Enantioselective Total Syntheses of [6*R*,7*R*] and [6*S*,7*S*] Tricyclic β-Lactams

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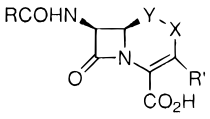
The reaction of Ox-glycyl chloride with a chiral imine derived from the combination of D-(*R*)-glyceraldehyde acetonide and protected D-threonine afforded optically active, highly functionalized *cis*-substituted β-lactams **11** and **12**. These β-lactams provide versatile intermediates for the syntheses of biologically important carbacephalosporins, isooxacephems, and other multicyclic β-lactams. Desilylation and oxidation of **12** with Dess−Martin periodinane followed by intramolecular cyclization produced a novel tricyclic β-lactam **17** and a 1-(hydroxymethyl)-*O*-2-isocephem **18** with [6*R*,7*R*] absolute configuration. Removal of the Ox protecting group and acylation of **17** in a one-pot reaction followed by saponification furnished the target salt **24**. Alternatively, reaction of phthaloylglycyl chloride with the chiral imine derived from the combination of L-(*S*)-glyceraldehyde acetonide and protected D-threonine gave only one enantiomeric azetidinone **27** in high yield. Further manipulation of **27** provided a new tricyclic β-lactam **39** with [6*S*,7*S*] absolute configuration which satisfies the stereochemistry typically required for antibacterial activity. This synthetic procedure provides a short, versatile and enantioselective method of preparing polycyclic β-lactams. Biological testing of these tricyclic β-lactams indicated that salt **39** has potential inhibitory activity against four typical strains of bacteria.

Introduction

For many years, the efforts of the organic synthetic community have been directed toward searching for new β-lactam antibiotics to meet the challenges of bacterial resistance to existing drugs. *O*-2-Isocephems,[1] a particular class of nuclear analogues of the cephalosporins, are but one group of the many structural types of β-lactams derived from extensive investigations. Structure−activity relationship studies of a series of *O*-2-isocephems have revealed promise for this class as orally absorbed antibiotics that exhibit comparable or better activity against some common pathogenic bacteria relative to the analogous cephalosporins. Additionally, the development of methodology for the preparation of multicyclic β-lactams has attracted considerable interest as the syntheses of a number of novel multicyclic β-lactams have been reported recently[2] and some of these compounds have potent biological activity.[2,3]



Cephalosporins: X = CH_2, Y = S
Carbacephems: X = Y = CH_2
O-2-Isocephems: X = O, Y = CH_2

It is well-known that the biological activity of β-lactam antibiotics and β-lactamase inhibitors most often is associated with a single enantiomer. Therefore, enantioselective synthesis of β-lactams is of great interest to organic and medicinal chemists. During the course of design, syntheses, and study of novel β-lactams in our laboratory, we sought to investigate approaches for asymmetric syntheses of biologically important carbacephalosporins, isooxacephems, and other multicyclic β-lactams in few overall steps. This paper describes a short, versatile, and enantioselective method for syntheses of polycyclic β-lactams and as a demonstration, we report herein the asymmetric synthesis of two novel tricyclic β-lactams.

Results and Discussion

One of the most direct routes to the β-lactam nucleus involves the Staudinger (ketene + imine) reaction.[4] The Ox group (4,5-diphenyl-1-oxazolin-2-one) is a versatile

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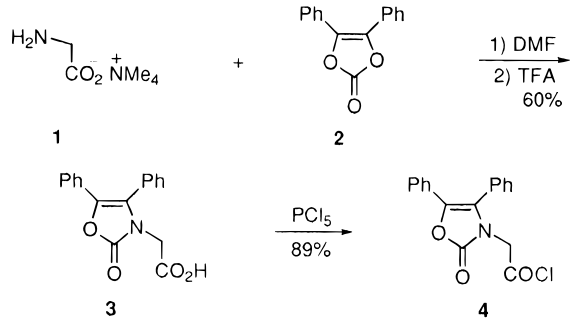
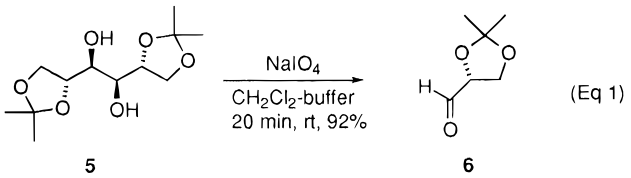
Scheme 1



and convenient protecting group.[5] It is very stable toward hydrolysis under general acidic or basic conditions, and Ox protected compounds tend to be crystalline, highly fluorescent solids. Thus, Ox-glycyl chloride was first chosen as the "ketene" component in this synthesis, and its preparation is shown in Scheme 1. Reaction of tetramethylammonium glycinate (**1**) with cyclic carbonate **2** gave Ox-glycine (**3**) in 60% yield.[6] Treatment of **3** with phosphorus pentachloride provided Ox-glycyl chloride **4** as a white crystalline solid in 89% yield.

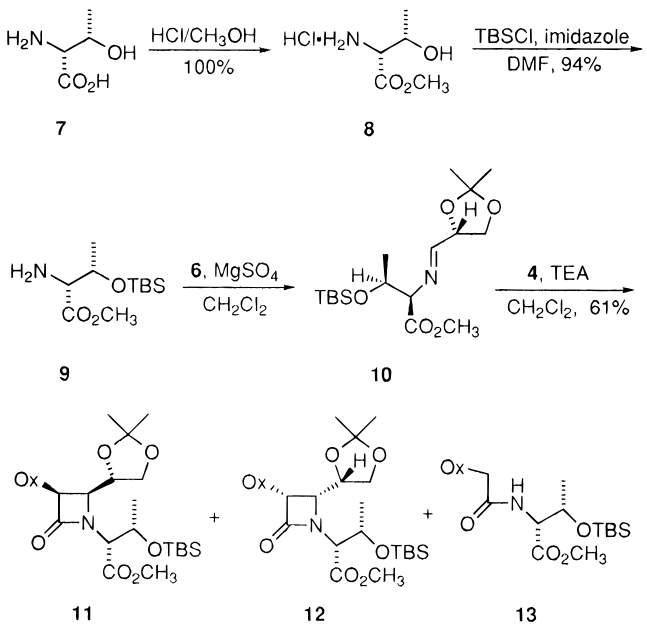
D-(*R*)-Glyceraldehyde acetonide **6** has been extensively used in the synthesis of natural products. Many of the known methods[7] for the preparation of D-(*R*)-glyceraldehyde acetonide (**6**) suffer from the use of hazardous reagents [$Pb(OAc)_4$], low yields, or inconvenient procedures. We investigated the process and found that oxidation of 1,2,5,6-di-*O*-isopropylidene-D-mannitol (**5**) with 1.25−1.3 equiv of $NaIO_4$ in a 3:1 mixture of methylene chloride and buffer (0.05 M potassium phosphate monobasic−sodium hydroxide buffer, pH 7) for 20 min afforded the desired aldehyde **6** in 92% yield. This solvent system (CH_2Cl_2 + buffer) is a key factor for the successful oxidation, and other solvents led only to diminished yields. The reaction has been performed several times, reproducibly providing **6** cleanly and in high yields (eq 1).



(Eq 1)

Use of imines derived from D-(*R*)-glyceraldehyde in the Staudinger reaction generally provides *cis*-β-lactams with good diastereoselectivity.[8] Threonine-derived imines also have been shown to give *cis*-β-lactams in the Staudinger reaction with increased diastereoselectivity when the size of the protecting group on the threonine hydroxyl group was increased.[9] We anticipated that by combining both chiral threonine and D-(*R*)-glyceraldehyde in a single imine, the Staudinger reaction would provide optically active *cis*-β-lactams with high functionality. As illustrated in Scheme 2, acid-catalyzed esterification of D-threonine (**7**) in methanol gave D-threonine methyl ester hydrochloride (**8**)[10] quantitatively. Silylation[11] of **8** with *tert*-butyldimethylsilyl chloride and imidazole in *N*,*N*-dimethylformamide afforded *O*-silyl ether **9** in 94% yield. Formation of chiral imine **10** was accomplished by treatment of a mixture of **9** and D-(*R*)-glyceraldehyde acetonide **6** with anhydrous magnesium sulfate. Subsequent annulation of **10** with Ox-glycyl chloride (**4**) in the presence of triethylamine provided a 1:2.9 mixture of diastereomeric β-lactams **11** and **12** in 61% yield, along with amide **13** as a byproduct in 21% yield.[12] Separation of **11** and **12** by flash column chromatography or preparative TLC was difficult. However, each pure enantiomer **11** or **12** could be obtained by recrystallization from a mixture of methylene chloride and hexanes. By carefully adjusting the ratio of methylene chloride and hexanes, β-lactam **12** was selectively crystallized.

Scheme 2



Upon examination of the proton NMR, the stereochemistry of each diastereomer (**11** and **12**) was found to be

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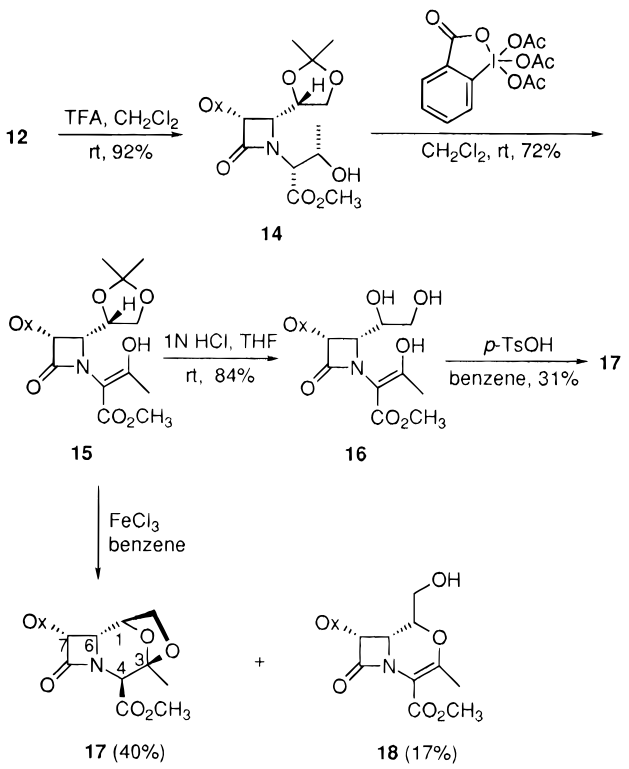
Scheme 3



cis with identical 5.4 Hz coupling constants for the C_3-C_4 protons. The absolute configuration of each diastereomer was determined by X-ray crystal structural analysis and chemical degradation.[12] These optically active monocyclic β-lactams containing functionality at both the β-lactam nitrogen and C-4 could be versatile precursors to many classes of fused-ring β-lactams. Although the stereochemistry about the β-lactam is opposite that usually observed in biologically active antibiotics, we initially intended to utilize the major product **12** to demonstrate the utility of such highly functionalized, yet readily available β-lactams, for the asymmetric syntheses of the corresponding *O*-2-isocephem derivatives.

As shown in Scheme 3, desilylation of **12** with 3 equiv of trifluoroacetic acid in methylene chloride gave β-hydroxy ester **14** in 92% yield after column chromatography. The oxidation of **14** to **15** proved to be troublesome. Swern oxidation[13] resulted in only recovery of the starting material. Oxidation of **14** with PCC in methylene chloride or with Brown's oxidant[14] was equally unsuccessful. Jones oxidation[15] gave the desired product **15** in low yields (10−19%). The problem was finally solved by using Dess−Martin periodinane.[16] Thus, β-hydroxy ester **14** was treated with 1.4 equiv of Dess−Martin periodinane in dry methylene chloride for 2 h, providing **15** in 72% yield.[17] The proton NMR spectrum of **15** showed a broad peak at 12.27 ppm corresponding to an enol hydroxy group, and its ^{13}C NMR spectrum showed two unsaturated carbon peaks at 100.06 and 178.02 ppm. This data indicates that compound **15** exists primarily in the enolic form. Hydrolysis of **15** with dilute aqueous hydrochloric acid in tetrahydrofuran afforded glycol **16** in 84% yield. Attempted cyclization of **16** by a Mitsunobu reaction[18] or TPP/I_2[19] was unsuccessful. However, refluxing **16** with *p*-toluenesulfonic acid in dry benzene for 1 h produced tricyclic β-lactam **17** in 31% yield. Furthermore, refluxing acetonide **15** with 1 equiv of ferric chloride[20] in dry benzene for 20 min provided the same product, tricyclic β-lactam **17**, in 40% yield, along with a bicyclic β-lactam, 1-(hydroxymethyl)-*O*-2-isocephem **18**, in 17% yield.

For antibacterial activity with β-lactam antibiotics, an acylated amino function α to the β-lactam carbonyl and a free carboxylic acid on the carbon atom adjacent to the azetidinone nitrogen are required.[21] To complete the total synthesis of a tricyclic β-lactam suitable for biological testing, our efforts at this point focused on removal of the Ox protecting group, followed by acylation to incorporate a biologically acceptable side chain and finally hydrolysis of the methyl ester to produce a free carboxylic acid or its sodium or potassium salt. It is known that the Ox group can be removed by reductive, oxidative, or photolytic processes.[5b,22] These methods have not been applied to highly functionalized β-lactams; therefore, model studies were performed to explore deprotection conditions. As outlined in Scheme 4, irradiation of **12** in methanol (Pyrex flask) with a 275-W sunlamp for 20 h gave a new compound. Its mass spectrum showed *m/e* 634 as the molecular weight corresponding to $C_{34}H_{42}N_2O_8Si$. Relative to the parent compound **12** ($C_{34}H_{44}N_2O_8Si$), two protons were lost. The proton NMR indicated that four aromatic protons had shifted downfield. Thus, the compound was assigned structure **19**. Catalytic hydrogenolysis of **11** was then tried using several catalysts, including 10% Pd/C, Pd black, 10% Pt/C, or 20% $Pd(OH)_2/C$[23] in tetrahydrofuran, methanol, ethyl acetate, or chloroform. The desired deprotected product **20** was obtained in good yield by hydrogenolysis over 10% Pd/C at 44 psi of hydrogen pressure in methanol containing acetic acid. Subsequent acylation of **20** with benzyl chloroformate, as a model acylating agent, and sodium bicarbonate as base provided compound **21**.

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(17) In this synthesis, Dess−Martin periodinane was prepared by following the original procedure[16a] with improvement: Reaction of potassium bromate (3.841 g, 0.023 mmol) with 2-iodobenzoic acid (4.216 g, 0.017 mol) gave 4.316 g (91%) of 1-hydroxy-1,2-benzodioxol-3(1*H*)-one 1-oxide, which was suspended in Ac_2O (14.776 g, 0.145 mol) and glacial HOAc (11.876 g, 0.198 mol) and stirred at 85 °C. After 10 min, the reaction mixture became homogeneous. The reaction was continued for another 2.5 h at 85 °C and allowed to stand then stood overnight at rt under N_2, and the periodinane was crystallized. Filtration under N_2 and washing the crystals with anhydrous ether (3 × 7 mL) afforded 5.596 g (86%) of Dess−Martin periodinane: mp 132−134 °C (lit.[16a] mp 133−134 °C).

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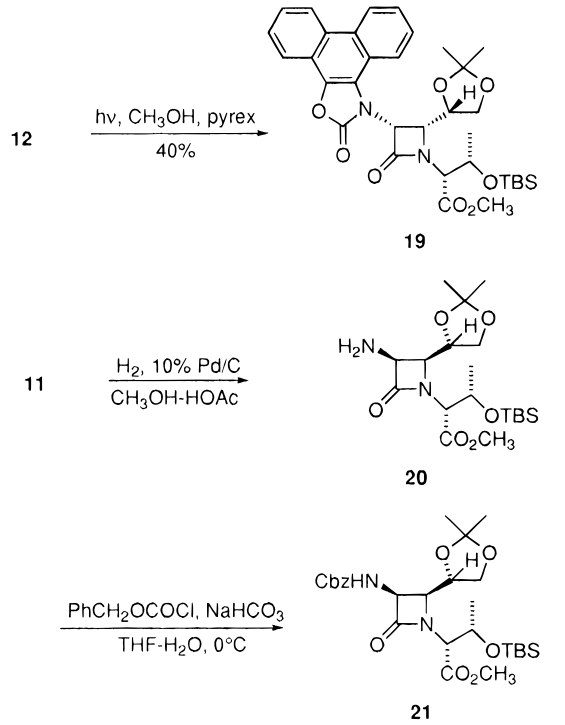
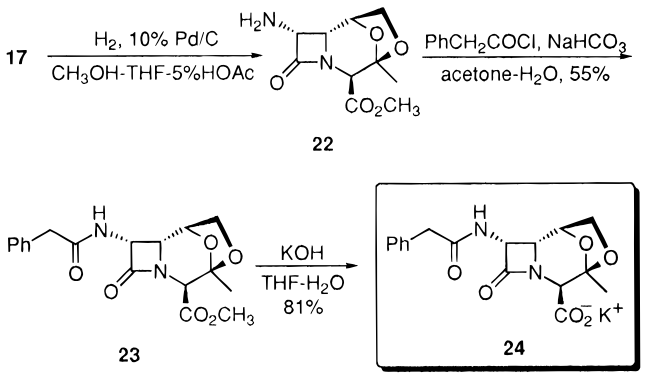
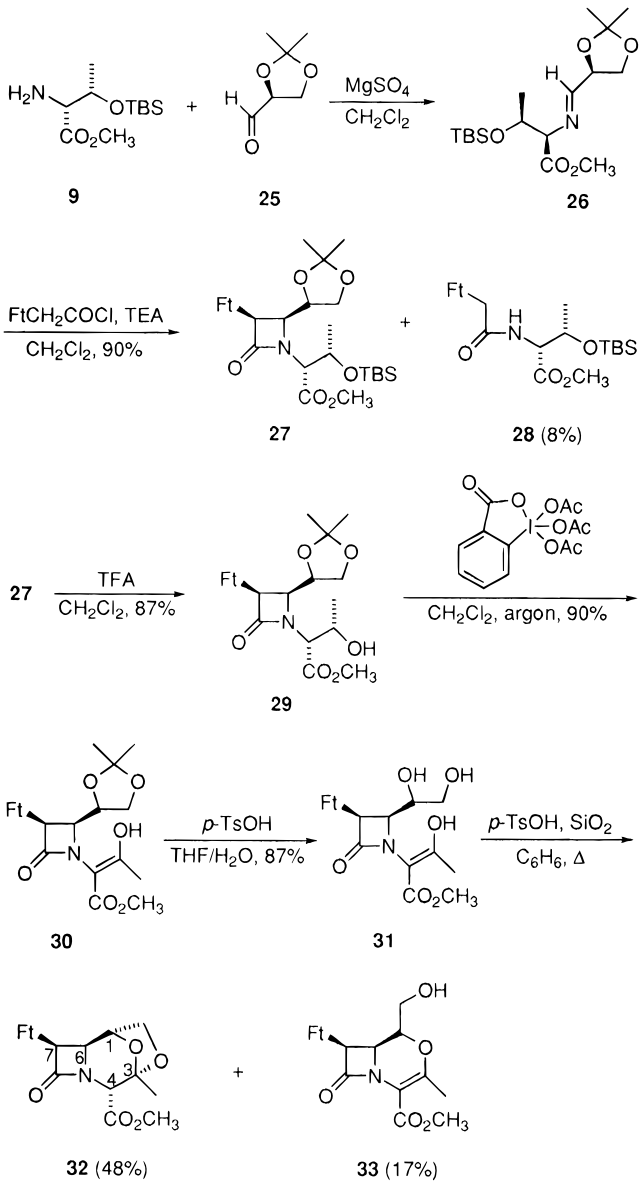
Scheme 4



Scheme 5



Scheme 6



The model experiments revealed that use of methanol containing a weak acid as solvent was necessary to effect hydrogenolytic removal of the Ox group from a highly functionalized β-lactam. Application of the same conditions described above to tricyclic β-lactam **17** was attempted but thwarted by solubility problems in methanol. Further study of the solvents used in the deprotection revealed that hydrogenolysis of **17** over 10% Pd/C in a 1:1:0.1 mixture of methanol/tetrahydrofuran/5% acetic acid at 52 psi hydrogen pressure smoothly afforded **22**. Subsequent Schotten−Baumann acylation[24] of crude **22** with phenylacetyl chloride gave the desired phenylacetamido compound **23** in 55% overall yield. Hydrolysis of **23** with 1 equiv of potassium hydroxide in a 1:1 mixture of tetrahydrofuran and water provided the corresponding potassium salt **24**, with [6*R*,7*R*] absolute configuration, in 81% yield (Scheme 5).

Based on the successful synthesis of [6*R*,7*R*]-tricyclic β-lactam **24** described above, we next turned our attention to the synthesis of the [6*S*,7*S*]-tricyclic β-lactam **39** which has the correct absolute configuration usually required for antibacterial activity.

The synthesis of chiral β-lactams with complete diastereoselectivity has been achieved by the cycloaddition of acid chlorides with imines derived from L-(*S*)-glyceraldehyde and *cis* β-lactams with [3*S*,4*S*] absolute configuration were obtained in high optical yields by the Roche group.[25] Therefore, L-(*S*)-glyceraldehyde acetonide[26] in our synthetic strategy was chosen as the chiral aldehyde component to prepare the imine and phthaloylglycyl chloride[27] was used as the ketene precursor to determine if it would have any advantages over the use of the Ox-protected glycine derivative **4**. As shown in Scheme 6, starting from protected D-threonine **9** and L-(*S*)-glyceraldehyde acetonide **25**, chiral imine **26** was synthesized in quantitative yield. Subsequent reaction of imine **26** with *N*-phthaloylglycyl chloride derived from *N*-phthaloylglycine in the presence of triethylamine gave

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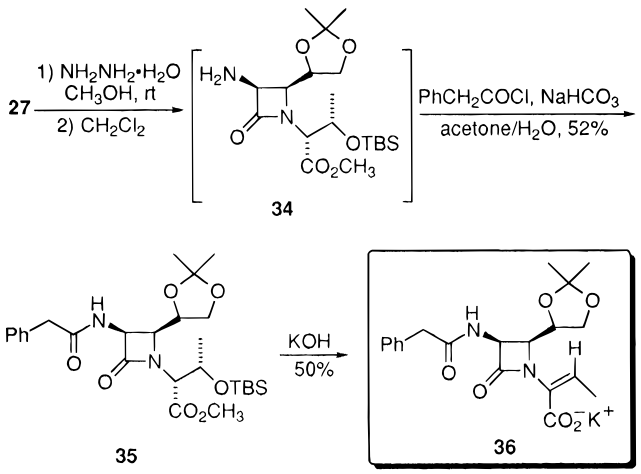
desired *cis* β-lactam **27** in 90% yield, along with amide **28** as a minor byproduct in 8% yield. The excellent yield of **27** as a single diastereomer represented a significant improvement over the related reaction of **4** with **10** which gave a lower yield of a mixture of diastereomers **11** and **12**. Desilylation of **27** with TBAF led to decomposition of the starting material, and no desired product could be detected. Treatment of **27** with 3 equiv of trifluoroacetic acid smoothly gave free hydroxy compound **29**. This deprotection was sensitive to the temperature of the reaction. When the reaction was carried out at rt for 1 h, desired product **29**, contaminated with the deacetonide byproduct, was isolated in a ratio of 3.6:1 as determined by proton NMR. Reducing the temperature to 0 °C and increasing the reaction time to 8 h gave the mixture in nearly the same ratio. However, when the reaction was run at 14 °C, desilylation gave **29** in 87% yield along with a trace of byproduct. Conversion of **29** to enol ester **30** was accomplished in 90% yield by oxidation of **29** with 1.7 equiv of Dess−Martin periodinane in dry methylene chloride. Deprotection of acetonide **30** with 1 N HCl in THF gave glycol **31** in 50% yield. TLC analysis showed the existence of decomposed material on the baseline. Alternatively, refluxing acetonide **30** with *p*-toluenesulfonic acid in a 1:1 mixture of THF and H_2O enhanced the yield of **31** from 50% to 87%.

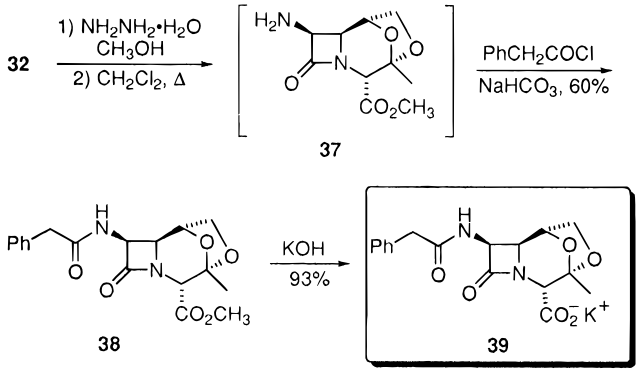
To construct the fused-ring β-lactams, the previous procedure described for the preparation of **17** and **18** was first followed. Acetonide **30** was refluxed with *p*-toluenesulfonic acid in benzene leading to decomposition. Use of ferric chloride instead of *p*-toluenesulfonic acid gave tricyclic β-lactam **32** in only 12% yield and 1-hydroxy-*O*-2-isocephem **33** in 4% yield. To improve the yields, we then chose glycol **31** as the substrate, and the cyclization was attempted under a variety of reaction conditions. Refluxing **31** with 1 equiv of *p*-toluenesulfonic acid and excess silica gel (EM Science, 230−400 mesh ASTM, SiO_2/**31** = 6/1) as a dehydration agent in dry benzene produced β-lactams **32** and **33** in 48% and 17% yield, respectively. It is worth noting that both compound **32** and **33** decomposed partly on silica gel during attempted standard flash chromatographic separation; therefore, it was necessary to use a short column for the isolation in order to minimize decomposition and obtain good yields.

With tricyclic β-lactam **32** in hand, it was possible at this point to attempt the removal of the phthalimido protecting group and attach a biologically active side chain. Ing-Manske's hydrazinolysis[28] of *N*-substituted phthalimides is often effective for removal of the phthalimido protecting groups and is used extensively in organic synthesis, but sometimes it was ineffective with phthalimido-containing penicillins and Δ^3-cephalosporins[29] due to the lack of selectivity. To observe the competitive effect of hydrazine on a highly functionalized β-lactam, a model study, shown in Scheme 7, was performed to explore the deprotection conditions. Interestingly, treatment of monocyclic β-lactam **27** with 1 equiv of hydrazine in methanol for 4 h at rt and then in methylene chloride for several days released the free amino compound **34** without destruction of the methyl ester or azetidinone ring. This deprotection selectivity might be attributed to the steric effect of the *O*-TBDMS function. Subsequent

Scheme 7



Scheme 8

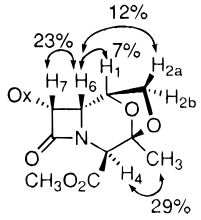


Schotten−Baumann acylation of crude **34** with phenylacetyl chloride produced the desired phenylacetamido product **35** in 52% overall yield. Hydrolysis of methyl ester **35** with 1 equiv of potassium hydroxide provided a new product. Proton NMR analysis showed that the *O*-silyl functional group was eliminated, and an olefin proton appeared as a quartet at 6.53 ppm. High resolution mass spectral analysis gave *m/e* 426 as the molecular ion corresponding to $C_{20}H_{23}N_2O_6K$ allowing assignment of the new product as structure **36**.

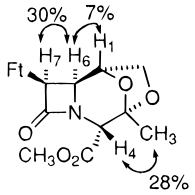
Application of the model deprotection conditions to tricyclic β-lactam **32** is outlined in Scheme 8. The free amino compound **37** was prepared by treatment of tricyclic β-lactam **32** with 1 equiv of hydrazine in a 1:1 mixture of methanol and methylene chloride at rt for 3 h, followed by refluxing in methylene chloride for 48 h and stirring for an additional 48 h at rt. Acylation of **37** *in situ* with phenylacetyl chloride and sodium bicarbonate gave 7-phenylacetamido tricyclic β-lactam **38** in 60% overall yield. Subsequent hydrolysis of **38** with 1 equiv of potassium hydroxide in a mixture of tetrahydrofuran and water provided target compound **39** in 93% yield.

Stereochemistry of Tricyclic β-Lactams 17 and 32. The configuration at C-3 and C-4 of tricyclic β-lactams **17** and **32** was determined by ^1H NMR and NOE experiments (Figure 1). When H_6 of **17** was irradiated, H_7, H_1, and H_{2a} were enhanced ca. 23%, 7%, and 12%, respectively, but no enhancement of H_4 could be observed. The α-orientation of H_4 was therefore determined. The same orientation of the methyl group on C-3 was unambiguously determined, since ca. 29% enhancement was observed for H_4 when the methyl was irradiated. Therefore, **17** possesses the 1*S*,3*R*,4*S*,6*R*,7*R* configuration.

(28) Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348.
(29) (a) Sheehan, J. C.; Cruickshank, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 3677, 3680, 3683. (b) Spry, D. O. *J. Am. Chem. Soc.* **1970**, *92*, 5006. (c) Lammert, S. R.; Kukolja, S. *J. Am. Chem. Soc.* **1975**, *97*, 5582.



17



32

Figure 1.

Also, irradiation of H_6 of **32** enhanced H_7 and H_1 ca. 30% and 7%, respectively, but no enhancement was observed for H_4. The β-orientation of H_4 was then determined. Irradiating the methyl on C-3 led to a 28% enhancement of H_4, which indicated that the methyl on C-3 has the same orientation as H_4. Hence **32** possesses the 1*R*,3*S*,4*R*,6*S*,7*S* configuration.

Biological Activity of 39. Monocyclic β-lactam **36** and enantiomeric tricyclic β-lactams **24** and **39** were tested for their antibacterial activity *in vitro*. Of these compounds, **39** exhibited significant inhibitory activity against *Streptococcus pneumoniae* (MIC 0.25 μg/mL) and moderate inhibitory activity against *Streptococcus pyogenes* (MIC 2 μg/mL), *Moraxella catarrhalis* (MIC 8 μg/mL), and *Staphylococcus aureus* (MIC 32 μg/mL). As expected, **24**, the "unnatural" enantiomer of **39**, was inactive against the same organisms.

Conclusion

A short, efficient, and enantioselective method of preparing multicyclic β-lactams has been developed. The synthetic procedure described here has successfully produced two enantiomeric tricyclic β-lactams. Starting from the Staudinger [2 + 2] cycloaddition of Ox-glycyl chloride with D-(*R*)-glyceraldehyde-derived imine or of phthaloylglycyl chloride with an optically active imine derived from a combination of L-(*S*)-glyceraldehyde and a D-threonine derivative, the asymmetric total syntheses of novel tricyclic β-lactams **24** and **39** were accomplished in only six and seven steps, respectively. Through the use of the versatile intermediates **11**, **12**, and **27** which have multiple functional groups attached to both the β-lactam nitrogen atom and the C-4 position, a number of bicyclic and polycyclic β-lactams may be created in relatively few steps. In addition, biological testing for these tricyclic β-lactams has demonstrated the potential possibility for this class as new members of the β-lactam antibiotic family.

Experimental Section

General Methods. Instruments and standard methods used have been described previously.[30] Solvents used in synthetic work were dried, when necessary, by standard methods.[31] Flash column chromatography was conducted on silica gel 60 (EM Science, 230−400 mesh ASTM). Analytical and preparative TLC was performed using commercially available aluminum-backed 0.2-mm silica gel 60 F_{254} plates (EM SEPARATIONS).

Ox-glycyl Chloride (4). Ox-glycine (**3**)[6] (3.540 g, 0.012 mol) and PCl_5 (2.499 g, 0.012 mol) in dry benzene (24 mL) were heated for 2 h at 65 °C (bath temperature) with stirring. The solvent was then removed under reduced pressure to give a crude solid, which was recrystallized from benzene and hexanes to yield 3.343 g (89%) of **4** as a crystalline solid: mp 108−110 °C; IR (KBr) 1792, 1760, 1600, 1500, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.57 (s, 2H), 7.1−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 51.7, 122.0, 124.4, 125.7, 126.9, 128.1, 128.4, 129.8, 130.2, 130.7, 135.3, 153.7, 169.5; MS(CI) *m/z* 314 (MH^+).

2,3-*O*-Isopropylidene-D-glyceraldehyde (6). To a solution of 1,2,5,6-di-*O*-isopropylidene-D-mannitol (**5**) (1.049 g, 4 mmol) in CH_2Cl_2 (6 mL) was added dropwise a suspension of $NaIO_4$ (1.07 g, 5 mmol) in 2 mL of buffer solution (0.05 M Na_2HPO_3−NaOH, pH 7) over a period of 10 min. The mixture was stirred for an additional 10 min at rt under N_2. TLC analysis indicated the reaction was complete. Na_2SO_4 was added and filtered, and the slurry residue was washed several times with CH_2Cl_2. The combined filtrate and washes were dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave 0.953 g (92%) of clean product **6** as a colorless oil: $[\alpha]^{23}_D$ +54.5° (*c* 2.7, C_6H_6) [lit.[7c] $[\alpha]^{23}_D$ +63.3° (*c* 1.25, C_6H_6)]; IR (neat) 2805, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.49 (s, 3H), 4.15 (m, 2H), 4.39 (m, 1H), 9.73 (d, 1H, *J* = 1.9 Hz); HRMS(CI) calcd for $C_6H_{11}O_3$ 131.0708, found 131.0707.

***O*-(*tert*-Butyldimethylsilyl)-D-threonine Methyl Ester (9).** To a mixture of D-threonine methyl ester hydrochloride (**8**) (7.10 g, 0.042 mol)[10] and imidazole (9.395 g, 0.138 mol) in dry DMF (30 mL) cooled to 0 °C was added TBDMSCl (6.981 g, 0.045 mol). The mixture was stirred for 30 min at 0 °C under N_2 and then allowed to warm to rt overnight. To this was added water (200 mL), and the mixture was extracted with ether (4 × 40 mL). The combined extracts were washed with H_2O (2 × 40 mL) and brine (40 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2−EtOAc (3:1) to give 9.829 g (94%) of **9** as a pale yellow oil: $[\alpha]^{23}_D$ +18.5° (*c* 1.3, $CHCl_3$); IR (neat) 3390, 3320, 1740, 1250, 1075, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.26 (d, 3H, *J* = 6.3 Hz), 1.62 (br, 2H), 3.29 (d, 1H, *J* = 2.7 Hz), 3.72 (s, 3H), 4.35 (dq, 1H, *J* = 2.7, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ −5.7, −4.8, 17.4, 20.4, 25.2, 51.4, 60.1, 69.0, 174.3; HRMS(CI) calcd for $C_{11}H_{26}NO_3Si$ 248.1682, found 248.1678.

Imine 10. A stirred solution of **9** (5.930 g, 0.024 mol) in dry CH_2Cl_2 (100 mL) was treated with $MgSO_4$ (9.268 g, 0.077 mol) at 0 °C under N_2. To this was added dropwise a solution of D-glyceraldehyde acetonide (**6**) (3.120 g, 0.024 mol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred for 4 h at 0 °C and then filtered, and the solvent was removed to give crude imine **10**, which was used in next step without further purification.

(3*S*,4*S*)- and (3*R*,4*R*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-*O*-[(*tert*-butyldimethylsilyl)oxy]propyl]-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-azetidin-2-one (11 and 12). To a solution of **10** (6.821 g, 0.019 mol) in dry CH_2Cl_2 (170 mL) at −18 °C was added TEA (2.327 g, 0.023 mol), followed by a solution of Ox-glycyl chloride (**4**) (5.347 g, 0.017 mol) in dry CH_2Cl_2 (30 mL) over a period of 20 min under N_2. The mixture was stirred for 2 h at the same temperature and then allowed to warm to 0 °C for 30 min. The reaction mixture was then washed with 5% citric acid solution (2 × 50 mL), saturated $NaHCO_3$ solution (50 mL), H_2O (50 mL), and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−EtOAc, 20:1) gave a mixture of **11** and **12** (6.598 g, 61%). Recrystallization of the mixture from CH_2Cl_2/hexanes afforded separate crops of pure **11** and **12** in a ratio of about 1:2.9. **11**: mp 71−73 °C; $[\alpha]^{21}_D$ −10.7° (*c* 1.0, CH_2Cl_2); IR (KBr) 1775, 1765, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.26 (s, 3H), 1.40 (d, 3H, *J* = 7.5 Hz), 1.42 (s, 3H), 3.73 (s, 3H), 3.95 (dd, 1H, *J* = 6.0, 8.8 Hz), 4.25 (dd, 1H, *J* = 6.0, 8.8 Hz), 4.48 (dd, 1H, *J* = 5.4, 9.3 Hz), 4.53 (m, 2H), 4.71 (m, 2H), 7.2−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −4.6, −4.5, 18.2, 20.6, 24.9, 26.0, 26.7, 52.2, 60.0, 60.8, 63.2, 68.9, 69.9, 74.7, 109.0, 123.5, 124.5, 126.5, 127.7, 127.8, 128.4, 129.4, 130.2, 130.8, 134.9, 154.0, 165.8, 168.9; HRMS(FAB) calcd for $C_{34}H_{45}N_2O_8Si$ 637.2945, found 637.2925. **12**: mp 198−199 °C; $[\alpha]^{21}_D$ +5.1° (*c* 1.0, CH_2Cl_2); IR (KBr) 1785, 1770, 1750, 1600, 1500, 1145, 1060 cm^{-1}; ^1H

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(31) *Purification of Laboratory Chemicals*, 2nd ed.; Perrin, D. D., Armarego, W. L. F., Perrin, D. R., Eds.; Pergamon: New York, 1980.

NMR ($CDCl_3$) δ 0.00 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 1.29 (s, 3H), 1.30 (d, 3H, J = 6.3 Hz), 1.34 (s, 3H), 3.64 (dd, 1H, J = 6.8, 8.3 Hz), 3.71 (s, 3H), 3.86 (dd, 1H, J = 5.6, 8.5 Hz), 3.97 (dd, 1H, J = 6.8, 8.3 Hz), 4.31 (d, 1H, J = 5.1 Hz), 4.51 (m, 1H), 4.67 (d, 1H, J = 5.4 Hz), 4.79 (m, 1H), 7.1−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.1, 17.7, 21.1, 24.7, 25.5, 26.3, 52.1, 57.8, 62.4, 65.7, 67.3, 74.6, 109.5, 122.5, 124.5, 125.8, 127.0, 128.2, 128.4, 129.9, 130.6, 130.6, 135.7, 153.0, 162.3, 168.8; HRMS(FAB) calcd for $C_{34}H_{45}N_2O_8Si$ 637.2945, found 637.2940. Anal. Calcd for $C_{34}H_{44}N_2O_8Si$: C, 64.12; H, 6.97; N, 4.40. Found: C, 63.95; H, 6.91; N, 4.29.

(3*R*,4*R*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-hydroxypropyl]-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (14). To a solution of **12** (636 mg, 1 mmol) in of CH_2Cl_2 (14 mL) was added trifluoroacetic acid (342 mg, 3 mmol). The solution was stirred for 1.5 h at rt and then diluted with CH_2Cl_2 (10 mL), washed with 10% aqueous $NaHCO_3$ solution (2 × 8 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−EtOAc, 19:1) gave 480 mg (92%) of **14** as a white solid: mp 162−163 °C; $[\alpha]^{23}_D$ −3.8° (*c* 0.5, CH_2Cl_2); IR (KBr) 3400, 1765, 1600, 1500, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.37 (s, 3H), 1.49 (d, 3H, J = 6.3 Hz), 3.51 (dd, 1H, J = 6.4, 8.2 Hz), 3.72 (dd, 1H, J = 5.4, 9.4 Hz), 3.77 (s, 3H), 3.99 (dd, 1H, J = 6.5, 8.2 Hz), 4.32 (d, 1H, J = 3.0 Hz), 4.45 (m, 1H), 4.74 (m, 1H), 4.80 (d, 1H, J = 5.3 Hz), 7.2−7.7 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 20.3, 25.1, 26.7, 52.8, 56.6, 61.70 65.7, 66.1, 67.3, 75.2, 110.1, 122.2, 124.6, 125.5, 126.8, 128.4, 128.6, 130.2, 130.5, 131.0, 136.1, 153.2, 163.9, 169.1; HRMS(FAB) calcd for $C_{28}H_{31}N_2O_8$ 523.2080, found 523.2090. Anal. Calcd for $C_{28}H_{30}N_2O_8$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.15; H, 5.90; N, 5.33.

(3*R*,4*R*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-hydroxyprop-1-enyl]-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (15). A solution of **14** (347 mg, 0.66 mmol) in dry CH_2Cl_2 (3 mL) was added to a stirred solution of Dess−Martin reagent[16,17] (381 mg, 0.9 mmol) in dry CH_2Cl_2 (7 mL). The reaction mixture was stirred for 2 h at rt under N_2 and then added to CH_2Cl_2 (10 mL) and a saturated $NaHCO_3$ (5 mL) solution containing saturated $Na_2S_2O_3$ (1 mL) solution. The mixture was stirred for 5 min. The organic layer was separated and washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−EtOAc, 19:1) gave 250 mg (72%) of **15** as a white solid: mp 95−97 °C; $[\alpha]^{23}_D$ +16.2° (*c* 0.45, CH_2Cl_2); IR (KBr) 3420, 1785, 1765, 1655, 1620, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.32 (s, 3H), 2.33 (s, 3H), 3.53 (dd, 1H, J = 5.9, 8.2 Hz), 3.73 (s, 3H), 3.91 (dd, 1H, J = 5.6, 9.4 Hz), 3.99 (dd, 1H, J = 6.4, 8.2 Hz), 4.72 (d, 1H, J = 5.6 Hz), 4.78 (m, 1H), 7.2−7.7 (m, 10H), 12.27 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 18.5, 25.1, 26.7, 52.0, 57.9, 63.5, 66.3, 74.6, 100.1, 110.0, 122.3, 124.6, 125.7, 126.8, 128.4, 128.6, 130.1, 130.7, 130.9, 136.2, 153.4, 163.0, 169.6, 178.0; HRMS(EI) calcd for $C_{28}H_{28}N_2O_8$ 520.1845, found 520.1832.

(3*R*,4*R*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-hydroxyprop-1-enyl]-3-(2-oxo-4,5-diphenyl-1-oxazolinyl)-4-[(*S*)-1,2-dihydroxyethyl]azetidin-2-one (16). To a solution of **15** (80 mg, 0.154 mmol) in THF (3 mL) was added 1 N HCl (3 mL). The mixture was stirred for 3 d at rt under N_2. The solvent was then removed under reduced pressure, and the residue was isolated by flash column chromatography on silica gel (CH_2Cl_2−CH_3OH, 20:1) to yield 62 mg (84%) of **16** as a white solid: mp 109−111 °C; $[\alpha]^{23}_D$ +25.1° (*c* 0.33, $CHCl_3$); IR (KBr) 3450, 1760, 1655, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.55 (dd, 1H, J = 5.3, 11.4 Hz), 3.69 (dd, 1H, J = 3.5, 11.4 Hz), 3.75 (s, 3H), 4.19 (t, 1H, J = 5.6 Hz), 4.27 (m, 1H), 4.73 (d, 1H, J = 5.6 Hz), 7.2−7.6 (m, 10H), 12.24 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8, 52.2, 58.7, 61.6, 64.6, 69.4, 100.5, 123.0, 124.7, 125.7, 126.8, 128.5, 128.6, 130.0, 130.6, 130.8, 136.3, 154.3, 163.0, 169.6, 177.3; HRMS(FAB) calcd for $C_{25}H_{25}N_2O_8$ 481.1611, found 481,1606.

[1*S*,3*R*,4*S*,6*R*,7*R*]-Tricyclic *β*-Lactam (17) and (1*S*,6*R*,7*R*)-1-(Hydroxymethyl)-*O*-2-isocephem (18). Method A. A solution of **16** (33 mg, 0.069 mmol) and *p*-toluenesulfonic acid monohydrate (11 mg, 0.058 mmol) in dry benzene (3 mL) was refluxed for 1 h using a Dean−Stark apparatus. The reaction mixture was then cooled to 0 °C, and saturated $NaHCO_3$ solution (2 mL) was added. After the mixture was stirred for 5 min, EtOAc (8 mL) was added. The organic layer was separated and washed with saturated $NaHCO_3$ (3 mL), H_2O (3 mL), and brine (3 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by preparative TLC (CH_2Cl_2−acetone, 20:0.8) gave 10 mg (31%) of **17** as a white solid: mp 271−273 °C. Anal. Calcd for $C_{25}H_{22}N_2O_7$: C, 64.92; H, 4.80; N, 6.06. Found: C, 65.05; H, 4.70; N, 6.06.

Method B. A mixture of acetonide **15** (104 mg, 0.2 mmol) and ferric chloride (33 mg, 0.2 mmol) in dry benzene (4 mL) was refluxed for 20 min under argon and then cooled to 0 °C, and 10% aqueous $NaHCO_3$ solution (2 mL) was added. After stirring for 3 min, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−THF, 20:0.5) gave 37 mg (40%) of **17** as a white solid and 16 mg (17%) of **18** as a pale yellow solid. **17**: mp 273−275 °C; $[\alpha]^{23}_D$ −130.7° (*c* 0.45, $CHCl_3$); IR (KBr) 1780, 1770, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H,), 3.61 (d, 1H, J = 5.0 Hz), 3.73 (s, 3H), 3.81 (d, 1H, J = 7.5 Hz), 3.89 (dd, 1H, J = 4.4, 7.5 Hz), 4.62 (s, 1H), 4.76 (d, 1H, J = 4.4 Hz), 4.94 (d, 1H, J = 5.0 Hz), 7.2−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 23.1, 52.5, 55.3, 61.2, 63.2, 69.5, 70.4, 105.1, 122.7, 124.6, 126.3, 127.1, 128.3, 128.5, 129.9, 130.6, 130.7, 135.6, 152.3, 165.8, 167.8; HRMS(FAB) calcd for $C_{25}H_{23}N_2O_7$ 463.1505, found 463.1484. **18**: mp 125−127 °C; $[\alpha]^{23}_D$ −57.6° (*c* 0.5, $CHCl_3$); IR (KBr) 3450, 1760, 1720, 1620, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.73 (dd, 1H, J = 5.1, 8.8 Hz), 3.80 (s, 3H), 3.93 (m, 2H), 4.86 (m, 1H), 5.02 (d, 1H, J = 5.1 Hz), 7.2−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.0, 51.2, 51.9, 61.2, 61.9, 75.0, 106.0, 123.1, 124.6, 126.1, 127.1, 128.3, 128.6, 130.0, 130.6, 130.7, 135.8, 153.8, 156.2, 160.5, 163.1; HRMS(FAB) calcd for $C_{25}H_{23}N_2O_7$ 463.1505, found 463.1506.

Photooxidation of Compound 12. A methanolic (1 mL) solution of **12** (10 mg, 0.016 mmol) in a Pyrex flask was irradiated with a 275-W sunlamp for 20 h. The solvent was removed, and the residue was purified by preparative TLC (hexanes−EtOAc, 6:4) to give 4 mg (40%) of **19** as a yellowish, viscous oil: IR (neat) 1780, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H), 1.17 (s, 3H), 1.22 (s, 3H), 1.45 (d, 3H, J = 6.0 Hz), 3.69 (m, 2H), 3.81 (s, 3H), 4.42 (dd, 1H, J = 5.4, 8.4 Hz), 4.52 (d, 1H, J = 5.0 Hz), 4.74 (m, 2H), 5.88 (d, 1H, J = 5.3 Hz), 7.72 (m, 4H), 8.03 (m, 1H), 8.13 (m, 1H), 8.70 (m, 1H), 8.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.0, 17.9, 21.4, 24.4, 25.8, 26.1, 52.3, 60.9, 61.9, 62.4, 65.6, 67.6, 75.0, 109.6, 119.6, 120.3, 120.3, 120.6, 123.2, 124.8, 126.0, 126.5, 127.6, 127.7, 128.0, 128.6, 128.8, 136.2, 153.9, 161.8, 169.0; HRMS(FAB) calcd for $C_{34}H_{43}N_2O_8Si$ 635.2789, found 635.2752.

(3*S*,4*S*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-O-[(*tert*-butyldimethylsilyl)oxy]propyl]-3-[*N*-(carbobenzyloxy)amino]-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (21). *β*-Lactam **11** (10 mg, 0.016 mmol) was dissolved in methanol (1 mL) containing 1 drop of glacial HOAc and hydrogenated over 10% Pd/C (3 mg) at 44 psi hydrogen pressure for 24 h. The reaction mixture was filtered through Celite and the solvent removed. The crude products containing **20** and bibenzyl were used directly in the following acylation step without further purification.

To a solution of the crude product **20** prepared above in THF (0.5 mL) and H_2O (0.4 mL) was added solid $NaHCO_3$ (2 mg, 0.023 mmol) followed by addition of benzyl chloroformate (3.5 μL, 0.023 mmol). The mixture was stirred in an ice bath for 30 min. H_2O (1 mL) was added and extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by preparative TLC (CH_2Cl_2−acetone, 20:0.8) gave 2 mg (23%) of **21**: IR (neat) 1780, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.25 (s, 3H), 1.33 (d, 3H, J = 6.5 Hz), 1.51 (s, 3H), 3.61 (dd, 1H, J = 7.9, 9.1 Hz), 3.73 (s, 3H), 3.91 (t, 1H, J = 7.6 Hz), 4.33 (dd, 1H, J = 1.4, 5.6 Hz), 4.52 (d, 1H, J = 2.4 Hz), 4.55 (m, 1H), 5.11 (m, 1H), 5.14 (s,

2H), 5.48 (dd, 1H, J = 5.6, 10.7 Hz), 5.94 (d, 1H, J = 10.7 Hz), 7.33 (m, 5H); MS(FAB) m/z 551 (MH^+), 493, 360, 159, 149, 91 (100%); HRMS(FAB) calcd for $C_{27}H_{43}N_2O_8Si$ 551.2789, found 551.2787.

[1*S*,3*R*,4*S*,6*R*,7*R*]-7-Phenylacetamido Tricyclic β-Lactam 23. Compound **17** (51 mg, 0.11 mmol) was dissolved in a mixture of CH_3OH−THF−5% HOAc (8 mL, 1:1:0.1) and hydrogenated over 10% Pd/C (20 mg) at 52 psi hydrogen pressure for 10 h. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The residual crude **22** was dissolved in acetone−H_2O (3 mL, 1:1). To this was added phenylacetyl chloride (16 μL, 0.12 mmol) followed by the addition of solid $NaHCO_3$ (10 mg, 0.12 mmol). The reaction mixture was stirred for 50 min in an ice bath. Water (2 mL) was added, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−THF, 20:1) gave 22 mg (55%) of **23** as a white solid: mp 59−61 °C; $[\alpha]^{22}_D$ −122.0° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1775, 1755, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 3H), 3.64 (dd, AB, 2H, J = 15.7 Hz), 3.77 (s, 3H), 3.85 (m, 3H), 4.35 (dd, 1H, J = 0.8, 5.3 Hz), 4.55 (s, 1H), 5.40 (dd, 1H, J = 4.6, 7.2 Hz), 6.09 (d, 1H, J = 7.2 Hz), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.3, 43.3, 52.5, 55.9, 59.3, 63.6, 68.6, 70.8, 105.0, 127.7, 129.2, 133.9, 167.8, 171.3, 171.9; HRMS(EI) calcd for $C_{18}H_{20}N_2O_6$ 360.1321, found 360.1330.

Potassium Salt 24. Potassium hydroxide (5.6 mg, 0.1 mmol) was dissolved in H_2O (1 mL). To a solution of **23** (7.2 mg, 0.02 mmol) in THF (0.2 mL) was added the KOH solution (0.2 mL, 0.02 mmol). The reaction mixture was stirred for 40 min at rt, diluted with H_2O (0.2 mL), and extracted with ether (3 × 0.5 mL) and EtOAc (0.5 mL). Removal of H_2O under reduced pressure gave 6.2 mg (81%) of **24** as a white solid: mp 186−190 °C; $[\alpha]^{22}_D$ −170.3° (*c* 0.35, CH_3OH); IR (KBr) 1755, 1655, 1605, 1380 cm^{-1}; ^1H NMR (CD_3OD) δ 1.69 (s, 3H), 3.64 (dd, 2H, J = 14.3 Hz), 3.75 (dd, 1H, J = 5.1, 7.4 Hz), 3.82 (m, 2H), 4.33 (s, 1H), 4.34 (d, 1H, J = 4.8 Hz), 5.31 (d, 1H, J = 4.6 Hz), 7.30 (m, 5H); ^{13}C NMR (CD_3OD) δ 24.4, 43.1, 57.4, 59.6, 67.2, 70.0, 72.1, 106.9, 128.0, 129.6, 130.2, 136.8, 174.0, 174.6, 174.7; HRMS(FAB) calcd for $C_{17}H_{17}N_2O_6K_2$ 423.0361, found 423.0357.

(3*S*,4*S*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-*O*-[(*tert*-butyldimethylsilyl)oxy]propyl]-3-phthalimido-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (27). Imine **26** was prepared by the reaction of protected D-threonine **9** (4.997 g, 0.02 mol) and L-(*S*)-glyceraldehyde acetonide **25** (2.630 g, 0.02 mol) in the presence of $MgSO_4$ (7.310 g, 0.06 mol) following the same procedure for the preparation of imine **10**. To a solution of imine **26** in dry CH_2Cl_2 (50 mL) cooled in an ice bath was added dropwise TEA (3.036 g, 0.03 mol) followed by addition of a solution of phthaloylglycyl chloride (5.575 g, 0.025 mol) in dry CH_2Cl_2 (20 mL) under argon. The reaction mixture was then stirred for 3 h, diluted with CH_2Cl_2 (80 mL), and washed with H_2O (100 mL), 1 N HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), H_2O (100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−EtOAc, 20:1) gave 9.902 g (90%) of **27** as a white solid: mp 55−57 °C; $[\alpha]^{22}_D$ +34.1° (*c* 3.7, $CHCl_3$); IR (KBr) 1775, 1745, 1725, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.24 (s, 3H), 1.28 (d, 3H, J = 6.2 Hz), 1.33 (s, 3H), 3.60 (dd, 1H, J = 5.9, 8.6 Hz), 3.71 (dd, 1H, J = 6.8, 8.6 Hz), 3.85 (s, 3H), 4.13 (dd, overlap with the peaks at 4.15 ppm, 1H, J = 5.5 Hz), 4.15 (d, 1H, J = 6.6 Hz), 4.53 (dt, 1H, J = 6.1, 6.6 Hz), 4.71 (p, 1H, J = 6.3 Hz), 5.36 (d, 1H, J = 5.4 Hz), 7.7−7.9 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.5, 17.8, 21.5, 24.8, 25.7, 26.4, 52.3, 54.6, 62.6, 64.3, 65.2, 67.2, 75.2, 109.6, 123.8, 131.4, 134.6, 163.2, 166.9, 168.6; HRMS (FAB) calcd for $C_{27}H_{39}N_2O_8Si$ 547.2476, found 547.2490.

(3*S*,4*S*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-hydroxypropyl]-3-phthalimido-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (29). To a solution of β-lactam **27** (2.184 g, 0.004 mol) in dry CH_2Cl_2 (50 mL) was added TFA (0.92 mL, 0.012 mol) dropwise at 14 °C under N_2. The solution was stirred for 4 h at 14 °C and then diluted with CH_2Cl_2 (70 mL), washed with H_2O (70 mL), 10% $NaHCO_3$ solution (70 mL), and brine (70 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−THF, 20:1) gave 1.503 g (87%) of **29** as a white solid: mp 72−73 °C; $[\alpha]^{22}_D$ −7.0° (*c* 1.0, $CHCl_3$); IR (KBr) 1770, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.42 (s, 3H), 1.44 (d, 3H, J = 6.6 Hz), 3.51 (dd, 1H, J = 5.8, 8.6 Hz), 3.73 (dd, 1H, J = 6.2, 8.6 Hz), 3.83 (s, 3H), 4.55 (m, 5H), 5.57 (d, 1H, J = 5.3 Hz), 7.7−8.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.2, 25.1, 26.3, 52.5, 54.8, 62.7, 63.0, 66.0, 67.3, 75.5, 110.5, 124.1, 131.2, 134.9, 166.2, 167.0, 169.2; HRMS(FAB) calcd for $C_{21}H_{24}N_2O_8$ 433.1611, found 433.1609.

(3*S*,4*S*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-hydroxyprop-1-enyl]-3-phthalimido-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (30). A suspension of **29** (0.877 g, 2.03 mmol) and Dess−Martin periodinane (1.463 g, 3.45 mmol) in dry CH_2Cl_2 (35 mL) was stirred for 2.5 h at rt under argon. Saturated $NaHCO_3$ solution (20 mL) and saturated $Na_2S_2O_3$ solution (10 mL) was added, and the reaction mixture was stirred vigorously for 5 min. The organic layer was separated and washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−THF, 20:1) gave 0.785 g (90%) of **30** as a white solid: mp 180−181 °C; $[\alpha]^{22}_D$ −17.7 (*c* 3.3, $CHCl_3$); IR (KBr) 1780, 1770, 1715, 1655, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.33 (s, 3H), 2.39 (s, 3H), 3.48 (dd, 1H, J = 8.5, 5.6 Hz), 3.72 (dd, 1H, J = 8.5, 6.4 Hz), 3.84 (s, 3H), 4.17 (dd, 1H, J = 9.5, 5.6 Hz), 4.39 (m, 1H), 5.44 (d, 1H, J = 5.6 Hz), 7.7−7.9 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.5, 25.2, 26.8, 52.2, 54.5, 62.9, 66.0, 75.4, 100.4, 109.9, 124.0, 131.2, 134.9, 163.9, 167.2, 169.7, 177.6; HRMS (EI) calcd for $C_{21}H_{22}N_2O_8$ 430.1376, found 430.1360.

(3*S*,4*S*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-hydroxyprop-1-enyl]-3-phthalimido-4-[(*R*)-1,2-dihydroxyethyl]azetidin-2-one (31). A solution of **30** (215 mg, 0.5 mmol) and *p*-toluenesulfonic acid (71 mg, 0.4 mmol) dissolved in THF (5 mL) and H_2O (5 mL) was refluxed for 18 h, and the solvent was then removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel, eluting with 1:1 CH_2Cl_2−THF, affording 170 mg (87%) of **31** as a white solid: mp 186−188 °C; $[\alpha]^{22}_D$ −15.8 (*c* 0.4, $CHCl_3$); IR (KBr) 3400, 1785, 1750, 1710, 1685, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (br, 1H), 2.41 (s, 3H), 2.67 (d, 1H, J = 3.8 Hz), 3.45 (m, 2H), 3.84 (s, 3H), 4.05 (m, 1H), 4.30 (dd, 1H, J = 7.3, 5.7 Hz), 5.49 (d, 1H, J = 5.7 Hz), 7.7−8.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.7, 52.3, 54.9, 61.0, 64.0, 70.4, 100.8, 124.0, 131.4, 134.9, 164.3, 167.6, 177.4; HRMS (FAB) calcd for $C_{18}H_{19}N_2O_8$ 391.1141, found 391.1142.

[1*R*,3*S*,4*R*,6*S*,7*S*]-Tricyclic β-Lactam (32) and 1-(Hydroxymethyl)-*O*-2-isocephem (33). A mixture of glycol **31** (78 mg, 0.2 mmol), *p*-TsOH (34 mg, 0.2 mmol), and silica gel (468 mg) in dry benzene (5 mL) was refluxed for 25 min. The solid was filtered and washed with EtOAc several times. The combined organic solvents were washed with 10% aqueous $NaHCO_3$ solution twice and brine, dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography on silica gel (CH_2Cl_2−THF, 20:1) gave 36 mg (48%) of **32** and 13 mg (17%) of **33** both as white solids. **32:** mp 235−236 °C; $[\alpha]^{22}_D$ +163.6° (*c* 0.75, $CHCl_3$); IR (KBr) 1790, 1770, 1725, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (s, 3H), 3.80 (s, 3H), 3.81 (m, 2H), 3.90 (d, 1H, J = 5.0 Hz), 4.51 (d, 1H, J = 3.9 Hz), 4.73 (s, 1H), 5.71 (d, 1H, J = 5.0 Hz), 7.7−8.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.2, 52.6, 54.90, 57.5, 63.1, 69.6, 70.7, 105.2, 124.0, 131.4, 134.7, 166.5, 167.2, 167.8; HRMS(FAB) calcd for $C_{18}H_{17}N_2O_7$ 373.1036, found 373.1015. **33**: mp 114−117 °C; $[\alpha]^{22}_D$ +50.1° (*c* 1.0, $CHCl_3$); IR (KBr) 3450, 1790, 1770, 1720, 1615, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.69 (d, 2H, J = 4.9 Hz), 3.77 (dd, 1H, J = 8.9, 5.0 Hz), 3.84 (s, 3H), 4.47 (dt, 1H, J = 8.9, 5.0 Hz), 5.83 (d, 1H, J = 5.2 Hz), 7.7−7.9 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.0, 51.1, 52.0, 57.6, 61.9, 75.1, 106.2, 123.9, 131.4, 134.7, 155.7, 161.6, 163.3, 167.4; HRMS (FAB) calcd for $C_{18}H_{17}N_2O_7$ 373.1036, found 373.1041.

(3*S*,4*S*)-1-[1(*R*)-(Methoxycarbonyl)-2(*S*)-*O*-[(*tert*-butyldimethylsilyl)oxy]propyl]-3-phenylacetamido-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one (35). To a solution of **27** (218 mg, 0.4 mmol) in CH_3OH (8 mL) was added

hydrazine monohydrate (22 mg, 0.44 mmol), and the mixture was stirred for 4 h at rt. The solvent was removed, and the residue was redissolved in of CH_2Cl_2 (8 mL). The solution was refluxed for 20 h and then stirred at rt for 5 d. The solid was filtered off, and the solvent was removed to give crude **34** which was then dissolved in a 1:1 mixture of acetone and H_2O (10 mL). To this was added phenylacetyl chloride (77 mg, 0.5 mmol) followed by addition of solid $NaHCO_3$ (42 mg, 0.5 mmol). The reaction mixture was stirred overnight at rt and then extracted with CH_2Cl_2 (4 × 5 mL). The combined extracts were washed with brine (8 mL), dried (Na_2SO_4), filtered, and concentrated. Isolation by flash column chromatography (CH_2Cl_2−THF, 20:1) gave 112 mg (52%) of **35** as a white solid: mp 93−95 °C; $[\alpha]^{22}_D$ +35.7° (*c* 1.5, $CHCl_3$); IR (KBr) 3270, 1780, 1755, 1655, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 1.18 (d, 3H, J = 6.2 Hz), 1.20 (s, 3H), 1.37 (s, 3H), 3.57 (dd, AB, 2H, J = 15.1 Hz), 3.63 (m, 2H), 3.72 (s, 3H), 3.81 (dd, 1H, J = 5.0, 7.5 Hz), 3.91 (d, 1H, J = 7.4 Hz), 3.95 (m, 1H), 4.62 (dq, 1H, J = 7.2, 6.2 Hz), 5.26 (dd, 1H, J = 5.2, 8.1 Hz), 6.48 (d, 1H, J = 8.1 Hz), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.3, 17.8, 21.5, 24.7, 25.7, 26.4, 43.5, 52.2, 56.6, 61.8, 65.3, 65.9, 67.2, 75.5, 109.5, 127.5, 129.1, 129.2, 134.1, 166.1, 169.0, 171.1; HRMS(FAB) calcd for $C_{27}H_{43}N_2O_7Si$ 535.2840, found 535.2857.

Salt 36. To a solution of **35** (10 mg, 0.02 mmol) in THF (0.2 mL) was added 0.1 M KOH solution (0.2 mL, 0.02 mmol), and the mixture was stirred for 45 min at rt and extracted with ether (4 × 0.4 mL) and EtOAc (0.4 mL). Removal of water under reduced pressure gave 4 mg (50%) of **36** as a white solid: mp 171−174 °C; $[\alpha]^{22}_D$ +41.5° (*c* 0.2, CH_3OH); IR (KBr) 1750, 1655, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.27 (s, 3H), 1.85 (d, 3H, J = 7.1 Hz), 3.38 (dd, 1H, J = 6.3, 8.5 Hz), 3.50 (dd, 1H, J = 6.6, 8.6 Hz), 3.56 (dd, AB, 2H, J = 14.0 Hz), 4.07 (m, 1H), 4.37 (dd, 1H, J = 5.4, 7.2 Hz), 5.23 (d, 1H, J = 5.4 Hz), 6.62 (q, 1H, J = 7.1 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.7, 25.5, 26.9, 43.8, 57.5, 62.5, 67.0, 76.7, 110.8, 128.2, 129.8, 130.2, 130.3, 133.1, 136.4, 167.5, 174.3; HRMS-(FAB) calcd for $C_{20}H_{24}N_2O_6K$ 427.1271, found 427.1270.

[1*R*,3*S*,4*R*,6*S*,7*S*]-7-Phenylacetamido Tricyclic β-Lactam (38). To a solution of **32** (74 mg, 0.2 mmol) in CH_3OH−CH_2Cl_2 (5 mL 1:1) was added hydrazine monohydrate (11 mg, 0.22 mmol), and the mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5 mL). Refluxing for 48 h and stirring for an additional 48 h at rt gave crude **37**. The same procedure for acylation of **34** was then followed, using phenylacetyl chloride (39 mg, 0.25 mmol) and solid $NaHCO_3$ (21 mg, 0.25 mmol) in a 1:1 mixture of acetone and H_2O (5 mL). The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2−EtOAc−CH_3OH, 3:1:0.1) affording 43 mg (60%) of **38** as a white solid: mp 64−65 °C; $[\alpha]^{22}_D$ +139.7° (*c* 0.8, $CHCl_3$); IR (KBr) 3300, 1775, 1755, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3H), 3.64 (dd, AB, J = 15.3 Hz), 3.76 (s, 3H), 3.83 (m, 3H), 4.35 (d, 1H, J = 4.9 Hz), 4.55 (s, 1H), 5.39 (dd, 1H, J = 4.6, 7.2 Hz), 6.25 (d, 1H, J = 7.2 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.3, 43.3, 52.5, 55.9, 59.3, 63.6, 68.6, 70.8, 105.0, 127.6, 129.1, 134.0, 167.8, 171.3, 171.9; HRMS-(FAB) calcd for $C_{18}H_{21}N_2O_6$ 361.1400, found 361.1409.

Salt 39. Following the same procedure for preparation of **36**, hydrolysis of **38** (7 mg, 0.02 mmol) in THF (0.2 mL) with 0.1 M KOH solution (0.2 mL, 0.02 mmol) gave 7 mg (93%) of **39** as a white solid: mp 185−187 °C; $[\alpha]^{22}_D$ +124.8° (*c* 0.25, CH_3OH); IR (KBr) 1755, 1655, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3H), 3.62 (dd, AB, 2H, J = 14.2 Hz), 3.75 (dd, 1H, J = 5.4, 7.3 Hz), 3.82 (d, 1H, J = 7.3 Hz), 3.83 (d, 1H, J = 4.4 Hz), 4.33 (s, 1H), 4.34 (d, 1H, J = 4.9 Hz), 5.31 (d, 1H, J = 4.8 Hz), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.4, 43.2, 57.4, 59.6, 67.3, 69.9, 72.1, 106.9, 128.0, 129.6, 130.2, 136.8, 174.0, 174.5; HRMS(FAB) calcd for $C_{17}H_{18}N_2O_6K$ 385.0802, found 385.0827.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **11**, **12**, **15**, **17**, **18**, **23**, **24**, **27**, **29**−**33**, **35**, **36**, **38**, and **39** (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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