Syntheses of Sugar-derived Heterotricyclic Lactams

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Following stereoselective addition of *N*-iodosuccinimide towards glycals and subsequent dehalogenation, glycosylimides **1** and **2** are obtained and converted by irradiation to yield the azepindione derivatives **3** and **4** and the [5.3.1.$0^{2,6}$] tricyclic alcohols **5** and **6**; their prolonged irradiation gives highly functionalised bridged heterotricyclic lactams **10** and **11** with a cyclopentane backbone.

Bi- and tri-cyclic azepindiones, especially the benzazepindione or benzodiazepine derivatives, are well-established pharmaceuticals with many applications ranging from psychopharmacy[1] to calcium antagonists in the treatment of cardiovascular diseases[2] as well as potent inhibitors of the HIV-1 reverse transcriptase.[3] The constant demand for new compounds containing the annelated azepine ring as well as the carboxamide[4] function prompted our interest in the syntheses of sugar-derived azepindiones. We report here the synthesis and structure elucidation of a new subclass of the 1,5-azepindione family.†

As known from previous investigations,[5] the glycosylimides may be selectively transformed in a Norrish type II process[6,7] towards tricyclic aminals or the azepindione derivatives, depending on both the individual monosaccharide and its protecting groups (Scheme 1).[5,8,9] Pentopyranose derivatives give exclusively lactams such as **3** or **4**. Hexopyranose compounds yield predominantly or exclusively tricyclic alcohols such as **5** or **6**.[5] *En route* to **5** or **6** the carbonyl group of the imide is alkylated intramolecularly and transformed stereoselectively into a bridgehead hemiaminal with another adjacent quaternary bridgehead. Therefore, the *exo* or *endo* product is possible and the NMR data are insufficient to prove the correct stereochemistry of this novel aminal. The absolute configuration of the crystalline tetraacetate **7** {81%, mp 196 °C, $[\alpha]_D^{20}$ 18 (*c* 1.18, $CHCl_3$)}‡ prepared by desilylation of **6** with tetrabutyl ammonium fluoride (TBAF) and subsequent acetylation with acetic anhydride at elevated temperature (Scheme 1), was established by X-ray analysis (Fig. 1).§ In accord with the difficult chemical substitution of the bridgehead alcohol in **5** or **6**, the X-ray data show only the *exo* product (Fig. 2). The alcohol group of **5** is caged by the sugar chair and the lactam ring, giving a chemical shift of δ 6.1 in Me_2SO and NOE effects with the H(8) and $H(10)_{eq}$ protons. The X-ray structure indicates a dihedral angle between the hemiaminal and the amide function of 103° [Fig. 1 : C(3)–N(2)–C(6)–O(25)]. Therefore, in contrast to the formation of **3** and **4**, an aza-analogous retro-aldol reaction of **5** or **6** to give the ketone **9** cannot occur due to stereoelectronic reasons. Apparently no ring strain is exerted in the [5.3.1.$0^{2,6}$]tricyclic ring system and thus compounds **5**–**7** are extraordinarily stable under various reaction conditions.

During prolonged irradiation of the methyl-protected imide **1**, in addition to **3** and **5** a highly polar new product **10** was obtained. The NMR data showed two new quaternary and functionalised carbons as well as new alcohol and NH moieties. This led to the proposed mechanism depicted in Scheme 1. The reaction proceeds *via* two stereoselective alkylations, first at C(2) and second at C(5) to give the lactams **10** and **11**. After transannular hemiaminal fragmentation to the azepindiones **3** and **4**, in a second Norrish type II reaction the excited ketone attacked the hydrogen at C(5) and a cyclopentane ring was formed. To confirm the second alkylation at C(5) the isolated azepindiones **3** and **4** were irradiated separately. After 120 h the

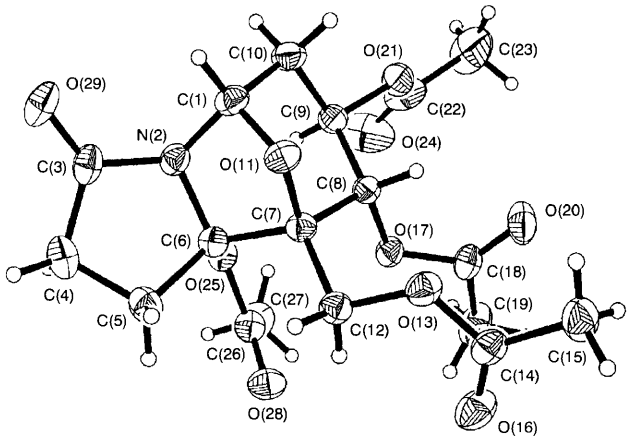
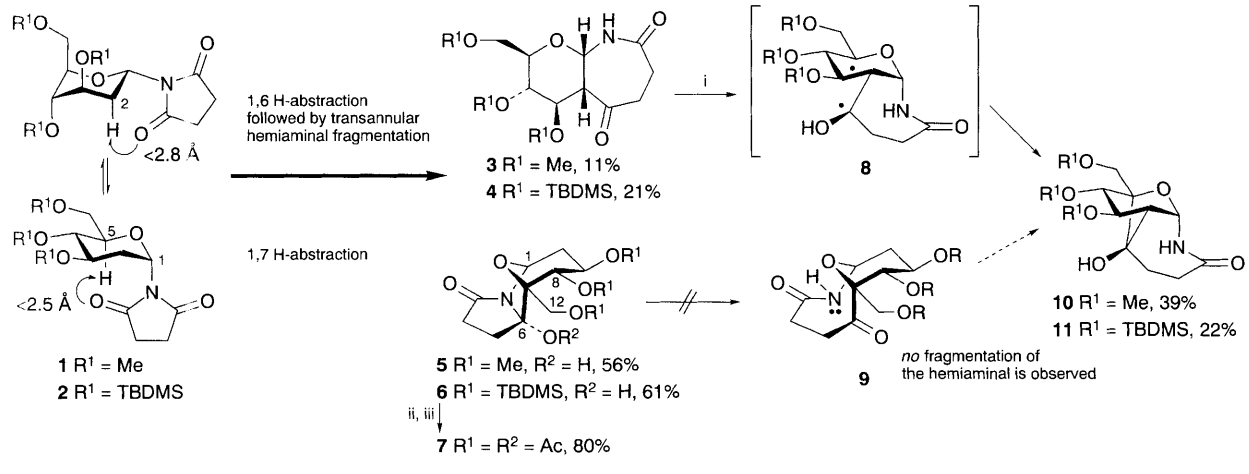


Fig. 1 X-Ray structure of **7**.[10,11] For orientation: acetates on the right, amide at the top left, hemiaminal at C(6).



Scheme 1 *Reagents and conditions*: i, 254 nm, MeCN; ii, TBAF, THF; iii, Ac_2O, Py, 60 °C

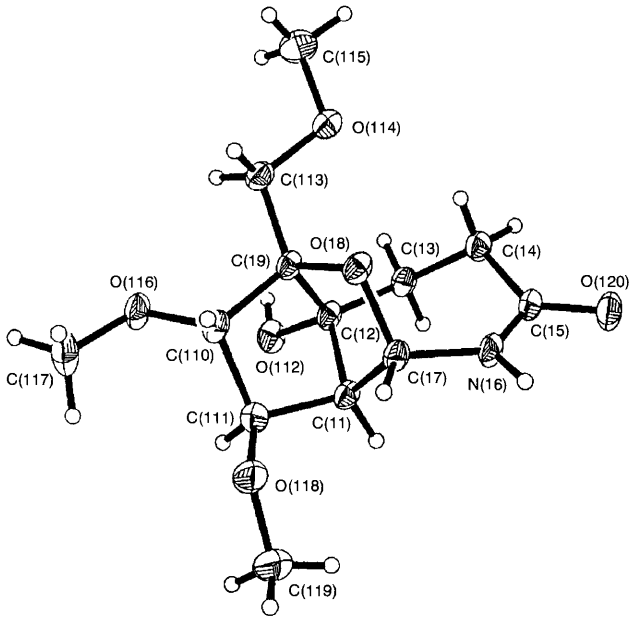


Fig. 2 X-Ray structure of **10**.[10,11] For orientation: top of the sugar chair with ring oxygen O(18).

alcohols **10** and **11** were isolated in moderate yields (39%, 22%) in addition to decomposition products. This may be attributed to the applied wavelength, as the absorption maximum of the carbonyl group is considerably lower than 254 nm. At this stage the NMR data were insufficient to establish the correct stereochemistry because there is no coupling with the two new quaternary and adjacent bridgeheads of the lactams **10** and **11** and no NOE effects were observed. The absolute configuration was determined by X-ray analysis of crystalline **10** (Fig. 2) {mp 205 °C, $[\alpha]_D^{20}$ 14 (*c* 0.53, $CHCl_3$)}.‡

The new bicyclic compounds **3** and **4** and the tricyclic **10** and **11** contain the carboxamide group as well as the functionalised azepinone ring annelated to the carbohydrate moiety. Further interest is focused on the new substructure present in these molecules. The ε-lactam is fused with the carboxamide group at the glycosidic position of the sugar. This stable annelated aminal structure present in both heterocycles is currently subject to a pharmaceutical screening process elsewhere.

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Footnotes

† Substructures of [5.4.0]-(**3**, **4**), [5.3.1.$0^{2,6}$]-(**5**–**7**), and [5.4.0.$0^{2,9}$]-(**10**, **11**) annelated lactam systems containing an α-oxo-aminal at the bridgehead have not been reported before.

‡ ^1H and ^{13}C NMR data of all new compounds (**3**, **5**, **7**, **10**, **11**) were in agreement with the structure, and their purity was proven by correct combustion analyses. The absolute configurations of **7** and **10** determined through Flack parameters correspond to the known chirality of these compounds.

§ *Crystal data for* **7** (CSD No. 401346): a = 8.405(1), b = 8.063(1), c = 14.791(1) Å, β = 93.06(1)°, V = 1000.9(2) Å^3, Z = 2, monoclinic, space group $P2_1$ (No. 4), 4033 independent reflections, R_{int} = 0.0156, R = 0.0537 for all reflections, S = 1.172, $\Delta\rho_{max}$ = 0.285, $\Delta\rho_{min}$ = −0.242 e Å^{-3}, Flack-parameter −0.02(21).[12]

For **10** (CSD No. 401347): a = 7.346(1), b = 10.9101(1), c = 17.631(1) Å, β = 91.55(1)°, V = 1412.5(3) Å^3, Z = 4, monoclinic, space group $P2_1$ (No. 4), 3135 independent reflections, R_{int} = 0.0104, R = 0.0466 for all reflections, S = 1.128, $\Delta\rho_{max}$ = 0.281, $\Delta\rho_{min}$ = −0.232 e Å^{-3}, Flack-parameter −0.06(21).[12]

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. Supplementary Crystallographic Data have also been deposited at the Fachinformationszentrum Karlsrühe. See Information for Authors, Issue No. 1.

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