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# STEREOSTRUCTURE OF NYSTATIN $A_1$: A SYNTHETIC ASSIGNMENT OF THE C1-C10 FRAGMENT

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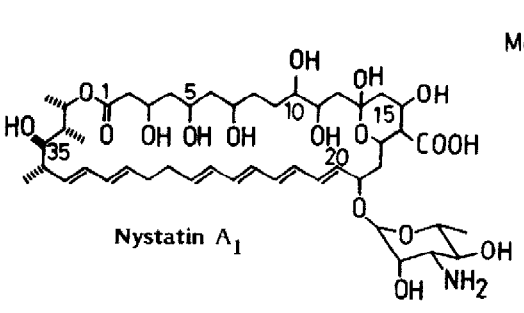
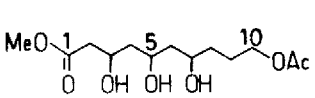
**Summary:** *The 3R, 5R and 7R configurations for nystatin $A_1$ have been assigned through a comparison of synthetic and natural fragment* **3**. *The key step of the synthetic sequence is a nucleophilic oxirane opening by an α-glycosyl copper reagent.*

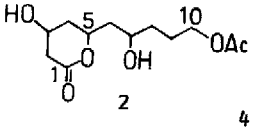
We recently reported[1] the 3R*, 5R* and 7R* relative configurations for nystatin $A_1$, a commonly used antibiotic in human therapy[2]. The stereochemical information was deduced by detailled proton-nmr analyses of the two degradation C1-C10 fragments, **1** and **2**. Exhaustive acetylation ($Ac_2O$, pyridine) and purification led to the unsaturated δ-lactone **3**, $[\alpha]_D^{20}$ -62° (c 0.23, $CHCl_3$).



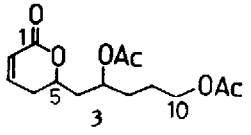
Nystatin $A_1$



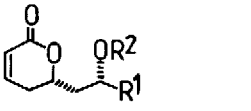
**1**



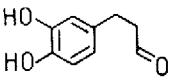
**2**



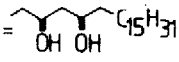
**3**



**4** $R^1$ = Me, $R^2$ =



**5** $R^1$ =

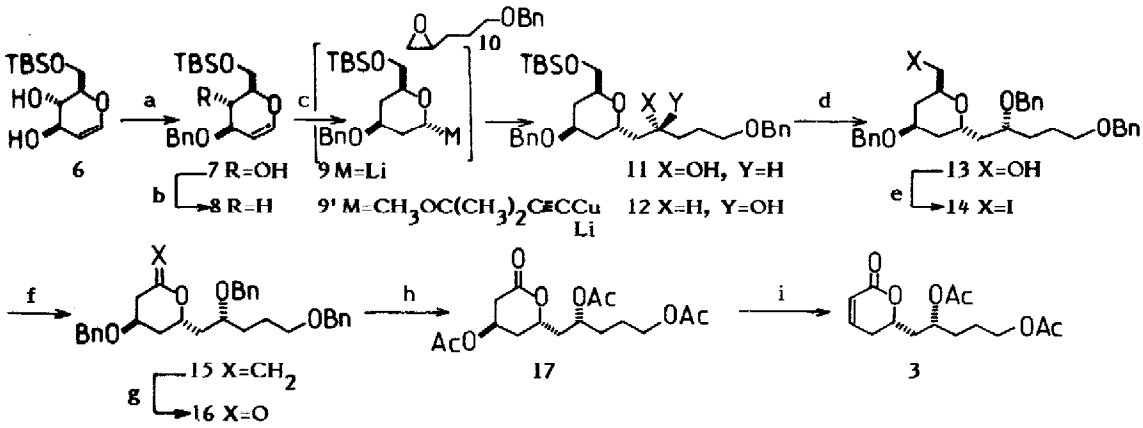


, $R^2$ = H

In order to determine the absolute configuration of this molecular segment of nystatin $A_1$, we undertook the synthesis of either **1**, **2** or **3**. Of the two possible enantiomeric candidates, the 3R,5R,7R compound was considered to be the most likely target for the synthetic work, based on the structural resemblance of nystatin $A_1$ to amphotericin B[3], and on the optical rotation of **3**, closely related to that of **4**[4], $[\alpha]_D$ -67° (c 2.3, $CHCl_3$), and **5**[5], $[\alpha]_D$ -34° (MeOH), the α,β-unsaturated δ-lactones of plant origin whose stereochemistry was recently established[6].

In continuation with our work on anionic anomeric species in the 2-deoxy series[7], we became interested in the possibility of expanding further their use in the synthesis of the 1,3-polyol systems. Within this context, an obvious strategy for preparing a C1-C10 nystatin $A_1$ segment which contains the required chiral centers would be to assemble a sugar-derived anionic compound (C1-C5)[8] with a suitable five-carbon epoxide (C6-C10)[8]. For the stereoselective carbon-carbon bond formation, we capitalized on the fact that the 2-deoxy glycosyl lithium[7] and copper[9] reagents are configurationally stable at low temperatures.

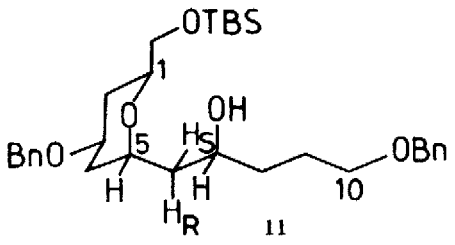
The known 6-O-silylated-D-glucal **6**[10], available in two steps from tri-O-acetyl-D-glucal, was regiospecifically benzylated at the 3-O-position via the stannylene procedure[11] to give the 3-O-



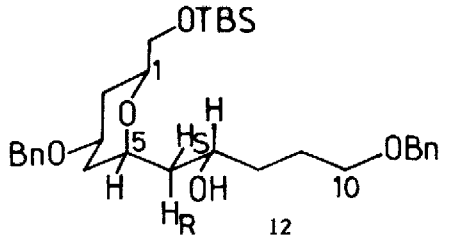

**Scheme:** (TBS = t-butyldimethylsilyl) (a) $Bu_2SnO$, $NBu_4Br$, BnBr, $PhCH_3$, 80°C, 18 h, 93%; (b) NaH, $CS_2$, r.t., 4 h then $CH_3I$, r.t., 18 h; $Bu_3SnH$, cat. AIBN, $PhCH_3$, reflux, 1.5 h, 73%; (c) HCl, $PhCH_3$, 1 min, -15°C then LN, THF, -78°C; $CH_3OC(CH_3)_2$ C≡CCu, THF, -78°C then **10**, $BF_3$:$Et_2O$, 5 equiv., -78 to 0°C, 1 h, 36%; (d) NaH, BnBr, DMF, 0°C, 1 h; $NBu_4F$, THF, r.t., 2 h, 86%; (e) $Ph_3P$, imidazole, $I_2$, $PhCH_3$, r.t., 3 h, 68%; (f) DBU, THF, reflux, 15 h; (g) $O_3$, $CH_2Cl_2$, 1 min, -78°C then $Me_2S$, 75% from **14**; (h) $H_2$, Pd/C, AcOEt, r.t. then $Ac_2O$, pyridine, r.t. quant.; (i) DBU, $PhCH_3$, r.t., 15 min.

benzylated glucal **7**[12] (93% yield, Scheme). Subsequent reductive removal of the C3 hydroxyl group by the xanthate protocol[13] provided the disymmetrically protected glycal **8** (73% yield), $[\alpha]_D$ -18° (c 0.86, $CHCl_3$) recently described by Paquette[14]. The unstable α-D-glycopyranosyl lithium derivative **9**, prepared by hydrochlorination in toluene[7] and reductive lithiation with lithium naphthalenide in THF at -78°C, was converted into the presumed mixed organocuprate reagent **9'**. Reaction of a THF solution of **9'** with the racemic epoxide **10**, in the presence of the $BF_3$:$OEt_2$ complex[16] (5 equiv.) at -78°C led to the diastereoisomeric alcohols **11** and **12**[17] (36% yield from glycal **8**). Despite the moderate yield[18] of this reaction, two interesting features are worth mentioning. The α-C-glycosidic products were the only coupling products formed, without any of the -compounds being detected. This was confirmed by oxidation of alcohols **11** and **12** which led to a single ketone[19]. The known[7] configurational stability of the initial lithiated species is thus preserved during the course of the following anionic modifications. A noticeable degree, although modest (**11**:**12** ratio, 3:2), of stereoselectivity in the desired sense was observed by the reaction of the chiral anionic species with the racemic epoxide. The kinetic preference may well become synthetically useful with an appropriate structural modification of the reactants.

The configuration at C7 (nystatin numbering) was unambiguously established by proton-nmr analysis of **11** and **12** in $CDCl_3$[19] (or $C_6D_6$) solution. The values of the $^3J$ and $^4J$ coupling constants demonstrate that the tetrahydropyran ring adopts a chair conformation. The assignment of the coupling constants for $H_R$ at C6 ($J_{6R,7}$ 2.2, $J_{5,6R}$ 2.5 and $J_{6R,6S}$ 14.8 Hz in **11**; $J_{5,6R}$ 3.8, $J_{6R,7}$ 8.4 and $J_{6R,6S}$ 14.5 Hz in **12**) and $H_S$ at C6 ($J_{6S,7}$ 9.4, $J_{5,6S}$ 11.4 and $J_{6R,6S}$ 14.8 Hz in **11**; $J_{6S,7}$ 3.1, $J_{5,6S}$ 10.8 and $J_{6R,6S}$ 14.5 Hz in **12**) is only compatible with the configuration shown (see below) where the C6-C10 appendage appears to take an extended zig-zag conformation, or a slight deviation from it in compound **11**. In the latter case, an intramolecular hydrogen bonding between O5 and the hydroxyl group at C7 stabilizes the conformation observed as already detected in this type of situation[1]. The unwanted isomer was transformed ($Ph_3P$, DEAD, PhCOOH, THF, r.t.) to the one desired using the Mitsunobu reaction[20].




11




12

Benzylation of **11** and subsequent desilylation with $NBu_4F$ in THF afforded the primary alcohol **13** converted to iodide **14** using the standard methodology[21]. DBU in THF easily eliminated hydrogen iodide from **14** and the unsaturated compound **15** was immediately ozonolyzed to give lactone **16**, $[\alpha]_D^{20}$ +3° (c 0.65, $CHCl_3$) after reductive workup. Lactone **16** has the full structure and substitution pattern of the C1-C10 nystatin $A_1$ segment.

For purposes of comparison with degradation product **3**, benzyl ethers were hydrogenolyzed in ethyl acetate and the resulting triol acetylated. This sensitive triacetate **17**, contaminated by a small amount of α,β-unsaturated lactone **3**, was readily converted into **3** by a brief treatment with DBU in toluene. Synthetic **3**[22] showed identical chromatographic and spectroscopic data and the same optical rotation, $[\alpha]_D$ -64° (c 0.11, $CHCl_3$) as compound **3** derived from nystatin $A_1$.

In conjunction with previous studies[1], the 3R, 5R and 7R configurations for the antibiotic nystatin $A_1$ are thus established[23]. Complete stereostructure of nystatin $A_1$ is described in the following communication.

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8. These numbers refer to the nystatin $A_1$ numbering.
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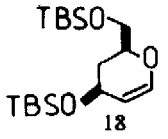
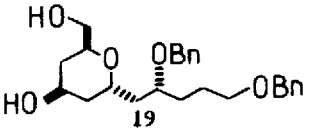
17. Purification of the coupling compounds **11** and **12** was greatly facilitated by acetylation of the crude product and isolation of the obtained acetates. Chromatography of the deacetylated mixture afforded alcohols **11** $[\alpha]_D^{20}$ +19° (c 1.6, $CHCl_3$), and **12** $[\alpha]_D^{20}$ +21° (c 1.17, $CHCl_3$).
18. The disilylated glycal **18** gave much better results. Selective displacement at the primary position of diol **19** (e.g., step e, in Scheme) under a variety of conditions was however unmanageable in our hands due to a competitive displacement of the hydroxyl at position 3 (glycal numbering) and/or the 3,6-anhydro ring formation.



**18**



**19**

19. Selected $^1$H-nmr data (nystatin $A_1$ numbering is used): **11** ($CDCl_3$): δ 1.36 (m, $J_{6R,7}$ 2.2, $J_{5,6R}$ 2.5, $J_{6R,6S}$ 14.8 Hz, H6R); 1.44 (dt, $J_{1,2a}$ = $J_{2a,3}$ = 8.5, $J_{2a,2e}$ 13.1 Hz, H2a); 1.85 (ddd, $J_{6S,7}$ 9.4, $J_{5,6S}$ 11.4, $J_{6R,6S}$ 14.8 Hz, H6S); 1.94 (m, $J_{2e,4e}$ ~1, $J_{1,2e}$ = $J_{2e,3}$ = 3.9; $J_{2a,2e}$ 13.1 Hz, H2e); 4.26 (m, $J_{5,6R}$ 2.5, $J_{4,5}$ 4.5, $J_{4',5}$ ~5, $J_{5,6S}$ 11.4 Hz, H5). **12** ($CDCl_3$): δ 1.39 (ddd, $J_{5,6R}$ 3.8, $J_{6R,7}$ 8.4, $J_{6R,6S}$ 14.5 Hz, H6R); 1.44 (dt, $J_{1,2a}$ = $J_{2a,3}$ = 8.0; $J_{2a,2e}$ 13.5 Hz, H2a); 1.89 (ddd, $J_{6S,7}$ 3.1, $J_{5,6S}$ 10.8, $J_{6S,6R}$ 14.5 Hz, H6S); 1.96 (dt, $J_{1,2e}$ = $J_{2e,3}$ = 3.9, $J_{2a,2e}$ 13.5 Hz, H2e); 4.37 (m, $J_{5,6R}$ 3.8, $J_{4,5}$ ~5, $J_{4',5}$ ~6, $J_{5,6S}$ 10.8 Hz, H5). Ketone derived from **11**, **12** ($C_6D_6$): δ 1.58 (m, $J_{2e,4e}$ 1.7, $J_{3,4e}$ = $J_{4e,5}$ = 4.3, $J_{4a,4e}$ 13.3 Hz, H4e); 1.70 (ddd, $J_{4a,5}$ 4.9, $J_{3,4a}$ 8.7, $J_{4a,4e}$ 13.3 Hz, H4a); 2.03 (dd, $J_{5,6S}$ 6.0, $J_{6R,6S}$ 15.2 Hz, H6S); 2.51 (dd, $J_{5,6R}$ 8.2, $J_{6R,6S}$ 15.2 Hz, H6R); 4.55 (m, $J_{4e,5}$ 4.3, $J_{4a,5}$ 4.9, $J_{5,6S}$ 6.0, $J_{5,6R}$ 8.2 Hz, H5). **16** ($CDCl_3$): δ 1.68 (ddd, $J_{3,4a}$ 3.8, $J_{4a,5}$ 11.7, $J_{4a,4e}$ 13.7 Hz, H4a); 2.11 (m, $J_{2e,4e}$ 1.7, $J_{4e,5}$ 2.9, $J_{3,4e}$ 3.8, $J_{4a,4e}$ 13.7 Hz, H4e); 2.64 (dd, $J_{2a,3}$ 5.2, $J_{2a,2e}$ 12.5 Hz, H2a); 2.75 (ddd, $J_{2e,4e}$ 1.7, $J_{2e,3}$ 4.0, $J_{2a,2e}$ 12.5 Hz, H2e); 3.95 (m, $J_{3,4a}$ = $J_{3,4e}$ = 3.8, $J_{2e,3}$ 4.0, $J_{2a,3}$ 5.2 Hz, H3); 4.80 (m, $J_{4e,5}$ 2.9, $J_{5,6}$ 6.1, $J_{5,6'}$ 6.7, $J_{4a,5}$ 11.7 Hz, H5).
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21. P.J. Garegg and B. Samuelson, J. Chem. Soc., Chem. Commun., (1979) 979-980.
22. $^1$H-Nmr ($CDCl_3$) of **3**: δ 1.87 (ddd, $J_{6R,7}$ 4.0, $J_{5,6R}$ 6.9, $J_{6R,6S}$ 14.7 Hz, H6R); 2.05 and 2.08 (2 s, Ac); 2.18 (ddd, $J_{5,6S}$ 6.5, $J_{6S,7}$ 9.1, $J_{6R,6S}$ 14.7 Hz, H6S); 2.31 (m, $J_{2,4a}$ = $J_{3,4a}$ = 2.6, $J_{4a,5}$ 11.5, $J_{4a,4e}$ 18.5 Hz, H4a); 2.49 (m, $J_{2,4e}$ 1.2, $J_{4e,5}$ 4.0, $J_{3,4e}$ 6.1, $J_{4a,4e}$ 18.5 Hz, H4e); 4.07 (m, H10,10'); 4.49 (m, $J_{4e,5}$ 4.0, $J_{5,6S}$ 6.5, $J_{5,6R}$ 6.9, $J_{4a,5}$ 11.5 Hz, H5); 5.10 (m, H7); 6.02 (ddd, $J_{2,4e}$ 1.2, $J_{2,4a}$ 2.5, $J_{2,3}$ 10.0 Hz, H2) and 6.87 (ddd, $J_{3,4a}$ 2.5, $J_{3,4e}$ 6.1, $J_{2,3}$ 10.0 Hz, H3).
23. After this work was completed, an investigation appeared which arrived at the same conclusion by a synthesis of an enantiomeric form of the C1-C10 fragment of nystatin $A_1$: K.C. Nicolaou and K.H. Ahn, Tetrahedron Lett., 30 (1989) 1217-1220.

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