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SYNTHESIS AND STEREOCHEMICAL ASSIGNMENT OF THE C_1-C_{10} FRAGMENT OF NYSTATIN A_1

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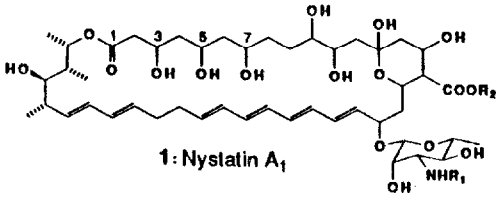
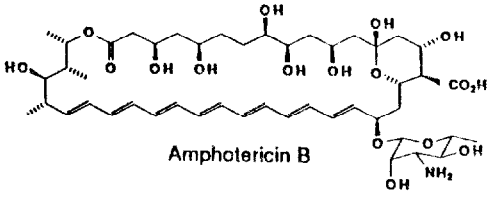
Summary. *Compound **8** representing the C_1-C_{10} fragment of nystatin A_1 has been synthesized from nystatin A_1 by degradation and by total synthesis. Comparison of the two samples revealed the 3R, 5R, 7R stereochemistry for the three nystatin A_1 centers.*

Nystatin A_1 (**1**)[1] is a clinically used polyene macrolide antibiotic of considerable importance. Despite its widespread use in medicine, however, its stereochemistry remains only partially known[1]. Our efforts in the area of polyene macrolide antibiotics, which recently culminated in the total synthesis[2] of amphotericin B (**2**) and its aglycon, are now directed towards the total synthesis and structural elucidation of nystatin A_1 (**1**). A recent communication[3] regarding the relative stereochemistry of the hydroxyl groups of the C_1-C_{10} fragment of nystatin A_1 (**4**) prompted us to report our investigations in this area which resulted in the synthesis and absolute stereochemical assignment of this fragment.

The C_1-C_{10} fragment of nystatin A_1 (**1**) was excised from the natural product by the sequence depicted in **Scheme 1**. Thus, nystatin A_1 (**2**)[4] was monoacetylated in methanol with acetic anhydride to give the acetamide **2** which was then methylated with diazomethane leading to methyl ester **3** (78% from **1**). Basic methanolysis of **3** under carefully controlled conditions led to compound **4** (30% yield



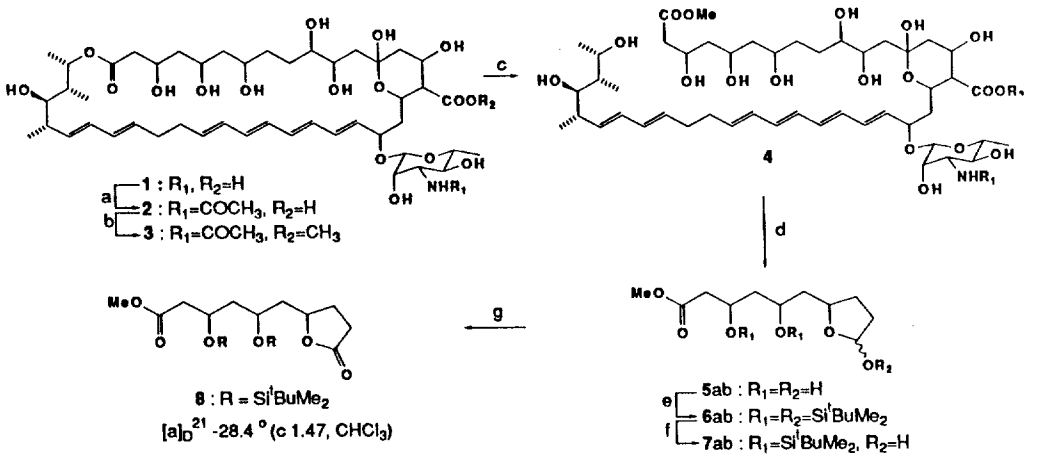
1: Nystatin A_1



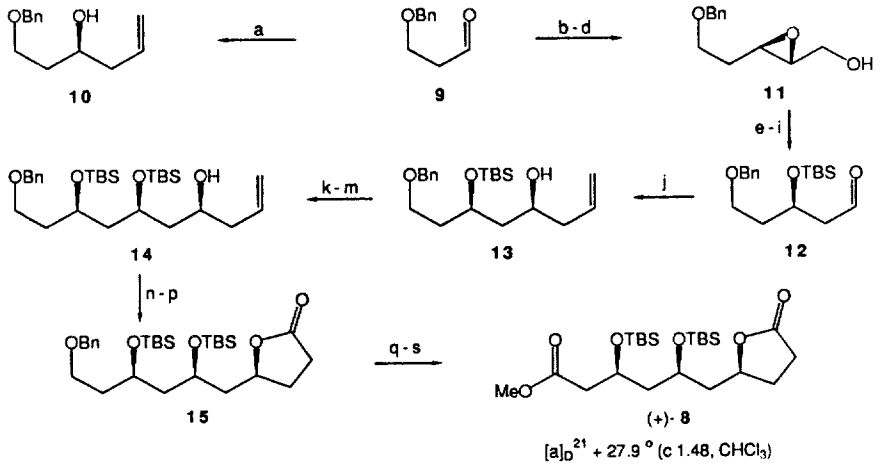
Amphotericin B

plus 26% recovered starting material) which was then cleaved at the 1,2-diol site with $NaIO_4$ in aqueous methanol furnishing the trihydroxy compound **5ab** (43%) as a mixture of lactol epimers (*ca* 2.5:1 by ^1H NMR). In addition to **5ab**, a second major product was obtained in this reaction which was presumed to be the other expected fragment of the molecule, although it has not yet been fully characterized. Compound **5ab** was then persilylated with $^tBuMe_2SiCl$-imidazole to afford trisilyl ether **6ab** which was selectively converted to lactol **7ab** (mixture of epimers; *ca* 2.5:1 by ^1H NMR) by exposure to mildly acidic conditions (AcOH-THF-H_2O, 66%). Finally, oxidation of **7ab** with pyridinium chlorochromate afforded γ-lactone **8**[5] in 96% yield $[\alpha]_D^{21}$ -28.4° (C 1.47, $CHCl_3$)]. In order to determine the relative and absolute stereochemistry of **8** synthetic studies were undertaken. In considering likely stereochemical candidates for **8**, our first suspect was the all-syn-3R,5R,7R compound due to the similarities of nystatin A_1 (**1**) to amphotericin B, although by no means this analogy precluded other possible structures[6]. It was also decided that Brown's allyl $(Ipc)_2$ borane reagents[7] would be used to provide the necessary asymmetric induction and flexibility in constructing the requisite stereoisomers. However, due to the higher optical purity of the commercially available[8] to us (-)-reagent at the time, we proceeded initially to build the 3S,5S,7S compound as depicted in **Scheme 2**.

Aldehyde **9** (**Scheme 2**) was initially reacted with the allyl Brown reagent derived from (-)-B-Ipc_2OMe and CH_2=$CHCH_2MgBr$ giving hydroxy compound **10** in 80% yield but only in 74% ee. On the other hand standard elaboration of **9** to epoxy alcohol **11** via the Sharpless epoxidation procedure[10] resulted in 77% overall yield and 91% ee[9]. The later sequence with the higher ee was therefore utilized in the synthesis of **8**. Thus, **11** was regioselectively opened to the corresponding 1,3-diol with REDAL[11] (95%) and then elaborated to aldehyde **12** by standard chemistry as outlined in **Scheme 2** (82% overall yield). Addition of the allyl Brown reagent derived from (-)-B-Ipc_2OMe and CH_2=$CHCH_2MgBr$ then led to compound **13** in 92% yield and 83% diastereomeric excess[12]. Careful flash column chromatography produced pure **13** from which pure **14** was generated by (a) protection; (b) ozonolysis-PPh_3 (c) reiteration of the Brown addition process and (d) chromatography (88% overall yield). The conversion of **14** to the desired target **8** for comparison with the degradatively derived material proceeded through intermediate **15** as follows: (a) temporary protection of the alcohol as ethoxyethyl ether (b) hydroboration of the olefin with 9-BBN followed by basic hydrogen peroxide work-up; (c) PCC oxidation of the alcohol with concomitant deprotection-cyclization-oxidation to afford **15** (44% overall yield); (d) hydrogenolysis of the benzyl ether; and (e) oxidation of the resulting primary alcohol, first to the aldehyde (PDC, CH_2Cl_2) and then directly[13] to the methyl ester **8** (58% overall yield). Synthetic **8** exhibited identical chromatographic and spectroscopic data as degradatively derived **8**, but opposite optical rotation $[\alpha]_D^{21}$ + 27.9° (c 1.48, $CHCl_3$)]. The CD spectra[14] of the two samples also exhibited opposite cotton effect reinforcing the conclusion of their enantiomeric nature. Therefore, based on the expected stereochemical course of the Sharpless[10] and Brown[7,6] reactions employed, the 3R,5R,7R absolute stereochemistry is assigned for fragment (-)-**8** and the corresponding nystatin A_1 (**1**) stereogenic centers. Work towards the complete stereochemical assignments and total synthesis of nystatin A_1 is continuing[14,15].



Scheme 1. Degradation of nystatin A_1 to compound 8. Reagents and conditions: (a) 2.0 equiv Ac_2O, MeOH, 0 °C, 1 h; (b) excess CH_2N_2, THF-MeOH, 25 °C, 1 h, 78% from 1; (c) 1.2 equiv K_2CO_3, MeOH, 25 °C,12 h, 30%, plus 26% recovered starting material; (d) 2.0 equiv $NaIO_4$, MeOH-H_2O(20:1), 25 °C, 30 min, 43%; (e) 5.0 equiv $^tBuMe_2SiCl$, imidazole, DMAP, cat., DMF, 25 °C, 12 h. 100%, (f) AcOH-THF-H_2O(3:3:1), 0 - 25 °C, 1 h, 66% (g) 2.5 equiv PCC, 4A molecular sieve, CH_2Cl_2, 25 °C, 1 h, 96%.



Scheme 2. Synthesis of 3S,5S,7S C_1-C_{10} fragment (+)-8 from 3-benzyloxypropanal 9. Reagents and conditions: (a) 1.1 equiv $Ipc_2BCH_2CH{=}CH_2$(from (-)-methoxydiisopinocampheylborane and $BrMgCH_2CH{=}CH_2$), Et_2O, -78 - 25 °C, 2 h; 30% H_2O_2-3N-NaOH, 50 °C, 2 h, 74%; (b) 1.0 equiv $(EtO)_2P(O)CH_2COOEt$, ^tBuOK, THF, -78 °C, 30 min, 91%; (c) 2.5 equiv DIBAL, $PhCH_3$, -78 - -45 °C, 2 h, 95%; (d) 0.12 equiv L-(-)-DET, 0.10 equiv $Ti(O\text{-}iPr)_4$, 2.0 equiv ^tBuOOH, 20% wt 4A molecular sieve, 0.1 M in CH_2Cl_2, -20 °C, 12 h, 89%; (e) 1.5 equiv REDAL, THF, -20 °C, 12 h, 95%; (f) 1.1 equiv ^tBuCOCl, pyridine, -20 °C, 10 min, 89%; (g) 1.2 equiv $^tBuMe_2SiCl$, imidazole, DMAP, cat., DMF, 25 °C, 12 h, 98%; (h) 2.5 equiv DIBAL, THF-hexane, -78 °C, 1 h, 96%; (i) 1.1 equiv $(COCl)_2$, 2.5 equiv DMSO, 5.0 equiv Et_3N, CH_2Cl_2, -78 - 0 °C, 1 h, 98%; (j) same as a, 92%; (k) same as g, 98%; (l) O_3, CH_2Cl_2-MeOH(100:1), -78 °C, ; 2.0 equiv Ph_3P, 25 °C, 2 h, 94%; (m) same as a, 95%; (n) 1.2 equiv $CH_2{=}CHOCH_2CH_3$, PPTS, cat., CH_2Cl_2, 25 °C, 30 min, 71%; (o) 1.5 equiv 9-BBN, THF, 0 - 25 °C, 3 h, 92%; (p) 5.0 equiv PCC, 4A molecular sieve, 25 °C, 1 h, 68%; (q) H_2, $Pd(OH)_2$, cat.,THF, 25 °C, 3 h, 94%; (r) 4.0 equiv PDC, 4A molecular sieve, CH_2Cl_2, 25 °C, 1.5 h, 78%; (s) 6.0 equiv PDC, 6.0 equiv MeOH, DMF, 25 °C, 24 h, 78%.

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4. We thank Dr. C. Cimarusti, E.R. Squibb, P.O. Box 4000, Princeton, NJ 08054, for generous samples of nystatin A_1 (**1**).

5. Rf = 0.36 (silica, 20% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (m, 1 H, *H*-7), 4.21 (m, 1 H, *H*-3), 3.93 (m, 1 H, *H*-5), 3.64 (s, 3 H, $COOCH_3$), 2.51-2.47 (m, 3 H, H-2, H-9), 2.42 (dd, J = 11.5, 5.5 Hz, 1 H, H-2), 2.31 (m, 1 H, CH_2), 1.96-1.72 (m, 5 H, CH_2), 0.86, 0.83 (singlets, 9 H each, ^{t}*Bu*), 0.06, 0.04, 0.03, 0.02 (singlets, 3 H each, Si*Me*$_2$). IR (neat) νmax 1783 (γ-lactone), 1744 cm^{-1} (COOMe); HRMS Calcd for $C_{23}H_{46}O_6Si_2$: 474.2830, found: 474.2841.

6. This caution was recently emphasized and justified by S.L. Schreiber and Goulet in their elegant studies on mycoticin A and B: (a) Schreiber, S.L; Goulet, M.T. *Tetrahedron Lett.* **1987**, *28*, 6001.

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8. Aldrich Co; $[\alpha]_D^{25}$ -73.7° (c=1, THF) for (-)-B-methoxydiisopinocampheylborane.

9. Enantiomeric excess (% ee) was determined by ^{19}F NMR spectroscopy using the Mosher ester: Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.*, **1969**, *34*, 2543.

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12. The diastereomeric excess was determined by ^{1}H NMR spectroscopy. Based on this value (83%), a 91% ee was calculated for the asymmetric induction of the second stereogenic center in **13**.

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14. Degradatively derived **8** showed a positive Cotton effect, whereas the synthetic material exhibited a negative Cotton effect. We thank Professor K. Nakanishi and W.T. Wiesler of Columbia University for the measurements of the CD spectra.

15. All new compounds exhibited satisfactory spectroscopic and/or analytical and exact mass data.

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