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SYNTHESIS OF 2,2-DIMETHYL-1-CARBAPENAM DERIVATIVES *VIA* AN INTRAMOLECULAR MICHAEL-TYPE REACTION

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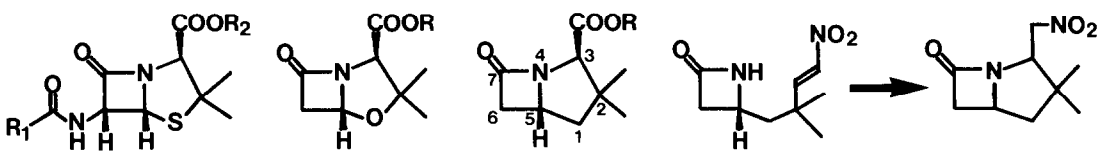
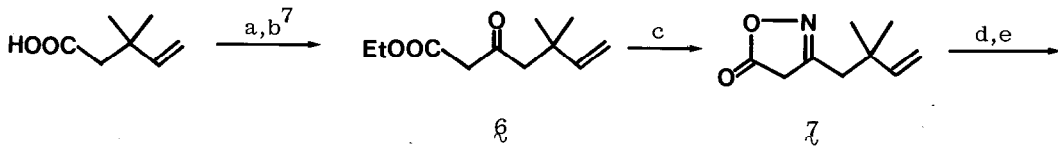
Summary: The synthesis of 2,2-dimethyl-1-carbapenam derivatives *via* an intramolecular Michael-type condensation reaction is described.

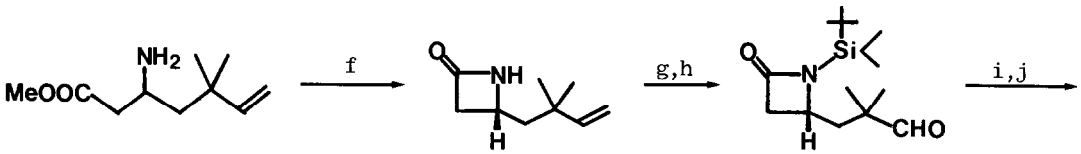
The discoveries of "non classical" β-lactam antibiotics, *e. g.* thienamycin[1] and clavulanic acid,[2] aroused considerable interest in the preparation of penicillin (1) analogues, in which the sulfur atom has been replaced by oxygen or carbon. Some reports have been published dealing with the successful synthesis of compounds having 2,2-dimethyl-1-oxapenam ring system 2.[3] Although considerable efforts were made towards the preparation of 1-carbapenem derivatives related to thienamycin, including our recent works on the synthesis of 1,1-dimethyl-1-carbapenems,[4] no synthetic approach towards 2,2-dimethyl-1-carbapenam (3) derivatives has been reported. The synthesis of 3 is interesting not only because of the structure-activity relationship between nuclear analogues of penicillins but also providing opportunities to find out a new method for the construction of the bicyclic ring system. Here we report the first synthesis of 2,2-dimethyl-1-carbapenam derivatives. In considering the synthetic approaches for 3, we planned to construct the bicyclic nucleus by forming N - C-3 bond by an intramolecular Michael-type reaction (4 → 5). The carbapenam 5, containing a potential carboxylic acid group at C-3, was expected to be a precursor for our target.



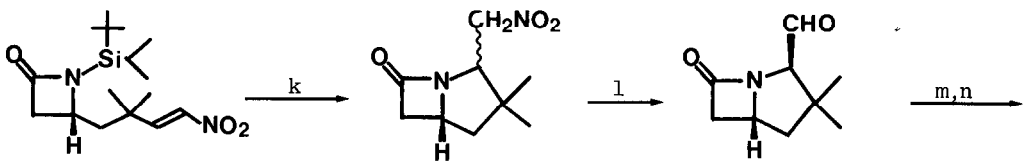
The azetidinone 9[5,6] with an olefinic side chain at C-4 position was prepared from 3,3-dimethyl-4-pentenoic acid[8] in six steps as shown in the scheme. The procedures that we have reported previously[9] have been adopted for the preparation of 9. After the protection of nitrogen of 9 with *tert*-butyldimethylsilyl group, the terminal double bond was cleaved oxydatively to afford the aldehyde 10.[10] Nitromethylation of 10 followed by dehydration gave the single unsaturated nitro compound 11. The coupling constant (14 Hz) in its NMR spectrum between the olefinic protons of 11 indicated the *trans* geometry of the unsaturated nitro group. By the action of potassium fluoride, desilylation occured and gave the epimeric mixture (*ca.* 2:1) of bicyclic nitro compound 5. It is evident that monocyclic intermediate, 4, cyclized simultaneously under the reaction conditions. On the other hand, acid catalyzed desilylation (HCl, MeOH,



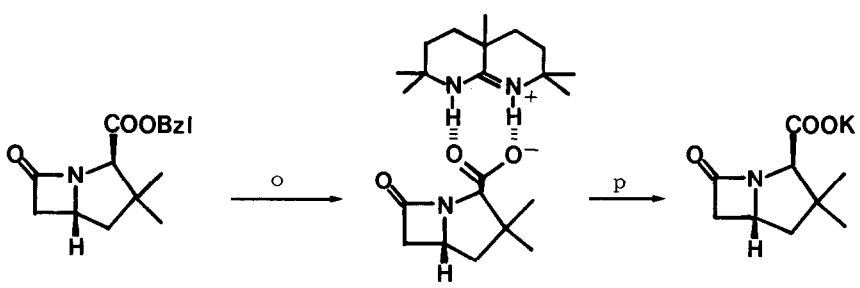
6 7



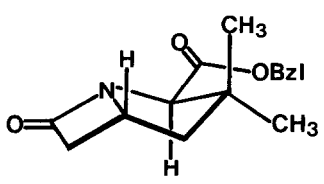
8 9 10



11 5 12



13 14 15



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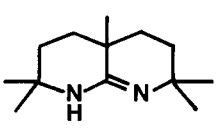

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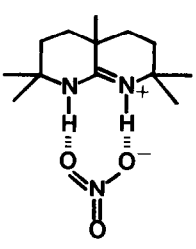

18

0°) of 11 afforded a product which was found to be more polar than 5 on TLC. The product was considered to be monocyclic azetidinone 4, and isomerized completely to the bicyclic carbapenam 5 during the column chromatography on silica gel. The method for the conversion of primary and secondary nitroalkanes into the corresponding aldehydes and ketones is well established.[11] In order to get aldehyde 12, we chose the ozonolysis of nitronate salt, prepared from the isomeric mixture of nitro compound 5 and amidine 17.[12] Another product of this reaction was the amidine salt of nitric acid 13, which was separated from 12 by column chromatography on silica gel. From the NMR spectrum, the resulting aldehyde 12 was found to be a single isomer, suggesting epimerization of the aldehyde group in the unstable isomer occured under the experimental conditions. Catalytic oxygenation[13] of the aldehyde in the presence of sodium bicarbonate gave a good yield of sodium salt of corresponding carboxylic acid, which was purified as a benzyl ester 13. The conformational feature of penicillins is well investigated by NMR Nuclear Overhauser Effect (NOE).[14] The relative configuration of the C-3 and C-5 positions of the carbapenams was clarified similarly by NOE experiment for the ester 13.[15] Irradiation of the high-field methyl peak resulted 10% increase in the intensity for C-5H, whereas the increase in that of C-3H was found negligible. These results indicate that the methyl group is located in the same side (β) as C-5H. Alternatively, saturation of the low-field methyl group (which must be assigned the α orientation) increases the intensity of C-3H by 13%, while no effect was observed with C-5H. These results indicate that the C-3-benzyloxycarbonyl group and the C-5H are in the *cis* orientation, which represents the thermodynamically preffered situation of the carboxylate group. Furthermore, these results suggest the *exo*-envelope conformation depicted in formula 16 is preferable for the ester 13, as reported for phenoxymethyl penicillin sulfoxide and sulfone derivatives, while phenoxymethyl penicillin derivative has been reported to possess an *endo*-envelope conformation.[14] Deprotection of the ester function in 13 was readily accomplished by a manner similar to that we have reported previously,[4b] and the resulting amidine salt 14 was converted into potassium salt 15 in good yield. The extention of this synthetic method for the total synthesis of 2,2-dimethyl-1-carbapenams with an amino group at C-6 position is the next problem.

At a concentration of 50 μg/ml, compounds 14 and 15 were found inactive against Gram positive and Gram negative organisms.

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4. (a) M. Shibuya and S. Kubota, *Tetrahedron Letters*, 21, 4009 (1980); (b) M. Shibuya and S. Kubota, *Tetrahedron Letters*, in press.
5. Satisfactory IR (JASCO DS-701G), mass (JEOL JMS-D300), and NMR (JEOL PS-100 for ^{1}H NMR and/or JEOL FX-200 for ^{13}C NMR) spectral data were obtained for each isolated synthetic intermediate. The substances described are *dl*-mixtures, but the enantiomer related to

penicillins is depicted for convenience.

6. Selected data, **9** : ν ($CHCl_3$) 3420 and 1755 cm^{-1}; δ ($CDCl_3$) 1.05 (6H, s), 1.67 (2H, d, J = 6), 2.55 (1H, ddd, J = 1, 2.5, and 15), 3.05 (1H, ddd, J = 2, 5, and 15), 3.64 (1H, m), 4.80∿5.95 (3H, m), and 6.60 (1H, br). **10** : mp 31∿32°; ν ($CHCl_3$) 1737 and 1727 cm^{-1}; δ ($CDCl_3$) 0.25 (6H, s), 0.96 (9H, s), 1.10 (6H, s), 1.58 (1H, dd, J = 11 and 13.5), 2.09 (1H, dd, J = 2 and 13.5), 2.56 (1H, dd, J = 3 and 15), 3.10 (1H, dd, J = 5 and 15), 3.48 (1H, m), and 9.46 (1H, s). **11** : mp 62∿63°; ν ($CHCl_3$) 1730, 1525, and 1352 cm^{-1}; δ ($CDCl_3$) 0.22 (3H, s), 0.24 (3H, s), 0.96 (9H, s), 1.19 (6H, s), 1.64 (1H, dd, J = 11 and 14), 2.00 (1H, dd, J = 2 and 14), 2.58 (1H, dd, J = 3 and 15), 3.14 (1H, dd, J = 5 and 15), 3.45 (1H, m), 6.86 (1H, d, J = 14), and 7.17 (1H, d, J = 14). **5** : ν ($CHCl_3$) 1760 and 1562 cm^{-1}. **12** : ν ($CHCl_3$) 1763 and 1730 cm^{-1}; δ ($CDCl_3$) 1.10 (3H, s), 1.35 (3H, s), 1.50 (1H, dd, J = 9 and 12), 2.02 (1H, dd, J = 5 and 12), 2.70 (1H, dd, J = 2 and 16), 3.30 (1H, dd, J = 5 and 16), 3.77 (1H, d, J = 2.5), 3.96 (1H, m), and 9.55 (1H, d, J = 2.5). **13** : ν ($CHCl_3$) 1755 cm^{-1}; δ ($CDCl_3$) 0.96 (3H, s), 1.32 (3H, s), 1.46 (1H, dd, J = 9 and 12.5), 2.01 (1H, dd, J = 5 and 12.5), 2.60 (1H, dd, J = 2 and 16), 3.24 (1H, dd, J = 5 and 16), 3.95 (1H, m), 4.06 (1H, s), 5.14 (2H, s), and 7.34 (5H, s); ^{13}C NMR δ ($CDCl_3$) 23.6 and 28.1 (CH_3), 42.5 and 47.2 (C-1 and C-6), 51.2 and 68.7 (C-5 and C-3), 52.0 (C-2), 66.8 (OCH_2), 128.4, 128.5, 128.6, and 135.4 (Ph), 169.9 and 176.2 (C=O). **14** : mp 162∿170°(dec); ν ($CHCl_3$) 1745 and 1660 cm^{-1}; δ ($CDCl_3$) 1.14 (3H, s), 1.30 (9H, s), 1.36 (3H, s), 1.38 (6H, s), 1.20∿2.10 (10H, m), 2.54 (1H, dd, J = 2 and 16), 3.17 (1H, dd, J = 4.5 and 16), 3.92 (1H, m), 3.96 (1H, s), and 11.58 (2H, br). **15** : mp 285∿290°(dec); ν (KBr) 1735 and 1603 cm^{-1}; δ (D_2O) 1.12 (3H, s), 1.40 (3H, s), 1.59 (1H, dd, J = 9 and 12.5), 2.14 (1H, dd, J = 5 and 12.5), 2.78 (1H, dd, J = 2 and 16), 3.30 (1H, dd, J = 4.5 and 16), 3.91 (1H, s), and 4.02 (1H, m).
7. Experimental conditions and yields, (a) $SOCl_2$, reflux, 93%; (b) 2 equiv $LiCH_2COOEt$, -78°, THF, 88%; (c) $NH_2OH{\cdot}HCl$, pyridine, 50°, 90%; (d) Na, *iso*-PrOH, reflux; (e) MeOH, HCl, rt, 80% from **7**; (f) mesitylmagnesium bromide, CH_2Cl_2, rt, 55%; (g) *tert*-butyldimethylsilyl chloride, N,N-diisopropylethylamine, DMF, 0°, 98%; (h) O_3, MeOH, -30° → Me_2S, rt, 87%; (i) CH_3NO_2, piperidine, 85%; (j) Ac_2O, pyridine, rt, 72%; (k) KF, MeOH, 0°, 15 min, 78%; (l) 3,3,6,9,9-pentamethyl-2,10-diaza-bicyclo-[4.4.0]-1-decene **17**, O_3, MeOH, -60° → Me_2S, rt, 62%; (m) Pt, O_2, H_2O/acetone (2:1 v/v), $NaHCO_3$, rt, 5h; (n) benzyl bromide, DMF, rt, 3h, 93% from **12**; (o) 10% Pd-C, H_2, THF, **17**, rt, 10 min, 88%; (p) potassium 2-ethylhexanoate, ether/THF (1:1 v/v), rt, 5 min, 96%.
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10. Direct ozonolysis of **9** was unsuccessful because of instability of the product.
11. N. Kornblum and A. S. Erickson, *J. Org. Chem.*, 46, 1037 (1981) and references cited therein.
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15. NOE experiment was carried out in argon-sparged solution (sample concentration, 14% w/v) with TMS as an internal lock in $CDCl_3$ using JEOL PS-100 instrument. The values of intensity increase contain ±2% experimental error.

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