*Tetrahedron* Vol. 48, No. 44, pp. 9801-9808, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00
Pergamon Press Ltd

# Iterative Diastereoselective Reduction of Hydroxy Diketoesters to all 1,3,5 Syn Triols: Synthesis of $C_1$-$C_{10}$ Fragment of Nystatin $A_1$

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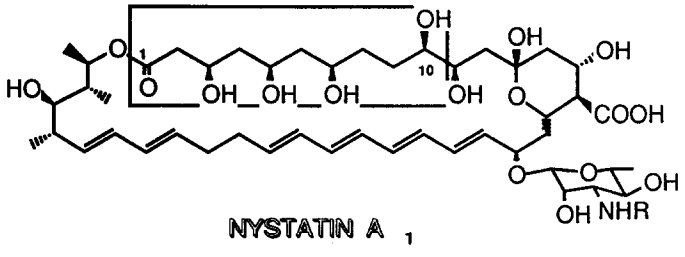
(*Received in UK 27 July* 1992)

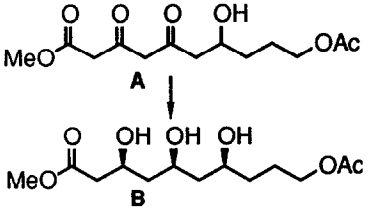
***Abstract:*** *the iterative diastereoselective reduction of a model hydroxy 3,5 diketo ester to the corresponding skipped 1,3,5 triol ester was studied in different conditions. The use of $NaBH_4/Ti(OiPr)_4$ in THF leads with good stereoselection to the syn-syn triol ester as the main product; the described method has been applied to an extremely short synthesis of the $C_1$-$C_{10}$ fragment (in racemic form) of the macrolide antibiotic Nystatin $A_1$.*

Stereocontrolled synthesis of polyether, polyoxy and polyene macrolide antibiotics has received conspicuous attention in the recent years. A striking feature of many natural substances within the polyene macrolides is the presence of a long chain with alternating hydroxyl functions, so called "skipped" polyols or 1,3 polyols.

Among the class of polyene macrolide antibiotics the complete stereostructure of Nystatine $A_1$[1], used in human therapy, has been recently assigned by a proton NMR study.[2] The $C_1$-$C_{10}$ fragment shows a *syn-syn* relationship between the three hydroxyl groups as demonstrated by two independent syntheses.[3]




NYSTATIN A $_1$

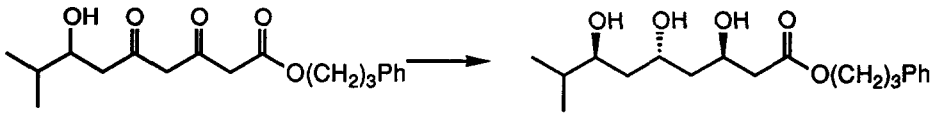



Many synthetic methodologies have been recently developed for the stereoselective synthesis of 1,3 polyols[4]: among them very significant results were obtained by reduction of acyclic β-hydroxy ketones or ketoesters, leading to the corresponding *syn* or *anti* 1,3 diols.[5]

An attractive alternative to the referenced methods[4] to prepare the $C_1$-$C_{10}$ fragment of Nystatin $A_1$ could be a sequential diastereoselective reduction of a β-hydroxy diketoester of type A: this should afford, with the

correct relative configuration in a straightforward step , the triol **B** which has been already characterized as an isolated fragment from Nystatin $A_1$. A pioneering work in a related iterative reduction was done by Evans[6], with the application of his methodology (intramolecular reduction mediated by $Me_4NHB(OAc)_3$)[7] to the iterative reduction of 3-phenylpropyl-7-hydroxy-3,5-dioxo-8-methyl nonanoate to the corresponding 1,3,5 *anti-anti* triol ester (see figure 1).

**Figure 1**



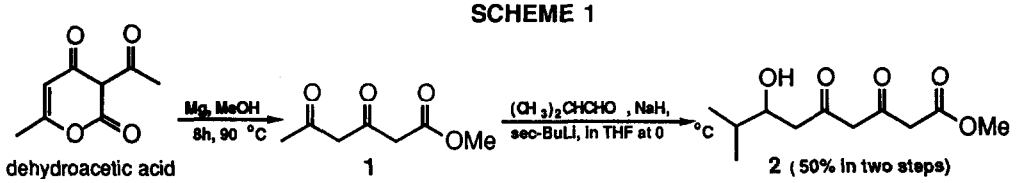

3-phenylpropyl 7-hydroxy-
3,5-dioxo-8-methyl nonanoate

*anti-anti*

Unfortunately the model compound used by Evans requires several steps to be prepared in very low yield.[6] Therefore the hydroxy diketo ester **2** (see scheme 1) was chosen as model for our initial studies because of its easy availability by a short synthetic sequence and with the possibility of comparing the final triols with the corresponding lactones already obtained and characterized .[6]

The following short preparation (scheme 1) was used to prepare our model compound **2** (methyl 7-hydroxy-3,5-dioxo-8-methylnonanoate) starting from the commercially available dehydroacetic acid.This was transformed[8] to the diketoester **1**, and then condensed (as trianion) with isobutyraldehyde affording, in reasonable yield, compound **2**.

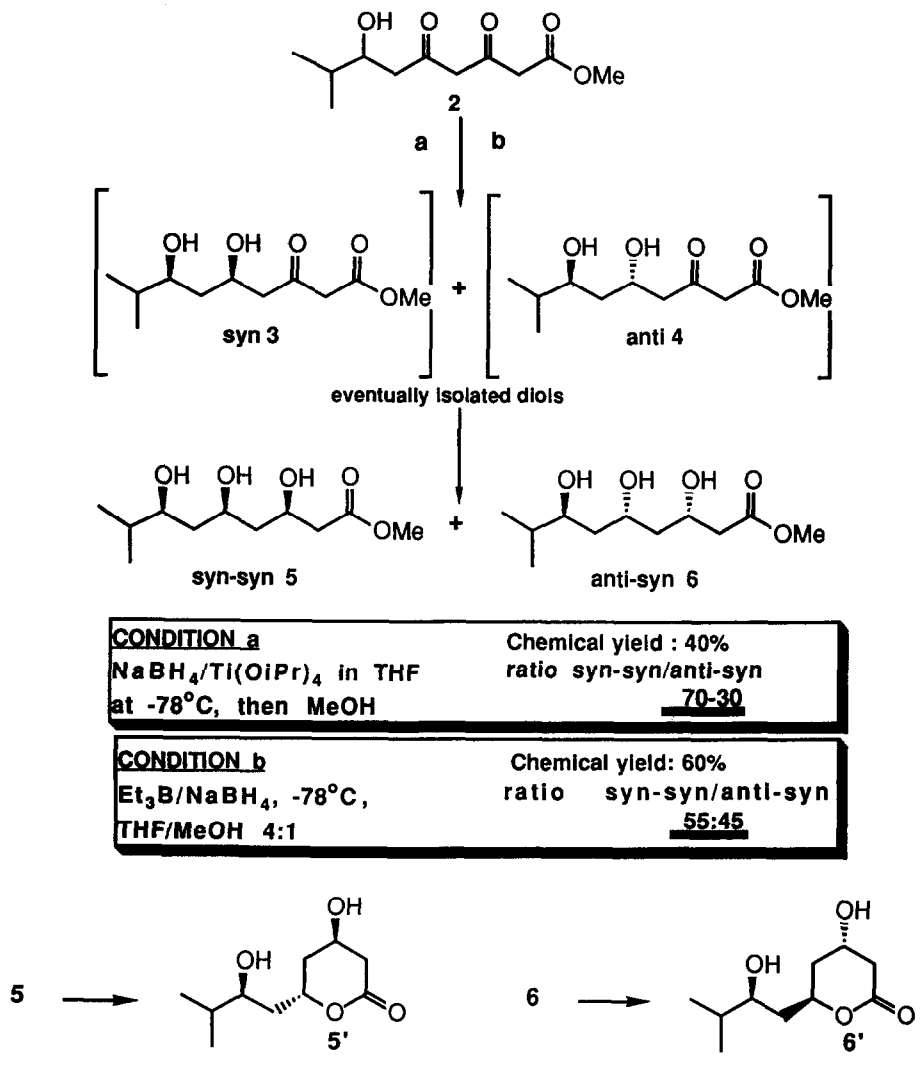
**SCHEME 1**




dehydroacetic acid **1** **2** ( 50% in two steps)

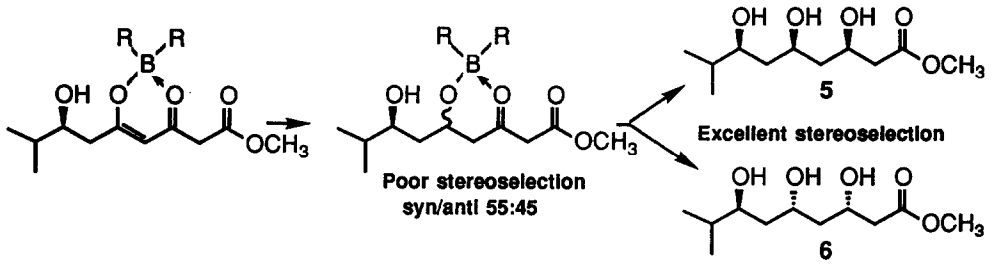
The model compound **2** was then subjected to the iterative reduction (see Scheme 2) using two different procedures, both employing a chelate-controlled intermolecular addition of hydride: **condition a**, developed by us[9] and **condition b**, the well known Merck procedure.[10] The described conditions and the chemical and diastereoselective yields were obtained after exhaustive studies in order to drive the reaction to completion[11], with the formation of two diastereoisomers (*syn-syn* **5** and *anti-syn* **6**) . The reaction can also be stopped (see experimental) in order to isolate the intermediate diols **3** and **4**; the ratio between the *syn* diol **3** and *anti* diol **4** was similar to those obtained for the final triols( **condition a**, *syn/anti* 70:30; **condition b**, *syn/anti* 57:43). This result clearly indicates that , in both the conditions used, the second reduction was more diastereoselective than the first one. The assignment of the correct relative configuration was demonstrated by transformation of the triols **5** and **6** to the corresponding lactones **5'** and **6'** (HF in $CH_3CN$, see experimental) which were shown to be identical to those already described.[6]

**SCHEME 2**



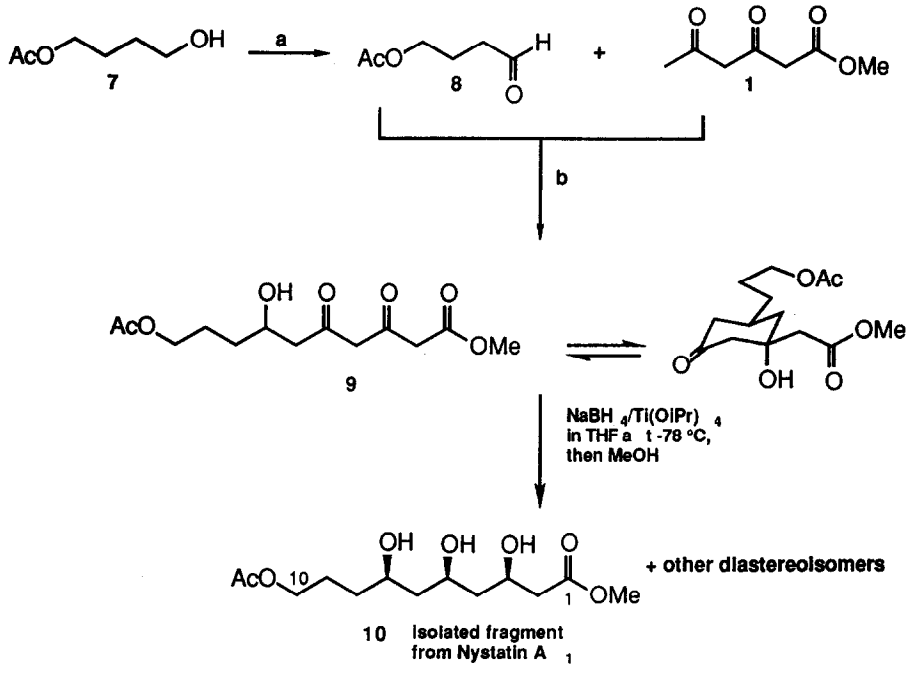

Quite surprisingly the Merck procedure did not give an acceptable stereoselection as shown in other cases.One reason for this outcome (which is in sharp contrast with other results, ref.6) can be assumed in a favored chelation between the two carbonyl groups (one in enol form), which leads to an obvious non stereoselective reduction of the first carbonyl (see figure 2).This type of chelation, with the use of the Merck procedure, has been already described in the reduction of 3,5 diketo esters.[12] The second reduction was indeed diastereoselective as expected, leading to the all *syn* compound **5** and to the *anti-syn* **6** in almost identical ratio.

## Figure 2




With these results in our hands we decided to achieve the synthesis of the $C_1$-$C_{10}$ fragment of Nystatin $A_1$ by the sequential diastereoselective reduction of the hydroxy diketoester **9**.

## SCHEME 3




a) PCC, in $CH_2Cl_2$ (86 %). b) NaH, s-BuLi, in THF at -35 °C, 5 min, 32%).

**9** was easily synthesized as shown in the scheme 3. Aldehyde **8** was prepared from the known monoacetyl 7[13] via PCC oxidation.The trianion of **1** (already prepared, see scheme 1 ) was condensed with the aldehyde **8** affording the desired compound **9**, which was shown to be a mixture of acyclic and hemiketal tautomers. Finally **9** was reduced in the described conditions and the crude mixture of triols was chromatographed on silica

gel affording in a 41% yield a major product.The $^1$H-NMR spectrum of this compound **10** (in $C_6D_6$) showed the same spectroscopic data described for the isolated fragment of Nystatin $A_1$.[14] Other diastereomeric compounds (not separated) were also recovered : the ratio between the *syn-syn* triol ester **10** and the other diastereoisomers was 88:12.

In conclusion the described sequence represents a straightforward synthesis of $C_1$-$C_{10}$ fragment of Nystatin $A_1$ with the application of a novel sequential diastereoselective reduction. Starting from an appropriate chiral hydroxyester such as **9** this synthesis will allow the fragment **10** to be obtained in optically active form and studies are in progress on this direction as well on the the improvement of the iterative diastereoselective reduction.

## EXPERIMENTAL

**GENERAL:** Flash chromatography was carried out on silica gel (Merck (70-230 mesh). Deactivated silica gel was used in some separations ( prepared by treatment with 2N HCl and then washed with $H_2O$ until neutrality and dried in air). TLC analyses were carried out on Merck Kieselgel 60 F-254 plates, monitoring the plates with U.V. lamp, $I_2$ exposure and $H_2SO_4$ 2N spraying and heating. All the solvents used were distilled and dried before use. $^1$H-NMR spectra were recorded on a Varian Gemini (200 MHz) instrument with a $CDCl_3$ solution and $CHCl_3$ as internal standard or otherwise noted.$^{13}$C-NMR spectra were determined on the same instrument (50.3 MHz) .

**Methyl-7-hydroxy-3,5-dioxo-8-methyl nonanoate 2** : compound **1** ( 635 mg, 4 mmol,prepared according to ref. 8) was slowly added to a vigorously stirred suspension of NaH (160 mg, 5 mmol) in dry THF( 25 mL) at 0 °C under a nitrogen atmosphere. After evolution of $H_2$ was ceased sec-BuLi ( 8 mmol of a 1.4M solution in cyclohexane) was dropwise added over 10 min. After 15 min to the red suspension isobutyraldehyde (250 mg, 4 mmol) was neat added: the mixture was stirred for 2 min and then quenched with 1N solution of $NaHSO_4$ (30 mL). The mixture was raised at room temperature and then diluted with $Et_20$ ( 100 mL) and the organic layer separated. The aqueous layer was extracted twice with AcOEt (100 mL); the combined organic layers were washed with phosphate buffer solution (30 mL, pH 7) and the aqueous layer was extracted twice with AcOEt. All the organic layers were dried over anhyd $Na_2SO_4$ and then concentrated in vacuo affording 2 g of a red oil. The crude product was purified by chromatography (hexanes/AcOEt 7:3 as eluent) on deactivated silica gel ( see general ) affording 490 mg (53% yield) of compound **2** , as yellow oil. $^1$H-NMR : 5.7 (s, 0.3H); 5.6 (s, 0.7H). 5.0 (bs, OH); 3.9 (m, 1H); 3.7 (s, 3H); 3.3 (s, 2H); 2.8-2.0 ( m, 4H); 1.7 (e, J = 6.3 Hz, 1H); 0.9 ppm( 2d, J= 6.3 Hz, 6H). $^{13}$C-NMR: 206.30; 172.67; 101.13; 97.50; 74.40; 60.04; 52.39; 51.00; 44.48; 44.23; 33.05; 18.31; 18.28 ppm.

**General procedure for the reduction the hydroxy diketo ester 2 (condition a):** in a round bottom flask under nitrogen atmosphere with magnetic stirring, hydroxy diketoester **2** ( 101 mg, 0.44 mmol was added in dry THF (10 mL). The solution was then cooled at - 78 °C and added of $Ti(OiPr)_4$ (0.53 mmol). After 30 min $NaBH_4$ (3 mmol) was added and the reaction was stopped after 6 h (TLC monitoring) in order to isolate the intermediates diols **3** and **4** (quenching with saturated $NH_4Cl$ solution).The reaction mixture was raised at room temperature and extracted with AcOEt (three times). The organic layers were dried over anhyd $Na_2SO_4$ and

evaporated in vacuo affording the crude products (diols) which were purified by silica gel chromatography (hexanes/AcOEt 7:3 as eluent). Following this procedure the diols **3** ( 48 mg) and **4** (20 mg) were obtained in a ratio 70/30 with an overall yield of 68 %.

**Diol syn 3**: $^1$H-NMR: 5.2 (d, J= 2.5 Hz, OH); 4.15 (m, 1H); 3.84 (m, 1H); 3.7 (s, 3H); 2.58 (s, 2H); 2.0-1.2 (m, 6H); 0.8 ppm (2d, J= 8.7 Hz, 6H). $^{13}$C-NMR; 172.75; 96.87; 69.77; 65.45; 52.14; 45.08; 41.39; 34.98; 32.72; 18.47; 18.38 ppm.

**DIol anti 4**: $^1$H-NMR: 4.7 (d, J= 2.3 Hz, OH); 4.15 (e, J= 4.6 Hz, 1H); 3.71 (s, 3H); 3.53 (ddd, J= 11.8, 8.6, 2.5 Hz, 1H); 2.65 (d, J= 14.8, 1H); 2.56 ( d, J= 14.8 Hz, 1H); 2.12 ( ddd, J= 24.7, 4.9, 1.7 Hz, 1H); 1.96 (m, 1H); 1.61 (e, J= 8.6 Hz, 1H); 1.4-0.95 (m, 2H); 0.9 ppm (2d, J= 8.6 Hz, 6H). $^{13}$C-NMR: 173.15; 96.44; 73.95; 65.28; 52.13; 45.12; 44.03; 33.77; 32.67; 18.63 ppm.

If the reaction must be driven to the final triols, after 6 h MeOH (0.5 mL) was added and the reaction was left overnight (18 h ) at - 78 °C. After TLC monitoring the reaction was stopped with gaseous $CO_2$ until neutrality. Then $H_20$ ( 2 mL) was added and the mixture was diluted with AcOEt. After evaporation of the organic solvents the aqueous residue was filtered, washed with hot AcOEt and extracted with AcOEt (twice).The collected organic layers, dried over anhyd $Na_2SO_4$, were concentrated in vacuo affording a crude mixture of products, which was chromatographed on silica gel (hexanes/ AcOEt 6:4 as eluent).The pure triols **5** (28 mg) and **6** (12 mg) were obtained in a ratio 70:30 with an overall yield of 41 %.

**Triol syn-syn 5**: $^1$H-NMR: 4.3 (m, 1H, ); 4.1 (m, 1H); 3.9 (bs, OH); 3.68 (s, 3H); 3.65 (m, 1H); 3.1 (bs, OH); 2.5 (m, 2H); 1.4-1.8 (m , 5H, OH); 0.9 ppm (2d, J= 6.2 Hz, 6H). $^{13}$C-NMR: 173.20; 77.45; 73.18; 68.68; 51.72; 42.74; 41.31; 39.61; 33.95; 18.00; 17.30 ppm.

**Triol anti-syn 6**: $^1$H-NMR: 4.3 -4.1 (m, 2H, OH); 4.0 (bs, OH); 3.69 (s, 3H); 3.65 (m, 1H); 2.8 (bs, OH); 2.48 (m, 2H); 1.5-1.8 (m, 5H); 0.92 ppm (d, J= 6.5 Hz, 3H); 0.88 ppm (d, J= 6.5 Hz, 3H); . $^{13}$C-NMR: 173.21; 73.45; 70.05; 68.96; 51.78; 41.72; 41.35; 39.39; 33.64; 18.33; 17.65 ppm.

**Syn-syn lactone 5'**: triol **5** (15 mg) was added to $CH_3CN$ ( 4 mL) in a round bottom flask under argon atmosphere. Then HF (0.5 mL of a 40% aqueous solution) was added with stirring. After 2 h (TLC monitoring) the reaction was stopped by elution with AcOEt (50 mL); the organic phase was washed with saturated $Na_2CO_3$ and then with brine until neutrality. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The crude product was purified by chromatography (AcOEt/$CHCl_3$ 7:3 as eluent) affording pure **11** as on oil (11 mg, 75%). $^1$H-NMR: 4.93 (m, 1H); 4.39 (m, 1H); 3.6 (m, 1H); 2.7-2.5 (m, 2H); 2.2 (bs, 2OH); 2.1 (m, 1H); 1.9-1.6 (m, 4H); 0.91 (d, J= 6.9 Hz, 3H); 0.88 ppm(d, J= 6.9 Hz, 3H) (see ref. 6 for comparable data).

**Anti-syn lactone 6'** : triol **6** (5 mg) was treated as above described for compond **5**, afforging pure **6'** (4 mg, 83%). $^1$H-NMR: 5.0 (m, 1H); 4.35 (m, 1H); 3.74 (m, 1H); 3.0 (bs, OH); 2.6-2.7 (m, 2H); 1.82 (bs, OH); 2.0-1.5 (m, 5H ); 0.9 ppm (2d, J= 6.7 Hz, 6H). (see ref. 6 for comparable data).

**Procedure for the reduction of the hydroxy diketester 2 (condition b)**[10]: a solution of $Et_3B$ (0.5 mL of a 1M solution in THF) was added to a mixture of THF (4 mL) and MeOH (1 mL) at room temperature under argon. After stirring for one hour, the mixture was cooled at - 78 °C, followed by the addition of compound **2** ( 100 mg, 0.45 mmol) and the stirring was continued for 30 min. Then $NaBH_4$ (1.5 mmol) was added and the mixture was stirred for 3-8 h. The reaction mixture was quenched with $CO_2$ after diluting with AcOEt . The mixture was then filtered and the organic layer was dried and evaporated in vacuo. The residue was then azeotroped a few times with MeOH until boron-containing compounds were removed. If the reaction was stopped after 3 h, the diols **3** and **4** were isolated in a ratio 57:43 (overall yield 65%). If the reaction was continued for 8 h, the triols **5** and **6** were isolated in a ratio 55:45 ( overall yield 60%).

**4-acetoxy butanal 8**: alcohol **7**[13] (2 g, 15.15 mmol) dissolved in $CH_2Cl_2$ (15 mL), was added to a vigorously stirred suspension of PCC ( 4.9 g, 22.8 mmol) in $CH_2Cl_2$ (30 mL) at room temperature. After 3 h, (TLC monitoring) $Et_2O$ ( 50 mL) was added and the supernatant liquid was decanted. The insoluble residue was washed with $Et_2O$ (5 for 20 mL) and the combined organic fractions were passed through a short pad of Florisil. The filtrate was concentrated in vacuo affording crude aldehyde **8** (1.7 g, 86%) which was used without purification. $^1$H-NMR: 9.8 (s, 1H); 4.08 (t, J= 4.8 Hz, 2H); 2.57 (t, J= 7.7 Hz, 2H); 2.1 (s, 3H); 1.8 ppm (m, 2H). $^{13}$C-NMR: 201.90; 171.95; 63.70; 40.71; 25.45; 21.47 ppm.

**Methyl 10-acetoxy-7-hydroxy-3,5-dioxodecanoate 9** : compound **1** ( 608 mg, 3.85 mmol,prepared according to ref. 8) was slowly added to a vigorously stirred suspension of NaH (145 mg, 4.8 mmol) in dry THF( 35 mL) at 0 °C under a nitrogen atmosphere. After evolution of $H_2$ was ceased sec-BuLi ( 8.5 mmol of a 1.4M solution in cyclohexane) was dropwise added over 10 min. After 15 min the red suspension was cooled at - 35 °C and then aldehyde **8** (500 mg, 3.85 mmol) was neat added: the mixture was stirred for 2 min and then quenched with 1N solution of $NaHSO_4$ (30 mL). The mixture was raised at room temperature, diluted with $Et_20$ ( 100 mL) and the organic layer separated. The aqueous layer was extracted twice with AcOEt (100 mL); the combined organic layers were washed with phosphate buffer solution (30 mL, pH 7) and the aqueous layer was extracted twice with AcOEt. All the organic layers were dried over anhyd $Na_2SO_4$ and then concentrated in vacuo affording 1.5 g of a red oil. The crude product was purified by chromatography on deactivated silica gel (hexanes/AcOEt 8:2 as eluent) affording 345 mg (32% yield) of compound **9** , as yellow oil. $^1$H-NMR: 5.6 (s, 0.5 H); 5.4 ( s, 0.5H); 4.63 (m, 1H); 4.1 (bt, J= 7.0 Hz, 2H); 3.8 (s, 3H); 3.71 (m, 2H); 3.2-3.5 (s, 1H); 2.11 (s, 3H); 2.05 (m, 2H); 2.0-1.5 ppm (m, 4H). $^{13}$C-NMR: 174.87; 171.64; 104.50; 79.65; 64.54; 63.97; 52.71; 29.79; 24.90; 24.28; 21.12 ppm.

**Reduction of the hydroxy diketoester 9**: the reduction was carried out on compound **9** (100mg, 0.35 mmol) in the same conditions described for compound **2** ( **condition a**, see above). After 15 h the reaction was stopped (TLC monitoring) and the crude mixture was chromatographed on silica gel (hexanes/AcOEt, 6:4 as eluent) affording as the main product compound **10** ( 32 mg, 41 %) together with an unseparable mixture of diastereoisomers ( 6 mg) with a ratio of 88:12.

**Triol syn-syn 10**: $^1$H-NMR (in $C_6D_6$): 4.3 (bs, OH); 4.06 (t, J= 6.6 Hz, 2H); 4.01 (m, 1H); 3.80 (m, 1H); 3. 68 (m, 1H); 3.6 (bs, OH); 3.28 (s, 3H); 3.25 bs, OH); 2.24 ( dd, J= 7.8, 16.5 Hz, 1H); 2.08 (dd, J= 3.9,

16.5 Hz, 1H); 1.71 (s, 3H); 1.6-1.7 (m, 2H); 1.25-1.4 (m, 4H); 1.0-1.16 ppm (m, 2H).$^{13}$C-NMR ($CDCl_3$): 173.28; 171.54; 72.98; 71.70; 68.76; 64.42; 51.81; 43.12; 42.55; 41.16; 33.93; 24.41; 20.82 ppm, (see reference 14 for comparable data).

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15. This work was partially supported by C.N.R. "Progetto Chimica Fine e Secondaria".