Synthesis of 3-Amino-4-Methylidene-2-Azetidinone *via* a Thermal Elimination Reaction

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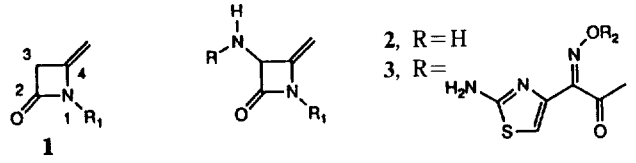
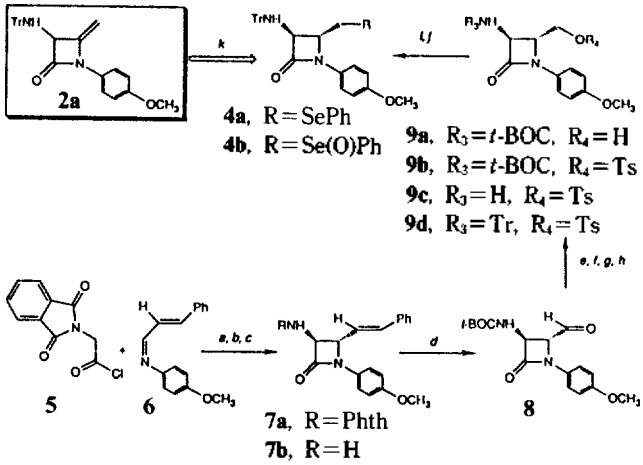
Recently, Joyeau, R. *et al.* reported the synthesis of 4-methylene-2-azetidinone analogue **1** from vinylic halide precursors by a 4-*exo*-trig cyclization.[1] No substitution on C3 position exhibited neither antimicrobial nor anti-β-lactamase activity. As part of project on the synthesis of new monobactams, introduction of amino group at C3 position provides a better antibacterial activity. Not only Azthreonam (α-methyl on C4 position) has good antibacterial activity but other β-methyl isomer also shows good activity. In addition, it has been great interest to synthesize 3-amino-4-methylene-2-azetidinone itself, we have attempted to prepare 4-methylene-2-azetidinones **2**, especially, which has aminothiazolesubstituted monobactams **3** on C3 position.[2-4]



1

2, R=H
3, R=

Figure



4a, R=SePh
4b, R=Se(O)Ph

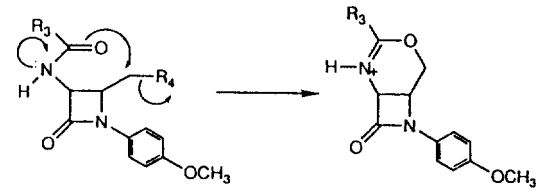
9a, R_3=*t*-BOC, R_4=H
9b, R_3=*t*-BOC, R_4=Ts
9c, R_3=H, R_4=Ts
9d, R_3=Tr, R_4=Ts

5 **6** **8**

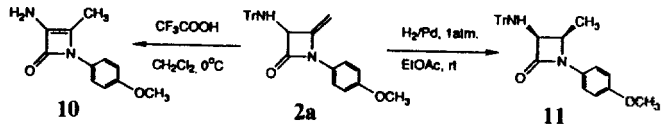
7a, R=Phth
7b, R=H
7c, R=*t*-BOC

(a) Et_3N, CH_2Cl_2, 0℃, 2 h, 42%, (b) CH_3NHNH_2, CH_2Cl_2, 0℃, 16 h, (c) *t*-Bu-OCOOCOO-*t*-Bu, CH_2Cl_2, r.t., 16 h, 62% (steps (b) and (c)), (d) OsO_4, $NaIO_4$, H_2O/THF(1:1.8), r.t., 18 h, 98%, (e) $NaBH_4$, THF-H_2O (1:1), 0℃, 2 h, 61%, (f) *p*-TsCl, pyridine, room temperature, 16 h, 97%, (g) CF_3COOH, 0℃, 30 min, 99%, (h) TrCl, Et_3N, DMF, −20℃, 30 min, then room temperature, 16 h, 97%, (i) PhSeSePh, $NaBH_4$, EtOH/THF, 50℃, 6 h, 63%, (j) $NaIO_4$, MeOH/H_2O (6:1), r.t., 5 h, 99%, (k) Na_2CO_3, toluene, reflux, 10 h, 48%. Phth=phthaloylimino, *t*-BOC=*t*-butoxycarbonyl, Tr=triphenylmethyl.

Scheme 1



Scheme 2



10 **2a** **11**

Scheme 3

The target *exo*- methylidene compound **2a** could be synthesized from *trans*-selenium oxide **4d** as outlined in retrosynthetic form in Scheme 1. One approach that appeared attractive was to eliminate good leaving group such as iodo, tosyl, mesyl, and oxyselenyl on 4-methyl derivatives. Our initial attempts to prepare this *exo*-methylene compound from iodo-, tosyl-, and mesyl-methyl analogues by a elimination reaction, were unsuccessful. We found that the thermal elimination of selenium oxides **4b** afforded 3-amino-4-*exo*-methylene-2-azetidinone **2a**.

Trans-aldehyde **8** was most conveniently prepared in fairly good yield using [2+2] cyclization, followed by dephthalation, protection with *t*-BOC, and oxidation with OsO_4 and $NaIO_4$. Yield of [2+2] cyclization was only 42% but *trans* isomer **7a** was exclusively formed without detecting any *cis* isomer. Aldehyde **8** was reduced to alcohol **9a** by $NaBH_4$. Tosylation of alcohol and the exchange of *t*-BOC of 3-amino group to trityl afforded tosylate **9d**. Selenization with diphenyl diselenide and mild oxidation of selenide with $NaIO_4$ provided selenium oxide **4b**[5] in high yield.

Selection of substituents on 3-position, herein, were important in an elimination reaction. In case that the protecting group of 3-amino has nucleophilicity, intramolecular nucleophilic attacking of the protecting group could be occurred toward leaving group on 4-methyl, forming a 6-membered ring (Scheme 2). As benzyloxycarbonyl (CBZ), *t*-BOC, and phthalimide protective group, which have carbonyl, could not be used, we used trityl protected selenium oxide **4b**[5] at an elimination step.

The thermal elimination reaction of *trans*-phenylselenoxo compound **4b** was performed in toluene solution in the presence of Na_2CO_3. After refluxing for 10 h, extraction (CH_2Cl_2), flash column chromatography (SiO_2), and recrystallization (Et_2O) provided 3-amino-4-methylidene-2-azetidinone **2a** as an white crystal (48%). The total synthesis involved 11 steps, providing 4.4% overall yield from **5** and **6**.

We have tried to remove protecting groups of **2a** (Scheme 3). First, the treatment of trifluoroacetic acid in dichloromethane gave detritylated as well as endoisomerized product **10**. Compound **10** was stable and its ring system would be interested for antibacterial activity of its derivatives. The alternative approach to remove trityl group was done by hydrogenation with Pd catalyst, but provided hydrogenated product **11**.

In conclusion, we have synthesized 4-methylidene β-lactam derivative **2a** with amino group on C3 positiion by thermal

elimination reaction from *trans*-isomer. Further studies on the removal of protecting groups as well as the attachment of suitable groups on N1 and C3 position to the synthesis of useful monobactam antibiotics are currently in progress.

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References

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4. Other syntheses of β-lactam ring using [2+2] cyclization; (a) G. I. Georg, P. He, J. Kant, and J. Mudd, *Tetrahedron Lett.*, **31**, 4167 (1990); (b) D. Kronenthal, C. Y. Han, and M. K. Taylor, *J. Org. Chem.*, **47**, 2765 (1982).
5. All compounds described were chracterized by NMR, IR, and mass spectral data. Selected physical date are as follow: **2a**: mp. 180-1℃; IR (KBr) 1682, 1789, 3053, 3359 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.53 (d, 1, J=8.7 Hz NH), 2.86 (d, 1, J=3.0 Hz, $=CH_2$), 3.76 (s, 3, OCH_3), 4.20 (d, 1, J=3.0 Hz, $=CH_2$), 4.67 (d, 1, J=8.7 Hz, NHCH), 6.83-7.71 (m, 19, aromatic H); ^{13}C-NMR (200 MHz, $CDCl_3$, off resonance spectrum) δ 56.1 (q, OCH_3), 68.0 (d, NHCH), 71.8 (s, CPh_3), 82.1 (t, $=CH_2$), 115.2 (d, aromatic CH), 122.4 (d, aromatic CH), 127.4 (d, aromatic CH), 128.9 (d, aromatic CH), 129.3 (s, $C=CH_2$), 129.5 (d, aromatic CH) 146.8 (s, aromatic C), 149.5 (s, aromatic C), 159.2 (s, aromatic C), 170.6 (s, CO); mass spectrum (CI, 200 eV), m/z (relative intensity) 447 (M^++1, 3), 418 (8), 271 (7), 243 (100), 167 (8). **4a**: mp. 137-8℃; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.60 (dd, 1, J=3.0, 13.8 Hz, CH_2Se), 2.92 (dd, 1 J=3.0, 13.8 Hz, CH_2Se), 3.59-3.61 (m, 1, C_4H), 3.74 (s, 3, OCH_3), 3.77 (brs, 1, NH), 4.26 (s, 1, C_3H), 6.69-7.57 (m, 24, aromatic H); mas spectrum (CI, 200 eV), m/z (relative intensity) 605 (M^++1, 0.4), 603 (M^++1, 0.4), 576 (0.4), 527 (0.4), 475 (2), 447 (2), 271 (13), 244 (100), 243 (100), 203 (13), 189 (26), 167 (100). **4b**: mp. 116-9℃; m/z (relative intensity) 605 (M^++1, 2), 603(M^++1, 1), 576 (1), 527 (3), 475 (5), 447(7), 271 (34), 244 (100), 243 (100), 203 (13), 189 (8), 167 (100).

Synthesis of Fosfazinomycin B

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Fosfazinomycin B (**1**), methyl arginylmethylhydrazinohydroxyphosphonohydroxyacetate, is a new antifungal substance isolated from the fermentation broth of *Streptomyces lavendofoliae*[1-3]. It is a tripeptide which contains a carbon-phosphorus-amine bond. Most of the organic compounds in nature are composed of carbon-carbon bond. But it has been proved that the compounds having carbon-phosphorus bond are also stable. Recently aminophosphonic acids and their derivatives have attracted attention because of their antibacterial, herbicidal, pesticidal, anticancer and enzyme inhibitory activities, and particularly their structural similarity to the biologically important amino acids. Since 2-aminophosphonic acid (2-AEPn) was isolated from sheep rumen in 1959 by Horiguchi and his coworkers[4], twenty six aminophosphonic acids and their derivatives have been discovered form living organisms. Aminophosphonic acids are also discovered in mammalian tissues like human muscles, sheep liver, and ox brain[5-11]. Their concentrations in human tissues, in heart and skeletal muscles was higher than in liver and brain.

Here we report the synthesis of Fosfazinomycin B (**1**) from methyl methylhydrazinobenzyloxyphosphonoacetate (**2**)[12] which has carbon-phosphorus bond. N-Carbobenzyloxynitroarginine (**4**) was prepared in 82% yield from protecting guano group and amino group of L-arginine (**3**) by treatment with nitric acid and carbobenzyloxychloride, successively. The peptide (**5**) was prepared by coupling of acetate (**2**) with **4** in the presence of ethyl chloroformate in 67% yield. Fosfazinomycin B (**1**) was obtained by hydrogenation in 62% yield. In conclusion. Fosfazinomycin B (**1**), a new kind of phosphorus compound was synthesized from methyl methylhydrazinobenzyloxyphosphonoacetate efficiently in 4 steps in 24% overall yield.

Experimental

N-Carbobenzyloxynitroarginine(4). To a 250 m*l* three neck round-bottomed flask. 12.5 g (0.057 mol) of nitroarginine[12], 18.9 g (0.135 mol) of potassium carbonate and 100 m*l* of distilled water were added. With stirring at 0℃, the solution was added with 8.54 m*l* (0.06 mol) of benzyl chloroformate was added carefully through a dropping funnel over 30 minutes. After being stirred for 4 hours, the reaction mixture was washed with chloroform and ether successively, nd acidified with dilute HCl solution. White oily organic layer was extracted with ethyl acetate, and the extract was dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation *in vacuo*, the crude product was chromatographed on a silica gel column by eluting with ethyl acetate. The major compound eluted from the column was