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A NOVEL SYNTHESIS OF THE CARBAPEN-2-EM RING SYSTEM

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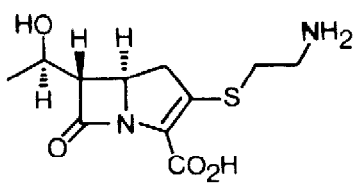
A new synthesis of the carbapenem ring system, as found in thienamycin and related natural products, has been developed. The key step involves a highly efficient carbene insertion reaction which produces the bicyclic ring system by forming the N-C3 bond.

Thienamycin (1), a highly potent and broad spectrum β-lactam antibiotic,[1] was recently isolated[2] from fermentations of the soil microorganism Streptomyces cattleya. It was the first structurally-determined[3] member of a growing family of natural products[4] that contain the novel carbapen-2-em ring system. The unprecedented biological activity of these compounds has prompted considerable synthetic activity which has resulted in total syntheses of thienamycin[5] and simpler carbapenem based analogs.[6,7] A common feature of these synthetic approaches is the formation of the C2-C3 bond as the penultimate step in the construction of the bicyclic nucleus. We now report a novel and highly efficient carbene insertion reaction (**2** → **3**)[8] which produces the bicyclic nucleus by forming the N-C3 bond.



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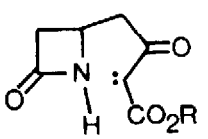

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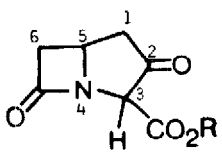

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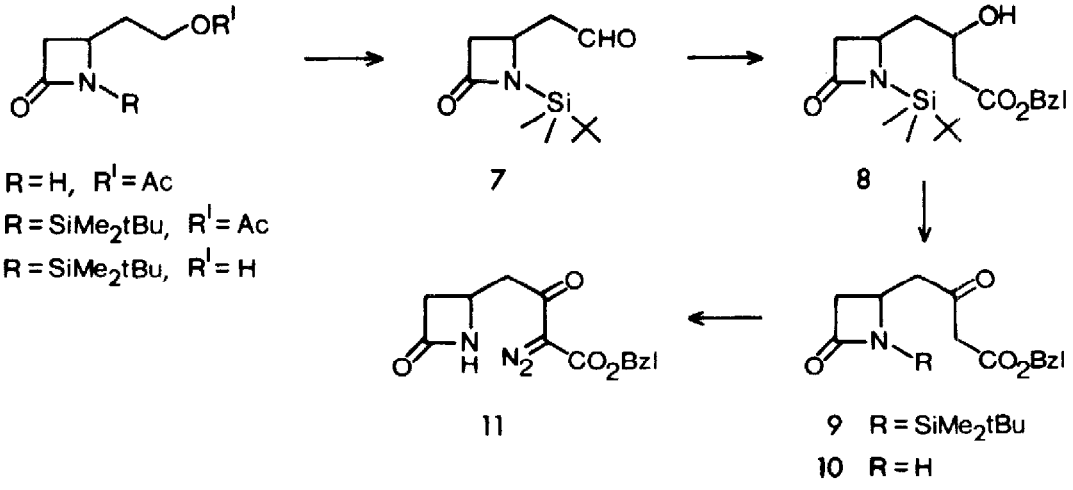
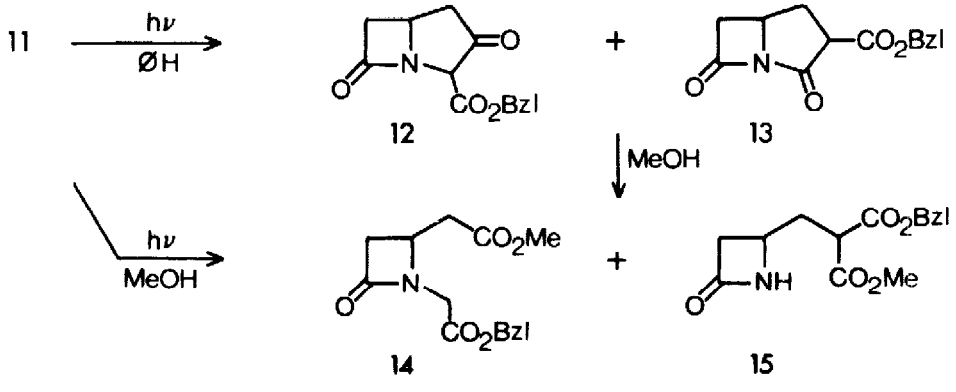
The requisite carbene precursor, α-diazo-β-ketoester **11**, was prepared in a straightforward manner from acetoxyethyl azetidinone **4**.[5] Protection of the nitrogen atom was achieved by silylation (t-BuMe$_2$SiCl, Et$_3$N, DMF, 0° to rt, 97%). We have found that the tert-butyldimethylsilyl group is ideal for this purpose since it is conveniently introduced, stable to most synthetic operations, and easily removed by mild acid hydrolysis. Deacetylation of **5**[9,10] (cat. NaOMe, MeOH, 0°, 55%) provided alcohol **6**[11] which was oxidized to aldehyde **7**[12] with Collins reagent[13] ($CrO_3 \cdot 2C_6H_5N$, CH_2Cl_2, rt, 74%). The remaining carbon framework was introduced by condensation of **7** with the lithium enolate of benzyl acetate (LDA, THF, -78°, 96%). Oxidation[13] of the resulting diastereomeric alcohols **8** gave **9** (73%) which was desilylated (1N HCl, MeOH, rt, 91%) to β-ketoester **10**. The carbene precursor **11** was then prepared by diazo exchange with p-carboxylbenzenesulfonyl azide[14] (Et$_3$N, MeCN, 0° to rt, 75%).

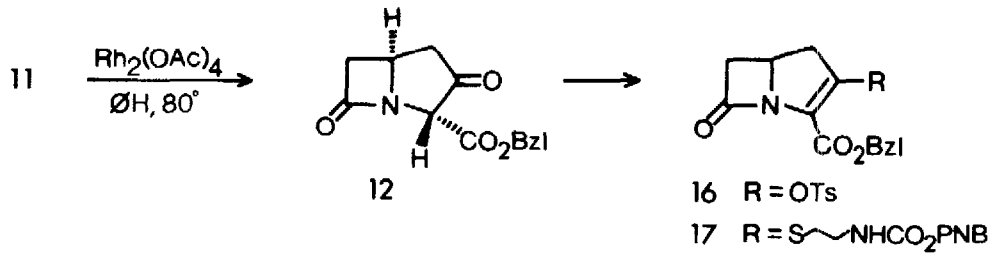


The decomposition of diazo ketoester **11** was examined both photochemically and catalytically. Photolysis (pyrex filter, ØH, rt) gave a 1:9 mixture of the desired product **12** and the relatively unstable imide isomer **13**. These products were readily distinguished by IR spectroscopy, the desired product showing a lactam carbonyl absorption near 1780 cm^{-1} and the isomer an 1825 cm^{-1} absorption. The bicyclic imide presumably arises by photolytic Wolff rearrangement[15] to a ketene intermediate which is trapped intramolecularly. Further evidence for the bicyclic structures was obtained by methanolysis of the photolysis mixture to give an easily separable, 1:9 mixture of diester **14**[16] and malonate **15**.



Metal catalyzed decomposition of the diazo ketoester proved more fruitful. After evaluation of a number of catalysts, we found that rhodium(II) acetate[17] (ca. 300:1 substrate-catalyst, ØH, 80°) effected the ring closure to **12** in near quantitative yield. Pure bicyclic ketoester **12** was obtained by direct crystallization (77-85%) as a single isomer having the thermodynamically preferred exo carboxylate orientation[18] as shown. No evidence for the enol tautomer was observed in either the crystalline or solution state. To our knowledge, this is the most efficient ring closure to a highly strained and reactive bicyclic β-lactam yet developed.

The bicyclic ketoester **12** was readily converted into carbapenems bearing the 2-thia substitution pattern found in thienamycin. Tosylation (Ts_2O, iPr_2NEt, CH_2Cl_2, 0°, 67%) provided the vinyl tosylate **16** which underwent selective addition of mercaptans to the 2-position. For example, condensation of **16** with N-(p-nitrobenzyloxycarbonyl) cysteamine (iPr_2NEt, DMF, -15°) afforded the thienamycin related derivative **17**. The extension of this methodology to the total synthesis of (+)-thienamycin and analogs will be the subject of forthcoming publications.



References and Notes

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2) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff and J. Birnbaum, J. Antibiot., **32**, 1 (1979).

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4) Other members of this family include epithienamycins A-D, P. J. Cassidy, E. O. Stapley, R. Goegelman, T. W. Miller, B. Arison, G. Albers-Schonberg, S. B. Zimmerman and J. Birnbaum, Abstract 81, 17th Intersci. Conf. Antimicr. Agents and Chemother., New York, N. Y., 1977; olivanic acids MM4550, MM13902, and MM17880, A. G. Brown, D. F. Corbett, A. J. Eglington and T. T. Howorth, J. C. S. Chem. Comm., 523 (1977) and D. F. Corbett, A. J. Eglington and T. T. Howorth, ibid., 953 (1977); and PS-5, K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, T. Ishikura and J. Lein, J. Antibiot., **31**, 480 (1978).

5) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard and B. G. Christensen, J. Amer. Chem. Soc., **100**, 313 (1978).

6) L. D. Cama and B. G. Christensen, ibid., **100**, 8006 (1978).

7) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale and R. Southgate, J. C. S. Chem. Commun., 236 (1979).

8) A related approach was used to construct the oxapenam ring system; L. D. Cama and B. G. Christensen, Tetrahedron Letters, 4233 (1978).

9) All new compounds gave IR, PMR, and mass spectra and elemental or high resolution mass spectral analyses consistent with the assigned structures.

10) Selected physical data. **5:** mp 36-37°; ν (film) 1740 cm^{-1}; δ ($CDCl_3$) 0.25 (s, 6, $2CH_3$), 0.98 (s, 9, $3CH_3$), 1.97 (m, 2, CH_2), 2.05 (s, 3, $COCH_3$), 2.67 (dd, 1, J = 2.8 and 15.2, H3a), 3.20 (dd, 1, J = 5.1 and 15.2, H3b), 3.62 (m, 1, H4), and 4.12 (t, 2, J = 6.1, CH_2OAc). **7:** mp 49-50°; ν ($CHCl_3$) 1735 and 1725 cm^{-1}; δ ($CDCl_3$) 0.23 (s, 3, CH_3), 0.27 (s, 3, CH_3), 0.98 (s, 9, $3CH_3$), 2.63 (ddd, 1, J = 1.2, 8.7, and 17.5, H4'a), 2.65 (dd, 1, J = 2.8 and 15.8, H3a), 3.07 (ddd, 1, J = 1.2, 4.3, and 17.5, H4'b), 3.37 (dd, 1, J = 5.5 and 15.8, H3b), 3.97 (m, 1, H4), and 9.78 (t, 1, J = 1.2, CHO). **9:** mp 41.5-43°; ν (CH_2Cl_2) 1740 and 1720 (sh) cm^{-1}; δ ($CDCl_3$) 0.18 (s, 3, CH_3), 0.22 (s, 3, CH_3), 0.97 (s, 9, $3CH_3$), 2.53 (dd, 1, J = 2.8 and 15.7, H3a), 2.63 (dd, 1, J = 9.5 and 17.5, H4'a), 3.13 (dd, 1, J = 3.9 and 17.5, H4'b), 3.28 (dd, 1, J = 5.3 and 15.7, H3b), 3.47 (s, 2, $COCH_2CO$), 3.88 (m, 1, H4), 5.17 (s, 2, $CH_2\phi$), and 7.33 (s, 5, C_6H_5). **11:** mp 102-103°; ν (CH_2Cl_2) 3405, 2133, 1758, 1712, and 1645 cm^{-1}; δ ($CDCl_3$) 2.63 (ddd, 1, J = 1.2, 2.6, and 15.0, H3a), 2.97 (dd, 1, J = 8.6 and 18.0, H4'a), 3.15 (ddd, 1, J = 2.3, 4.8, and 15.0, H3b), 3.40 (dd, 1, J = 4.6 and 18.0, H4'b), 3.98 (m, 1, H4), 5.27 (s, 2, $CH_2\phi$), 6.13 (m, 1, NH), and 7.38 (s, 5, C_6H_5). **12:** mp 100-102°; ν (CH_2Cl_2) 1770 and 1741 cm^{-1}; ν (CCl_4) 1783, 1773, and 1744 cm^{-1}; δ ($CDCl_3$) 2.43 (dd, 1, J = 8.0 and 19.1, H1a), 2.94 (dd, 1, J = 6.5 and 19.1, H1b), 2.99 (dd, 1, J = 2.0 and 16.0, H6β), 3.68 (dd, 1, J = 5.0 and 16.0, H6α), 4.18 (m, 1, H5), 4.76 (s, 1, H2), 5.23 (s, 2, $CH_2\phi$), and 7.40 (s, 5, C_6H_5). **16:** mp 103-105°; ν (CH_2Cl_2) 1786 and 1723 cm^{-1}; δ ($CDCl_3$) 2.44 (s, 3, CH_3), 3.03 (dd, 1, J = 3.0 and 17.0, H6β), 3.16 (dd, 1, J = 8.5 and 18.7, H1a), 3.32 (dd, 1, J = 10.0 and 18.7, H1b), 3.55 (dd, 1, J = 5.5 and 17.0, H6α), 4.21 (m, 1, H5), 5.14 (ABq, 2, J = 12, $CH_2\phi$), 7.35 (s, 5, C_6H_5), 7.26 and 7.75 (two d's, 4, J = 9, C_6H_4).

11) The N-tert-butyldimethylsilyl group is also subject to strong base cleavage as evidenced by formation of some 4-hydroxyethyl azetidinone in this reaction.

12) Aldehyde **7** has also been prepared from 4-allylazetidinone[7] by successive N-silylation and ozonolysis; F. DiNinno, unpublished results.

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14) J. B. Hendrickson and W. A. Wolf, ibid., **33**, 3610 (1968).

15) H. Meier and K. Zeller, Angew. Chem. Int. Edit., **14**, 32 (1975).

16) Bicyclic ketoester **12** is subject to facile retro-Dieckmann ring opening by a variety of nucleophiles. For example, treatment with cysteamine in DMF leads to a β-mercaptoethyl amide analogous to **14**.

17) Rhodium(II) acetate is an efficient catalyst for the insertion of diazoacetate into RX-H bonds; R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert and P. Teyssie, Tetrahedron Letters, 2233 (1973) and R. Paulissen, E. Hayez, A. J. Hubert and P. Teyssie, Tetrahedron Letters, 607 (1974).

18) Structure **12** has been confirmed by single crystal X-ray analysis; J. M. Hirshfield and J. P. Springer, unpublished results. Computer modeling studies suggest that the exo isomer is preferred over the endo isomer by ca. 4.5 kcal $mole^{-1}$.

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