intensity (spectra not shown), demonstrating the population shift from unhydrated ≥Si–OH species (at about 2 ppm) to I (at 7 ppm). Detailed investigations of this type and analogous experiments with other bases are in progress.

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Iterative Butenolide Construction of Polypropionate Chains

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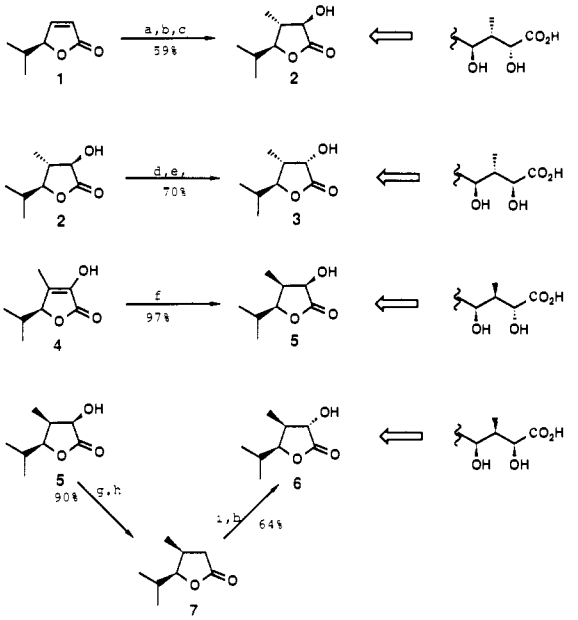
Sequences of alternating secondary methyl and hydroxyl groups are typical of the polypropionate-derived chains found, for example, in many macrolide antibiotics. Although much fascinating chemistry has been brought to bear on the stereochemical problems which these structures pose, this has not yet led to a reliable and generally applicable method.[1]

We now wish to report such a method[2] and demonstrate its usefulness by the synthesis of the C_7–C_{13} fragment of erythronolide A.

The method proceeds through two stages: First, stereoselective addition of a methyl and of a hydroxyl group to a 5-substituted butenolide leads to 3-hydroxy-4-methyl-2-furanones (e.g., **1** and **2**). Second, elaboration to the next butenolide (e.g., **5** to **11**) once again sets the stage for the introduction of methyl and hydroxyl groups. Stereoselective synthesis of each of the four possible 5-alkyl-3-hydroxy-4-methylfuranone diastereomers (e.g., **2**, **3**, **5**, and **6**), coupled with the appropriate butenolide elaborations, allows any regular polypropionate stereoisomer to be constructed.[2]

We now illustrate the first stage below using a model with a 5-isopropyl group. Butenolide **1**[3] served as the starting material for construction of two of the four possible 3-hydroxy-4-methyl-2-furanone diastereomers. The 3β,4α,5β-furanone **2** was obtained, starting with the conjugate addition of tris(thiophenyl)methyllithium.[4] The bulky 4-tris(thiophenyl)methyl substituent now directed the in situ MoOPH[5] oxidation of the resulting enolate to the β-face, so that removal of the thiophenyl substituents (Raney nickel) gave the desired 3β-hydroxy-4α-methyl-2-furanone **2**.[6] Simply inverting the secondary hydroxyl group[7] of furanone **2** led to the 3α,4α,5β-furanone **3**.[8]



(a) $LiC(SPh)_3$, THF, −78 °C; (b) MoOPH 0 °C; (c) Raney nickel, EtOH; (d) DEAD, PPh_3, PhCOOH, THF; (e) K_2CO_3, MeOH; (f) 5% Rh/alumina, H_2, MeOH; (g) MsCl, Et_3N; (h) 2% Na(Hg), NaH_2PO_4, MeOH, 0 °C; (i) LDA, THF, −78 °C.

The two remaining 3-hydroxy-4-methyl-2-furanone diastereomers were prepared from 3-hydroxybutenolide **4**.[9] Hydrogenation of **4** with rhodium on alumina[10] gave the 3β,4β,5β-furanone **5**.[11] The final diastereomer, 3α,4β,5β-furanone **6**, was formed by inversion of the secondary hydroxyl group in furanone **5** or, alternatively, by deoxygenation of furanone **5** to furanone **7**, followed by reoxidation of the corresponding enolate with MoOPH reagent.[12]

These highly effective routes (stereoselectivity ≥40:1) to the four possible -hydroxy-4-methyl diastereomers of a 5-substituted 2-furanone complete the first stage of the method. The second stage, which makes the method iterative, requires elaboration of any given 3-hydroxyfuranone to the next butenolide or 3-hydroxybutenolide (cf. **1** and **4**). Note that every new cycle incorporates the two centers created on the furanone template into the growing C5 substituent at the same time as it sets the stage for creation of the next two centers.

Conversion of **5** to **11** illustrates the "butenolide elaboration". In situ protection of **5** as the trimethylsilyl ether,[13] addition of ethyl acetate anion, and basic methanolysis gave bicyclic hemiketal **8**. Hemiketal **8** is in equilibrium with the corresponding monocyclic tetronic acid and could be transformed to **9** by phase-transfer benzylation, followed by acylation of the secondary alcohol. Hydrogenation of **9** with rhodium on alumina removed the benzyl group and saturated the double bond to give **10**. Elimination of

† National Science Foundation predoctoral fellow, 1981–1984.

(1) See, inter alia: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Heathcock, C. H. *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Vol. 2. Heathcock, C. H. *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3. Mukaiyama, T. *Org. React. (N. Y.)* **1982**, *28*, 203.

(2) An overview of this work was presented at the International Symposium on Organic Chemistry of Medicinal Natural Products in Shanghai, China, November 10, 1985: Stork, G.; Rychnovsky, S. D., *Pure Appl. Chem.* **1986**, *58*, 767. For recent lactone-based approaches to acyclic stereocontrol, see: Hanessian, S.; Murry, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, 5623, 5627, 5631. Hanessian, S.; Murray, P. J. *Can. J. Chem.* **1986**, *64*, 2231. Ziegler, F. E.; Kneisley, A. *Heterocycles* **1987**, *25*, *105* and references cited therein.

(3) Butenolide **1** was prepared from methylpropanal by Schlessinger's procedure: Herrman, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544.

(4) Manas, A.-R. B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216.

(5) (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (b) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(6) (a) Analysis of the product by gas chromatography showed less than 1% of any other of the stereoisomers of **2**. (b) ^1H NMR of **2** ($CDCl_3$) δ 4.03 (d, J = 10.5 Hz, 1 H), 3.83 (dd, J = 4.4, 9.6 Hz, 1 H), 2.8 (s, 1 H), 2.25 (m, 1 H), 1.98 (m, 1 H), 1.24 (d, J = 6.5 Hz, 3 H), 1.04 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H).

(7) Mitsunobu, O. *Synthesis* **1981**, *13*, 1.

(8) ^1H NMR of **3** ($CDCl_3$) δ 4.47 (d, J = 8.0 Hz, 1 H), 3.93 (dd, J = 3.2, 7.6 Hz, 1 H), 2.79 (s, 1 H), 2.56 (m, 1 H), 1.86 (m, 1 H), 1.12 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H).

(9) Hydroxybutenolide **4** was prepared from methylpropanal and diethyl oxalylpropionate by the procedure of Anderson: Anderson, J. R.; Edwards, R. L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 215.

(10) (a) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 499. (b) Schlessinger, R. H.; Damon, R. E. *Tetrahedron Lett.* **1975**, 4551.

(11) (a) Analysis of the product by gas chromatography showed a 40:1 mixture of **5** and **3**. (b) ^1H NMR of **5** ($CDCl_3$) δ 4.55 (d, J = 6.7 Hz, 1 H), 3.84 (dd, J = 3.8, 10.5 Hz, 1 H), 2.96 (s, 1 H), 2.73 (m, 1 H), 1.88 (m, 1 H), 1.07 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H).

(12) (a) Analysis of the product from MoOPH oxidation of **7** by gas chromatography showed less than 1% of lactone **5**. (b) ^1H NMR of **6** ($CDCl_3$) δ 4.38 (t, J = 6.8 Hz, 1 H), 4.09 (d, J = 6.1 Hz, 1 H), 3.62 (s, 1 H), 2.55 (m, 1 H), 1.93 (m, 1 H), 1.10 (d, J = 7.3 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H).

(13) Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807.

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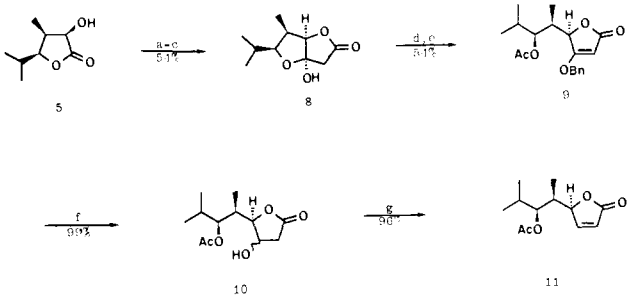
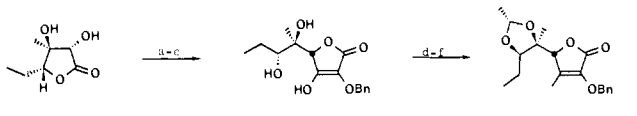
water by treatment with methanesulfonyl chloride and triethylamine then completed the construction of butenolide **11** (cf. **1**).



(a) Me_3SiNMe_2, THF; (b) $LiOC(OEt)CH_2$, THF, −78 °C; (c) K_2CO_3, MeOH; (d) $PhCH_2Br$, Na_2CO_3, Bu_4NBr, CH_2Cl_2/H_2O; (e) Ac_2O, Et_3N, DMAP; (f) 5% Rh/alumina, H_2, MeOH; (g) MsCl, Et_3N.

Conversion of **12** to **14** illustrates the "hydroxybutenolide elaboration". Protection of (+)-dihydroxyfuranone **12**[14] as the bis(trimethylsilyl) ether, addition of the anion of ethyl (benzyloxy)acetate,[15] and basic methanolysis gave tetronic acid **13**. The 4-methyl group was introduced by phase-transfer phosphorylation (diphenyl chlorophosphate) of the ethylidene acetal of **13**, followed by nickel acetylacetonate catalyzed coupling with dimethylzinc.[16] The resulting 3-hydroxybutenolide benzyl ether **14** is the operational equivalent of **4**.

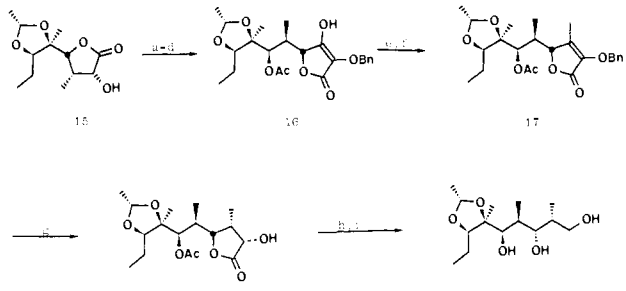


(a) Me_3SiCl, imidazole, DMF; (b) LiHMDS, $EtOC(O)CH_2OCH_2Ph$, THF, −50 °C; (c) K_2CO_3, MeOH; (d) acetal, CSA, CH_2Cl_2; (e) $(PhO)_2P(O)Cl$, Na_2CO_3, CH_2Cl_2/H_2O, Bu_4NBr; (f) Me_2Zn, $Ni(AcAc)_2$ Et_2O.

The successful conversions of **5** to **11** and of **12** to **14** complete the second stage of the general method. Every successive cycle produces butenolides which are identical with **1** or **4** except for the detailed structure of the side chains, and the method should therefore be generally applicable.

Dihydroxyfuranone **12** was selected to illustrate the hydroxybutenolide elaboration because one more cycle, starting with butenolide **14**, leads to the C_7–C_{13} fragment of erythronolide A. Hydrogenation of **14** with rhodium on alumina removed the benzyl ether and saturated the double bond to give the 3-hydroxy-4-methyl-2-furanone **15**: mp 101–102 °C, $[\alpha]_D^{24}$ −33° (*c* 0.42, MeOH). A second hydroxybutenolide homologation sequence was applied to furanone **15**. Protection, butenolide elaboration, and hydrogenation, along the lines described for dihydroxyfuranone **12**, gave the 3-hydroxy-4-methyl-2-furanone **18**: mp 126–130 °C, $[\alpha]_D^{24}$ + 55° (*c* 0.32, MeOH). The hydroxybutenolide homologation and reduction sequences starting with dihydroxyfuranone **12** and with hydroxyfuranone **15** proceeded in 64% and 40% overall yields, respectively.

Further elaboration to erythronolide A, which is described in the following communication[17] in this issue, required triol **19** This was readily available from furanone **18** by lithium aluminum



(a) Me_3SiNMe_2, THF; (b) LiHMDS, $EtOC(O)CH_2OCH_2Ph$, THF, −50 °C; (c) K_2CO_3, MeOH; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (e) $(PhO)_2P(O)Cl$, Na_2CO_3, CH_2Cl_2/H_2O, Bu_4NBr; (f) Me_2Zn, $Ni(acac)_2$, Et_2O; (g) 5% Rh/alumina, H_2, MeOH; (h) LAH, THF, HOAc, H_2O, $NaIO_4$; (i) $NaBH_4$, EtOH.

hydride reduction, in situ sodium periodate oxidation, and sodium borohydride reduction. The resulting triol **19** has the correct stereochemistry of the C_7–C_{13} fragment of erythronolide A.[17]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for the financial support of this work.

Supplementary Material Available: Experimental details for an iterative butenolide construction of polypropionate chains (30 pages). Ordering information is given on any current masthead page.

Concise Total Synthesis of (+)-(9*S*)-Dihydroerythronolide A

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We wish to report a total synthesis of (+)-(9*S*)-dihydroerythronolide A (**1**),[1] which also constitutes a formal total synthesis of erythromycin A (**2**).[2,3] The synthesis illustrates the usefulness

† National Science Foundation predoctoral fellow, 1981–1984.

(1) For the preparation of **1** [(+)-(9*S*)-9-deoxo-9-hydroxyerythronolide A] from erythromycin A, see: Jones, P. H.; Rowley, E. K. *J. Org. Chem.* **1968**, *33*, 665. Also see ref 2d, footnote 4.

(2) (a) For recent reviews of synthetic work in this area, see: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics, Chemistry, Biology and Practice*; Academic: New York, 1984; Chapter 4. Total synthetic work directed toward erythronolide A and erythromycin: (b) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (c) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggei, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (d) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213. (e) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215. (f) Hanessian, R.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 1111. (g) Hanessian, R.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843. (h) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686. (i) Heathcock, C. H.; Hagan, J. P.; Young, S. D.; Pilli, R.; Bai, D.-L.; Märki, H.-P.; Kees, K.; Badertscher, U. *Chem. Scr.* **1985**, *25*, 39. (j) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095. (k) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810. (l) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2814. (m) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818.

(14) Dihydroxyfuranone **12** was prepared in three steps and 43% overall yield from ethyl (4*R*)-4-hydroxy-2-hexynoate (available in 80% ee by Midland's procedure: Midland, M. M.; Tramontano, A. *Tetrahedron Lett.* **1980**, 3549) by the previously described method (Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951). Dihydroxyfuranone **12** was recrystallized to optical purity: mp 76–77.5 °C, $[\alpha]_D^{22}$ +84.6° (*c* 1.36, methanol).

(15) Meinwald, J.; Dugan, A. J.; Adams, M. A. *Tetrahedron Lett.* **1978**, 4327.

(16) For a related transformation, see: Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *61*, 2530. For a $Ni(acac)_2$-catalyzed conjugate addition of dimethylzinc to an unsaturated ketone, see: Greene, A. E.; Langard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *40*, 931.

(17) Stork, G.; Rychnovsky, S. D., following paper in this issue.

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