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AN EFFICIENT ENANTIOSELECTIVE SYNTHESIS OF THE CARBAPENAM-2-ONE SYSTEM. AN APPROACH TO (+)-THIENAMYCIN AND RELATED CARBAPENEMS#

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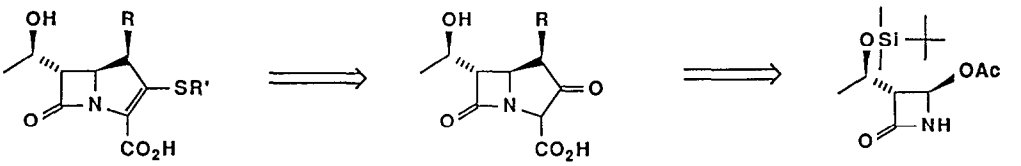
SUMMARY: Cycloaddition of the enantiomeric 4-acetoxy-2-azetidinone (**5**) with the 2-siloxy-1,3-butadiene (**8**) gives the carbacephem **9** which is cleaved **via** ozone and cyclized to the carbapenem system (+)-**13** in 30% overall yield.

The extensive activity directed toward the carbapenem systems (**1, 2**) due to their highly important antibiotic properties,[2] has resulted in a large number of synthetic achievements.[3] In fact, the β-methyl derivative **2** is currently considered the flagship of the new generation of potent and stable carbapenems.[4]

Many of the synthetic approaches to **1** and **2** are based on the highly versatile penultimate precursors **3** and **4** which in turn usually arise **via** a number of synthetic steps from the readily available azetidinone, **5**.[5]

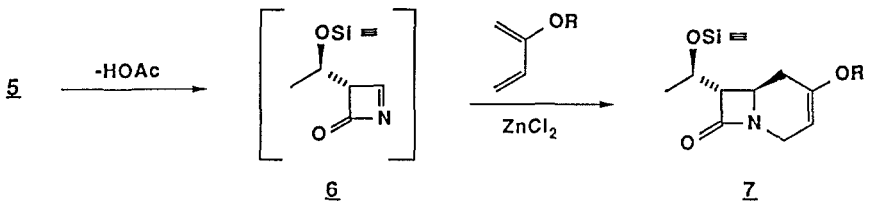


1, R = H, R' = $CH_2CH_2NH_2$ **3**, R = H **5**

2, R = Me, R' = $CH_2C(=NH)NMe_2$ **4**, R = Me

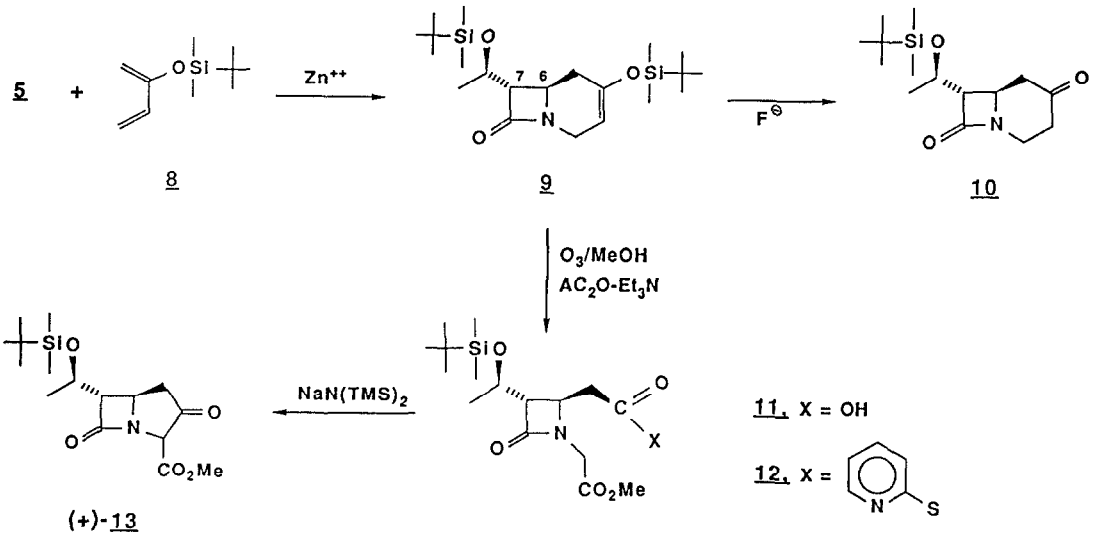
Recently, a report by one of us (YU)[6] described the first cycloaddition of dienes to **5**, presumably **via** the often postulated azetinone **6**, to furnish cycloadducts **7**, albeit in poor yields

#Dedicated to Professor Tetsuji Kametani on the occasion of his 70th birthday.



(16-20%). The process was stimulated by the earlier work of Danishefsky[7] and Weinreb[8,9] who successfully implemented hetero-Diels-Alder reactions with imines and Lewis acid catalysts.

We now wish to describe our efforts in enhancing the cycloaddition of **5** to a 2-siloxydiene **8** and in a rather efficient manner carry this forward to the optically pure title compound (O-silylated methyl ester of **3**). Our four step sequence begins by heating a mixture of azetidinone **5** with 1.5 equiv of the siloxydiene **8**[10] and 0.7 eq of fused $ZnCl_2$ in dry acetonitrile at reflux for 3 h, whereupon an additional 0.5 equiv of diene was introduced and heated for 3 h. Workup (aqueous quench, extraction with CH_2Cl_2, drying K_2CO_3, solvent removal) gave the carbacephem system **9** (54-65% yield), mp 74-75° C after chromatography (sg, 15% EtOAc-hexane); $[\alpha]^{22}_D$ + 56.1° (c 0.86, $CHCl_3$).[11] The **trans**-stereochemistry for H_6-H_7 was assigned by its coupling of 1.5 Hz and the



regiochemistry was confirmed by identity to **10** with that previously reported.[6] Treatment of the crystalline carbacephem **9** with ozone in 80% CH_2Cl_2-MeOH (-78° C) containing a few drops of 0.1% solution of Sudan III dye (Aldrich--Solvent Red 23) and worked up by modifying the procedure of Schreiber,[12] gave the acid-ester **11** (85%, mp 106-107° C; $[\alpha]^{22}_D$ + 6.43°) after chromatography (sg, 2% MeOH-$CHCl_3$).[13]

In order for the acid-ester **11** to be set to undergo a Dieckmann cyclization, a number of diesters were prepared, but all failed to cyclize. Similarly, mixed anhydrides were also disappointing in this respect. The thiopyridine ester[14] **12** was therefore prepared in analogy to earlier work[15] with phenyl thioesters) using triphenylphosphine-2,2'-dipyridyldisulfide, CH_2Cl_2, 25°. The thioester **12** was isolated (94%, oil; $[\alpha]^{22}_D$ + 31.37°, c 0.5, $CHCl_3$) after flash chromatography (Amicon 20-45 μ silica gel, 45% EtOAc-hexane). The Dieckmann cyclization was carried out with 1.1 equiv of sodium bis(trimethylsilyl)amide in THF at -30° and afforded the carbapenem-2-one, **13** after flash chromatography (Merck 40 μ silica gel, 25% EtOAc hexane); 60-65% yield, colorless oil; $[\alpha]^{22}_D$ + 121.3° (c, 0.72, $CHCl_3$).[16]

Thus, the four step sequence from the azetidinone **5** to the carbapenem-2-one bicyclic system (+)-**13** was accomplished in 30+% overall yield. Studies are continuing to apply this route to the β-methyl analog **4** and other derivatives which would be applicable to this cycloaddition process.

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9. For an excellent review of heterodienophiles in Diel-Alder reactions see Weinreb, S. M.; Staib, R. R. ***Tetrahedron 1982,*** **38**, 3087.

10. Prepared in 75-81% yield following the literature procedure; Vedejs, E. et. al, ***J. Org. Chem. 1986,*** **51,** 1556.

11. **Analytical data 9**: IR (CCl_4): 1762, 1665. ^{1}H-NMR ($CDCl_3$): δ 0.07 (s, 6 H), 0.13 (s, 3 H), 0.15 (s, 3 H), 0.86 (s, 9 H), 0.92 (s, 9 H), 1.23 (d, J = 6.1 Hz, 3 H), 2.24 (ddd t, J = 17.0, 8.0, 2.5, 2.2 Hz, 1 H), 2.22 (m, 1 H), 2.74 (dd, J = 5.3, 1.2 Hz, 1H), 3.49 (dd t, J = 17.0, 2.5, 2.2 Hz, 1 H), 3.58 (ddd, J = 1.5, 8.0, 6.0 Hz, 1 H), 4.13 (ddd, J = 17.0, 2.5, 2.2 Hz, 1 H), 4.18 (m, 1 H), 4.85 (ddd, J = 2.5, 2.5, 2.5, Hz, 1 H). ^{13}C-NMR, -5.0, -4.6, -4.4, -4.3, 22.7, 25.5, 25.6, 33.9, 37.3, 47.1, 65.8, 66.9, 99.3, 147.8, 166.7. Calcd for $C_{21}H_{41}NO_3Si$. Found: C 60.42; H, 10.12; N, 3.22.

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13. This material cannot be recrystallized due to scrambling of the ester; it was flash chromatographed using W. R. Grace 951 silica gel. **Physical data**: ^{1}H-NMR ($CDCl_3$): δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.86 (s, 9 H), 1.23 (d, J = 6.2 Hz, 3 H), 2.18-2.92 (m, 3 H), 3.71 (s, 3H), 3.94, 4.15 (ABq, J = 18.0 Hz, 2 H), 4.21 (m, 2 H). IR (KBr) 3400-3500, 1772, 1723, 1702 cm^{-1}. Calcd. for $C_{16}H_{29}NO_6Si$. Found: C 53.12; H, 8.08; N, 3.71.

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16. **Physical data (+)-13**: IR (CCl_4) 1770, 1745. ^{1}H-NMR ($CDCl_3$): δ 0.090 (s, 3 H), 0.092 (s, 3 H), 0.89 (s, 9 H), 1.27 (d, J = 6.3 Hz, 3 H), 2.42 (dd, J = 7.8, 18.9 Hz, 1 H), 2.87 (dd, J = 6.7, 18.9 Hz, 1 H), 3.12 (dd, J = 2.0, 5.1 Hz, 1 H), 3.77 (s, 3 H), 4.14 (m, 1 H), 4.31 (m, 1 H), 4.66 (s, 1 H). Calcd. for $C_{16}H_{27}NO_5Si$. Found: C, 56.27; H, 7.97; N, 4.10.

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