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A New Synthesis of 1β-Methylcarbapenems Using NBS-Promoted Cyclization as a Key Step

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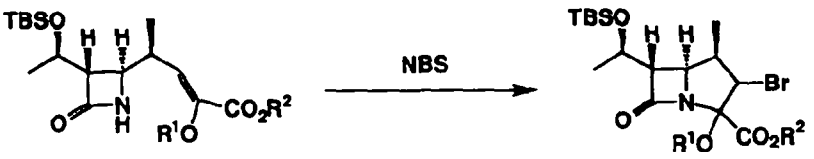
Abstract: A novel construction of 1β-methylcarbapenem skeleton has been achieved by use of *N*-bromosuccinimide(NBS)-promoted cyclization as a key step. The mechanism of the stereospecific cyclization leading to 1β-methylcarbapenam is also discussed.

1β-Methylcarbapenems have attracted much attention recently because of their potent and broad-spectrum antibacterial activities in addition to their chemical and metabolic stability.[1] The 1β-methylcarbapenem skeletons having a bicyclic ring system have been synthesized by the excellent methodologies based on the Rh(II)-catalyzed carbene insertion,[1,2] the intramoleculer Wittig reaction,[3] the Dieckmann condensation[4] and the Eschenmoser sulfide contraction.[5] In connection with our synthetic studies in search of a new carbapenem having potent antibacterial activity, we now report a conceptually new synthetic method of 1β-methylcarbapenem skeleton based on a novel ring construction utilizing NBS-promoted cyclization as a key step.

It is well-documented that the halonium ion-induced cyclization leading to lactams is quite convenient in the synthesis of nitrogen-containing heterocycles such as alkaloids[6] because of the mild reaction conditions and simplicity of the procedure. Although 5-endo-trigonal mode is unfavorable in the construction of a 5-membered ring system,[7] we anticipated that cyclization of α-alkoxy enoate **A** leading to the desired carbapenam **B** would proceed smoothly due to the effect of the electron-donating alkoxy group which could stabilize the developing positive charge on the carbon α to the ester group (Scheme 1).

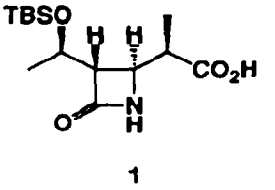
Scheme 1



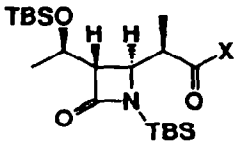
A **B**

R^1, R^2: alkyl group TBS: *tert*-butyldimethylsilyl

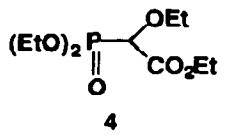
First of all, propionic acid derivative **1**[8,9] was treated sequentially with *N*, *N'*-carbonyldiimidazole and EtSH, followed by *N*-silylation with TBSOTf in the presence of 2,6-lutidine to give **2** in 81% yield. Compound **2** was then reduced according to the Fukuyama's method(Et_3SiH/10% Pd-C)[10] to aldehyde **3** in quantitative yield. Aldehyde **3** was treated with the sodium salt of phosphate **4** at 0 °C to give a mixture of the (*Z*)-isomer **5a** and the (*E*)-isomer **5b** in 85% yield in a ratio of 2:1. *N*-TBS group of **5a** was selectively cleaved with *n*-Bu_4NF in the presence of AcOH to give the (*Z*)-isomer **6a**.[11] (*E*)-Isomer **6b** was also obtained from **5b** under the same conditions.



1



2: X = SEt
3: X = H



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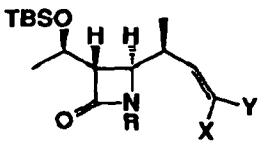
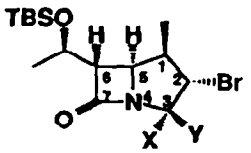
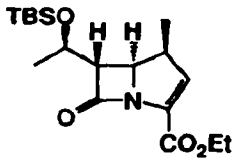


5a: R = TBS, X = OEt, Y = CO_2Et
5b: R = TBS, X = CO_2Et, Y = OEt
6a: R = H, X = OEt, Y = CO_2Et
6b: R = H, X = CO_2Et, Y = OEt



7a: X = OEt, Y = CO_2Et
7b: X = CO_2Et, Y = OEt



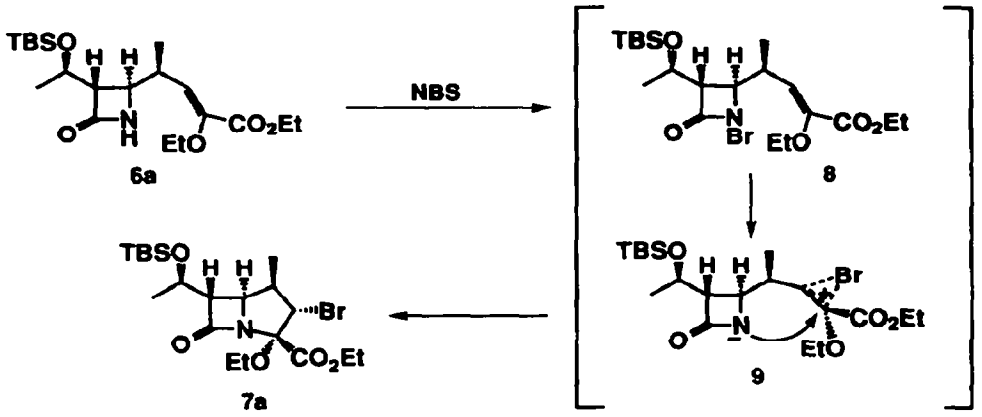
10

We next examined the NBS-promoted cyclization of **6** leading to **7**. Treatment of **6a** with 1 eq of NBS in CH_3CN at room temperature gave the cyclized product **7a** as a sole product in quantitative yield via 5-endo-trigonal mode cyclization.[12] In a similar way, the (*E*)-isomer **6b** was subjected to the cyclization reaction, resulting in the formation of the C_3-epimer **7b** in quantitative yield.[13] The stereochemistry of **7a** and **7b** was determined by both the NOE experiment and the X-ray crystallographic analysis.[14]

In order to gain an insight into the mechanism of this cyclization, we tried to isolate a reaction intermediate. When the reaction was carried out at 0 °C for 5 min and subsequently quenched with 0.2 M phosphate buffer (pH 7.0), a mixture of the *N*-brominated compound **8**[15] and **7a** in a ratio of 1:1 was obtained; when the reaction was further continued under the same reaction conditions, **8** was gradually converted to **7a**. These results indicate that the reaction is initiated by bromination of the nitrogen atom. The bromonium ion would then migrate to the olefin π-bond from the less hindered α-face to form the bridged bromonium ion intermediate **9**. Subsequently, the resulting anion on the amide nitrogen would attack on the carbon α to ethoxy group, giving the *anti* adduct **7a** (Scheme 2).

With the desired carbapenam **7a, b** in hand, we next examined conversion to the carbapenem. After several trials, **10**, which is an important precursor for the synthesis of carbapenems,[16] was obtained in 75% yield by treatment of **7a** with CH_3COCl-NaI in CH_3CN.[17] Epimer **7b** was also converted to **10** under the same reaction conditions.

Scheme 2 Plausible mechanism of the NBS-promoted cyclization



In summary, we found a convenient method for the construction of 1β-methylcarbapenam skeleton using the novel NBS-promoted cyclization reaction. Further transformation of the functionalized carbapenams **7** into other useful 1β-methylcarbapenems is now under investigation.

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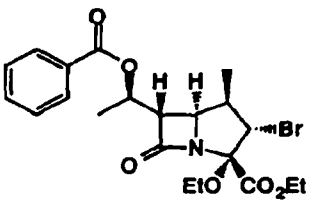
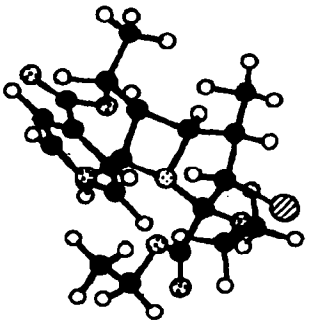
11. The regiochemistry of **6a** and **6b** was determined on the basis of ^{1}H NMR spectra; the vinyl protons of **6a** and **6b** appeared at δ 5.93 and δ 4.81, respectively. For **6b**, NOE (14.9%) was observed between vinyl proton and EtO-methylene protons.
12. A typical procedure is as follows: to a solution of **6a** (50 mg, 0.125 mmol) in CH_3CN (2 ml) was added NBS (25 mg, 0.138 mmol) all at once at 20 °C and the mixture was stirred for 30 min. The mixture was poured into saturated aqueous $Na_2S_2O_3$ and extracted with AcOEt. The organic layer was washed with H_2O, with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (*n*-hexane:AcOEt = 10:1) to give **7a** (58 mg, 97%) as a syrup.
^{1}H NMR spectrum of **7a** (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.16 (d, *J*=6.2Hz, 3H), 1.20 (t, *J*=7.0Hz, 3H), 1.23 (d, *J*=7.0Hz, 3H), 1.32 (t, *J*=7.1Hz, 3H), 2.62-2.83 (m, 1H), 3.20 (t, *J*=3.7Hz, 1H), 3.78-4.05 (m, 3H), 4.18 (d, *J*=11.3Hz, 1H), 4.15-4.38 (m, 3H).
13. ^{1}H NMR spectrum of **7b** (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.20 (d, *J*=7.4Hz, 3H), 1.21 (d, *J*=6.0Hz, 3H), 1.30 (t, *J*=6.9Hz, 3H), 1.36 (t, *J*=7.1Hz, 3H), 2.68-2.81 (m, 1H), 3.13 (dd, *J*=5.4, 3.1Hz, 1H), 3.75 (d, *J*=10.8Hz, 1H), 3.85-4.37 (m, 6H).
14. The stereochemistry at C_2 of **7a** and **7b** was unambiguously determined on the basis of ^{1}H NMR spectra; NOE between H_2 and H_6 was observed (5.4% for **7a** and 4.1% for **7b**). The stereochemistry at C_3 of these epimers was confirmed by the X-ray crystallographic analysis of 6-(1-benzoyloxy)ethyl derivative **11** which was easily obtainable from **7a**. Full crystal data for **11** has been deposited at the Cambridge Crystallographic Data Centre.



11



15. ^{1}H NMR spectrum of **8** (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.10-1.36 (m, 12H), 2.66-2.85 (m, 1H), 3.16 (t, *J*=2.5Hz, 1H), 3.77-4.05 (m, 3H), 4.19-4.42 (m, 3H), 6.03 (d, *J*=10.2Hz, 1H). The related acylhypoiodide intermediate was suggested in the iodolactonization: P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
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