Asymmetric Synthesis of (1′*R*,3*R*,4*R*)-4-Acetoxy-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-azetidinone and Other 3-(1′-Hydroxyethyl)-2-azetidinones from (*S*)-(+)-Ethyl 3-Hydroxybutanoate: Formal Total Synthesis of (+)-Thienamycin

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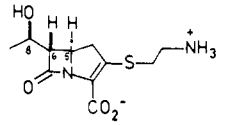
Abstract: The synthesis of (1′*R*,3*R*,4*R*)-4-acetoxy-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-azetidinone, an important precursor for the synthesis of carbapenems and penems, is detailed. The methodology utilized relies on the addition, cyclization reaction between the dianion of (*S*)-(+)-ethyl 3-hydroxybutanoate and *N*-arylaldimines. The syntheses of other useful optically active 3-(hydroxyethyl)-2-azetidinones are presented. A study of factors influencing the stereochemistry in the addition, cyclization reaction for the formation of 3-(1′-hydroxyethyl)-2-azetidinones is detailed.

Thienamycin (**1**), discovered in 1976, is a novel β-lactam antibiotic[1] isolated from *Streptomyces cattleya*.[2] It possesses exceptional potency and a wide spectrum of antibacterial activity. Of note also is its stability against β-lactamases. However, the isolation of thienamycin (**1**) afforded, unfortunately, low yields, quite contrary to the usual high-yield fermentation processes of other noted β-lactam antibiotics. Outstanding biological properties, low fermentation yields, and its unique structure consisting of a highly strained 1-carbapenem ring system concomitant with three chiral centers have made thienamycin (**1**) and related β-lactam antibiotics, such as the penems **2** and the olivanic acids **3** (epithienamycin C and D) and **4** (epithienamycin A, B, E, and F; R_1 = H, SO_3H), a special challenge in organic synthesis.[3]



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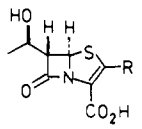

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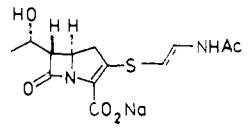

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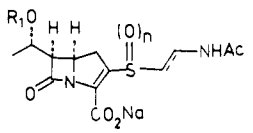

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Most especially, the control of the relative and absolute stereochemistry at the three contiguous chiral centers remains a difficult synthetic task.[4] Thienamycin (**1**) and the unnatural penems **2** require the 6α-(8*R*-(hydroxyethyl)) side chain and the olivanic acids **3** and **4** the 6α- and 6β-(8*S*-(hydroxyethyl)) side chains, respectively. Because of the inherent instability of the bicyclic β-lactam ring system in **1–4** and related systems, strategies toward their total synthesis usually first focus on the elaboration of the correct stereochemistry at the three chiral centers. The ring closure toward formation of the bicyclic ring system is performed as late as possible in the synthetic scheme.

In several approaches, the hydroxyethyl side chain has been introduced stereoselectively by aldol condensation[5] between enolates of suitable racemic and optically active 2-azetidinones or methyl 6-bromopenicillanate[6] and acetaldehyde or an acetaldehyde equivalent. Higher ratios of the desired trans-*R* isomer could be obtained in a two-step sequence by stereoselective reduction of trans-acetylated 2-azetidinones and 6-diazopenicillanate.[6a,7]

Other strategies involved the incorporation of the hydroxyethyl group prior to the construction of the β-lactam ring system. For example, chiral building blocks D-glucose,[8] L-threonine,[9] and D-allothreonine[10] have been utilized. 1,3-Dipolar cycloadditions of nitrile oxides and nitrones with crotonates also resulted in a stereo- and enantiocontrolled introduction of the 3-(hydroxyethyl)

(1) For recent reviews on β-lactam antibiotics, see: Morin, R. B.; Gorman, M. *Chemistry and Biology of β-Lactam Antibiotics*; Academic: New York, 1982; Vol. 1–3. Brown, A. G.; Roberts, S. M. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; The Royal Society of Chemistry: Burlington House, London, 1984. Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1985; p 1.

(2) Kahan, J. S.; Kahan, F.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.

(3) For reviews on the synthesis of carbapenem β-lactam antibiotics, see: Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2, p 227. Hoppe, D. *Nachr. Chem., Tech. Lab.* **1982**, *30*, 24. Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. For a review on penems, see: Ernest, I. In *Chemistry and Biology of the β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2, p 315. Also see: Afonso, A.; Hon, F.; Weinstein, J.; Ganguly, A.; McPhail, A. T. *J. Am. Chem. Soc.* **1982**, *104*, 6138.

(4) For a recent review on the stereospecific construction of chiral β-lactams, see: Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103. Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498.

(5) For leading references, see: Bouffard, F. A.; Salzmann, T. N. *Tetrahedron Lett.* **1985**, *26*, 6285. Hamlet, A. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 411.

(6) For the conversion of penicillins to thienamycin and penems, see: (a) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765. (b) DiNinno, F.; Beattie, T. R.; Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960. (c) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K. J.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2505. (d) Maruyama, H.; Hiraoka, T. *J. Org. Chem.* **1986**, *51*, 399. (e) Alpegiani, M.; Bedeschi, A.; Giudici, F.; Perrone, E.; Franceschi, G. *J. Am. Chem. Soc.* **1985**, *107*, 6398. (f) Brown, B. B.; Volkmann, R. A. *Tetrahedron Lett.* **1986**, *27*, 1545.

(7) (a) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (b) Nago, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673.

(8) Durette, P. L. *Carbohydr. Res.* **1982**, *100*, C27–C30. Ikota, N.; Yoshino, O.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 1929. Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R. *Can. J. Chem.* **1982**, *60*, 2292. Knierzinger, A.; Vasella, A. *J. Chem. Soc., Chem. Commun.* **1984**, 9.

(9) For leading references, see: (a) Maruyama, H.; Shiozaki, M.; Hiraoka, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3264. (b) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, n. *J. Am. Chem. Soc.* **1985**, *107*, 1438. (c) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *Lect. Heterocycl. Chem.* **1985**, *8*, 43.

(10) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Chem. Lett.* **1983**, 169.

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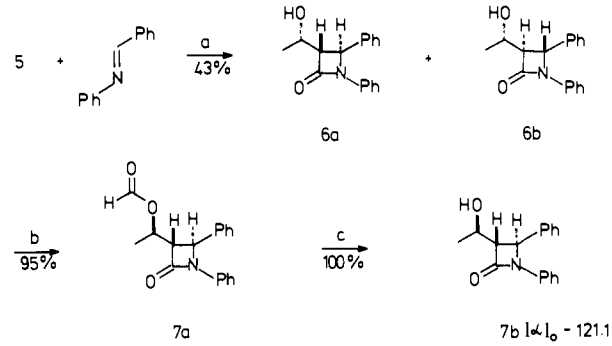
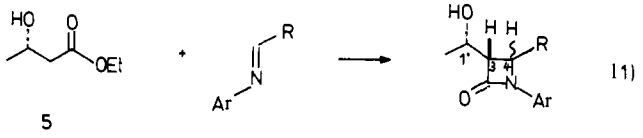
Scheme I[a]



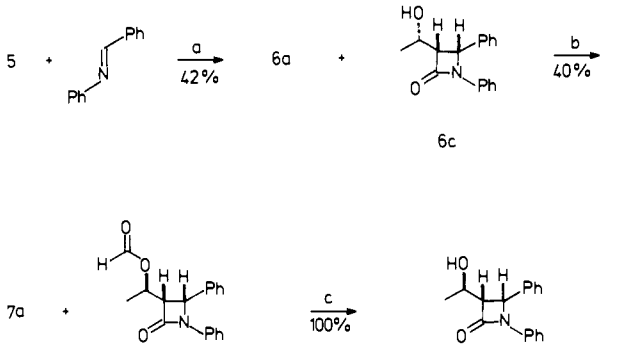
[a] (a) Method B, −20–25 °C; (b) PPh_3, diethyl azodicarboxylate (DEAD), HCO_2H, 0–25 °C, 1.5 h; (c) MeOH, HCl, 25 °C, 1.5 h.

side chain of the 2-azetidinones prior to β-lactam formation.[11] Another approach involves a cycloaddition reaction between diketene and an aldimine containing the 1-(−)-menthyl ester group as a chiral auxiliary. The resulting *trans*-3-acetyl-2-azetidinone was stereoselectively reduced to form the desired (1′-hydroxyethyl)-2-azetidinone.[12] Optically active ketene derived from α-bromo-3-hydroxybutyric acid chloride has also recently[13] been used in a ketene imine cycloaddition reaction for the synthesis of penems.

Recently, we[14,15] and others[16] have demonstrated that readily available optically active esters of 3-hydroxybutyric acid[17] can be used in a convergent approach toward the stereo- and enantiocontrolled synthesis of 3-(1′-hydroxyethyl)-2-azetidinones (eq 1). We would like now to report the full details of this approach, as well as the successful implementation of this chemistry for the formal total synthesis of (+)-thienamycin (**1**).



Scheme II[a]



[a] (a) Method B, −20–25 °C; (b) PPh_3, diethyl azodicarboxylate (DEAD), HCO_2H; 0–25 °C, 1.5 h; (c) MeOH, HCl, 25 °C, 1.5 h.

Results and Discussion

It is well-known that the dianion of β-hydroxy esters can be α-alkylated to yield threo products with high diastereoselectivity.[18] The easy availability of optically active *S*- and *R*-configurated esters of 3-hydroxybutyric acid, therefore, provides access toward reaction products with high diastereomeric and enantiomeric purity. We rationalized that we could utilize this methodology in a novel approach toward the synthesis of 3-(1′-hydroxyethyl)-2-azetidinones by dianion arylaldimine condensation and that we would be able to effectively control the relative and the absolute stereochemistry at the carbon atoms 1′ and 3 at the β-lactam ring system. We also envisioned the possibility of controlling the stereochemistry at carbon 4 via an aldol-like transition state as proposed for the diastereoselective aldol condensation to obtain reaction products with either cis or trans stereochemistry at the β-lactam ring. In model studies[15c] with benzylideneaniline (Scheme I). the dianion of racemic and *S*-configurated ethyl 3-hydroxybutanoate (**5**) was reacted between −20 °C and room temperature for 5 h in the presence of hexamethylphosphoric triamide as a cosolvent (method B), generating a mixture of azetidinones **6a** and **6b** in chemical yields of 43% (racemic) and 38% (optically active).[19] The major isomer *trans*-**6a** (90–95%) was assigned the (1′*S*,3*S*,4*S*) configuration, the minor isomer *trans*-**6b** (5–10%) the (1′*S*,3*R*,4*R*) configuration.[7,20] No cis isomer was detected under these reaction conditions. After inversion of the configuration at the hydroxyethyl side chain, the

(11) Kametani, T.; Huang, S.-P.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060. Kametani, T.; Nagahara, T.; Suzuki, Y.; Yokohama, S.; Huang, S.-P.; Ihara, M. *Tetrahedron* **1981**, *37*, 715. Kametani, T.; Huang, S.-P.; Nagahara, T.; Yokohama, S.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 964. Kametani, T.; Nagahara, T.; Ihara, M.; *J. Chem. Soc., Perkin Trans. 1* **1981**, 3048. Kametani, T.; Nagahara, T.; Honda, T. *J. Org. Chem.* **1985**, *50*, 2327.

(12) Sunagawa, M.; Goda, K.; Enomoto, M.; Sasaki, A. *Heterocycles* **1984**, *21*, 430.

(13) Lombardi, P.; Colombo, M.; Crugnola, M.; Franceschi, G. Br. Patent 2144419A, 1985.

(14) Preliminary accounts of this work have been presented: Georg, G. I. *Abstracts of Papers*, 188th National Meeting of the American Chemical Society, Philadelphia, PA; American Chemical Society: Washington, DC, 1984; ORGN 118. Georg, G. I.; Gill, H. S.; Gerhardt, C. *Abstract of Papers*, 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, Canada, 1985; G3-27. Georg, G. I.; Gill, H. S. *Abstract of Papers*, 190th National Meeting of the American Chemical Society, Chicago, IL; American Chemical Society: Washington, DC, 1985; ORGN 69.

(15) (a) Georg, G. I.; Gill, H. S. *J. Chem. Soc., Chem. Commun.* **1985**, 1433. (b) Georg, G. I.; Gill, H. S.; Gerhardt, C. *Tetrahedron Lett.* **1985**, *26*, 3903. (c) Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 3779.

(16) (a) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. (b) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927. (c) Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, *26*, 937. (d) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523. (e) Chiba, T.; Nakai, T. *Chem. Lett.* **1985**, 651. (f) Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647. (g) Hart, D. J.; Ha, D.-C. *Tetrahedron Lett.* **1985**, *26*, 5493. (h) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, 1343. (i) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2149. (j) Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153.

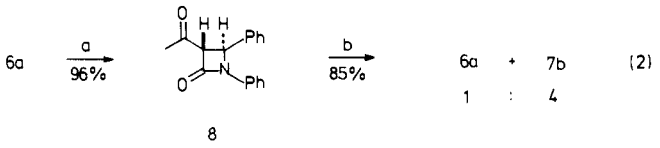
(17) (a) *S* Enantiomer: Seebach, D.; Sutter, M. A.; Weber, R. H.; Zueger, M. F. *Org. Synth.* **1984**, *63*, 1. Wipf, B.; Kupfer, E.; Bertazzi, R.; Leuenberger, H. G. W. *Helv. Chim. Acta* **1983**, *66*, 485. (b) *R* Enantiomer: Seebach, D.; Zueger, M. *Helv. Chim. Acta* **1982**, *65*, 495. Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, *65*, 293. Ethyl (*S*)-3-hydroxybutanoate, methyl (*R*)-3-hydroxybutanoate, and (*R*)-3-hydroxybutyric acid are commercially available from Fluka. (*S*)-3-Hydroxybutyric acid, sodium salt and (*R*)-3-hydroxybutyric acid, sodium salt are available from Aldrich.

(18) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825; (b) **1980**, *63*, 1383. (c) Frater, G. *Tetrahedron Lett.* **1981**, *22*, 425. (d) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197. (e) Kraus, G. A.; Taschner, M. J. *Tetrahedron Lett.* **1977**, 4575.

(19) Throughout our work we observed lower yields when optically active ethyl 3-hydroxybutanoate (both commercially available material and product prepared by bakers' yeast reduction in our laboratory) was utilized as compared to racemic starting material. It has been pointed out by Seebach (ref 17a) that (*S*)-(+)-ethyl 3-hydroxybutanoate may undergo transesterification/oligomerization at room temperature. This may be the reason for the lower yields observed. β-Lactams **6**, **7**, and **9** were synthesized from (*S*)-(+)-ethyl 3-hydroxybutanoate with an enantiomeric excess of 86%, as obtained by bakers' yeast reduction. The optical rotations of **6**, **7**, and **9** were taken after recrystallization. β-Lactams **6a**, **7a**, and **7b** contain small amounts (<5%) of the corresponding trans β-lactams with opposite stereochemistry at the β-lactam ring. We were not able to separate these isomers by chromatography or recrystallization.

(20) Otto, H. H.; Mayrhofer, R.; Bergmann, H. J. *Liebigs Ann. Chem.* **1983**, 1152. The assignment of the diastereoisomers was made by Otto, correlating the chemical shifts of **6a** and **7b** with the analogue chemical shifts of (8*R*)- and (8*S*)-thienamycins, penicillins, and cepholosporins. The signals for the methyl group and the proton signal at C_4 in α-*S* derivatives such as **6a** are generally found to resonance at lower field than the corresponding α-*R* derivatives such as **7b**. In order to confirm these assignments, we subjected **6a** and **7b** to mesylation, followed by β-elimination with sodium bicarbonate (see ref 27). As expected, β-lactam **6a** produced the (*Z*)-ene [^{1}H NMR ($CDCl_3$) δ 2.04 (d, J = 7.8 Hz, 3 H, CH_3), 5.73 (q, d, $J_{8,9}$ = 7.6, $J_{5,8}$ = 0.9 Hz, 1 H, CH=C)] and β-lactam **7b** the (*E*)-ene [^{1}H NMR ($CDCl_3$) δ 1.58 (d, J = 8.0 Hz, 3 H, CH_3), 6.33 (q, d, $J_{8,9}$ = 7, $J_{5,8}$ = 1.6 Hz, 1 H, CH=C)]. The ^{1}H NMR data for the (*Z*)- and (*E*)-enes correlated very well with the chemical shift values reported for similar 2-azetidinones.[27]

desired trans-*R* isomer **7b** was obtained in 95% overall yield from **6a** via **7a** according to the Mitsunobu procedure, using triphenylphosphine, diethyl azodicarboxylate, and formic acid, followed by acid hydrolysis.[21] An alternative but less satisfactory approach toward **7b** involved oxidation with pyridinium chlorochromate[22] of **6a** to furnish the 3-acetyl derivative **8** in 96% yield and subsequent reduction with diisopropylamine–borane[6a] to give **6a**/**7a** in a 1:4 ratio (eq 2).



(2)

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(a) Pyridinium chlorochromate, CH_2Cl_2, 25 °C, 15 h; (b) diisopropylamine–borane, magnesium trifluoroacetate, ether, 25 °C, 75 min.

The reaction temperature during the dianion imine addition, cyclization greatly influenced the stereochemistry of the resulting products (Scheme II). Quenching the reaction mixture at −20 °C after 7 h gave a 3:2 ratio of *trans*-**6a** and *cis*-**6c** (42% yield). After formation of the inverted formyl esters, *trans*-**7a** and *cis*-**9a** could be separated by column chromatography. Hydrolysis of **9a** quantitatively yielded *cis*-**9b**. The initial model studies presented here demonstrated the great potential for the synthesis of optically active 3-(1′-hydroxyethyl)-2-azetidinone precursors with correct absolute stereochemistry of type **7b** for the elaboration of (+)-thienamycin (**1**) and the penems **2**, of type **6a** for *trans*-olivanic acids **3**, and of the enantiomer of **9b** for *cis*-olivanic acids **4**.[15c] Subsequently, we investigated the dianion imine addition, cyclization under a variety of reaction conditions and with several aldimines (Table I of the supplementary material). The dianion imine reaction with benzylideneaniline (run 1, Table I) was performed with lithium diisopropylamide and lithium isopropylcyclohexylamide as a base for the dianion formation without any noticeable effect on the stereochemical outcome of the reaction. Utilization of the *tert*-butyl ester instead of ethyl 3-hydroxybutanoate (run 1, Table I) also gave essentially the same result. Increasing the reaction time to 20 h at 25 °C (run 4, Table I) produced **6a** and **6b** in a 2:1 ratio (see also run 23 in the 4-furyl series). Without hexamethylphosphoric triamide as a cosolvent (method A), the reaction with benzylidineaniline (run 5, Table I) gave a 1:4 ratio of *trans*-**6a** and *cis*-**6c**.

Generally, in all reactions (runs 2, 11, 18, and 19 in Table I) lower reaction temperatures favored formation of cis products, and small changes in temperature influenced the distribution of product ratios.[23] Because of the influence of the reaction temperature on the stereoselectivity of the reaction, we believe that kinetic and thermodynamic factors play an important role in the consequential stereochemistry.[15c,24]

One possible mechanism for the formation of the trans products would involve epimerization at position 3 of the β-lactam ring via enolate formation to give **6b** or at position 4 to give **6a** via anion formation stabilized by the neighboring amide functionality. We, therefore, subjected a 1:1 mixture of β-lactams *cis*-**6c** and *trans*-**6a** at 25 °C for 2 h to 1.5 equiv of lithium isopropylcyclohexylamide in the presence of 1.5 equiv of hexamethylphosphoric triamide without noticeable epimerization. When we increased the amount of hexamethylphosphoric triamide to 2.2 equiv and the reaction time to 4.5 h, we observed a 30% decrease of the *cis*-**6c** isomer (80-MHz NMR). Since we also had a loss of 33% in chemical yield during the reaction due to decomposition, we do not believe that cis–trans isomerization at C_3 or C_4 occurred in the case of β-lactam **6**. The presence of hexamethylphosphoric triamide, therefore, seems to promote formation of a transition state leading toward product **6a** (see also run 22, Table I).

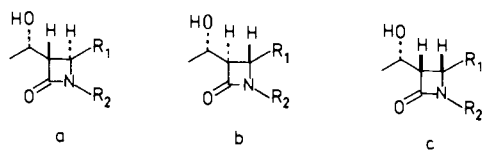


Figure 1.

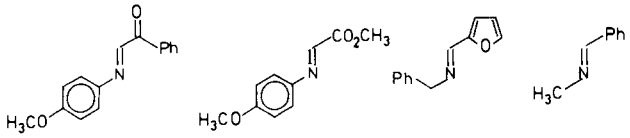


Figure 2.

Product distribution is, however, not only influenced by the reaction conditions but also even more so by the imine substituents. Introduction of a *p*-methoxyphenyl moiety, for example, as in β-lactam **10** (R_1 = Ph, R_2 = 4-MeOPh; Figure 1) gave a 3:3:1 ratio of **10a**, **10b**, and **10c** (run 6, Table I) when reacted under identical reaction conditions as previously employed for the formation of **6a**. Again, lower temperature (run 8, Table I) and omission of hexamethylphosphoric triamide (run 7, Table I) showed a strong preference for the formation of *cis*-**10c**. Isomer **10b** should conceivably be derived from **10c** by cis–trans isomerization via enolate formation. As before, we therefore subjected the cis isomer **10c** to treatment with lithium isopropylcyclohexylamide (1.5 equiv) in the presence of hexamethylphosphoric triamide to establish whether cis–trans isomerization had occurred after product formation. The reaction mixture was quenched after 2 h at 25 °C, but no cis–trans isomerization could be detected. Additionally, *cis*-**11c** (R_1 = CH=CHPh, R_2 = 4-MeOPh; Figure 1) was treated under the same conditions for 6 h at 25 °C; no isomerization was detected. Because of these results, we are of the opinion that isomerization does not occur after product formation but could rather happen at the ring-open stage, after addition of the imine but before ring closure to the β-lactam ring system. Hexamethylphosphoric triamide and higher reaction temperatures seem to promote the observed epimerization (runs 6, 9, 10, and 11; Table I).

In the 4-furyl series (runs 18–23, Table I) we found that we obtained larger amounts of *trans*-**a** products with increased OMe substitution at the *N*-aryl group in the presence of hexamethylphosphoric triamide. Omission of hexamethylphosphoric triamide produced a *trans*-**a**:*cis*-**c** ratio of 1:1 (run 19, Table I) when a *N*-(4-methoxyphenyl) substituent was employed. The diastereomeric ratios in the 4-vinyl series (runs 9–16, Table I), however, did not depend on the substitution pattern on the *N*-aryl ring, nor was the stereochemistry dependent on the nature of the vinyl substituents explored. Again, the presence of hexamethylphosphoric triamide and a higher reaction temperature promoted formation of the undesired *trans*-**b** isomer (runs 9–11, Table I). The best reaction conditions for the formation of **11a** and **11c** (R_1 = CH=CHPh, R_2 = 4-MeOPh; Figure 1) were found (run 13, Table I) in quenching the reaction mixture at +10 °C after 2.5 h to give 6:4 to 4:6 mixtures of **11a** and **11c** in yields between 77% and 99%. Employing the above reaction conditions for the formation of 4-(phenylethynyl)-2-azetidinone **15** (R_1 = C≡C—Ph, R_2 = 4-MeOPh; Figure 1) produced **15a** and **15c** in a 2:3 ratio but only in a moderate yield of 32%. In addition to the imines

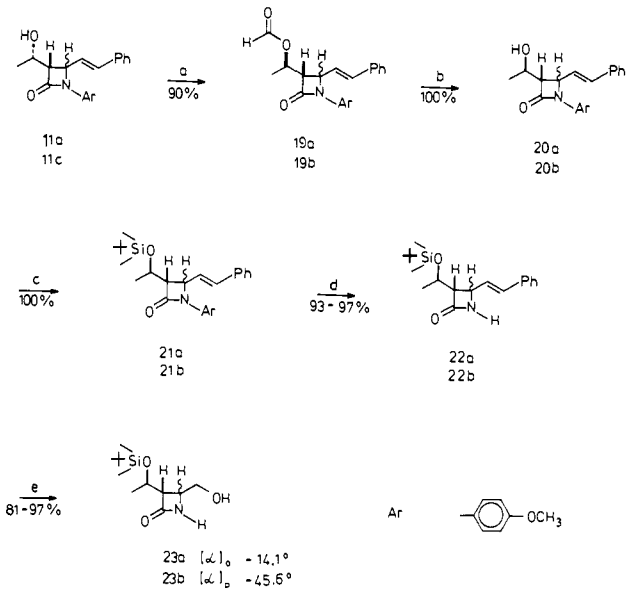
(21) Melillo, D. G.; Liu, T.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. Melillo, D. G.; Liu, T.; Sletzinger, M.; Shinkai, I.; Ryan, K. *Tetrahedron Lett.* **1980**, *21*, 2783.

(22) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.

(23) Addition of the imine was usually performed at −78 °C, then the temperature was raised to −20 °C (see experimental procedures), and the mixture was warmed slowly to quenching temperature. In run 19 (Table I) a 1:1 mixture of *trans*-**16a** and *cis*-**16c** was observed under these conditions. However, addition of the imine at −20 °C under otherwise identical conditions resulted in a 10:3:3 mixture of **16a**, **16b**, and **16c**.

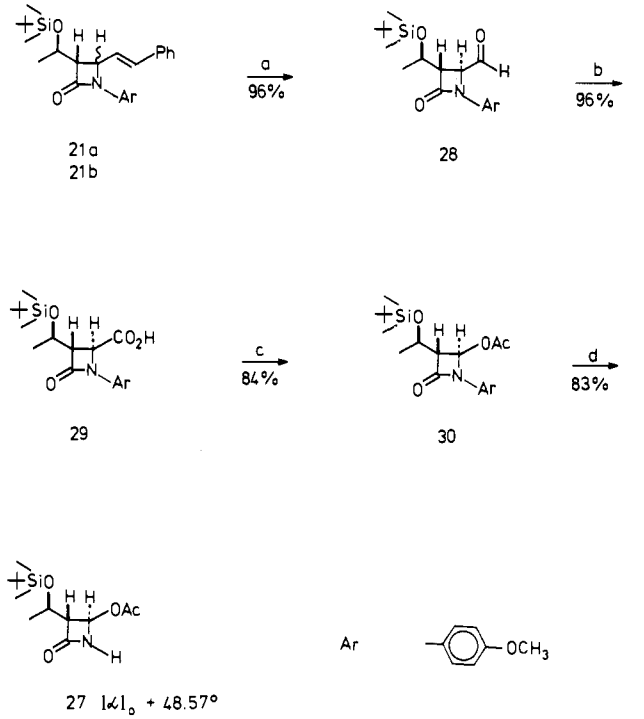
(24) It has been generally assumed that deprotonation of β-hydroxy esters leads toward the formation of chelated (*Z*)-enolates. See: ref 18e and Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 80. α-Alkylation of chelated β-hydroxy esters should produce high levels of 1,2-diastereoselection *regardless* of enolate geometry. Studies concerning the influence of enolate geometry on the stereoselectivity of β-lactams for simple enolates have been reported by Hart; see ref 16a. Studies toward the elucidation of enolate geometry of 3-hydroxybutanoates, imine geometry, reaction rates, and their influence on the stereochemistry of the β-lactams are currently under investigation.

Scheme III[a]



[a] (a) PPh_3, diethyl azodicarboxylate (DEAD), HCO_2H, 0–25 °C, 1.5 h; (b) MeOH, HCl, 25 °C, 15 h; (c) dimethylformamide (DMF) *tert*-butyldimethylsilyl chloride, imidazole, 25 °C, 3 h; (d) ammonium cerium(IV) nitrate, −20 °C, 40 min, CH_3CN, H_2O; (e) O_3, $NaBH_4$, CH_2Cl_2, −78–0 °C.

Scheme IV[a]



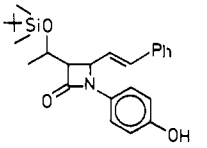
[a] (a) Osmium tetroxide, sodium periodate, THF/H_2O, 25 °C, 22 h; (b) potassium permanganate, THF/H_2O, 25 °C, 5 h; (c) lead tetraacetate, DMF/H_2O, 70 °C, 45 min; (d) ammonium cerium(IV) nitrate, CH_3CN/H_2O, −10 °C, 12 min.

in Table I, we explored the dianion imine reaction with the imines detailed in Figure 2; we did not, however, observe any β-lactam formation. Apparently, neither an aliphatic substituent[25] at the imine nitrogen nor a carbonyl group at the imine carbon seems to be compatible with the reaction conditions employed.

In conclusion, we have demonstrated that the diastereomeric distribution of isomers **a**, **b**, and **c** (Figure 1) in the dianion imine condensation depends greatly on the two imine substituents for the reaction. Hexamethylphosphoric triamide seems to promote the formation of transition states favoring the formation of *trans*-**a** products in the case of β-lactams **6** (R_1 and R_2 = Ph; Figure 1) and **18** (R_1 = furyl, R_2 = 3,4,5-$(MeO)_3$Ph; Figure 1). With other imines hexamethylphosphoric triamide and higher reaction temperatures facilitate epimerization at C_3, as our results suggest, possibly prior to ring closure of the β-lactam ring system.

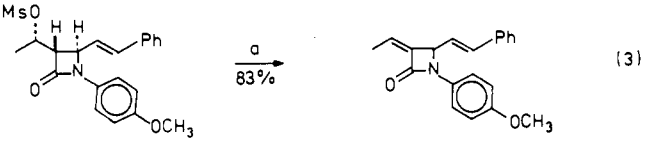
After these initial studies concerning the scope of the reaction, the influence of the imine substituents, and the reaction conditions on the stereochemical outcome of the reaction, we proceeded to unequivocally confirm the absolute stereochemistry of our products by synthesizing useful thienamycin precursors. The first synthetic target was the known 4-(hydroxymethyl)-2-azetidinone **23a**, which could be achieved in a six-step sequence[15a] in an overall yield of 33% (Scheme III). (*S*)-(+)-Ethyl 3-hydroxybutanoate of 86% optical purity[17a] was used in this reaction as obtained from reduction of ethyl acetoacetate using bakers' yeast.

Dianion imine condensation with *N*-anisylcinnamylideneimine gave a 1:1 mixture of trans and cis β-lactams **11a** and **11c** in 77% yield.[19] Mitsunobu inversion of **9** clearly gave the inverted (*R*)-(hydroxyethyl)azetidinones **19** in up to 90% yield. As a side product[26] we also isolated the enelactam **25**[27] in yields ranging from 3% to 12%. After acid hydrolysis of **19**, the hydroxyl group in **20** was protected as *tert*-butyldimethylsilyl ether to yield **21a** and **21b**. Subsequently, **21a** and **21b** were subjected separately to oxidative dearylation with ammonium cerium(IV) nitrate[28] to obtain the N-unprotected β-lactams *trans*-**22a** and *cis*-**22b** in 93% yield.[29] Taking into account reaction temperature and reaction time, we also isolated various amounts (0–12%) of O-demethylated side products **26**.[30]



26

Ozonolysis of **22a** and **22b** followed by reductive workup with sodium borohydride[31] produced the 4-(hydroxymethyl)-2-azeti-



(a) $NaHCO_3$, MeOH, 65 °C, 2 h.

(25) For utilization of *N*-alkyl imines in enolate imine condensations, see: Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643.

(26) β-Hydroxy esters are known to form elimination products under Mitsunobu conditions. Mitsunobu, O. *Synthesis* **1981**, 1.

(27) Anti elimination of (8*S*,6*S*)-configurated 3-(hydroxyethyl)azetidinones is expected to produce *Z*-configurated enelactams. Because of ambiguous chemical shifts, we confirmed the structure of **25** according to a protocol (eq 3) reported by Merck. Johnston, D. B. R.; Schmitt, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313.

(28) (a) Fukuyama, T.; Frank, R. K.; Jewell, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 2122. (b) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(29) Optical rotations of intermediates **21** and **22** were taken after recrystallization; intermediates **23** were synthesized from recrystallized **22** and purified by column chromatography.

(30) Early quenching of the reaction mixtures in the oxidation reactions with ammonium cerium(IV) nitrate produced up to 20% oxidatively demethylated products of type **26**. Resubjecting the phenol **26** to ammonium cerium(IV) nitrate gave the expected product **22**. Mechanistic studies for oxidative demethylation of 1,4-dimethoxybenzenes have been shown to proceed via aryl–oxygen cleavage. Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227. Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627. The isolation of phenol **26** indicates the possibility of alkyl–oxygen cleavage as a competing mechanism for the oxidative dearylation of *N*-aryl β-lactams.

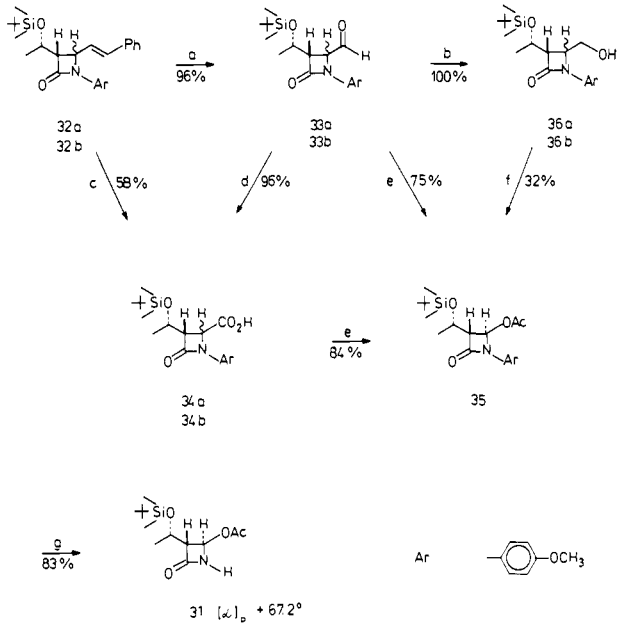
dinone *trans*-**23a** in 97% yield and *cis*-**23b** in 81% yield. The overall yields from (*S*)-ethyl 3-hydroxybutanoate were 33% for *trans*-**23a** and 26% for *cis*-**23b** and are comparable to those from other reported methods for the synthesis of thienamycin precursors. The optical rotation for **23a** was found to be identical with the literature value[32] for (1′*R*,3*S*,4*S*)-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(hydroxymethyl)-2-azetidinone synthesized from L-threonine. The absolute stereochemistry of the cis products was later established (Scheme IV) by cis–trans isomerization at C_4. Intermediates **23a** and the enantiomer of **23b** should be convertible to thienamycin (**1**) and *cis*-olivanic acids **4**, respectively, by stepwise carbon chain elongation according to a procedure published by Merck.[33]

It has become evident that the 4-acetoxy derivative **27** (Scheme IV) is the key intermediate for the synthesis of thienamycin (**1**) and related penems. The side chain as needed for the ring closure toward formation of the penem system can be introduced in a one-step sequence through a Lewis acid catalyzed displacement at position 4 with the appropriate silyl enol ether.[34] The synthesis of **27** via the 3-hydroxybutanoate route is detailed in Scheme IV.[35]

Oxidative cleavage of the double bond in optically active azetidinone **21** with osmium tetroxide and sodium periodate[36] yielded aldehyde **28** in 96% yield as a single trans isomer. Optimal conditions for the transformation of aldehyde **28** to carboxylic acid **29** were found to be oxidation with potassium permanganate, which proceeded in 96% yield. Oxidative decarboxylation of acid **29** with lead tetraacetate[34b] produced the *trans*-4-acetoxy derivative **30** in 84% yield. Attempts to introduce the side chain according to the Merck procedure[34] at this stage with the *N*-(4-methoxyphenyl) substituent still in place failed to produce the desired chain-elongated product. Oxidative dearylation[29] with ammonium cerium(IV) nitrate of **30** then produced the 4-acetoxy-2-azetidinone **27** in 83% yield, identical in all respects with the material previously described by other authors. The optical rotation of our product with $[\alpha]_D$ +48.57° compared favorably with other reported values such as $[\alpha]_D$ +47.9° from D-allothreonine,[37] $[\alpha]_D$ +47.2° from L-threonine,[9a] and $[\alpha]_D$ +50.0° from 6-aminopenicillanic acid.[6c] The overall yield for **27** in eight steps from optically active 3-hydroxybutanoate was 44% and 58% with racemic material due to the differences in yield associated with the first step of the synthesis of 77% vs. quantitative yield.[19] This is, to our knowledge, the most efficient methodology developed yet for the synthesis of this important key intermediate for the synthesis of 3-(hydroxyethyl)penems. Since **27** has previously been converted to (+)-thienamycin,[33,34b] its synthesis constitutes a formal, total synthesis of (+)-thienamycin.

Following now the methodology as optimized for the synthesis of *R*-configurated 3-(hydroxyethyl)-4-acetoxy-2-azetidinone **27**, we also prepared the optically active *S*-configurated azetidinone **31** (Scheme V) as a precursor for the synthesis of olivanic acids **3**. Protection of the hydroxyethyl group of **11** as *tert*-butyldimethylsilyl ether **32** proceeded quantitatively. Oxidative cleavage of the double bond in **32** with osmium tetroxide and sodium periodate resulted in the formation of aldehydes **33a** and **33b**, in 96% yield. Oxidation with potassium permanganate gave the

Scheme V[a]



[a] (a) Osmium tetroxide, sodium periodate, THF/H_2O, 25 °C, 22 h; (b) sodium borohydride, ethanol, 0 °C, 2 h; (c) potassium permanganate, sodium periodate, 25 °C, 20 h; (d) potassium permanganate, THF/H_2O, 25 °C, 5 h; (e) lead tetraacetate, CH_3CN, 70 °C, 3 h; (f) lead tetraacetate, cupric acetate, CH_3CN, reflux, 13 h; (g) ammonium cerium(IV) nitrate, CH_3CN/H_2O, −10 °C, 12 min.

carboxylic acids **34** in high yield (96%). The cis–trans mixture **34** underwent oxidative decarboxylation with lead tetraacetate to produce 84% of the trans-configurated 4-acetoxy derivative **35**. Again, oxidative dearylation with ammonium cerium(IV) nitrate generated the *S*-configurated 4-acetoxy-2-azetidinone **31** in 83% yield. Comparison of the optical rotation of **31**, $[\alpha]_D$ +67.2°, with the literature value[38] of $[\alpha]_D$ +67.9° (as obtained from 6-aminopenicillanic acid) demonstrated an optical purity of 99% for **31**.

Additionally, to the above described methodology we considered shorter, but lower yielding, pathways toward the synthesis of **31**: direct oxidative decarboxylation of the aldehydes **33** and the hydroxymethyl derivatives **36** (both racemic) produced **35** in 75% and 32% yield, respectively. Cleavage of the double bond in **32** toward the formation of acids **34** with potassium permanganate and sodium periodate proved to be not as efficient (58% yield) as the two-step sequence via aldehyde–carboxylic acid (92% overall yield).

The overall optimized yield for optically active **31** was 50% and 64% for the racemic material.[19] β-Lactam **31** can be converted to epithienamycin C and D according to the Merck methodology.[33,34b] With this paper we believe to have demonstrated and verified the potential of the 3-hydroxybutanoate route for the construction of optically active 3-(hydroxyethyl)-2-azetidinones. The attractive features are the utilization of readily available optically active starting material and high diastereo- and enantioselectivity as well as overall good yields.

Experimental Section

General Procedures for the Dianion Imine Condensation, Method A. To a stirred solution of *N*-isopropylcyclohexylamine (0.622 g, 0.724 mL, 4.4 mmol) in tetrahydrofuran (5.0 mL) at −78 °C (dry ice/acetone bath), *n*-butyllithium (4.0 mmol) in hexanes was added dropwise. After 15 min, neat ethyl 3-hydroxybutanoate (0.2643 g, 0.26 mL, 2.0 mmol) was added slowly. The temperature of the reaction mixture was then kept at −20 °C (dry ice/carbon tetrachloride bath) for 60–90 min, and the mixture was then recooled to −78 °C. A solution of the appropriate imine (2 mmol) in THF (3.0 mL) was added dropwise over a period of 5 min. The

(31) Georg, G.; Durst, T. *J. Org. Chem.* **1983**, *48*, 2092.
(32) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron* **1984**, *40*, 1795. Shiozaki, M.; Ishida, N.; Hiraoka, T.; Yanagisawa, H. *Tetrahedron Lett.* **1981**, *22*, 5205.
(33) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(34) (a) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379. (b) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293. See also ref 6a. (c) The importance of acetoxy derivative **27** has recently been underscored with its utilization in the synthesis of β-methyl 1-carbapenems. Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675 (see also ref 7b).
(35) In this sequence (Scheme IV) we utilized 100% optically pure ethyl (*S*)-3-hydroxybutanoate. The optical rotations of our products were taken after purification by column chromatography without recrystallization.
(36) Cavalleri, B.; Ballotta, R.; Lancini, G. C. *J. Heterocycl. Chem.* **1972**, 979.
(37) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. *Tetrahedron* **1983**, *39*, 2399.
(38) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1981**, *29*, 2899.
(39) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.

−78 °C cooling bath was replaced by a −20 °C bath, and the reaction mixture was allowed to warm up to +10 °C gradually. After 2.5 h the reaction was quenched with saturated ammonium chloride solution (20 mL), and the reaction mixture was extracted with ether (3 × 20 mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting oil was purified by column chromatography on silica gel using ethyl acetate/hexane mixtures as eluents.

Method B. This method is the same as described in method A with the exception of the addition of the imine in a solution of hexamethylphosphoric triamide (0.72 g, 0.7 mL, 4.0 mmol) and tetrahydrofuran (3.0 mL). For the reaction time and temperature, see Table I in the supplemental material.

(1′*S*,3*S*,4*R*)-3-(1′-Hydroxyethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (11a) and (1′*S*,3*S*,4*S*)-3-(1′-Hydroxyethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (11c). **Method A**: colorless oil; yield[19] 99% (racemic), 77% (optically active) 1:1 ratio of **11a** and **11c**; $[\alpha]_D$ +21.00° (*c* 1.39, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 and 1.38 (d, J = 6.0 Hz, 3 H, CH_3), 2.20 (br s, 1 H, OH), 3.08 (dd, J = 2.0, 6.0 Hz, 1 H, C-H_3), 3.38 (dd, J = 6.0, 6.7 Hz, 1 H, CH_3), 3.68 (s, 3 H, OCH_3), 3.9–4.3 (m, 1 H, CH), 4.4 (dd, J = 2.0, 10 Hz, 1 H, C-H_4), 4.65 (dd, J = 6.0, 10 Hz, 1 H, C-H_4), 6.0–7.3 (m, 11 H, vinyl H and ArH); EIMS, *m/e* (relative intensity) 323 (M^+, 42), 279 (18), 236 (45), 202 (39), 174 (31), 149 (50), 131 (38), 91 (45), 43 (100); HRMS, $C_{20}H_{21}NO_3$ requires *m/e* 323.1520, found 323.1520. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.00; H, 6.91; N, 4.20.

(1′*R*,3*S*,4*R*)- and (1′*R*,3*S*,4*S*)-3-((Formyloxy)ethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (19a and 19b). Experimental procedures as described for the formation of **7a**: yield 90%; IR ($CHCl_3$) 1740, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 and 1.46 (d, J = 6.5 Hz, 3 H, CH_3), 3.14 and 3.60 (dd, J = 2.5, 8 Hz; dd, J = 6 Hz, 1 H, C-H_3), 3.63 (s, 3 H, OCH_3), 4.46 and 4.59 (dd, J = 2.5, 10 Hz; dd, J = 6, 10 Hz, 1 H, C-H_4), 5.2–5.6 (m, 1 H, CH), 6.17 and 6.18 (dd, J = 10, 20 Hz, 1 H, CH), 6.5–7.5 (m, 10 H, ArH, CH), 7.60 and 7.77 (s, 1 H, HCO_2); EIMS, *m/e* 351 (M^+), 149 (base); HRMS, $C_{21}H_{21}NO_4$ requires *m/e* 351.1469, found 351.1478.

(1′*R*,3*S*,4*R*)- and (1′*R*,3*S*,4*S*)-3-(1′-Hydroxyethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (20a and 20b). Experimental procedure as described for **7b**: quantitative yield; IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 and 1.43 (d, J = 6 Hz, 3 H, CH_3), 1.98 and 2.25 (br d, 1 H, OH), 3.10 and 3.45 (m and dd, J = 6.0, 10 Hz, 1 H, C-H_3), 3.73 (s, 3 H, OCH_3), 4.0–4.85 (m, 1 H, CH), 6.0–7.5 (m, 11 H, ArH, CH); EIMS, *m/e* 323 (M^+), 43 (base); HRMS, $C_{20}H_{21}NO_3$ requires *m/e* 323.1520, found 323.1520.

(1′*R*,3*S*,4*R*)- and (1′*R*,3*S*,4*S*)-3-(1′-((*tert*-Butyldimethylsilyl)-oxy)ethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (21a and 21b). To a solution of a 1:1 mixture of **20a** and **20b** (1.63 g, 5.04 mmol) in dimethylformamide (8 mL), imidazole (0.858 g, 12.60 mmol) and *tert*-butyldimethylsilyl chloride (0.912 g, 6.05 mmol) were added at 25 °C. The reaction mixture was stirred for 22 h and poured into water (60 mL). After extraction with hexanes (4 × 40 mL), the combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. Purification and separation of **21a** and **21b** were achieved through column chromatography on silica gel with ethyl acetate/hexanes (1:1) to yield 2.20 g (100%) of **21a** and **21b** (ratio 1.05:1). **21a**: mp 124 °C (petroleum ether/methylene chloride); $[\alpha]_D$ −108.9° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 0.83 (s, 9 H, *t*-Bu), 1.28 (d, J = 6.0 Hz, 3 H, CH_3), 3.05 (br t, J = 1.8, 4.0 Hz, 1 H, C-H_3), 3.73 (s, 3 H, OCH_3), 4.1–4.5 (m, 1 H, CH), 4.65 (dd, J = 1.8, 8 Hz, 1 H, C-H_4), 6.25 (dd, J = 8, 16 Hz, 1 H, CH), 6.75–7.3 (m, 10 H, ArH, CH). **21b**: colorless oil; $[\alpha]_D$ +49.76° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.86 (s, 9 H, *t*-Bu), 1.28 (d, J = 6.5 Hz, 3 H, CH_3), 3.41 (t, J = 7.8, 4.2 Hz, 1 H, C-H_3), 3.68 (s, 3 H, OCH_3), 4.16–4.56 (m, 1 H, CH), 4.56–4.81 (m, 1 H, C-H_4), 6.4–7.4 (m, 11 H, ArH, CH); EIMS, *m/e* 437 (M^+), 73 (base); HRMS, $C_{26}H_{35}NO_3Si$ requires *m/e* 437.2384, found 437.2382.

(1′*R*,3*S*,4*R*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(2′-phenylethenyl)-2-azetidinone (22a). A solution of β-lactam **21a** (80 mg, 0.183 mmol) in acetonitrile (20 mL) was cooled for 2 min in a −20 °C cooling bath (carbon tetrachloride/dry ice), and then an aqueous solution (10 mL) of ammonium cerium(IV) nitrate (200 mg, 0.365 mmol) was added dropwise to the reaction mixture over a period of 3 min. The reaction mixture was stirred at −20 °C for 15 min before more solid ammonium cerium(IV) nitrate (100 mg, 0.182 mmol) was added to the reaction mixture. In case the water froze, the reaction vessel was removed from the cooling bath for a short time and recooled after the ice had dissolved. After an additional 25 min at −20 °C, thin-layer chromatography showed that the starting material had been consumed. The reaction was quenched in saturated sodium bicarbonate solution (60 mL), and the mixture was extracted 3 times with methylene chloride. The combined organic layers were dried over magnesium sulfate, filtered, and evaporated under reduced pressure to yield a brown oil. Flash chromatography on silica gel using ethyl acetate/hexanes (3:7) as eluent yielded 53.6 mg (93%) of **22a** as colorless crystals: mp 85–86 °C (petroleum ether/methylene chloride); $[\alpha]_D$ +40.7° (*c* 0.856, $CHCl_3$); IR ($CHCl_3$) 3430, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.80 (s, 9 H, *t*-Bu), 2.90 (dd, J = 2, 4 Hz, 1 H, C-H_3), 3.93–4.38 (m, 2 H, CH and C-H_4), 5.83 (br s, 1 H, NH), 6.15 (dd, J = 8.0, 16.0 Hz, 1 H, CH), 6.55 (d, J = 16.0 Hz, 1 H, CH), 7.2 (s, 5 H, ArH); EIMS, *m/e* 316 (M^+ − 15), 75 (base); CIMS (NH_3), *m/e* 332 (M^+ + 1), 274 (base); HRMS, $C_{18}H_{26}NO_2Si$ (M − 15) requires *m/e* 316.1731, found 316.1725.

(1′*R*,3*S*,4*S*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(2′-phenylethenyl)-2-azetidinone (22b). Same experimental procedure as described for **22a**: yield 96%; mp 79–80 °C (petroleum ether/methylene chloride); $[\alpha]_D$ −45.90° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3432, 1752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.80 (s, 9 H, *t*-Bu), 1.15 (d, J = 6 Hz, 3 H, CH_3), 3.25 (m, 1 H, C-H_3), 3.95–4.4 (m, 2 H, CH and C-H_4), 5.88 (br s, 1 H, NH), 6.35–7.4 (m, 7 H, CH and ArH); EIMS, *m/e* 316 (M^+ − 15), 75 (base); CIMS (NH_3), *m/e* 332 (M^+ + 1), 274 (base); HRMS, $C_{18}H_{26}NO_2Si$ (M − 15) requires *m/e* 316.1731, found 316.1725.

(1′*R*,3*S*,4*S*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(hydroxymethyl)-2-azetidinone (23a). β-Lactam **22a** (0.05 g, 0.151 mmol) dissolved in a mixture of methylene chloride (20 mL) and methanol (0.2 mL) was cooled to −78 °C, and ozone was introduced until the blue color persisted for 5 min. The excess of ozone was removed in a stream of nitrogen, and dimethyl sulfide (0.04 mL, 0.54 mmol) was added to the reaction mixture. After the mixture was stirred at −20 °C for 15 min, sodium borohydride (0.05 g, 1.32 mmol) in ethanol (20 mL) was added dropwise, and then the mixture was stirred an additional 35 min. The reaction mixture was poured into a saturated ammonium chloride solution (10 mL), extracted with methylene chloride (3 × 10 mL), dried with magnesium sulfate, and evaporated under reduced pressure. Flash chromatography on silica gel with ethyl acetate as eluent yielded 0.038 g (97%) of **23a**: mp 87–88 °C; $[\alpha]_D$ −14.11° (*c* 0.595, $CHCl_3$); IR ($CHCl_3$) 3457, 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, *t*-Bu), 1.24 (d, J = 6 Hz, 3 H, CH_3), 2.27 (br s, 1 H, OH), 2.92 (dd, J = 2.0, 6.0 Hz, 1 H, C-H_3), 3.79 (m, 3 H, CH_2, C-H_4), 4.19 (m, 1 H, CH), 6.09 (br s, 1 H, NH); EIMS, *m/e* 244 (M^+ − 15), 75 (base); CIMS (NH_3), *m/e* 260 (M^+ + 1), 75 (base); HRMS, $C_{11}H_{22}NO_3Si$ (M − 15) requires *m/e* 244.1368, found 244.1353.

(1′*R*,3*S*,4*R*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-(hydroxymethyl)-2-azetidinone (23b). Experimental procedure as described for **23a**: yield 81%; mp 93–94 °C; $[\alpha]_D$ −45.63° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3446, 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, *t*-Bu), 1.31 (d, J = 6.0 Hz, 3 H, CH_3), 3.26 (m, 2 H, OH and C-H_3), 3.84 (m, 3 H, CH_2 and C-H_4), 4.34 (m, 1 H, CH), 5.96 (br s, 1 H, NH); EIMS, *m/e* 244 (M^+ − 15), 75 (base); CIMS (NH_3), *m/e* 260 (M^+ + 1), 75 (base); HRMS, $C_{11}H_{22}NO_3Si$ (M − 15) requires *m/e* 244.1368, found 244.1356.

(1′*R*,3*R*,4*R*)-4-Acetoxy-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-azetidinone (27). Ammonium cerium(IV) nitrate (130 mg, 0.24 mmol) dissolved in water (0.3 mL) was added to a cooled (−10 °C) solution of β-lactam **30** (24.3 mg, 0.06 mmol) in acetonitrile (1.5 mL). The reaction mixture was stirred at −10 °C for 12 min and then poured into a mixture of ether (4 mL), saturated aqueous sodium bicarbonate solution (2 mL), and 10% sodium bisulfite (5 mL). The ether layer was separated, washed twice with 10% sodium bicarbonate solution (3 mL), dried, and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using ethyl acetate/hexanes (2:3) as eluent resulted in 14.3 mg (83%) of azetidinone **27** as colorless crystals: mp 104.5–106 °C; $[\alpha]_D$ +48.57° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3430, 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, *t*-Bu), 1.25 (d, J = 6.5 Hz, 3 H, CH_3), 2.10 (s, 3 H, $COCH_3$), 3.20 (dd, J = 1.5, 3.5 Hz, 1 H, C-H_3), 4.30 (m, 1 H, CH), 5.99 (d, J = 1.5 Hz, 1 H, C-H_4), 7.30 (br s, 1 H, NH).

(1′*R*,3*S*,4*S*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-formyl-1-(4′-methoxyphenyl)-2-azetidinone (28). Same experimental procedure as detailed for β-lactam **33**: yield 96%; $[\alpha]_D$ −36.8° (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.80 (s, 9 H, *t*-Bu), 1.41 d, J = 6.3 Hz, 3 H, CH_3), 3.61 (dd, J = 2.3, 7.5 Hz, 1 H, C-H_3), 3.74 (s, 3 H, OCH_3), 4.15 (m, 1 H, CH), 4.27 (dd, J = 2.3, 3.15 Hz, 1 H, C-H_4), 6.86 (d, J = 8.7 Hz, 2 H, ArH), 7.28 (d, J = 8.7 Hz, 2 H, ArH); EIMS, *m/e* 363 (M^+), 75 (base); HRMS, $C_{19}H_{29}NO_4Si$ requires *m/e* 363.1874, found 363.1875.

(1′*R*,3*S*,4*S*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(4′-methoxyphenyl)-2-azetidinone-4-carboxylic Acid (29). Same procedure as

detailed for β-lactam **34** from β-lactam **33**: yield 96%, colorless crystals; mp 167–168.5 °C; $[\alpha]_D$ −96.58° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 1760 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.79 (s, 9 H, *t*-Bu), 1.33 (d, *J* = 6.3 Hz, 3 H, CH_3), 3.44 (m, 1 H, C-H_3), 3.83 (s, 3 H, OCH_3), 4.44 (m, 1 H, CH), 4.68 (d, *J* = 1.8 Hz, 1 H, C-H_4), 6.90 (d, *J* = 8.7 Hz, 2 H, ArH), 7.31 (d, *J* = 8.7 Hz, 2 H, ArH), 9.75 (br s, 1 H, CO_2H); EIMS, *m/e* 379 (M^+), 322 (base); HRMS, $C_{19}H_{29}NO_5Si$ requires *m/e* 379.1813, found 379.1813.

(1′*R*,3*R*,4*R*)-4-Acetoxy-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(4′-methoxyphenyl)-2-azetidinone (30). Experimental procedure as detailed for the formation of **35** from β-lactam **34**: yield 84%, colorless crystals; mp 70–72 °C (ethyl acetate/hexanes); $[\alpha]_D$ −66.83° (*c* 1.21, $CHCl_3$); IR ($CHCl_3$) 3430, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.78 (s, 9 H, *t*-Bu), 1.35 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.10 (s, 3 H, $COCH_3$), 3.18 (d, *J* = 3 Hz, 1 H, C-H_3), 3.73 (s, 3 H, OCH_3), 4.35 (m, 1 H, CH), 6.25 (s, 1 H, CH_4), 6.74 (d, *J* = 10.4 Hz, 2 H, ArH), 7.25 (d, *J* = 10.4 Hz, 2 H, ArH); EIMS, *m/e* 393 (M^+), 43 (base); HRMS, $C_{20}H_{31}NO_5Si$ requires *m/e* 393.1970, found 393.1962.

(1′*S*,3*R*,4*R*)-4-Acetoxy-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-azetidinone (31). For the experimental procedure, see β-lactam **27**: yield 83%, colorless oil; $[\alpha]_D$ +67.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3430, 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, *t*-Bu), 1.31 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.13 (s, 3 H, $COCH_3$), 3.28 (dd, *J* = 1.5, 3.15 Hz, 1 H, C-H_3), 4.30 (m, 1 H, CH), 5.85 (d, *J* = 1.5 Hz, 1 H, C-H_4), 6.65 (br s, 1 H, NH); EIMS, *m/e* 230 (M^+ − 57), 75 (base); CIMS, *m/e* 272 (M^+ − 15), 159 (base). Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.62; H, 8.71; N, 4.88. Found: C, 54.70; H, 8.41; N, 4.80.

(1′*S*,3*S*,4*R*)- and (1′*S*,3*S*,4*S*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(4′-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (32a and 32b). For the experimental procedure, see β-lactam **21**. Quantitative yield, 1:1 mixture of **32a** and **32b**. **32a**: IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, *t*-Bu), 1.35 (d, *J* = 5.7 Hz, 3 H, CH_3), 3.12 (dd, *J* = 1.9, 3.3 Hz, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 4.20 (m, 1 H, CH), 4.45 (dd, *J* = 1.9, 5.7 Hz, 1 H, C-H_4), 6.20 (dd, *J* = 7.6, 16 Hz, 1 H, CH), 6.65–7.45 (m, 10 H, CH and ArH); HRMS, $C_{26}H_{35}NO_3Si$ requires *m/e* 437.2384, found 437.2397. **32b**: IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, *t*-Bu), 1.35 (d, *J* = 5.7 Hz, 3 H, CH_3), 3.45 (dd, *J* = 3.8, 4.2 Hz, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 4.30 (m, 1 H, CH), 4.65 (dd, *J* = 4.2, 6.0 Hz, C-H_4), 6.40 (dd, *J* = 6.6, 16 Hz, 1 H, CH), 6.67 (d, *J* = 8 Hz, 2 H, ArH), 6.95 (d, *J* = 8 Hz, 2 H, ArH), 7.35 (br s, 6 H, CH, ArH). Anal. Calcd for $C_{26}H_{35}NO_3Si$: C, 71.35; H, 8.00; N, 3.20. Found: C, 71.48; H, 7.89; N, 3.28.

(1′*S*,3*S*,4*S*)- and (1′*S*,3*S*,4*R*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-formyl-1-(4′-methoxyphenyl)-2-azetidinone (33a and 33b). A solution of a 1:1 mixture of **32a** and **32b** (50.0 mg, 0.15 mmol) in tetrahydrofuran/water (6 mL, 1.8:1) containing osmium tetroxide (0.015 mmol, 2.5 wt % solution in *tert*-butyl alcohol) and sodium periodate (127.8 mg, 0.6 mmol) was stirred vigorously at 25 °C for 22 h under a blanket of nitrogen. The colorless precipitate was filtered off and washed twice with ether (5 mL). The organic layer was separated, washed 2 times with 10% sodium bicarbonate solution (3 mL), dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield a dark brown oil. Purification by column chromatography on silica gel using ethyl acetate/hexanes (1:4) as eluent gave 51.8 mg (96%) of **33a** and **33b** as a light-yellow oil. **33a**: $[\alpha]_D$ +107.67° (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.84 (s, 9 H, *t*-Bu), 1.47 (d, *J* = 6.5 Hz, 3 H, CH_3), 3.66 (dd, *J* = 2.5, 7.5 Hz, 1 H, C-H_3), 3.78 (s, 3 H, OCH_3), 4.0–4.38 (m, 2 H, CH and C-H_4), 6.81 (d, *J* = 8 Hz, 2 H, ArH), 7.22 (d, *J* = 8 Hz, 2 H, ArH), 9.91 (d, *J* = 2.5 Hz, 1 H, CHO). **33b**: $[\alpha]_D$ −20.66° (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.11 (s, 6 H, $Si(CH_3)_2$), 0.73 (s, 9 H, *t*-Bu), 1.31 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.32 (m, 1 H, C-H_3), 3.71 (s, 3 H, OCH_3), 4.20 (m, 2 H, CH, C-H_4), 6.79 (d, *J* = 7.8 Hz, 2 H, ArH), 7.17 (d, 7.8 Hz, 2 H, ArH), 9.71 (d, *J* = 3.1 Hz, 1 H, CHO); EIMS, *m/e* 363 (M^+), 75 (base); HRMS, $C_{19}H_{29}NO_4Si$ requires *m/e* 363.1860, found 363.1859.

(1′*S*,3*S*,4*S*)- and (1′*S*,3*S*,4*R*)-3-(1′-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(4′-methoxyphenyl)-2-azetidinone-4-carboxylic Acid (34a and 34b). A solution of aldehydes **33a** and **33b** (300 mg, 0.83 mmol) in tetrahydrofuran/water (15 mL, 1.8:1) was stirred in the presence of potassium permanganate (520 mg, 3.20 mmol) and potassium carbonate (730 mg, 5.2 mmol) at 25 °C under an inert atmosphere. After 2 h additional potassium permanganate (31.5 mg, 0.2 mmol) was added and the reaction mixture stirred an additional 3 h. The brown precipitate was filtered off, and the tetrahydrofuran was evaporated under reduced pressure. The aqueous layer was washed twice with ether (5 mL) and then acidified with 6 N hydrochloric acid to pH 4. Extraction of the aqueous layer with ether (3 × 5 mL), drying of the combined organic layers over magnesium sulfate, and removal of the ether under reduced pressure yielded 315 mg (96%) of **34a** and **34b**. **34a**: colorless crystals; mp 156–157 °C; $[\alpha]_D$ +87.78° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $Si(CH_3)_2$), 0.79 (s, 9 H, *t*-Bu), 1.35 (d, *J* = 6.0 Hz, 3 H, CH_3), 3.41 (m, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 4.30 (m, 2 H, CH and C-H_4), 6.80 (d, *J* = 7.3 Hz, 2 H, ArH), 7.26 (d, *J* = 7.3 Hz, ArH), 7.75 (br s, 1 H, CO_2H); EIMS, *m/e* 379 (M^+), 75 (base). Anal. Calcd for $C_{19}H_{29}NO_5Si$: C, 60.13; H, 7.70; N, 3.69. Found: C, 60.20; H, 7.48; N, 3.80. **34b**: oil; $[\alpha]_D$ −24.62° (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.15 (s, 6 H, $Si(CH_3)_2$), 0.80 (s, 9 H, *t*-Bu), 1.35 (d, *J* = 6.0 Hz, 3 H, CH_3), 3.45 (m, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 3.95–4.6 (m, 2 H, CH and C-H_4), 6.35–7.5 (m, 4 H, ArH), 7.85 (br s, 1 H, CO_2H); HRMS, $C_{19}H_{29}NO_5Si$ requires *m/e* 379.1813, found 379.1802.

(1′*S*,3*R*,4*R*)-4-Acetoxy-3-(1′-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(4′-methoxyphenyl)-2-azetidinone (35). The acids **34a** and **34b** (10.2 mg, 0.026 mmol) were dissolved in dimethylformamide/acetic acid (5 mL). After addition of lead tetraacetate (240 mg, 0.54 mmol) the mixture was stirred at 70 °C for 45 min under a blanket of nitrogen. The hot solution was poured into water (20 mL), and the aqueous layer was extracted with ether (3 × 5 mL). The dried (magnesium sulfate) organic layers were evaporated under reduced pressure to give a dark-brown oil. Column chromatography on silica gel with ethyl acetate/hexanes as eluent produced 8.46 mg (84%) of pure **35** as a light-yellow oil: $[\alpha]_D$ −14.92° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.78 (s, 9 H, *t*-Bu), 1.35 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.1 (s, 3 H, $COCH_3$), 3.18 (m, 1 H, C-H_3), 3.73 (s, 3 H, OCH_3), 4.35 (m, 1 H, CH), 6.2 (br s, 1 H, C-H_4), 6.80 (d, *J* = 10.4 Hz, 2 H, ArH), 7.25 (d, *J* = 10.4 Hz, 2 H, ArH); EIMS, *m/e* 393 (M^+), 43 (base); HRMS, $C_{20}H_{31}NO_5Si$ requires *m/e* 393.1970, found 393.1962.

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Supplementary Material Available: Table I and experimental procedures and spectral data for the synthesis of β-lactams outlined in Scheme I, eq 2, Scheme II, and Table I (10 pages). Ordering information is given on any current masthead page.