A Facile Synthesis of 2-*exo*-Methylenepenam; a Potent Intermediate for Syntheses of New β-Lactamase Inhibitors

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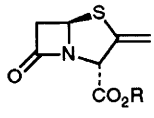
A convenient synthesis of 2-*exo*-methylenepenams **1** is performed by reductive cyclization of allenecarboxylates **8** in a $BiCl_3$/Zn bimetal redox system; subsequent manipulation of the 2-*exo*-methylene moiety of **1** opens new entries to β-lactam antibiotics and/or β-lactamase inhibitors.

The 2-*exo*-methylenepenam framework **1** represents a structural hybrid of those of clavulanic acid **2**, sulbactam **3a** and its analogues **3b** and **c**, which are natural and semi-synthetic inhibitors of certain β-lactamases.[1] One can, therefore, hope that the 2-*exo*-methylenepenam **1** might exhibit similar potent inhibitory activity toward β-lactamases. Furthermore, **1** is a new strategic intermediate, which can open new entries to potent β-lactamase inhibitors through manipulation of the *exo*-methylene moiety. Although two different synthetic schemes of 6-amide-substituted *exo*-methylenepenams have been reported so far by Baldwin *et al.*[2] and our group,[3] the synthesis of the 6-unsubstituted *exo*-methylenepenam **1** has not yet been realized.[4] Herein, we disclose the first synthesis of the 6-unsubstituted 2-*exo*-methylenepenam **1** based on a newly devised methodology for construction of the 2-*exo*-methylenepenam framework (Scheme 1) as well as preliminary experiments to demonstrate the synthetic potentiality of **1** (Scheme 2).

The key strategy of the construction of 2-*exo*-methylenepenam framework **1** involves the reductive cleavage of the phenylsulfonylthio moiety of allenecarboxylates **8** into the



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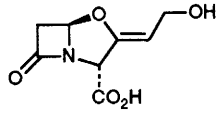

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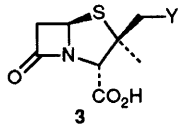

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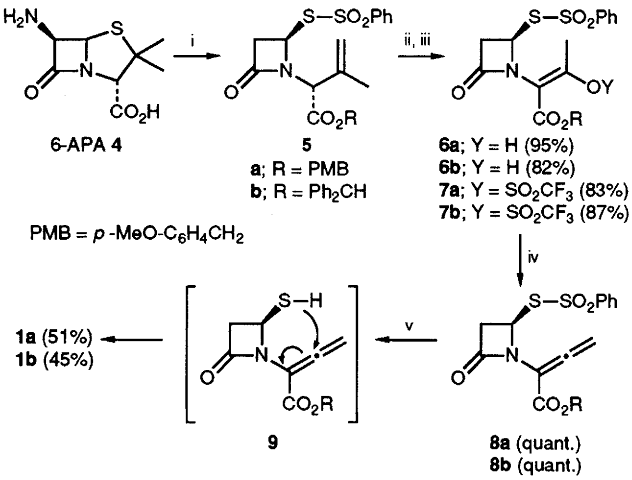
Sulbactam **a**; Y = H
BL-P2013 **b**; Y = Cl
YTR-830H **c**; Y = 



Scheme 1 *Reagents*: i, according to refs. 5, 6 and 7; ii, O_3; iii, Tf_2O, Et_3N; iv, Et_3N; v, $BiCl_3$, Zn

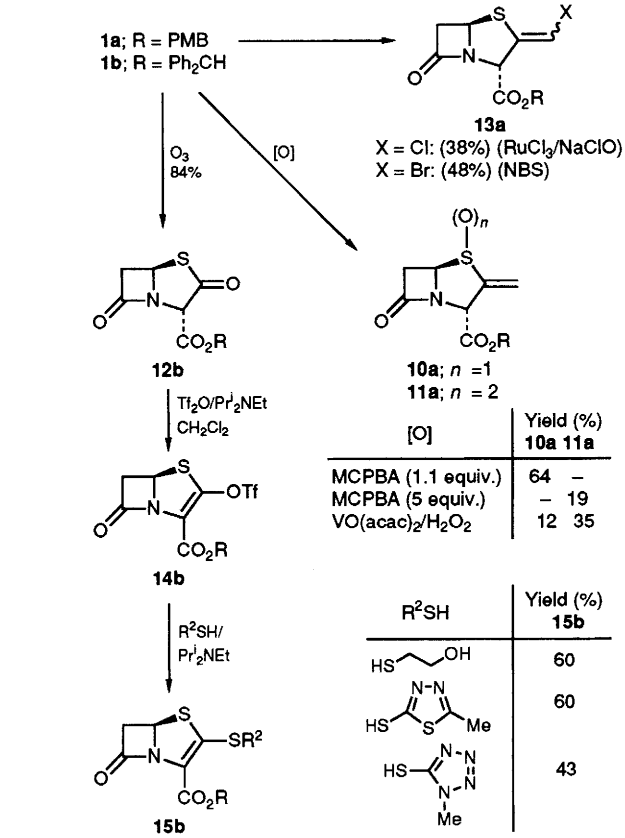
corresponding thiols **9** and subsequent intramolecular Michael-type addition of the thiol moiety to the allenecarboxylate group (Scheme 1). The allenecarboxylates **8** were prepared starting from 6-aminopenicillanic acid (6-APA) **4**. Thus, ozonolysis of azetidinones **5**, derived from **4** according to the reported procedure[5–7] in a mixed solvent of CH_2Cl_2 and methanol (2 : 1) at −78 °C afforded enols **6** (82 ~ 95%), which were subsequently treated with trifluoromethanesulfonic anhydride in CH_2Cl_2 containing triethylamine at −78 °C to give the corresponding triflates **7** (83 ~ 87%). 1,2-Elimination of the triflates **7** with triethylamine in tetrahydrofuran (THF) at −20 °C proceeded smoothly to give the allenecarboxylates **8** in almost quantitative yields.

The reductive cyclization of the allenecarboxylates **8** into the 2-*exo*-methylenepenams **1** was performed successfully in a bismuth(III) chloride/zinc bimetal redox system.† A mixture of the allenecarboxylates **8**, bismuth(III) chloride (2 equiv.) and zinc (8 equiv.) in THF was stirred at room temp. for 1 h to afford the corresponding 2-*exo*-methylenepenams **1** (45–51%). Although the role of the metal salt and metal is not clear at present, both components are indispensable since lack of each of them resulted in the recovery of **8**.

Thus obtained 2-*exo*-methylenepenams **1** are key intermediates for the synthesis of various new members of β-lactam antibiotics and/or β-lactamase inhibitors, since manipulation of the C-2 *exo*-methylene moiety can offer new entries to this goal as illustrated in Scheme 2. At first, we investigated chemoselective oxidation of **1** by using various oxidizing agents. Oxidation of **1a** with *m*-chloroperbenzoic acid (MCPBA) (1.1 equiv.) in CH_2Cl_2 at 5 °C for 1 h afforded sulfoxide **10a** (64%). Treatment of **1a** with an excess of (MCPBA) (5 equiv.) provided the corresponding sulfone **11a** (19%). Oxidation of **1a** in acetone with aq. 30% hydrogen peroxide (10 equiv.) in the presence of $VO(acac)_2$ (0.1 equiv.) (Hacac = pentane-2,4-dione) at room temp. for 10 h also provided **11a** (35%) together with **10a** (12%). In contrast, reaction of **1a** with sodium hypochlorite and a catalytic amount of ruthenium(III) chloride in CH_2Cl_2 gave 2-(chloromethylene)penam **13a** (X = Cl) in 38% yield. The corresponding bromide **13a** (X = Br) was obtained by the reaction of **1a** with *N*-bromosuccinimide (NBS) in 48% yield. On the other hand, ozonolysis of **1b** (R = $PhCH_2$) in a mixed solvent of CH_2Cl_2 and methanol at −78 °C proceeded in a chemoselective manner to afford 2-oxopenam **12b** (84%).

Transformation of **12b** into 2-substituted penems **15b** was successfully performed as follows: Treatment of **12b** with

† The combination of bismuth(III) chloride/zinc is the best of choice among the metal salt/metal combinations so far examined, *e.g.* $BiCl_3$/Sn (7%), and $TiCl_4$/Zn (none).



Scheme 2

trifluoromethanesulfonic anhydride (Tf_2O) in CH_2Cl_2 containing *N*-ethyl-*N*-diisopropylamine at −78 °C, afforded triflate **14b**, which was subsequently treated with thiols (R^2SH) in CH_2Cl_2 containing *N*-ethyl-*N*-diisopropylamine to give the corresponding 2-substituted penems **15b** (60 ~ 43%).

Thus far obtained penams **1**, **10**, **11**, **13** and penems **15** are potent candidates for the precursors of new members of β-lactamase inhibitors. Details of their bioassay results will be reported in due course.

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