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A Convenient Synthesis of 2-*exo*-Methylene Penam, A Potent Intermediate for New β-Lactam Antibiotics Synthesis

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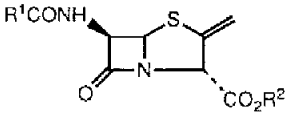
Abstract: A convenient synthesis of 2-exo-methylene penams 1 was performed by transformation of thiazoline-azetidinones, derived from penicillin G, through intramolecular Michael addition. Manipulation of the exo-methylene moiety of 1 opened new entries to 2-oxopenam and 2β-thiomethyl substituted penams, respectively.

2-*exo*-Methylene penam framework **1** represents a structural hybrid of those of penicillin **2** and clavulanic acid **3**. Recently, Baldwin and his group have reported the first synthesis of **1** (R^1 = $PhOCH_2$) through decarboxylative Pummerer-type reaction of penicillin-2-carboxylate elaborated from penicillin **2** and its preliminary bioassay results indicating that 2-*exo*-methylene penam **1** (R^1 = $PhOCH_2$; R_2 = H) has comparable antibacterial activity to natural penicillin V.[1] However, no further investigation on modification of the 2-*exo*-methylene penam framework leading to potent new β-lactam antibiotics has not appeared yet presumably because of the laborious multi-step operation (8 steps) and the low overall yield (< 6% from **2**). Although several 2-*exo*-alkylidene penams have been prepared through different pathways,[2] so far explored procedures can not be applied to prepare the parent system **1**. We therefore investigated an alternative short-cut route to **1** from penicillin **2** as illustrated in Scheme 1. Herein, we describe a straight forward synthesis of **1** as well as preliminary experiments to demonstrate potentiality of **1** in new β-lactam antibiotics synthesis.



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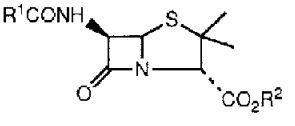

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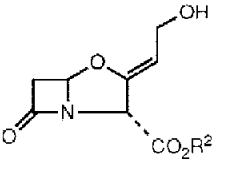

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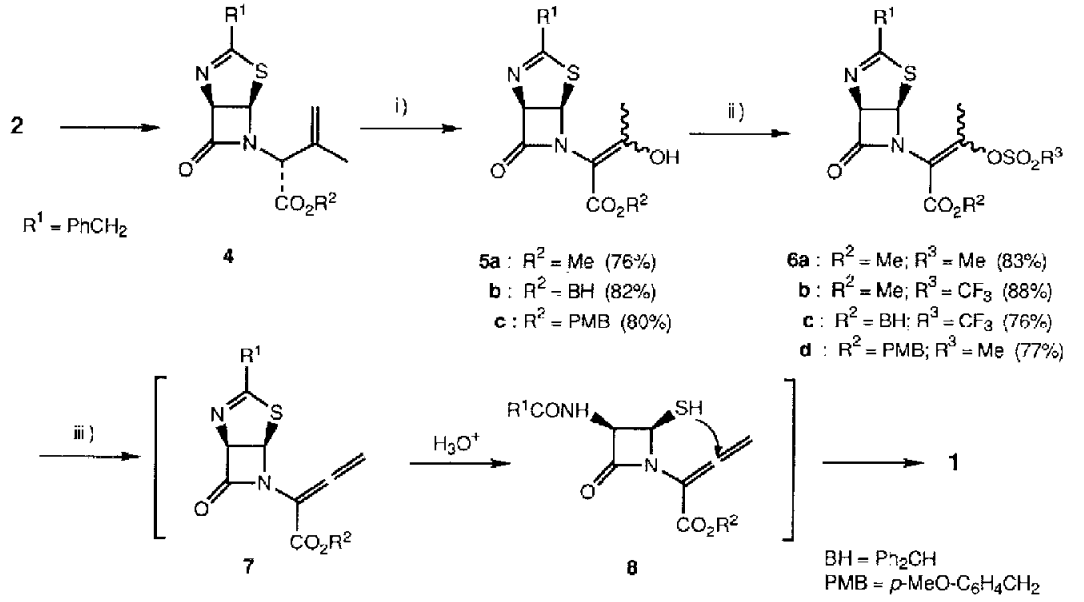
The key strategy of the construction of 2-*exo*-methylene penam framework **1** involves 1,2-elimination of sulfonates **6** (R^3 = Me, CF_3) to allene carboxylates **7** followed by hydrolysis of the thiazoline ring affording thiols **8** which, in turn, lead to 2-*exo*-methylene penam **1** by intramolecular Michael addition of the thiol moiety to the allene carboxylate group (Scheme 1). The sulfonates **6** (R^3 = Me or CF_3) were prepared by ozonolysis of thiazoline-azetidiones **4**, derived from penicillins **2** by Cooper's procedure,[3] and subsequent reaction of enols

5 with trifluoromethanesulfonic anhydride (or methanesulfonyl chloride) and triethylamine in THF at -40 °C for 1 h. The 1,2-elimination of the sulfonates **6** into allene carboxylates **7** was attempted by treatment with triethylamine (2 equiv.) in DMF at -20 °C for 0.2-0.5 h. Then, the reaction was quenched with aqueous 10% hydrochloric acid (or 60% perchloric acid) and the usual workup gave the *exo*-methylene penams **1**[4] in 55-80% yields without isolation of any detectable amounts of **7**[5] (Table 1). The direct transformation of **6** to **1** by the one-pot process can be reasonably understood by assuming that during the reaction and/or the workup process, the sulfonates **6** successively undergo 1,2 elimination (**6**→**7**), hydrolysis of thiazoline moiety (**7**→**8**) and intramolecular Michael addition (**8**→**1**).



i) O_3/CH_2Cl_2-MeOH (2:1), - 78 °C; ii) $MeSO_2Cl$ or $(CF_3SO_2)_2O$/Et_3N/THF, - 40 °C, 1h; iii) Et_3N/DMF, - 20 °C; H_3O^+.

Scheme 1

Table 1. One-Pot Transformation of Sulfonates **6** into 2-*exo*-Methylene Penams **1**[a)]

Entry	Sulfonate **6**	Time/h	H_3O^+ [b)]	Yield/%[c)]
1	**6a**	0.5	10% HCl	80
2	**6b**	0.2	60% $HClO_4$	75
3	**6c**	0.2	"	66
4	**6d**	0.2	"	55

a) Carried out in the manner as described in the text.

b) The reaction was quenched with acids (10 vol/vol %) at -20 °C.

c) Based on HLPC: YMC-PACK AM-312 ODS (6Φ x 150 mm); MeCN/H_2O (70/30).

Thus far obtained 2-*exo*-methylene penams **1** are potent intermediates for new β-lactam antibiotics synthesis. In fact, ozonolysis of **1** (R^1 = $PhCH_2$; R^2 = BH) in CH_2Cl_2-methanol (2:1) at -78 °C afforded 2-oxopenam **9** (60%),[6] while oxidation of **1** (R^1 = $PhCH_2$; R^2 = PMB) with *m*-chloroperbenzoic acid (mCPBA) (1.1 equiv.) in CH_2Cl_2 at 5 °C for 0.5 h afforded the corresponding sulfoxide **11** (84%) and excess mCPBA (5 equiv.) provided sulfone **12** (44%). The 2-oxopenam **9** is a promising precursor of 2-substituted penems **10**.[6] On the other hand, the sulfoxide **11** carries vinylsulfoxide moiety which can be expected to work as a powerful Michael acceptor. Indeed, elongation of the C(2)-side chain of **11** was performed successfully by Michael addition of thiols (R^4SH) to **11** in THF in the presence of sodium hydride (0.2 equiv.) at -50 °C for 1 h. The reaction proceeded in a stereospecific manner to afford 2β-thiomethyl substituted penams **13**[7], exclusively (Table 2). Subsequent reduction of the sulfoxides **13** with phosphorus tribromide in DMF at -30 °C for 1 h afforded the corresponding 2β-thiomethylpenams **14** (74-85%),[8] a new class of β-lactam antibiotics.[9]

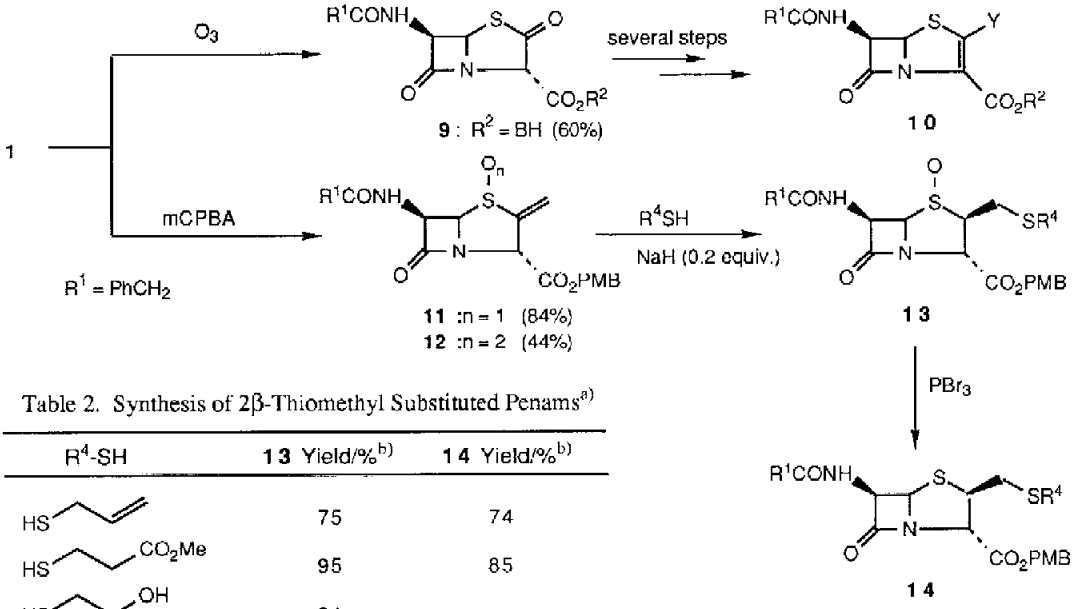


Table 2. Synthesis of 2β-Thiomethyl Substituted Penams[a)]

R^4-SH	**13** Yield/%[b)]	**14** Yield/%[b)]
HS	75	74
HS, CO_2Me	95	85
HS, OH	91	
HS, NHAc, CO_2Me	95	

a) Carried out in the manner as described in the text.
b) Isolated yields after column chromatography (SiO_2).

Scheme 2

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References

1) J. E. Baldwin, A. K. Forrest, S. Ko and L. N. Sheppard, *J. Chem. Soc. Chem. Commun.*, **1987**, 81.

2) J. L. Douglas, A. Martel, G. Garon, and M. Menard, *Can. J. Chem.*, **62**, 2282 (1984); N. F. Osborne, *J. Chem. Soc. Perkin Trans. I*, **1982**, 1429; P. C. Cherry, D. N. Evans, C. E. Newall, and N. S. Watson, *Tetrahedron Lett.*, **21**, 561 (1980); P. Lombardi, G. Franceschi, and F. Arcamone, *Tetrahedron Lett.* **1979**, 3777.

3) R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **92**, 2575 (1970).

4) *exo*-Methylene Penam **1a:** (R^1=$PhCH_2$, R^2=Me): ^1H NMR ($CDCl_3$: 300 MHz) δ 7.40~7.23 (m, 5H), 6.07 (d, 1H, *J* = 8.4 Hz), 5.77 (dd, 1H, *J* = 4.1, 8.4 Hz), 5.60 (d, 1H, *J* = 4.1 Hz), 5.40 (t, 1H, *J* = 0.6 Hz), 5.28 (t, 1H, *J* = 0.6 Hz), 5.19 (t, 1H, *J* = 0.6 Hz), 3.78 (s, 3H), 3.63 (s, 2H); IR (KBr) 3309, 1794, 1756, 1666, 1537 cm^{-1}; *exo*-Methylene Penam **1b**: (R^1=$PhCH_2$, R^2=BH): ^1H NMR ($CDCl_3$: 300 MHz) δ 7.40~7.22 (m, 15H), 6.85 (s, 1H), 6.08 (d, 1H, *J* = 9 Hz), 5.77 (dd, 1H, *J* = 4, 9 Hz), 5.61 (d, 1H, *J* = 4 Hz), 5.37 (bs, 1H), 5.27 (bs, 2H), 3.63 (s, 2H); IR (KBr) 3335, 1801, 1743, 1666, 1621, 1531, cm^{-1}; *exo*-Methylene Penam **1c**: (R^1=$PhCH_2$, R^2=PMB): ^1H NMR ($CDCl_3$: 300 MHz) δ 7.40~6.85 (m, 9H), 6.07 (d, 1H, *J* = 9 Hz), 5.75 (dd, *J* = 4.2, 9 Hz), 5.57 (d, 1H, *J* = 4.2 Hz), 5.35 (t, 1H, *J* = 1.4 Hz), 5.24 (t, 1H, *J* = 1.4 Hz), 5.18 (t, 1H, *J* = 1.4 Hz), 5.11 (s, 2H), 3.80 (s, 3H), 3.61 (s, 2H); IR (KBr) 3309, 1801, 1743, 1666, 1627, 1531 cm^{-1}.

5) Although all attempts to isolate intermediary allene carboxylates **7** failed due to the lability in aqueous media even under neutral or basic conditions, the formation of **7** (R^1=$PhCH_2$, R^2=BH) before quenching the reaction with aqueous perchloric acid was confirmed by ^1H NMR spectra: ($CDCl_3$: 300 MHz) δ 7.20~7.05 (m, 15H), 6.68 (s, 1H), 5.87 (d, 1H, *J* = 4 Hz), 5.82 (d, 1H, J = 4 Hz), 5.62, 5.54 (ABq, 2H, *J* = 15.5 Hz), 3.76, 3.64 (ABq, 2H, *J* = 16.4 Hz).

6) V. M. Girijavallabham, S. W. McCombie, P. Pinto, S. Lin, and R. Versace, *J. Chem. Soc. Chem. Commun.*, **1987**, 691; H. H. Wasserman and W. T. Han, *J. Am. Chem. Soc.*, **107**, 1444 (1985); L. Ghosez, J. Marchand-Brynaert, J. Vekemans and S. Bogdan, *Tetrahedron*, **39**, 2493 (1983); M. Cossement, J. Marchand-Brynaert, S. Bogdan and L. Ghosez, *Tetrahedron Lett.*, **24**, 2563 (1983); J. Marchand-Brynaert and L. Ghosez *Tetrahedron Lett.*, **21**, 3085 (1980).

7) Michael Adduct **13** (R^1=$PhCH_2$, R^2=PMB, R^3=$CH_2CH_2CO_2CH_3$): ^1H NMR ($CDCl_3$, 200 MHz): δ 7.38~7.21 (m, 7H), 7.06 (d, 1H, *J* = 10.6 Hz), 6.90~6.85 (m, 2H), 6.03 (dd, 1H, *J* = 4.5, 10.6 Hz), 5.20, 5.09 (ABq, 2H, *J* = 11.7 Hz), 4.85 (d, 1H, *J* = 4.5 Hz), 4.55 (d, 1H, *J* = 9.3 Hz), 3.80 (s, 3H), 3.78 (q, 1H, *J* = 9.3 Hz), 3.69 (s, 3H), 3.57 (s, 2H), 3.01 (d, 2H, *J* = 9.3 Hz), 2.71 (t, 2H, *J* = 6.9 Hz), 2.53 (t, 2H, *J* = 6.9 Hz); IR ($CHCl_3$): 1798, 1738, 1682, 1613, 1518 cm^{-1}.

8) 2β-Thiomethylpenam **14** (R^1=$PhCH_2$, R^2=PMB, R^3=$CH_2CH_2CO_2CH_3$): ^1H NMR ($CDCl_3$, 200 MHz): β 7.23-7.41 (m, 7H), 6.84-6.92 (m, 2H), 6.30 (d, 1H, *J* = 8.8 Hz), 5.64 (dd, 1H, *J* = 4.1, 8.8 Hz), 5.33 (d, 1H, *J* = 4.1 Hz), 5.12 (s, 2H), 4.96 (d, 1H, *J* = 2.3 Hz), 4.07 (ddd, 1H, *J* = 2.3, 6.4, 8.9 Hz), 3.81 (s, 3H), 3.71 (s, 3H), 3.64 (s, 2H), 2.71-2.79 (m, 2H), 2.35-2.61 (m, 4H).

9) The stereochemistry of **13** and **14** was confirmed by 2D NMR experiments (NOESY). Antibacterial activity of the corresponding carboxylic acids of **11-14** as well as their inhibitory effects toward β-lactamase will be reported in due course.

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