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Synthesis of the C_1-C_{10} Fragment of the Macrolide Antibiotic Nystatin A_1 from a Chiral Building Block Obtained via Chemoenzymatic Approach

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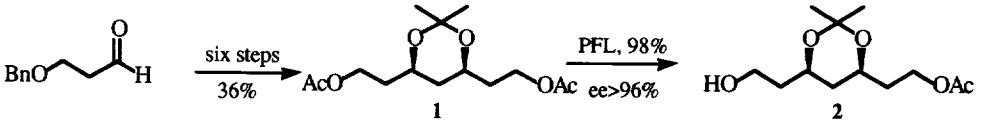
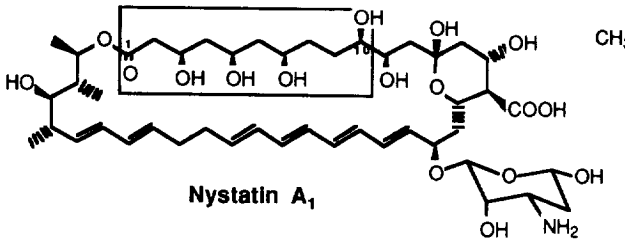
Abstract: a novel synthesis of C_1-C_{10} fragment of Nystatin A_1 was accomplished: the synthetic sequence utilized, as chiral building block, a protected *syn* 1,3 polyol previously obtained by chemoenzymatic route. The final fully protected fragment was then transformed to a known lactone in order to demonstrate the correct relative and absolute configuration.

Recent reports from this laboratory[1,2] have described the preparation and the utilisation of a new chiral building block, the (3S,5R) polyol **2**, which was obtained via biocatalytic desymmetrization of the meso precursor **1**. Optically active compound **2** can now be prepared in a seven step sequence from 3-benzyloxypropanal[3] (easily prepared from commercially available 3-benzyloxypropanol), on a multi-gram scale and with improved yield with respect to our previous report.[4]

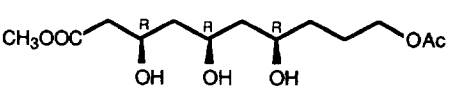
SCHEME 1



The title compound **2** has been already transformed into a series of mevinic acid analogues[2] and represents also an immediate precursor of the C_1-C_7 fragment of Amphotericin B.[5] To demonstrate the synthetic utility of compound **2**, we have directed our efforts to the synthesis of the C_1-C_{10} fragment of Nystatina A_1,



Nystatin A_1



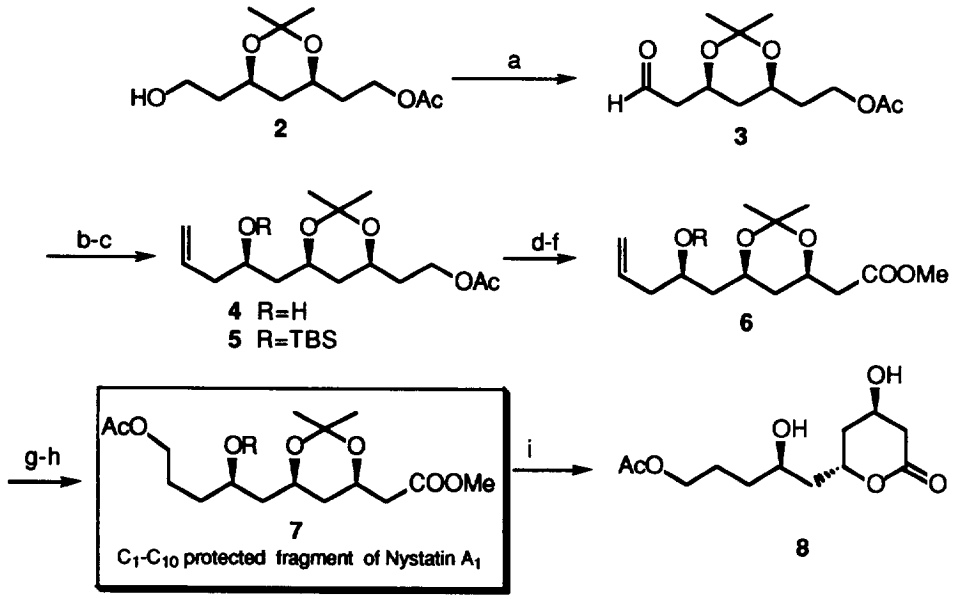
C_1-C_{10} fragment

poliene macrolide antibiotic used in human therapy,[6] whose complete structure has been recently assigned by spectroscopic and synthetic studies.[7]

In order to demonstrate the absolute configuration of the C-3, C-5 and C-7 carbons one enantioselective synthesis of the C_1-C_{10} fragment appeared,[8] together with an alternative approach which led to a partial fragment.[9] These two studies demonstrated the correct relative and absolute configuration of the C_1-C_{10} fragment previously proposed[10]: subsequently our shorter synthetic approach was published,[11] although in a racemic version.

The synthetic route is outlined in Scheme 2, starting from chiral compound **2**. In order to introduce the required third hydroxyl group with the correct absolute (R) stereochemistry, we decided to utilise Brown's allyl $(Ipc)_2$ borane reagent[12]: this way also a three carbons chain could be added to obtain the final C-10 chain.

SCHEME 2



a. PCC, NaOAc in CH_2Cl_2, 89%, r.t., 3h . **b**. $Ipc_2BCH_2CH{=}CH_2$ (from (+)-methoxydiisopino campheylborane and $BrMgCH_2CH{=}CH_2$) Et_2O, -78 °C, 1h ; 8-HQ MeOH, t.a., 12h, 60%. **c**. 2,6-lutidina, TBDMSTf, in CH_2Cl_2, -78°C, 45 min, 91%. **d**. Na, dry MeOH , r.t. 24 h, 100%. **e**.PDC in DMF, r.t., 24h, 62%. **f**. CH_2N_2 in ether, r.t. 30 min., 96%. **g**. BH_3 in THF, 0-25°C, then $NaOH/H_2O_2$, 70%. **h**. Ac_2O, Py, r.t., 99%. **i**. HF/CH_3CN, r.t., 1h, 76%.

To this end, compound **2** was oxidised with PCC/NaOAc system[13] to the corresponding aldeyde **3**, with good yield. Then aldeyde **3** was added of the allyl borane reagent (derived from (+)-B-Ipc_2OMe and $BrMgCH_2CH{=}CH_2$), with subsequent oxidative work up with 8-HQ.[14] The two diastereoisomers (de=80%)[15]

can be separated by flash chromatography and the desired polyol **4** was obtained,[16] after purification, in 60% overall yield.

Compound **4** was then protected as TBS ether to **5** (91% yield), deacetylated (Na in anhydrous MeOH), oxidised and methylated to yield the ester **6** (53% overall yield from **4**). The final hydroboration with usual regioselective commercial 9-BBN gave only 10% overall yield of the compound **7**. Therefore **6** was treated with diborane solution (BH_3/THF) followed by basic work up affording, in a reasonable 70% yield, the final alcohol. Quantitative acetylation produced the fully protected fragment **7** of Nystatin A_1, suitable for further elaboration.[17]

In order to confirm the relative and absolute configuration (3R, 5R, 7R) of the C_1-C_{10} protected fragment **7**, this was then transformed into the known lactone **8**, which has been isolated as degradation product of Nystatin, and structurally elucidated both by ^{1}H-NMR studies[7] and partial synthesis.[9] To this end the acidic deblocking of all the protective groups and the subsequent lactonization were carefully accomplished with aqueous HF in CH_3CN solution. The ^{1}H-NMR values as well as the optical rotation data[18,19] of our lactone **8** were found in nice agreement with the literature data .[10]

In conclusion we have showed that the optically active building block **2** is a precursor for the synthesis of the C_1-C_{10} fragment of Nystatin A_1 in a fully protected form. This approach represents an alternative synthesis of this fragment, and is currently under investigation for the preparation of longer polyol fragment of the hydrophilic part of the Nystatin A_1. [20,21]

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2. Bonini, C.; Racioppi, R.; Righi, G.; Rossi, L.; Viggiani, L. *Tetrahedron : Asymmetry*, **1993**, *4*, 793.
3. 3-benzyloxypropanal has also been the starting material for the enantioselective synthesis of the C_1-C_{10} fragment of Nystatin A_1, see below ref. 8.
4. The overall reaction sequence from 1-benzyloxy propanediol, already described in the experimental section of ref.2, was improved in many reaction steps (which are practically nearly quantitative): a major limitation for a further improvement appears the aldol condensation of 1-benzyloxypropionaldehyde, with the dianion of methyl acetoacetate. Anyway the yield of this reaction was improved up to 48%.
5. For the total synthesis of Amphotericin B see Nicolaou, K.C.; Daines, R.A.; Ogawa, Y.; Chakraborty, T.K. *J. Am. Chem.* Soc. **1988**, *110*, 4696 and previous work therein reported. For a complete list of references on the Amphotericin B chemistry see: Furstner, A.; Baumgartner, J.; *Tetrahedron* , **1993**, *49* , 8541.
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13. The need for buffered conditions was imposed by labile acid acetonide function. Other methodologies (i.e. Swern oxidation) did not give better results.
14. Since the traditional oxidative work-up (NaOH, H_2O_2) leads to a difficult separation of compound **4** with Ipc_2OH, the alternative methodology with 8-hydroxyquinoline was used (see Brown, H.C.; Racherta, U.S.; Liao, Y.; Khanna, V.V. *J. Org. Chem.*, **1992**, *57*, 6608).
15. The diastereomeric excess was determined by ^{1}H-NMR spectroscopy.
16. Compound **4**: ^{1}H-NMR: ($CDCl_3$): 5.75-5.92 (m, 1H), 5.05-5.18 (m, 2H), 4.16 (t, 2H, J= 5.7 Hz), 4.0.8-4.16 (m, 1H), 3.9-4.04 (m, 1H), 3.88 (M, 1H), 3.43 (bs, 1H), 2.18-2.32 (m, 2H), 2.05 (s, 3H), 1.77 (m, 2H) 1.46 (s, 3H), 1.58-1.68 (m, 2H), 1.38 (s, 3H), 1.28-1.33 ppm (m, 2H). ^{13}C-NMR ($CDCl_3$): 170.93, 134.82, 117.32, 98.79, 70.73, 69.95, 65.99, 60.77, 42.43, 42.04, 37.18, 35.38, 30.16, 20.67, 19.83 ppm. $[a]_D$= -10.4° (c= 1.1%, $CHCl_3$).
17. Compound **7**: ^{1}H-NMR: ($CDCl_3$): 4.2-4.32 (m, 1H), 4.03 (t, 2H, J= 6.7 Hz), 3.87-4.05 (m, 1H), 3.72-3.85 (m, 1H), 3.66 (s, 3H), 2.54 (dd, 1H, J= 15.26, 6.7 Hz), 2.36 (dd, 1H, J= 15.74, 6.7 Hz), 2.02 (s, 3H), 1.4-1.8 (m, 6H), 1.42 (s, 3H), 1.33 (s, 3H), 1.11-1.28 (m, 2H), 0.86 (s, 9H), 0.02 ppm (s, 6H). ^{13}C-NMR ($CDCl_3$): 171.29, 171.02, 99.61, 68.16, 65.91, 65.74, 64.53, 51.53, 43.49, 41.26, 36.80, 33.10, 30.04, 25.02, 24.21, 20.9, 19.58, -4.47ppm. $[a]_D$= + 5.9° (c= 2.2 %, $CHCl_3$).
18. Compound **8:** ^{13}C-NMR ($CDCl_3$): 171.20, 169.72, 74.98, 68.96, 64.34, 62.66, 42.86, 38.56, 36.05, 33.81, 24.77, 20.97 ppm. $[a]_D$= + 16° (c= 0.5 %, $CHCl_3$). lit. [10] $[a]_D$= + 15° ($CHCl_3$).
19. Following the same scheme, but using (-)-B-Ipc_2OMe (see scheme 2, step **b**) we have also obtained the other diastereoisomer of compound **8** (3R,5R,7S), which shows different pattern of ^{1}H-NMR spectrum in comparison with **8**. Further details will be given in a forthcoming paper.
20. All new compounds exhibited satisfactory spectroscopic exact mass data.
21. This work was partially supported by a MURST 40% grant.

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