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3-Methyl-γ-butyrolactone as a Source of 2-Methyl-3-hydroxyketones and 2-Methyl-1,3-diols: A Synthesis of the C_{19}-C_{27} Fragment of Rifamycin S by Linear Iteration

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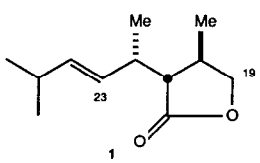
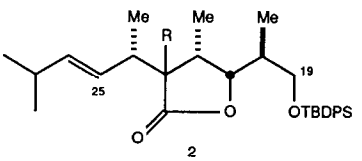
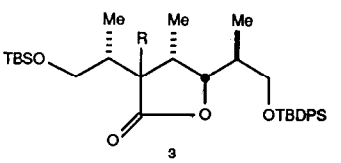
Abstract: 3-Methyl-γ-butyrolactone has been employed as a source of 2-methyl-3-hydroxyketones after functioning as a template for the preparation of enantiomerically pure propionate chains. This method is exemplified by the preparation of the C_{19}-C_{27} propionate fragment utilized by Kishi in his synthesis of rifamycin S.

The 2-methyl-3-hydroxyketone functionality is prevalent in polypropionate-derived natural products, of which pikromycin, oleandomycin and erythromycin are representative.[2] This functionality also manifests itself in the guise of hemiketals (e.g., elaiophylin)[3] and spiroketals (e.g., calcimycin).[4] Moreover, 2-methyl-3-hydroxyketones can serve as a source of 2-methyl-1,3-diols by virtue of their stereocontrolled reduction.[5]

In this Letter we describe a method for the generation of 1-methyl-2-hydroxyketones from R-3-methyl-γ-butyrolactone, a template that has been shown to provide polypropionate fragments[6], and ultimately, natural products[7] of high enantiomeric purity. The utility of this method is exemplified by the synthesis of silyl ether **13**, an intermediate in Kishi's landmark synthesis[8] of rifamycin S, through a triple, linear iteration technique.







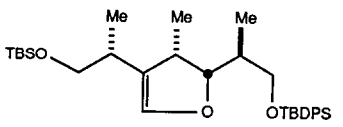
a, R = β-H
b, R = α-H

The known[6] lactone **2a**, prepared by linear iteration from lactone **1**, was converted (O_3, $MeOH/CH_2Cl_2$, $NaHCO_3$, -78°C; $NaBH_4$, 0° →25°C; TBSOTf, Et_3N, CH_2Cl_2, 0°C, 3h) to the

differentially protected bis-silyl ether **3** in 85% yield. Reduction (DIBAL, CH_2Cl_2, -78°C, 1.5h) of the lactone functionality provided a mixture of hemiacetals (δ5.24 and 5.13, hemiacetal methine-H), which, was dehydrated (MsCl, Et_3N, CH_2Cl_2, 0°C, 2h) to give the dihydrofuran **4** (^1H NMR: δ 6.01, s, 1H, vinyl; IR: 1647 cm^{-1}). Ozonolysis (3:1 MeOH/CH_2Cl_2, solid $NaHCO_3$, -78°C; DMS, -78°C →25°C) afforded ketoformate **5a**, which was converted to hydroxyketone **5b** with half saturated methanolic ammonia in 82% yield from lactone **2a**.

Having established the feasibility of forming 3-hydroxyketones, a more challenging target was chosen, namely, Kishi's tetrapropionate intermediate **13**. Accordingly, 2,3-trans-trisubstituted lactone **2b** was prepared for a second iteration. Lactone **2b** was transformed into diacetate **6** by the Criegee sequence (MeLi, ether, 0°C, 2 h; 30% H_2O_2, HOAc/THF, 0°C → 25°C, 18 h; Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C (1 h), 25°C (3 h); 8 volumes of CH_2Cl_2, reflux, 18 h) in 46% yield along with the formation of cis-2,3-trisubstituted lactone **2a**.

The appearance of the cis-lactone is a result of enolization during the methyllithium addition to the trans-2,3-trisubstituted lactone **2b**. Lactone **2a** can be equilibrated (t-BuOK, t-BuOH) to afford a 1:1 mixture of readily separable lactones **2a** and **2b**. Cleavage of diacetate **6a** (DIBAL, CH_2Cl_2, -78°C, 45 min) and acetonide formation provided olefin **6b** (69%).



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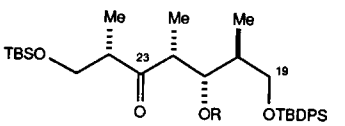
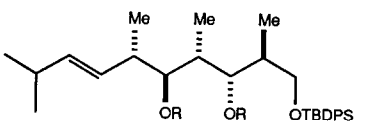
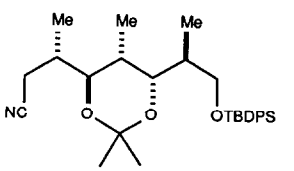


5a, R = CHO
b, R = H



6a, R = Ac
b, R = CMe_2



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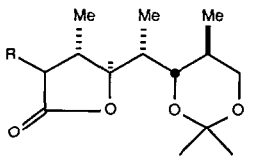
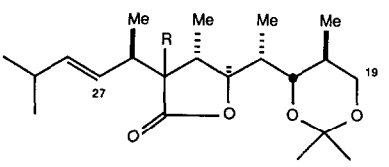
Formation of the third lactone template proceeded as follows. Ozonolysis of olefin **6a** (vide supra), reduction ($LiAlH_4$, Et_2O, 0°C →25°C, 45 min) tosylation (p-TsCl, pyr., 25°C, 20 h), and cyanide displacement (NaCN, DMSO, 25°C, 40h) gave nitrile **7** (IR: 2248 cm^{-1}) in 67% overall yield. While acidic medium had served admirably for nitrile hydrolysis in the iteration of lactone **1**, only a complex mixture of products could be obtained from nitrile **7** in acidic medium. Therefore, the nitrile was subjected to alkaline hydrolysis (KOH, DEG, 200°C, 48 h) and the crude base soluble products were subjected to lactonization/ketalization ($Me_2C(OMe)_2$, p-TsOH, 25°C, 48 h) in 95% yield from nitrile **7** to provide iterated lactone **8a**.

Introduction of the fourth and final propionate unit was accomplished by palladium-

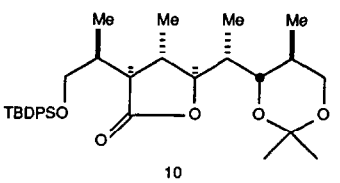
mediated alkylation with the diethyl phosphate of S-2-methyl-4(E)-hexen-3-ol (>95% ee).[7b,9] Carbomethoxylation (2.0 eq. LDA, THF, -78°C; 1.0 equiv. $NCCO_2Me$, -78°C, 1 h) of lactone **8a** gave the lactonic ester **8b** (93%), which was subjected to alkylation (NaH, THF, 25°C, 1.5 h; 15 mol% $Pd(Ph_3P)_4$, 15 mol% Ph_3P; 4.5 equiv. of S-phosphate; 0°C, 1 h, then 25°C, 3 h) to give a 56/44 mixture of olefins **9a** in 98% yield. Krapcho decarbomethoxylation[10] (LiCl, H_2O, DMSO, 190°C, 3 h) of the mixture afforded lactones **9b** and **9c**, which upon equilibration (t-BuOK, t-BuOH/ether, 25°C, h) produced a 98/2 ratio (capill. gc) (87%) of 2,3-trans-trisubstituted lactone **9b** and its cis counterpart, respectively. The formation of silyl ether **10** (81%) from lactone **9b** was achieved by the ozonolysis procedure described for lactone **2a**, except that silylation was accomplished with tert-butyldiphenylsilyl chloride (DMF, imidazole, DMAP, 25°C, 18h).



8a, R = H
b, R = CO_2Me



9a, R = CO_2Me
b, R = α-H
c, R = β-H



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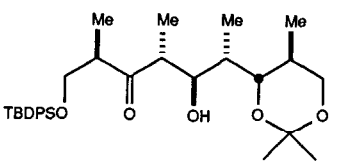

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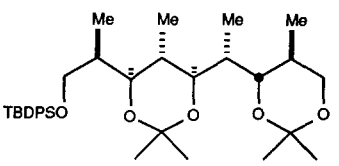

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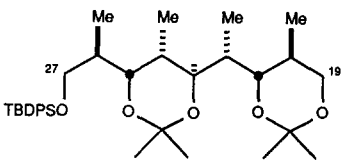

13

With all of the stereocenters of tetrapropionate **13** in place in lactone **9b** except for C_{25}, the correction of this stereogenic center was addressed. Although the "contrathermodynamic epimerization" procedure[11] would have served to convert the more stable trans-2,3-trisubstituted lactone **9b** to the less stable cis isomer **9c**, the latter compound being a candidate for the Criegee sequence, we chose to investigate the reduction of C_{25} ketone **11**, in light of the high stereoselectivity reported by Masamune[12] and Hanessian[13] in the DIBAL reduction of the C_{23} keto compounds used in their syntheses of the rifamycin S propionate chain. The conversion of lactone **10** to hydroxyketone **11** (79% yield) was accomplished by the sequence of reactions described for **3** → **5b**, with the exception that the dehydration was

conducted for 30 minutes at 0°C followed by 30 minutes at 25°C.

Surprisingly, reduction (DIBAL, CH_2Cl_2, -78°C, 1 h) of ketone **11** gave two diols that were converted ($Me_2C(OMe)_2$, p-TsOH, 25°C, 18 h) to bis-acetonide **12** (47%) and the desired bis-acetonide **13** (42%), which was identical by ^1H NMR (250 MHz) and high resolution mass spectroscopy with an authentic sample. In a similar fashion, DIBAL reduction of C_{23} hydroxyketone **5b**, gave a ~ 1:1 mixture of diols. The reason for the lack of selectivity in these reductions is, at this time, unclear.

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