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A NOVEL SYNTHESIS OF THE CARBAPEN-2-EM DERIVATIVES

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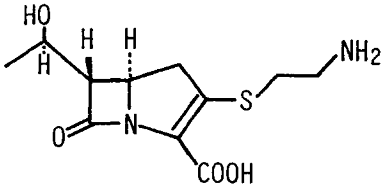
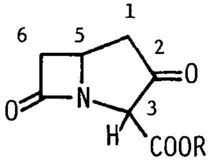
Summary: A new synthesis of the carbapen-2-em ring system, the basic nucleus of thienamycin and its relatives, is described.

The highly potent antibacterial activities of thienamycin (1) and related natural products[1] have attracted considerable interest in the synthesis of the novel carbapen-2-em derivatives[2]. One of the most successful strategies for the construction of the carbapen-2-em ring system involves an intramolecular carbene insertion reaction to produce carbapenams of type 2, which are readily converted into the 2-thia substituted carbapen-2-ems as found in thienamycin[2f]. In this communication, we also report a simple and high-yielding synthesis of the carbapenams of type 2. The key step involves a Dieckmann-type condensation reaction[3] of the monocyclic β-lactams 3, which are conveniently synthesized by an application of the Ugi reaction[4] using isonitriles as β-lactam forming reagents.



1



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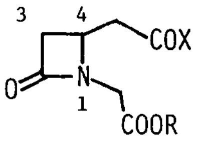
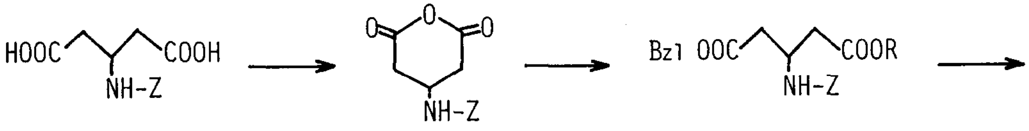


3

The starting material, the mono *t*-butyl ester of 3-aminoglutaric acid, was prepared in a straightforward manner from N-benzyloxycarbonyl 3-aminoglutaric acid (4)[5]. The compound 4 was converted (Ac_2O, 40°C) into the anhydride 5, which was heated (110°C, 10 min) with benzyl alcohol to give the monobenzyl ester 6[6], mp 94-96°. Treatment of 6 with isobutylene (H_2SO_4, CH_2Cl_2, 20°C), following hydrogenolysis of 7 (10% Pd/C, EtOH) gave the mono t-butyl ester 8, mp 175-177° (decomp.), in 55% yield from 4.

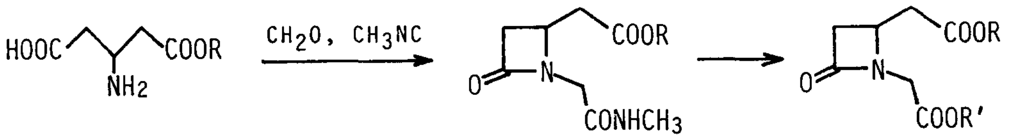
The three component condensation reaction of 8 with formaldehyde and methyl isonitrile readily proceeded in methanol at room temperature to produce the desired β-lactam 9[7] (66%). The selective cleavage of the amide bond of 9 was achieved via the imino chloride. The compound 9 was first treated with PCl_5 (pyridine, CH_2Cl_2, 0°C), and successively with methanol. The acidic work-up of the reaction mixture gave the methyl ester 10 (84%). The methyl ester 10 was then transformed in 73% yield into the benzyl ester[8] 11 by saponification



4

5

6, R = H
7, R = Bu^t



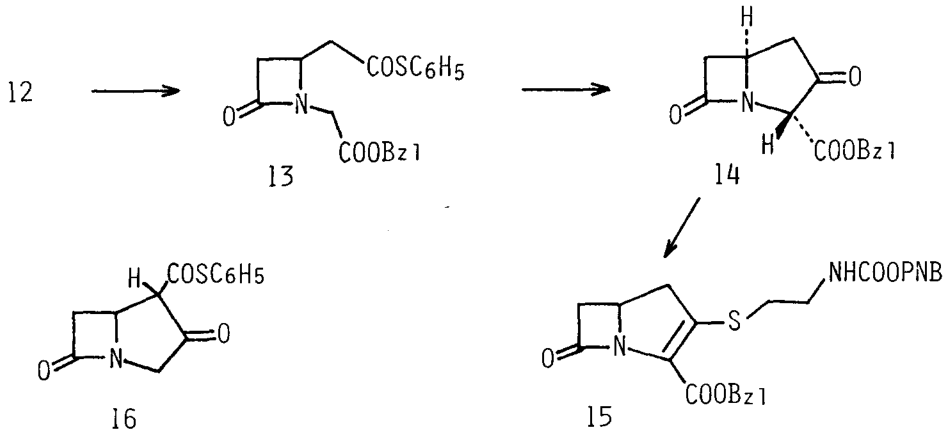
8, R = Bu^t

9, R = Bu^t

10, R = Bu^t, R'=CH_3
11, R = Bu^t, R'=Bzl
12, R = H, R'= Bzl

(1M KOH, MeOH, 0°C), followed by treatment of the potassium salt with benzyl chloride (TMEDA, DMF, 20°C). Removal of the t-butyl group of 11 was cleanly effected with 70% aqueous trifluoroacetic acid (20°C, 1 hr) to give the acid 12[9]

Dieckmann-type condensation reaction was examined on the active esters of the acid 12, including the acid chloride. Best results were obtained when the phenyl thioester of 12 was used. Thus, the acid 12 was converted into the acid chloride [$(COCl)_2$, pyridine, benzene], which was treated with thiophenol to yield the phenyl thioester 13[10] (95%). Treatment of 13 with 3.5 mol. equiv.[11] of $LiN[Si(CH_3)_3]_2$ (THF, -78°C, 5min), following column chromatography on silica gel gave the desired bicyclic ketoester 14[12] (79%), which was a single and thermodynamically stable isomer as shown[2f]. This reaction was highly regio-



13 14 15 16

selective[13], and the isomeric ketoester 16 was not detected in the reaction mixture.

The bicyclic keto ester 14 was then converted [(1) $(PhO)_2P(O)Cl$, i-Pr_2NEt, CH_3CN,-5°C, (2) $HSCH_2CH_2NHCOOPNB$, i-Pr_2NEt, CH_3CN, 0°C] into the carbapenem 15[14] in a similar manner to the method reported by Christensen et.al.[2f]. Total synthesis of thienamycin using this methodology is now in progress.

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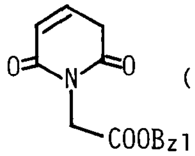
3. Recently, a similar Dieckmann-type condensation reaction has been reported in the synthesis of the 1,1-dimethyl substituted derivatives of the carbapenam 2; M. Shibuya, "Nagai Memorial Symposium", Tokushima, Japan, Dec., 1980.

4. I. Ugi and C. Steinbrukner, *Chem. Ber.*, 94, 2802 (1961); I. Ugi and E. Wishhöfen, *ibid.*, 95, 136 (1962); I. Ugi, *Angew. Chem.*, 74, 9 (1962).
5. H. Feuer and W.A. Swarts, *J. Am. Chem. Soc.*, 77, 5427 (1955); S.G. Cohen and E. Khedouri, *ibid.*, 83, 1093 (1961).
6. All new compounds had elemental analysis or exact parent mass spectrum measurements consistent with the proposed structures.
7. The compound 9: mp 75.5-78°; ν(nujol) 1770, 1730, and 1655 cm^{-1}; δ(100 MHz, $CDCl_3$) 1.45 (s, 9, t-Bu), 2.57 (dd, 1, J=16.4 and 5.8, H4'), 2.73 (dd, 1, J=16.4 and 6.3, H4'), 2.76 (dd, 1, J=14.9 and 3.5, H3), 2.82 (d, 3, J=4.9, $NHC\underline{H}_3$), 3.21 (dd, 1, J=14.9 and 5.1, H3), 3.88 (s, 2, $NC\underline{H}_2CO$), 4.03 (m, 1, H4), and 6.27 (m, 1, NH).
8. An attempt to prepare the benzyl ester 11 directly from 9 via the imino chloride was unsuccessful.
9. The compound 12: mp 138-139.5°; ν(nujol) 1752, 1745, and 1700 cm^{-1}.
10. The compound 13: mp 77-80°; ν(nujol) 1755, 1735, and 1720 cm^{-1}; δ(100 MHz, $CDCl_3$) 2.75 (dd, 1, J=14.9 and 2.4, H3), 2.92 (dd, 1, J=16.6 and 2.2, H4'), 3.23 (dd, 1, J=14.9 and 5.4, H3), 3.25 (dd, 1, J=16.6 and 2.2, H4'), 4.06 (ABq, 2, $NC\underline{H}_2CO$), 4.20 (m, 1, H4), 5.13 (s, 2, $OC\underline{H}_2Ar$), and 7.32, 7.39 (each s, Ar).
11. When equimolar amount of the base was used, no reaction occured at -78°C, but warming of the reaction mixture to 0°C resulted in near quantitative formation of the β-lactam cleavage product (i); ν(CH_2Cl_2) 1755, 1730, and 1690 cm^{-1}; m/e 259 (M^+).



(i)

12. The physical data of the bicyclic ketoester 14 corresponded well with those reported by Christensen et.al.[2f]; 14: mp 105-106° (Lit[2f]. mp 100-102°); ν(CH_2Cl_2) 1772 and 1746 cm^{-1}; ν(CCl_4) 1785, 1775, and 1746 cm^{-1}; δ(100 MHz, $CDCl_3$) 2.36 (dd, 1, J=18.8 and 7.8, H1), 2.85 (dd, 1, J=18.8 and 6.5, H1), 2.90 (dd, 1, J=16.1 and 2.0, H6β), 3.58 (dd, 1, J=16.1 and 4.9, H6α), 4.09 (m, 1, H5), 4.72 (s, 1, H3), 5.18 (s, 2, $C\underline{H}_2Ar$), and 7.34 (s, 5 Ar).
13. After the completion of this work, a regioselective Dieckmann-type condensation reaction with half-thiol diester has been reported; Y. Yamada, T. Ishii, M. Kimura, and K. Hosaka, *Tetrahedron Letters*, 22, 1353 (1981).
14. The compound 15: pale yellow powder; ν(CH_2Cl_2) 1785 and 1730 cm^{-1}; δ(100 MHz, $CDCl_3$) 2.92 (dd, 1, J=16.4 and 2.9, H6β), 2.88-3.10 (m, 2, $SC\underline{H}_2CH_2N$), 3.16 (broad dd, 2, J=16 and 9.7, H1), 3.30-3.53 (m, 2, $SCH_2C\underline{H}_2N$), 3.48 (dd, 1, J=16.4 and 5.3, H6α), 4.18 (m,· 1, H5), 5.19 and 5.29 (each s, $OC\underline{H}_2Ar$), and 7.27-8.26 (Ar).

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