Synthesis of 2-*exo*-Methylenepenam by Reductive 1,2-Elimination and S-S Bond Fission in a $PbBr_2$/Al Bimetal System

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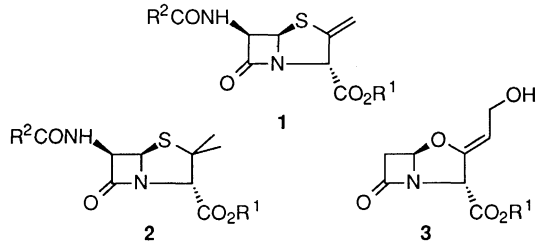
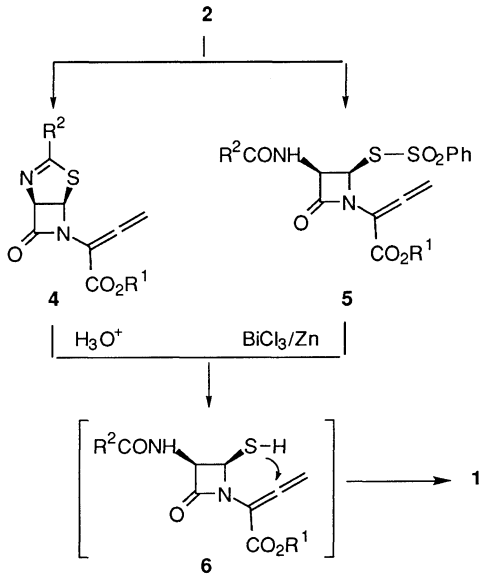
A convenient synthesis of 2-*exo*-methylenepenam was performed by reductive elimination of a 3,4-disubstituted chlorine atom(s) and/or a triflate moiety and S-S bond fission of the phenylsulfonylthio group of *p*-methoxybenzyl 3,4-dichloro or 4-chloro-3-(trifluoromethylsulfonyloxy)-2-[4-(phenylsulfonylthio)-2-oxoazetidin-1-yl]-2-butenoate derived from penicillin G in a lead(II) bromide/aluminum bimetal redox system.

2-*exo*-Methylenepenam framework **1** represents a structural hybrid of those of penicillin **2** and clavulanic acid **3**.[1] Because of the unique structure, 2-*exo*-methylenepenam **1** may stand for a new candidate of potent broad-spectrum antibiotics in its own right as well as a strategic intermediate for the synthesis of penem and penam families of β-lactam antibiotics through manipulation of the *exo*-methylene moiety.[2-4]



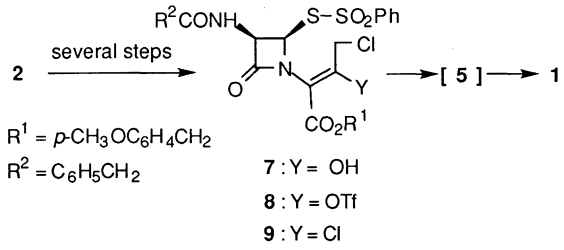
The first synthesis of **1** based on decarboxylative Pummerer-type reaction of penicillin-2-carboxylic acid elaborated from penicillin V has been reported by Baldwin and his group.[2] Recently, we have envisioned another synthetic scheme of **1** relying on intramolecular Michael-type addition of 2-(4-mercapto-2-oxoazetidin-1-yl)-2,3-butadienoate **6** (Scheme 1).[3,4] Thus far explored procedures are, however, not necessarily satisfactory in a practical sense because the former consists of multi-step operation (8 steps), resulting in low over-all yield (< 6%) and the latter involves intermediates **4**[3] or **5**[4] which are not always easy to handle owing to the lability under ambient conditions. We therefore investigated an alternative route to **1** and developed a direct conversion of 3,4-disubstituted 2-[4-(phenylsulfonylthio)-2-oxoazetidin-1-yl]-2-butenoates **8** and **9**, derived from penicillin G, into **1** by treatment with a lead(II) bromide/aluminum bimetal redox in DMF, in which, both reductive fission of the phenylsulfonylthio moiety and 1,2-elimination of the 3,4-disubstituted butenoate groups would occur, affording **1** *via* **5** (Scheme 2). Herein, we disclose the new device for the construction of the 2-*exo*-methylenepenam framework.

The 3,4-dichloro-2-butenoate **9** (R^1 = $PhCH_2$; R^2 = PMB) is stable enough to survive for several days under ambient conditions and can be easily prepared from penicillin G; thus, reaction of enol **7**, derived from penicillin G according to the



Scheme 1.

reported procedure,[5] with trifluoromethanesulfonic anhydride and triethylamine (1.5 molar amounts each) in dichloromethane at -78 ℃ for 1 h afforded the corresponding trifluromethanesulfonate **8** (95%) which was, in turn, treated with lithium chloride (10 molar amounts) in NMP containing aluminum chloride (3 molar amounts) at room temperature for 4 h to give the 3,4-dichloro-2-butenoate **9** (83%).[6]



Scheme 2.

The conversion of **9** into **1** was successfully achieved by one-pot reaction: thus, a mixture of **9**, lead(II) bromide and aluminum (1:1:5 molar ratio)[7] in DMF was stirred for 1 h at room temperature. Workup of the mixture gave 82% yield of the desired product **1** as colorless crystals. The lead(II) bromide /aluminum combination is the best choice among so far examined metal salts/metal combinations: metal salt/metal (% yield based on HPLC): $PbCl_2$/Al (65%) > $PbBr_2$/Zn (59%) > $SnCl_2$/Al (52%) > $BiCl_3$/Zn (43%) > $BiCl_3$/Al (40%) > $SnCl_2$/Mg (35%) > $TiCl_4$/Mg (20%) > $SnCl_2$/Zn (10%) > $NiCl_2$(bpy)/Zn (7%) >

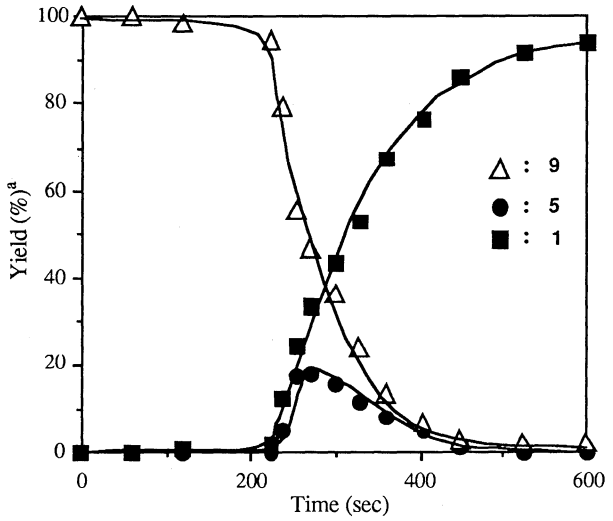


Figure 1. Time course of the reductive cyclization of 3,4-dichloro-2-butenoate **9** to 2-*exo*-methylenepenam **1** *via* allenecarboxylate **5**. [a]Determined by HPLC; column: YMC-Pack® AM-312 ODS (6.0 Φ x 150 mm); mobile phase: CH_3CN/H_2O = 65/35; flow rate: 1 mL min^{-1}; detection wavelength: 254 nm.

$TiCl_4$/Al (6%) > $PbBr_2$/Sn (--), $BiCl_3$/Sn (--), $PbBr_2$/Mg (--).

The time course of the reductive cyclization of **9** to **1** was monitored by HPLC (Figure 1), showing that after a few minutes induction period, the reaction occurred smoothly and most of **9** was converted to **1** in ten minutes. Notably, during the course of the reaction, the allenecarboxylate **5** was formed and finally disappeared. This fact can be reasonably explained by assuming that reductive 1,2-elimination of the 3,4-dichloro-2-butenoate group of **9**, leading to **5**, and subsequent reductive fission of the phenylsulfonylthio moiety of **5** would take place in a $PbBr_2$/Al system to afford **6** which would, in turn, undergo ring closure leading to **1**.

In a similar manner, reductive cyclization of the triflate **8** was also achieved successfully; thus, reaction of **8** with lead(II) bromide (1 molar amount) and aluminum (5 molar amounts) in DMF at room temperature for 2 h afforded **1** in 74% yield.

In conclusion, the reductive cyclization of **8** or **9** through reductive 1,2-elimination and subsequent S-S bond fission in a lead(II) bromide/aluminum system may open a practical and straightforward synthetic route to the 2-*exo*-methylenepenam **1**.

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References and Notes

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6 The reaction proceeded in a stereo specific manner to give the corresponding *E*-isomer **9**, exclusively: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64, 3.69 (ABq, *J* = 17.0 Hz, 2H), 3.80 (s, 3H), 4.27 (d, *J* = 12.3 Hz, 1H), 4.70 (d, *J* = 12.3 Hz, 1H), 4.73 (dd, *J* = 5.5, 7.5 Hz, 1H), 5.09, 5.19 (ABq, *J* = 12.0 Hz, 2H), 5.87 (d, *J* = 5.5 Hz, 1H), 5.99 (d, *J* = 7.5 Hz, 1H), 6.91-7.73 (m, 14H). The stereochemistry was tentatively assigned by comparison of the ^{1}H NMR spectra with those of (*E*)- and (*Z*)-isomers of 1-[3-chloro-1-(*p*-methoxybenzyloxycarbonyl)-2-(diphenylmethyloxy)-1-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinones: H. Tanaka, M. Taniguchi, Y. Kameyama, M. Monnin, S. Torii, M. Sasaoka, T. Shiroi, S. Nagao, T. Yamada, and Y. Tokumaru, *Bull. Chem. Soc. Jpn.*, **68**, 1385 (1995).

7 The direct transformation of **9** to **1** was achieved in 76% yield by use of 0.1 molar amount of lead(II) bromide and 5 molar amounts of aluminum. The presence of lead(II) bromide is indispensable for this reaction, since in the absence of lead(II) bromide, most of **9** was recovered intact. The role of lead(II) bromide in the lead(II) bromide/aluminum bimetal redox system will be discussed in due course.