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AN EFFICIENT SYNTHESIS OF A KEY INTERMEDIATE FOR OPTICALLY ACTIVE 5,6-CIS-CARBAPENEM ANTIBIOTICS

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Summary: A versatile intermediate (**18**) for optically active 5,6-cis-carbapenem antibiotics was synthesized with a highly regioselective intramolecular aldol condensation as a key step.

Since the discovery of 5,6-cis-carbapenems, represented by C-19393 H_2[1] (carpetimycin A[2]), they have attracted much attention as synthetic targets because of their potent and broad antibacterial activity. Several synthetic methods of constructing 5,6-cis-carbapenems have been reported.[3]

In the preceding papers,[4] we described a stereoselective synthesis of racemic 5,6-cis-carbapenems *via* reductive desulfurization utilizing an organotin hydride. Since then our efforts have been concentrated on preparing a chiral 5,6-cis-carbapenem with a functional group, in addition to a hydroxy group, in the C-6 side chain to obtain new carbapenem antibiotics with improved biological activity. Here we report a novel stereocontrolled synthesis of **18** which may serve as a potential intermediate for this purpose.

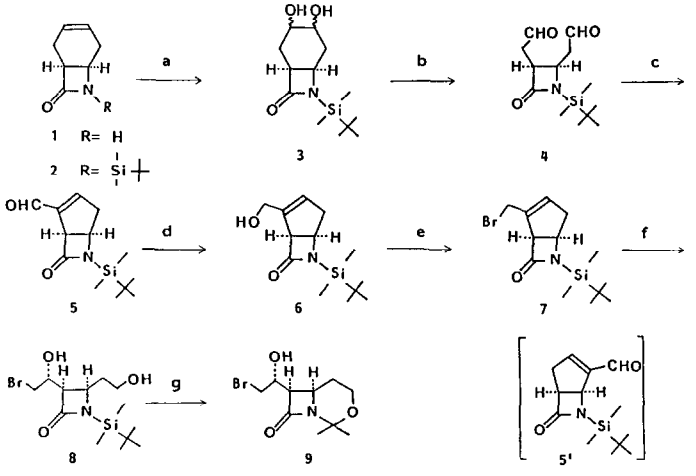
The starting material selected for our initial investigation (shown in Scheme I) was easily available 8-oxo-7-azabicyclo[4.2.0]oct-2-ene (**1**).[5] **1** was treated with tert-butyldimethylsilyl chloride-Et_3N and then with N-methylmorpholine N-oxide and osmium tetroxide[6] to afford cis-diol **3** in 63 % yield. Treatment of **3** with $HIO_4 \cdot 2H_2O$ gave dialdehyde **4**. Reaction conditions were examined to convert **4** into **5** selectively. First, the rather unstable dialdehyde **4** was treated with morpholine-camphoric acid[7] to give *ca.* 1:1 mixture of **5** and **5'**. Then, by employing piperidine-acetic acid,[8] **5** was obtained highly regioselectively but in a low yield (after reduction with $NaBH_4$, **6**[9] was isolated in 16 % yield). But when the dialdehyde **4** was treated with dibenzylammonium trifluoroacetate,[10] the intramolecular aldol condensation proceeded highly regioselectively and gave **5** exclusively in a good yield (**5'** was not observed by 90 MHz NMR and by HPLC). We presume that this high selectivity might be due to the bulkiness of the tert-butyldimethylsilyl group and the amine component. Unstable α,β-unsaturated aldehyde **5** was reduced with $NaBH_4$ to **6** without isolation (57 % yield from **3**). **6** was converted into the

bromide **7** with N-bromosuccinimide-dimethyl sulfide[11] in 67 % yield. **7** was subjected to ozonolysis, then, to reduction with $NaBH_4$ to afford diol **8** in 97 % yield (for the stereochemistry vide post). **8** was deprotected with potassium fluoride and then treated with 2,2-dimethoxypropane ($BF_3 \cdot OEt_2$, CH_2Cl_2) to give acetonide **9**[12] in 59 % yield.

This sequence of reactions was applied to the optically active compound (**17**) to obtain **18** with optical activity. **17** was prepared from the racemic compound **10** by successfully combining optical resolution and effective conversion of both enantiomers (**11a**[13] and **11b**[13b]) into the desired optically active compound **13** (Scheme II). Thus, resolution of **10** was effected with cinchonidine to give chiral **11a** [28 %, $[\alpha]_D^{25}$+3.36°(c=1.24, $CHCl_3$)] and its enantiomer **11b** [27 %, $[\alpha]_D^{25}$-3.44°(c=1.685, $CHCl_3$)]. **11a** was converted into **12** by Curtius rearrangement in 79 % yield, then **12** was hydrolyzed to **13**[$[\alpha]_D^{25}$ +36.4°(c=0.45, H_2O)] in 76 % yield. **13** was transformed to the optically active β-lactam **17**[14] [mp 163-164°C, $[\alpha]_D^{25}$-28.6°(c=0.585, $CHCl_3$)] with Ph_3P-$(PyS)_2$/ CH_3CN.[15] On the other hand **11b** was also converted into **13** [$[\alpha]_D^{25}$+36.6°(c=0.56, H_2O)] via esterification (92 %), hydrolysis (93 %), Curtius rearrangement (96 %), and deprotection (73 %). The merit of this method is that both the enantiomers (**11a** and **11b**) resolved from **10** are utilized in preparing the optically active compound **17**.

Application of the same sequence of reactions employed in the preparation of **9** from **1** to the optically active compound **17** gave the desired optically active compound **18** [mp 141-142°C, $[\alpha]_D^{25}$+13.0°(c=0.54, $CHCl_3$)].

Scheme I



a) OsO_4, N-methylmorpholine N-oxide, acetone-H_2O
b) $HIO_4 \cdot 2H_2O$, THF
c) $(PhCH_2)_2\overset{+}{N}H_2 \cdot CF_3COO^-$, benzene
d) $NaBH_4$, MeOH
e) NBS, MeSMe, CH_2Cl_2
f) 1) O_3, MeOH 2) $NaBH_4$, MeOH
g) 1) KF, MeOH 2) 2,2-Dimethoxypropane, $BF_3 \cdot OEt_2$, CH_2Cl_2

The stereochemistry of **18** was confirmed to be 6R, 7R, 9R by a single crystal X-ray analysis[16] (Fig. I). The reduction of ozonide of chiral **7** with $NaBH_4$ was proved to proceed selectively to give 9R stereochemistry. Since the bromo atom in the side chain is susceptible to nucleophiles (including H^-), compound **18** serves as an efficient intermediate for preparing new type of carbapenems (**19**) with a variety of functional groups in the C-6 side chain (Scheme III). The synthesis and biological properties of such 5,6-cis-carbapenems will be reported in due course.

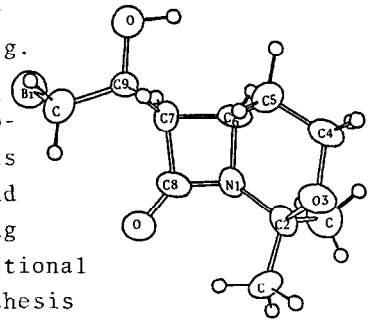
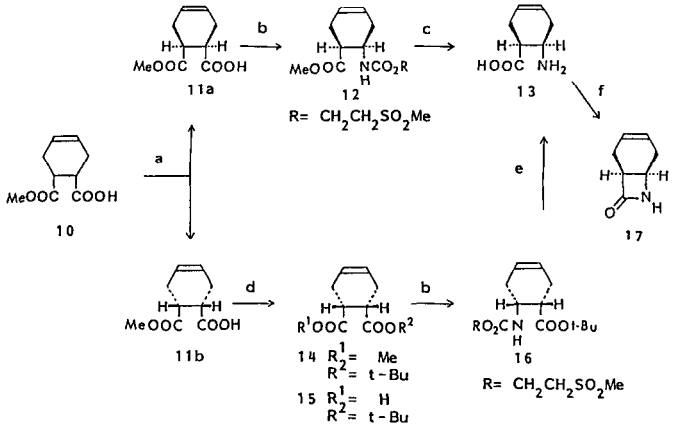


Figure I
ORTEP view of **18**

Scheme II



a) Optical resolution with cinchonidine, Me_2CO

b) 1) ClCOOEt, Et_3N 2) NaN_3, $n\text{-}Bu_4NHSO_4$, CH_2Cl_2 3) 100°C, toluene 4) $MeSO_2CH_2CH_2OH$

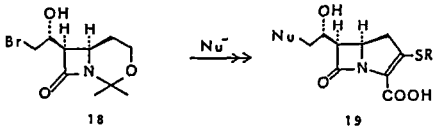
c) aq. NaOH

d) 1) isobutene, H_2SO_4, CH_2Cl_2 2) aq. NaOH

e) 1) aq. NaOH 2) CF_3COOH

f) PySSPy, Ph_3P, CH_3CN

Scheme III



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9) ^{13}C-NMR ($CDCl_3$) δ: -5.17 (s, SiMe), -5.59 (s, SiMe), 26.23 (q, 3xMe), 37.27 (t, C_4), 52.52 (d, C_5), 60.73 (t, $\underline{C}H_2O$), 63.99 (d, C_3), 140.72 (s, C_2), 175.79 (s, C_7).

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12) mp 133-135°C, IR ν_{max}^{KBr} : 1740 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ: 1.40, 1.69 (each 3H, 2xs, 2xMe), 1.7-2.0 (2H, m, C_4-H_2), 2.5 (1H, br, OH), 3.29 (1H, dd, J=11, 6Hz, C_7-H), 3.5-4.3 (6H, m, C_4-H_2, C_6-H, CH-O, CH_2Br).

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