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Palladium(II)-Assisted Carboacylation of Enamides To Produce Functionalized β-Amino Acids. Synthesis of Relays to (±)-Thienamycin

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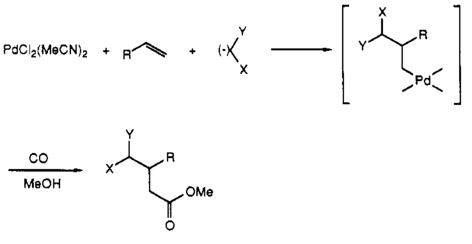
Alkylation of benzyl vinylcarbamate with sodium benzyl acetoacetate in the presence of palladium(II) chloride, followed by carbonylation (CO/MeOH), produced a highly functionalized β-amido ester that was converted, using conventional organic synthetic methodology, into a relay to (±)-thienamycin.

Olefins coordinated to palladium(II) salts are generally reactive toward nucleophiles[1] and undergo facile alkylation by stabilized carbanions[2] to produce unstable (σ-alkyl)palladium(II) complexes. These readily undergo carbon monoxide insertion,[3] to result in overall "carboacylation" of the alkene (eq 1). With enamides as the olefin (R = NHCOR), attack occurs exclusively α to the nitrogen, and carbonylation produces highly functionalized β-amino acid derivatives. Since β-amino acids can be cyclized to β-lactams,[4] and since β-lactams are potentially biologically active and of current interest,[5] this unusual approach to this class of compounds was examined.



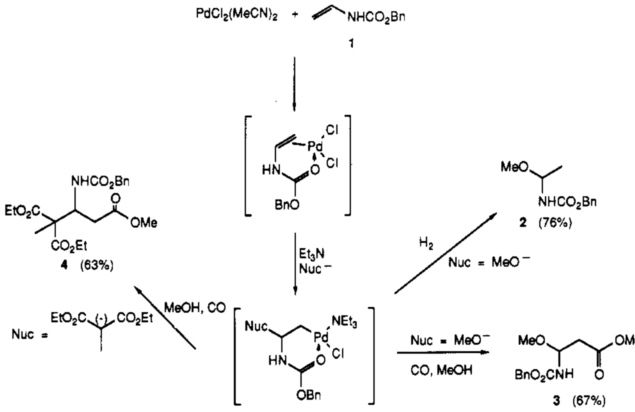
(1)

Results and Discussion

The enamide substrate chosen for these studies was benzyl vinylcarbamate (**1**),[6] since the (benzyloxy)carbonyl group on nitrogen could be easily removed by hydrogenolysis. This compound was readily synthesized by a Curtius reaction of acryloyl azide with benzyl alcohol. Palladium-assisted alkoxylation and alkylation proceeded smoothly, producing unstable (σ-alkyl)palladium(II) complexes. These underwent cleavage with hydrogen without debenzylation, or underwent carbonylation under mild conditions (Scheme I), to produce the functionalized carbamates **2**–**4** in overall good yield.

For determination of the utility of these compounds for the preparation of β-lactams convertible to (±)-thienamycin,[7] triester **4** was hydrogenolyzed to produce the free amino triester. This compound was rather unstable and difficult to purify. Further, all attempts to effect β-lactam formation (e.g., NaH, RMgX,[4] Et_3Al[8]) resulted instead in decomposition, with recovery of large amounts of diethyl methylmalonate. Clearly the stability of the malonate anion (a requirement for efficient olefin alkylation[2]) was the cause of this facile carbon–carbon bond cleavage. Two approaches to the desired functionalized β-lactams, both depending on conversion of the stabilized carbanion fragment to a poor leaving group prior to β-lactam formation, have been developed and are summarized in Scheme II.

Scheme I



Benzyl acetoacetate was chosen as the alkylating agent, since reduction of the keto group and debenzylation would be facile and would convert this fragment into a poor leaving group, facilitating β-lactam formation. Palladium-assisted carboacylation of carbamate **1** with benzyl acetoacetate was very efficient, producing the highly functionalized keto diester carbamate **5**, in excellent yield, as a ~1:1 mixture of diastereoisomers, in one step. Reduction of the keto group with sodium borohydride in methanol,[9] silylation of the resulting alcohol,[10] and double debenzylation (H_2, Pd/C) produced amino acid **6** in 67% overall yield from **5**. This material consisted of only two of the four possible diastereoisomers, in a 2:1 ratio. Cyclization using classical DCC coupling methodology[11] produced the desired β-lactam **7** in 59% yield after chromatographic separation from dicyclohexylurea. This material was a *single* (racemic) diastereoisomer of the trans β-lactam, having the relative stereochemistry of (±)-*epi*-

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[1] For reviews, see: (a) Hegedus, L. S. Nucleophilic Attack on Transition Metal Organometallic Compounds. In *The Chemistry of the Metal-Carbon Bond*, Vol. 2; Hartley, F. R., Patai, S., Eds.; John Wiley and Sons: New York, 1985; pp 401–512. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985; pp 59–116. (c) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: 1987; pp 825–859.

[2] Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973.

[3] Hegedus, L. S.; Darlington, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 4980.

[4] For example: (a) Shono, T.; Tsubata, K.; Okmaga, N. *J. Org. Chem.* **1984**, *49*, 1056. (b) Kametani, T.; Huang, S.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060.

[5] Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.

[6] (a) Hart, D.; vonDormat, A. E. *Bull. Soc. Chim. Belg.* **1956**, *65*, 291. (b) Wolfrom, J.; McFadden, R.; Chaney, T. *J. Org. Chem.* **1961**, *26*, 2597.

[7] Ratcliffe, R. W.; Albers-Schönberg, G. The Chemistry of Thienamycin and Other Carbapenem Antibiotics. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 227–310.

[8] (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (b) Cainelli, G.; Contento, M.; Drusiani, A.; Panunzio, M. *J. Chem. Soc., Chem. Commun.* **1985**, 240.

[9] House, H. O.; Babad, H.; Toothill, R. B.; Noltes, A. W. *J. Org. Chem.* **1962**, *27*, 4141.

[10] (a) Ireland, R. E.; Wardle, R. B. *J. Org. Chem.* **1987**, *52*, 1780. (b) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

[11] Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.

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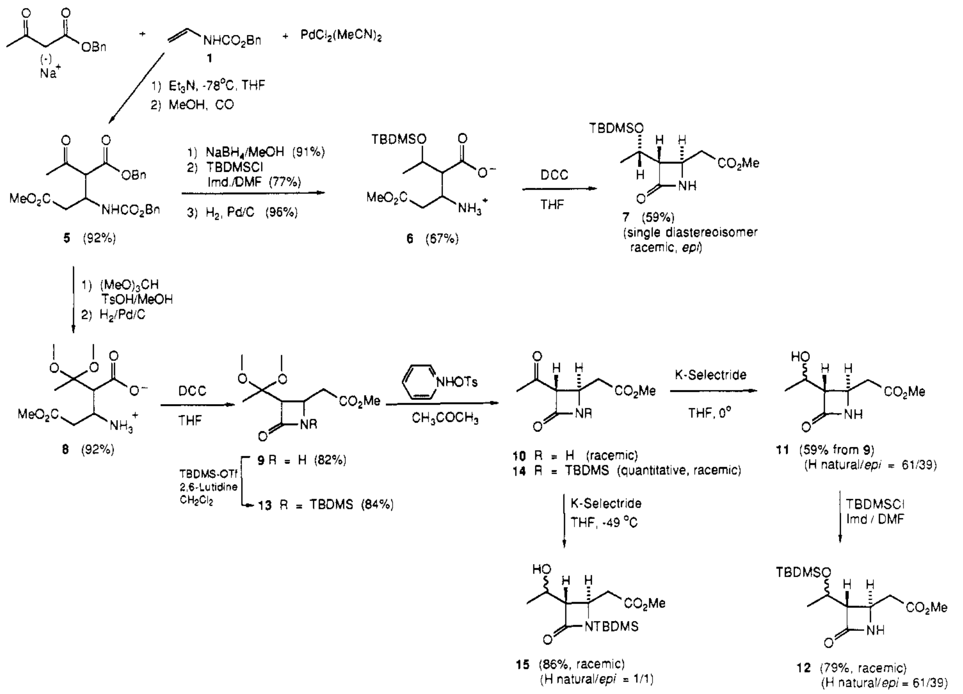
Scheme II



thienamycin epimeric at the hydroxy-bearing carbon of the hydroxyethyl side chain. Inversion of configuration at this position has previously been efficiently accomplished by using a modified Mitsunobu reaction,[12] and the enantiomerically pure 1*S*, 3*S*, 4*R* alcohol analogue of **7** has been converted to biologically active 1-β-methylcarbapenems.[12] Thus, the above route affords rapid access to a single (racemic) diastereomeric precursor to this class of compounds.

An alternative approach, which permitted some control of stereochemistry in the hydroxyethyl side chain, was required to directly achieve the relative stereochemistry found in (±)-thienamycin. This problem has traditionally been addressed by utilizing stereocontrolled reductions of *trans*-3-ketoazetidinones such as **10** or **14**. For 3-ketoazetidinones, the trans isomer is the thermodynamically favored one,[13] and generation of the ketone carbonyl *after* the β-lactam-forming step would permit equilibration to the more stable trans isomer and provide a suitable substrate for stereoselective side-chain reduction studies. Accordingly, the keto group of **5** was converted to its acetal,[14] and the free amino acid **8** was produced in excellent overall yield by hydrogenolytic double debenzylation. Cyclization as above (DCC) produced β-azetidinone **9** in excellent yield. Removal of the acetal with pyridinium tosylate[15] in acetone produced exclusively the trans isomer of azetidinone **10** (racemic) in excellent yield. This material was somewhat unstable and difficult to handle so it was directly reduced to (hydroxyethyl)azetidinone **11**.

Stereocontrolled reduction of β-keto lactams such as **10** and **14** has been the subject of extensive studies,[13,16-18] and the stereoselectivity of the reduction was highly sensitive to reaction conditions. In particular, it has been reported that in related systems, the stereoselectivity is proportional to the temperature of the reaction.[16] With unprotected keto lactam **10**, modest (61:39 natural/epi) selectivity was observed when the reduction was performed at 0 °C in THF. When the temperature was increased to 25 °C, however, none of the desired product was produced. The ^{1}H NMR spectrum of the crude product mixture indicated that concurrent reduction of the ester side chain had occurred. Protection of the β-lactam nitrogen atom with a *tert*-butyldimethylsilyl group, followed by removal of the acetal group, gave keto lactam **14**. Reduction of **14** at −49 °C gave an 86% yield of product **15** as a 53:47 mixture of diastereomers, while at 0 °C, a 15% yield of desired product was produced with diastereoselectivity similar to that obtained in the reduction of the unprotected keto lactam. Again, overreduction of the system intruded at these higher temperatures and acceptable stereocontrol could not be achieved.

The relative stereochemistries of **7**, **11**, and **12** were assigned by comparison of their spectroscopic properties with those reported for identical materials prepared by totally different routes. Thus, the major epimer of **11** had properties identical with those reported for the natural C-1′ epimer of this material,[19] while the minor component corresponded to the compound having the opposite configuration at C-1′.[19] O-Silylation of **11** gave **12**. The major epimer of **12** had properties identical with those reported for optically active material having the natural *R* configuration at C-1′,[12] while the minor epimer of **12** was identical with compound **7**, confirming the stereochemistry assigned to this material above.

Intermediates such as **7**, **11**, **12**, and **14** have previously been converted to (±)-thienamycin.[12,19,20] The palladi-

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[12] Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

[13] See, for example: Chiba, T.; Nakai, T. *Chem. Lett.* **1985**, 651.

[14] Wenkert, E.; Goodwin, T. E. *Synth. Commun.* **1977**, *7*, 409.

[15] Sterzycki, R. *Synthesis* **1979**, 724.

[16] Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208.

[17] Shih, D. H.; Fayter, J. A.; Cama, L. D.; Christensen, B. G.; Hirshfield, J. *Tetrahedron Lett.* **1985**, *26*, 583.

[18] Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1986**, *27*, 6241.

[19] Fetter, J.; Lempert, K.; Kajtar-Peredy, M.; Simig, G. *J. Chem. Soc., Perkin Trans. I* **1988**, 1135.

[20] (a) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961. (b) Andrus, A.; Christensen, B. G.; Heck, J. V. *Tetrahedron Lett.* **1984**, *25*, 595. (c) Iimori, T.; Shibasaki, M. *Ibid.* **1985**, *26*, 1523. (d) Hatanaka, M. *Ibid.* **1987**, *28*, 83. (e) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Ibid.* **1985**, *26*, 4739. (f) Shinkai, I.; Liu, T.; Reamer, R. A.; Stetzinger, M. *Tetrahedron Lett.* **1982**, *23*, 4899.

um-assisted carboacylation reported herein provides an efficient route to highly functionalized early precursors to this class of compounds.

Experimental Section

General. For purification of crude reaction mixtures, radial-layer chromatography (Chromatotron Model 7924) using Merck silica gel 60PF or column chromatography using Alfa 70-μm silica gel was used in most cases. Analytical thin layer chromatography was performed by using Merck precoated silica gel F-254 plates; products were observed by using ultraviolet light or iodine.

Materials. Tetrahydrofuran (Mallinckrodt) and diethyl ether (Mallinckrodt) were predried over CaH_2 and distilled from benzophenone ketyl under a nitrogen atmosphere prior to use. Hexane (technical grade) and trimethyl orthoformate (Aldrich) were distilled at atmospheric pressure. Methylene chloride (technical), ethyl acetate, and methanol (Mallinckrodt) were distilled from CaH_2. Acetone (technical) was distilled from $CaCl_2$. Triethylamine (Aldrich) and 2,6-lutidine (Eastman) were distilled from KOH. Pyridinium tosylate[15] was prepared according to literature procedures. Benzyl acetoacetate was prepared by transesterification of ethyl acetoacetate (Baker) and benzyl alcohol (Mallinckrodt). Palladium chloride–bis(acetonitrile) complex was prepared by stirring palladium chloride (Engelhardt) in acetonitrile overnight and removing the excess solvent by rotary evaporation. Sodium hydride (50% in oil, Alfa), carbon monoxide (Matheson), *p*-toluenesulfonic acid monohydrate (Aldrich), 5% palladium on carbon (Lancaster Synthesis), dicyclohexylcarbodiimide (Aldrich), K-Selectride (1 M in THF, Aldrich), and tetra-*n*-butylammonium fluoride (1 M in THF, Lancaster Synthesis) were used without further purification.

Benzyl Vinylcarbamate.[6] Acryloyl chloride (10.0 mL, 123 mmol), diluted with 30 mL of toluene, was added dropwise to a cooled (0 °C) solution of sodium azide (9.58 g, 147 mmol) in 50 mL of distilled water. The mixture was stirred vigorously at 0 °C for 5 h. The organic layer was separated and washed with 10 mL of 10% aqueous sodium carbonate and then with 10-mL portions of cold distilled water until addition of dilute aqueous silver nitrate to the washings failed to give a precipitate. The organic solution was dried ($MgSO_4$) before use in the subsequent step.

The toluene solution of acryloyl azide was added dropwise to a stirred and heated (100 °C) mixture of hydroquinone (609 mg, 5.52 mmol), pyridine (600 μL, 7.42 mmol), and benzyl alcohol (15.3 mL, 148 mmol). The mixture was stirred for 30 min at 110 °C after completion of addition, and then the toluene was removed by rotary evaporation. The product was distilled from the resulting residue (bp 120 °C, 0.5 mmHg), giving 15.0 g (69%) of a colorless solid, mp 43–44 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33 (br s, 5 H, Ar), 6.75 (m, 1 H, C*H*NH), 6.60 (br s, 1 H, NH), 5.12 (s, 2 H, CH_2Ph), 4.45 (d, 1 H, *J* = 17 Hz, =CH_2, cis), 4.30 (d, 1 H, *J* = 8 Hz, =CH_2, trans). IR ($CDCl_3$): ν 3440, 3060, 2950, 1725 (CO) cm^{-1}.

Benzyl (1-Methoxyethyl)carbamate (2). Benyl vinylcarbamate (0.09 g, 0.5 mmol), $PdCl_2\cdot(CH_3CN)_2$ (0.13 g, 0.5 mmol), and triethylamine (0.10 g, 1.0 mmol) were combined in 10 mL of methanol and cooled to 0 °C under argon. The flask was then charged with hydrogen (1 atm), and stirring was continued for 40 min at 0 °C. Palladium metal was then observed to precipitate, and the reaction mixture was filtered through Celite. Removal of the solvent in vacuo provided a yellow oil. Chromatography on silica gel using 5% EtOAc in hexanes gave 0.08 g (76%) of **2** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (d, 3 H, *J* = 8 Hz, CH_3), 3.37 (s, 3 H, OCH_3), 5.05 (m, 1 H, N*H*), 5.12 (s, 2 H, CH_2Ph), 5.25 (m, 1 H, C*H*), 7.38 (s, 5 H, Ar *H*). IR ($CDCl_3$): ν 3340, 3042, 2995, 2943, 1725 (CO), 1605, 1528, 1460, 1403, 1340, 1235, 1070 cm^{-1}. Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.16; H, 7.18; N, 6.70. Found: C, 63.18; H, 7.05; N, 6.60.

Methyl 3-Methoxy-3-[[(benzyloxy)carbonyl]amino]propionate (3). $PdCl_2\cdot(CH_3CN)_2$ (0.13 g, 0.5 mmol) was stirred with argon-saturated THF (10 mL). Benzyl vinylcarbamate (0.11 g, 0.6 mmol) in 5 mL of THF was added to the orange $PdCl_2\cdot(CH_3CN)_2$ suspension. Stirring at ambient temperature for 10 min provided a homogeneous red-brown solution. The solution of the Pd(II)–olefin complex was cooled to −78 °C, and triethylamine (0.10 g, 1.0 mmol) in 2 mL of THF was added dropwise. After being stirred at −78 °C for 20 min, $NaOCH_3$ (0.5 mmol, 0.5 mL of a 1 M methanol solution) was added slowly over 5 min. The orange solution was allowed to warm to −60 °C, and carbon monoxide was introduced. After being stirred for 30 min at −60 °C, the cold bath was removed, and the homogeneous orange solution warmed slowly to room temperature. Black Pd(0) began to precipitate after about 15 min, and the reaction mixture was stirred for an additional 2 h. Filtration of the black suspension through Celite and evaporation of the solvent provided a yellow oil. Purification by flash chromatography (hexanes/EtOAc, SiO_2) provided 0.90 g (67%) of **3** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.65 (d, 2 H, *J* = 6 Hz, C$H_2CO_2CH_3$), 3.32 (s, 3 H, OCH_3), 3.65 (s, 3 H, CO_2CH_3), 5.12 (s, 2 H, CH_2Ph), 5.25 (m, 1 H, C*H*NH), 6.08 (br s, 1 H, N*H*), 7.32 (s, 5 H, Ar *H*). IR (CCl_4): ν 3410, 2930, 1725 (CO), 1490, 1435, 1195, 1075, 1040 cm^{-1}. Anal. Calcd for $C_{13}H_{17}O_5N$: C, 58.40; H, 6.41; N, 5.24. Found: C, 57.98; H, 6.14; N, 5.14.

Methyl 3-[[(Benzyloxy)carbonyl]amino]-4,4-dicarbethoxypentanoate (4). Preparation of Sodium Diethyl Methylmalonate. Diethyl methylmalonate (1.74 g, 10.0 mmol) in 10 mL of THF was added dropwise to a suspension of NaH (0.25 g, 10.5 mmol) in 10 mL of THF. Considerable H_2 was evolved during the addition. The mixture was stirred at room temperature for 2 h before using. **Preparation of the Pd(II)–Olefin Complex.** $PdCl_2\cdot(CH_3CN)_2$ (0.26 g, 1.0 mmol) was stirred with nitrogen-saturated THF (20 mL). Benzyl vinylcarbamate (0.21 g, 1.2 mmol) in 5 mL of THF was added to the orange $PdCl_2\cdot(CH_3CN)_2$ suspension. Stirring at ambient temperature for 10 min provided a homogeneous red-brown solution. The solution of the Pd(II)–olefin complex was cooled to −78 °C, and triethylamine (0.20 g, 2.0 mmol) in 2 mL of THF was added dropwise. After being stirred at −78 °C for 20 min, the homogeneous orange solution was warmed to −60 °C. Sodium diethyl methylmalonate (1.2 mmol, 2.4 mL of a 0.5 M THF solution) was added dropwise over a 5-min period, and stirring was continued at −60 °C for 30 min. Methanol (2 mL) was added via syringe, a CO-filled balloon was attached with a needle through the serum cap, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 16 h and was filtered through Celite to remove the Pd(0) that had precipitated. The filtrate was evaporated and a yellow-green oil was isolated. Unreacted diethyl methylmalonate was removed by Kugelrohr distillation (110 °C, 0.5 mmHg), and the remaining residue was purified by flash chromatography (5% EtOAc in hexanes, SiO_2). A colorless oil was obtained (0.26 g, 63%). ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.20 (t, 3 H, OCH_2CH_3, *J* = 7.1 Hz), 1.27 (t, 3 H, OCH_2CH_3, *J* = 7.1 Hz), 1.49 (s, 3 H, CH_3), 2.62 (m, 2 H, CH_2CO), 3.62 (s, 3 H, OCH_3), 4.12 (q, 2 H, OCH_2CH_3, *J* = 7.1 Hz), 4.20 (q, 2 H, OCH_2CH_3, *J* = 7.1 Hz), 4.63 (ddd, 1 H, C*H*, *J* = 4.6, 4.6, 10.1 Hz), 5.07 (s, 2 H, CH_2Ph), 5.64 (d, 1 H, N*H*, *J* = 10.1 Hz), 7.30 (br s, 5 H, Ar *H*). IR (film): ν 3360, 2980, 2950, 1735 (CO), 1505, 1465, 1455, 1440, 1385, 1370, 1340, 1305 cm^{-1}. Anal. Calcd for $C_{20}H_{27}O_8N$: C, 58.65; H, 6.65; N, 3.42. Found: C, 58.90; H, 6.39; N, 3.69.

Methyl 3-[[(Benzyloxy)carbonyl]amino]-4-carbobenzoxy-5-oxohexanoate (5). A solution of $PdCl_2\cdot(CH_3CN)_2$ (2.438 g, 9.40 mmol) in argon-saturated THF (250 mL) was stirred under argon for 10 min. Benzyl vinylcarbamate (3.1g, 17mmol) was added. The mixture was stirred for 10 min and then cooled to −78 °C. Triethylamine (1.3 mL, 18 mmol) was added dropwise over 10 min; then the mixture was stirred for an additional 10 min. A precooled (−78 °C) THF solution of sodium benzyl acetoacetate (prepared from sodium hydride) was added over 10 min. The mixture was stirred at −78 °C for 2 h; then precooled methanol (140 mL, −78 °C) was added, the atmosphere evacuated and replaced with carbon monoxide twice, and the mixture was allowed to slowly warm to 22 °C. After being stirred for 12 h at 22 °C, the black slurry was filtered through Celite to remove the palladium metal and the filtrate was concentrated by rotary evaporation to give the crude product. Purification by column chromatography (silica gel, 3:1 hexane/diethyl ether, R_f = 0.62 with ether) gave 3.69 g (92%) of **5** as a ~1:1 mixture of diastereoisomers. ^{1}H NMR (270 MHz, $CDCl_3$/TMS): δ 7.32 (m, 10 H, Ar H), 5.88, 5.79 (2 d, 1 H, *J* = 9.7 Hz, NH), 5.10 (m, 4 H, CH_2Ph), 4.77, 4.67 (m, 1 H, C*H*NH), 4.09, 4.05 (2 d, 1 H, *J* = 6.4, 5.1 Hz, C*H*C(O)), 3.62, 3.61 (2 s, 3 H, CH_3O), 2.73, 2.61 (m, 2 H,

$CH_2CO_2CH_3$), 2.23, 2.19 (2 s, 3 H, $CH_3C(O)$). ^{13}C NMR (67.9 MHz, $CDCl_3$/TMS): δ 202.4, 201.3 ($CH_3C(O)$), 171.3, 171.0 (CH_3O_2C), 168.4, 167.5 (BnO_2CCH), 155.6, 155.4 (BnO_2CNH), 136.2, 134.9, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9 (Ar C), 67.5, 67.4, 66.9 (CH_2Ph), 61.3, 60.3 ($CHC(O)$), 51.8 (CH_3O), 47.4, 46.8 ($CHNH$), 37.5, 36.7 ($CH_2CO_2CH_3$), 30.3, 29.2 ($CH_3C(O)$). IR (film): ν 3363 (NH), 2951, 1726 (CO) cm^{-1}. Mass Spectrum (NH_3, CI): m/z 428 (M + 1). Anal. Calcd for $C_{23}H_{25}O_7N$ (427.45): C, 64.63; H, 5.90; N, 3.28. Found: C, 64.75; H, 5.93; N, 3.29.

Methyl 3-[[(Benzyloxy)carbonyl]amino]-4-carbobenzoxy-5-hydroxyhexanoate. A solution of **5** (2.30 g, 5.38 mmol) in methanol (150 mL) was cooled to 0 °C and stirred as sodium borohydride (102 mg, 2.70 mmol) was added. After being stirred for 7 h at 0 °C, the mixture was acidified with 5% aqueous HCl to pH 5 and concentrated by rotory evaporation. The product was dissolved in diethyl ether, washed with distilled water, dried ($MgSO_4$), concentrated by rotary evaporation, and dried in vacuo, giving 2.35 g of crude material. The ^1H NMR spectrum of this material indicated the reaction was 66% complete. Repetition of the reaction conditions using 139 mg (3.67 mmol) of sodium borohydride and isolation gave 2.27 g of 92% pure product as a 2:1 mixture of diastereoisomers contaminated with diethyl ether. ^1H NMR (270 MHz, $CDCl_3$/TMS): δ 7.34 (m, 10 H, Ar H), 5.86, 5.68 (2 d, 1 H, J = 9.3, 9.7 Hz, NH), 5.10 (m, 4 H, OCH_2Ph), 4.44 (m, 1 H, $CHNH$), 4.02 (m, 1 H, $CHOH$), 3.62, 3.61 (2 s, 3 H, CH_3O), 2.82 (m, 1 H, $CHCO_2Bn$), 2.6 (m, 2 H, $CH_2CO_2CH_3$), 2.34 (br s, 1 H, OH), 1.26, 1.23 (2 d, 3 H, J = 6.7, 7.3 Hz, CH_3CH). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 173.2, 171.2 (CO_2CH_3, CO_2Bn), 156.7, 155.6 ($NHCO_2Bn$), 136.3, 135.2, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0 (Ar C), 67.2, 66.9, 66.8, 66.7, 65.3 (CH_2Ph and $CHCO_2Bn$), 54.8, 54.5 ($CHOH$), 51.8 (CH_3O_2C), 47.5, 47.3 ($CHNH$), 37.5, 36.6 ($CH_2CO_2CH_3$), 21.8, 21.2 (CH_3CH). IR (film): ν 3417 (br), 2952, 1721 (CO) cm^{-1}. This material was used without further purification.

Methyl 3-[[(Benzyloxy)carbonyl]amino]-4-carbobenzoxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoate. The product from above (490 mg, 1.14 mmol) was mixed with imidazole (311 mg, 4.57 mmol) and *tert*-butyldimethylsilyl chloride (340 mg, 2.26 mmol) in dimethylformamide (12 mL). After being stirred for 24 h at room temperature, the mixture was diluted with diethyl ether and washed with 5% aqueous HCl, distilled water, and saturated aqueous $NaHCO_3$. The organic solution was dried ($MgSO_4$), concentrated by rotary evaporation, and dried in vacuo, giving 772 mg of crude material. Column chromatography (silica gel, 2:1 hexane/diethyl ether, R_f = 0.75 with diethyl ether) gave 478 mg (77%) of product as a ~2:1 mixture of diastereoisomers. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 7.38 (m, 10 H, Ar H), 5.85, 5.65 (2 d, 1 H, J = 9.8, 9.2 Hz, NH), 5.10 (m, 4 H, OCH_2Ph), 4.36 (m, 1 H, $CHNH$), 4.13 (m, 1 H, $CHOSi$), 3.59, (s, 3 H, CH_3O_2C), 2.79, 2.62 (2 dd, 1 H, J = 8.5, 4.0 Hz, $CHCO_2Bn$), 2.51 (dd, 1 H, J = 15.8, 6.3 Hz, $CH_2CO_2CH_3$), 2.31 (dd, 1 H, J = 15.8, 7.9 Hz, $CH_2CO_2CH_3$), 1.26 (d, 3 H, J = 6.0 Hz, CH_3CH), 0.80 (m, 9 H, $(CH_3)_3C$), 0.08 (m, 6 H, $(CH_3)_2Si$). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 173.3 ($CHCO_2Bn$), 170.5 (CO_2CH_3), 155.5 ($NHCO_2Bn$), 136.4, 135.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7 (Ar C), 68.1 ($CHCO_2Bn$), 66.5 (CH_2Ph), 56.0 ($CHOSi$), 51.5 (CH_3O_2C), 46.8 ($CHNH$), 38.7 ($CH_2CO_2CH_3$), 25.5 ($(CH_3)_3C$), 21.6 (CH_3CH), 17.7 ($(CH_3)_3C$), −4.3, −5.4 ($(CH_3)_2Si$). IR (film): ν 3419 (br), 2953, 1724 (CO) cm^{-1}. This material, shown to be >95% pure by ^1H NMR, was used without further purification.

Methyl 3-Amino-4-(hydroxycarbonyl)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexanoate (6). The starting material (96 mg, 0.18 mmol) in methanol (5 mL) was flushed with argon; then 5% palladium on carbon (38 mg, 0.018 mmol) was added. The atmosphere was evacuated and replaced with hydrogen gas twice. After being stirred for 15 h at room temperature, the black slurry was filtered through Celite and concentrated by rotary evaporation to give 58 mg of 95% pure product as a 2:1 mixture of diastereoisomers contaminated with methanol. ^1H NMR (300 MHz, D_2O): δ 4.29 (dq, $^1/_3$ H, J = 6.5, 4.3 Hz, $CHOSi$), 4.16 (dq, $^2/_3$ H, J = 6.4, 6.4 Hz, $CHOSi$), 3.89 (dt, $^1/_3$ H, J = 9.4, 3.1 Hz, $CHNH_3^+$), 3.74 (dt, $^2/_3$ H, J = 8.2, 4.8 Hz, $CHNH_3^+$), 3.58 (s, 3 H, CH_3O), 2.78 (dd, 1 H, J = 17.8, 4.3 Hz, CH_2), 2.67 (dd, 1 H, J = 18.4, 8.4 Hz, CH_2), 2.59 (dd, $^1/_3$ H, J = 10.7, 6.6 Hz, $CHCO_2^-$), 2.35 (dd, $^2/_3$ H, J = 6.7, 4.9 Hz, $CHCO_2^-$), 1.12 (d, 1 H, J = 6.0 Hz, CH_3CH), 1.10 (d, 2 H, J = 6.0 Hz, CH_3CH), 0.71 (m, 9 H, $(CH_3)_3C$), −0.03 (m, 6 H, $(CH_3)_2Si$). IR (film): ν 3420 (br), 2950, 1730 (CO) cm^{-1}. This material was used without further purification.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-oxo-[2α,3β(*S)]-(±)-2-azetidineacetic Acid, Methyl Ester (7).** A mixture of the amino acid **6** (55 mg, 0.17 mmol) and dicyclohexylcarbodiimide (93 mg, 0.45 mmol) in THF (10 mL) was stirred for 18 h. The slurry was filtered through Celite, the solvent was removed by rotary evaporation, diethyl ether was added, and the slurry was filtered again. Column chromatography (silica gel, 2:1 hexane/diethyl ether) gave 32 mg of 95% pure trans isomer contaminated with diethyl ether. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 6.15 (br s, 1 H, NH), 4.20 (dq, 1 H, J = 3.6, 6.3 Hz, $CHCH_3$), 3.88 (ddd, 1 H, J = 8.6, 5.3, 2.3 Hz, H-4), 3.72 (s, 3 H, CH_3O_2C), 2.95 (dd, 1 H, J = 2.9, 2.9 Hz, H-3), 2.76–2.54 (m, 2 H, CH_2), 1.30 (d, 3 H, J = 6.6 Hz, CH_3CH), 0.88 (s, 9 H, $(CH_3)_3C$), 0.08 (s, 6 H, $(CH_3)_2Si$). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 171.5 (CO_2CH_3), 167.6 (C(O)N), 65.0, 63.5 ($CHCH_3$, C-3), 51.9 (CH_3CO_2), 46.2 (C-4), 39.1 (CH_2), 25.7 ($(CH_3)_3C$), 20.5 (CH_3CH), 18.0 ($C(CH_3)_3$), −4.3, −5.0 ($(CH_3)_2Si$). This material was identical with the minor isomer of compound **12**.

Methyl 3-[[(Benzyloxy)carbonyl]amino]-4-carbobenzoxy-5,5-dimethoxyhexanoate. A solution of starting material (1.485 g, 3.47 mmol), trimethyl orthoformate (5.0 mL), methanol (5.0 mL), and *p*-toluenesulfonic acid monohydrate (27 mg, 14 mmol) was heated at reflux with stirring under argon for 6 h and then stirred at 22 °C for 10 h. The mixture was transferred to a separatory funnel with diethyl ether (50 mL) and then washed with dilute aqueous sodium hydroxide (25 mL) and distilled water (25 mL). The organic layer was dried ($MgSO_4$) and then concentrated in vacuo to give 1.72 g of 90% pure product as a ~3:1 mixture of diastereoisomers contaminated with methanol. ^1H NMR (200 MHz, $CDCl_3$/TMS): δ 7.32 (m, 10 H, Ar H), 5.88 (d, 1 H, J = 9.5 Hz, NH), 5.09 (m, 4 H, CH_2Ph), 4.42 (m, 1 H, $CHNH$), 3.64, 3.58 (2 s, 3 H, CH_3O_2C), 3.46, 3.37 (2 d, 1 H, J = 10.6, 7.4 Hz, $CHCO_2Bn$), 3.15, 3.14 (2 s, 6 H, $(CH_3O)_2C$), 2.70 (dd, 1 H, J = 16.6, 5.3 Hz, CH_2), 2.57 (dd, 1 H, J = 16.6, 5.8 Hz, CH_2), 1.48, 1.41 (2 s, 3 H, $CH_3C(OCH_3)_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 171.5, 171.3 (CH_3O_2C), 170.9, 170.2 ($CHCO_2Bn$), 155.5, 155.2 ($NHCO_2Bn$), 136.5, 135.6, 135.4, 128.3, 128.1, 127.9 (Ar C), 101.8, 101.1 ($CH_3C(OCH_3)_2$), 66.5 (CH_2Ph), 53.1, 52.7 ($CHCO_2Bn$), 51.5 (CH_3O_2C), 48.2, 48.1 ($(CH_3O)_2C$), 47.2, 46.9 ($CHNH$), 37.8, 37.1 ($CH_2CO_2CH_3$), 18.4, 17.7 ($CH_3C(OCH_3)_2$). IR (film): ν 3363 (br), 2952, 1736 (CO), 1715 (sh), 1700 (sh) cm^{-1}. Mass Spectrum (NH_3, CI): m/z 442 ([M + 1] − MeOH). This material was used without further purification.

Methyl 3-Amino-5,5-dimethoxy-4-(hydroxycarbonyl)hexanoate (8). A solution of starting material (113 mg, 0.239 mmol) in methanol (6 mL) was saturated with argon; then 5% palladium on carbon (65 mg, 0.031 mmol) was added. The atmosphere over the solution was evacuated and replaced with hydrogen gas twice. The mixture was stirred at room temperature under an atmosphere of hydrogen for 6 h. Filtration through Celite followed by concentration in vacuo gave 58 mg of 94% pure product contaminated with toluene. ^1H NMR (200 MHz, D_2O): δ 3.97 (dt, 1 H, J = 6.9, 2.5 Hz, $CHNH_3^+$), 3.66 (s, 3 H, CH_3O_2C), 3.22, 3.21 (2 s, 6 H, $(CH_3O)_2C$), 2.73 (m, 3 H, $CHCO_2^-$ and CH_2), 1.44 (s, 3 H, $CH_3C(OCH_3)_2$). This material was carried on without further purification.

3-(1,1-Dimethoxyethyl)-4-oxo-2-azetidineacetic Acid, Methyl Ester (9). A mixture of 8 (0.990 g, 3.97 mmol), THF (110 mL), and dicyclohexylcarbodiimide (1.482 g, 7.18 mmol) was stirred at room temperature for 24 h. Glacial acetic acid (0.75 mL, 13 mmol) was added and the mixture stirred for 15 min. Filtration through Celite and concentration by rotary evaporation gave the crude product. Column chromatography (silica gel, 3:1 hexane/ethyl acetate, R_f = 0.41 with ethyl acetate) gave 749 mg (82%) of the trans isomer, along with minor amounts of the cis isomer. Trans isomer. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 6.13 (br, 1 H, NH), 3.94 (ddd, 1 H, J = 9.2, 4.6, 2.6 Hz, H-4), 3.72 (s, 3 H, CH_3O_2C), 3.25 (s, 6 H, $(CH_3O)_2C$), 3.16 (d, 1 H, J = 2.5 Hz, $CHC(OCH_3)_2$), 2.84 (dd, 1 H, J = 16.6, 3.0 Hz, CH_2), 2.55 (dd, 1 H, J = 16.6, 10.3 Hz, CH_2), 1.44 (s, 3 H, $CH_3C(OCH_3)_2$). In addition, minor signals due to the cis isomer were present: δ 4.35 (ddd, J = 7.8, 5.3, 2.6 Hz, H-4), 2.79 (dd, J = 16.2, 4.6 Hz, CH_2), 2.61 (dd, J = 16.7, 9.2 Hz, CH_2). Trans isomer. ^{13}C NMR (75.5

MHz, $CDCl_3$/TMS): δ 171.0 (CH_3O_2C), 166.1 (C(O)NH), 99.0 ($C(OCH_3)_2$), 62.4 (C-3), 51.5 (CH_3O_2C), 48.7, 48.4 ($(CH_3O)_2C$), 46.6 (C-4), 38.8 (CH_2), 19.4 ($CH_3C(OCH_3)_2$). In addition, minor signals (~15%) due to the cis isomer were present: δ 172.0, 166.9, 99.6, 58.9, 47.1, 39.2, 20.0. IR (film): ν 3303 (br), 2951, 1760 (C(O)N), 1735 (CO_2R) cm^{-1}. Mass spectrum (EI): *m/z* 199 (M − CH_3OH). This material, shown to be >95% pure by ^{1}H NMR, was carried forward without further purification.

3-(1-Oxoethyl)-4-oxo-[2α,3β]-2-azetidineacetic Acid, Methyl Ester (10). A solution of **9** (93 mg, 0.40 mmol), acetone (3 mL), and pyridinium tosylate (30 mg, 0.12 mmol) was stirred under reflux for 2 h. The solvent was removed by rotary evaporation; chloroform (3 mL) was added and then removed by rotary evaporation, giving crude product used without further purification in the subsequent reaction. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.62 (br s, 1 H, NH), 4.30 (ddd, 1 H, *J* = 8.2, 5.5, 2.7 Hz, H-4), 3.96 (d, 1 H, *J* = 2.5 Hz, H-3), 3.70 (s, 3 H, CH_3O), 2.75 (dd, 1 H, *J* = 16.6, 5.4 Hz, CH_2), 2.64 (dd, 1 H, *J* = 16.6, 8.3 Hz, CH_2), 2.32 (s, 3 H, $CH_3C(O)$). ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 199.3 ($CH_3C(O)$), 170.7 (CH_3O_2C), 162.8 (C(O)NH), 68.6 (C-3), 51.8 (CH_3O), 45.9 (C-4), 38.3 (CH_2), 29.4 ($CH_3C(O)$). IR (film): ν 3250 (br), 2954, 1769 (C(O)N), 1732 (CO_2R), 1712 (CO) cm^{-1}.

3-(1-Hydroxyethyl)-4-oxo-[2α,3β]-2-azetidineacetic Acid, Methyl Ester (11).[19] A solution of crude material **10** in THF (4 mL) was cooled in an ice bath, a 1 M THF solution of K-Selectride (1.0 mL, 1.0 mmol) was added dropwise with stirring over 10 min, and then the mixture was stirred at 0 °C for 90 min. Glacial acetic acid (0.25 mL, 4.3 mmol) was added, and the mixture was diluted 4-fold with ethyl acetate, filtered through Celite, and concentrated by rotary evaporation. Chloroform (2 mL) was added; then the mixture was filtered through Celite and concentraed again, giving the crude product. Column chromatography (silica gel, 10% ethyl acetate in chloroform, R_f = 0.21 in ethyl acetate) gave 46 mg of 95% pure trans azetidinone as a 61:39 mixture of diastereoisomers at the hydroxy position contaminated with EtOAc. The major isomer had properties identical with those reported for the natural C-1′ epimer of this material (except our δ 3.96 ppm vs reported δ 3.87 ppm).[19] The minor component corresponded to the compound having the opposite configuration at C-1′.[19] Major diastereoisomer. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ 6.70 (br s, 1 H, NH), 4.18 (m, 1 H, CHOH), 3.96 (dt, 1 H, *J* = 7.0, 2.0 Hz, H-4), 2.88 (dd, 1 H, *J* = 6.0, 2.0 Hz, H-3), 2.72 (m, 2 H, CH_2), 1.30 (d, 3 H, *J* = 7.0 Hz, CH_3CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.8, 171.4 (CH_3O_2C), 168.6, 168.0 (C(O)NH), 65.3, 65.1 (CHOH), 64.0, 63.0 (C-3), 52.0, 51.9 (CH_3O), 47.6, 46.9 (C-4), 39.1, 38.9 (CH_2), 21.1, 20.9 (CH_3CH). IR (film): ν 3346 (br), 2955, 1734 (CO) cm^{-1}. Minor diastereoisomer. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.11 (br s, 1 H, NH), 4.12 (m, 1 H, CHOH), 3.83 (ddd, 1 H, *J* = 7.9, 6.0, 2.1 Hz, H-4), 3.70 (s, 3 H, CH_3O), 2.91 (dd, 1 H, *J* = 6.1, 2.3 Hz, H-3), 2.70 (m, 2 H, CH_2), 2.30 (br s, 1 H, OH), 1.31 (d, 3 H, *J* = 6.6 Hz, CH_3CH).

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-oxo-[2α,3β]-2-azetidineacetic Acid, Methyl Ester (12). A solution of starting material **11** (60 mg, 0.32 mmol) in dimethylformamide (3 mL), imidazole (86 mg, 1.3 mmol), and *tert*-butyldimethylsilyl chloride (92 mg, 0.61 mmol) was stirred for 22 h at room temperature. The mixture was diluted with diethyl ether (30 mL) and then washed with 5% aqueous HCl (10 mL) and distilled water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give the crude material. Column chromatography (silica gel, 5:1 hexane/ethyl acetate, R_f = 0.53 in ethyl acetate) gave 68 mg (70%) of product as a 61:39 mixture of natural[12]:epi diastereoisomers. The major isomer had properties identical with those reported for optically active material having the natural *R* configuration at C-1′.[12] The minor isomer was identical with compound **7**. ^{1}H NMR (270 MHz, $CDCl_3$/TMS): δ 6.42 (br s, 1 H, NH), 4.19 (dq, 1 H, *J* = 6.0, 6.0 Hz, CHOSi), 3.97 (ddd, $^2/_3$ H, *J* = 2.2, 3.9, 9.4 Hz, H-4), 3.87 (dt, $^1/_3$ H, *J* = 1.9, 5.7 Hz, H-4), 3.72 (s, 3 H, CH_3O_2C), 2.94 (m, $^1/_3$ H, H-3), 2.82 (dd, $^2/_3$ H, *J* = 2.1, 4.9 Hz, H-3), 2.64 (m, 2 H, CH_2), 1.31 (d, 1 H, *J* = 6.3 Hz, CH_3CH), 1.21 (d, 2 H, *J* = 6.3 Hz, CH_3CH), 0.88 (s, 9 H, $(CH_3)_3C$), 0.08 (m, 6 H, $(CH_3)_2Si$). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 171.5, 171.4 (C(O)N), 167.9, 167.7 (CO_2R), 65.3, 65.0, 64.0, 63.6 ($CHCH_3$, C-3), 51.8 (CH_3O_2C), 46.7, 46.1 (C-4), 39.4, 39.1 (CH_2), 25.6 ($(CH_3)_3C$), 22.3, 20.5 (CH_3CH), 17.9, 17.8 ($C(CH_3)_3$), −4.4, −5.1 ($(CH_3)_2Si$). IR (film): ν 3268 (br), 2955, 1766 (C(O)N), 1741 (CO_2R) cm^{-1}. Anal. Calcd for $C_{14}H_{27}O_4NS$ (301.46): C, 55.78; H, 9.03; N, 4.65. Found: C, 56.00; H, 9.00; N, 4.63. Mass spectrum (NH_3, CI): *m/z* 319 (M + 1).

1-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-3-(1,1-dimethoxyethyl)-4-oxo-2-azetidineacetic Acid, Methyl Ester (13). A solution of starting material **9** (86 mg, 0.37 mmol) in 4 mL of CH_2Cl_2, 2,6-lutidine (87 μL, 0.75 mmol), and *tert*-butyldimethylsilyl triflate (128 μL, 0.56 mmol) was stirred at room temperature for 30 min and then diluted with 10 mL of CH_2Cl_2 and washed with 10 mL of distilled water. The aqueous layer was washed with 10 mL of CH_2Cl_2, and the organic layers were combined, dried ($MgSO_4$), and dried in vacuo to give crude product. Filtration through a short bed of silica gel gave 108 mg (84%) of product as a mixture of cis and trans isomers with >95% purity. ^{1}H NMR (200 MHz, $CDCl_3$/TMS): δ 4.24 (m, $^1/_2$ H, H-4), 3.94 (ddd, $^1/_2$ H, *J* = 2.7, 4.6, 7.1 Hz, H-4), 3.70 (s, 3 H, CH_3O_2C), 3.41 (d, 1 H, *J* = 2.8 Hz, H-3), 3.23 (m, 6 H, $(CH_3O)_2C$), 2.66 (m, 2 H, CH_2), 1.49, 1.39 (2 s, 3 H, $CH_3C(OCH_3)_2$), 0.97, 0.96 (2 s, 9 H, $(CH_3)_3C$), 0.27–0.20 (m, 6 H, $(CH_3)_2Si$). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 171.8, 171.6, 170.9, 170.2 (C(O)N, CO_2CH_3), 100.2, 99.4 ($C(OCH_3)_2$), 63.5, 59.0 (C-3), 51.5, 51.3 (CH_3O_2C), 49.9–48.7 (C-4, $(CH_3O)_2C$), 40.0, 35.8 (CH_2), 26.1, 25.9 ($(CH_3)_3C$), 19.6, 19.5 ($CH_3C(OCH_3)_2$), 18.4, 18.2 ($C(CH_3)_3$), −5.7 to −5.9 ($(CH_3)_2Si$). IR (film): ν 2953, 1748 (CO) cm^{-1}. Mass spectrum (NH_3, CI): *m/z* 314 (M − CH_3O).

1-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-3-(1-oxoethyl)-4-oxo-[2α,3β]-2-azetidineacetic Acid, Methyl Ester (14). A solution of starting material **13** (108 mg, 0.313 mmol) and pyridinium tosylate (34 mg, 0.14 mmol) in 4 mL of acetone was stirred under reflux for 2 h and then filtered through a short bed of silica gel. Concentration in vacuo gave an essentially quantitative yield (94 mg) of product as the trans isomer with >95% purity. ^{1}H NMR (270 MHz, $CDCl_3$/TMS): δ 4.25 (ddd, 1 H, *J* = 2.7, 3.8, 9.5 Hz, H-4), 4.20 (d, 1 H, *J* = 2.6 Hz, H-3), 3.68 (s, 3 H, CH_3O_2C), 2.85 (dd, 1 H, *J* = 3.8, 15.7 Hz, CH_2), 2.55 (dd, 1 H, *J* = 9.5, 15.8 Hz, CH_2), 2.31 (s, 3 H, $CH_3C(O)$), 0.95 (s, 9 H, $(CH_3)_3C$), 0.27, 0.21 (2 s, 6 H, $(CH_3)_2Si$). ^{13}C NMR (67.9 MHz, $CDCl_3$/TMS): δ 199.1 ($CH_3C(O)$), 170.0 (CH_3O_2C), 167.3 (C(O)N), 70.0 (C-3), 51.7 (CH_3O_2C, 47.5 (C-4), 39.0 (CH_2), 29.6 ($CH_3C(O)$), 26.0 ($(CH_3)_3C$), 18.3 ($C(CH_3)_3$), −5.7, −5.8 ($(CH_3)_2Si$). IR (film): ν 2952, 2859, 1748 (CO), 1713 (CO) cm^{-1}.

1-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-3-(1-hydroxyethyl)-4-oxo-[2α,3β]-2-azetidineacetic Acid, Methyl Ester (15). A solution of starting material **14** (110 mg, 0.37 mmol) in 4 mL of THF was cooled for 15 min in a −49 °C acetonitrile/dry ice bath; then K-Selectride (1 M in THF) was added dropwise over 10 min, followed by stirring 3 h in the cold bath. Glacial acetic acid (60 μL, 1.05 mmol) was added dropwise. After being stirred for 10 min, ethyl acetate (20 mL) was added and the mixture allowed to warm to room temperature. Filtration through Celite followed by concentration in vacuo gave the crude product. Column chromatography (silica gel, 10% ethyl acetate in $CHCl_3$, R_f = 0.71 with ethyl acetate) gave 95 mg (86%) of trans product as a 53:47 mixture of diastereoisomers at the hydroxy position. ^{1}H NMR (200 MHz, $CDCl_3$/TMS): δ 4.10 (m, 1 H, CHOSi), 3.81 (m, 1 H, H-4), 3.73 (s, 3 H, CH_3O_2C), 3.19 (d, 1 H, *J* = 3.2 Hz, OH), 2.93 (dd, 1 H, *J* = 2.2, 8.2 Hz, H-3), 2.91 (dd, 1 H, *J* = 3.8, 16.3 Hz, CH_2), 2.54 (dd, 1 H, *J* = 10.6, 16.5 Hz, CH_2), 1.32 (d, 3 H, *J* = 6.3 Hz, CH_3CH), 0.96, 0.95 (2 s, 9 H, $(CH_3)_3C$), 0.26, 0.22 (2 s, 6 H, $(CH_3)_2Si$). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS): δ 172.1, 171.8 (C(O)N), 170.5, 170.4 (CO_2CH_3), 66.6, 65.5 (CHOSi), 63.8, 63.5 (C-3), 52.1, 51.7 (CH_3O_2C), 50.1, 49.1 (C-4), 40.8, 39.7 (CH_2), 26.1 ($(CH_3)_3C$), 21.0 (CH_3CH), 18.3, 18.1 ($C(CH_3)_3$), −5.5 to −6.0 ($(CH_3)_2Si$). IR (film): ν 3468 (br), 2955, 1739 (CO) cm^{-1}. Anal. Calcd for $C_{14}H_{27}O_4NSi$ (301.46): C, 55.78; H, 9.03; N, 4.65. Found: C, 55.60, H, 8.94; N, 4.62. Mass spectrum (NH_3, CI): *m/z* 301 (M + 1).

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