Asymmetric Total Synthesis of an Important 3-(Hydroxymethyl)carbacephalosporin

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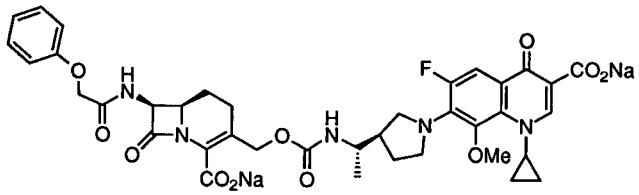
Carbacephalosporins have gained much attention as important antibacterial agents. Recently, 3-(hydroxymethyl)carbacephalosporins have been linked to quinolones for the production of multifunctional antibiotics. A short, practical asymmetric total synthesis of carbacephalosporin **3**, suitable for conjugating to other chemical moieties, is reported. The synthesis was achieved by Mitsunobu cyclization of dipeptide **12**, prepared from L-*erythro*-*anti*-β-hydroxy-α-amino acid **11**, and subsequent Horner−Wadsworth−Emmons cyclization of ketone **16**.

Introduction

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. Several groups have been approaching this problem through the synthesis of dual-action antibiotics that incorporate a β-lactam antibiotic covalently linked to a quinolone antibiotic. Dual-action drugs in which penems, carbapenems, and cephalosporins are linked to quinolones through carbamate, ester, or quaternary ammonium moieties have been reported.[1−6] Most recently, the Proctor and Gamble group has described the synthesis of highly active carbacephalosporin quinolonyl conjugate **1**.[7−9] We also have reported on the synthetic progress toward novel carbacephalosporin−quinolone dual-action antibiotic **2**.[10]



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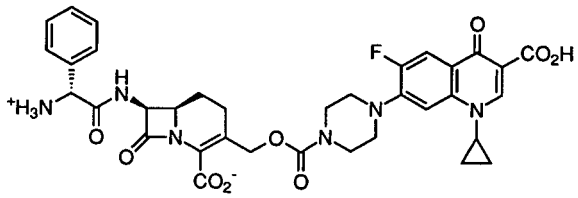

2

These recent reports demonstrate the continued interest in carbacephalosporin antibiotics. Although our group[11] and others[12−17] have reported racemic syntheses of carbacephalosporins, there have been few asymmetric routes.[12,18−24] We now report a short, practical asymmetric total synthesis of carbacephalosporin **3** that could be elaborated to a variety of dual-drug and siderophore−drug[25−36] conjugates of interest. Although we have

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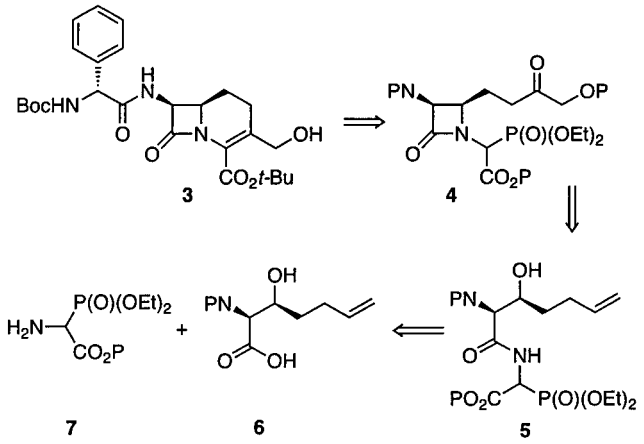
Scheme 1



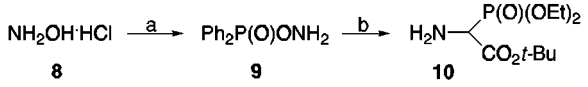
chosen to incorporate the D-phenylglycine side chain found in the commercial carbacephalosporin, Lorabid, the design of our synthetic route will accommodate numerous substitutions and elaborations of the amino side chain in either the final compound or in precursor **20**. The 3-(hydroxymethyl) chemical handle allows for convenient incorporation into valuable multifunctional compounds such as **1** and **2**.

Results and Discussion

Retrosynthetic analysis of **3** revealed that this important carbacephalosporin could be constructed from β-lactam **4**, which is directly obtainable from dipeptide **5** (Scheme 1). The synthesis of **5** required an appropriately substituted L-*erythro*-*anti*-β-hydroxy-α-amino acid, which is the only requirement for the preparation of carbacephalosporin **3** in optically active form if the β-lactam is prepared by $N-C_4$ bond closure.[37] In previous studies, our laboratory has shown that an enzymatic approach could be used to synthesize these amino acids.[38] The stereochemistry of the carbacephalosporin is determined by choosing the appropriate β-hydroxy-α-amino acid (i.e. **6**).

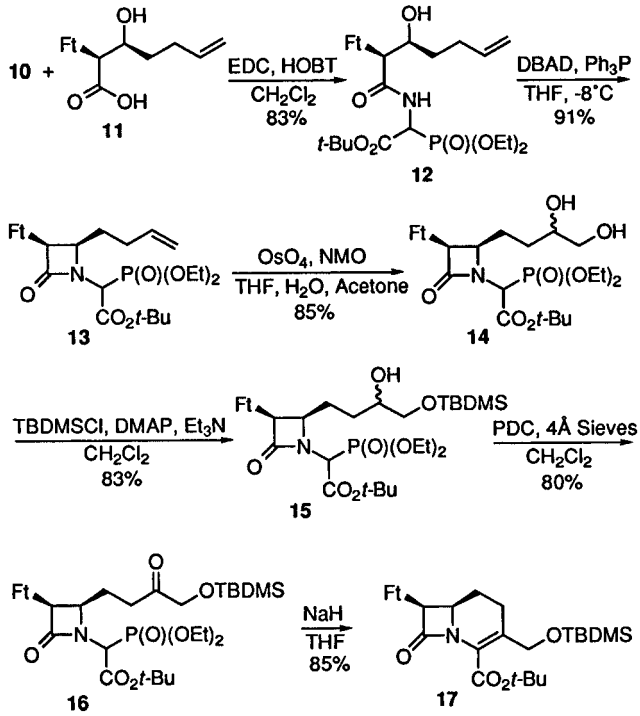
With β-hydroxy-α-amino acid **11** made available through methodology developed by our group,[39] aminophosphonoacetate **10** was the only remaining starting material needed for preparation of the key dipeptide. *O*-(Diphenylphosphinyl)hydroxylamine (**9**) was prepared in 66% yield from hydroxylamine hydrochloride and diphenylphosphinic chloride according to the method of Colvin.[40] Treatment of *tert*-butyl diethylphosphonoacetate with sodium hydride followed by **9** afforded racemic aminophosponoacetate **10** in 50% yield (Scheme 2). Although the use of racemic **10** immediately introduced a diastereomeric mixture when coupled to **11**, it should be noted that the introduction of diastereomers was not a serious problem since those centers were later destroyed.

Scheme 2[a]



[a] Reaction conditions: (a) NaOH, dioxane, $Ph_2P(O)Cl$; -8 °C, 5 min, 66%; (b) $CH_2(P(O)(OEt)_2)(CO_2$-*tert*-butyl), NaH, THF, 0 °C; **9**, THF, -78 °C, 2 h, rt, 16 h, 50%.

Scheme 3



Next, with both starting materials in hand, the synthesis of the carbacephalosporin framework was efficiently carried out (Scheme 3). Dipeptide **12** was obtained in 83% yield by coupling β-hydroxy-α-amino acid **11** to **10** with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT). Cyclization of **12** using Mitsunobu conditions,[37,41] di-*tert*-butyl azadicarboxylate (DBAD) and triphenylphosphine, afforded β-lactam **13** in 91% yield. The expected cis stereochemistry was confirmed by proton NMR with $J = 5.7$ Hz for the C_3-C_4 protons. β-Lactam **13** was then dihydroxylated by treatment of OsO_4 and *N*-methylmorpholine *N*-oxide in a mixture of aqueous tetrahydrofuran and acetone[42] to provide a mixture of diastereomeric diols **14** in 85% crude yield.

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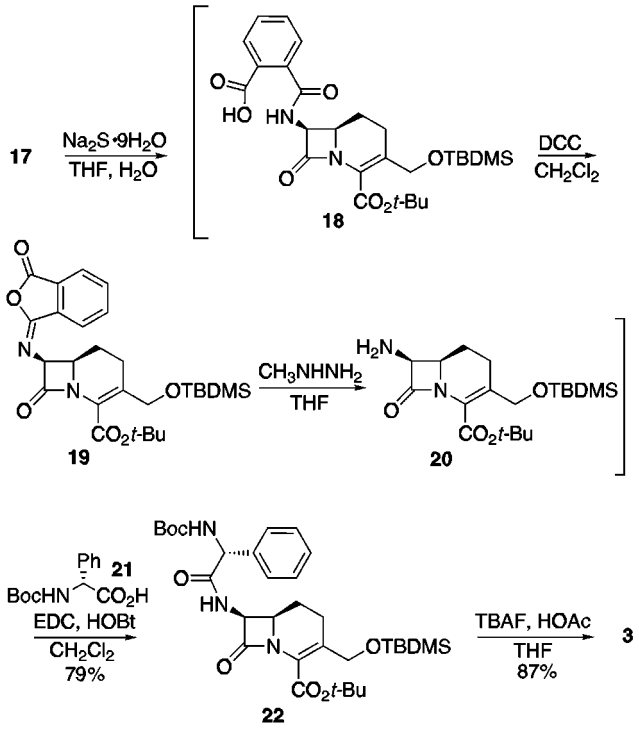
Using *tert*-butyldimethylsilyl chloride and a catalytic amount of (dimethylamino)pyridine,[43] this crude mixture of diastereomers was selectively silylated to give an 83% yield (based on recovered starting material) of **15**. Treatment of **15** with PDC and 4 Å molecular sieves afforded ketone **16** in 80% yield. Horner−Wadsworth−Emmons cyclization of the sodium salt of ketone **16** provided carbacephalosporin **17** as a single diastereomer in 85% yield.

Next, the removal of the phthalimido protecting group of **17** followed by elaboration of the carbacephalosporin side chain was necessary. The usual method of phthalimido deprotection involving treatment with hydrazine or methylhydrazine has not typically worked for these bicyclic β-lactams since the azetidinone carbonyl function is more reactive toward the hydrazine than the phthalimido carbonyl. In fact, all of our attempts to deprotect phthalimido carbacephalosporin **17** with methylhydrazine have resulted in opening of the β-lactam ring. Therefore, the three-step deprotection methodology of Kukolja et al. was utilized.[44] In this method, to enhance the activity of the phthalimido function relative to the β-lactam, the imido functionality was first converted to the corresponding isoimide.

Treatment of phthalimido protected **17** with sodium sulfide in THF and water provided phthalamic acid derivative **18** in quantitative yield. Compound **18** was then treated with *N*,*N*-dicyclohexylcarbodiimide (DCC) in dichloromethane to give phthalisoimide **19**, which was taken on directly to the next step without further purification. Treatment of **19** with methylhydrazine in dry THF afforded deprotected carbacephalosporin **20**, which was also used directly without further purification. Coupling of **20** to *N*-(*tert*-butyloxycarbonyl)-D-phenylglycine (**21**)[35] using EDC and HOBT in dichloromethane gave Boc-D-phenylglycylamino carbacephalosporin **22** in 79% overall yield for the four steps beginning with **17**. Finally, compound **22** was treated with tetrabutylammonium fluoride (TBAF) and acetic acid in THF to give molecule **3** as a single diastereomer in 87% yield (Scheme 4).

We have described the efficient asymmetric total synthesis of an important carbacephalosporin and its precursors. These compounds are ideal for evaluation as antibiotics as well as for construction of multifunctional conjugates and prodrugs.

Scheme 4



Experimental Section

General Methods. Instruments and general methods used have been described previously.[45]

***tert*-Butyl α-Amino(diethylphosphono)acetate (10).** Sodium hydride (0.87 g, 60% dispersion in mineral oil, 22 mmol) was suspended in anhydrous THF (100 mL) and cooled to 0 °C. *tert*-Butyl diethylphosphonoacetate (5.0 g, 20 mmol) was added, and stirring was continued for 0.5 h at 0 °C. The resulting solution was transferred via cannula to a stirred suspension of **9**[40] (4.6 g, 20 mmol) in anhydrous THF (100 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C and then allowed to warm to rt and stir for 16 h. Excess THF was removed, and the residue was taken up in dichloromethane (150 mL) and extracted with aqueous *p*-TsOH (5%, 3 × 75 mL). The aqueous extracts were made basic (pH = 8) by treatment with solid potassium biphosphate. This solution was then extracted with dichloromethane (3 × 75 mL), dried ($MgSO_4$), filtered, and evaporated to afford 2.62 g (50%) of **10** as a yellow oil. No further purification was necessary. Spectroscopic data were equivalent to the known compound:[46,47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (q, 2H, J = 7.2 Hz), 4.18 (q, 2H, J = 7.2 Hz), 3.86 (d, 1H, J = 19.8 Hz), 2.16 (br s, 2H), 1.50 (s, 9H), 1.36 (t, 3H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.24, 82.59, 63.06, 63.04, 62.97, 62.95, 55.08, 53.23, 27.87, 16.44, 16.36; IR (TF) 3433, 2982, 1736, 1642 cm^{-1}; HRMS calcd for $C_{10}H_{23}NO_5$ 268.1314, found 268.1295.

***erythro*-*N*-[*tert*-Butyl-2-(diethylphosphono)-2-acetyl]-2-phthalimido-3-hydroxy-7-heptenoamide (12)**. To a solution of β-hydroxy amino acid **11**[39] (1.95 g, 6.74 mmol) in dichloromethane (20 mL) was added a solution of **10** (1.80 g, 6.74 mmol) in dichloromethane (30 mL) followed by HOBT (1.14 g, 80%, 6.74 mmol). The reaction mixture was cooled to 0 °C, and EDC (1.94 g, 10.1 mmol) was added. After being warmed to rt and stirred for 18 h, the reaction mixture was diluted with dichloromethane (50 mL), washed with 1 M citric acid (2 × 50 mL), aqueous saturated sodium bicarbonate (2 × 50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (silica gel; eluted with 50−75% ethyl acetate/hexanes gradient) afforded 3.02 g (83%) of **12** as a white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, 1H, J = 49, 9.5 Hz), 7.89−7.73 (m, 4H), 5.84−5.70 (m, 1H), 5.13−4.93 (m, 3H), 4.76−4.73 (m, 1H), 4.25−4.10 (m, 5H), 2.34−2.12 (m, 2H), 1.58−1.54 (m, 2H), 1.51 and 1.48 (s, 9H, due to diastereomers), 1.39−1.30 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.91, 167.84, 167.82, 167.78, 167.71, 165.11, 164.94, 137.80, 134.23, 134.19, 131.73, 131.68, 123.60, 123.57, 115.10, 83.64, 83.56, 68.71, 68.54, 64.02, 63.93, 63.80, 63.71, 63.66, 63.62, 63.57, 63.54, 57.53, 57.19, 52.70, 52.61, 50.77, 50.68, 33.31, 33.25, 28.88, 28.78, 27.77, 16.37, 16.29, 16.25, 16.16; IR (TF) 3300, 3070, 2980, 1720, 1690, 1520, 1380 cm^{-1}; HRMS calcd for $C_{25}H_{36}N_2O_9P$ 539.2158, found 539.2139.

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***N*-[*tert*-Butyl-2-amino-2-(diethylphosphono)acetyl]-3-phthalimido-4-[4-(1-butenyl)]azetidin-2-one (13).** Dipeptide **12** (3.97 g, 7.38 mmol) was dissolved in anhydrous THF (30 mL) and cooled to −8 °C. To this stirred solution was added triphenylphosphine (3.88 g, 14.8 mmol) in anhydrous THF (20 mL) followed by DBAD (3.40 g, 14.8 mmol) in anhydrous THF (20 mL). After the solution was warmed to rt and stirred for 16 h, the THF was removed and the resulting oil was triturated with ether and seeded with a crystal of triphenylphosphine oxide. The crystallized triphenylphosphine oxide byproduct was filtered, and the filtrate was concentrated. Two separations via flash chromatography (silica gel; eluted with 5−20% THF/dichloromethane gradient) afforded 3.50 g (91%) of **13** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.75 (m, 4H), 5.71−5.56 (m, 1H), 5.46 and 5.45 (dd, 1H, J = 18 Hz, J = 5.7 Hz due to both diastereomers), 5.07 and 5.07 (d, 1H, J = 24.6 Hz, due to both diastereomers), 4.91−4.81 (m, 2H), 4.55−4.49 (m, 1H), 4.35−4.20 (m, 4H), 2.42−1.80 (m, 4H), 1.55 and 1.54 (s, 9H, due to both diastereomers), 1.45−1.35 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.22, 167.20, 165.27, 165.18, 164.66, 164.58, 163.96, 163.91, 163.84, 163.78, 136.89, 136.85, 134.44, 131.52, 123.74, 123.71, 115.34, 115.30, 84.20, 83.78, 63.64, 63.62, 63.56, 63.53, 63.44, 63.36, 63.27, 60.52, 60.48, 60.06, 57.00, 56.94, 54.61, 53.77, 52.66, 51.74, 30.00, 29.72, 28.20, 27.97, 27.87, 27.38, 16.43, 16.35, 16.23; IR (TF) 2980, 1770, 1720, 1380, 1260, 1150 cm^{-1}; HRMS calcd for $C_{25}H_{33}N_2O_8P$ 521.2053, found 521.2081.

***N*-[*tert*-Butyl-2-amino-2-(diethylphosphono)acetyl]-3-phthalimido-4-[4-[1-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxybutyl]]azetidin-2-one (15)**. To a stirred solution of **13** (1.57 g, 3.02 mmol) in THF (10 mL), water (10 mL), and acetone (1 mL) was added NMO-monohydrate (0.600 g, 4.44 mmol) followed by OsO_4 (0.010 g). After being stirred at rt for 2 h, the reaction was quenched with sodium metabisulfite (1.5 g) and stirred for 30 min. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and evaporated to give 1.431 g (85%) of *N*-[*tert*-butyl-2-amino-2-(diethylphosphono)acetyl]-3-phthalimido-4-[4-(1,2-dihydroxy butyl)]azetidin-2-one (**14**) as a crude tan oil. The diastereomeric mixture of compounds was taken on to the next step with no further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.75 (m, 4H), 5.49−5.40 (m, 1H), 5.15−5.01 (m, 1H), 4.57−4.48 (m, 1H), 4.38−4.15 (m, 4H), 3.58−3.20 (m, 3H), 2.30−2.12 (m, 2H), 1.78−1.60 (m, 2H), 1.54−1.53 (m, 9H), 1.48−1.35 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.23, 167.15, 165.46, 165.37, 165.23, 165.15, 164.60, 164.56, 164.52, 164.48, 163.95, 163.90, 163.57, 163.51, 163.49, 163.42, 134.40, 131.51, 123.67, 84.49, 84.08, 84.03, 71.63, 71.49, 70.85, 70.72, 66.51, 66.35, 66.19, 65.62, 64.20, 64.15, 64.10, 63.98, 63.89, 63.85, 63.75, 63.37, 63.32, 63.28, 63.22, 61.00, 60.78, 60.39, 60.21, 57.04, 56.91, 54.59, 54.50, 53.66, 53.60, 52.62, 52.52, 51.62, 51.54, 29.43, 29.35, 28.99, 27.93, 27.82, 25.00, 24.72, 24.58, 24.00, 16.38, 16.31, 16.24, 16.20; IR (TF) 3450, 2950, 1770, 1720, 1390, 1250, 1150 cm^{-1}; HRMS calcd for $C_{25}H_{35}N_2O_{10}P$ 555.2108, found 555.2108.

To a stirred solution of **14** (0.735 g, 1.33 mmol) in dry dichloromethane (15 mL) was added triethylamine (0.19 mL, 1.4 mmol), *N*,*N*-(dimethylamino)pyridine (0.007 g, 0.05 mmol), and *tert*-butyldimethylsilyl chloride (0.200 g, 1.33 mmol). After being stirred at rt for 20 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated, washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated. Radial chromatography using a Chromatotron (4 mm silica plate; eluted with 10−15% THF/dichloromethane gradient and then 10% MeOH/dichloromethane) afforded 0.534 g (83% based on recovered starting material) of a diastereomeric mixture of **15** as a light yellow gum and 0.199 g of recovered starting material: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.72 (m, 4H), 5.50−5.41 (m, 1H), 5.12−5.02 (m, 1H), 4.58−4.46 (m, 1H), 4.34−4.18 (m, 4H), 3.50−3.37 (m, 2H), 3.26−3.15 (m, 1H), 2.40−2.10 (m, 2H), 1.88−1.80 (m, 2H), 1.54−1.53 (m, 9H), 1.46−1.34 (m, 6H), 0.81−0.80 (m, 9H), −0.04−−0.06 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.37, 167.31, 167.21, 165.48, 165.38, 165.29, 165.21, 164.73, 164.65, 164.58, 164.00, 163.94, 163.87, 163.82, 163.74, 163.69, 134.36, 134.27, 134.22, 131.67, 131.58, 123.66, 123.63, 123.55, 84.24, 84.21, 83.84, 71.11, 70.99, 70.76, 67.13, 67.10, 66.88, 63.78, 63.69, 63.62, 63.60, 63.53, 63.36, 63.28, 57.09, 57.00, 54.62, 54.58, 53.76, 53.71, 52.66, 52.62, 51.72, 51.68, 29.21, 28.96, 28.93, 28.71, 27.97, 27.86, 27.65, 25.77, 25.18, 24.92, 24.38, 24.17, 18.14, 16.44, 16.37, 16.28, −5.52; IR (TF) 3500, 1780, 1730, 1390, 1310, 1250, 1160 cm^{-1}; HRMS calcd for $C_{31}H_{49}N_2O_{10}PSi$ 669.2972, found 669.2957.

***N*-[*tert*-Butyl-2-amino-2-(diethylphosphono)acetyl]-3-phthalimido-4-[4-[1-[(*tert*-butyldimethylsilyl)oxy]-2-oxobutyl]]azetidin-2-one (16).** To a stirred solution of **15** (1.68 g, 2.52 mmol) in dry dichloromethane (30 mL) was added pyridinium dichromate (1.89 g, 5.03 mmol) and powdered 4 Å molecular sieves (8 g). After being stirred at rt for 2 h, the reaction mixture was diluted with ether (100 mL) and filtered through a pad of Celite and silica gel. Radial chromatography of the crude reddish-brown oil using a Chromatotron (4 mm silica plate; eluted with 8% THF/dichloromethane) gave 1.35 g (80%) of **16** as a tan gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.73 (m, 4H), 5.43 and 5.43 (dd, 1H, J = 5.4, 16.8, 5.4, 18 Hz due to both diastereomers), 5.08 and 5.07 (d, 1H, J = 22.8, 24.3 Hz due to both diastereomers), 4.55−4.47 (m, 1H), 4.31−4.18 (m, 4H), 4.04−4.02 (m, 2H), 2.60−2.25 (m, 2H), 1.93−1.77 (m, 2H), 1.54 and 1.53 (s, 9H, due to both diastereomers), 1.44−1.34 (m, 6H), 0.84 (s, 9H), −0.01 and −0.02 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.02, 208.93, 167.16, 165.07, 164.63, 164.56, 164.04, 134.46, 131.52, 123.80, 123.75, 84.27, 83.98, 69.06, 63.72, 63.64, 63.39, 63.29, 60.58, 60.22, 57.03, 34.35, 34.25, 27.98, 27.88, 25.69, 22.47, 21.70, 18.19, 16.37, −5.65; IR (TF) 2990, 2850, 1770, 1720, 1470, 1390, 1250, 1150 cm^{-1}; HRMS calcd for $C_{31}H_{47}N_2O_{10}PSi$ 667.2816, found 667.2818.

***tert*-Butyl (7*S*,6*R*)-7-phthalimido-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-carba-1-dethia-3-cephem-4-carboxylate (17).** To a suspension of sodium hydride (0.036 g, 60% dispersion in mineral oil, 0.91 mmol) in anhydrous THF (3 mL) cooled to 0 °C was added compound **16** (0.603 g, 0.904 mmol) in anhydrous THF (3 mL). After being stirred for 30 min the reaction mixture was allowed to warm to rt and stir an additional 1.5 h. The reaction mixture was then diluted with ether (15 mL) and treated with brine (5 mL). The resulting two-phase mixture was separated, and the aqueous layer was further extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to give a white solid. Recrystallization from ether and hexanes yielded 0.329 g (71%) of **17** as white crystals. Radial chromatography using a Chromatotron (1 mm silica plate; eluted with 2:1 hexanes:ethyl acetate) of the mother liquor afforded an additional 0.064 g of **17** as a white solid. Total yield for the reaction was 85%: $[\alpha]^{26}_D$ −9.3° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.74 (m, 4H), 5.58 (d, 1H, J = 5.1 Hz), 4.80 (d, 1H, J = 14.2 Hz), 4.38 (d, 1H, J = 14.2 Hz), 3.90 (ddd, 1H, J = 5.0, 5.0 Hz, J = 10.6 Hz), 2.55−2.30 (m, 2H), 2.00−1.85 (m, 2H), 1.55 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.47, 160.98, 160.81, 135.33, 134.50, 131.54, 123.73, 123.10, 82.54, 62.06, 56.93, 53.25, 27.95, 25.86, 24.11, 20.38, 18.26, −5.37, −5.41; IR (TF) 2955, 2860, 1775, 1725, 1470, 1385, 1160 cm^{-1}; HRMS calcd for $C_{27}H_{36}N_2O_6Si$ 512.2343, found 512.2325; mp 147−150 °C. Anal. Calcd for $C_{27}H_{36}N_2O_6Si$: C, 63.26; H, 7.08; N, 5.46. Found: C, 63.37; H, 7.01; N, 5.22.

***tert*-Butyl (7*S*,6*R*)-7-[[*N*-(*tert*-Butyloxycarbonyl)-D-phenylglycylamino]amino]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-carba-1-dethia-3-cephem-4-carboxylate (22).** Phthalimido-protected carbacephalosporin **17** (0.513 g, 1.00 mmol) was dissolved in a 1:1 mixture of THF/H_2O (20 mL) and cooled to 0 °C. To this stirred solution was added $Na_2S{\cdot}9H_2O$ (0.240 g, 1.00 mmol). After 15 min, the reaction was treated with 0.5 M citric acid until pH = 3.5. The resulting mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), filtered, and evaporated to give

0.530 g (100%) of *tert*-butyl (7*S*,6*R*)-7-*N*-phthalamic acid-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-carba-1-dethia-3-cephem-4-carboxylate (**18**) as a white gum. No further purification was necessary: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.47 (m, 5H), 5.48 (dd, 1H, J = 6.9, 4.8 Hz), 4.76 (d, 1H, J = 14.1 Hz), 4.20 (d, 1H, J = 14.1 Hz), 3.80 (ddd, 1H, J = 11.6, 4.8, 4.8 Hz), 2.43−2.36 (m, 2H), 2.02−1.93 (m, 2H), 1.21 (s, 9H), 0.87 (s, 9H), 0.037 and 0.019 (2s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.96, 170.30, 165.15, 160.70, 138.20, 137.08, 132.52, 130.29, 130.04, 128.96, 128.59, 122.10, 81.99, 61.75, 59.02, 52.79, 27.64, 25.84, 24.14, 21.14, 18.24, −5.37; IR (TF) 3050−3400 (br), 2980, 1750, 1710, 1390, 1365, 835 cm^{-1}; HRMS calcd for $C_{27}H_{38}N_2O_7SiNa$ 553.2346, found 553.2316.

To a stirred solution of **18** (0.530 g, 1.00 mmol) in dry CH_2Cl_2 (20 mL) cooled to 0 °C was added DCC (0.217 g, 1.05 mmol). After 30 min, the reaction was warmed to rt and stirred for an additional 30 min. The reaction mixture was again cooled to 0 °C and filtered to remove dicyclohexylurea (DCU) byproduct. The filtrate was evaporated, giving crude *tert*-butyl (7*S*,6*R*)-7-phthalisoimido-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-carba-1-dethia-3-cephem-4-carboxylate (**19**) as a yellow solid that was used in the next step without further purification. ^{1}H NMR of the crude product indicated mostly phthalisomide **19** with only slight contamination of DCC and DCU.

To a stirred solution of phthalisoimide **19** (1.00 mmol, assuming a quantitative yield in the previous step) in dry THF (20 mL) cooled to −8 °C was added methylhydrazine (0.53 mL of 1.9 M solution in THF, 1.0 mmol). After 10 min, the THF was removed, and the residue was taken up in $CHCl_3$. After the solids were filtered off, the filtrate was concentrated to give crude *tert*-butyl (7*S*, 6*R*)-7-amino-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-carba-1-dethia-3-cephem-4-carboxylate (**20**) as a yellow foam that was used in the next step without further purification.

To a stirred solution of *N*-(*tert*-butyloxycarbonyl)-D-phenylglycine[35] (0.251 g, 1.00 mmol) in dry CH_2Cl_2 (20 mL) were added amino carbacephalosporin **20** (1.00 mmol, assuming a quantitative yield in the previous step) and HOBT (0.17 g, 80%, 1.0 mmol). This solution was cooled to 0 °C, and EDC (0.230 g, 1.20 mmol) was added. After being warmed to rt and stirred for 6 h, the reaction mixture was filtered to remove solids. The filtrate was diluted with CH_2Cl_2 (40 mL), washed with 1 M citric acid (2 × 40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (silica gel; eluted with 3:1 hexanes:ethyl acetate) gave 0.488 g (79% overall yield starting with phthalimido protected carbacephalosporin **17**) of **22** as a white foam: $[\alpha]^{26}_D$ −17° (*c* 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 6.93 (br s, 1H), 5.74 (d, 1H, J = 6.0 Hz), 5.37 (dd, 1H, J = 7.6 Hz, J = 4.9 Hz), 5.17 (br s, 1H), 4.69 (d, 1H, J = 14.1 Hz), 4.33 (d, 1H, J = 14.1 Hz), 3.72 (ddd, 1H, J = 11.4, 4.8 Hz, J = 3.4 Hz), 2.39 2.20 (m, 2H), 1.70−1.56 (m, 2H), 1.48 (s, 9H), 1.41 (s, 9H), 0.88 (s, 9H), 0.050 and 0.038 (2s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.71, 164.84, 160.82, 154.86, 138.11, 136.87, 129.04, 128.47, 127.17, 122.42, 82.33, 80.24, 61.83, 58.95, 58.32, 52.79, 28.29, 27.87, 25.87, 23.83, 20.33, 18.27, −5.38, −5.42; IR (TF) 3310 (br), 2980, 2940, 1750, 1710, 1540, 1490, 1365, 1160, 840 cm^{-1}; HRMS calcd for $C_{32}H_{49}N_3O_7SiNa$ 638.3237, found 638.3234. Anal. Calcd for $C_{32}H_{49}N_3O_7Si$: C, 62.41; H, 8.02; N, 6.82. Found: C, 62.21; H, 7.87; N, 6.79.

***tert*-Butyl (7*S*,6*R*)-7-[[*N*-(*tert*-Butyloxycarbonyl)-D-phenylglycylamino]amino]-3-(hydroxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylate (3).** To THF (4 mL) cooled to 0 °C was added TBAF (0.63 mL of 1 M solution in THF, 0.63 mmol) followed by acetic acid (0.036 mL, 0.63 mmol). To this stirred solution was added compound **22** (0.257 g, 0.417 mmol) in THF (4 mL). After being stirred for 1 h at 0 °C, the reaction was warmed to rt and stirred for an additional 16 h. The reaction was quenched with brine (8 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered, and evaporated. Radial chromatography using a Chromatotron (2 mm silica plate; eluted with 1:1 hexanes:ethyl acetate) gave 0.181 g (87%) of **3** as a white foam: $[\alpha]^{26}_D$ −26° (c 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.30 (m, 5H), 7.16 (br s, 1H), 5.76 (d, 1H, J = 6.3 Hz), 5.43 (dd, 1H, J = 8.1 Hz, J = 4.8 Hz), 5.16 (br s, 1H), 4.43 (d, 1H, J = 12.0 Hz), 3.81−3.70 (m, 2H), 3.15 (br m, 1H), 2.55−2.47 (m, 1H), 2.18−2.06 (m, 1H), 1.62−1.55 (m, 1H), 1.50 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.77, 165.36, 161.66, 154.84, 138.12, 135.40, 129.02, 128.50, 127.15, 125.16, 83.44, 80.26, 61.57, 58.91, 58.50, 52.87, 28.29, 27.78, 25.68, 20.44; IR (TF) 3420, 3300, 2980, 1760, 1750, 1710, 1370, 1160 cm^{-1}; HRMS calcd for $C_{26}H_{35}N_3O_7Na$ 524.2373, found 524.2386.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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