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THE RING CLOSURE OF SUBSTITUTED AZETIDINONES: A NEW ROUTE TO [4.2.0] FUSED BETA-LACTAMS

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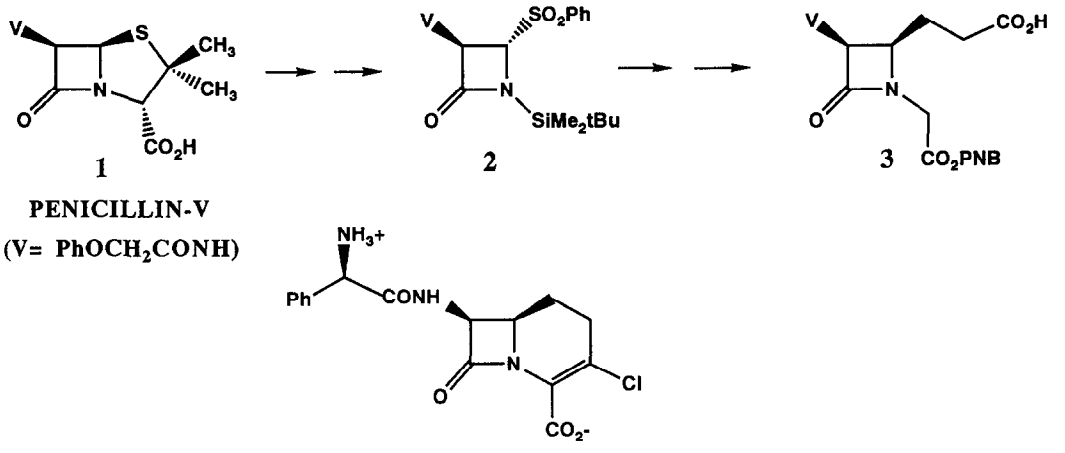
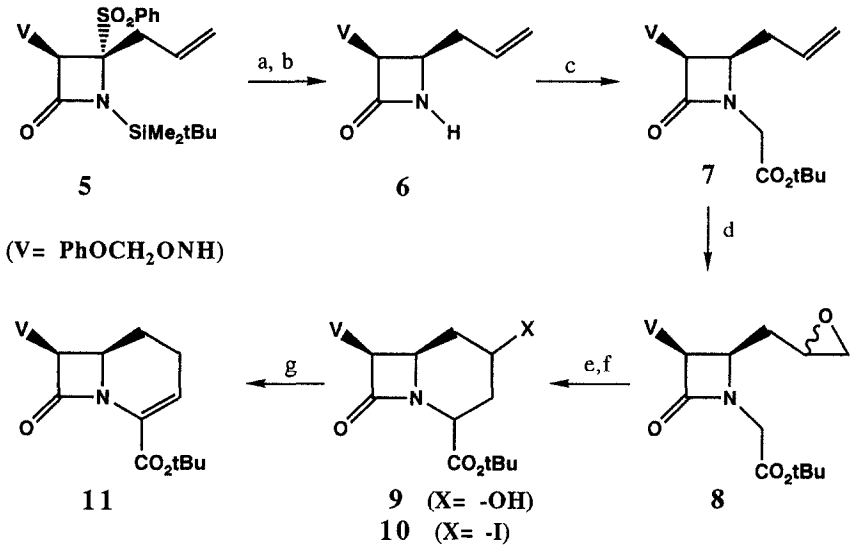
ABSTRACT: The synthesis of 1-carba-1-dethiacephalosporin nuclei is described. The new route utilizes a readily-available penicillin derivative as starting material and features an intramolecular ring closure to form the six-membered ring.

The importance of the 1-carba-1-dethiacephalosporins to the management of infectious diseases is highlighted by the recent introduction of Lorabid™ (loracarbef, **4**).[1] Of the many challenges encountered in developing such a compound for the marketplace, the chemical synthesis proved to be significant.[2] We recently described an alternate route to the synthesis of **4** which commenced with the stereoselective manipulation of penicillin.[3] This development allows for ready access to the azetidinone **3** which serves as a pivotal intermediate in the production synthesis of loracarbef.



Current work in these laboratories has been directed toward the development of an alternate synthesis of the 1-carba-1-dethiacephalosporin framework that may prove to be more expeditious.[4] To this end, we chose to examine the ring closure of various substituted azetidinones readily available in chiral form from penicillin

utilizing chemistry previously discussed.[3] One such available azetidinone is the allyl derivative **5**, obtained in 52% yield from phenyl sulfone **2**. Removal of the silyl group followed by stereoselective reductive desulfonation provided **6**. Alkylation of the azitidinone nitrogen (81%) followed by epoxidation of the terminal olefin with mCPBA (86%) provided the fully functionalized beta-lactam **8** as a 1:1 mixture of diastereomers. Although the isomers could be separated via HPLC, in practice the mixture was treated directly with two equivalents of lithium bis-(trimethylsilyl)amide in THF to provide the ring closed alcohol **9**. Although the stereochemistry of the appendages on the six membered ring has not been rigorously determined, it appeared that only a single isomer was isolated (NMR). Dehydration of the alcohol **9** via the iodide **10**[5] and isomerization of the double bond to the thermodynamically more stable Δ-3 isomer provided the 3-H-1-carba-1-dethiacephem **11** as the major product (2:1 Δ-3:Δ-2 by NMR). A 3-H derivative similar to this compound (phthalimido instead of V at C-7) was converted to loracarbef by the Kyowa Hakko group.[6] Although the yields of the final three steps are not high, they represent unoptimized conditions which should be readily improved upon.[7]



(a) 1N HCl; THF; rt (71%) (b) $Li(tBuO)_3AlH$; THF; 0°C (51%)
(c) $BrCH_2CO_2tBu$; Triton-B; DMF; 0°C (90%) (d) mCPBA; PhH; reflux (86%)
(e) $LiN(SiMe_3)_2$; THF; 0°C (20%); (f) PPh_3; I_2; pyridine; toluene; 80°C (26%)
(g) DBU; CH_2Cl_2 (60%)

The new methodology presented herein not only provides an alternate route to the synthesis of loracarbef, it also provides functionalized [4.2.0] beta-lactam systems which can be useful in the preparation of new antibacterial agents. We hope to report further developments of this chemistry in the near future.

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7. Data for compounds **5**-**11** are as follows (melting points are uncorrected):

   5: mp 94-96.5°C; IR ($CHCl_3$, cm^{-1}) 2970, 2940, 1770, 1698, 1519, 1495, 1310, 1155; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J=6 Hz, 2H), 7.78-7.58 (m, 3H), 7.26-6.94 (m, 3H), 7.10 (d, J=12 Hz, 1H), 6.64 (d, J=9 Hz, 2H), 6.26 (d, J=12 Hz, 1H), 5.80-5.64 (m, 1H), 5.31-5.24 (m, 1H), 4.95-4.86 (m, 1H), 4.36 (ABq, J=15 Hz, 2H), 3.22-3.10 (m, 1H), 2.14-2.06 (m, 1H), 1.11 (s, 9H), 0.48 (s, 3H), 0.44 (s, 3H); MS (FD) *m/z* 515 (M+1); UV (EtOH) 274nm (ε=1650), 267nm (ε=1930), 217nm (ε=15100); $[\alpha]^{25}_{365}$ +90.04° (c=1.144, MeOH).Anal. Calcd for $C_{26}H_{34}N_2O_5SSi$: C, 60.67; H, 6.66; N, 5.44. Found: C, 60.96; H, 6.84; N, 5.45.

   6: mp 142-144°C; IR ($CHCl_3$, cm^{-1}) 3023, 1773, 1688, 1600, 1524, 1496, 1237; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-6.89 (m, 6H), 6.10 (s, 1H), 5.79-5.64 (m, 1H), 5.41-5.33 (m, 1H), 5.17-5.04 (m, 2H), 4.54 (s, 2H), 4.00-3.92 (m, 1H), 2.39-2.28 (m, 1H), 2.18-2.04 (m, 1H); MS (FD) *m/z* 260 (M+); UV (EtOH) 275nm (ε=1180), 269nm (ε=1430); $[\alpha]^{25}_{365}$ +263.97° (c=1.038, DMSO). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.83; H, 6.16; N, 11.00.

7: (oil) IR (film, cm^{-1}) 2979, 1763, 1741, 1685, 1533, 1496, 1369, 1231, 1156; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-6.89 (m, 5H), 7.21 (d, J=9 Hz, 1H), 5.80-5.65 (m, 1H), 5.41 (dd, J=9 and 9 Hz, 1H), 5.13-5.06 (m, 2H), 4.50 (s, 2H), 4.16-4.10 (m, 1H), 3.90 (ABq, J=18 Hz, 2H), 2.30-2.26 (m, 2H), 1.45 (s, 9H); MS (FAB) m/e 375 (M+1); HRMS (FAB) *m/z* (M+1) calcd 375.1919, obs 375.1909; UV (EtOH) 276nm (ε=1123), 269nm (ε=1357), 202nm (ε=15012); $[\alpha]^{25}_{365}$ +63.00° (c=1.00, DMSO).

8: (oil) IR ($CHCl_3$, cm^{-1}) 3419, 2984, 1765, 1738, 1690, 1236, 1225; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.50 (m, 1H), 7.38-6.90 (m, 5H), 5.46-5.38 (m, 1H), 4.54 (s, 2H), 4.36-3.76 (m, 3H), 2.95-2.86 (m, 1H), 2.80-2.71 (m, 1H), 2.55-2.39 (m, 1H), 2.18-1.70 (m, 2H), 1.47 (s, 9H); MS (EI) *m/z* 391 (M+1); HRMS (FAB) m/e (M+1) calcd 391.1869, obs 391.1879; UV (EtOH) 275nm (ε=1050), 268nm (ε=1260); $[\alpha]^{25}_{365}$ +65.30° (c=0.536, DMSO).

9: mp 175-177°C; IR (KBr, cm^{-1}) 3372, 3238, 2984, 1757, 1721, 1676, 1523, 1400, 1270, 1246, 1159; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J=7.1 Hz, 1H), 7.32-6.88 (m, 5H), 5.24 (dd, J=6.7 and 6.1 Hz, 1H), 4.50 (s, 2H), 3.92-3.82 (m, 1H), 3.79-3.69 (m, 2H), 2.10-1.99 (m, 3H), 1.82-1.72 (m, 1H), 1.49 (s, 9H), 1.23-1.15 (m, 1H); MS (FD) *m/z* 390 (M+), 333 [(M+) -57]; UV (EtOH) 275nm (ε=1180), 269nm (ε=1420); $[\alpha]^{25}_{365}$ +325.49° (c=0.510, DMSO). Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.33; H, 6.74; N, 6.95.

10: mp >82°C (d); IR ($CHCl_3$, cm^{-1}) 1766, 1734, 1689, 1496, 1258, 1154; ^1H NMR (300 MHZ, $CDCl_3$) δ 7.75 (d, J=6 Hz, 1H), 7.32-7.24 (m, 2H), 7.03-6.98 (m, 1H), 6.87 (d, J=9 Hz, 2H), 5.28-5.24 (m, 1H), 4.72-4.70 (m, 1H), 4.47 (s, 2H), 4.07-4.00 (m, 2H), 2.13-1.95 (m, 4H), 1.51 (s, 9H); MS (FAB) *m/z* 501 (M+1); UV (EtOH) 275nm (ε=1360), 268nm (ε=1760); $[a]^{25}_{365}$ +176.2° (c=0.545, DMSO).

11: ^1H NMR (300MHZ, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.08-6.99 (m, 2H), 6.89 (d, J=7.7 Hz, 2H), 6.33-6.27 (m, 1H), 5.43-5.38 (m, 1H), 4.53 (s, 2H), 3.90-3.82 (m, 1H), 2.46-2.20 (m, 2H), 1.99-1.88 (m, 1H), 1.51 (s, 9H),1.42-1.25 (m, 1H).