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STEREOCONTROLLED ENTRY TO 1-OXAPENAMS AND 1-OXACEPHEMS FROM CARBOHYDRATES

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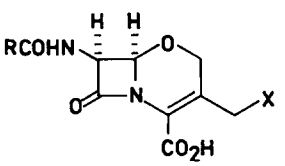
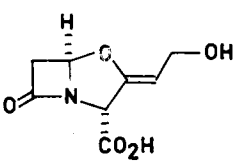
Abstract - N-Benzyl-2-carboxy-2-deoxypento and hexopyranosylaminolactams readily available *via* addition of trichloroacetyl isocyanate to substituted glycals, were transformed into enantiomerically pure N-benzyl-4-alkoxy-3-hydroxymethylazetidinones-2. The transformation involved the glycolic cleavage which was followed by sodium borohydride reduction. The above compounds can serve as starting materials for the synthesis of 1-oxapenams and 1-oxacephems.

The synthesis of 1-oxapenams and 1-oxacephems, which are exemplified here by structures 1-3, carries with itself a stereochemical problem of stereocontrolled formation of a desired configuration at the carbon atom bearing oxygen and nitrogen atoms. Similar problem has been encountered during the synthesis of N-glycoside type compounds. Therefore, planning an entry to 1-oxa-analogs of β-lactam antibiotics we directed our attention toward sugar precursors.



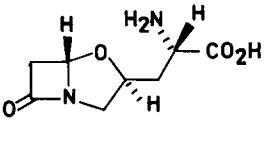
1-oxacephalosporins

1



clavulanic acid

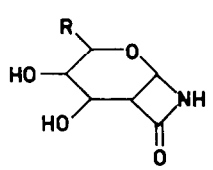
2



clavalanine (Ro 22-5417)

3

Recently, we have reported a simple synthesis of sugar β-lactams 4 *via* (2+2)cycloaddition of trichloroacetyl isocyanate to glycals.[1] Owing to the high stereoselectivity of this process and to a variety of sugar precursors available, compounds 4 can be used as a wide base for stereocontrolled synthesis of selected β-lactams with 1-oxabicyclic structure. In this paper we describe a general synthetic scheme based on readily available compounds 5 and 6.

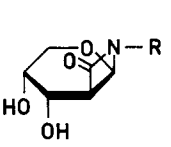


4: R=H, CH_3, CH_2OH

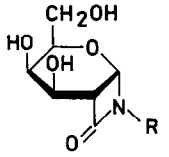
β-Lactams 5 and 6 were benzylated at the nitrogen atom in the three steps procedure[2] to give 7 and 8 respectively in 84% overall yield.

Glycolic cleavage of a vic-diol grouping with sodium periodate under standard conditions.[3] leads to the formation of reactive dialdehyde 9 which further undergoes an intramolecular aldol

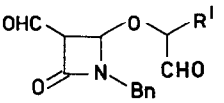
condensation. Therefore, control of the reaction time, temperature, and pH is necessary in order to achieve desired product.



5: R=H
7: R=Bn



6: R=H
8: R=Bn

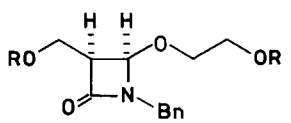


9: R′=H
10: R′=CH_2OH

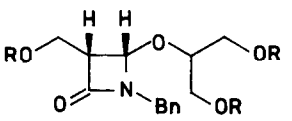
A solution of 7 (ca. 2%) in methanol/water (1:1) treated with sodium periodate (1 mol equiv.) at -5^{o}, in the presence of ammonium sulfate (3 mol equiv.) afforded the dialdehyde 9 which was immediately reduced, without isolation, with sodium borohydride to give the diol 11 with 3S, 4R configuration at the azetidinone ring; 82%, $(\alpha)_D$ $+52.4^{o}$ (c 1.7, $CHCl_3$). Compound 8 under the same conditions gave a triol 12 with 3R, 4S configuration; 78%, $(\alpha)_D$ -33.0^{o} (c 1, MeOH). On the other hand, oxidation of 7 in methanol/water solution at -5^{o}, in the presence of sodium hydrogencarbonate (pH 8), followed by sodium borohydride reduction[4] furnished a mixture of *trans* compound 13 with 3R, 4R configuration, $(\alpha)_D$ $+35.0^{o}$ (c 1, MeOH), and two bicyclic compounds: 14 m.p. 175-176°, $(\alpha)_D$ -68.0^{o} (c 1, MeOH), and 15 m.p. 89-91°, $(\alpha)_D$ -51.5^{o} (c 1, MeOH), in a ratio of about 5:3:1 respectively. Prolongation of the reaction time, owing to the reversibility of the base catalyzed aldol condensation led after 20 h to a 1:1 mixture of compounds 14 and 15 (85%).

The structure and configuration of β-lactams 11 - 15 were proved on the basis of analytical and spectral data taken for the respective acetates 16 - 20.[5]

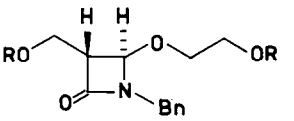
The methodology showed by us opens an attractive access to a variety of 1-oxapenams and 1-oxacephems, and offers full stereocontrol at the carbon atom being crucial for biological activity of β-lactam antibiotics.



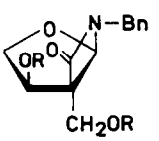
11: R=H
16: R=Ac



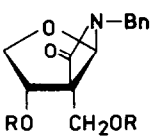
12: R=H
17: R=Ac



13: R=H
18: R=Ac



14: R=H
19: R=Ac



15: R=H
20: R=Ac

ACKNOWLEDGMENT

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REFERENCES

1. M. Chmielewski and Z. Kałuza, *J. Org. Chem.*, 51, 2395 (1986); M. Chmielewski and Z. Kałuza, *Carbohydr. Res.*, to be published; M. Chmielewski, Z. Kałuza, W. Abramski, D. Mostowicz, B. Hintze, and C. Bełzecki, *Bull. Polon. Acad.: Chem.*, to be published.

2. Trimethylsilyl chloride and pyridine silylation of 5 and 6 was followed with benzylation in boiling benzene in the presence of potassium carbonate and tetrabutylammonium bromide as a catalyst. Methanolysis of crude persilylated compounds in the presence of DOWEX 50 WX 8 ion exchange resin afforded 7 and 8 respectively (84%).
7: m.p. 134-135°; $[\alpha]_D$ -92.2° (c 1, CH_2Cl_2); ir ($CHCl_3$): 1760 cm^{-1}; ^{1}H-n.m.r. (DMSO-d_6): 3.15 (t, 1 H, J_{12}= 4.33, J_{23}= 4.52 Hz, H-2), 3.45 (dd, 1 H, H-5), 3.53 (dd, 1 H, H-5′), 3.63 (m, 1 H, H-4), 3.85 (m, 1 H, H-3), 5.14 (d, 1 H, H-1).
8: m.p. 112-114°; $[\alpha]_D$ +81.7° (c 1, MeOH); ir (nujol): 1730 cm^{-1}; ^{1}H-n.m.r. (DMSO-d_6): 2.76 (t, 1 H, J_{12}= 4.5, J_{23}= 5.3 Hz, H-2), 3.1 - 3.3 (m, 3 H, H-5, 6, 6′), 3.38 (d, 1 H, J_{34}= 3.8 Hz, H-4), 3.52 (dd, 1 H, H-3), 4.99 (d, 1 H, H-1).

3. R. D. Guthrie, *Methods Carbohydr. Chem.*, Ed. R. L. Whistler, Academic Press 1962, Vol I, (125) 445.

4. It was essential to reduce the dialdehyde 9 with sodium borohydride 30 min after the periodate cleavage of the diol grouping in 7. Prolongation of the reaction time led to the selfcondensation of 9 .

5. Analytical and spectral data of compounds 16 - 20:
16: colorless syrup; $[\alpha]_D$ +12.0° (c 1.7, $CHCl_3$); ir ($CHCl_3$): 1755 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.54 (m, 1 H, H-3), 3.59, 4.11 (2m, 4 H, OCH_2CH_2OAc), 4.37 (dd, 1 H, J_{3A}= 8.3, J_{AB}= 11.7 Hz, CH_AH_BOAc), 4.44 (dd, 1 H, J_{3B}= 5.0 Hz, CH_AH_BOAc), 4.86 (d, 1 H, J_{34}=3.8 Hz, H-4).
17: colorless syrup; $[\alpha]_D$ -10.0° (c 1.4, $CHCl_3$); ir ($CHCl_3$): 1760 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.55 (m, 1 H, J_{3A}= 8.1, J_{3B}= 4.9, J_{34}= 3.9 Hz, H-3), 3.76 [m, 1 H, $OCH(CH_2OAc)_2$], 3.9 - 4.2 (m, 4 H, $2CH_2OAc$), 4.33, 4.48 (m, 2 H, CH_AH_BOAc), 5.06 (d, 1 H, H-4).
18: colorless syrup; $[\alpha]_D$ +39.1° (c 0.34, $CHCl_3$); ir ($CHCl_3$): 1760 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.33 (m, 1 H, H-3), 3.62, 4.15 (2m, 4 H, OCH_2CH_2OAc), 4.28 (m, 1 H, CH_AH_BOAc) 4.77 (d, 1 H, J_{34}= 1.0 Hz, H-4).
19: m.p. 49-51°; $[\alpha]_D$ -71.0° (c 1, MeOH); ir ($CHCl_3$): 1770 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.85, 4.43 (2dd, 2 H, H-5, 5′), 4.34, 4.56 (2d, 2 H, CH_2OAc), 5.04 (dd, 1 H, H-4), 5.25 (s, 1 H, H-1).

20: m.p. 69-71°; $[\alpha]_D$ -54.0° (c 1, MeOH); ir ($CHCl_3$): 1765 cm^{-1}; ^1H-n.m.r. ($CDCl_3$): 4.16 (m, 2 H, H-5, 5'), 4.41, 4.48 (2d, 2 H, CH_2OAc), 5.44 (m, 1 H, H-4), 5.44 (s, 1 H, H-1).

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