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Radical Rearrangement: A Strategy for Conversion of Cephalosporin to 1-Carba(dethia)cephalosporin

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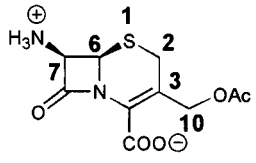
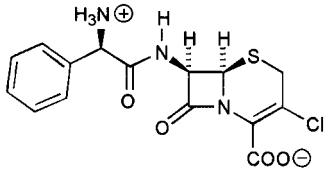
Abstract—A radical rearrangement approach to semisynthesis of the carbacephem class of β-lactam antibiotics is reported. The crucial bond construction in assembly of the carbacephem framework was accomplished by intramolecular C–C bond formation between an azetidin-2-one-4-yl and a pendant diene ester. This reactive intermediate was generated by fragmentation of a cephem derived radical followed by loss of sulfur dioxide. The radical precursor was prepared in 63% yield over four steps and the subsequent rearrangement reaction provided carbacephem products in a single step at 23% yield.

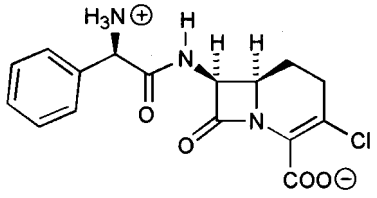
An investigation of the 1-carba(dethia)cephem (carbacephem) class of antibiotics identified loracarbef (Lorabid®), a compound of sufficient interest to support development to commercialization. Loracarbef is a potent antibacterial agent,[1] is well absorbed following oral administration,[2] and exhibits an astonishing degree of chemical stability. The seemingly conservative atom interchange that differentiates cephems and carbacephems, substitution of carbon for sulfur at position 1 adjacent to the bridgehead, profoundly influences the chemical properties of the bicyclic β-lactam nucleus without adversely affecting the antibacterial characteristics.[3]



cephalosporin nucleus
(cephem)



cefaclor
(cephem)



loracarbef
(carbacephem)

Because loracarbef and other members of the carbacephem class of compounds differ from their fermentation derived analogs (e.g. cefaclor) by the carbon substitution, they are available only through lengthy syntheses.[4]

One well-established approach to enantiospecific synthesis of new bicyclic β-lactams is through structural modification of inexpensive fermentation products such as penicillin and cephalosporin.[5] Even though all classes of β-lactam antibiotics have been synthesized in this way, the routes from penicillin to carbacephems are cumbersome.[6] Nonetheless, obvious structural similarity between the bicyclic core structures of cephems and carbacephems strongly suggests the possibility of finding an atom efficient chemical transformation that would connect the two β-lactam ring systems. As an extension of our program to investigate new radical based synthetic methodology for installation of carbon–carbon bonds at C4 of azetidin-2-one derivatives,[7] we envisaged a homolytic retrosynthetic disconnection in a generalized target structure such as **1** (Scheme 1). Sufficiently nucleophilic carbon-centered radicals react readily with electron deficient olefins.[8] Furthermore, inspection of molecular models suggests that cyclization of **2** would be facilitated by very favorable orbital overlap in the proposed transition state. However, consideration of synthetic schemes for generation of **2** immediately reveals two significant challenges. First, generation of a radical such as **2** from a monocyclic precursor by the usual reductive processes would likely be precluded by preferential reduction of the diene ester. Secondly, stereoselective introduction of the diene ester would require multistep transformations of known penicillin-derived azetidinone intermediates and thus compromise the potential efficiency of the overall process.

Keywords: cephalosporins; radicals; rearrangements.
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† Deceased.

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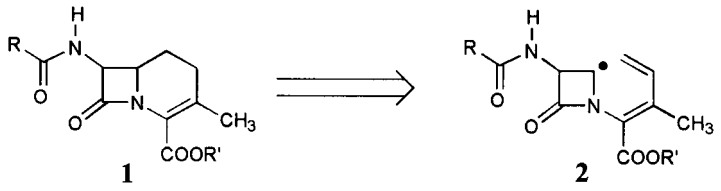


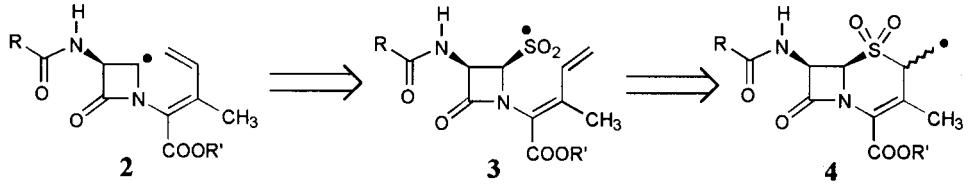
Scheme 1.

The propensity of β-sulfenyl, sulfinyl and sulfonyl carbon radicals toward fragmentation[9] offers the possibility of a very efficient approach to **2** wherein a potential method for stereoselective synthesis of the required diene ester substituent is embedded in methodology for generation of **2** (Scheme 2). Presumably **2** could be formed on loss of SO_2 from sulfinyl radical[10] **3** which, in turn, could result from fragmentation of cephem sulfone radical **4**.

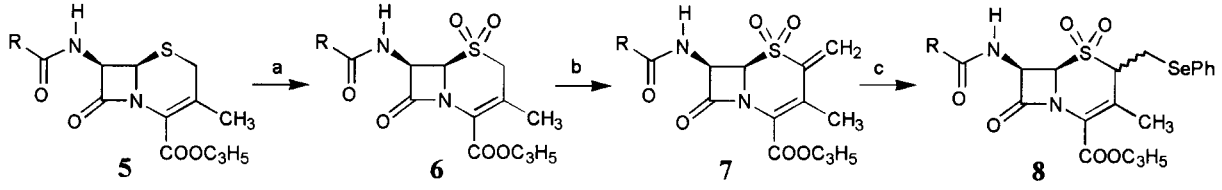
Thus, a carbon-centered radical exocyclic at C2 in a cephalosporin sulfone contains all of the structural and electronic elements necessary to drive a rearrangement to the corresponding carbacephem radical. Synthesis of a precursor to **4** presents no synthetic difficulties of consequence. We now report demonstration of a pathway for the direct conversion of a cephalosporin to the corresponding carbacephem.

We chose 7-phenoxyacetamido-10-desacetoxycephalosporin allyl ester **5** as a model substrate for investigation of the proposed activation–rearrangement sequence. This simple cephalosporin is easily synthesized in high yield by classical procedures[11] from either the 10-desacetoxy cephalosporin nucleus or penicillin. The straightforward process for activation of the cephem is outlined below (Scheme 3). Only a standard tributyltin hydride reduction of **8** seemed to be required for generation of **4** and initiation of the proposed rearrangement.

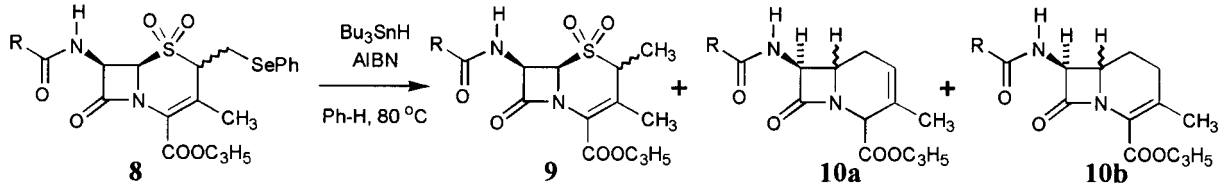
When **8** was subjected to variations on the standard radical ring closure conditions[12,13] (tributyltin hydride, 2,2′-azobisisobutyronitrile [AIBN], benzene, 80°C), **9** was observed as the major product (60–70%) accompanied by the desired carbacephem compounds **10** (15–25%), numerous minor products and, curiously, gas evolution. The major features of the reaction outcome are illustrated in Scheme 4. As expected, the carbacephem products were formed as a mixture of all possible ring junction and double bond isomer combinations. The 6,7-*trans* ring junction was favored and the Δ^2 (non-conjugated) double bond isomer predominated regardless of ring junction stereochemistry. Furthermore, the C2 epimers of **9** appeared to interconvert upon chromatography. This phenomenon caused substantial difficulty in chromatographic detection of the carbacephem reaction products and resulted in tedious purification.



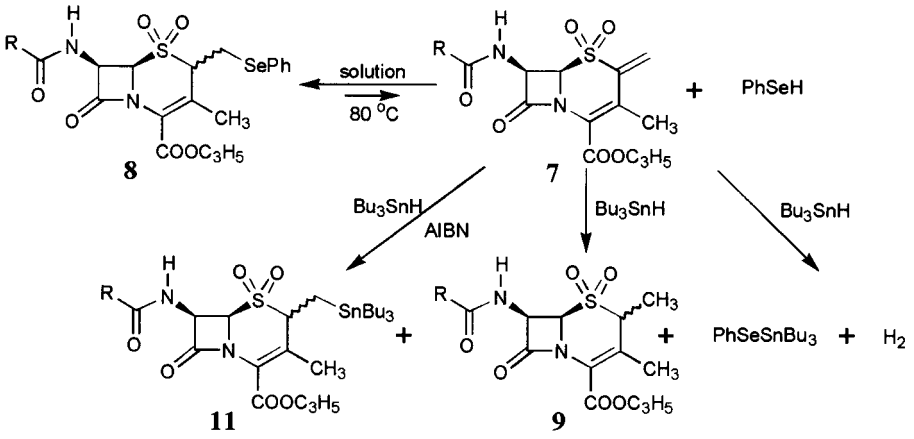
Scheme 2.



Scheme 3. Conditions: (a) 2.2 equiv. *m*-CPBA; DMF–EtOAc=1:1, 0°C; 94%. (b) 37% aq. formaldehyde; Me_2NH_2Cl; THF; 25°C; 92%. (c) PhSeH; CH_3CN; 25°C; 83% R=$PhOCH_2$.



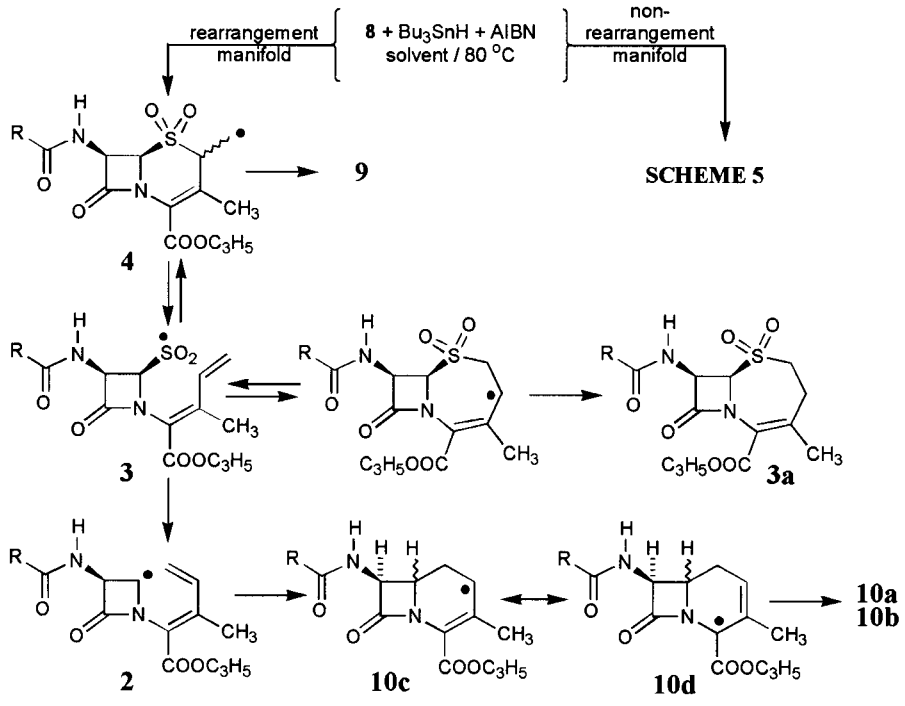
Scheme 4.



Scheme 5.

A large matrix of reaction conditions was explored including variations on solvent, reaction temperature, concentration and energy source with no significant variation in the results. The simplest explanation that could account for the major observed products and for the large amount of direct reduction product **9** would be to assume that quenching of radical **4** by tributyltin hydride is faster than the proposed fragmentation and rearrangement. Premature reduction is often a shortcoming of synthetic routes based on radical cyclizations. However, very slow addition of the tributyltin hydride and high dilution failed to change the product distribution significantly. Furthermore, when the reaction was conducted with or without AIBN in the presence of a chain-terminating 10% (v/v) nitrobenzene, **9** was still produced. Finally, the gas evolution phenomenon is unexplained by simple premature hydrogen atom transfer. Together these results suggest that other chemistry is operative in the rearrangement reaction mixture at a rate or rates competitive with the radical chain process.

Tributyltin hydride reacts with carboxylic acids in the absence of radical initiators to form tributyltin carboxylates and hydrogen.[14] The C2 methine proton of **8** and selenophenol both represent acids that might exhibit similar reactivity with tributyltin hydride. As a test of this hypothesis, cephalosporin sulfone **9** was heated with 1 equiv. of tributyltin hydride in toluene at 95°C for 1 h. No gas evolution was observed and no evidence for enolstannyl ether formation could be found in the ^{1}H NMR spectrum of an aliquot concentrate. Upon addition of one equivalent of selenophenol, gas evolution commenced and $(n\text{-Bu})_3$Sn-SePh was formed. Thus, a mechanistic rationale emerges to account for the inescapably large amount of direct reduction product (Scheme 5). Presumably when **8** is heated in



Scheme 6.

solution, an equilibrium is established between **8** and **7** plus selenophenol. Tributyltin hydride can then react with the free selenophenol by chemistry that is not part of the desired radical chain pathway. This process could account for the (hydrogen) gas evolution and a large fraction of the $(n\text{-Bu})_3$SnSePh. Tributyltin hydride can react with **7** as well to afford **9**, the same product that results from premature hydrogen atom transfer to **4** in the radical chain manifold. Tributyltin radical itself can react with **7** through the radical chain process. When the exomethylene cephem **7** was treated independently with tributyltin hydride in toluene at 110°C, **9** was the exclusive product; in the presence of AIBN both reduction product **9** and the $Bu_3Sn^{\cdot}$ addition product **11** were formed. Indeed **11** was always isolated in varying amounts from rearrangement reaction mixtures.

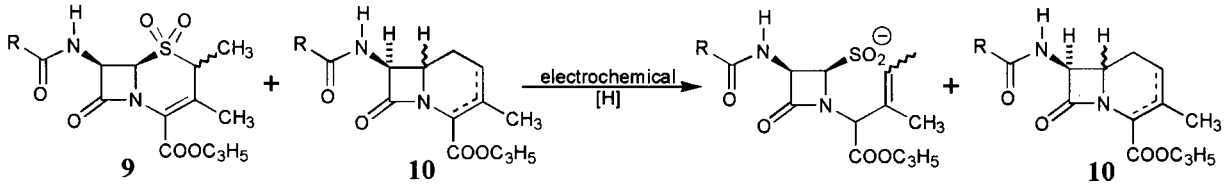
Radical **4** is most likely involved in a fragmentation/readdition equilibrium with **3** that supports both direct reduction and carbacephem formation (Scheme 6). The latter product can only result from displacement of the equilibrium by loss of SO_2 from **3**. Considering the non-radical chain pathway for degradation of **8**, the rate constant[15] of ca. 2×10^6 M^{-1} s^{-1} for depletion of **4** by $(n\text{-Bu})_3$Sn–H, and our observed formation of carbacephem product at 15–25%, we conclude that loss of SO_2 from **3** is quite an efficient process. We expected that closure of the sulfonyl radical **3** onto the terminus of the diene ester would be unfavorable based on steric as well as radical philicity considerations. However, the reaction mixture produced a very small amount of material that is isomeric with **9** and exhibits an AA′BB′ pattern centered around 2.9δ in place of the diastereotopic methyl doublets of **9** at 1.5δ in the ^{1}H NMR spectrum. We tentatively assign the structure **3a** to this substance. We were unable to find any product attributable either to 5-*exo* ring closure or to hydrogen atom transfer to **2** by $(n\text{-Bu})_3$Sn-H, suggesting that 6-*endo* ring closure of **2** to the carbacephem radicals **10c** and **10d** is very fast.

The C2 epimers of **9** appeared to interconvert under all chromatographic conditions examined, effectively obscuring chromatographic observation of reaction progress and initially confounding product isolation. A simple expedient rendered the carbacephem products of the reaction more readily available for isolation and analysis. All cephem sulfones were eliminated from the crude reaction mixtures by reductive opening of their dihydrothiazine rings through the use of electrochemical methods[16] followed by extractive removal of the resulting azetidin-2-one-4-sulfinic acid salts (Scheme 7).

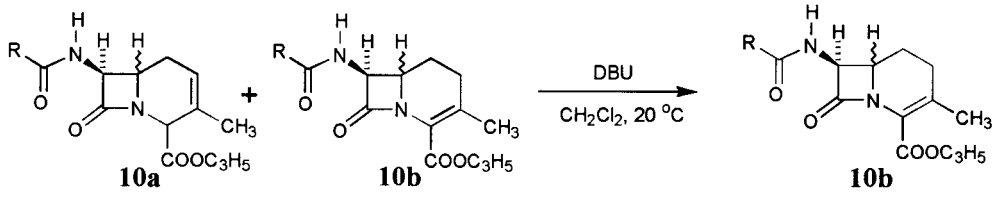
The carbacephem product is a mixture of ring junction and double bond isomers that largely favors the *trans* ring junction (86:14) and the Δ^2 double bond isomer (88:12). The *trans* preference in the ring junction stereochemistry is easily rationalized by assuming preferential approach of the diene ester terminus from the less hindered face of the azetidin-2-one-4-yl **2**. Presumably the distribution of the double bond isomers is reflective of a spin density ratio that favors the capto-dative radical stabilization[17] at C4 (**10d**) over carbonyl conjugation stabilization at C2 (**10c**).

Finally, we required a transformation of the major carbacephem product, the Δ^2 isomers, to the biologically active Δ^3 isomers. Isomerization of double bond mixtures of cephalosporin to the biologically active Δ^3 form is accomplished by a two step process of oxidation at sulfur (Δ^2 cephalosporin sulfoxides are unknown) followed by a return to the sulfide oxidation state under neutral or acidic conditions.[18] Obviously this sequence cannot be applied to the carbacephem ring system. We found, in contrast to the cephalosporin system, that treatment of the carbacephem isomer mixture with catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane results in a simplification of **10a/10b** to the pair of ring junction diastereomers at C6 (**10b**), each with the double bond migrated completely to the Δ^3 position (Scheme 8).

We have illustrated a straightforward approach to carbacephem synthesis that is based on the close structural relationship between the target molecule and the naturally occurring molecules that are readily available from fermentation as starting materials. In concept the cephem-to-carbacephem pathway involves only regioselective addition



Scheme 7.



Scheme 8.

of a single carbon atom to the cephalosporin nucleus, removal of the sulfur atom and specific reconnection of the remaining components. There are strategic advantages of this approach to synthesis of carbacephems over others that have been recorded. High yield fermentation is the source for several important aspects of the carbacephem product: fifteen of sixteen atoms in the nucleus core structure, the absolute stereochemistry and the legendary β-lactam that is responsible for biological activity. Following some simple adjustments to the natural product, transformation of cephem framework to the corresponding carbacephem framework can be accomplished in a single step. Thus, strategic validation of the radical rearrangement approach to carbacephem synthesis has been fully realized. Certain tactical issues, most notably radical generation methodology and control of ring junction diastereoselection, remain to be addressed and are currently under investigation.

Experimental

Allyl (6*R*,7*R*) 7-phenoxyacetamido-10-desacetoxyceph-3-em-4-carboxylate (5). To a slurry of 7-amino-desacetoxycephalosporanic acid (42.8 g, 200 mmol) in a mixture of dioxane (400 mL) and water (200 mL) was added dropwise with stirring 2N aqueous sodium hydroxide (100 mL, 200 mmol). The reaction mixture became a brown homogeneous solution after ca. 30 min. One dropping funnel was charged with phenoxyacetyl chloride (29 mL, 210 mmol) in dioxane (130 mL); another was charged with 2N aqueous sodium hydroxide (110 mL, 220 mmol). The reaction vessel was cooled in an ice bath and simultaneous additions of acid chloride solution and hydroxide solution were rate adjusted to maintain pH=8–9 (meter). When the acid chloride addition was complete, the pH was adjusted to 8.5, the cooling bath was removed, and stirring continued for 1 h at ambient temperature. After removal of most of the dioxane in vacuo, the aqueous solution was extracted once with ether and taken directly to the esterification reaction.

Tetrabutylammonium hydrogen sulfate (71.3 g, 210 mmol) was dissolved in water (300 mL) and the pH adjusted to 7.5 with 2N aqueous sodium hydroxide (meter). The aqueous acylation reaction mixture and the tetrabutylammonium sulfate solution were combined in a separatory funnel and extracted with three portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated to a brown oil. The oily salt was dissolved in acetone (150 mL) and the solution cooled in an ice bath. Allyl bromide (19.5 mL, 225 mmol, purified by filtration through activity I neutral alumina immediately prior to use) was added dropwise. Upon completion of the addition, the cooling bath was removed and the reaction mixture stirred at ambient temperature for 2 h. After removal in vacuo of most of the acetone, the thick brown oil was diluted with ether/dichloromethane (3:1=v/v) and extracted twice with pH 7 buffer and once with saturated brine. The organic phase was dried ($MgSO_4$), treated with decolorizing carbon, and concentrated to 65.2 g (84%) of **5** as a yellow solid. The crude material, contaminated by several percent of Δ^2 isomer, was taken directly to the oxidation step. The analytical sample was prepared by recrystallization from isopropyl ether/dichloromethane which afforded **5** as a white crystalline solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.05 (d, J=8.4 Hz, 1H), 7.29 (td, J=1.1, 7.3 Hz, 2H), 6.98–6.92 (m, 3H), 6.01–5.88 (m, 1H), 5.67 (dd, J=4.4, 8.1 Hz, 1H), 5.38 (dd, J=1.5, 17.2 Hz, 1H), 5.24 (dd, J=1.5, 10.2 Hz, 1H), 5.12 (d, J=4.8 Hz, 1H), 4.71 (dd, J=1.5, 4.0 Hz, 2H), 4.63 (d, J=3.7 Hz, 2H), 3.52 (q, J=17.9 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.5, 164.0, 161.6, 157.7; MS (FAB) m/z 389.1 (97%, M+H); IR (KBr) ν_{max} 3273 (m), 1762 (s), 1719 (s), 1671 (s), 1543 (m), 1496 (m), 1385 (m), 1221 (s) cm^{-1}; $[\alpha]_D^{20}$=+1205.1 (c=1 DMSO); UV–vis (EtOH, nm) 268 (6643).

Allyl (6*R*,7*R*) 7-phenoxyacetamido-1,1-dioxo-10-desacetoxyceph-3-em-4-carboxylate (6). To a solution of **5** (15.0 g, 38.6 mmol) in DMF (160 mL) at ice bath temperature was added *m*-chloroperoxybenzoic acid (85% technical, 17.7 g, ca. 85 mmol) in ethyl acetate (160 mL) dropwise at such a rate as to maintain a reaction temperature of 10–15°C. After the addition was complete, the cooling bath was removed and stirring continued at ambient temperature for 3 h. The reaction mixture was diluted with ethyl acetate and extracted three times with N HCl/saturated brine=1:1 (v/v), once with N sodium thiosulfate, twice with saturated aqueous sodium bicarbonate once with saturated brine. The organic phase was dried ($MgSO_4$) and concentrated to a tan solid. Recrystallization from isopropyl ether/dichloromethane provided 13.1 g (81%) of **6** as an off-white crystalline solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.57 (d, J=9.5 Hz, 1H), 7.29 (td, J=1.1, 5.5 Hz, 2H), 7.00–6.90 (m, 3H), 6.07 (dd, J=4.8, 9.1 Hz, 1H), 6.00–5.88 (m, 1H), 5.39 (dd, J=1.5, 17.6 Hz, 1H), 5.26 (dd, J=1.5, 10.2 Hz, 1H), 4.74 (dd, J=1.5, 5.5 Hz, 2H), 4.66 (q, J=8.78 Hz, 2H), 4.32 (q, J=18.3 Hz, 2H), 2.01 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.1, 163.9, 160.7, 157.3; MS (FAB) m/z 421.1 (74%, M+H); IR (KBr) ν_{max} 3394 (m), 1764 (s), 1726 (s), 1525 (s), 1329 (s), 1227 (s), 1128 (s) cm^{-1}; $[\alpha]_D^{20}$=−279.4 (c=1 DMSO); UV–vis (EtOH, nm) 261 (8638).

Allyl (6*R*,7*R*) 7-phenoxyacetamido-1,1-dioxo-2-methylene-10-desacetoxyceph-3-em-4-carboxylate (7). To a solution of **6** (43.0 g, 102 mmol) in dioxane (600 mL) was added an excess of aqueous formaldehyde (37% solution, 150 mL) and dimethylamine hydrochloride (12.6 g, 155 mmol). After stirring at ambient temperature 1.5 h, tlc analysis (1:1=EtOAc–hexanes, double elution) indicated complete reaction. After approximately half of the dioxane had been removed in vacuo, (some precipitate deposited) the remaining mixture was diluted with ethyl acetate and extracted with N HCl and brine. The aqueous phase was back extracted with two portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated to a solid. Crystallization from isopropyl ether/dichloromethane (two crops) provided a total of 40.3 g (91%) of **7** as an off-white crystalline solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.77 (dd, J=3.3, 9.5 Hz, 1H), 7.33–7.26 (m, 2H), 7.00–6.89 (m, 3H), 6.58 (d, J=2.6 Hz, 1H), 6.50 (d, J=2.6 Hz, 1H), 6.19–6.13 (m, 1H), 6.03–5.09 (m, 1H), 5.62 (t, J=4.8 Hz, 1H), 5.41 (dt, J=1.8, 17.2 Hz, 1H), 5.29 (dt, J=1.5, 10.6 Hz, 1H), 4.80–4.74 (m, 2H), 4.68 (dd, J=3.7, 9.5 Hz, 2H), 2.16 (s, 3H); ^{13}C

NMR (DMSO-d_6, 75 MHz) δ 168.2, 163.1, 161.0, 157.4; MS (FAB) *m/z* 587.1 (100%, M+matrix), 433.1 (26%, M+H); IR (KBr) ν_{max} 3398 (m), 1772 (s), 1732 (s), 1715 (s), 1534 (s), 1322 (s), 1312 (s), 1143 (s) cm^{-1}; $[\alpha]_D^{20}=-132.4$ (*c* 1 DMSO); UV–vis (EtOH, nm) 261 (8038), 305 (2216).

Allyl (6*R*,7*R*) 7-phenoxyacetamido-1,1-dioxo-2-phenylselenomethyl-10-desacetoxyceph-3-em-4-carboxylate (8). To a stirred solution of **7** (1.30 g, 3.0 mmol) in dry acetonitrile was added selenophenol (0.35 mL, 3.3 mmol) in one portion. After ca. 30 min, a colorless crystalline solid formed and was collected. The filtrate was concentrated to a yellow solid. The yellow solid was triturated with ether, collected and combined with the crystalline material to give, after drying in vacuo, a total of 1.47 g (83%) of white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.61 (d, *J*=9.5 Hz, 1H), 7.65–7.56 (m, 2H), 7.37–7.21 (m, 5H), 7.02–6.88 (m, 3H), 6.24 (dd, *J*=4.8, 9.5 Hz, 1H), 6.01–5.86 (m, 1H), 5.76 (d, *J*=4.8 Hz, 2H), 5.44–5.24 (m, 2H), 4.82–4.60 (m, 4H), 3.78 (dd, *J*=5.1, 14.3 Hz, 1H), 3.36 (dd, 4.4, 14.6 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.1, 164.0, 160.7, 157.4; MS (FAB) *m/z* 591.1 (70%, M+H); IR (KBr) ν_{max} 3384 (m), 1767 (s), 1726 (s), 1600 (m), 1528 (m), 1496 (m), 1324 (m), 1231 (m), 1109 (m), 1060 (m) cm^{-1}.

Radical Rearrangement of 8. A slurry of **8** (3.04 g, 5.14 mmol) and AIBN (0.851 g, 5.19 mmol) in benzene (190 mL) was heated to reflux. Tributyltin hydride (3.3 mL, 11.9 mmol) was added dropwise over ca. 5 min. After 1.5 h, tlc analysis (60:40=EtOAc–hexanes) indicated complete consumption of **8**. The reaction mixture was cooled, concentrated in vacuo, and partitioned between acetonitrile and hexanes. The acetonitrile solution was concentrated to an orange oil and submitted to flash chromatography on silica gel using an elution gradient of hexanes to ethyl acetate. The early elution product, **11**, and representative fractions containing chromatographically pure **9** were collected for characterization. The remainder of the material (1.74 g) was taken directly to electrochemical reduction for removal of cephalosporin sulfones.

Allyl (6*R*,7*R*) 7-phenoxyacetamido-1,1-dioxo-2-tributylstannylmethyl-10-desacetoxyceph-3-em-4-carboxylate (11). Yellow oil; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.56 (d, *J*=10.2 Hz, 1H), 7.32–7.26 (m, 2H), 7.00–6.92 (m, 3H), 6.12 (dd, *J*=4.4, 9.9 Hz, 1H), 6.02–5.89 (m, 1H), 5.39–5.25 (m, 2H), 5.04 (d, *J*=4.4 Hz, 1H), 4.68–4.67 (m, 3H), 1.74 (s, 2H), 1.64–1.38 (m, 8H), 1.37–1.21 (m, 9H), 0.95–0.84 (m, 15H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.9, 165.9, 163.7, 157.2, 139.4, 132.7, 129.5, 128.5, 121.4, 118.8, 64.2, 59.8, 53.9, 28.3, 26.6, 16.9, 13.5, 10.2, 6.6; MS (ESI) *m/z* 725.2 (100%, M+H), 723.3 (63%, M−H); IR ($CHCl_3$) ν_{max} 2959 (m), 1797 (m), 1746 (m), 1697 (m), 1521 (m), 1495 (m), 1315 (m), 1241 (m), 1136 (m) cm^{-1}; UV–vis (EtOH, nm) 247 (0.2768).

Allyl (6*R*,7*R*) 7-phenoxyacetamido-1,1-dioxo-2-methyl-10-desacetoxyceph-3-em-4-carboxylate (9). Waxy off-white solid (data reported for the major diastereomer); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.68 (d, *J*=9.1 Hz, 1H), 7.32–7.26 (m, 2H), 7.00–6.90 (m, 3H), 6.16 (dd, *J*=4.8, 9.5 Hz, 1H), 5.98–5.87 (m, 1H), 5.57 (d, *J*=4.8 Hz, 1H), 5.39 (dd, *J*=1.5, 17.2 Hz, 1H), 5.26 (dd, *J*=1.5, 10.2 Hz, 1H), 4.74 (dd, *J*=1.5, 5.5 Hz, 2H), 4.65 (s, 2H), 4.12 (q, *J*=7.0 Hz, 1H), 2.06 (s, 3H), 1.55 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.2, 168.0, 164.1, 163.5, 161.0, 161.0, 157.4; MS (ESI) *m/z* 435.1 (100%, M+H); IR ($CHCL_3$) ν_{max} 3410 (m), 1789 (m), 1722 (m), 1518 (m), 1328 (m), 1230 (m) 759 (m) cm^{-1}; UV–vis (EtOH, nm) 263 (8537).

Electrochemical removal of sulfones and double bond isomerization. The partially purified rearrangement product (1.74 g) and tetrabutylammonium tosylate (1.80 g) were dissolved in a mixture of DMF (50 mL) and methanol (30 mL). The solution was placed in an electrochemical cell[19] consisting of a Hg pool cathode and a Pt wire anode. The system was cooled to 0–5°C and thoroughly purged of oxygen by conducting an Ar stream through the reaction mixture; purging was continued during the course of the reaction. The reduction was performed at a constant potential of −1.4 V. When **9** had been consumed as judged by tlc analysis (60:40=EtOAc–hexanes) the reaction mixture was concentrated in vacuo, redissolved in dichloromethane and then extracted with N HCl, saturated aqueous $NaHCO_3$, and saturated brine. The organic phase was dried (Na_2SO_4) and concentrated to an oil which was taken directly to the next step. The crude reduction product (498 mg) was dissolved in dichloromethane (20 mL) and treated at room temperature with DBU (42 mg, 0.3 mmol). After 1.5 h, the reaction mixture was extracted with N HCl, dried (Na_2SO_4), and concentrated to an oil. The crude product was purified by flash chromatography to afford 377 mg of 6*R* (*trans*) carbacephem and 61 mg of 6*S* (*cis*) carbacephem (23% of **10** based on **8**).

Allyl (6*R*,7*R*) 7-phenoxyacetamido-10-desacetoxy-1-carba-(dethia)ceph-3-em-4-carboxylate (10). Yellow oil; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.88 (d, *J*=8.8 Hz, 1H), 7.30 (td, *J*=1.8, 8.4 Hz, 2H), 6.96 (td, *J*=0.73, 7.3 Hz, 3H), 5.99–5.87 (m, 1H), 5.38 (dd, *J*=1.5, 17.2 Hz, 1H), 5.38 (dd, *J*=3.7, 5.1 Hz, 1H), 5.22 (dd, *J*=1.5, 10.2 Hz, 1H), 4.68 (d, *J*=5.5 Hz, 2H), 4.58 (s, 2H), 3.78 (ddd, *J*=5.1, 5.1, 10.2 Hz, 1H), 2.32–2.27 (m, 2H), 1.94 (s, 3H), 1.79–1.63 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.2, 165.0, 161.8, 157.6; MS (FAB) *m/z* 371.1 (93%, M+H); IR ($CHCl_3$) ν_{max} 3416 (m), 3026 (m), 1764 (s), 1689 (s), 1523 (m), 1496 (m), 1389 (m) cm^{-1}; UV–vis (EtOH, nm) 268 (9191).

Allyl (6*S*,7*R*) 7-phenoxyacetamido-10-desacetoxy-1-carba-(dethia)ceph-3-em-4-carboxylate (10). Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, *J*=7.3 Hz, 1H), 7.41–7.29 (m, 2H), 7.12–7.00 (td, *J*=1.1, 7.3 Hz, 1H), 6.97–6.85 (dd, *J*=1.1, 8.8 Hz, 2H), 6.09–5.88 (m, 1H), 5.41 (dd, *J*=1.5, 17.2 Hz, 1H), 5.27 (dd, *J*=1.1, 10.2 Hz, 1H), 4.82 (dd, *J*=1.83, 7.3 Hz, 1H), 4.76 (d, *J*=1.5, 5.9 Hz, 1H), 4.52 (s, 2H), 3.50 (ddd, *J*=2.2, 3.7, 11.3 Hz, 1H), 2.44–2.47 (m, 2H), 2.00 (s, 3H), 1.82–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 161.2, 160.2, 156.9; MS (FD) *m/z* 371 (100%, M+H); IR ($CHCl_3$) ν_{max} 3019 (s), 1763 (s), 1688 (s), 1524 ((m), 1495 (s), 1441 (m), 1390 (m), 1233 (s) cm^{-1}; UV–vis (EtOH, nm) 268 (7620).

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