Halide-Terminated *N*-Acyliminium Ion−Alkyne Cyclizations: A New Construction of Carbacephem Antibiotics

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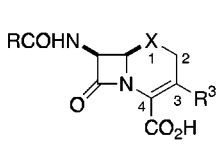
Received August 1, 1997[⊗]

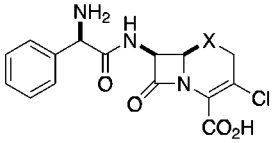
A series of 4-(3-alkynyl)azetidinones **13** was prepared from 4-(phenylsulfonyl)azetidine-2-one (**9**) and isopropyl glyoxylate hydrate. The 3-pentynyl (**13a**) and 4-phenyl-3-butynyl (**13b**) azetidinone acetates underwent 6-exo cyclization when treated with 3 equiv of $SnCl_4$ at 0 °C to provide 3-(1-chloroalkylidene)carbacephems **15a** (65%) and **15b** (33%) respectively. In contrast, the 3-butynyl (**13d**) and 4-(trimethylsilyl)-3-butynyl (**13c**) azetidinone acetates underwent 7-endo cyclization under similar conditions to give 1-azabicyclo[5.2.0]nonenes **14a** (11%) and **14b** (71%), respectively. Beginning with penicillin degradation product **18**, the more elaborate 3-pentynyl azetidinone cyclization substrate **27** was prepared in seven steps. Exposure to **27** to 3 equiv of $SnCl_4$ in CH_2Cl_2 at 0 °C for 6 h, followed by allowing the reaction mixture to warm to rt, provided the desired 3-(1-chloroethylidene)carbacephem **28** in 60% yield and high (>99%) enantiometric purity. Cleavage of the chloroethylidene group of **28** with ozone gave 3-hydroxy carbacephem **29** in 77% yield. Since this intermediate has been converted in three steps to loracarbef (**3**), a new formal total synthesis of this carbacephem antiboitic was concluded.

Introduction

For over 50 years, β-lactam antibiotics have been indispensable in man's war against bacterial pathogens. One recent development in this area was the introduction of carbocyclic analogues of natural penicillins and cephalosporins. Christensen and colleagues at Merck were the first to describe carbacephem analogues **1** of the widely employed cephalosporin class of antibiotics **2**.[2] In 1992 loracarbef (Lorabid, **3**), the carbacephem analogue of one of the most widely prescribed cephalosporin antibiotics cefaclor (Ceclor, **4**), was introduced by Eli Lilly & Co. Loracarbef, the first carbacephem antibiotic to be marketed in the United States, is an orally active, broad spectrum antibiotic that is approved for treatment of infections of the upper and lower respiratory and urinary tracts and skin infections.[3] It has a similar pharmacological profile to cefaclor and, as is typical of carbacephems, displays greater chemical stability than the parent cephem.



1 X = CH_2 carbacephem
2 X = S cephalosporin



3 X = CH_2 loracarbef
4 X = S cefaclor

To date, carbacephems are available only by total or semi synthesis. Numerous methods for constructing carbacephems have been reported[4,5] since the original total synthesis was disclosed in 1972[2a] and the first enantioselective synthesis in 1985.[6] Most syntheses of carbacephems assemble the six-membered ring last, with formation of the N−C(4) and C(3)−C(4) σ bonds being the most common.[4]

Numerous disclosures from our laboratories have demonstrated the utility of nucleophile-promoted iminium ion−alkyne cyclizations for the synthesis of nitrogen heterocycles.[7] Nucleophile participation in Mannich cyclizations can regulate regio- and stereochemistry, allowing simple alkynes to be employed as cyclization components rather than more elaborate π-nucleophiles such as unsaturated silanes or stannanes. To develop fully this chemistry, we have recently been examining the role that external nucleophiles can play in related cyclization reactions initiated by *N*-acyliminium ions.[8] As a further development of this theme, a new route to carbacephems is suggested in Scheme 1. Involvement of an external nucleophile in the pivotal cyclization of glyoxylate-derived *N*-acyliminium ion **6** would yield a 3-alkylidenecarbacepham **7**.[9,10] Oxidative cleavage of the alkylidene unit of **7** would provide a 3-hydroxycarbacephem,[11] an intermediate that has been widely employed

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.

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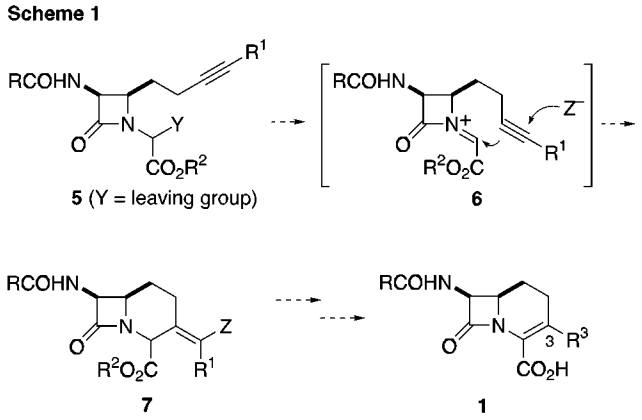
S0022-3263(97)01433-3 CCC: $14.00

Scheme 1

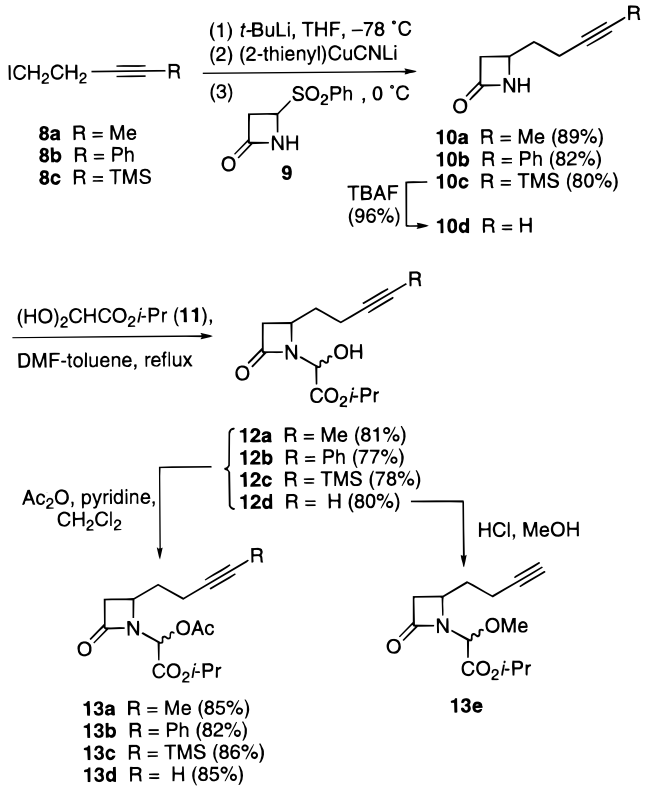


to prepare other 3-substituted carbacephems.[12] Alternatively, the alkylidene functionality might be elaborated to provide access to less common carbacephem analogues. In this paper, we report the successful development of this new route to carbacephems and illustrate its potential utility by a short enantioselective formal total synthesis of loracarbef (**3**).[13]

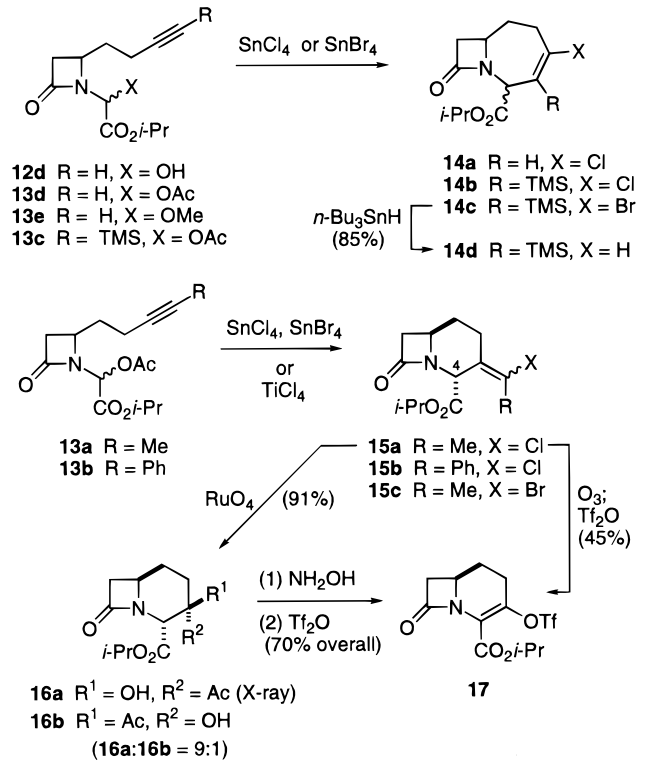
Results and Discussion

Initial Model Studies. Our first objective was to determine which structural features were required for the alkyne to cyclize in the desired 6-*exo* mode (**6** → **7**). With this aim, a representative set of 4-(3-alkynyl)-azetidinones was prepared from 4-(phenylsulfonyl)azetidin-2-one (**9**),[14] an intermediate that has been employed extensively as a precursor of 4-substituted azetidin-2-ones.[15] Thienyl cyano cuprates ($R_2CuLi{\cdot}LiCN$)[16] derived from homopropargyl iodides **8a**−**c**[17] coupled efficiently with **9** to give alkynyl azetidinones **10a**−**c** in high yields (Scheme 2). Subsequent desilylation of **10c** with TBAF efficiently provided 3-butynylazetidinone **10d**. Condensation of **10a**−**d** with isopropyl glyoxylate hydrate **11**[18] yielded hemiaminals **12a**−**d**, which were acetylated with acetic anhydride to afford **13a**−**d** in 63−69% yield for the two steps. The related α-methoxy ester **13e** was readily obtained by exposure of **12d** to methanolic HCl.

Scheme 2



Scheme 3



Our initial attempts to cyclize the 4-(3-butynyl)azetidin-2-one derivatives **12d**, **13d**, or **13e** in CH_2Cl_2 at low temperature with 1 equiv of typical Lewis acids were unsuccessful (Scheme 3). Under more forcing conditions (3 equiv of $SnCl_4$, 0 °C, 6 h), acetate precursor **13d** was transformed to a single bicyclic product (**14a**) in low (11%) yield. The addition of external nucleophiles, such as NaI,

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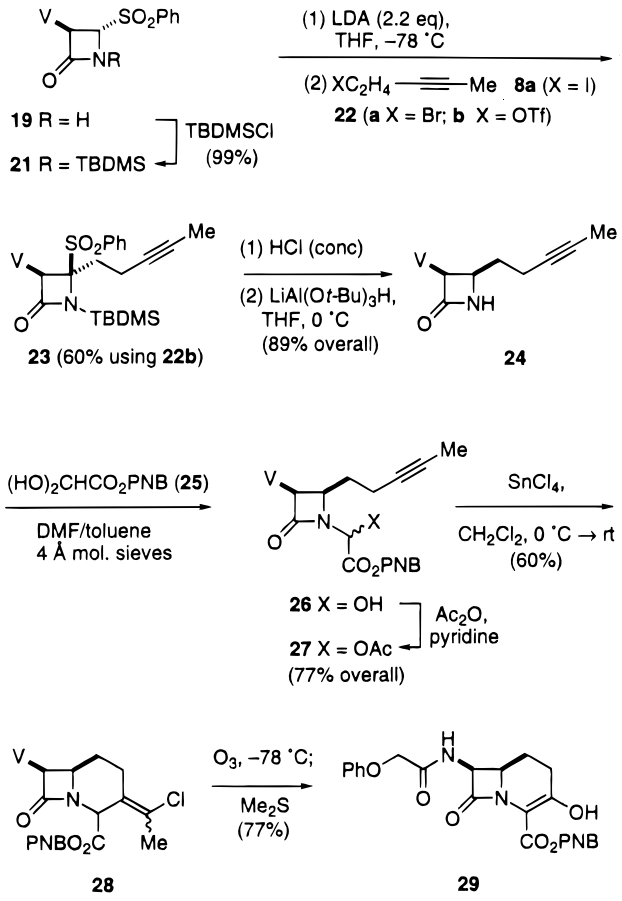
Scheme 4[a]

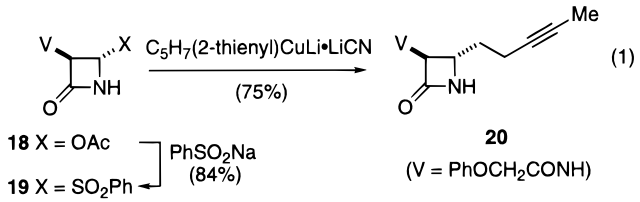


[a] V = $PhOCH_2CONH$. PNB = *p*-nitrobenzyl.

n-Bu_4NBr, or *n*-Bu_4NI, had no beneficial effect. That **14a** had the 1-azabicyclo[5.2.0]nonene skeleton resulting from 7-*endo* cyclization was apparent from the magnitude of the ^1H NMR coupling constant of the vinylic hydrogen (δ 5.94, J = 6 Hz). Not surprisingly, silyl alkyne analogue **13c** also underwent 7-*endo* cyclization when exposed to $SnCl_4$ or $SnBr_4$ under similar conditions. Cyclization of the silyl derivative was cleaner and provided azabicyclo[5.2.0]nonenes **14b** and **14c** in yields of 71 and 39%, respectively. The structure of **14c** was secured by treatment with *n*-Bu_3SnH to give **14d**, which showed a diagnostic doublet of doublets for the vinylic hydrogen in the ^1H NMR spectrum at δ 5.05 (J = 8.2, 5.0 Hz).

In marked contrast, the 3-pentynyl (**13a**) and 4-phenyl-3-butynyl (**13b**) azetidinone acetates underwent 6-*exo* cyclization when treated with 3 equiv of $SnCl_4$ at 0 °C to provide the desired 3-(1-chloroalkylidene)carbacephems **15a** (65%) and **15b** (33%). In each case, a 4:1 mixture of isomers was produced. Exposure of **13a** to 2 equiv of $TiCl_4$ delivered **15a** in similar yield (59%), while the corresponding bromo derivative **15c** was obtained in 51% yield (a 6.5:2.5:1 mixture of isomers) when **13a** was treated at 0 °C with 4 equiv of $SnBr_4$. The isomers of **15a** could be separated by column chromatography, and each showed a diagnostic ^1H NMR singlet for a vinylic methyl group at ~δ 2.1, although only the major isomer showed a NOE enhancement between this signal and the C(4) methine hydrogen. That at least the major isomers of **15a** and **15c** had the carbacepham skeleton was first confirmed by ozonolysis of the isomer mixtures to yield an unstable enolic β-keto ester, which provided triflate derivative **17** in ~45% yield after reaction with Tf_2O and *i*-Pr_2EtN. Definitive evidence that the isomers of **15a** differed only in stereochemistry of the 1-chloroethylidene unit was obtained by treatment of the separated isomers of **15a** with RuO_4.[19] From each isomer, an identical 9:1 mixture of α-hydroxy ketones **16a** and **16b** was obtained. The major isomer **16a** provided single crystals, thus allowing structural assignments to be unambiguously secured by X-ray analysis.[20] Beckmann fragmentation of the oxime derivatives of **16** with Tf_2O provided a second, less conventional, way to secure triflate **17**.[21]

Synthesis of Carbacephem 29 and Formal Asymmetric Total Synthesis of Loracarbef. The next challenge was to see if this new construction of carbacephems would also succeed with more relevant substrates containing a 3-acylamino side chain and a carboxylic acid protecting group that could be removed without damaging the carbacephem skeleton. These studies began with (3*R*,4*R*)-3-(phenoxyacetamido)-4-acetoxyazetidin-2-one (**18**), which is readily available by the chemical degradation of penicillin V.[22] Not surprisingly, condensation of the homopropargyl cuprate derived from iodide **8a** with sulfone derivative **19**[23] provided the 3,4-*anti* product **20** (eq 1).



We turned to an alkylation−reduction sequence introduced by Morin and co-workers for incorporating the 3-pentynyl substituent at C(4).[23] Alkylation was first attempted by generating the dianion of *N*-silyl sulfone **21** with 2.2 equiv of LDA in THF at −78 °C (Scheme 4), followed by addition of 1-iodo-3-pentyne (**8a**) or 1-bromo-3-pentyne (**22a**). The homopropargyl bromide was completely unreactive toward this dianion. Iodide **8a**, while unreactive at −78 °C, produced trace amounts of alkylation product **23** when the reaction mixture was allowed to warm to −20 °C for 2 h. When the more reactive 3-pentynyl triflate (**22b**)[24] was employed, alkylation occurred smoothly at −78 °C to deliver **23** in a 60% yield. Although the relative stereochemistry of this product was not determined, a single stereoisomer was formed and is presumed, on the basis of literature precedent,[23] to be as depicted in **23**. Desilylation of **23** by brief treatment with concentrated HCl, followed by reductive removal of the phenyl sulfone with lithium tri-*tert*-butoxyaluminum hydride provided the desired *cis*-disubstituted β-lactam **24** ($J_{3,4}$ = 5 Hz) in good yield.

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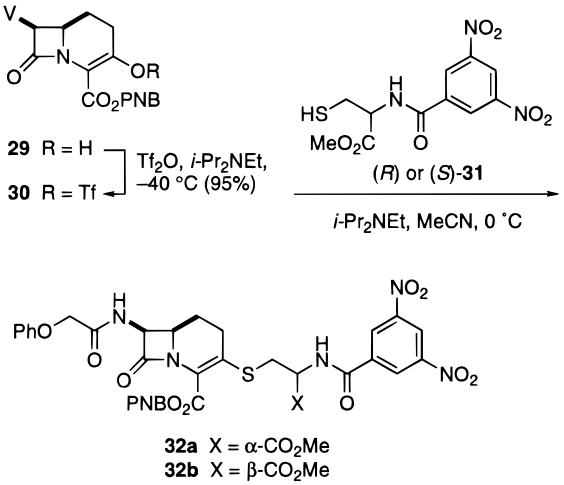
Scheme 5[a]



[a] V = $PhOCH_2CONH$. PNB = *p*-nitrobenzyl.

Condensation of freshly prepared *p*-nitrobenzyl (PNB) glyoxylate hydrate (**25**)[25] with azetidinone **24** provided a mixture of hemiaminals **26**, which were acetylated to provide acetates **27** (a 4:1 mixture of diastereomers) in 70% overall yield from **24**. Exposure of **27** to 3 equiv of $SnCl_4$ in CH_2Cl_2 at 0 °C for 6 h, followed by allowing the reaction mixture to warm to rt, provided the desired 3-(1-chloroethylidene)carbacephem **28** in 60% yield. We were delighted to find that this key conversion proceeded as efficiently with the more elaborate substrate **27** as it did in the less-functionalized model series. The stereostructure of **28** was assigned in analogy with our earlier model studies. Cleavage of the chloroethylidene group by exposure of **28** to an excess of ozone in $MeOH-CH_2Cl_2$ at −78 °C followed by treatment with Me_2S gave the known 3-hydroxy carbacephem **29** in 77% yield after flash chromatography. Since this intermediate has been converted in three steps to loracarbef (**3**),[13a] a new formal total synthesis of this carbacephem antibiotic was concluded.

The high enantiomeric purity of **29** was confirmed as shown in Scheme 5. Reaction of **29** with 1.1 equiv of Tf_2O and excess *i*-Pr_2EtN in CH_2Cl_2 at −40 °C formed the known enol triflate **30**.[26] Carbacephem 3-triflates have proven to be useful intermediates for synthesis of a wide variety of 3-substituted carbacephems, owing to their ready participation in transition metal-mediated cross-couplings and direct nucleophilic substitution reactions.[12] Condensation of **30** with the individual enantiomers of protected cysteine **31**[27] provided the diastereomeric vinylogous cysteine thioesters **32a** and **32b** in near quantitative yield. These products were readily resolved by reverse-phase HPLC and each showed a diastereomeric purity of >99%.

Conclusions

A new method for constructing carbacephems has been developed in which the C(3)−C(4) σ-bond is formed by a chloride-terminated *N*-acyliminium−alkyne cyclization. Using this approach, late intermediate **29** of an earlier Lilly synthesis of loracarbef (**3**) was prepared in high enantiomeric purity in seven steps, and 19% overall yield, from readily available (3*R*,4*S*)-3-(phenoxyacetamido)-4-(benzenesulfonyl)-azetidin-2-one (**19**). The success of the key cyclization reaction with a substrate as highly functionalized as **27** suggests that chloride-terminated *N*-acyliminium ion−alkyne cyclizations could find wide application in the construction of complex azacyclic molecules.

Experimental Section[28]

4-(3-Pentynyl)azetidin-2-one (10a). A solution of 1-iodo-3-pentyne (**8a**) (9.2 g, 47 mmol) in dry ether (50 mL) was added dropwise to a solution of *tert*-butyllithium (54 mL, 92 mmol, 1.7 M solution in pentane) and dry ether (50 mL) at −78 °C. The solution was stirred for 2 h and then added by cannula to a solution of lithium 2-thienylcyanocuprate (200 mL, 50 mmol, 0.25 M solution in THF) at −78 °C and the resulting brown solution was warmed to 0 °C, and maintained at this temperature for 1 h. The resulting cuprate solution was cooled to −78 °C, and a solution of 4-(phenylsulfonyl)azetidinone (4.00 g, 18.9 mmol) in dry THF (50 mL) was added. The solution was stirred at 0 °C for 3 h and then quenched with saturated aqueous NH_4Cl (200 mL). The precipitate was removed by filtration and washed with EtOAc (100 mL). The combined filtrates were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give 2.81 g of a light brown oil. Purification by flash chromatography on silica gel (1:1 hexanes−EtOAc) gave azetidinone **10a** as a light yellow oil (2.3 g, 88%): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.35 (br s, 1H), 3.68−3.78 (m, 1H), 3.08 (ddd, J = 14.8, 5.0, 2.1 Hz, 1H), 2.61 (ddd, J = 14.8, 2.3, 1.3 Hz, 1H,), 2.16−2.26 (m, 2H), 1.70−1.80 (m, 5H); ^{13}C NMR ($CDCl_3$,125 MHz) δ167.9, 77.4, 76.9, 47,6, 43.5, 34.1, 16.1, 3.4; IR (film) 3420, 3246, 1750 cm^{-1}; MS (CI) *m/e* 138.0913 (138.0919 calcd for $C_8H_{12}NO$, MH).

Isopropyl 2-Hydroxy-2-[4-(3-pentynyl)-2-oxoazetidin-1-yl]acetate (12a). A mixture of isopropyl glyoxylate hydrate (**11**, 1.5 g, 11 mmol) and toluene (100 mL) was heated at reflux in a Dean−Stark apparatus for 1 h. A solution of azetidinone **10a** (1.0 g, 7.3 mmol) and toluene (10 mL) was then added, and the resulting solution was heated at reflux for 3 h. Toluene was removed by rotary evaporation, and the residue was dissolved in ether (150 mL) and washed with H_2O (5 × 20 mL) and brine (3 × 20 mL). The combined aqueous washings were extracted with ether (2 × 40 mL), and the combined ether extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography on silica gel (1:1 hexanes−EtOAc) gave **12a** (1.49 g, 80%), a 1.2:1 mixture of stereoisomers (^1H NMR analysis), as a colorless oil that was contaminated with a small amount of glyoxylate **11**. **12a**: ^1H NMR ($CDCl_3$, 500 MHz) (major isomer) δ 5.34 (s, 1H), 5.14 (septet, J = 6.3 Hz, 1H), 4.23 (br s, 1H), 3.80−3.88 (m, 1H), 3.00−3.12 (m, 1H), 2.73 (dd, J = 4.0, 2.6 Hz, 1H), 2.11−2.27 (m, 2H), 1.88−2.10 (m, 1H), 1.55−1.80 (m, 4H), 1.25−1.34 (m, 6H); (minor isomer) δ 5.29 (s, 1H), 5.12 (septet, J = 6.8 Hz, 1H), 3.91−3.40 (m, 1H), 2.68 (dd, J = 4.0, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 168.3, 167.3, 166.9, 77.4, 77.2, 76.9, 72.1, 71.7, 71.4, 71.3, 51.4, 50.2, 42.8, 42.6, 33.0, 32.4, 25.5, 21.7, 21.6, 15.4, 15.3, 3.4; IR (film) 3390, 1750, 1738 cm^{-1}; MS (CI) *m/e* 254.1398 (254.1391 calcd for $C_{13}H_{20}NO_4$, MH).

Isopropyl 2-Acetoxy-2-[4-(3-pentynyl)-2-oxoazetidin-1-yl]acetate (13d). Acetic anhydride (670 μL, 7.1 mmol) and a few milligrams of DMAP were added to a solution of **12d** (1.2 g, 4.7 mmol), pyridine (2 mL), and CH_2Cl_2 (10 mL) at 0 °C.

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(28) The procedure we employed to purify THF, CH_2Cl_2 and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. Triethylamine−pyridine, diisopropylethylamine, diisopropylamine, and acetonitrile were distilled from CaH_2 at atmospheric pressure. Tin tetrachloride was purchased from Aldrich Chemical Co. and was distilled from P_2O_5 at atmospheric pressure. Other general experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

The reaction was maintained at rt overnight. The solution was diluted with ether (50 mL), washed with 1 M HCl (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography on silica gel (3:1 hexanes−EtOAc) gave acetate **13d** (1.2 g, 86%), a 1.2:1 mixture of stereoisomers (^{1}H NMR analysis), as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer) δ 6.24 (s, 1H), 4.98−5.10 (m, 1H), 3.78−3.85 (m, 1H), 3.05 (t, J = 15.4 Hz, 1H), 2.69 (dd, J = 15.2, 2.8 Hz, 1H), 1.90−2.10 (m, 6H), 1.50−1.70 (m, 4H), 1.15−1.25 (m, 6H); (minor isomer) δ 6.07 (s, 1H), 3.88−3.93 (m, 1H), 3.08 (t, J = 5.4 Hz, 1H), 2.75 (dd, J = 15.3, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 167.2, 166.4, 164.6, 163.9, 76.9, 72.3, 72.1, 70.7, 51.9, 51.7, 42.9, 32.7, 31.8, 21.5, 21.4, 20.5, 20.4, 15.1, 14.9, 3.3; IR (film) 1780, 1745, 1736 cm^{-1}; MS (CI) *m/e* 296.1502 (296.1496 calcd for $C_{15}H_{22}NO_5$, MH).

Isopropyl 4-chloro-9-oxo-1-azabicyclo[5.2.0]non-3-ene-3-carboxylate (14a). Tin tetrachloride (320 μL, 2.7 mmol) was added dropwise to a solution of acetate **13d** (250 mg, 0.8 mmol) and CH_2Cl_2 (9 mL) at 0 °C, and the reaction was maintained at this temperature for 6 h. The reaction was then poured into a mixture of saturated aqueous $NaHCO_3$ (15 mL) and ether (50 mL) and stirred for 15 min. The layers were separated, the aqueous slurry was extracted with ether (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography on silica gel (2:1 hexanes−EtOAc) gave recovered **13d** (63 mg, 29%) and azabicyclo[5.2.0]non-3-ene **14a** (25 mg, 12%) as a single stereoisomer (^{13}C NMR analysis): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94 (d, J = 6.0 Hz, 1H), 5.07 (d, J = 6.0 Hz, 1H), 5.03 (septet, J = 6.2 Hz, 1H,), 4.24−4.30 (m, 1H), 3.17 (dd, J = 14.8, 4.9 Hz, 1H), 2.32−2.40 (m, 2H), 2.67 (dd, J = 14.8, 2.2 Hz, 1H), 2.18−2.25 (m, 1H), 1.78−1.86 (m, 1H), 1.27 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 165.7, 137.7, 122.2, 69.9, 52.5, 51.9, 43.1, 34.2, 31.2, 21.7, 21.6; IR (film) 1750, 1736 cm^{-1}; MS (CI) *m/e* 258.0890 (258.0896 calcd for $C_{12}H_{17}ClNO_3$, MH).

Isopropyl 3-(1-Chloroethylidene)-1-carba-1-dethiacepham-4-carboxylate (15a). Tin tetrachloride (900 μL, 7.7 mmol) was added dropwise to a solution of acetate **13d** (1.0 g, 3.4 mmol) and CH_2Cl_2 (30 mL) at 0 °C, and the reaction was maintained at this temperature for 6 h. Workup as described for **14a** and purification of the residue by flash chromatography on silica gel (2:1 hexanes−EtOAc) gave **15a** (597 mg, 65%), a 4:1 mixture of stereoisomers (integration of ^{1}H NMR signals at 5.6 and 5.2 ppm), as a colorless oil. The isomers were separated by flash chromatography on silica gel (6:1 hexanes−EtOAc) for characterization. Major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.22 (s, 1H), 4.98 (septet, J = 6.4 Hz, 1H), 3.82−3.90 (m, 1H), 3.10−3.19 (m, 2H), 2.55 (dd, J = 14.9, 1.6 Hz, 1H), 2.22 (s, 3H), 2.15−2.20 (m, 1H), 2.00−2.10 (m, 1H), 1.28−1.38 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 166.2, 129.3, 124.9, 69.5, 52.6, 46.8, 43.9, 30.5, 25.2, 23.0, 21.6, 21.5; IR (film) 1750, 1655 cm^{-1}; MS (EI) *m/e* 271.0965 (271.0975 calcd for $C_{13}H_{18}ClNO_3$, M). Anal. Calcd. for $C_{13}H_{18}ClNO_3$: C, 57.45; H, 6.76; N, 5.15. Found: C, 57.32; H, 6.60; N, 5.05. Minor isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 (s, 1H), 4.98 (septet, J = 6.2 Hz, 1H), 3.75−3.83 (m, 1H), 3.15 (dd, J = 14.7, 4.7 Hz, 1H), 2.67−2.78 (m, 1H), 2.55 (d, J = 14.7 Hz, 1H), 2.10−2.20 (m, 5H), 1.25−1.40 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 165.8, 128.3, 125.4, 69.4, 53.9, 46.6, 44.0, 30.9, 24.9, 22.2, 21.6; MS (CI) *m/e* 272.1054 (272.1053 calcd for $C_{13}H_{19}ClNO_3$, MH).

Isopropyl 3-Ethanoyl-3-hydroxyl-1-carba-1-dethiacepham-4-carboxylate (16a and 16b). Following the general procedure of Sharpless, a solution of $RuCl_3 \cdot H_2O$ (8 mg, 0.4 mmol) and H_2O (2 mL) was added to the stereoisomeric mixture of vinyl chlorides **15a** (500 mg, 1.8 mmol), $NaIO_4$ (1.6 g, 6.9 mmol), CCl_4 (4 mL), and MeCN (4 mL) at rt. After 5 min, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with a 5% aqueous solution of $Na_2S_2O_3$ (2 × 10 mL). The combined aqueous extracts were extracted with CH_2Cl_2 (10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give hydroxy ketones **16** (451 mg, 94%), a 9:1 mixture of stereoisomers (signals at δ 4.79 and 4.48), as a colorless solid. The ^{1}H NMR spectrum showed a third minor component.

An analytical sample of the major isomer **16a** was prepared by flash chromatography (1:1 hexanes−EtOAc) and recrystallization from CH_2Cl_2-hexane: mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.95 (septet, J = 6.3 Hz, 1H), 4.90 (br s, 1H), 4.49 (s, 1H), 3.83−3.89 (m, 1H), 3.16 (dd, J = 14.7, 4.6 Hz, 1H), 2.71 (dd, J = 14.7, 1.3 Hz, 1H), 2.33 (s, 3H), 2.20 (td, J = 13.6, 4.2 Hz, 1H), 1.85−2.20 (m, 2H), 1.75−1.80 (m, 1H), 1.25 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.4, 168.2, 167.1, 77.2, 69.9, 58.5, 45.9, 44.4, 27.2, 25.6, 23.9, 21.7, 21.4; IR ($CHCl_3$) 1737 cm^{-1}; MS (EI) *m/e* 269.1258 (269.1263 calcd for $C_{13}H_{19}NO_5$, M).

Isopropyl 3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (17). A solution of **15a** (80 mg, 0.29 mmol) and CH_2Cl_2−MeOH (1:1, 10 mL) was saturated with ozone at 78 °C. After the observation of a deep blue color, excess ozone was flushed from the solution with nitrogen, and Me_2S (150 μL, 2.0 mmol) was added. The reaction was warmed to rt and conentrated to give 39 mg of a yellow oil. The crude enol was dissolved in CH_2Cl_2 (5 mL) and *i*-Pr_2EtN (150 μL, 0.86 mmol) and trifluoromethanesulfonic anhydride (50 μL, 0.30 mmol) were added at 0 °C. The reaction was allowed to warm to rt, and after 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography on silica (1:2 EtOAc−hexanes) gave 47 mg (45%) of triflate **17** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.22 (septet, J = 6.3 Hz, 1H), 3.64−3.74 (m, 1H), 3.35 (dd, J = 15.7, 5.3 Hz, 1H), 2.71 (dd, J = 15.7, 2.4 Hz, 1H), 2.58−2.65 (m, 2H), 2.30−2.40 (m, 1H), 1.62−1.80 (m, 1H), 1.33 (t, J = 6.1, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 158.8, 141.3, 123.8, 120.4, 71.1, 46.1, 43.4, 26.3, 26.2, 21.5, 21.3; IR (film) 1789, 1770, 1728 cm^{-1}; MS (EI) *m/e* 357.0481 (357.0481 calcd for $C_{12}H_{14}F_3NO_6S$, M).

3-Pentynyl Trifluoromethanesulfonate (22b). Following the general procedure of Hanack,[29] a solution of 3-pentyn-1-ol (4.21 g, 50.0 mmol), 2,6-lutidine (7.0 mL, 60 mmol), and dry CH_2Cl_2 was cooled to 0 °C. Trifluoromethanesulfonic anhydride (freshly distilled from P_2O_5, 10 mL, 60 mmol) was added dropwise by syringe over 10 min, and after 30 min, the reaction mixture was concentrated and the resulting red syrup was partitioned between pentane (250 mL) and water (50 mL). The organic layer was separated, washed with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to afford a red oil. Filtration through a short column of basic alumina (pentane) gave 9.90 g (91%) of the known[30] triflate **22b** as a somewhat unstable orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.52 (t, J = 6.8 Hz, 2H), 2.63−2.70 (m, 2H), 1.78 (t, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 118.6 (q), 79.3, 74.5, 71.7, 22.3, 3.3; IR (film) 1208, 947 cm^{-1}; MS (EI) *m/e* 216.0075 (216.0068 calcd for $C_6H_7F_3O_3S$, M), 133, 105, 99, 66. Anal. Calcd for $C_6H_7F_3O_3S$: C, 33.34; H. 3.26; Found: C, 33.29; H, 3.31.

(3*R*,4*S*)-1-(*tert*-Butyldimethylsilyl)-3-(phenoxyacetamido)-4-(benzenesulfonyl)-4-(3-pentynyl)azetidin-2-one (23). A THF solution of LDA (1.7 mL, 0.89 mmol, 0.52 M solution in THF) was added dropwise by syringe over 15 min to a solution of **21** (190 mg, 0.400 mmol, 0.1 M) and dry THF (4 mL) at −78 °C. After 30 min, a solution of freshly prepared triflate **22b** (96.0 mg, 0.44 mmol) and THF (0.5 mL) was added dropwise by cannula. After 30 min at −78 °C, the reaction was quenched by adding saturated aqueous NH_4Cl (1 mL) and the resulting mixture was allowed to warm to rt. Concentration gave a reddish oil, which was dissolved in EtOAc (200 mL) and washed with H_2O (3 × 10 mL) and brine (2 × 10 mL). After drying ($MgSO_4$), concentration afforded 230 mg of a red foamy solid, which was chromatographed on

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(30) Hanack, M.; Collins, C. J.; Stutz, H.; Benjamin, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 2356.

silica gel (2:1:0.02 hexanes−EtOAc−Et_3N) to afford **23** (130 mg, 60%) as a colorless solid: mp 142−143 °C; $[\alpha]^{24}_D$ +100.7°, $[\alpha]^{24}_{577}$ +103.1°, $[\alpha]^{24}_{546}$ +119.6°, $[\alpha]^{24}_{435}$ +222.7°, $[\alpha]^{24}_{405}$ +275.6° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (d, J = 11 Hz, 1H), 8.00 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.9 Hz, 2H), 7.13 (t, J = 8.0 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 6.29 (d, J = 11 Hz, 1H), 4.54 (d, J = 15.5 Hz, 1H), 4.31 (d, J = 15.0 Hz, 1H), 2.16−2.28 (m, 3H), 1.18−1.28 (m, 1H), 1.73 (s, 3H), 1.09 (s, 9H), 0.46 (s, 3H), 0.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 167.8, 156.7, 136.1, 134.3, 130.4, 129.6, 129.2, 122.0, 114.1, 83.3, 80.8, 77.2, 66.8, 60.8, 26.6, 25.5, 19.8, 15.0, 3.4, −4.6, −4.7; IR (KBr) 3681, 1770, 1698 cm^{-1}; MS (FAB) *m/e* 541.2183 (541.2192 calcd for $C_{28}H_{37}N_2O_5SSi$, MH). Anal. Calcd for $C_{28}H_{36}N_2O_5SSi$: C, 58.20; H, 6.38; 5.90; Found: C, 58.07; H, 6.33; N, 5.98.

(3*R*,4*R*)-3-(Phenoxyacetamido)-4-(3-pentynyl)azetidin-2-one (24). Concentrated HCl (3.4 mL, 41 mmol) was added to a solution of **23** (2.21 g, 4.09 mmol) and THF (5 mL) at rt. After 30 min, saturated aqueous $NaHCO_3$ solution (10 mL) was carefully added and the resulting mixture was extracted with EtOAc (4 × 50 mL). The organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$) and concentrated to give 1.7 g of the corresponding 1-unsubstituted azetidinone as an unstable yellow solid, which was used immediately without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 10.0 Hz, 1H), 7.73 (t, J = 7.3 Hz, 1H), 7.63 (t, J = 7.5 Hz, 2H), 7.37 (s, 1H), 7.23 (t, J = 8.3 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 2H), 5.76 (d, J = 10.0 Hz, 1H), 4.56 (d, J = 15.3 Hz, 1H), 4.49 (d, J = 15.9 Hz, 1H), 2.36−2.37 (m, 2H), 2.20 (dt, J = 15.0, 5.3 Hz, 1H), 1.72 (t, J = 1.9 Hz, 3H), 1.61−1.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 164.7, 156.7, 134.8, 133.4, 130.4, 129.7, 129.4, 122.2, 114.4, 79.1, 78.8, 70.6, 66.9, 61.7, 26.4, 25.1, 14.7; IR (CH_2Cl_2) 3666, 3394, 1798, 1699 cm^{-1}; MS (FAB) *m/e* 449.1150 (449.1147 calcd for $C_{22}H_{22}N_2O_5SNa$, MNa).

A THF solution of lithium tri-*tert*-butoxyaluminum hydride (4.1 mL, 1 M, 4.1 mmol) was added dropwise by syringe over 15 min to a solution of this product (1.7 g) and dry THF (40 mL) at 0 °C. After 45 min, the reaction was quenched with saturated aqueous sodium potassium tartrate (10 mL). The resulting aluminum salts were removed by filtration and washed with CH_2Cl_2 (4 × 40 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried ($MgSO_4$), and concentrated to give 1.6 g of a crude yellow solid. Recrystallization of this product from 10:1 hexanes−CH_2Cl_2 gave **24** (1.05 g, 90% over two steps) as a colorless crystalline solid: mp 159−160 °C; $[\alpha]^{24}_D$ +73.2°, $[\alpha]^{24}_{577}$ +73.5°, $[\alpha]^{24}_{546}$ +84.6°, $[\alpha]^{24}_{435}$ +141.9°, $[\alpha]^{24}_{405}$ +161.4° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.7 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 6.42 (br s, 1H), 5.34 (dd, J = 8.1, 5.2 Hz, 1H), 4.54 (s, 2H), 4.00 (app quintet, J = 4.7 Hz, 1H), 2.17−2.20 (m, 2H), 1.75 (t, J = 2.4 Hz, 3H), 1.61−1.67 (m, 1H), 1.48−1.53 (m, 1H); ^{13}C NMR (CD_3CN, 125 MHz) δ 169.7, 167.7, 158.5, 130.6, 122.6, 115.6, 78.7, 77.0, 67.8, 58.9, 54.2, 54.1, 30.6, 16.0; IR (CH_2Cl_2) 3685, 3413, 1776, 1694 cm^{-1}; MS (FAB) *m/e* 287.1398 (287.1396 calcd for $C_{16}H_{19}N_2O_3$, MH).

***p*-Nitrobenzyl 2-Hydroxy-2-[(3*R*,4*R*)-3-(phenoxyacetamido)-4-(3-pentynyl)-2-oxoazetidin-1-yl]acetate (26).** Following the general procedure of Woodward,[31] a mixture of **24** (400 mg, 1.40 mmol), *p*-nitrobenzyl glyoxylate hydrate (**25**, 650 mg, 2.86 mmol), dry DMF (5 mL), dry toluene (10 mL), and 4 Å molecular sieves (2 g, activated for 8 h at 150 °C and 0.1 mm) was stirred at rt for 8 h. The reaction mixture was then filtered through a pad of Celite, the residue was washed with EtOAc (3 × 100 mL), and the combined eluents were concentrated (50 °C, 1 mm) to give 1.40 g of a mixture of the crude hemiaminal **26** and **25**; this yellow oil was used without further purification. A pure sample of **26**, a 2:1 mixture of diastereomers (^{1}H NMR analysis), was obtained as a light yellow oil by flash chromatography (1:1 EtOAc−hexanes): ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer) δ 8.19 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.01 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 8.2 Hz, 2H), 5.33 (s, 1H), 5.32 (s, 2H), 5.27−5.31 (m 1H), 4.50 (s, 2H), 4.18 (dd, J = 12.2, 6.5 Hz, 1H), 2.11−2.20 (m, 2H), 1.57−1.89 (m, 5H); (minor isomer) 8.22 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.07 Hz, 2H), 5.65 (s, 1H), 4.09 (dd, J = 12.1, 6.3 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 125 MHz) (major isomer) 169.2, 169.0, 166.5, 157.5, 148.3, 142.0, 130.1, 129.4, 124.1, 122.5, 115.0, 77.5, 77.1, 73.4, 67.4, 67.6, 58.4, 57.9, 28.8, 15.9, 3.94 ppm; (minor isomer) δ 169.1, 167.9, 167.1, 142.2, 124.2, 129.0, 77.0, 72.6, 67.5, 58.1, 29.0, 15.7 ppm; IR (film) 3333, 1756, 1682 cm^{-1}; MS (FAB) *m/e* 518.1541 (518.1539 calcd for $C_{25}H_{25}N_3O_8Na$, MNa).

***p*-Nitrobenzyl 2-Acetoxy-2-[(3*R*,4*R*)-3-(phenoxyacetamido)-4-(3-pentynyl)-2-oxoazetidinon-1-yl]acetate (27).** Acetic anhydride (660 μL, 7.0 mmol) was added rapidly to a solution of the crude hemiaminal **26** (1.40 g, ca. 1.4 mmol), pyridine (570 μL, 7.0 mmol), and CH_2Cl_2 (50 mL) at rt. After 30 min, the reaction was diluted with EtOAc (200 mL), washed with water (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to give 750 mg of a yellow oil. Flash chromatography on silica gel (2:1 hexanes−EtOAc) gave 581 mg (77% over two steps) of **27**, a 2:1 mixture of diastereomers (^{1}H NMR analysis), as an off-white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer) δ 8.23 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.12 (d, J = 8.3 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.91 (d, J = 7.8 Hz, 2H), 6.24 (s, 1H), 5.40 (dd, J = 8.4, 5.6 Hz, 1H), 5.33 (s, 2H), 4.55 (s, 2H), 4.19 (dd, J = 6.0, 1.4 Hz, 1H), 2.19 (s, 3H), 2.00−2.11 (m, 2H), 1.74 (s, 3H), 1.51−1.71 (m, 2H); (minor isomer) δ 6.50 (s, 1H), 4.14 (dd, J = 5.7, 1.5 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) (major isomer) δ 169.7, 169.1, 166.6, 165.0, 157.5, 148.3, 142.2, 130.1, 129.2, 124.1, 122.6, 115.0, 77.2, 77.1, 72.8, 67.6, 67.1, 58.7, 58.6, 28.3, 20.6, 15.6, 3.54; (minor isomer) 169.6, 169.0, 166.4, 164.5, 142.1, 129.0, 124.2, 77.5, 77.1, 72.2, 67.0, 58.5, 29.0, 20.7, 15.7; IR (film) 3356, 1766, 1682 cm^{-1}; MS (FAB) *m/e* 560.1661 (560.1645 calcd for $C_{27}H_{27}N_3O_9Na$, MNa). Anal. Calcd for $C_{27}H_{27}N_3O_9$: C, 60.33; H, 5.06; N, 7.57; Found: C, 60.07; H, 5.07; N, 7.57.

***p*-Nitrobenzyl (7*R*,8*R*)-3-(1-Chloroethylidene)-7β-(phenoxyacetamido)-1-carba-1-dethiacepham-4-carboxylate (28).** A CH_2Cl_2 solution of $SnCl_4$ (2.3 mL, 1.0 M, 2.3 mmol) was added dropwise to a solution of **27** (403 mg, 0.750 mmol) and dry CH_2Cl_2 (3 mL) at 0 °C. After 6 h, the cooling bath was removed and after 15 min the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting emulsion was diluted with EtOAc (20 mL) and stirred vigorously for 30 min. The organic layer was separated, and the aqueous layer was washed with EtOAc (3 × 50 mL). The remaining aqueous slurry was dissolved in 1 M HCl (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to give, after flash chromatography on silica gel (2:1 hexanes−EtOAc), **28** (235 mg, 61%), a 5:1 mixture of what are assumed to be double-bond stereoisomers (^{1}H NMR analysis), as a yellow foam: ^{1}H NMR (major isomer) ($CDCl_3$, 500 MHz) δ 8.23 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.12 (d, J = 7.1 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.4 Hz, 2H), 5.39 (s, 1H), 5.26−5.39 (m, 1H), 5.25 (s, 2H), 4.52 (s, 2H), 4.07−4.15 (m, 1H), 3.18 (dt, J = 14.9, 3.4 Hz, 1H), 2.24 (d, J = 1.0 Hz, 3H) 2.02 (m, 1H), 1.86 (dt, J = 13.2, 4.1 Hz, 1H), 1.29−1.22 (m, 1H); (minor isomer) δ 8.22 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 6.9 Hz, 1H), 5.79 (s, 1H), 2.73 (dt, J = 14.8, 3.3 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (major isomer) ($CDCl_3$, 125 MHz) δ 168.6, 167.4, 165.5, 156.8, 147.9, 141.9, 130.5, 129.8, 128.3, 124.2, 124.0, 122.4, 114.6, 67.0, 66.0, 58.1, 52.9, 52.4, 24.8, 24.1, 23.1; (minor isomer) δ 167.6, 165.1, 142.2, 129.5, 124.5, 65.8, 58.3, 53.4, 52.7, 25.1, 24.5, 22.3; IR (CH_2Cl_2) 3683, 3415, 1767, 1694 cm^{-1}; MS (FAB) *m/e* 514.1372 (514.1371 calcd for $C_{25}H_{25}N_3O_7Cl$, MH), Anal. Calcd for $C_{25}H_{24}ClN_3O_7$: N_3O_7-CC, 58.43; H, 4.74; N, 8.18; Found: C, 58.24; H, 4.87; N, 7.96.

***p*-Nitrobenzyl (7*R*,8*R*)-7β-(Phenoxyacetamido)-3-hydroxy-1-carba-1-dethia-3-cephem-4-carboxylate (29).** A solution of **28** (105 mg, 0.204 mmol) and 1:1 CH_2Cl_2−MeOH (10 mL) was saturated with ozone at −78 °C. After the observation of a deep blue color, excess ozone was flushed from

(31) Earnest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.

the solution with nitrogen and Me_2S (150 μL, 2.0 mmol) was added. The reaction was warmed to rt and concentrated to give a yellow oil, which was dissolved in EtOAc (50 mL) and washed with water (3 × 5 mL) and brine (1 × 5 mL), and dried ($MgSO_4$). Concentration, followed by rapid chromatography of the residue on silica gel (1:1 EtOAc−hexanes, then 10:1 $CHCl_3$−MeOH), afforded the known enol **29** (81 mg, 77%) as an unstable yellow oily solid: $[\alpha]^{24}_D$ +34.3°, $[\alpha]^{24}_{577}$ +37.0°, $[\alpha]^{24}_{546}$ +42.7° (*c* 0.5, THF); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.04 (s, 1H), 8.21 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.49−7.54 (m, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.04 (t, J = 7.2 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 5.51 (d, J = 13.5 Hz, 1H), 5.35−5.37 (m, 1H), 5.26 (d, J = 13.5 Hz, 1H), 4.55 (s, 2H), 3.87−3.89 (m, 1H), 2.46−2.55 (m, 2H), 1.95−2.01 (m, 1H), 1.82−1.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.9, 166.7, 166.1, 165.2, 156.8, 147.7, 142.3, 129.8, 128.2, 123.7, 122.4, 114.6, 103.2, 67.0, 65.5, 57.1, 52.2, 25.6, 21.3; IR (CH_2Cl_2) 3685, 3414, 1770, 1732 cm^{-1}; MS (FAB) *m/e* 468.1400 (468.1406 calcd for $C_{23}H_{22}N_3O_8$, MH).

***p*-Nitrobenzyl (7*R*,8*R*)-7*β*-(Phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (30).** A CH_2Cl_2 solution of trifluoromethanesulfonic anhydride (freshly distilled from P_2O_5, 230 μL, 23 μmol, 0.10 M solution in CH_2Cl_2) was rapidly added to a solution of **29** (10 mg, 21 μmol) and triethylamine (250 μL, 25 μmol, 0.1 M solution in CH_2Cl_2) and CH_2Cl_2 (5 mL) at −40 °C. After 15 min, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the extracts were combined, washed with brine (1 × 5 mL), dried ($MgSO_4$), and concentrated to give 12 mg (95%) of the known triflate **30** as a yellow oil.

***p*-Nitrobenzyl 3-[[(2*R*)-2-[(3,5-dinitrobenzoyl)amino]-2-(methoxycarbonyl)ethyl]thio]-(7*R*,8*S*)-7*β*-(phenoxyacetamido)-1-carba-1-dethia-3-cephem-4-carboxylate (32a).** A solution of **30** (18 mg, 30 μmol), *i*-Pr_2NEt (300 μL of a 0.10 M solution in MeCN), and dry MeCN (5 mL) was cooled to 0 °C in an ice bath. A solution of (*R*)-**31** (9.8 mg, 30 μmol) and dry MeCN (1 mL) was added rapidly, and after 10 min, water (5 mL) was added to the pink reaction mixture. The resulting mixture was then extracted with EtOAc (3 × 20 mL). The organic extracts were collected, washed with brine (1 × 5 mL), dried ($MgSO_4$), and concentrated to give 40 mg of a tan oil. Purification of this oil by flash chromatography on silica gel (1:1 hexanes−EtOAc) gave **32a** (23 mg, 98%) as a yellowish oil, which rapidly forms a solid hydrate on standing. Reverse-phase HPLC analysis of **32a** (Alltima C_{18}, 10 μM, 2:1 MeOH−H_2O) indicated the presence of a single diastereomer: mp 238 °C (dec); $[\alpha]^{24}_D$ +6.9°, $[\alpha]^{24}_{577}$ +7.1°, $[\alpha]^{24}_{546}$ +5.26° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.29 (d J = 2.0 Hz, 2H), 9.21 (d, J = 1.6 Hz, 1H), 8.97 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 13.1 Hz, 1H), 5.48 (d, J = 13.5 H, 1H), 5.39 (t, J = 6 Hz, 1H), 5.33−5.36 (m, 1H), 4.57 (s, 2H), 3.95 (dd, J = 11.6, 4.0 Hz, 1H), 3.82 (dd, J = 14.5, 1.5 Hz, 1H), 3.61 (s, 3H), 3.00 (dd, J = 14.7, 5.6 Hz, 1H), 2.92 (dd, J = 18.9, 3.4 Hz, 1H), 2.37 (ddd, J = 18.6, 12.4, 5.7 Hz, 1H), 2.08−2.11 (m, 1H), 1.52−1.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 168.8, 164.5, 162.2, 162.1, 158.6, 148.6, 147.8, 141.8, 137.0, 129.9, 129.5, 128.8, 127.9, 126.9, 123.7, 122.5, 121.3, 114.5, 67.1, 66.8, 58.6, 52.9, 51.9, 32.9, 29.6, 28.0, 22.0; IR (CH_2Cl_2) 3683, 3415, 1776, 1738, 1716 cm^{-1}; MS (FAB) *m/e* 778.1531 (778.1540 calcd for $C_{34}H_{30}N_6O_{14}S$, M), 778, 713, 588, 391, 335. Anal. Calcd for $C_{34}H_{32}N_6O_{15}S$ (**32a**·H_2O): C, 51.25; H, 4.04; N, 10.55; S, 4.02. Found: C, 51.44; H, 3.98; N, 10.39; S, 3.95.

Diastereomer **32b** was prepared in an identical fashion from **30** and (*S*)-**31**. Reverse-phase HPLC analysis (Alltima C_{18}, 10 μM, 2:1 MeOH−H_2O) indicated the presence of a single diastereomer: mp 120−125 °C; $[\alpha]^{24}_D$ −58.1°, $[\alpha]^{24}_{577}$ −60.1°, $[\alpha]^{24}_{546}$ −73.8°, $[\alpha]^{24}_{435}$ −218.1°, $[\alpha]^{24}_{405}$ −300.7° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.13 (s, 1H), 9.02 (s, 2H), 8.59 (d, J = 7.7 Hz, 1H), 8.18 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.09 (d, J = 6.4 Hz, 1H), 7.04 (t, J = 7.1 Hz, 1H), 6.90 (d, J = 7.9 Hz, 2H), 5.42 (d, J = 13.1 Hz, 1H), 5.34 (d, J = 13.1 Hz, 1H), 5.23 (t, J = 5.6 Hz, 1H), 5.06 (t, J = 3.6 Hz, 1H), 4.48 (s, 2H), 3.83 (m, 1H), 3.84 (s, 3H), 3.45 (dd, J = 14.3, 4.0 Hz, 1H), 3.31 (dd, J = 14.3, 3.8 Hz, 1H), 2.74 (dd, J = 18.9, 2.9 Hz, 1H), 2.39−2.44 (m, 1H), 1.51−1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 168.9, 163.9, 162.9, 162.8, 156.8, 148.7, 147.1, 141.6, 136.6, 129.8, 129.2, 129.0, 127.6, 126.1, 123.7, 122.4, 121.3, 114.6, 67.9, 66.9, 58.8, 53.1, 33.0, 29.7, 27.9, 25.6, 22.3; IR (CH_2Cl_2) 3685, 3600, 3413, 1777, 1749, 1716, 1694, 1678 cm^{-1}; MS (FAB) *m/e* 801 (MNa).

Acknowledgment. This research was supported by a grant from the National Heart, Lung, and Blood Institute (HL-25854) and postdoctoral fellowships to E.M. (Rotary Club) and M.I.R. (Fonds National Suisse de la Recherche Scientifique). NMR and mass spectra were determined using instruments acquired with the assistance of NSF and NIH shared instrumentation grants. We particularly thank Drs. Larry C. Blaszczak and Matthew J. Fisher of the Lilly Research Laboratories for samples of (3*R*,4*R*)-3-(phenoxyacetamido)-4-acetoxyazetidin-2-one (**18**) and Drs. Lowell Hatfield and John Gardner of the Lilly Research Laboratories for advice.

Supporting Information Available: Experimental procedures and characterization data for **10bcd**, **12bcd**, **13bcd**, **14bcd**, **15bc**, **19**, **21**, **25**, and **31** and ^{1}H NMR spectra (500 MHz in $CDCl_3$) of **10abcd**, **12abcd**, **13abcd**, **14acd**, **15bc**, **16a**, **17**, **24**, **26**, **32a**, and **32b** (33 pages). This material is containing 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.

JO971433W