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Stereospecific Synthesis of *dl*-Triacetyldaunosamine

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Daunosamine triacetate was synthesized via a stereospecific non-carbohydrate approach. The *N*-benzoyl-β-amino lactone (**9**) could be an interesting intermediate for the very important and highly deoxygenated amino sugar, 4-deoxydaunosamine.

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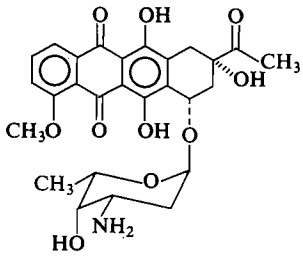
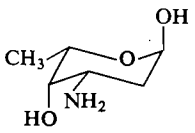
On a synthétisé le triacétate de la daunosamine par une approche stéréospécifique n'impliquant pas de carbohydrates. La *N*-benzoyl β-amino lactone (**9**) pourrait s'avérer être un intermédiare interessant pour la synthèse du sucre aminé très important et très désoxygené qu'est la désoxy-4 daunosamine.

[Traduit par le journal]

The antileukemic drug daunomycin (daunorubicin), **1**, is split into daunomycinone and the amino sugar daunosamine, **2**, on mild acid hydrolysis (1). In a previous communication, an approach to the aglycone daunomycinone (2) was described; we now wish to disclose the total synthesis of triacetyldaunosamine.



1



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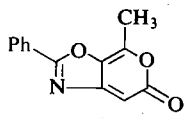

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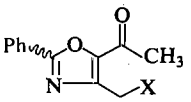
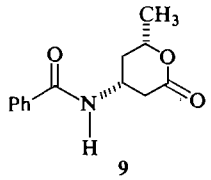


4 X = H
5 X = Br
6 X = CN
7 X = $COOCH_3$
8 X = COOH

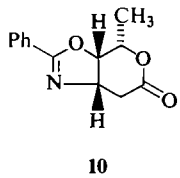
L-Daunosamine has been synthesized by Goodman and co-workers (3) and the *N*-acyl derivatives of the unnatural D-isomer were also prepared by Baer *et al.* (4) and by Richardson (5), all starting from natural sugars. In our route, a substituted oxazolo-α-pyrone **3** served as the key intermediate. It was envisaged that catalytic hydrogenation of **3** would furnish the lactone corresponding to daunosamine provided that all *cis*-addition of hydrogen to the unsaturated system is operative.

The synthesis of **3** was initiated by the preparation of the oxazole **4** (ν_{CO} 1680 cm^{-1}; δ 2.48 (3H, s), 2.52 (3H, s), 7.3–7.6 (3H, m), and 7.9–8.2 (2H, m); *m/e* 201 (M^+)) by benzoyloxylation of 2,4-pentanedione morpholine enamine (6). Compound **4** was selectively brominated at the 'benzylic' position with NBS to give **5** (m.p. 108–110 °C; ν_{CO} 1680 cm^{-1}; δ 2.57 (3H, s), 4.75 (2H, s), 7.3–7.6 (3H, m), and 7.9–8.2 (2H, m); *m/e* 279, 281 (M^+)). Conversion of the bromide **5** into the nitrile **6** could not be achieved by conventional procedure, presumably owing to the high acidity of the 'benzylic' hydrogens of **6** which reacted further, uncontrollably. However, nitrile **6** (ν 2270 and 1680 cm^{-1}; δ 2.67 (3H, s), 412 (2H, s) 7.3–7.6 (2H, m), and 7.9–8.2 (2H,

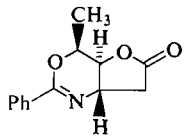
m); *m/e* 226 (M^+)) was obtained by cyanide displacement in a sealed tube employing liquid hydrogen cyanide as a cosolvent (KCN:HCN–Et_2O, 75 °C, 36 h). Reaction of **6** with hydrogen chloride-saturated methanol gave the methyl ester **7** (ν_{CO} 1740 and 1680 cm^{-1}; δ 2.57 (3H, s) 3.75 (3H, s), 4.5 (2H, s), 7.3–7.6 (3H, m), and 7.9–8.2 (2H, m); *m/e* 259 (M^+)) which was hydrolyzed to the carboxylic acid **8** (m.p. 194 °C dec.; ν_{CO} 1725 and 1683 cm^{-1}) by HCl in aqueous HOAc at ambient temperature. This acid underwent decarboxylation readily on heating to regenerate the oxazole **4**, therefore it must be handled with care. Treatment of **8** with thionyl chloride in anhydrous chloroform afforded the desired oxazolo-α-pyrone (m.p. 185–187 °C dec.; ν 1740 and 1690 cm^{-1}; δ 2.517 (3H, d, J = 0.8 Hz) and 6.158 (1H, q, J = 0.8 Hz); *m/e* 227 (M^+)).



9

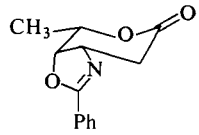


10

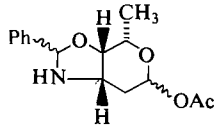


11

Attempts at hydrogenating **3** using Adams catalyst in ethyl acetate resulted in the generation of the benzamide **9** (ν_{CO} 1730 and 1670 cm^{-1}) and its hexahydro derivative. Hydrogenolysis could be avoided when the reduction was carried out with 5% Rh/Al_2O_3 as catalyst. The product retained a C=N bond and its structure **10** was supported by spectral data, especially its mass spectrum. It was thermodynamically unstable, and was converted upon heating into a γ-lactone **11** (ν_{CO} 1760 cm^{-1}). This facile transformation suggested that **10** indeed possesses an all *cis* stereochemistry whose preferred conformation is **10***a* with the oxygen atom of the oxazoline ring assuming an axial orientation, whereas both the nitrogen and the methyl group are equatorial. In view of the occurrence of this rearrangement,



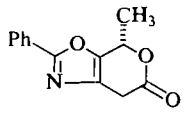
10*a*



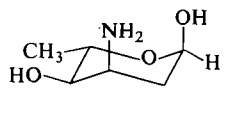
12

the lactone carbonyl was reduced by sodium di(2-methoxyethoxy) aluminum hydride to the lactol and then acetylated [Ac_2O-pyr]. Further hydrogenation (5% Rh/Al_2O_3 in EtOAc) of this lactol acetate gave compound **12**. The benzylidene group was removed by acid treatment and the crude product was reacetylated to yield the triacetyl derivatives. Preparative t.l.c. on silica gel permitted the isolation of triacetyldaunosamine. Identification of this final product was by spectral comparison (i.r., m.s.) with a sample derived from natural sources.

Borohydride reduction of the ketoester **8** afforded lactone **13** which could be a useful synthetic intermediate of ristosamine **14** (7). All new compounds gave satisfactory analysis or exact mass molecular ions.



13



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