

**Regiochemical Control in the Hemiacetalization of a  
Dihydroxydialdehyde. An Application of the Use of Homochiral  
3-Methyl- $\gamma$ -butyrolactones to the Construction of Homochiral  
Tripropionate Units.**

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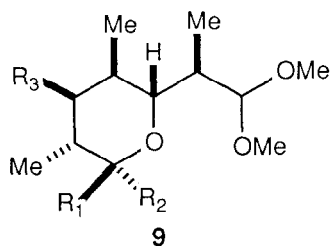
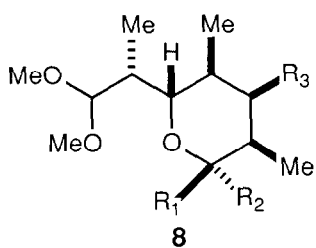
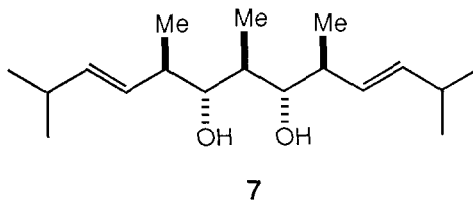
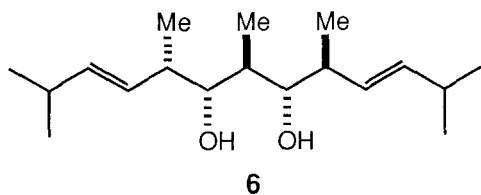
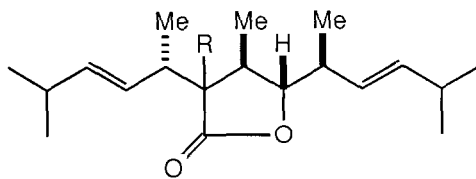
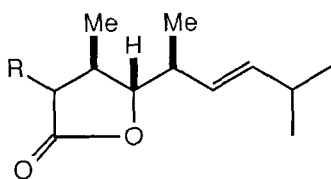
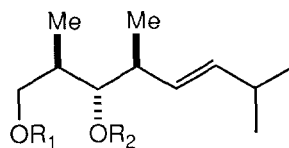
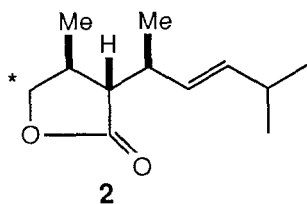
**Abstract:** A method for the inversion of lactone homochirality and subsequent chain extension of dipropionate to tripropionate units is discussed. The synthetic sequence leads to (+)-methyl Prelog-Djerassi lactic acid.

The utility of homochiral 3-methyl- $\gamma$ -butyrolactone as a template for the synthesis of dipropionate units has been demonstrated.<sup>1a</sup> The extension of this methodology into an iterative process that can provide tripropionate units is the subject of this Letter.

Claisen rearrangement of the diethylortholactone of S-3-methyl- $\gamma$ -butyrolactone<sup>2</sup> with R-2-methylhex-4(E)-en-3-ol (1)<sup>3,4</sup> (toluene, cat.  $(\text{CH}_3)_3\text{CCO}_2\text{H}$ , reflux) provided the lactone 2 as virtually the sole product (%ds > 97.5%, 83%).<sup>5</sup> A reaction sequence was sought that would transpose the element of  $\text{CO}_2$  in lactone 2 and thereby permit further chain extension at the starred carbon of lactone 2. A formal Baeyer-Villiger oxidation of the lactone was accomplished by a modification of the previously reported Criegee procedure.<sup>1</sup> Thus, the lactone was converted (MeLi,  $\text{Et}_2\text{O}$ ,  $-18^\circ\text{C}$ ; 30%  $\text{H}_2\text{O}_2$ , THF, HOAc,  $0^\circ\text{C}$ ;  $\text{Ac}_2\text{O}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ;  $\text{LiAlH}_4$ ;  $\text{H}_3\text{O}^+$ ) to the diol 3a in 81% yield. The  $\text{LiAlH}_4$  reduction served to generate the diol from the mixture of acetates 3b,c, a reduction that also produced acetal 3d. Although a hydrolysis was required to liberate additional diol from the acetal, this route proved superior to saponification, a process which generated unacceptable quantities of elimination products. The lactone transformation was completed by selective tosylation of the primary alcohol (TsCl, pyr.,  $25^\circ\text{C}$ , 16h), cyanide displacement (NaCN, DMSO  $25^\circ\text{C}$ , 3 days), and hydrolysis (1N HCl/aq. MeOH, reflux, 3.5h), affording the inverted lactone 4a in 81% yield from the diol. The lactone 4a was readily carbomethoxylated by modification<sup>6</sup> of the procedure of Mander<sup>7</sup> (2 equiv. LDA,  $-20^\circ\text{C}$ , 1h;  $-78^\circ\text{C}$ , HMPA,  $\text{NCCO}_2\text{Me}$ , 1.5h), giving rise to a 13:1

mixture of lactonic esters **4b** in 92% yield. R-alcohol **1** ( $\%ee=80$ ) was converted into its diethylphosphate ( $n\text{-BuLi}$  ether;  $(\text{EtO})_2\text{POCl}$ ;  $0^\circ\text{C}$  (0.5h),  $25^\circ\text{C}$  (2.5h)) and then added to the sodium anion of lactonic esters **4b** ( $\text{NaH}$ , THF; 5 mol %  $\text{Pd}(\text{Ph}_3\text{P})_4$ ; 5 mol %  $\text{Ph}_3\text{P}$ ;  $0^\circ\text{C}$  (1h),  $25^\circ\text{C}$  (2h)) providing a 2:1 mixture of alkylation products **5a**. Decarboxylation<sup>8</sup> ( $\text{LiCl}$ ,  $\text{H}_2\text{O}$ , DMSO;  $200^\circ\text{C}$ ; 3h) of the mixture afforded, at this juncture, seemingly pure ( $^1\text{H}$  NMR) trans-lactone **5b** and cis-lactone **5c** in 91% and 4% yields, respectively, for the two steps. When the Criegee carbon extrusion process was performed on the major component, a mixture of the diol **6** (48%), meso-diol **7** (5%), and acetaldehyde acetals of **6** and **7** (28%) was produced. Liberation of the diols from the acetals was a sluggish process owing to the limited solubility of the acetals in several hydrolytic media. The lactone that provided diol **7** could not be readily identified by  $^1\text{H}$  NMR but was undoubtedly the contaminant in the  $^{13}\text{C}$  NMR spectrum of lactone **5b**.<sup>9</sup>

Diol **6** was subjected to ozonolysis ( $\text{O}_3$ , MeOH; DMS;  $p\text{-TsOH}$ , MeOH,  $(\text{MeO})_3\text{CH}$ ) giving two of the four methoxypyrans (**8a,b-9a,b**) arising from the two modes of acetalization and two possible anomers of each. Although the pure major isomer (33%) and minor isomer (30%) could be converted to the same ~1:1 mixture of acetals, this equilibration did not necessarily preclude structural isomerization (**8a,b**  $\leftrightarrow$  **9a,b**) as opposed to anomerization (**8a**  $\leftrightarrow$  **8b**, **9a**  $\leftrightarrow$  **9b**). The minor component of the mixture was assigned structure **8a** because its axial anomeric methine proton appeared as a doublet at  $\delta 4.41$  ( $J=8.7$  Hz). The major component's methine proton absorbed at  $\delta 4.56$  ( $J=2.9$  Hz), a value compatible with the other three isomers. The stereochemistry was confirmed by removing the possibility of structural isomerization. Thus, hydroxy acetal **8a** was deoxygenated ( $n\text{-BuLi/THF}$ ;  $\text{PhOCSCl}^{10}$ ;  $n\text{-Bu}_3\text{SnH}$ , AIBN, toluene,  $90^\circ\text{C}$ , 6h) to afford acetal **8c**, which upon acid catalysis ( $p\text{TsOH}$ , MeOH) was interconvertible with acetal **8d**, the deoxygenation product of the major hydroxy acetal **8b**. Both compounds are, therefore, the thermodynamically more stable isomers having all ring carbons equatorially disposed, as compared with the anomers **9a,b** which bear an axial substituent adjacent to the anomeric center.<sup>11</sup> The acetal **8c** was readily converted to the lactone ( $\text{O}_3$ , EtOAc,  $-78^\circ\text{C}$ , 1.5h; TFA/THF,  $0^\circ\text{C}$ , 3h) by the method of Deslongchamps<sup>12</sup> in 56% yield from alcohol **8a**. The absolute and relative stereochemistries of the lactonic acetal were further supported by its oxidation ( $\text{O}_3$ , HOAc,  $25^\circ\text{C}$ , 30h) to the methyl ester of the Prelog-Djerassi lactonic acid ( $[\alpha]_D^{25} + 36.4^\circ$  ( $\text{CHCl}_3$ , c, 0.055; lit.<sup>13</sup>  $[\alpha]_D^{25} + 38^\circ$  ( $\text{CHCl}_3$ , c, 1.03)<sup>14,15</sup>).



- a, R<sub>1</sub> = H, R<sub>2</sub> = OMe, R<sub>3</sub> = OH**  
**b, R<sub>1</sub> = OMe, R<sub>2</sub> = H, R<sub>3</sub> = OH**  
**c, R<sub>1</sub> = H, R<sub>2</sub> = OMe, R<sub>3</sub> = H**  
**d, R<sub>1</sub> = OMe, R<sub>2</sub> = H, R<sub>3</sub> = H**

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**References and Notes:**

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5. The %ds=% of major diastereomer in the mixture. Thaisrivongs, S.; Seebach, D., *J. Am. Chem. Soc.*, **1983**, 105, 7407.
6. Two equivalents of LDA are required with the lactone. Cf. ref. 6 and Ziegler, F. E.; Wang, T.-F., *Tetrahedron Lett.*, **1985**, 26, 2291.
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9. The meso diol **7** arises from the minor amount of S-phosphate. Little racemization of the  $\pi$ -allyl complexes occurs (see preceding Letter). The ratio of the acetals of **6** and **7** was undetermined. The %ee of R-alcohol **1** was not determined directly, but was inferred from the ratio of **6/7**, assuming equal rates of hydrolysis of the diastereomeric acetals.
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15. All new compounds gave satisfactory spectroscopic and/or combustion data.

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