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SYNTHESIS OF SOME 4-ACYLOXY-7-OXO-1-AZABICYCLO [3.2.0]HEPT-2-ENE-2-CARBOXYLATES

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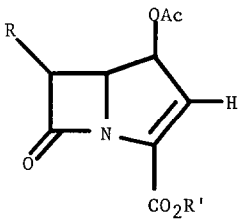
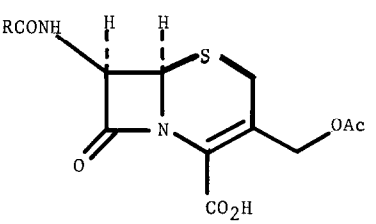
Summary: Allylic oxidation of 4-allyl-1-dimethyl-t-butylsilylazetidin-2-ones (5,7) gave the 4-(1-hydroxyprop-2-ene-1-yl) derivatives (6,8). Radical benzoyloxylation of the silylated 8-oxo-7-azabicyclo[4.2.0]oct-3-ene (18) provided four allylic monobenzoates. Progression of (8) and (29) afforded, respectively, 4-acyloxy olivanic acid analogues containing **trans-** (16) and **cis-** (31) substituents at C-6.

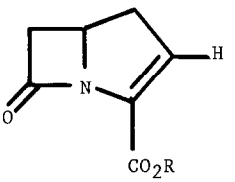
4-Acyloxy olivanic acids (1), together with corresponding derivatives in the 1-carbadethiacephem series,[1] may be envisaged as activated 'endo-substituted' analogues of the naturally occurring 3-acetoxymethyl cephems (2). Recently preparations of a simple



(1)



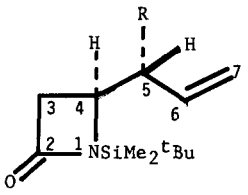
(2)



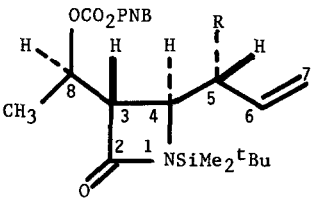
(3) R = PNB
(4) R = Na

acetoxy derivative (1; R = H, R' = PNB) from 4-vinyl azetidinone,[2] and of 4-hydroxy and 4-methoxy variants of (1)[3] have been described.

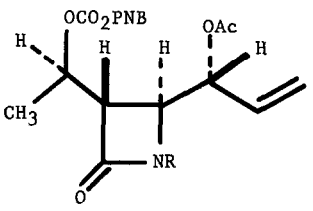
We now report our syntheses of type (1) derivatives employing allylic oxidation reactions of olefinic precursors. Owing to the labile nature of the parent ester (3) and its sodium salt (4),[4] we were unable to achieve allylic oxidation or bromination of the bicyclic species. Surprisingly, 1-dimethyl-t-butylsilyl-4-allyl azetidinones were resistant to radical bromination (NBS, AIBN, PhH, Δ). However, silylated azetidinones (5) and (7)[5] were oxidised under Sharpless' conditions (SeO_2, t-BuO_2H , MDC, 50°C)[6,7] to give alcohols (6)[8] and (8), respectively (**ca** 35%). Product (8) was a mixture of alcohol epimers (8:1 ratio). On the basis of coupling constant data,[9] we assign the (3RS, 4RS, 5SR, 8SR) stereochemistry to the major isomer. Acetylation (Ac_2O, MDC, Et_3N, DMAP) of the latter gave (9) (86%). Desilylation (KF, MeOH) to (10) (71%) and conversion **via** glyoxylate (11) to phosphorane (12)



(5) R = H
(6) R = OH

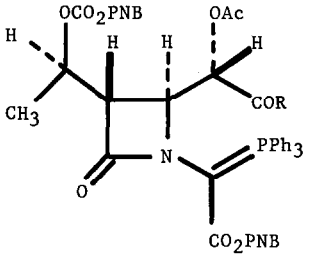


(7) R = H
(8) R = OH
(9) R = OAc

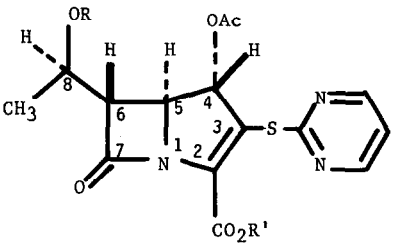


(10) R = H
(11) R = CH(OH) CO_2PNB
(12) R = $C(PPh_3)CO_2PNB$

PNB = p-$NO_2C_6H_4CH_2$ throughout



(13) R = OH
(14) R = S



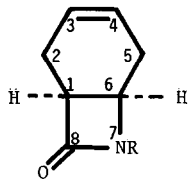
(15) R = PNBOCO, R' = PNB
(16) R = H , R' = Na

Reagents: (12→13); i, O_3, EtOAc, TFA, -70°C. ii, m-CPBA, 86%. (13→14); i, $(EtO)_2POCl$ (1.2 equiv), Et_3N, THF, room temp., 2h. ii, Lithium 2-pyrimidinyl thiolate (1.2 equiv) 5h. (14→15); toluene, Δ, 2.5h, 68%. (15→16) H_2, Pd-C, H_2O-diox, 2.5h, 77%.

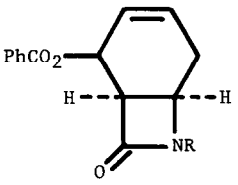
followed our established procedures.[4] Ozonolysis of the double bond followed by oxidative work-up of the ozonide gave carboxylic acid (13). Conversion to the 2-pyrimidinyl thioester (14), and subsequent cyclisation in refluxing toluene gave the (4RS, 5SR, 6SR, 8RS) bicyclic azetidinone (15). Hydrogenolysis provided sodium salt (16) in good yield. In contrast to its 4-unsubstituted counterpart, prepared previously in these laboratories,[10] salt (16) did not possess broad spectrum antibacterial activity. However, spectroscopic evidence did indicate that the compound was unstable in aqueous solution.

Previously, we have described[4] a strategy for the preparation of **cis**- carbapenem analogues from the cyclohexa-1,4-diene-derived β-lactam (17). N-Silylation of this material (Me_2Bu^tSiCl, imidazole, DMF) provided a substrate (22) amenable to Kharasch-Sosnovsky oxidation ($PhCO_3Bu^t$, CuCl, PhH, Δ, 24h).[11, 12] This afforded all four regioisomeric monobenzoates (23) (25%), (24) (17%), (25) (18%), and (26) (20%).[13] [A similar reaction of the 1-diphenyl-t-butylsilyl azetidinone (27) directed the oxidation to favour (28) (35%) at the expense of the corresponding 5-benzoyloxy isomer (29)]. Desilylation (KF, MeOH) gave unprotected isomers (18 - 21).[14]

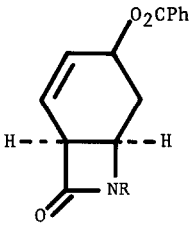
Isomer (21) was elaborated to phosphorane (30).[4] A subsequent ozonolysis - cyclisation sequence [i, O_3, TFA, EtOAc, -70°C; ii, Ph_3P, -70-0°C; iii, $NaHCO_3$ (aq)] gave



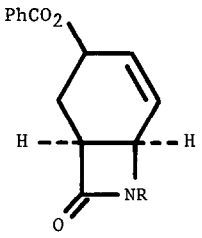
(17) R = H
(22) R = $SiMe_2{}^tBu$
(27) R = $SiPh_2{}^tBu$



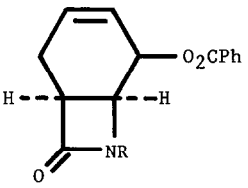
(18) R = H
(23) R = $SiMe_2{}^tBu$
(28) R = $SiPh_2{}^tBu$



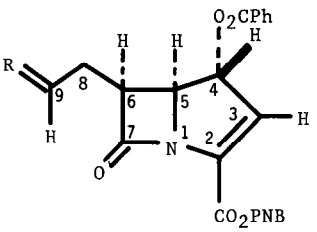
(19) R = H
(24) R = $SiMe_2{}^tBu$



(20) R = H
(25) R = $SiMe_2{}^tBu$



(21) R = H
(26) R = $SiMe_2{}^tBu$
(29) R = $SiPh_2{}^tBu$
(30) R = $C(PPh_3)CO_2PNB$



(31) R = O
(32) R = $CHCO_2CH_3$

the bicyclic aldehyde - benzoate (31) (59%). This 4-benzoyloxy olivanate derivative was characterised further by reaction with carbomethoxymethylenetriphenyl phosphorane, yielding the acrylate (32) (66%). We have also studied isomers (18) and (19) as potential precursors of bicyclic β-lactams and will present the results in our full paper.

References and Notes

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8. All compounds prepared are racemic; where it is necessary to indicate relative stereochemistry, one isomer is depicted. All new compounds were homogeneous (tlc or hplc) and exhibited satisfactory spectral properties.

9. Selected ^{1}H m.r. data for major isomer (9): $\delta(CDCl_3)$ 3.69 (1H, t, $J \simeq 2.5$ Hz, 4-H), 4.41 (1H, br d, J 6Hz, 5-H). Decoupling experiments show $^3J_{4,5} \simeq 1$-2 Hz. Inspection of models indicates that a dihedral angle $\theta \simeq 80$-100° (Karplus equation) is best accommodated for the (3RS, 4RS, 6SR, 8SR) relative stereochemistry.

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13. Although we are reluctant to assign the stereochemistries of (23-26) from coupling constant data, we have in each case rigorously proved the regiochemistry of substitution by ^{1}H decoupling experiments. Each was a single stereoisomer.

14. We have also obtained a corresponding series of allylic bromides from (22) (NBS, AIBN, PhH, Δ).

15. Both **cis**- carbapenem systems (31) and (32) showed $^3J_{5,6} = 6$Hz, and $^3J_{4,5\alpha} = 7.5$Hz. Since (32) was unaffected on treatment with DBU in ethyl acetate at room temperature, we consider that the benzoyloxy group adopts the thermodynamically favourable 4α-configuration.

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