Hydrogenolysis-Isomerization-Reduction of Propargyl Acetate, and Regio- and Stereoselective Hydrogenation of Dienyl Ester for the Synthesis of 1β-Methylcarbapenem Precursor

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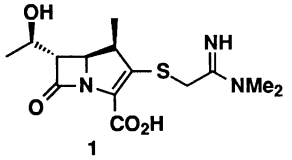
A straightforward synthetic route of 1β-methylcarbapenem precursor is established by hydrogenolysis-isomerization-reduction process of propargyl acetate or by regio- and stereoselective hydrogenation process of dienyl ester with complete stereoselectivity.

Carbapenems have received considerable attention in the β-lactam antibiotics due to high antibacterial activity.[1] Among them thienamycin and imipenem constitute the most representative ones, but they are chemically unstable and metabolized by renal dehydropeptidase I, a hydrogenase from fungus.[1] On the other hand, 1β-methylcarbapenem **1** possesses chemical and metabolic stability. For these reasons, synthetic methods have been investigated since the discovery by Merck group.[1] Control of the stereochemistry of the methyl group at the 1-position is the most important but difficult step.[2] Stereoselective hydrogenation has offered one of the main methods for the control of the stereochemistry of C-1 methyl group.[3] For this purpose, the side chain at the 5-position has been fixed as cyclic intermediate **2** in order to achieve high stereoselectivity, and the aminal fixing the side chain was removed after the reduction. Therefore more straightforward methods have been desired. Hydrogenation of the substrate having acyclic side chain was previously reported, but it utilized a double differentiation method involving a chiral substrate and a chiral ligand.[3d] On the other hand, the use of a substrate possessing a stationary conformation, such as a dienyl ester, would give the desired 1β-methyl derivative with high stereoselectivity in the hydrogenation reaction without conversion to the cyclic intermediate or utilizing a double differentiation method. The hydrogenation reaction might proceed with high stereoselectivity, because the most stable conformation of dienyl ester is expected as **3**[4] by MM-2 calculation, and it can be fixed due to the conjugated system of two olefins and an ester. Moreover, if the hydrogenation of dienyl ester proceeds regioselectively at the terminal olefin, it would give an α,β-unsaturated ester. The conversion of α,β-unsaturated ester to β-keto ester derivative is well known, and the β-keto ester is a useful synthetic intermediate of 1β-methylcarbapenem. We have already reported stereodivergent synthesis of β-lactams by the addition of metal enolate to a chiral imine.[5] In this letter, we wish to report a straightforward synthetic method of 1β-methylcarbapenem intermediate by regio- and stereoselective hydrogenation of dienyl ester.



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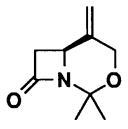

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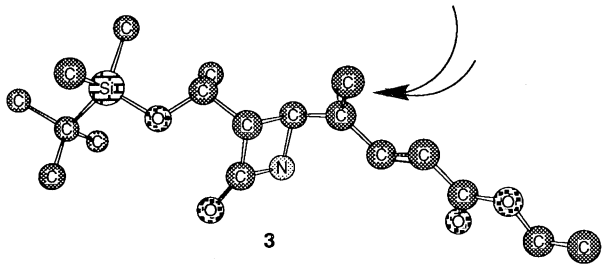

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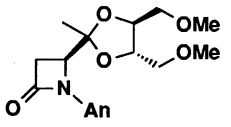
The starting material *R*-**5** was obtained as a single diastereomer from 3-unsabstituted β-lactam **4**.[6] Protection of the hydroxyl group of **5**[7] was carried out in a usual manner with TBDMSCl (3 eq) and imidazole (2 eq) in DMF at ambient temperature.



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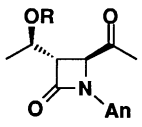
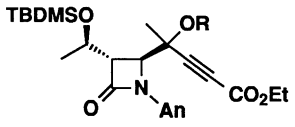


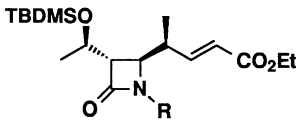
R-**5** R : H
6 R : TBDMS

For introduction of three carbon unit to construct a carbapenem framework, ethyl propiolate was selected for the following transformation to α,β-unsaturated ester **9a**. The addition reaction of ethyl propiolate to the acetyl carbonyl group of **6** proceeded to give alcohol **7** in 99% yield [LDA (2 eq), ethyl propiolate (2 eq) in THF at -78 ~ -40 °C for 1.5 h], which was treated with 2 eq acetic anhydride and 1.5 eq of 4-*N*,*N*-dimethylaminopyridine (DMAP) as a base in CH_2Cl_2 for 13 h to give propargyl acetate **8** in 99% yield. Hydrogenolysis of the acetate **8** with palladium catalyst was carried out with 4 eq of formic acid in the presence of $Pd(OAc)_2$ (5 mol%)-PPh_3 (50 mol%) in 1,4-dioxolane at 90 °C for 10 h to give directly α,β-unsaturated ester **9a** in 87% yield in a single step procedure.[8] Examination of the ^{1}H-NMR (270 MHz) spectrum revealed that the reduction proceeded in a highly stereoselective manner to give β-isomer as a sole product, and other isomers such as the corresponding α-isomer, acetylenic- **10**, and allenic-type derivatives **11** could not be detected. Deprotection of the *p*-methoxyphenyl group of **9a** with 2 eq of cerium(IV) diammonium nitrate (CAN) in acetonitrile-water at -20 °C for 0.5 h gave **9b** in 61% yield.

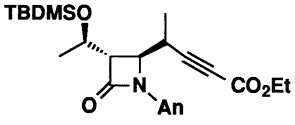
On the other hand, a stepwise method was investigated in order to clarify the reaction pathway of the above hydrogenolysis-isomerization-reduction reaction. The use of 2 eq of formic acid at 90 °C for 22 h gave dienyl ester **12** exclusively in 98% yield, whereas the reaction at lower temperature gave the mixture of dienyl ester **12** and allenyl ester **11**. Deprotection of *p*-methoxyphenyl group of **12** with 5 eq of CAN in acetonitrile-water at -20 ~ -10 °C for 0.5 h gave **13** in 76% yield. The regio- and stereoselective hydrogenation of



7 R : H
8 R : Ac



9a R : An
9b R : H



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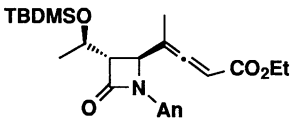

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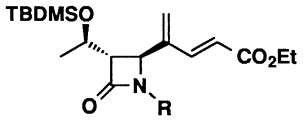
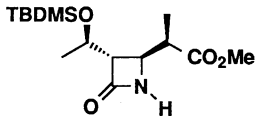
dienyl ester **13** was achieved by the use of 5% Pd/C (1 mol%) as catalyst in THF under hydrogen (1 atm) for 1.5 h to give α,β-unsaturated ester **9b**[9] in 95% yield with complete stereoselectivity, and other isomers could not be detected by ^{1}H-NMR (270 MHz). The absolute configuration of the 1-position of **9b** was established to be *S* by its conversion to the known compound **14**[1] with a catalytic amount of $RuCl_3$ and a stoichiometric amount of $NaIO_4$ in CH_3CN/ CCl_4/ H_2O at rt[10] for 2 h followed by esterification with diazomethane in THF. By the present two-step procedure, the total yield was increased.

Thus the pathway of the one step transformation of propargyl acetate **8** to α,β-unsaturated ester **9b** is concluded to involve allenyl ester **11**, which was isomerized to thermodynamically more stable dienyl ester **12**, and then reduced to α,β-unsaturated ester **9a** in the presence of an exess amount of formic acid.

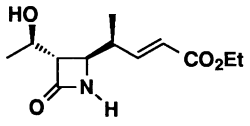


12 R : An
13 R : H



14
$[\alpha]_D^{23}$ -33 (c 0.02, $CHCl_3$)

Desilylation of **9b** was conducted with 2N HCl in MeOH at ambient temperature for 10 h to give the hydroxyethyl derivative **15** in 82% yield. Compound **15** was subjected to the Tsuji method[11] for the preparation of β-keto carbonyl compounds to give β-keto ester **16**. The reaction was carried out with 20 mol% of sodium tetrachloropalladate(II) and 1.5 eq of *tert*-butyl hydroperoxide in acetic acid and water at 70 °C to give **16** in 71% yield. The β-keto ester **16**[12] is known as a useful intermediate for the synthesis of 1β-methylcarbapenem.[1]



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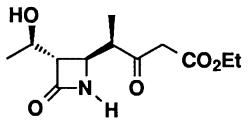

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In summary, we have developed a novel synthetic method of 1β-metylcarbapenem precursor employing the hydrogenolysis-isomerization-reduction process or regio- and stereoselective hydrogenation process as the crucial step. In contrast to the previous reported procedures, the present strategy used an acyclic intermediate for the stereoselective hydrogenation of the side chain, which could avoid some additional steps necessary for the conventional cyclic strategy.

References and Notes

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

2 F. Shirai and T. Nakai, *Tetrahedron Lett.*, **29**, 6461 (1988); Y. Nagao, T. Kumagai, Y. Nagase, S. Tamai, Y. Inoue, and M. Shiro, *J. Org. Chem.*, **57**, 4232 (1992); J. S. Prasad and L. S. Liebeskind, *Tetrahedron Lett.*, **28**, 1857 (1987), and the references cited therein.

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4 The most stable conformation was calculated with CAche™ system, and **3** was drawn with CSC Chem 3D™.

5 T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron Lett.*, **32**, 7563 (1991); T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron*, **48**, 5629 (1992); M. Shimizu, Y. Ukaji, J. Tanizaki, and T. Fujisawa, *Chem. Lett.*, **1992**, 1349; T. Fujisawa, R. Hayakawa, and M. Shimizu, *Tetrahedron Lett.*, **33**, 7903 (1992); T. Fujisawa, M. Ichikawa, Y. Ukaji, and M. Shimizu, *Tetrahedron Lett.*, **34**, 1307 (1993); T. Fujisawa, K. Higuchi, and M. Shimizu, *Synlett*, **1993**, 59; T. Fujisawa, D. Sato, and M. Shimizu, *BioMed. Chem. Lett.*, **3**, 2343 (1993); M. Shimizu, T. Ishida, and T. Fujisawa, *Chem. Lett.*, **1994**, 1403.

6 The starting β-lactam *R*-**5** was prepared as follows: acetylation of **4** at the 3-position with acetylimidazole (85%) followed by stereoselective reduction of methyl ketone at the 3-position with DIBAL (79%, 1'*R* : 1'*S* = 76 : 24). The chiral dioxolane was removed with CF_3SO_3H in 2-butanone (97%).

7 *R*-**5**, ^{1}H-NMR(270 MHz, $CDCl_3$) δ 1.38 (d, *J*=6.6Hz, 3H), 1.76 (bs, 1H), 2.25 (s, 3H), 3.17 (dd, *J*=2.6, 2.6Hz, 1H), 3.78 (s, 3H), 4.30-4.37 (m, 1H), 4.57 (d, *J*=2.6Hz, 1H), 6.85 (d, *J*=8.9Hz, 2H), 7.20 (d, *J*=8.9Hz, 2H); IR (neat) 3420, 2900, 1740, 1520, 1250 cm^{-1}; $[\alpha]_D^{23}$ -98.6 (c 0.10, $CHCl_3$).

8 J. Tsuji and T. Yamakawa, *Tetrahedron Lett.*, **20**, 613 (1979).

9 ^{1}H-NMR(270 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.80 (s, 9H), 1.07 (d, *J*=4.0Hz, 3H), 1.09 (d, *J*=3.6Hz, 3H), 1.22(t, *J*=7.1Hz, 3H), 2.33-2.48 (m, 1H), 2.75-2.77 (m, 1H), 3.54 (dd, *J*=2.3, 5.0Hz, 1H), 4.09-4.17 (m, 3H), 5.81 (d, *J*=14.5Hz, 1H), 5.88 (bs, 1H), 6.80 (dd, *J*=7.9, 7.9Hz, 1H); IR(neat) 3300,2950, 1760, 1740, 1260, 1170, 840 cm^{-1}; $[\alpha]_D^{23}$ -22 (c 0.02, $CHCl_3$).

10 H. Fliri and C. -P. Mak, *J. Org. Chem.*, **50**, 3438 (1985).

11 J. Tsuji, H. Nagashima, and K. Hori, *Chem. Lett.*, **1980**, 257.

12 ^{1}H-NMR(270 MHz, $CDCl_3$) δ 1.22-1.31 (m, 9H), 1.83 (s, 1H), 2.90-2.98 (m, 2H), 3.55 (dd, *J*=15.7, 9.9Hz, 2H), 3.76-3.83 (m, 1H), 4.17-4.23 (m, 3H), 6.39 (bs, 1H); IR (neat) 3300, 2950, 1740, 1300, 1180, 750 cm^{-1}.