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An Efficient and Stereoselective Synthesis of the 1β-Methylcarbapenem Key Precursor

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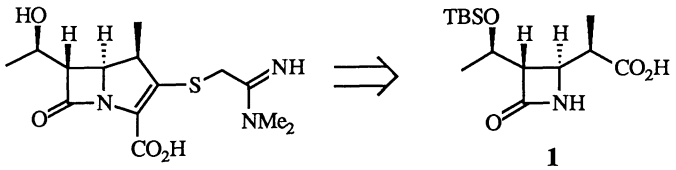
The key precursor for the preparation of 1β-methylcarbapenem antibiotic was stereoselectively synthesized from (+)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone by employing an intermolecular carbenoid displacement reaction as a key step.

Since a synthesis of the potent broad spectrum antibiotic 1β-methylcarbapenem, exhibiting remarkable dehydropeptidase-I stability and enhanced chemical stability, has been reported by Merck group,[1] considerable effort has been devoted towards the synthesis of its key precursor, (3S,4S)-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (**1**), and a number of chiral stereoselective synthesis of **1** have been appeared to date.[2]

As a part of our continuing studies directed towards the synthesis of carbapenem antibiotics, we also became interested in developing a method for the stereoselective synthesis of 1β-methylcarbapenems, and here report an efficient preparation of **1**.



1

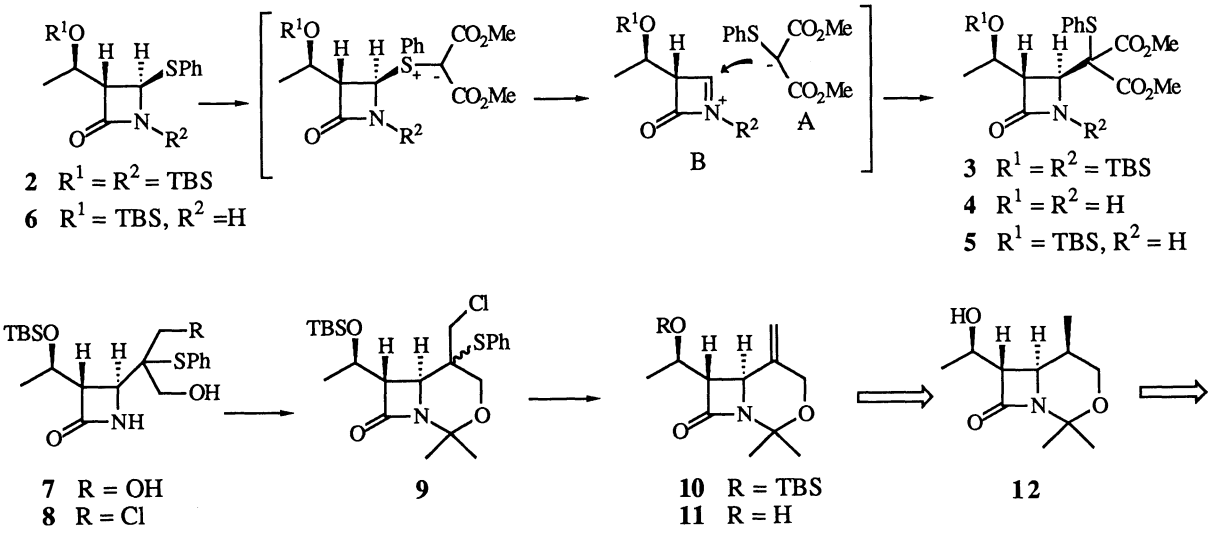
TBS = *t*-butyldimethylsilyl

Our synthesis involved the stereoselective carbon-carbon bond formation at the 4-position of an azetidin-2-one using a carbenoid displacement reaction of 3-hydroxyethyl-4-phenylthio-2-azetidinone derivatives with dimethyl α-diazomalonate in the presence of rhodium acetate as a key step.[3]

Thus, the sulfide **2** easily derived from (+)-4-acetoxy-3-[(R)-1-t-butyldimethylsilyloxy)ethyl]-2-azetidinone[4] was treated with dimethyl α-diazomalonate in benzene-dichloromethane (1:1, v/v) under reflux in the presence of a catalytic amount of rhodium acetate to give the carbon-introduced product **3** as the sole product in 82% yield, where the stereochemistry at the

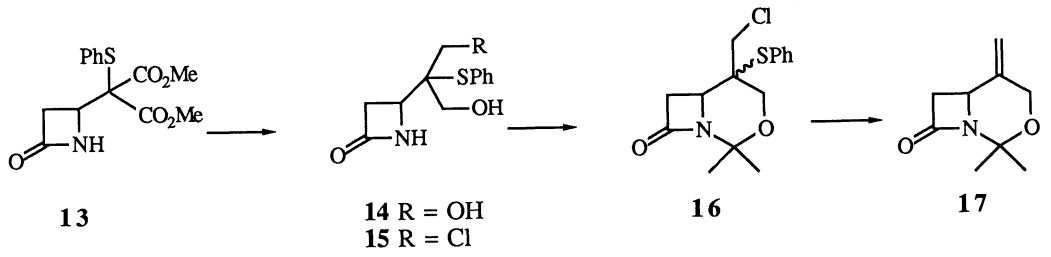
4-position was controlled in the Michael addition of nucleophile (A) to the intermediate (B) affording the 3,4-trans-2-azetidinone. Deprotection of the silyl groups of **3** by treatment with hydrochloric acid in methanol furnished **4**, which on silylation with t-butyldimethylsilyl chloride in N,N-dimethylformamide in the presence of imidazole provided the diester **5** [5] in nearly quantitative overall yield from 3. The compound 5 could more directly be prepared from mono-silylated sulfide **6** by the application of the above carbenoid displacement reaction in 46% yield in one-step.

The desired starting material bearing all the carbon-framework in hands, we focused our attention to introduce the 1β-methyl function. Diisobutylaluminum hydride reduction of the diester **5** in tetrahydrofuran at -78 °C afforded the diol **7**,[6] in 54% yield, which on exposure with 1 equiv. of methanesulfonyl chloride in pyridine gave the mono-chloride **8** in 76% yield. After conversion of **8** into the acetonide **9** [7] by treatment with 2,2-dimethoxypropane in dichloromethane in the presence of boron trifluoride etherate as a catalyst, the introduction of exo-methylene function was attempted by employing a radical elimination process.[8] Heating of the chloride **9** with tri-n-butyltin hydride in the presence of AIBN in benzene provided the expected olefin **10** exhibiting the spectroscopic data identical with those reported,[9] in 78% yield, whose desilylation with tetra-n-butylammonium fluoride gave the alcohol **11**.



Since the stereoselective reduction of **11** to **12** and its further conversion into **1** has already been achieved by Merck group,[9] this synthesis constitutes its formal synthesis.

Similarly, the diester **13** obtained from the reaction of 4-phenylthio-2-azetidinone with dimethyl α-diazomalonate was also converted into the corresponding exo-methylene derivative **17** [10] via the diol **14**,[11] and the chlorides **15** [12] and **16** under the same reaction conditions as described for the preparation of the hydroxyethyl derivative **10**.



13 **14** R = OH, **15** R = Cl **16** **17**

In summary, we could disclose five-steps synthesis of **12**, a key precursor for the synthesis of 1β-methylcarbapenems, from **6**.

References

1) D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, Heterocycles, 21, 29 (1984).

2) Y. Ito and S. Terashima, Yuki Gosei Kagaku Kyokai Shi, 47, 606 (1989) and references cited therein.

3) T. Kametani, N. Kanaya, T. Mochizuki, and T. Honda, Heterocycles, 19, 1023 (1982); T. Honda, Yakugaku Zasshi, 109, 345 (1989) and references cited therein.

4) T. Kametani, S.-D. Chu, and T. Honda, J. Chem. Soc., Perkin Trans.1, 1988, 1593;This compound is also commercially available from Kanegafichi Kagaku Kogyo Co. Ltd.

5) Compound **5**; ^{1}H NMR($CDCl_3$, 270 MHz):δ 0.07(s, 3H, Me), 0.08(s, 3H, Me), 0.88 (s, 9H, ^{t}Bu), 1.13(d, J=6.1 Hz, 3H, Me), 3.24(br s, 1H, 3-H), 3.62(s, 3H, Me), 3.66(s, 3H, Me), 4.24(dq, J=1.8 and 6.1 Hz,1H,CHOSi), 4.36(d, J=1.8 Hz, 4-H), 5.77(br s, 1H, NH), 7.20-7.50(m, 5H, SPh); IR($CHCl_3$):3400,1740,1720 cm^{-1}; HRMS: m/z Found: 410.1097. Calcd for $C_{18}H_{24}NO_6SiS(M^+-{}^t Bu)$: 410.1092.

6) Compound **7**; ^{1}H NMR($CDCl_3$, 270 MHz):δ 0.07(s,3H,Me), 0.08(s, 3H, Me), 0.86(s, 9H, ^{t}Bu), 1.28(d,J=6.1 Hz, 3H, Me), 3.30(br s, 2H, OH), 3.47(dd, J=1.8 and 5.8 Hz, 3-H), 3.54(d, J=11.6 Hz, 1H, CHHO), 3.63(d, J=11.6 Hz, 1H, CHHO), 3.70 (d, J=11.6 Hz, 1H, CHHO), 3.83(d, J=11.6 Hz, 1H, CHHO), 4.08(dq, J=5.8 and 6.1 Hz, 1H, MeCHO), 7.40-7.70(m, 5H, SPh);HRMS: m/z Found: 354.1189.

Calcd for $C_{16}H_{24}NO_4SiS(M^+-{}^tBu)$: 354.1194.

7) Compound 9; ^1H NMR($CDCl_3$, 270 MHz):δ 0.06(s, 3H, Me), 0.12(s, 3H, Me), 0.89 (s, 9H, ^tBu), 1.35(d, J=6.1 Hz, 3H, Me), 1.23(s, 3H, Me), 1.68(s, 3H, Me), 3.53(dd, J=2.4 and 2.5 Hz, 1H, 7-H), 3.57(d, J=12.2 Hz, 1H, CHH), 3.73(d, J=12.2 Hz,1H, CHH), 3.76(d, J=12.2 Hz, 1H, CHH), 3.82(d, J=12.2 Hz, 1H, CHH), 4.08(d, J=2.5 Hz, 1H, 6-H), 4.28(dq, J=2.5 and 6.1 Hz, 1H, MeCHO), 7.26-7.68 (m, 5H, SPh); IR($CHCl_3$): 1730 cm^{-1}; HRMS: m/z Found: 454.1639. Calcd for $C_{22}H_{33}NO_3SiSCl(M^+-{}^tBu)$: 454.1639.

8) A. G. M. Barrett, D. H. R. Barton, R. Bielski, and S. W. McCombie, J. Chem. Soc., Chem. Commun., 1977, 866; B. Lythgoe and I. Waterhouse, Tetrahedron Lett., 1977, 4223; T. Kametani, S.-D. Chu, A. Itoh, T.-C. Wang, A. Nakayama, and T. Honda, J. Chem. Soc.,Chem. Commun., 1988, 544.

9) L. M. Fuentes, I. Shinkai, A. King, R. Purick, R. A. Reamer, S. M. Schmitt, L. Cama, and B. G. Christensen, J. Org. Chem., 52, 2563(1987).

10) Compound 17; ^1H NMR($CDCl_3$, 270 MHz):δ 1.45(s, 3H, Me), 1.73(s, 3H, Me), 2.78(dd, J=4.9 and 15.3 Hz, 1H, 7-H), 2.87(dd, J=2.4 and 15.3 Hz, 1H, 7-H), 3.53-3.83(m, 2H, 2-H_2), 4.05(dd, J=2.4 and 4.9 Hz, 1H, 6-H), 4.98(br s, 1H, olefinic proton), 5.12(br s, 1H, olefinic proton); IR($CHCl_3$): 1740 cm^{-1}; HRMS: m/z Found: 152.0708. Calcd for $C_8H_{10}NO_2(M^+-Me)$: 152.0709.

11) Compound 14; mp 130-134 °C: ^1H NMR(CD_3OD, 400 MHz): δ 2.89(dd, J=5.1 and 14.9 Hz, 1H, 3-H), 3.26(dd, J=2.4 and 14.9 Hz, 1H, 3-H), 3.31(m, 2H, OH), 3.57 (d, J=11.5 Hz, 1H, CHH), 3.63(d, J=11.5 Hz, 1H, CHH), 3.66(d, J=11.5 Hz, 1H, CHH), 3.73(d, J=11.5 Hz, 1H, CHH), 3.90(dd, J=2.4 and 5.1 Hz, 1H, 4-H), 7.32-7.64(5H, m, SPh); HRMS: m/z Found: 253.0767. Calcd for $C_{12}H_{15}NO_3S(M^+)$: 253.0772.

12) Compound 15; ^1H NMR($CDCl_3$, 270 MHz):δ 3.08(ddd, J=3.1, 4.9 and 15.3 Hz, 1H, 3-H), 3.30(dd, J=2.4 and 15.3 Hz, 1H, 3-H), 3.74(d, J=11.6 Hz, 1H, CHH), 3.89 (d, J=12.2 Hz, 1H, CHH), 3.75-3.85(m, 2H, CH_2), 4.01(dd, J=2.4 and 4.9 Hz, 1H, 4-H), 6.05(br s, 1H, NH), 7.36-7.62(m, 5H, SPh).

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