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A FACILE SYNTHESIS OF BENZYL 3,7-DIOXO-1-AZABICYCLO[3.2.0]HEPTANE-2-CARBOXYLATE. A POTENTIAL PRECURSOR OF THIENAMYCIN AND CLAVULANIC ACID ANALOGS

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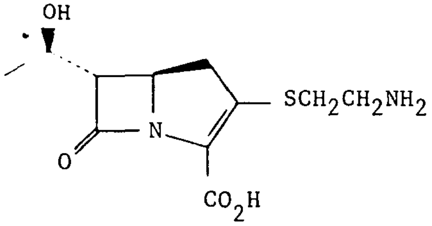
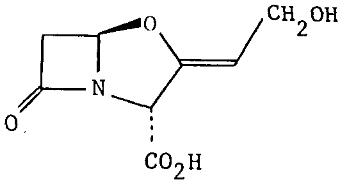
A novel, high yield synthesis of the 1-carbapenam ring system 3 is described in which the entire carbon framework is introduced in a single step from simple precursors.

Thienamycin (1) and clavulanic acid (2), new naturally occurring β-lactams with interesting biological activities, have been the subjects of considerable total synthetic effort. The 1-carbapenam ring system 3 is an attractive synthetic objective since it should be convertible into derivatives of both thienamycin and 1-carbaclavulanic acid. The synthesis of 3 (R=CH_3, $CH_2C_6H_5$) has been reported recently by three groups.[1-3] A novel, shorter route to 3 which produces its entire carbon framework in a single, high yield step from simple, inexpensive precursors is described here.



1



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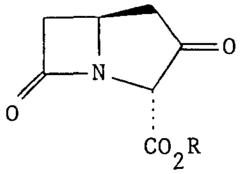
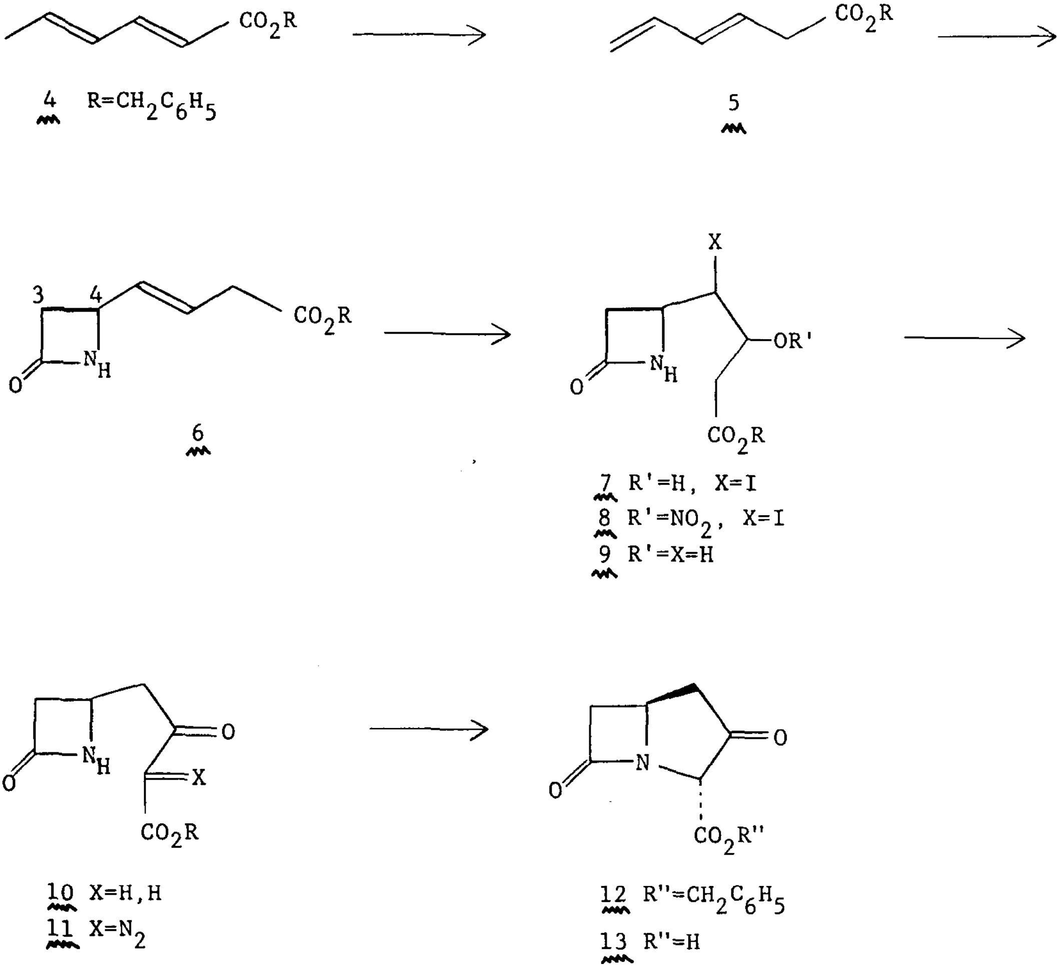


3

Benzyl sorbate 4 was isomerized to 3,5-hexadienoate 5 by kinetically quenching its lithium enolate (formed using LDA, HMPA, THF, -78°) with acetic acid.[4-6] This diene reacted smoothly with chlorosulfonyl isocyanate (CH_2Cl_2, $0^{\circ} \rightarrow$ rt) to give β-lactam 6 in 90% yield after a reductive workup (Na_2SO_3, K_2HPO_4, H_2O, rt).[7] Iodohydrin 7 (diastereomeric mixture) was prepared selectively from 6 in 79% yield (Ag_2O, HBF_4, I_2, H_2O, DME); none of the other regioisomer could be detected. The regiochemical assignment for 7 was supported by a PMR decoupling experiment on iodonitrate 8 (also a diastereomeric mixture of a single regioisomer) which was prepared similarly ($AgNO_3$ replaced Ag_2O + HBF_4). Reduction (nBu_3SnH, $(\emptyset CO_2)_2$, $\emptyset CH_3$, reflux) of 7 afforded alcohol 9 (78%)

which was converted to ketoester 10 in 46% yield by oxidation with Collins reagent ($CrO_3.2C_5H_5N$, CH_2Cl_2, rt). The ketoester also was prepared from 7 by Jones oxidation followed by reduction ($TiCl_3$, H_2O, CH3CN, rt). Diazo group transfer from tosyl azide to 10 (Et_3N, CH_3CN, rt)[8] produced 11 (78%) which underwent rhodium-catalyzed ring-closure[9] under very mild conditions ($Rh_2(OAc)_4$, CH_2Cl_2, rt, 20 min.) to give 12 in 96% yield. This molecule proved to be quite labile, and several attempts to convert it to the corresponding acid (13) were unsuccessful due to decomposition.



4 R=$CH_2C_6H_5$

5

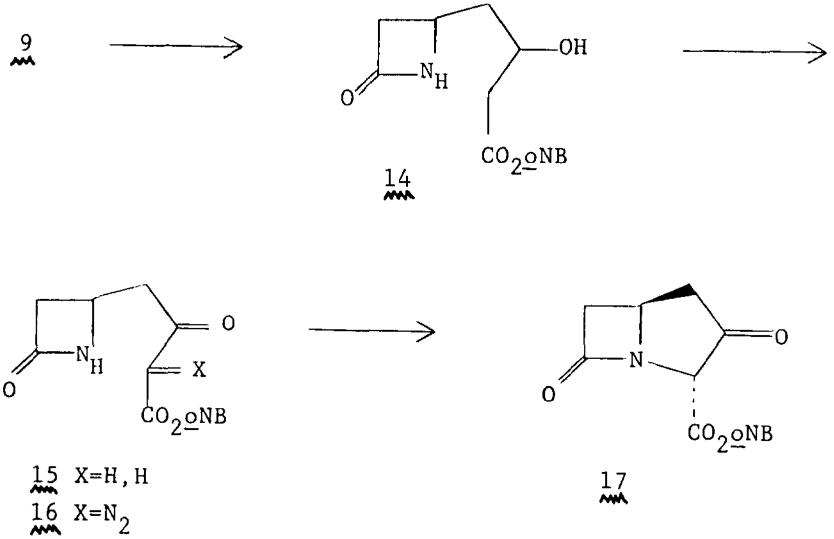
6

7 R'=H, X=I
8 R'=NO_2, X=I
9 R'=X=H

10 X=H,H
11 X=N_2

12 R''=$CH_2C_6H_5$
13 R''=H

In order to prepare **13**, an ester more readily cleaved than benzyl appeared necessary. Therefore, the photo-labile *o*-nitrobenzyl ester was produced. Careful hydrolysis of **9** (KOH, H_2O, THF, 2.5 hr. at max. pH 12.5) followed by esterification of the resulting potassium salt with *o*-nitrobenzyl bromide (DMF, rt) gave **14** which was then converted to **17** in a manner analogous to that used in the benzyl ester series [Jones oxidation to **15** (53%), diazo exchange to **16** (65%) and ring closure (43%)]. Attempts to prepare acid **13** from **17** were also unsuccessful.



9

14

15 X=H,H

16 $X=N_2$

17

Various derivatives of **3** have been reported including analogs of thienamycin.[1,3] Some of these compounds were sufficiently stable to alkali to allow the ester group to be hydrolyzed by the careful addition of base. Conversion of **12** to 1-carbaclavulanic acid derivatives remains to be reported.

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References and Notes

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5. All new compounds gave IR, NMR (^1H and ^{13}C) and elemental or high resolution mass spectral analyses consistent with the assigned structures.
6. Selected physical data. **4**: bp 124-8°C at 0.6 mm; ν (film) 1709 cm^{-1}. **5**: bp 125-8°C at 1.0 mm; ν (film) 1724 cm^{-1}; δ ($CDCl_3$) 3.12 (d, 2, J = 6.0, CH_2CO_2), 5.10 (s, 2, $\underline{CH_2}\phi$), 5.13 (m, 2, $\underline{CH_2}$ = CH), 6.00 (m, 3, CH_2=$\underline{CH}$-$\underline{CH}$=$\underline{CH}$-), 7.33 (s, 5, C_6H_5). **6**: mp 47.5-9°C; ν (CH_2Cl_2) 3410, 1765, 1735 cm^{-1}; δ ($CDCl_3$) 2.58 (ddd, 1, J = 1.5, 2.8 and 15,H_{3a}), 3.10 (d, 2, J = 5.0, CH_2CO_2), 3.13 (ddd, 1, J = 1.5, 5.0 and 15, H_{3b}), 4.05 (m, 1, H_4), 5.12 (s, 2, $\underline{CH_2}\phi$), 5.76 (m, 2, CH=CH), 6.75 (m, 1, NH), 7.33 (s, 5, C_6H_5). **7** (diastereomeric mixture): ν (CH_2Cl_2) 3600-3200, 1761, 1733 (sh) cm^{-1}; δ ($CDCl_3$) 2.80 (m, 4, H_{3a}, H_{3b}, CH_2CO_2), 3.6 - 4.4 (br m, 4, H_4, $\underline{CH}$I-$\underline{CH}$O$\underline{H}$), 5.11 (s, 2, $\underline{CH_2}\phi$), 6.33 and 6.63 (br m, 1, NH). **8** (diastereomeric mixture): ν (CH_2Cl_2) 1773, 1733, 1647 cm^{-1}; δ ($CDCl_3$) 2.90 (m, 4, H_{3a}, H_{3b}, CH_2CO_2), 3.58 (m, 1, H_4), 4.25 (m, 1, CHI), 5.15 (s, 2, $\underline{CH_2}\phi$), 5.31 (m, 1, $CHONO_2$), 6.23 and 6.63 (br m, 1, NH) 7.35 (s, 5, C_6H_5). **9** (diastereomeric mixture): mp 80.5-1.5°C (single diastereomer from EtOAc); ν (CH_2Cl_2) 1747, 1725 (sh) cm^{-1}; δ ($CDCl_3$) 1.72 (t, 2, J=7.0, $\underline{CH_2}$CHOH), 2.52 (d, 2, J = 6.5, CH_2CO_2), 2.53 (m, 1, H_{3a}), 3.05 (m, 1, H_{3b}), 3.45-4.30 (m, 3, H_4, C$\underline{H}$O$\underline{H}$), 5.10 (s, 2, $\underline{CH_2}\phi$), 6.68 (m, 1, NH), 7.27 (s, 5, C_6H_5). **10**: mp 54-6°C. Other physical data for **10**-**12** agreed with those reported for these compounds.[1,2] **14** (mixture of diastereomers): mp 96.5-107.5°C. **16**: mp 142-3°C. **17**: mp 151-2°C. Spectra of **14**-**17** closely resembled those of the corresponding benzyl esters with the expected differences.
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