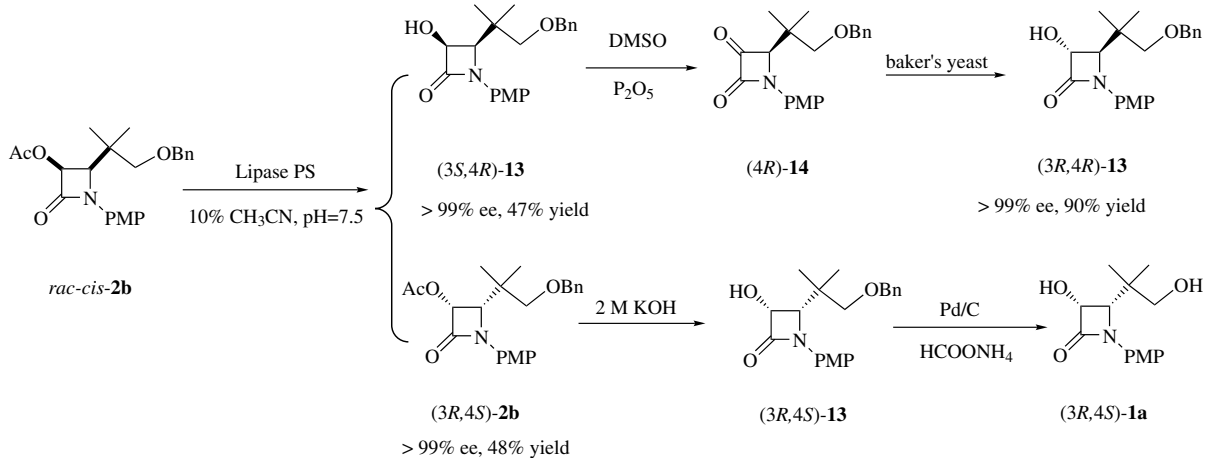
The cleavage of the benzyl group, particularly in sensitive molecules such as β-lactams, can be difficult, and the commonly used H_2–Pd/C hydrogenation[24] was ineffective in the deprotection of (3*R*,4*S*)-**13**. Among the deprotection methods investigated, homogeneous hydrogenation with ammonium formate as the hydrogen source turned out to be fast and reliable[25] (Scheme 3). The same deprotection

[‡] This notion was supported by the observation that when the Staudinger reaction was carried out with the imine that was purified by chromatography during which a significant proportion of the *Z* imine was removed the proportion of *cis*-β-lactam was greatly enhanced.

[§] The enantiopurity of these compounds was initially established by the NMR analysis of their Mosher[33] derivatives.



Scheme 2. Synthesis of 3-acetoxy β-lactam *rac-cis*-**2b**.

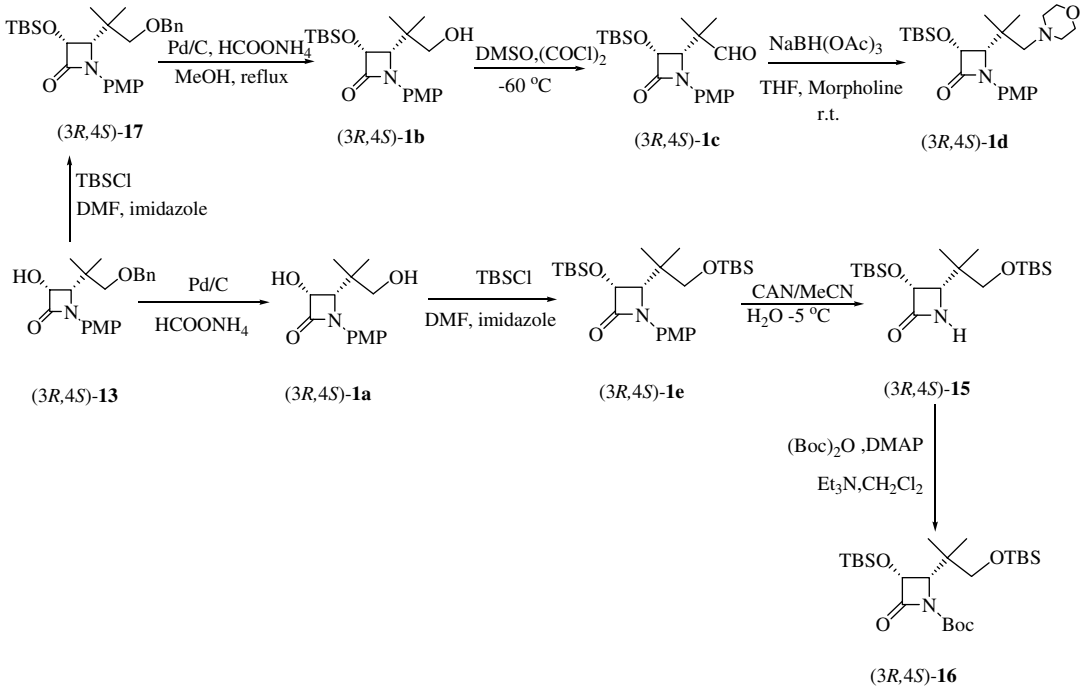


Scheme 3. Preparation of (3*R*,4*S*)-**13**, (3*S*,4*R*)-**13**, and (3*R*,4*R*)-**13**.

method was also effective with the *t*-butyldimethyl silyl (TBS) derivative (3*R*,4*S*)-**17**, making it suitable for the preparation of compound (3*R*,4*S*)-**1b** (Scheme 4). Having identified a good deprotection method, compounds (3*R*,4*S*)-**13** and (3*R*,4*S*)-**17** were converted to (3*R*,4*S*)-**1a** and (3*R*,4*S*)-**1b**, respectively, as shown in Scheme 4.

In the following steps, enantiomer (3*R*,4*S*)-**1a** was protected with two equivalents of TBSCl to (3*R*,4*S*)-**1e** and the *N*-*p*-methoxyphenyl (PMP) group was removed with ammonium cerium nitrate (CAN) to give (3*R*,4*S*)-**15** in high yield. The subsequent protection of the amide amine group in (3*R*,4*S*)-**15** as the corresponding *N*-Boc derivative yielded (3*R*,4*S*)-**16**, which is poised for coupling with baccatin III toward a new paclitaxel analogue (Fig. 2).

It has been shown that the introduction of a morpholine group into four new taxane analogues (non-side chain) provides enhanced biological activity of these analogues compared to paclitaxel and docetaxel, especially vis a vis the resistant cancer cell lines expressing P-glycoproteins (PC-12, PC-6/VCR29-9, and PC-6/VP1-1).[27,28] In light of the above, a paclitaxel analogue bearing a morpholine group in the C-13 side chain became an attractive target and we decided to extend our synthesis to incorporate morpholine into the C-13 side chain of the precursor β-lactam **1d**. The synthesis of the latter compound from (3*R*,4*S*)-**13** was achieved in 30% yield after four steps, as shown in Scheme 4. The 3-hydroxy group of (3*R*,4*S*)-**13** was protected by TBSCl to give (3*R*,4*S*)-**17** in 96% yield. The following debenzylation successfully produced (3*R*,4*S*)-**1b**, although compared to the earlier described hydrogenation of (3*R*,4*S*)-**13** to (3*R*,4*S*)-**1a**, debenzylation of (3*R*,4*S*)-**17** required more palladium and a longer reaction time. Subsequent Swern oxidation (DMSO/$(COCl)_2$)[19] of (3*R*,4*S*)-**1b** at −50 °C to −60 °C gave aldehyde (3*R*,4*S*)-**1c** in 92% yield. To introduce the morpholine group we carried out reductive amination using sodium triacetoxylborohydride ($NaBH(OAc)_3$),[29] as reducing agent in the presence of excess morpholine. Under these conditions, aldehyde



Scheme 4. Synthesis of (3*R*,4*S*)-**1b**–**e** and (3*R*,4*S*)-**16**.

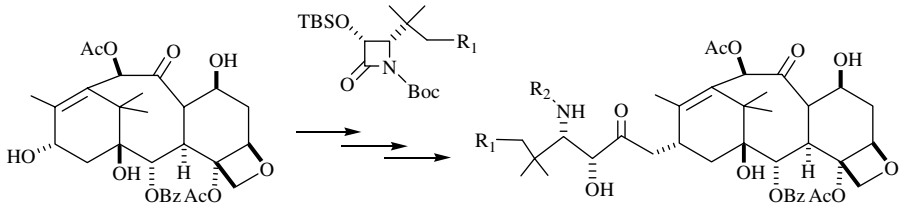


Figure 2. Paclitaxel analogues with novel C-13 side chains are formed by coupling baccatin III with suitably substituted β-lactams according to Holton's protocol.[26] Several protection and deprotection steps are involved.

(3*R*,4*S*)-**1c** was converted to (3*R*,4*S*)-**1d** in 53% yield. Other reductive amination methods employing toxic $NaBH_3CN$[30] or neat $Ti(OiPr)_4$ in the presence of $NaBH_3CN$[31] gave lower yields.

3. Conclusion

Useful chiral building blocks for the synthesis of paclitaxel analogues and other pharmaceutically important compounds were prepared in enantiopure form (99% ee) via a simple and efficient synthesis followed by lipase-catalyzed kinetic resolution. A protocol was established for oxidation of compound (3*S*,4*R*)-**13** to the corresponding 3-oxo-β-lactam (4*R*)-**14** and its subsequent conversion by baker's yeast to the *trans*-(3*R*,4*R*) isomer. The synthesis of the morpholine substituted β-lactam **1d** was carried out. However, to obtain the corresponding *N*-Boc derivative, ready for coupling with baccatin III, several protection and deprotection steps will need to be optimized.

4. Experimental

4.1. General

Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter operating at room temperature. IR spectra were recorded as thin films on NaCl plates on a Mattson Satellite FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at room temperature on a Bruker 250, 400, and 500 MHz FT-NMR spectrometer; chemical shifts are reported in ppm using Me_4Si as internal standard. *J* values are expressed in Hertz. Enantiomeric excess was determined by chiral HPLC analysis or by NMR analysis of the Mosher [(*R*)-MTPA-Cl] derivatives [compounds (3*R*,4*S*)-**13**, (3*S*,4*R*)-**13**, and (3*R*,4*R*)-**13**]. Chiral-phase HPLC analyses were performed on a (*S*,*S*)-Whelk-O 1 column (25 cm × 4.6 mm, Regis Technologies Inc.) using hexane–isopropanol (90:10) as the mobile phase on an Agilent

HPLC 1100. A UV detector set at 254 nm was used to monitor the reactions.

All solvents and chemicals were purchased from Sigma–Aldrich and Fisher Scientific (Canada). All solvents used were purified and dried by standard methods. Lipase PS was a gift from Amano Enzyme USA Co. Baker's yeast was purchased from the bulk food store Bulkbarn.

4.2. 5,5-Dimethyl-2-phenyl-1,3-dioxane 9[32]

Camphorsulfonic acid (0.22 g, 0.95 mol) was added to a solution of neopentyl glycol **7** (8.32 g, 0.08 mol) and benzaldehyde dimethyl acetal **8** (12.8 mL, 0.09 mol) in methylene chloride (220 mL) containing activated 4 Å molecular sieves (10 g). GC and TLC show complete conversion after 30 min of reaction. The molecular sieves were filtered and washed with methylene chloride (20 mL × 3). The filtrate was washed with 10% sodium bicarbonate and brine, dried over magnesium sulfate, and filtered. Evaporation under vacuum afforded **9** (14.9 g, 99% yield) as colorless crystals; mp 30–31 °C; IR ($CHCl_3$) γ_{max}/cm^{-1} 3066, 3036, 2953, 2868, 1456, 1390, 1216, 1105, 1022; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, s, CH_3), 1.30 (3H, s, CH_3), 3.65 (2H, d, $J = 10.8$, CH_2), 3.77 (2H, d, $J = 11.0$, CH_2), 5.39 (1H, s, C*H*), 7.37 (3H, dd, $J = 6.7$, $J = 8.1$, Ar*H*), 7.51 (2H, d, $J = 6.7$, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.9 (*C*H_3), 23.1 (*C*H_3), 30.2 (*C*Me$_2$), 77.7 (O*C*H$_2$), 101.8 (H*C*Ph), 126.2, 128.3, 128.7, 138.8; HRMS: $C_{12}H_{16}O_2$ (M+), calcd: 192.11504, found: 192.11502.

4.3. 3-(Benzyloxy)-2,2-dimethylpropan-1-ol 10[32]

Lithium aluminum hydride (1.98 g, 0.052 mol) was added to a solution of **9** (10.0 g, 0.052 mol) in 1:1 diethyl ether and methylene chloride (200 mL) cooled to −10 °C. Aluminum chloride (6.95 g, 0.052 mol) in 40 mL of diethyl ether was then added and the resulting mixture was stirred at −10 °C for 10 min. The reaction was allowed to warm to room temperature, then it was heated at reflux. Reflux was continued until GC shows complete conversion (4 h). After the reaction was cooled to −10 °C and diluted with 50 mL of ethyl acetate the reaction was hydrolyzed with water (150 mL) and extracted with ethyl acetate. The combined organic layers were washed sequentially with 10% sodium bicarbonate solution and brine, dried over magnesium sulfate, and filtered. Evaporation under vacuum gave **10** (9.35 g, 93% yield) as a colorless oil; IR ($CHCl_3$) γ_{max}/cm^{-1} 3349, 2982, 2940, 2839, 1725, 1513, 1249, 1173; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (6H, s, (CH_3)$_2$), 2.68 (1H, s, O*H*), 3.32 (2H, s, CH_2), 3.45 (2H, s, CH_2), 4.51 (2H, s, OCH_2Ph), 7.32 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8 (*C*H_3), 36.2 (*C*Me$_2$), 71.6 (*C*H$_2$OH), 73.5 (*C*H$_2$Ph), 79.3 (*C*H$_2$OCH$_2$Ph), 127.4, 127.6, 128.4, 138.2; HRMS: $C_{12}H_{18}O_2$ (M+), calcd: 194.13068, found: 194.13067.

4.4. 3-(Benzyloxy)-2,2-dimethylpropanal 11[19]

A solution of oxalyl chloride (4.9 g, 0.025 mol) in dry methylene chloride (63 mL) was placed in a flame-dried 250 mL three-neck round-bottom flask equipped with a thermometer and two pressure-equalizing dropping funnels containing dimethyl sulfoxide (3.6 mL, 0.051 mol) dissolved in methylene chloride (12 mL) and benzyl ether alcohol **10** (4.9 g, 0.025 mol) dissolved in methylene chloride (25 mL), respectively. The reaction mixture was cooled to −60 °C and the DMSO solution was added over a period of 5 min, followed by the alcohol solution (10 min). After stirring at −60 °C for 30 min, triethylamine (18 mL, 0.13 mol) was added and stirring was continued for an additional 45 min when GC shows a complete conversion. After the reaction was warmed to room temperature, water (40 mL) was added and stirred for 10 min, followed by addition of 2 M HCl (30 mL). The solution was extracted with methylene chloride, washed with brine, dried over magnesium sulfate, and filtered. Evaporation under vacuum gave **11** (6.0 g, 92% yield) as a colorless oil; IR ($CHCl_3$) γ_{max}/cm^{-1} 3349, 2982, 2940, 2839, 1725, 1513, 1249, 1173; ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (6H, s, (CH_3)$_2$), 3.45 (2H, s, OCH_2), 4.51 (2H, s, OCH_2Ph), 7.30 (5H, s, Ar*H*), 9.57 (1H, s, C*H*O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.3 (*C*H_3), 43.4 (*C*Me$_2$), 73.4 (*C*H$_2$O), 76.5 (O*C*H$_2$Ph), 127.5, 127.6, 128.3, 138.0, 182.2; HRMS: $C_{12}H_{16}O_2$ (M+), calcd: 192.1150, found: 192.1142.

4.5. (*E*)-*N*-(3-(Benzyloxy)-2,2-dimethylpropylidene)-4-methoxybenzenamine 12

To a 5% solution of the corresponding aldehyde **11** (4.239 g, 0.022 mol), in methylene chloride (18 mL) were added *p*-anisidine (2.883 g, 0.022 mol) and 4 Å molecular sieves (9 g). The resulting suspension was stirred at room temperature for 2 h until TLC shows complete conversion. The molecular sieves were filtered and thoroughly washed with methylene chloride (20 mL). The combined organic solutions were concentrated under vacuum to give imine **12** (6.2 g, 95% yield) as a light yellow liquid; IR ($CHCl_3$) γ_{max}/cm^{-1} 3031, 2961, 2930, 2858, 3708, 1731, 1648, 1504, 1454, 1244, 1101, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (6H, s, CH_3), 3.51 (2H, s, OCH_2), 3.83 (3H, s, OCH_3), 4.56 (2H, s, CH$_2$Ph), 6.85 (2H, d, $J = 8.9$, Ar*H*), 7.00 (2H, d, $J = 8.8$, Ar*H*), 7.32 (5H, s, Ar*H*), 7.89 (1H, s, N=C*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.7 (*C*H_3)$_2$, 28.4 (*C*Me$_2$), 55.9 (O*C*H$_3$), 75.3 (O*C*H$_2$Ph), 80.0 (*C*H$_2$O), 163.7 (*C*H=N), 127.5, 127.6, 128.3, 138.0 (*C*–Ph), 115.6, 123.3, 141.3, 159.2 (*C*–Ph–OMe).

4.6. *cis*-(±)-3-Acetoxy-4-(2-benzyloxy-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2-one *rac*-*cis*-2b

Crude imine **12** (10.8 g, 0.036 mol) and dry triethylamine (25 mL, 0.18 mol) in dry methylene chloride (100 mL) were cooled to −10 °C and treated under a nitrogen atmosphere with carboxylic acid chloride **6** (12.3 g, 0.09 mol) in dry methylene chloride (65 mL). After complete addition, the solution was warmed to room temperature and stirred for 3 h. The reaction mixture was hydrolyzed with 2 M HCl, and extracted with methylene chloride (100 mL × 2). The combined organic layers were washed with saturated sodium carbonate solution (50 mL × 2), dried over magnesium sulfate, filtered, and evaporated to dryness. Crystallization from hexane and ethyl acetate gave *rac*-

2b-*cis* (11.9 g, 75% yield) as white crystals; mp 78–79 °C; IR ($CHCl_3$) γ_{max}/cm^{-1} 2961, 2934, 2871, 1758, 1513, 1373, 1221, 1112; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.15 (3H, s, CH_3CO), 3.17 (2H, dd, $J = 9.1$, $J = 9.0$, CCH_2), 3.79 (3H, s, OCH_3), 4.39 (2H, q, $J = 11.9$, OCH_2Ph), 4.69 (1H, d, $J = 5.5$, NCH), 6.17 (1H, d, $J = 5.5$, CHO), 6.83 (2H, d, $J = 9.0$, ArH), 7.34–7.38 (7H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4 (*C*H_3), 20.8 (*C*H_3), 21.5 (*C*H_3CO), 38.4 (*C*Me$_2$), 55.4 (O*C*H_3), 61.7 (N*C*H), 73.1 (O*C*H_2Ph), 73.4 (*C*HO), 77.6 (C*C*H_2O), 114.2, 121.2, 127.4, 127.7, 128.4, 130.3, 138.1, 157.1, 163.9, 169.1; HRMS: $C_{23}H_{27}NO_5$ (M+), calcd: 397.18893, found: 397.18891.

4.7. General procedure for lipase resolution of racemic *cis* 3-acetoxy-β-lactams

Amano PS lipase (2 g) was suspended in a 0.2 M potassium phosphate buffer (pH 7.5) (27 mL). 3-Acetoxy-β-lactam *rac*-**2b**-*cis* (2 g, 0.005 mol) in 10% acetonitrile (3 mL) was added to the reaction mixture. The reaction was vigorously stirred at room temperature for 72 h until the reaction proceeded to 48% conversion (by chiral HPLC analysis). The mixture was extracted with ethyl acetate (30 mL × 3) and the combined ethyl acetate layers were washed with brine and dried over magnesium sulfate. Removal of the solvent afforded a mixture of unreacted 3-acetoxy-β-lactam and hydrolyzed product 3-hydroxy-β-lactam. Separation by flash chromatography on a silica gel column (hexane–ethyl acetate = 4:1 to 2:1) gave enantiopure 3-hydroxy-β-lactam (3*S*,4*R*)-(−)-**13** (0.83 g, 47% yield) and the unreacted 3-acetoxy-β-lactam (3*R*,4*S*)-(+)-**2b** (0.95 g, 48% yield). Chemical hydrolysis of the latter gave (3*R*,4*S*)-(+)-**13** in 92% yield.

4.7.1. (3*S*,4*R*)-(−)-4-(2-Benzyloxy-1,1-dimethylethyl)-3-hydroxy-1-(4-methoxyphenyl)azetidin-2-one 13. White crystals; mp 133–134 °C; $[\alpha]_D^{20} = -77.1$ (*c* 1.0, CH_2Cl_2). IR ($CHCl_3$) γ_{max}/cm^{-1} 3344, 2943, 2876, 1726, 1512, 1243; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, s, CCH_3), 1.20 (3H, s, CCH_3), 3.10 (1H, d, $J = 9.5$, CCH_2), 3.48 (1H, d, $J = 9.3$, CCH_2), 3.78 (3H, s, OCH_3), 4.24 (1H, d, $J = 5.5$, NCH), 4.57 (2H, s, OCH_2Ph), 4.95 (1H, dd, $J = 5.4$, $J = 11.5$, OHCH), 5.40 (1H, d, $J = 11.3$, OH), 6.83 (2H, d, $J = 9.0$, ArH), 7.19 (2H, d, $J = 9.0$, ArH), 7.39 (5H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6 (*C*H_3), 27.2 (*C*H_3), 38.9 (C*C*H_3), 55.4 (O*C*H_3), 66.8 (N*C*H), 74.1 (HO*C*H), 74.6 (O*C*H_2Ph), 77.3 (C*C*H_2O), 114.2, 121.6, 128.3, 128.6, 128.7, 130.3, 136.2, 156.8, 168.4; HRMS: $C_{21}H_{25}NO_4$ (M+), calcd: 355.1783, found: 355.1776.

4.7.2. (3*R*,4*S*)-(+)-4-(2-Benzyloxy-1,1-dimethylethyl)-3-acetoxy-1-(4-methoxyphenyl)azetidin-2-one 2b. Colorless crystals; mp 85–86 °C; $[\alpha]_D^{20} = +51.0$ (*c* 1.0, CH_2Cl_2).

4.8. (3*R*,4*S*)-(+)-3-Hydroxy-4-(2-benzyloxy-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2-one 13

3-Acetoxy-β-lactam (3*R*,4*S*)-(+)-**2b** (2 g, 0.005 mol) was dissolved in tetrahydrofuran (40 mL) and cooled to 0 °C. The reaction mixture was slowly treated with 2 M KOH (20 mL) and stirred at 0 °C until TLC indicated complete conversion (2 h). The reaction was quenched with water (20 mL) and extracted with ethyl acetate (40 mL × 2). The combined organic layers were washed with brine, and dried over magnesium sulfate, filtered, and concentrated. Crystallization from hexane and ethyl acetate yielded (3*R*,4*S*)-(+)-**13** (1.65 g, 92% yield) as colorless crystals; mp 138–140 °C; $[\alpha]_D^{20} = +78.0$ (*c* 1.0, CH_2Cl_2). Spectra are identical to those of (3*S*,4*R*)-(−)-**13**.

4.9. (3*R*,4*S*)-(+)-3-Hydroxy-4-1,1-dimethyl-2-hydroxyethyl)-1-(4-methoxyphenyl)azetidin-2-one 1a

Ammonium formate (0.41 g, 0.006 mol) and palladium on activated carbon (1.2 g, 10 wt %) were added to a solution of β-lactam (3*R*,4*S*)-(+)-**13** (1.1 g, 0.03 mol) in dry methanol (15 mL). The reaction was stirred at reflux for 20 min when TLC indicated complete conversion. The mixture was acidified with 2 M HCl to pH ~ 3, and then extracted with ethyl acetate (40 mL × 3). The organic layers were combined and washed with brine, dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product. Crystallization with methylene chloride yielded products (3*R*,4*S*)-(+)-**1a** (0.398 g, 50% yield) as colorless crystals; mp 162–164 °C; $[\alpha]_D^{20} = +70.2$ (*c* 1.0, CH_2Cl_2). IR ($CHCl_3$) γ_{max}/cm^{-1} 3369, 2960, 2933, 1727, 1512, 1247, 1126, 1033; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, s, CH_3), 1.13 (3H, s, CH_3), 3.26 (1H, d, $J = 10.5$, NCH), 3.72 (3H, s, OCH_3), 3.73 (1H, d, $J = 10.2$, CHOH), 4.23 (2H, d, $J = 5.3$, CH_2), 4.94 (1H, s, OH), 6.30 (1H, s, OH), 6.83 (2H, d, $J = 10.0$, ArH), 7.23 (2H, d, $J = 10.0$, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.5 (*C*H_3), 26.5 (*C*H_3), 39.4 (*C*), 55.5 (O*C*H_3), 66.6 (N*C*H), 67.5 (OH*C*H), 76.5 (*C*H_2), 114.3, 122.4, 129.4, 157.3, 169.7 (*CO*); HRMS: $C_{14}H_{19}NO_4$ (M^+), calcd: 265.1001, found: 265.1006.

5. (3*R*,4*S*)-(+)-4-(2-Benzyloxy-1,1-dimethylethyl)-3-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-azetidin-2-one 17

3-Hydroxy-β-lactam (3*R*,4*S*)-(+)-**13** (1.1 g, 0.03 mol) was dissolved in dimethylformamide (2 mL). *tert*-Butyldimethylsilyl chloride (0.73 g, 0.036 mol) and imidazole (2.5 equiv) were added. The mixture was stirred at 35 °C until TLC indicated complete conversion (4 h). The reaction was quenched with water and extracted with methylene chloride (15 mL × 3). The combined organic extracts were washed three times with water and brine, dried over magnesium sulfate. Filtration and concentration gave (3*R*,4*S*)-(+)-**17** (1.3 g, 97% yield) as a colorless oil; $[\alpha]_D^{20} = +52.1$ (*c* 1.2, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 2955, 2931, 2857, 1753, 1513, 1248, 1132; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (3H, s, CH_3), 1.20 (3H, s, CH_3), 3.11 (1H, d, $J = 9.3$, OCH_2), 3.47 (1H, d, $J = 9.3$, CCH_2), 3.78 (3H, s, OCH_3), 4.35 (1H, d, $J = 5.5$, NCH), 4.57 (2H, s, OCH_2Ph), 4.96 (1H, dd, $J = 5.4$, $J = 11.3$, CHOH), 5.40 (1H, d, $J = 11.3$, OH), 6.83 (2H, d, $J = 9.0$, ArH), 7.20 (2H, d, $J = 9.0$, ArH), 7.39 (5H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.4 (Si*C*H$_3$), −4.6 (Si*C*H$_3$), 18.1 (Me$_3$*C*Si), 20.4 ((*C*H$_3$)$_2$C), 21.2 ((*C*H$_3$)$_2$C),

25.7 ((*C*H$_3$)$_3$CSi), 39.6 (*C*(CH$_3$)$_2$), 55.4 (OCH$_3$), 61.9 (NCH), 73.0 (HOCH), 76.1 (OCH$_2$Ph), 78.0 (CCH$_2$O), 114.0, 120.6, 127.3, 127.5, 128.4, 131.2, 138.4, 156.5, 167.4; HRMS: $C_{27}H_{39}NO_4Si$ (M+), calcd: 469.2648, found: 469.2648.

5.1. (3*R*,4*S*)-(+)-3-(*tert*-Butyldimethylsilanyloxy)-4-(1,1-dimethyl-2-hydroxy-ethyl)-1-(4-methoxyphenyl)azetidin-2-one 1b

Ammonium formate (820 mg, 13 mmol) and palladium on activated carbon (1.5 g, 10 wt %) were added to a solution of (3*R*,4*S*)-(+)-**17** (499 mg, 1 mmol) in dry methanol (20 mL). The reaction was stirred under reflux for 30 min when TLC indicated complete conversion. The mixture was acidified with 2 M HCl to pH ~ 3, and then extracted with ethyl acetate (40 mL × 3). The organic layers were combined and washed with brine, dried over magnesium sulfate, filtered, and evaporated to dryness. Separation of the crude residue by flash column chromatography (hexane–ethyl acetate = 6:1 to 4:1) followed by crystallization with methylene chloride yielded (3*R*,4*S*)-(+)-**1b** (230 mg, 57%) as colorless crystals; mp 103–104 °C; $[\alpha]_D^{20} = +53.7$ (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 3417, 2956, 2931, 2858, 1738, 1513, 1248, 836; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (9H, s, C(C*H*$_3$)$_3$), 1.02 (3H, s, C*H*$_3$), 1.11 (3H, s, C*H*$_3$), 3.40 (2H, q, OC*H*$_2$), 3.78 (1H, s, OC*H*$_3$), 4.39 (1H, d, *J* = 5.5, NC*H*), 5.02 (1H, d, *J* = 5.5), 6.86 (2H, d, *J* = 9.0, Ar*H*), 7.37 (2H, d, *J* = 9.0, Ar*H*), 7.39; ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.4 (SiCH$_3$), 84.6 (SiCH$_3$), 18.1 (Me$_3$*C*Si), 20.8 ((*C*H$_3$)$_2$C), 21.1 ((*C*H$_3$)$_2$C), 25.7 ((*C*H$_3$)$_3$CSi), 39.5 (C(*C*H$_3$)$_2$), 55.5 (OCH$_3$), 62.9 (NCH), 69.8 (HOCH), 114.2, 121.0, 131.0, 156.8, 167.1 (*C*ON); HRMS: $C_{20}H_{33}NO_4Si$ (M+), calcd: 379.21790, found: 379.21787.

5.2. (3*R*,4*S*)-(+)-3-(*tert*-Butyldimethylsilanyloxy)-4-(1-formyl-1,1-dimethylmethyl)-1-(4-methoxyphenyl)azetidin-2-one 1c[19]

A solution of oxalyl chloride (0.134 mL, 1.74 mmol) in dry methylene chloride (12 mL) was placed in a 50 mL three-neck round-bottom flask equipped with two dropping funnels containing DMSO (0.265 mL, 3.76 mmol) dissolved in methylene chloride (4 mL) and (3*R*,4*S*)-(+)-**1b** (660 mg, 1.88 mmol) dissolved in methylene chloride (8 mL), respectively. When the reaction mixture was cooled to −60 °C, the DMSO solution was added to the mixture, stirred for 5 min; then, the alcohol solution was added over a period of 10 min. After stirring at −60 °C for 1 h, triethylamine (1.368 mL, 9.88 mmol) was added and stirred for an additional 4 h at room temperature. When TLC indicated complete conversion, water (10 mL) was added and stirred for 10 min, followed by addition of saturated ammonium chloride solution (10 mL). The solution was extracted with methylene chloride (25 mL × 3), washed with brine, dried over magnesium sulfate, and filtered. Evaporation under vacuum gave (3*R*,4*S*)-(+)-**1c** (600 mg, 83%) as colorless crystals; mp 110–111 °C; $[\alpha]_D^{20} = +56.4$ (*c* 1.05, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 2955, 2932, 2857, 1756, 1724, 1513, 1466, 1384, 1249, 1180, 1129, 894, 837, 783; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (3H, s, CH$_3$Si), 0.22 (3H, s, CH$_3$Si), 0.92 (9H, s, (C*H*$_3$)$_3$CSi), 1.21 (3H, s, C*H*$_3$C), 1.24 (3H, s, C*H*$_3$C), 3.78 (3H, s, OC*H*$_3$), 4.55 (1H, d, *J* = 5.5, NC*H*), 5.02 (1H, d, *J* = 5.5, C*H*OH), 6.85 (2H, d, *J* = 8.6, Ar*H*), 7.27 (2H, d, *J* = 8.6, Ar*H*), 9.64 (1H, s, C*H*O); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.5 (SiCH$_3$), −4.8 (SiCH$_3$), 18.1 (Me$_3$*C*Si), 19.3 (*C*H$_3$C), 22.1 (*C*H$_3$C), 25.6 ((*C*H$_3$)$_3$CSi), 48.0 (*C*(CH$_3$)$_2$), 55.4 (OCH$_3$), 64.1 (NCH), 76.2 (OCH), 114.3, 114.5, 121.1, 122.7, 130.3, 156.9 (*C*–Ph), 166.3 (*C*O), 204.3 (*C*HO); HRMS: $C_{21}H_{33}NO_4Si$ (M+), calcd: 391.21787, found: 391.21824.

5.3. (3*R*,4*S*)-(+)-3-(*tert*-Butyldimethylsilanyloxy)-4-(1,1-dimethyl-2-morpholinethyl)-1-(4-methoxyphenyl)azetidin-2-one 1d[30]

Aldehyde (3*R*,4*S*)-(+)-**1c** (541 mg, 1.43 mmol) was dissolved in MeOH (4 mL), to this solution were added morpholine (0.36 mL, 4.2 mmol), AcOH (0.075 mL, 1.43 mmol), and NaBH(OAc)$_3$ (417 mg, 2 mmol). With ice cooling, the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane–ethyl acetate = 4:1) to give (3*R*,4*S*)-(+)-**1d** (340 mg, 53% yield) as a colorless solid; mp 90–91 °C; $[\alpha]_D^{20} = +48.7$ (*c* 1.5, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 2956, 2931, 2857, 1749, 1512, 1378, 1247, 1131, 1036, 888, 836, 782; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (3H, s, SiC*H*$_3$), 0.25 (3H, s, SiC*H*$_3$), 0.95 (6H, s, (C*H*$_3$)$_3$CSi), 1.01 (3H, s, C*H*$_3$CC), 1.04 (3H, s, C*H*$_3$CC), 2.21 (1H, *J* = 13.8, OC*H*$_2$Ph), 2.56 (1H, d, *J* = 13.8, OC*H*$_2$Ph), 2.43–2.48 (4H, m, C*H*$_2$NC*H*$_2$), 3.65–3.66 (4H, m, C*H*$_2$OC*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 4.27 (1H, d, *J* = 5.5, NC*H*), 4.96 (1H, d, *J* = 5.5, OC*H*), 6.83 (2H, d, *J* = 8.8, Ar*H*), 7.28 (2H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.4 (SiCH$_3$), −4.4 (SiCH$_3$), 18.1 (Me$_3$*C*Si), 22.4 ((*C*H$_3$)$_2$C), 25.2 ((*C*H$_3$)$_2$C), 25.7 ((*C*H$_3$)$_3$CSi), 40.3 (*C*Me$_2$), 55.4 (OCH$_3$), 56.2 (*C*H$_2$NCH$_2$), 65.7 (NCH), 76.5 (HOCH), 65.0 (CCH$_2$O), 67.3 (*C*H$_2$OCH$_2$), 114.0, 121.7, 130.9, 156.6 (*C*–Ph), 167.4 (*C*O); HRMS: $C_{24}H_{40}N_2O_4Si$ (M+), calcd: 448.27572, found: 448.27602.

5.4. (3*R*,4*S*)-(+)-3-(*tert*-Butyldimethylsilanyloxy)-4-(2-(*tert*-butyldimethylsilanyloxy)-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2-one 1e

Hydroxy-β-lactam (3*R*,4*S*)-(+)-**1a** (1.06 g, 0.004 mol) (1.0 equiv) was dissolved in dimethylformamide (2 mL). *tert*-Butyldimethylsilyl chloride (1.32 g, 0.009 mol) and imidazole (4 equiv) were added. The mixture was stirred at 35 °C until TLC indicated complete conversion (4 h). The reaction was quenched with water and extracted with methylene chloride (20 mL × 3). The combined organic extracts were washed with water (15 mL × 3) and brine, and dried over magnesium sulfate. Filtration and concentration gave (3*R*,4*S*)-(+)-**1e** (1.4 g, 72% yield) as colorless crystals; mp 82–83 °C; $[\alpha]_D^{20} = +34.8$ (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 2955, 2931, 2857, 1753, 1513, 1248, 1132; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (6H, s, C*H*$_3$Si), 0.24

(6H, s, CH_3Si), 0.95 (18H, s, (CH_3)$_3$C), 3.15 (1H, d, $J = 10.1$, CHOBn), 3.32 (1H, d, $J = 10.1$, CHOBn), 3.77 (3H, s, OCH_3), 4.42 (1H, d, $J = 5.5$, NCH), 4.98 (1H, d, $J = 5.5$, CHO), 6.80 (2H, d, $J = 8.9$, ArH), 7.30 (2H, d, $J = 8.9$, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.5 (CH$_3$Si), −5.4 (*C*H$_3$Si), −5.4 (*C*H$_3$Si), −4.6 (*C*H$_3$Si), 18.1 (Me$_3$*C*), 18.3 (Me$_3$*C*), 19.5 (*C*H$_3$C), 20.8 (*C*H$_3$C), 25.7 ((*C*H$_3$)$_3$C), 25.9 ((*C*H$_3$)$_3$C), 39.3 (*C*(Me)$_2$), 55.4 (O*C*H$_3$), 61.3 (N*C*H), 76.0 (O*C*H), 70.5 (*C*H$_2$), 113.9, 120.3, 131.5, 156.4 (*C*–Ph), 167.5 (*CO*). HRMS: $C_{26}H_{47}NO_4Si_2$ (M+), calcd: 493.30435, found: 493.30518.

5.5. (3*R*,4*S*)-(+)-3-(*tert*-Butyldimethylsilanyloxy)-4-(2-(*tert*-butyldimethylsilanyloxy)-1,1-dimethylethyl)azetidin-2-one 15

A solution of β-lactam (3*R*,4*S*)-(+)-**1e** (262 mg, 0.531 mmol) in acetonitrile (25 mL) was cooled to −10 °C. CAN (1.016 g, 1.858 mmol) (3.5 equiv) in distilled water (14 mL) was added dropwise to the solution over the period of 1 h. The reaction mixture was diluted with distilled water (10 mL) and stirred at −10 °C for 20 min. Then, the mixture was extracted with ethyl acetate (50 mL × 3), and the combined organic layers were washed with 5% sodium bisulfite solution (25 mL), 10% sodium carbonate solution (25 mL), 5% sodium bisulfite solution (25 mL), and brine (25 mL). The organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum. Purification of the crude products by flash chromatography on silica gel (hexane–ethyl acetate = 7:1) as eluting solvent gave the N-H-lactam (3*R*,4*S*)-(+)-**15** (152.3 mg, 74% yield) as colorless crystals; mp 97–98 °C; $[\alpha]_D^{20} = +47.1$ (*c* 0.25, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 3232, 2955, 2930, 2858, 1763, 1472, 1254, 1190, 196, 890, 837, 729, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (6H, s, CH_3Si), 0.19 (6H, s, CH_3Si), 0.87 (9H, s, (CH_3)$_3$C), 0.92 (9H, s, (CH_3)$_3$C), 1.02 ((CH_3)$_2$C), 3.26 (1H, d, $J = 9.6$, (CH)$_2$O), 3.40 (1H, d, $J = 9.6$, (CH)$_2$O), 3.56 (1H, d, $J = 5.0$, NCH), 4.87 (1H, d, $J = 5.0$, CHO), 5.88 (NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.6 ((*C*H$_3$)$_2$Si), −5.5 (*C*H$_3$Si), −4.6 (*C*H$_3$Si), 18.0 (Me$_3$*C*Si), 18.3 (Me$_3$*C*Si), 19.3 (*C*H$_3$C), 19.9 (*C*H$_3$C), 25.7 ((*C*H$_3$)$_3$C), 25.9 ((*C*H$_3$)$_3$C), 37.3 (*C*(Me)$_2$), 60.5 (N*C*H), 78.3 (O*C*H), 73.2 (*C*H$_2$), 169.5 (*CO*); HRMS: $C_{19}H_{41}NO_3Si_2$ (M+), calcd: 387.26251, found: 387.26272.

5.6. (3*R*,4*S*)-(+)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilanyloxy)-4-(2-(*tert*-butyldimethylsilanyloxy)-1,1-dimethylethyl)azetidin-2-one 16

Triethylamine (4 equiv) was added dropwise to a stirred solution of N-H-β-lactam (3*R*,4*S*)-(+)-**15** (775 mg, 2 mmol), di-*tert*-butyl-dicarbonate (808 mg, 4 mmol) (2 equiv), and DMAP (0.3 equiv) in 15 mL of dry methylene chloride at room temperature. After the addition of amine, the reaction mixture was monitored by TLC until complete conversion was indicated. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL), and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with saturated aqueous NH_4Cl (50 mL × 2) and brine solution, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel (hexane–ethyl acetate = 8:1) to afford (3*R*,4*S*)-(+)-**16** (917 mg, 94% yield) as a colorless oil; $[\alpha]_D^{20} = +57.1$ (*c* 1.01, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 2956, 2931, 2858, 1808, 1729, 1472,1318, 1256, 1156, 1095, 838, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.17 (3H, s, CH_3Si), −0.18 (6H, s, CH_3Si), −0.05 (3H, s, CH_3Si), 0.70 (9H, s, (CH_3)$_3$CSi), 0.72 (9H, s, (CH_3)$_3$CSi), 0.82 (1H, s, CH_3C), 0.85 (1H, s, CH_3C), 1.31 (9H, s, (CH_3)$_3$CO), 3.20 (1H, d, $J = 9.5$, (CH)$_2$O), 3.41 (1H, d, $J = 9.5$, (CH)$_2$O), 3.93 (1H, d, $J = 6.6$, NCH), 4.72 (1H, d, $J = 6.6$, CHO); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.5 ((*C*H$_3$)$_2$Si), −5.5 (*C*H$_3$Si), −4.7 (*C*H$_3$Si), 18.0 (Me$_3$*C*Si), 18.3 (Me$_3$*C*Si), 20.1 (*C*H$_3$C), 22.7 (*C*H$_3$C), 25.6 ((*C*H$_3$)$_3$CSi), 25.9 ((*C*H$_3$)$_3$CSi), 27.9 ((*C*H$_3$)$_3$CO), 39.4 (*C*(Me)$_2$), 63.2 (N*C*H), 76.1 (O*C*H), 83.0 (Me$_3$*C*O), 69.6 (*C*H$_2$), 149.1 (COO), 167.8 (*CO*); HRMS: $C_{24}H_{49}NO_5Si_2$ (M+), calcd: 487.31491, found: 487.31496.

5.7. (4*R*)-(+)-4-(2-Benzyloxy-1,1-dimethylethyl)-1-(4-methoxyphenyl)azetidin-2,3-dione 14

Phosphorus pentoxide (568 mg, 1.5 equiv) was added to dry DMSO (15 mL) and stirred at room temperature for 10 min. The starting material (3*S*,4*R*)-(−)-**13** (710 mg, 2 mmol) dissolved in 6 mL of DMSO, was added dropwise. The resulting mixture was stirred at room temperature, until TLC indicated complete conversion (24 h). The reaction was quenched with cooled saturated $NaHCO_3$ solution and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with water (20 mL × 3) to remove excess DMSO, then, washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (hexane–ethyl acetate = 8:1) and crystallized from hexane and ethyl acetate to give (4*R*)-(+)-**14** (310 mg, 55% yield) as yellow crystals; mp: 137–138 °C; $[\alpha]_D^{20} = +48.7$ (*c* 0.75, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 2962, 2930, 2874, 1813, 1759, 1512, 1464, 1251, 1113, 1030, 978, 830, 739, 604; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (3H, s, CH_3), 1.14 (3H, s, CH_3), 3.19 (1H, s, OCH_2Ph), 3.20 (1H, s, OCH_2Ph), 3.86 (3H, s, OCH_3), 4.49 (1H, s, CH_2OBn), 4.51 (1H, s, CH_2OBn), 4.78 (1H, s, NCH), 6.92 (2H, d, $J = 9.2$, ArH), 7.45 (2H, d, $J = 9.2$, ArH), 7.30–7.43 (5H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3 (*C*H$_3$), 23.7 (*C*H$_3$), 39.4 (*C*Me$_2$), 55.6 (O*C*H$_3$), 73.4 (O*C*H$_2$Ph), 75.8 (N*C*H), 76.9 (C*C*H$_2$O), 114.4, 121.1, 127.8, 128.5, 129.8, 137.6, 158.0 (*C*–Ph), 161.4 (CON), 194.4 (*C*OC); HRMS: $C_{20}H_{21}NO_4$ (M+), calcd: 339.14706, found: 339.14711.

5.8. (3*R*,4*R*)-(+)-3-Hydroxy-4-(1,1-dimethyl-2-benzyloxyethyl)-1-(4-methoxyphenyl)azetidin-2-one 13

Dry baker's yeast (7 g) was added to a solution of sucrose (26 g) in sterilized water (250 mL) contained in a 1 L flask with 500 mL working volume. The mixture was stirred vigorously at 30 °C for 30 min in order to activate the yeast. Compound (4*R*)-(+)-**14** (300 mg, 0.89 mmol), finely ground with 300 mg of β-cyclodextrin, was added to a fermenting yeast and the reaction was monitored by TLC. When the reaction reached 100% conversion (48 h), the reaction was stopped. The reaction mixture was saturated with sodium chloride and centrifuged at 3000*g* for 10 min

in order to remove yeast cells. The cell pellet was washed with ethyl acetate (50 mL × 3). The supernatant liquid was extracted continuously with ethyl acetate (250 mL) for 24 h and the combined extracts were washed with brine and dried over anhydrous $MgSO_4$. After removing the solvent under reduced pressure, the crude residue was purified by flash chromatography on silica gel (hexane–ethyl acetate = 6:1) to yield *trans*-3-hydroxy-β-lactams (3*R*,4*R*)-(+)-**13** (270 mg, 90% yield) as colorless crystals; mp 95–96 °C; $[\alpha]_D^{20} = +39.5$ (*c* 0.25, CH_2Cl_2); IR ($CHCl_3$) γ_{max}/cm^{-1} 3350, 2960, 2930, 2870, 1750, 1510, 1250; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, s, CH_3), 1.02 (3H, s, CH_3), 3.10 (1H, s, CH_2OBn), 3.11 (1H, s, CH_2OBn), 3.75 (3H, s, OCH_3), 4.13 (1H, s, NC*H*), 4.80 (1H, s, C*H*OH), 4.40 (1H, s, OCH_2Ph), 4.42 (1H, s, OCH_2Ph), 6.75 (2H, d, $J = 8.5$, Ar*H*), 7.16 (2H, d, $J = 8.5$, Ar*H*), 7.24–7.39 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6 (*C*H_3), 27.3 (*C*Me_2), 5.5 (O*C*H_3), 66.8 (N*C*H), 74.0 (HO*C*H), 74.6 (O*C*H_2Ph), 77.2 (C*C*H_2O), 114.2, 121.6, 128.3, 128.6, 128.7, 130.3, 136.2, 156.8, 168.4; HRMS: $C_{21}H_{25}NO_4$ (M+), calcd: 355.17857, found: 355.17838.

Acknowledgements

Financial support by the Natural Sciences and Engineering Research Council of Canada (M.M.K.), and the Medical Research Fund of New Brunswick (M.M.K.) are gratefully acknowledged. The authors are deeply grateful to Dr. D. L. Hooper for the NMR spectra recorded at the Atlantic Regional Magnetic Resonance Centre at Dalhousie University, Halifax, Canada.

References

1. Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681–1683.
2. Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. *J. Med. Chem.* **1992**, *35*, 4230–4237.
3. Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976–982.
4. Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305–2314.
5. Ojima, I.; Lin, S.; Slater, J. C.; Wang, T.; Per, P.; Bernacki, R. J.; Ferlinin, C.; Scambia, G. *Bioorg. Med. Chem.* **2000**, *8*, 1619–1628.
6. Forró, E.; Fütöp, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 93–102.
7. Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068–1075.
8. Spero, D. M.; Kapadia, S.; Farina, V. *Tetrahedron Lett.* **1995**, *36*, 4543–4546.
9. Yang, Y.; Wang, F. Y.; Rochon, F. D.; Kayser, M. M. *Can. J. Chem.* **2005**, *83*, 28–36.
10. Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 295–368.
11. Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684–6686.
12. Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399–8401.
13. Bauduin, G.; Bondon, D.; Pietrasanta, Y.; Pucci, B. *Tetrahedron* **1978**, *23*, 3269–3274.
14. Lee, A. S. Y.; Cheng, C. L. *Tetrahedron* **1997**, *53*, 14255–14262.
15. Mukaiyama, T.; Shiina, I.; Sakata, K.; Emura, T.; Seto, K.; Saitoh, M. *Chem. Lett.* **1995**, *24*, 179–180.
16. Green, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991, pp 128–134.
17. Calinaud, P.; Gelas, J. Synthesis of Isopropylidine, Benzylidine, and Related Acetals. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 3–33, and the references cited therein.
18. Lipták, A.; Imre, J.; Harangi, J.; Nánási, P.; Neszmélyi, A. *Tetrahedron* **1982**, *38*, 3721–3727.
19. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
20. Yang, Y.; Kayser, M. M.; Rochon, F. D.; Rodríguez, S.; Stewart, J. D. *J. Mol. Catal. B: Enzym.* **2005**, *32*, 167–174.
21. Kayser, M. M.; Drolet, M.; Stewart, J. D. *Tetrahedron: Asymmetry* **2005**, *16*, 4004–4009.
22. Kayser, M. M.; Yang, Y.; Mihovilovic, M. D.; Feicht, A.; Rochon, F. D. *Can. J. Chem.* **2002**, *80*, 796–800.
23. Yang, Y.; Kayser, M. M.; Hooper, D. *Chirality* **2005**, *17*, 131–134.
24. Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Thanh Nga, T. T. *J. Org. Chem.* **1997**, *62*, 8826–8833.
25. Díez, E.; Fernández, R.; Marqués-López, E.; Martín-Zamora, E.; Lassaletta, J. M. *Org. Lett.* **2004**, *6*, 2749–2752.
26. Holton, R. A.; Biediger, R. J.; Boatman, P. D. Semisynthesis of Taxol and Taxotere. In *Taxol®: Science and Applications*; Suffness, M., Ed.; CRC Press: New York, 1995; pp 97–121.
27. Takeda, Y.; Yoshino, T.; Uoto, K.; Chiba, J.; Ishiyama, T.; Iwahana, M.; Jimbo, T.; Tanaka, N.; Terasawa, H.; Soga, T. *Biorg. Med. Chem. Lett.* **2003**, *13*, 185–190.
28. Takeda, Y.; Uoto, K.; Iwahana, M.; Jimbo, T.; Nagata, M.; Atsumi, R.; Ono, C.; Tanaka, N.; Terasawa, H.; Soga, T. *Biorg. Med. Chem. Lett.* **2004**, *12*, 3209–3215.
29. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
30. Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789–795.
31. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552–2554.
32. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, *10*, 1593–1596.
33. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.