β-HYDROXY-δ-LACTONES AS CHIRAL BUILDING BLOCKS INVOLVING 1,3-DIHYDROXYL FUNCTIONS. 1. NEW STRATEGIES FOR STEREOSELECTIVE CONSTRUCTION OF 2-METHYL-3,5-DIHYDROXY ESTERS

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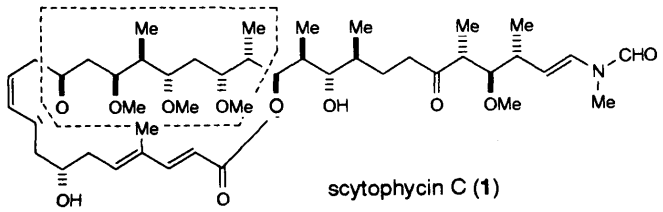
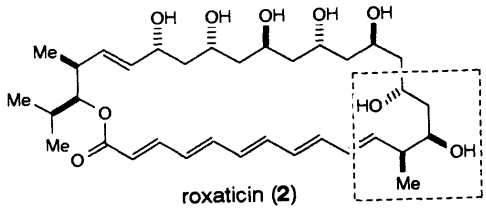
Four possible isomers of 2-methyl-3,5-dihydroxy ester derivatives, useful building blocks for natural product synthesis, were synthesized stereoselectively using C_3-hydroxyl-directed methylation of β-hydroxy-δ-lactone and β,δ-dihydroxy ester.

KEYWORDS β-hydroxy-δ-lactone; β,δ-dihydroxy ester; hydroxyl-directed methylation; scytophicin C; roxaticin; chiral building block; stereoselective synthsis

The 2-methyl-3,5-dihydroxy ester units **3** ~ **6** are useful building blocks in the total synthesis of poly-functionalized natural products such as scytophycin C (**1**),[1] roxaticin (**2**)[2] and the related biologically active compounds.[3] Essential for the synthesis of 2-methyl esters with sterically defined 3,5-dihydroxyl groups is the enantioselective aldol condensation of propionate equivalents[4] or crotyl boronates[4] involving a complex chiral auxiliary with an α-unsubstituted aldehyde **7** having a chiral hydroxyl group at the β-position. Thus, development of a simpler way to construct these building blocks is needed. We now report the practical strategies for synthesizing four possible isomers **3**,**4**,**5**, and **6** stereo-selectively combining several simple reactions effectively.

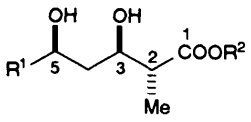


scytophycin C (**1**)

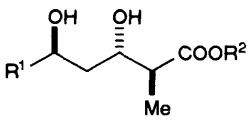


roxaticin (**2**)

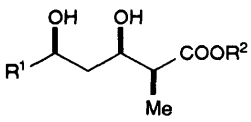
The key intermediates in our strategies are 3,5-*syn*-dihydroxy esters **9**[5] and 3,5-*anti* derivatives **10**[5], which are now easily obtained by diastereoselective reduction of the corresponding 5-hydroxy-3-ketoesters **8**[5,6] using the Prasad[7] or Evans[8] procedure. Among four possible isomers, 2,3-*anti* isomers **3** and **4** are usually prepared by direct methylation of trianion derived from **9** and **10**, respectively, since methylation of the dianions derived from β-hydroxy esters affords 2,3-*anti*-2-methyl-3-hydroxy esters.[9] In fact, when 3,5-dihydroxy esters **9** and **10** were triply deprotonated by using slightly enforced basic conditions [5 eq of LDA, -20°C in THF-HMPA (5 eq)] and then treated with methyl iodide at -78°C, the desired 2,3-*anti*-dihydroxy esters **3**[5,10] (R^2= Et ; 63 ~ 70%) and **4**[5,10] (R^2= Et ; 55 ~ 61%) were obtained accompanied with some nonreacting starting materials (10 ~ 20%). The diastereoselectivities of methylation were in the range of 5 ~ 9 : 1 in the 3,5-*syn*-dihydroxy esters **9** but were much higher (12 ~ 15 : 1) in the 3,5-*anti* derivatives **10**. The better selectivity with 3,5-*anti* may be explained by considering that the intramolecular chelated structure **ii** for the transition state in which the α-face is severely



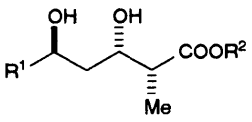
3 (2,3-*anti*-3,5-*syn*)



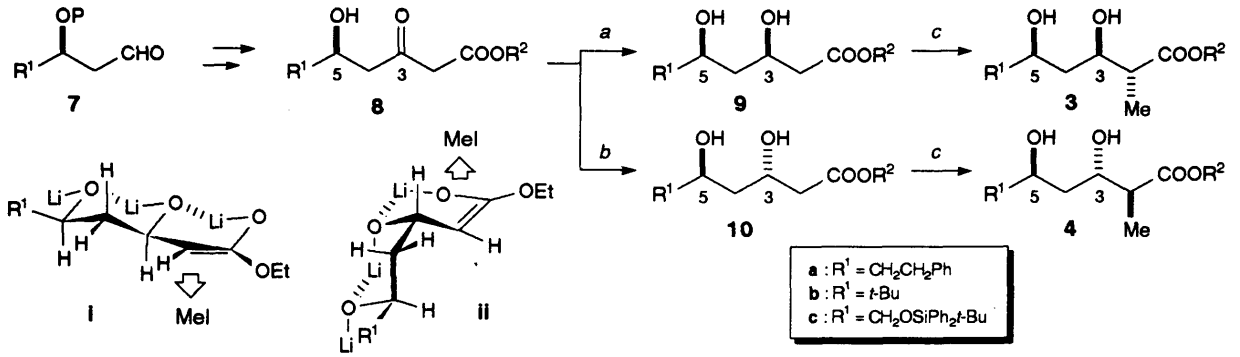
4 (2,3-*anti*-3,5-*anti*)



5 (2,3-*syn*-3,5-*syn*)



6 (2,3-*syn*-3,5-*anti*)

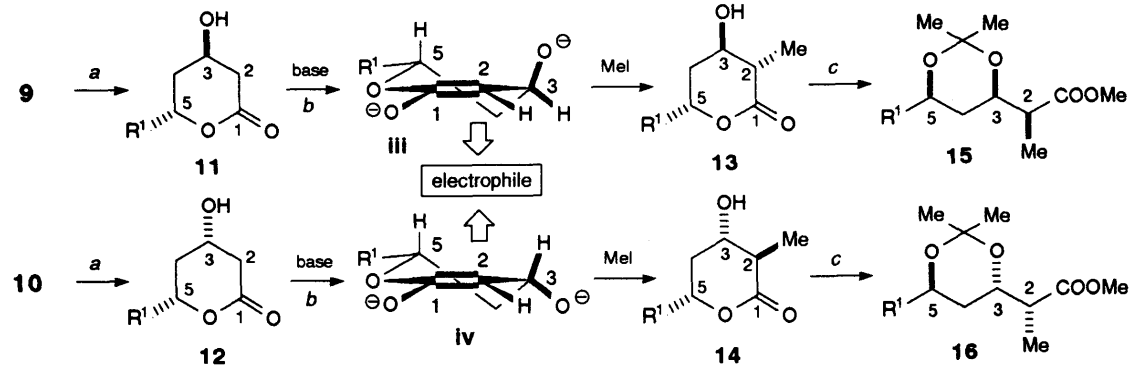


Reagents and conditions: (*a*) Et_2BOMe-$NaBH_4$, THF, -78°C; **9a**: 71% (3,5-*syn* : 3,5-*anti* = 25 : 1); **9b**: 75% (20 : 1); **9c**: 96% (30 : 1); (*b*) $Me_4NB(OAc)_3H$, AcOH-CH_3CN, 0°C; **10a**: 81% (3,5-*syn* : 3,5-*anti* = 1 : 9); **10b**: 70% (1 : 10); **10c**: 90% (1 : 12); (*c*) LDA (5 eq), THF-HMPA (5 eq), -20°C, 60 min then MeI (10 equiv), -78°C, 60 min; **3a**: 63% (2,3-*syn* : 2,3-*anti* = 5 : 1); **3b**: 70% (9 : 1); **3c**: 63% (6 : 1); **4a**: 58% (12 : 1); **4b**: 55% (15 : 1); **4c**: 61% (13 : 1).

hindered. However, in the linear transition state **i** from **9**, there is no such apparent steric effect.

On the other hand, further elaboration is neede for the synthesis of 2,3-*syn* esters **5** and **6**. We focussed our attention on the stereoselective methylation of β-hydroxy-δ-lactones **11**[5] and **12**[5] derived from **9** and **10**, respectively. They are regarded as a masked 3,5-dihydroxy acid having fixed conformation. The particular feature of this system is that dianions **iii** and **iv** derived from them can not form cyclic chelated structure as **i** and **ii** do, thus a different stereochemical entry is produced for the nucleophilic reactions at the C_2-positions. Alkylation is expected to take place from the opposite side of the sterically demanding 3-hydroxyl group (see **iii** and **iv**). In fact, such selectivity has occurred in the alkylation of the related β-hydroxy lactones.[11]

The starting β-hydroxy-δ-lactones have been synthesized in many laboratories[12] in connection with the synthesis of inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase.[13] However, note that although structure modification aiming to produce such hypocholesterolemic agents has often been tried, little attention has been paid to the further synthetic use of these unique units. The present work is the first report using the readily obtainable 5-substituted-3-hydroxy-δ-lactones **11** and **12** as key elements to prepare useful building blocks.



Reagents and conditions: (*a*) 1. LiOH, aqTHF, 0°C; 2. Reflux in benzene with MS-4A trap (in toluene for **c** series); **11a**: 85%; **11b**: 86%; **11c**: 85%; **12a**: 92%; **12b**: 89%; **12c**: 89%; (*b*) LDA (3 eq), THF-HMPA (5 eq), -40°C, 90 min then MeI (10 eq), -78°C, 60 min; **13a**: 90% (2α-Me : 2β-Me = 99 : 1); **13b**: 82% (20 :1); **13c**: 82% (33 : 1); **14a**: 81% (1 : 24); **14b**: 82% (1: 24); **14c**: 79% (1 : 18); (*c*) Dimethoxypropane, CSA, MeOH, CH_2Cl_2, room temp.; **15a**: 89%; **15b**: 47%; **15c**: 84%; **16a**: 75%;**16b**: 90%; **16c**: 88%

Lactones **11**[5] and **12**[5] were obtained from **9** and **10** by hydrolysis followed by azeotropic ring closure. Base treatment (3 eq of LDA, 5 eq of HMPA, THF, -40°C) and the subsequent MeI addition at -78°C afforded 2α-methyl lactones **13**[5] (>20 :1) and 2β-methyl lactones **14**[5] (>18 : 1), respectively, as expected. The stereochemistry of the newly introduced methyl group was directed in both cases mainly by the geometry of the C_3-hydroxyl group[14] and not by the C_5-substituent. The C_2-

methylated lactones thus obtained were then treated under the usual acetonide formation conditions (dimethoxypropane, CSA in CH_2Cl_2). Acid-catalyzed ring opening and acetonide formation proceeded simultaneously slowly affording the protected 2,3-*syn*-2-methyl-3,5-dihydroxy methyl esters **15**[5] and **16**[5], which are equivalent to **5** and **6**, respectively, in good yield.[15] Adding a small amount (ca. 2 eq) of methanol to the reaction solution slightly accelerated the reaction rate.

These stepwise strategies for constructing **3** ~ **6** are useful for securing a relatively large amount of stereo-chemically well defined isomers starting from the same β-hydroxy aldehyde **7** *via* **8**. In particular, when (*S*)-malic acid is used as the precursor for **7c**,[6] optically active **3c** ~ **6c** having functionality at the C_6-carbon can be prepared by this simple procedure. Further investigation of the nucleophilic reactions of β-hydroxy-δ-lactone dianion with other electrophiles and natural-product synthesis using the present methodology are now in progress.

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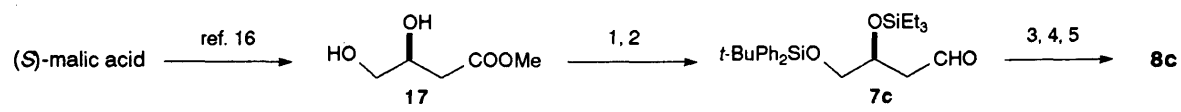
5) The structure of each new compound was confirmed by IR and ^{1}H-NMR (400 or 500MHz) spectra. Additionally, elemental analysis was carried out in the **c** series. Physical properties (melting point and optical rotation in $CHCl_3$ at 25°C) for selected compounds in the **c** series are: **8c**: oil, $[\alpha]_D$ -15.4° (*c* 3.34); **11c**: mp 116-117°C, $[\alpha]_D$ +11.3° (*c* 2.96); **12c**: mp 92.5-93°C, $[\alpha]_D$ +17.3° (*c* 3.24); **13c**: oil, $[\alpha]_D$ +14.3° (*c* 3.17); **14c**: mp 108-110°C, $[\alpha]_D$ +26.2° (*c* 0.69); **15c**: oil, $[\alpha]_D$ +4.4° (*c* 2.50); **16c**: oil, $[\alpha]_D$ -28.7° (*c* 3.00).
6) δ-Hydroxy-β-ketoesters **8a** and **8b** were prepared from 3-phenyl propionaldehyde and pivalaldehyde, respectively, by conden-sation with ethyl acetoacetate using NaH and *n*-BuLi as bases. Optically active **8c** was prepared from dihydroxy ester **17**[16] as follows: 1. *t*-$BuPh_2SiCl$, imidazole, DMF, 0°C then Et_3SiCl, 0°C (79%); 2. DIBAH, ether, -78°C (93%); 3. CH_3COOEt, LDA, THF, -78°C (92%); 4. PDC, MS-4A, CH_2Cl_2, room temp. (81%); 5. aqAcOH, THF, room temp. (96%). A shorter synthesis of the corresponding *t*-butyl ester of **8c** was reported recently.[12a]



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10) The stereostructure of C_2-methylated esters **3** and **4** was confirmed by comparing the NMR spectra of their cyclized products with those of **13** and **14**.
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14) The stereostructure of C_2-methylated lactones **13** and **14** was confirmed by NMR measurement. Although a rather larger coupling constant (ca. 7 Hz) exists between C_2-H and C_3-H in 3β-OH lactone **13**, an NOE (ca. 8%) on C_5-H by irradiation of C_2-H clearly suggests the α-configuration of C_2-methyl and the boat-like conformation of **13**. A quite reasonable $J_{2,3}$ value (ca. 10 Hz) was obtained in 3α-OH lactone **14**.
15) In **15b**, the yield was 47%. The by-products were the starting lactone **13** (20%) and the dehydrated product, α,β-unsaturated lactone (22%).
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