Pergamon

Tetrahedron Letters 39 (1998) 9–12

TETRAHEDRON
LETTERS

# Enantioselective Polyol Synthesis *via* the Cope Rearrangement of Chiral Aldol Products. A Synthesis of the $C_1$-$C_{10}$-Fragment of Nystatin $A_1$

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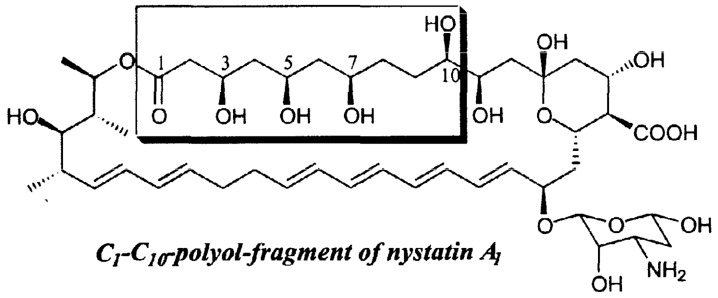
Received 25 August 1997; accepted 10 October 1997

**Abstract:** A stereoselective synthesis of a fully protected $C_1$-$C_{10}$-polyol-fragment of nystatin $A_1$ is described. The oxy-Cope rearrangement of the chiral aldol product **1** affords the aldehyde **3** as the key intermediate which is converted into the natural product fragment by enantioselective allylboration and intramolecular conjugate addition of a hemiacetal-alkoxide.

Nystatin $A_1$ is a member of the large group of over 200 polyene macrolide antibiotics which have been discovered so far.[1] Based upon their strong antifungal activity some of them like nystatin $A_1$ have become important clinical agents for the treatment of life-threatening fungal infections. The molecular structure of nystatin $A_1$ is devided into a polyene section of six double bonds and a polyol part of eight hydroxy groups which are positioned mainly in a 1,3-relationship. Such 1,3-diol motifs are also found in many other members of this class of natural products, thus the search for new stereoselective routes towards the synthesis of 1,3,5,..-polyol structures has been an area of active research for the past several years.[2]



*$C_1$-$C_{10}$-polyol-fragment of nystatin $A_1$*

We wish to present here a novel and stereoselective approach towards the $C_1$-$C_{10}$-polyol fragment of nystatin $A_1$[3] which is based on the Cope rearrangement of chiral aldol products.[4] This methodology was recently developed in our laboratory and has been successfully applied for the synthesis of enantiopure and highly substituted tetrahydropyrans[5] and piperidines.[6]

The chiral aldehyde **3** readily available *via* Cope rearrangement of aldol product **1** was envisaged as the key intermediate in our synthesis. It already contains three hydroxy groups of the $C_1$-$C_{10}$-fragment of nystatin $A_1$ in a masked form: the aldehyde to be converted into the $C_7$-hydroxy group by enantioselective allylboration, the phenyldimethylsilyl group to be traded for the $C_5$-hydroxy group by oxidative desilylation and the enoate moiety to be used for the introduction of the $C_3$-hydroxy group by conjugate addition of an oxa-nucleophile. The reason for the use of a 1-silyl-1,5-diene in this context is the poor performance of 1-alkoxy-1,5-dienes in the Cope rearrangement.[7]

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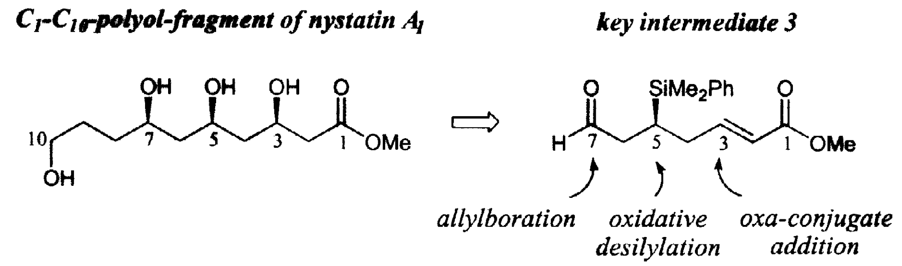
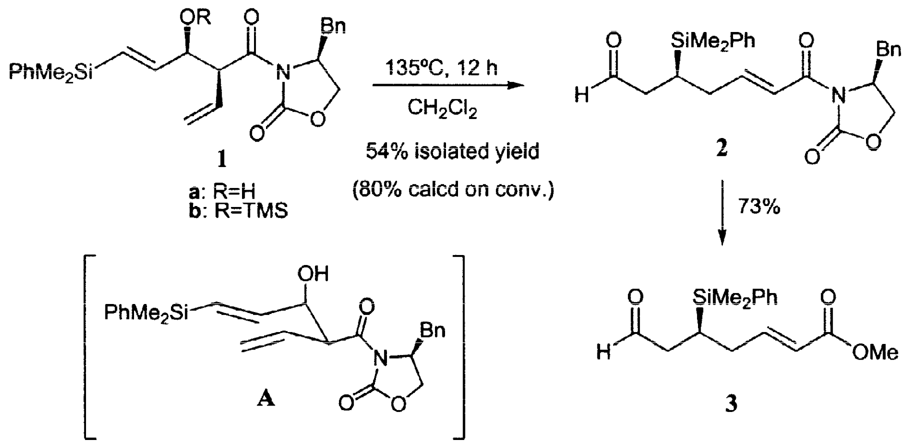
*PII:* S0040-4039(97)10455-5



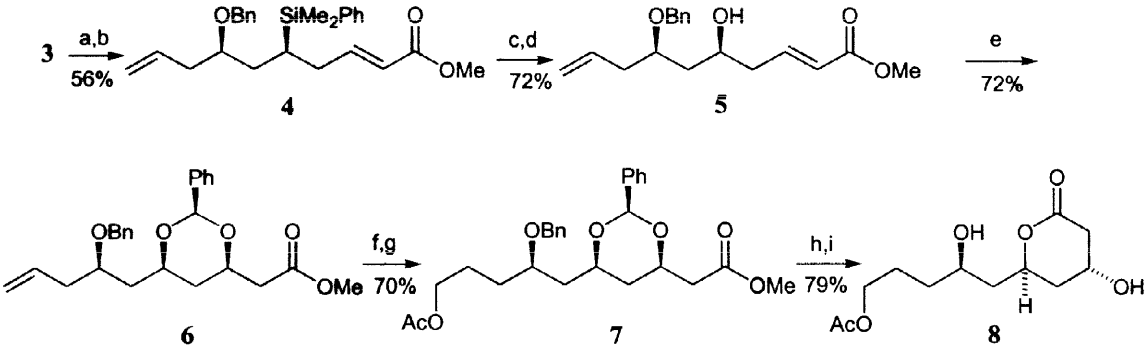
The aldol product **1a** was prepared in good yield according to the *Evans* asymmetric aldol methodology.[8] The standard silyloxy-Cope rearrangement of **1b** (R= $SiMe_3$) was complete within 20-30 min in toluene at 180°C (10:1 stereoselection). Apparently, the free activation energy of the sigmatropic rearrangement is significantly lower for the silyl-substituted 1,5-dienes compared to the alkyl-substituted ones.[9] Therefore, we reasoned that a Cope rearrangement of the unprotected aldol product **1a** (R= H) might be feasible with only minor amounts of retro-aldol products being produced. This side reaction usually prevents the use of the free aldol products in the Cope rearrangement. Under the optimized conditions ($CH_2Cl_2$, 135°C, 12 h) the desired product **2** was obtained in 54% yield as a single stereoisomer after chromatographic purification (Scheme 1). In addition, the corresponding retro-aldol products were isolated in 36% and 32% yield, respectively, and were routinely used for the aldol reaction again. Thus, the total yield for the oxy-Cope rearrangement calculated on conversion amounts to 80%. *This is the first example of a synthetically useful Cope rearrangement of an unprotected aldol product which we have encountered in our investigations so far.* We assume that the rearrangement proceeds through the depicted chairlike transition state **A** with an axial hydroxy and an equatorial carboximide group. Transesterification of the imide **2** (MgClOMe, $CH_2Cl_2$, 0°C) proceeded cleanly to furnish the methyl ester **3** in 73% yield.[10]



**Scheme 1**

With the key intermediate **3** available in enantiopure form and good overall yield we turned our attention to the elaboration of the $C_1$-$C_{10}$-fragment of nystatin $A_1$ (Scheme 2). Enantioselective allylation using *Brown's* allylbis(2-isocaranyl)borane[11] and benzylation ($Cl_3CC{=}NHOBn$, TfOH)[12] gave rise to **4** which already contains two chiral centers and constitutes the complete carbon backbone of the target molecule. Oxidative desilylation under retention of configuration *via* a two-step procedure (1. $BF_3$-AcOH, 2. $H_2O_2$, $NaHCO_3$)[13] produced the δ-hydroxy-α,β-enoate **5** in good overall yield. Treatment of **5** with benzaldehyde and KOtBu transformed the $C_5$-hydroxy group into the benzylidene hemiacetal alkoxide which now added to the enoate to install the protected $C_3$-hydroxy group *syn*-stereoselectively (25:1 stereoselection).[14] This conjugate addition is known to be thermodynamically controlled to deliver the dioxane **6**[15] with all substituents in equatorial positions.

**Scheme 2**



*Reagents and conditions:* a) allylbis(2-isocaranyl)borane, $Et_2O$, -78°C, 30 min, then $H_2O_2$, MeOH, rt, 30 min; b) $Cl_3CC{=}NHOBn$, TfOH, $CH_2Cl_2$, 0°C, 4 h; c) $BF_3(AcOH)_2$, $CH_2Cl_2$, rt, 5 min; d) $H_2O_2$, $NaHCO_3$, KF, MeOH, THF, rt, 5 h; e) KOtBu, PhCHO, $CH_2Cl_2$, 0°C, 1 h; f) $BH_3$-THF, THF, 0°C, 1 h, then $H_2O_2$, NaOH; g) $Ac_2O$, pyridine, rt, 6 h; h) Pd/C, $H_2$, EtOH; i) HF, $CH_3CN$, rt 1 h.

Finally, hydroboration of the terminal olefin and acetylation produced a fully protected, enantiopure $C_1$-$C_{10}$-polyol fragment of nystatin $A_1$ **7**. Upon hydrogenolysis and treatment with acid the benzyl protecting groups were removed and lactonization occurred to afford the known lactone **8**[16] whose spectroscopic and analytical properties were identical with the published data.[3]

In conclusion, we have achieved a very short and stereoselective synthesis of the $C_1$-$C_{10}$-polyol-fragment of nystatin $A_1$ with a highly selective and efficient oxy-Cope rearrangement of a chiral aldol product as the key step. The strategy presented here is expected to be applicable to the synthesis of even more complex polyol natural products which we are now actively pursuing.

**Acknowledgement.** This research has been supported by the Deutsche Forschungsgemeinschaft (Schn 441/1-1) and the Fonds der Chemischen Industrie. The Degussa AG is gratefully acknowledged for the donation of L-phenylalanine. We would like to thank Prof. Tietze for his generous support.

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15. $[a]_D^{20} = -13.0°$ ($c = 0.5$, $CHCl_3$); $^1H$ (200 MHz, $CDCl_3$): δ= 1.30-1.80 (m, 4 H, 4-$H_2$, 6-$H_2$), 2.04 (dt, *J*= 14.0, 7.0 Hz, 1 H, 8-H), 2.33-2.45 (m, 1 H, 8-H), 2.47 (dd, *J*= 15.5, 5.5 Hz, 1 H, 2-H), 2.70 (dd, *J*= 15.5, 7.0 Hz, 1 H, 2-H), 3.60-3.75 (m, 1 H, 7-H), 3.70 (s, 3 H, OMe), 3.95-4.10 (m, 1 H, 5-H), 4.18-4.35 (m, 1 H, 3-H), 4.46 (d, *J*= 15.5 Hz, 1 H, benzyl-H), 4.61 (d, *J*= 15.5 Hz, 1 H, benzyl-H), 5.11 (d, *J*= 17.0 Hz, 1 H, 10-H), 5.14 (dd, *J*= 10.5, 1.0 Hz, 1 H, 10-H), 5.54 (s, 1 H, acetal-H), 5.86 (ddt, *J*= 17.0, 10.5, 7.0 Hz, 1 H, 9-H), 7.28-7.38 (m, 10 H, phenyl-H); $^{13}C$ (50 MHz, $CDCl_3$): d= 36.84, 38.19, 39.80, 40.72 (C-2, C-4, C-6, C-8), 51.75 (OMe), 70.67 (benzyl-C), 73.15, 73.74, 74.38 (C-3, C-5, C-7), 100.6 (acetal-C), 117.5 (C-10), 126.0, 127.6, 128.0, 128.1, 128.4, 128.6, 138.4, 138.6 (phenyl-C), 134.5 (C-9), 171.2 (CO).
16. $[a]_D^{20} = +16.0°$ ($c = 0.8$, $CHCl_3$); $^1H$ (500 MHz, $CDCl_3$): δ= 1.50-1.65 (m, 2 H, 8-$H_2$), 1.67-1.86 (m, 4 H, 6-$H_2$, 9-$H_2$), 1.94 (dt, *J*= 14.0, 8.0 Hz, 1 H, 4-H), 2.07 (s, 3 H, OAc), 2.09 (mc, 1 H, 4-H), 2.65 (br d, *J*= 17.0 Hz, 1 H, 2-H), 2.71 (dd, J= 17.0, 4.0 Hz, 1 H, 2-H), 3.00-3.60 (br s, 2 H, 2x OH), 3.84 (mc, 1 H, 7-H), 4.09 (t, *J*= 6.0 Hz, 2 H, 10-$H_2$), 4.34-4.40 (m, 1 H, 3-H), 4.94 (mc, 1 H, 5-H); $^{13}$ C (125 MHz, $CDCl_3$): δ= 20.99, 24.71, 33.75, 35.51, 38.38, 42.75, 62.31, 64.36, 68.51, 75.00, 170.8, 171.4. All new compounds were fully characterized by IR, UV, MS, NMR and combustion analysis.