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An Intramolecular Addition-Elimination Strategy For The Synthesis Of Carbapenems

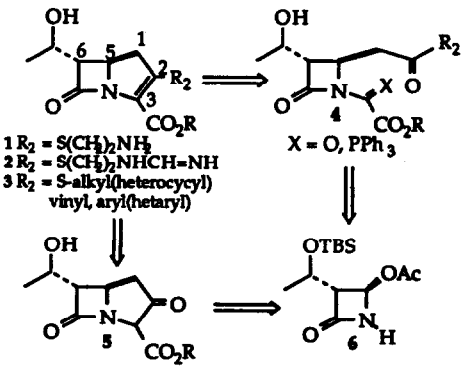
C. B. Ziegler, Jr.*, W. V. Curran, G. B. Feigelson, P. Bitha, P.Fabio, T. Strohmeyer, K. Short and Y-i. Lin

Medical Research Division, American Cyanamid Company,
Lederle Laboratories, Pearl River, NY 10965

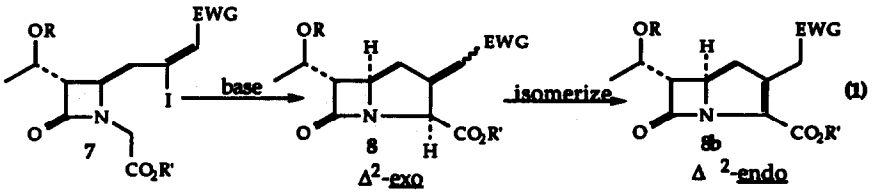
Abstract: The synthesis of 2-[(4-fluorophenylsulfonyl)methyl] carbapenem carboxylate **20** is described. The key step is a base mediated addition-elimination ring closure of a iodovinyl sulfone **12**.

The discovery of thienamycin **1**[1] and the subsequent development of its N-formimidoyl derivative imipenem[2] **2** triggered intense interdisciplinary interest in the field of carbapenem antibiotics. From a microbiological perspective, the carbapenems, as a class, represented a new frontier with few limitations as far as their broad spectrum antibacterial potency.[3] From an organic chemistry perspective, these compounds constituted a substantial synthesis challenge. Unlike the penicillins and the cephalosporins, the carbapenems are not products of semi-synthetic modification. Most carbapenem analog programs resort to total synthesis. In response to this challenge, several formal total syntheses of the carbapenem nucleus and analogs have been developed since 1978.[4] Nevertheless, the vast majority of carbapenem derivatives **3** that have been prepared result from two major syntheses that utilize intermediates **4**[5] or **5** (Scheme 1). Of these two, the synthesis via the β-ketoester **5**[6] is more versatile in terms of the diverse nature of synthetic analogues available from it. The synthesis of compounds **4** and **5** hinges on the commercially available 4-acetoxyazetidinone **6** which contains three contiguous chiral centers.

SCHEME 1



Our interest in studying the biological activity of 2-(alkylsubstituted) carbapenems[7,8] prompted us to search for an alternate entry to this class. One approach of particular interest was a two-step sequence driven by a base-mediated intramolecular addition-elimination reaction of an appropriately substituted 4-allylazetidinone **7** (to form **8**) followed by double bond isomerization to form the carbapenem **8b** (eqn.1).



EWG = electron withdrawing group

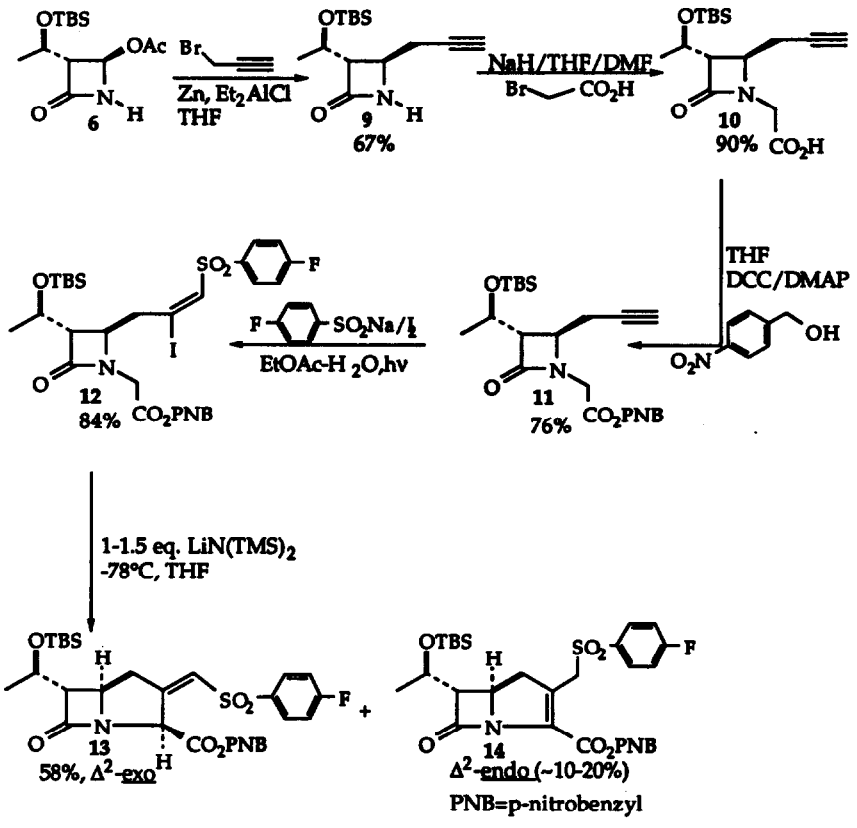
Our experience with intramolecular addition-elimination synthesis[8,9] in addition to Hanessian's earlier synthesis of the penem FCE-22101[10a] and of thienamycin[11] via an intramolecular Michael addition provided added precedent for our approach.[12] To test the strategy carbapenems were chosen where EWG = SO_2Ar. Herein is described an expedient five-step preparation of these compounds.

RESULTS AND DISCUSSIONS

An important prerequisite in our carbapenem addition-elimination synthesis strategy was the stereo-controlled design of suitably substituted allylic azetidinones **7** (EWG = SO_2Ar). The logical starting point for the preparation of such azetidinones **7** is the 4-acetoxyazetidinone **6**.[13] Thus, in a reaction amenable to scale-up, azetidinone **6** readily reacted with propargyl bromide in a Reformatsky-like reaction[14] facilitated by Et_2AlCl (Scheme 2). The resulting product, **9**, reflected a stereocontrolled, β-incorporation of the propargyl moiety (the only product observed).[15] The preference for β-face substitution is consistent with that observed in other reactions of **6** with organozinc[16] or organotin[17] reagents as well as Lewis acid enolates.[18,19] The 4-propargylazetidinone **9** was isolated in 67% yield following a simple recrystallization. Alkylation of the azetidinone nitrogen of **9** was achieved with bromoacetic acid and strong base. The free acid **10**, produced in 90% yield, was then esterified to the p-nitrobenzyl ester under standard conditions. The two-step alkylation-esterification sequence[20] gave an enhanced yield of **11** compared to the obvious and more direct azetidinone alkylation with the p-nitrobenzyl bromoacetate.[21]

A key reaction in this synthetic scheme was the chemo and regioselective "iodo-sulfonylation" of **11** to form the iodovinyl sulfone **12**. This method, a modification from that of Truce[22a,b] and later Koboyashi[22c], entailed heating the azetidinone **11** with excess iodine and sodium p-fluorophenylsulphinate in a biphasic system. We found that irradiation with a 300 Watt incandescent lamp positioned close enough to sustain a steady reflux expedited the formation of product sulfone **12** which was obtained in 86% yield.

SCHEME 2



With a reliable synthesis of the iodovinyl sulfone in hand, we next explored the intramolecular addition-elimination ring closure. On treatment with LiN(TMS)2 at -78°C the sulfone **12** cyclized to the Δ^2-exo carbapenem **13** in 58% yield following an acid quench and aqueous workup. Isolation of pure **13** required only a EtOAc/hexane trituration procedure. Lesser amounts of the Δ^2-endo product **14** (relative to **13**) are formed but remain in the mother liquor.[23] We obtained higher yields of **13** by choosing conditions that include: low temperatures (-90° to -78°C), short reaction times (0.3 to 1 h) and 1.3 to 1.5 equivalents of base. On the other hand, higher reaction temperatures, longer reaction times as well as more base increased the ratio of **14** to **13** but at the expense of the overall product yield.[24]

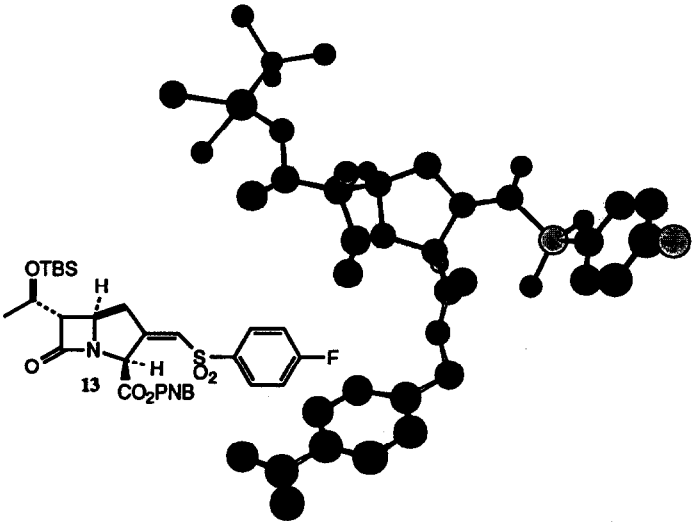


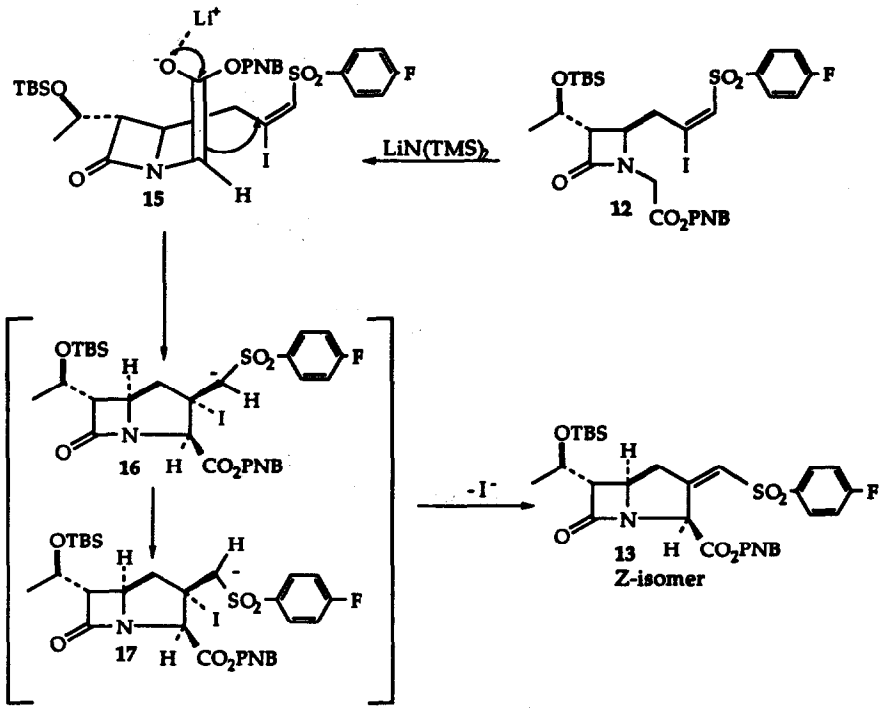
Figure 1. Solid-state structure of the major diastereomeric product isomer **13** from the intramolecular addition-elimination.

Initially, we were unsure of the stereochemical assignment of the Δ^2-exo isomer **13**, as ^{1}H NMR experiments on **13** proved inconclusive. However, a single crystal X-ray analysis of **13** revealed its absolute configuration (shown in Fig. 1). Interestingly, the Z double bond geometry presides in **13** and the more sterically congested β-orientation of the C-3 carboxylate is apparent.

Taking these two observations into consideration one can propose a probable mechanistic course for this cyclization. In Scheme 3 a stepwise addition-elimination sequence is presented to account for the stereochemical outcome observed in the Δ^2-exo product **13**. Base treatment of **12** most likely forms a reactive non-chelated ester enolate **15**. The conformation of this enolate ensures the β-orientation of the carboxylate on cyclization. This reasoning is quite similar to that originated by Hanessian in a conjugate addition strategy towards thienamycin.[11] Cyclization of **15** to **16** followed by bond rotation to **17** and subsequent iodide elimination would give the Z-isomer **13**. The actual mechanistic course operating here may indeed be more involved with other (concerted and/or reversible) pathways operating. The complexity of nucleophilic vinylic addition-elimination processes is well known and the mechanistic course of such reactions depends on the nucleophilic and vinylic substituents.[25]

In order to evaluate the microbiogical activity of the Δ^2-endo carbapenem **14** both of the protecting groups (TBS and PNB) were removed. Two routes, shown in Scheme 4, proved to be effective for generating the Δ^2-endo hydroxyethyl derivative **19**, starting from either **13** or **14**. Isomerization of **13** using Hunigs base in

SCHEME 3

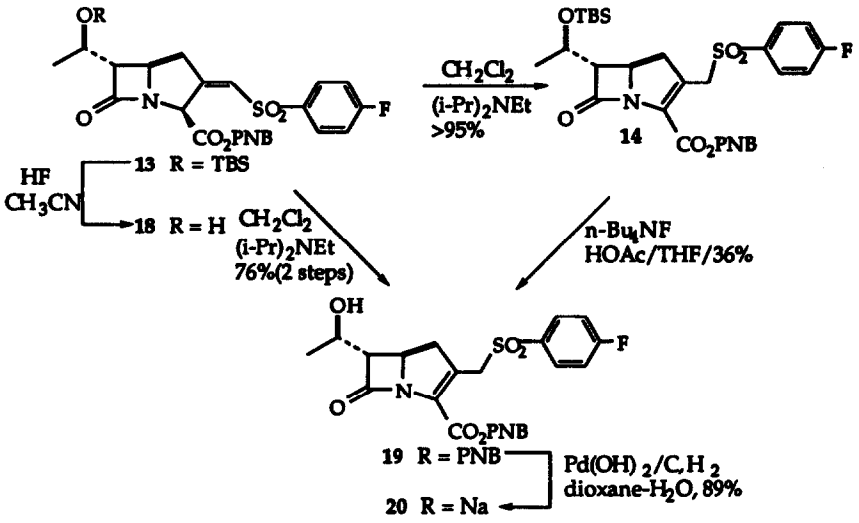


CH_2Cl_2 at room temperature gave **14** in quantitative yield. The Δ^2-endo isomer, when treated with buffered n-Bu_4NF,[3b] hydrolyzed to the hydroxyethyl derivative **18**. Alternatively, another method requiring dilute aqueous HF in CH_3CN[26] could be used in the TBS-hydrolysis of **13** to give **18**. Hunigs base isomerization of **18** afforded the Δ^2-endo carbapenem **19** in 76% yield for the 2-step process. Interestingly, the HF-CH_3CN method caused the decomposition of the Δ^2-endo isomer **14**.

In the final step of the synthesis, the Δ^2-endo carbapenem was hydrogenolysed in the presence of $NaHCO_3$ to yield the sodium salt **20** in 89% yield[27] following reverse phase chromatography. The microbiological activity of **20** was poor to moderate against a panel of Gram-negative and Gram-positive organisms, and substantially less active than imipenem **2**, the standard used for comparison.

The novel addition-elimination strategy reported herein compliments the existing carbapenem synthetic methods. Though not discussed, this method is general for a variety of aryl sulfones.

SCHEME 4



EXPERIMENTAL SECTION

Melting points are uncorrected. Elemental analyses were obtained for all new compounds are reported when possible. Chromatographic separations were done using either thin layer plates (Analtech silica gel GF), flash column-silica gel or reversed phase thin layer or preparative plates (Analtech RPS-F). NMR spectra were recorded using a NT-300 WB or a GE-300 Spectrometer. Mass spectra were recorded on a Finnigan Mat 90 (for chemical ionization spectra-CI and desorption chemical ionization - DCI) or a VG ZAB-SE spectrometer (for fast atom bombardment spectra-FAB). Sodium chloride was the matrix component for the FAB mass spectra. IR spectra were recorded on Perkin-Elmer Model 21 infrared spectrometer. The single crystal X-ray analysis was performed by Molecular Structure Corporation, 3200 Research Forest Dr., The Woodlands, TX.

(3S,4R)-3-[(1R)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-(2-propynyl)-2-azetidinone, 9. To a dry three neck round bottom flask equipped with a mechanical stirrer, 1000 ml addition funnel and thermometer was added 146.6 g zinc (2.25 mol) and 1L tetrahydrofuran. The suspension was stirred at 0° under an atmosphere of argon while 800 ml of diethylaluminum chloride (1.8M in toluene) was added via cannula. A solution of 320 g (1.11 mol) of [3S-[3a(S*),4beta]]-4-(acetyloxy)-3-[1-[[1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-2-azetidinone and 168 ml (1.51 mol) propargyl bromide (80% toluene solution) in 800 ml tetrahydrofuran was added via addition funnel over 90 minutes and the reaction mixture was stirred at 0°C for two hours, then at room temperature overnight. The reaction mixture was cooled to 0°C and 200 ml of pyridine was added dropwise over 50 minutes. The solution was then filtered through diatomaceous earth and washed with dichloromethane. The filtrate was concentrated in vacuo to 1L and the solid was dissolved in dichloromethane. The resulting solution was added

over 45 minutes to a stirred 3L slurry of ice/water and stirring was continued for an additional 30 minutes. The solution was filtered through hydrous magnesium silicate and the filtrate evaporated to afford 196.6 g (66.9%) after recrystallization from heptane: mp 116-117°C.
^{1}H NMR ($CDCl_3$) δ 0.078 (s, 6H), 0.877 (s, 9H), 1.23 (d, 3H), 2.05 (t, acetylenic H), 2.54 (m, 2H, propargyl CH_2), 2.90 (m, H_3), 3.86 (m, H_4), 4.21 (m, H), 5.98 (brs, OH).
^{13}C NMR ($CDCl_3$) δ 4.3 (2C, CH_3), 17.9 (quaternary). 22.6 (CH_3), 24.6 (propargyl C), 25.7 (3 CH_3), 48.8, 63.9 (azetidinone C's), 65.0 (COSi), 70.9 and 79.7 (acetylenic C's), 168.0 (CO); IR(KBr) cm^{-1} 3308 (alkyne), 3208 (NH), 3140 (NH), 2975, 2956, 2928, 2897, 2118 (alkyne), 1754 and 1723 (co-amide); Opt. Rotation (CH_3OH) $[a]_D^{25}$ = -6°±2 conc. = 0.612%; Anal. Calcd. for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.01. Found: C, 62.97; H, 9.32; N, 5.15.

(3S,4R)-3-[(1R)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-2-oxo-4-[2-propynyl-1-azetidineacetic acid, 10. A 4.48 g (93.3 mmol) suspension of prewashed sodium hydride (50% dispersed in oil) in 200 ml of anhydrous tetrahydrofuran was cooled in an ice bath under argon. To this suspension was added, over a 30 minute period, a solution of 10 g (37.5 mmol) azetidinone **9** and 6.22 g (44.7 mmol) bromoacetic acid in anhydrous tetrahydrofuran (125 ml). The resulting reaction mixture was stirred for an additional 20 minutes, then 16 ml of dry dimethylformamide was added dropwise. The ice bath was removed and the suspension was stirred overnight at room temperature. 1N Hydrochloric acid (100 ml) was slowly added to the suspension followed by 200 ml of water. The product was extracted in 3 x 300 ml of ethyl acetate. The organic phase was then washed with 2 x 200 ml of water, 2 x 200 ml of brine, dried over magnesium sulfate and filtered. The filtrate was evaporated to give, after recrystallization from hot hexane, 10.9 g of product **10** (90%): m.p. 86-88°C; ^{1}H NMR ($CDCl_3$) δ 0.07 (d, 6H, $2CH_3$), 0.9 (s, 9H, $3CH_3$), 1.24 (d, 3H, CH_3), 2.1 (t, acetylenic H), 2.6 (m, 2H, propargyl CH_2), 2.97 (dd, H_3), 4.0 (m, H_4), 4.14 (AB quartet, 2H, CH_2CO_2), 4.2 (p, CHO Si);
^{13}C NMR ($CDCl_3$) δ 5.6, -4.4 ($SiCH_3$), 17.8 (SiC), 22.3, 22.5, 25.6 ($3CH_3$), 42.0 ($\underline{CH_2}CO_2H$), 54.0 (C_4), 63.1, 65.3 (C_3 and CHOSi), 71.4, 79.4 (2 acetylenic), 168.33 (β-lactam CO), 172.4 (CO_2H); IR (KBr) cm^{-1} - 3277 (alkyne), 3400-2600 (broad-OH), 2968, 2932, 2858, 2124 (alkyne), 1755, 1702; MS (CI-Ammonia) (m/e). Anal Calcd. for $C_{16}H_{27}NO_4Si$: C, 59.04; H, 8.36; N, 4.30. Found: C, 58.90; H, 8.23; N, 4.29.

(3S,4R)-3-[(1R)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-2-oxo-4-(2-propynyl)-1-azetidineacetic acid,(4-nitrophenyl)methyl ester, 11. To a THF solution (25 ml) containing 1.38 g (4.65 mmol) of the acid **10**, and 0.782 g (5.1 mmol) p-nitrobenzyl alcohol was added 1.05 g (5.1 mmol) dicyclohexylcarbodiimide and 30 mg dimethylaminopyridine. The resulting reaction was stirred overnight and then filtered through a bed of diatomaceous earth. After the addition of EtOAc (50 ml) the organic solution was washed in sequence starting with water, 5% HOAc, water and finally brine. The organic solution was dried ($MgSO_4$) then filtered and following solvent removal the product was recrystallized from EtOAc/hexane to yield 1.62 g (76%) : m.p. 68-71°C; ^{1}H NMR ($CDCl_3$) δ 0.06 (2S, 6H, $2CH_3$), 0.86 (s, 9H, $3CH_3$), 1.24 (d, 3H, CH_3), 2.0 (t, 1H, acetylenic), 2.58 (m, 2H, propargyl CH_2), 2.95 (dd, H_4), 3.95 (m, H_4), 4.13 (d, 2H, CH_2N), 4.19 (m, CHOSi), 5.26 (d, CH_2O_2C), 7.52 (d, 2H), 8.23 (d, 2H); IR (KBr) cm^{-1}, 3223 (terminal acetylene), 3114, 3072, 2978, 2952, 2932, 1760, 1736, 1607; MS (CI-Ammonia) (m/e) : 478 (m + NH_4)$^+$, 461 (MH^+); Anal. Calcd. for $C_{23}H_{32}N_2O_6Si$: C, 59.98; H, 7.00; N, 6.08. Found: C, 59.93; H, 7.06; N, 6.22.

(3S,4R)-3-[(1R)-1-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]ethyl]-2-oxo-4-[3-[(4-fluorophenyl)-sulfonyl]-2-iodo-2(E)-propenyl]-1-azetidineacetic acid,(4-nitrophenyl)methyl ester, 12. A two-phase system containing ethyl acetate (50 ml), water (25 ml), the acetylene **11** (1.1 g - 2.25 mmol), iodine (0.61 g - 2.4 mmol), sodium 4-fluorophenylsulfinate (1.05 g - 5.8 mmol, Parish Chemical Co.), sodium acetate (475 mg - 5.8 mmol) and sodium bicarbonate (487 mg - 5.8 mmol) was prepared. The reaction mixture was degassed with argon and then irradiated with a 300 Watt lamp positioned close enough to sustain a steady reflux. The reaction progress was monitored by tlc (30% EtOAc - 70% hexane). After 0.5 h the iodine color had dissipated and the reaction was diluted with ethyl acetate (50 ml) then the aqueous portion separated. The EtOAc solution was washed with water then brine and finally dried. Purification of the product **12** via flash silica gel chromatography yielded 1.45 gm (84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), 0.87 (s, 9H, $3CH_3$), 1.25 (d, 3H, CH_3), 3.22 (dd, 1H, H_3), 3.35 (dd, 1H, allylic CH), 3.8 (dd, 1H, allylic CH), 4.05 (dd, 2H, CH_2CO_2), 4.2 (m, 2H, H_4 + CHOSi), 5.25 (s, 2H, CH_2O), 7.06 (s, vinyl H)7.25 (t, 2H, aromatic), 7.5 (d, 2H, aromatic), 7.9 (dd, 2H, aromatic), 8.2 (d, 2H, aromatic). IR (neat) cm^{-1}, 3105, 3045, 2954, 2930, 1760, 1590; MS (CI-Ammonia) (m/e) : 764 $(M + NH_4)^+$, 747 $[M+H]^+$.

(5R,6S)-3(Z)-[[4-Fluorophenyl]sulfonyl]methylene-6-[(1R)-1-[[(1,1-dimethylethyl)dimethyloxy]ethyl]-7-oxo-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 13. To an argon degassed THF solution (15 ml) of the iodovinyl sulfone, **12** (1.4 g - 1.93 mmol) stirring at -78°C was added $LiN(TMS)_2$ (2.5 mmol as a 1M THF solution) dropwise over a 5 min. period. The resulting reaction was stirred 45 min. and then quenched by the addition of acetic acid (0.2 ml - 3.3 mmol) followed by the addition of KH_2PO_4 (1.5 mmol as a 0.5 M aqueous solution). This mixture was then allowed to warm to 0° followed by an aqueous workup (EtOAc - water and then brine). After drying the organic solution (Na_2SO_4) the crude reaction product was isolated as an oil. Trituration of this oil (20% EtOAc/80% hexane) gave a yellow solid (675 mg - 58%) : ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H, $2CH_3$), 0.88 (s, 9H, $3CH_3$), 1.23 (d, 3H, CH_3), 2.6-3.0 (m,3H, H_6 and $2H_1$), 3.8 (m, H_5), 4.2 (p, CHOSi), 5.25 (s, H_3), 5.4 (s, 2H, CH_2O), 6.35 (s, vinyl H), 7.2 (t, 2H, aromatic), 7.68 (d, 2H, aromatic), 7.8 (dd, 2H, aromatic), 8.2 (d, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ -5.1, -4.4 ($2CH_3$), 17.9, 22.6, 25.6, 39.8, 53.2, 62.4, 65.4, 65.6, 66.4, 116.7 (2C), 123.6 (2C), 125.1, 128.8 (2C), 130.5 (2C), 136.1, 142.5, 147.7, 157.9 164.2, 166.6, 167.6, 171.7; IR (KBr) cm^{-1} 3103, 3078, 3073, 2955, 2930, 1771, 1744, 1591; MS (CI-Ammonia) (m/e) : 636 $(m + NH_4)^+$, 619 $(M+H)^+$; Anal. Calcd. for $C_{29}H_{35}FN_2O_8SSi$: C, 56.29; H, 5.70; N, 4.53. Found: C, 56.19; H, 5.72; N, 4.46.

Isomerization of the Δ^2-exo carbapenem, 13 to the Δ^2-endo isomer, 14. To a CH_2Cl_2 (2 ml) solution containing the Δ^2-exo isomer **13** (190 mg - 0.31 mmol) was added diisopropylethyl amine (1 ml). The resulting solution was heated at 35°C under an argon atmosphere for 5h. Evaporation of all volatiles left a solid residue whose proton NMR indicated a complete and clean transformation to the Δ^2-endo isomer **14**: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, CH_3), 0.09 (s, CH_3), 0.88 (s, 9H, $3CH_3$), 1.22 (d, 3H, CH_3), 3.08-3.35 (m, 3H allylic CH_2 and H_6), 4.28 (m, H_5), 4.52 (dd, 2H, CH_2SO_2), 5.15 (dd, 2H, CH_2O_2C), 7.18 (t, 2H, aromatic), 7.58 (d, 2H aromatic), 7.85 (dd, 2H, aromatic), 8.2 (d, 2H, aromatic).

(5R,6S)-3-[[4-Fluorophenyl)-sulfonyl]methyl]-6-[(1R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,(4-nitrophenyl)methyl ester, 19, *via* the Δ^2-exo isomer, 18. The Δ^2-exo isomer **13** (250 mg - 0.36 mmol) was dissolved in 2 ml CH_3CN. To this was added a CH_3CN solution (25 ml) containing 3.5 % HF (v/v). The starting material was consumed after 3h by tlc analysis (EtOAc). Solid $NaHCO_3$ (250 mg) was added and the resulting mixture was stirred 0.5h, followed by the removal of the solvent. The residue was triturated with EtOAc and the combined triturates were washed twice with water then brine and finally dried (Na_2SO_4). A small amount of the intermediate product **18** was purified via flash chromatography on a pad (2 cm) of silica gel: ^1H NMR ($CDCl_3$) δ - 0.09 (d, CH_3), 2.7 - 3.1 (m, 3H, allylic CH_2 and H_6), 3.8 (m, H_5), 5.28 (s, H_3), 5.4 (dd, 2H, aromatic), 7.7 (d, 2H, aromatic), 7.85 (dd, 2H, aromatic), 8.2 (d, 2H, aromatic).

The balance of the crude reaction product containing **18** was then dissolved in CH_2Cl_2 (5 ml) followed by the addition of diisopropylethylamine (5 ml). The reaction was stirred 4h at 20°. On workup, the solvent was removed in vacuo. The residue was then dissolved in EtOAc and washed with aqueous KH_2PO_4 (0.5 M) and then brine followed by $MgSO_4$ drying. Purification via flash chromatography (75% EtOAc-25% hexane) gave 138 mg (76% - 2 steps) product **19** : ^1H NMR ($CDCl_3$) δ 1.35 (d, 3H, CH_3), 3.15 (dd, 1H, H_1), 3.3 (dd, 1H, H_6), 3.35 (dd, H_1), 4.3 (m, 2H, H_5 and CHO), 4.52 (dd, 2H, CH_2SO_2), 5.15 (dd, 2H, CH_2O_2C), 7.15 (t, 2H, aromatic), 7.55 (d, 2H, aromatic), 7.85 (dd, 2H, aromatic), 8.23 (d, 2H, aromatic); IR (KBr) cm^{-1} 3534, 3507 (broad), 3106, 3073, 2971, 2934, 1782, 1717, 1590; MS (CI-Ammonia) no molecular ion observed.

Compound **19** was unstable at room temperature. Its half life was approximately 2-3 days at 20°. It could be stored indefinitely in a -20°C freezer.

Synthesis of compound 19 via the Δ^2-endo intermediate 14. The Δ^2-endo carbapenem **14** (190 mg - 0.31 mmol) was dissolved in THF (2 ml). To this was added acetic acid (186 mg - 3.1 mmol) and then n-Bu_4NF (1.55 mmol as a 1M THF solution). The resulting reaction was stirred 22 h at 20° followed by an aqueous workup (EtOAc). Purification of the product via flash silica gel column chromatography (50-75% EtOAc/hexane) resulted in the isolation of 57 mg hydroxyethyl carbapenem **19** (36%). The ^1H NMR of the title compound matched that from the previous experiment.

(5R,6S)-3-[[Fluorophenylsulfonyl]methyl]-6-[(1R)-1-hydroxyethyl]-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt, 20. The Δ^2-endo carbapenem **19** (1.0g - 1.98 mmol) was dissolved in dioxane (25 ml). To this was added an aqueous (11 ml) solution of $NaHCO_3$ (166.5mg - 1.98 mmol) and 10% palladium on charcoal (70 mg). This mixture was hydrogenolysed under H_2 (7 psi - Parr apparatus) for 1 h. The reaction mixture was filtered through a pad of diatomaceous earth and then extracted with EtOAc (30 ml, 3x). The aqueous portion was concentrated and the product was purified via preparative plate reversed phase chromatography (Analtech RPS-F, 500 μ , water/ethanol eluent 19:1). After aqueous extraction of the product from the plate 695 mg of product **20** (89%) was obtained as a sodium salt following lyophilization. The sodium salt **20** was contaminated with sodium 4-fluorophenyl sulfinate[27] (approx. 10-20% by NMR integration) : ^1H NMR (D_2O) d 1.22 (d, 3H, CH_3), 3.0 (m, 2H, allylic H_1), 3.35 (m, H_6), 4.1 (p, CHO), 4.5 (d, 1H, $CHSO_2$, the other H of the CH_2SO_2 absorbance was buried under the water peak at 4.8 ppm), 7.3 (t, 2H), 7.85 (dd, 2H); IR (KBr) cm^{-1} 3425 (broad), 3106, 2977, 1758, 1591; MS(FAB) m/e : 414(M + Na), 392 (M + H); MS(FAB) exact mass: Calcd. for: 414.0400. Found: 414.0400 ($M+Na^+$). IR (KBr) cm^{-1} 3420 (broad) 3080, 3060, 3020, 2955, 2850, 2600 (broad), 1740, 1667, 1600 . UV λ_{max} (H_2O) nm (ε) 218 (5960), 252(1640), 273(1880).

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