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SYNTHESIS OF ENANTIOMERICALLY PURE PRECURSORS OF CARBAPENEMS FROM CARBOHYDRATES

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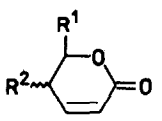
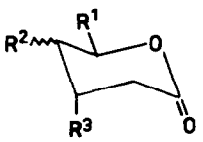
Abstract: Conjugate addition-rearrangement of N-p-metoxybenzylhydroxylamine to α,β-unsaturated sugar lactones followed by hydrogenolysis of the O-N bond in isoxazolidin-5-ones, and subsequent cyclization of the resulting β-amino acid, provides an effective route to 4-substituted azetidinones.

The Michael addition of hydrazoic acid or O-benzylhydroxylamine to the α,β-unsaturated lactones **1** proceeds exclusively anti with regard to the terminal acetoxymethyl group, to produce the unstable adduct **2**[1,2] which easily undergoes retro addition.



1



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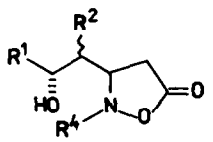
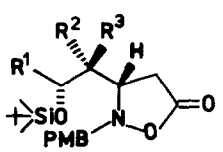


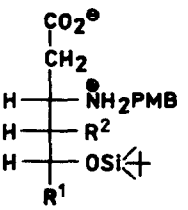
3

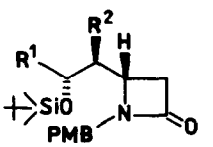
R^1=H, CH_2OAc; R^2=H, OAc; R^3=N_3, NHOBn; R^4=CH_3, C_6H_{11}, *p*-$CH_2C_6H_4OCH_3$(PMB)

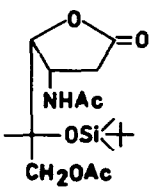
Owing to the rearrangement of the lactone ring to form the isoxazolidin-5-one, the conjugate addition of *N*-substituted hydroxylamines to compounds **1** provides an effective and a stereospecific route to the stable products **3** which can be utilized in the synthesis of selected structures.[3] The structural feature of **3**, such as the β-amino acid fragment present within the molecule, and the absolute configuration at the C-3 of the isoxalidin-5-one ring prompted us to investigate the sequence of reactions leading to the synthetic intermediate for the carbapenem antibiotics.

Isoxazolidin-5-ones bearing p-methoxybenzyl at the nitrogen atom **4-7**, prepared by the known procedure[3], were used for our studies.









4: R^1=R^2=R^3=H
5: R^1=CH_2OAc, R^2=R^3=H
6: R^1=CH_2OAc, R^2=H, R^3=OAc
7: R^1=CH_2OAc, R^2=OAc, R^3=H

8: R^1=R^2=H
9: R^1=CH_2OAc, R^2=H
10: R^1=CH_2OAc, R^2=OAc

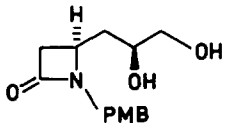
11: R^1=R^2=H
12: R^1=CH_2OAc, R^2=H
13: R^1=CH_2OAc, R^2=OAc

14

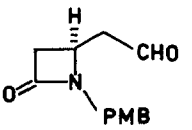
Compounds **4** - **6**, dissolved in methanol and hydrogenated over 10% Pd/C at r.t. for 30 min gave β-amino acids **8**, **9**, and **10** respectively in a good yield. Cyclization of **8**, **9** and **10** (0,12 mmol) in CH_2Cl_2 (20 ml) with 2-chloro-N-methylpyridinum iodide (0,13 mmol) and triethylamine (0,26 mmol) after 30 min afforded **11**, **12**, and **13** respectively.[4] In the case of **7**, the hydrogenation leads to the opening of the isoxazolidinone ring which is fol-

lowed by the rapid migration of the acetyl residue from the neighbouring oxygen to the nitrogen atom, and removal of the p-methoxybenzyl substituent. In the consequence, the subsequent cyclization affords the lactone **14**.[4]

The deacetylation of **12** with ammonia in methanol followed by the desilylation with tetrabutylammonium fluoride gives the diol **15**[4] which was subsequently subjected to the glycolic cleavage. Compound **15** (24 mg) dissolved in the methanol-water 1:1 mixture (2 ml) was treated with tetrabutylammonium metaperiodate (39 mg) and was left for 2 hrs. The standard work up and the chromatographic purification yielded **16** (18 mg, 89%).



15



16

In conclusion, we presented a new stereocontrolled approach to the carbapenem antibiotics from carbohydrate precursors,[5] which is the second example based on the Michael addition of hydroxylamine to the unsaturated esters.[6]

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References and notes

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3. I. Panfil, S. Maciejewski, C. Belżecki, M. Chmielewski, *Tetrahedron Lett.*, 30, 1527, (1989)
4. **11** : syrup; IR (film): 1760 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): 1.57 (m, 1H, H-1a'), 1.92 (m, 1H, H-1b'), 2.65 (dd, 1H, J 1.9, 14.6 Hz, H-3a), 2.95 (dd, 1H, J 5.0 Hz, H-3b), 3.59 (m, 1H, H-4), 3.62 (m, 2H, H-2a', 2b'), 3.78 (s, 3H, OCH_3), 4.04, 4.48 (2d, 2H, benzyl).
12 : syrup; $[\alpha]_D$ -10.6° (*c* 0.53, CH_2Cl_2); IR (film): 1760 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): 1.46 (ddd, 1H, H-1a'), 1.90 (ddd, 1H, H-1b'), 2.04 (s, 3H, OAc), 2.62 (dd, 1H, J 1.9, 14.5 Hz, H-3a), 3.01 (dd, 1H, J 4.9 Hz, H-3b), 3.58 (m, 1H, H-4), ~3.8 (m, 1H, H-2'), 3.80 (s, 3H, OCH_3), 3.88 (m, 2H, H-3a', 3b'), 4.07, 4.52 (2d, 2H, benzyl); MS m/z : 364 (M-57), 333 (M-88), 322 (M-99), 280 (M-141).
13 : syrup; $[\alpha]_D$+2.3° (*c* 0.53, CH_2Cl_2); IR (film): 1760 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): 2.04, 2.10 (2s, 6H, 2OAc), 2.81 (dd, 1H, J 5.1, 14.5 Hz, H-3a), 3.06 (dd, 1H, J 1.4 Hz, H-3b), 3,67 (m, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.86, 4.64 (2d, 2H, benzyl), 3.88 (dt, 1H, H-2'), 3.93 (dd, 1H, J 4.7, 11.5 Hz, H-3a'), 3.97 (dd, 1H, J 5.8 Hz, H-3b'), 5.17 (dd, 1H, J 1.4, 4.8 Hz, H-1'); MS m/z : 422 (M-57), 392 (M-99), 280 (M-141).
14 : m.p. 151-152°C; $[\alpha]_D$-71.2° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 3460 (NH), 1795 (C=O lactone), 1750 (acetyl), 1690 cm^{-1} (amide); ^{1}H-n.m.r. ($CDCl_3$) : 2.02, 2.08 (2s, 6H, 2 acetyl), 2.52 (dd, 1H, J 9.1, 17.4 Hz, H-2), 2.82 (dd, 1H, J 9.5 Hz, H-2'), 4.06 (ddd, 1H, J 2.2, 5.3, 7.2 Hz, H-5), 4.11 (dd, 1H, J 10.6 Hz, H-6), 4.25 (dd, 1H, H-6'), 4.72 (dd, 1H, J 7.9 Hz, H-4), 5.02 (m, 1H, H-3); MS m/z :360(M+1), 344(M-15), 302 (M-57), 260 (M-99).
15 : m.p. 85-86°C; $[\alpha]_D$ -4.5 (*c* 0.73, CH_2Cl_2); IR ($CHCl_3$); 1760 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$) : 1.44 (ddd, 1H, H-1a'), 1.86 (ddd, 1H, H-1b'), 2.69 (dd, 1H, J 2.2, 14.5 Hz, H-3a), 3.07 (dd, 1H, J 5.0 Hz, H-3b), 3.38 (bt, 1H, H-3a'), 3.57 (bd, 1H, H-3b'), 3.69 (m, 2H, H-4, 2'), 3.80 (s, 3H, OCH_3), 4.14, 4.51 (2d, 2H, benzyl); MS m/z : M^+, 265.0.
16 : syrup; $[\alpha]_D$ -4.0 (*c* 0.43, CH_2Cl_2; IR (film): 3400 (OH), 1740 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$) : 2.62 (ddd, 1H, J 0.8, 6.6, 18.1 Hz, H-1a'), 2.64 (dd, 1H, J 2.4, 14.8 Hz, H-3a), 2.73 (ddd, 1H, J 1.1, 6.3 Hz, H-1b'), 3.19 (dd, 1H, J 5.1 Hz, H-3b), 3.94 (m, H1, H-4), 4.21, 4.39 (2d, 2H, benzyl), 9.63 (t, 1H, H-2'), MS m/z : M^+233.
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6. S.W. Baldwin, J. Aube, *Tetrahedron Lett.*, 28, 179 (1987).

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