in 10.0 mL of a solvent was added 0.384 mL (4 mmol) of Me_3Al. The reaction vessel is partially immersed in a constant-temperature bath (30.00 ± 0.02 °C). After 5 h, phenylacetylene (0.222 mL, 2 mmol) was added. Aliquots were analyzed by GLC after quenching with 3 N HCl. The results were summarized in Table III.

Reaction of 1-Octyne with (*E*)-1-Octenyldiisobutylalane and Zirconocene Dichloride.[26] 1-Octyne (0.55 g, 5 mmol) in 5 mL of hexane was treated with 0.92 mL (5 mmol) of *i*-Bu_2AlH for 4 h at 50 °C.[25] Hexane was evaporated under reduced pressure. To the residue were sequentially added 5 mL of 1,2-dichloroethane, 0.55 g (5 mmol) of 1-octyne, and Cl_2ZrCp_2 (1.46 g, 5 mmol). After 12 h at room temperature, the reaction mixture was worked up as described earlier for the representative case. Distillation provided 278 mg (25%) of crude (*E*)-2-(*n*-hexyl)-1,3-decadiene: IR (neat) 3090 (w), 3020 (m), 2900 (s), 1770 (w), 1640 (w), 1605 (m), 1450 (s), 1375 (m), 960 (s), 875 (s), 720 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.87 (t, 6 Hz, 6 H), 1.1–1.65 (m, 16 H), 1.8–2.3 (m, 4 H), 4.83 (s, 2 H), 5.65 (dt, *J* = 16 and 7 Hz, 1 H), 6.05 (d, 16 Hz, 1 H).

^1H NMR Examination of Tri(*n*-propyl)alane and Zirconocene Dichloride. Tri(*n*-propyl)alane (0.474 mL, 2.5 mmol) and 0.73 g (2.5 mmol) of Cl_2ZrCp_2 were mixed in 10 mL of 1,2-dichloroethane at room temperature and examined 1 h later by ^1H NMR, which showed the following signals: ^1H NMR ($ClCH_2CH_2Cl$, C_6H_6) δ 0.13 (t, *J* = 7.5 Hz, 6 H), 0.7–1.1 and 1.2–1.7 (m, 15 H), 6.21 (s, 5.2 H), 6.44 (s, 4.5 H). The integration ratio of the two peaks at δ 6.21 and 6.44 indicates that Cl(*n*-Pr)$ZrCp_2$ and Cl_2ZrCp_2 were present in a ratio of 54:46. The ^1H NMR spectra of *n*-Pr_3Al and *n*-Pr_2AlCl in 1,2-dichloroethane are as follows: ^1H NMR of *n*-Pr_3Al ($ClCH_2CH_2Cl$, Me_4Si) δ 0.13 (t, *J* = 7.5 Hz, 6 H), 0.90 (t, *J* = 7.5 Hz, 9 H), 1.2–1.7 (m, 6 H); ^1H NMR of *n*-Pr_2AlCl ($ClCH_2CH_2Cl$, Me_4Si) δ 0.25 (t, *J* = 7.5 Hz, 4 H), 0.92 (t, *J* = 7.5 Hz), 6 H), 1.2–1.7 (m, 4 H).

^1H NMR Examination of Di(*n*-propyl)chloroalane and Zirconocene Dichloride. Di(*n*-propyl)chloroalane was generated by mixing 2 mmol of *n*-Pr_3Al and 1 mmol of $AlCl_3$ in 1,2-dichloroethane (3 mL). This solution was then added to 0.876 g (3.0 mmol) of Cl_2ZrCp_2 in 5 mL of 1,2-dichloroethane at room temperature. The following ^1H NMR spectrum did not show any change with time: ^1H NMR ($ClCH_2CH_2Cl$, Me_4Si) δ −0.05 (t, *J* = 7.5 Hz, 4 H), 0.90 (t, *J* = 7.5 Hz, 6 H), 1.43 (tq, *J* = 7.5 Hz, 4 H), 6.45 (s, 10 H). No other Cp signal was discernible.

Reaction of 1-Heptyne with Di(*n*-propyl)chloroalane and Zirconocene Dichloride. To a mixture of 0.262 mL (2.0 mmol) of 1-heptyne and 0.584 g (2.0 mmol) of Cl_2ZrCp_2 in 8 mL of 1,2-dichloroethane was added at room temperature *n*-Pr_2AlCl generated from 0.252 mL (1.33 mmol) of *n*-Pr_3Al and 0.089 g (0.67 mmol) of $AlCl_3$ in 2 mL of 1,2-dichloroethane. The progress of reaction was monitored by GLC examination of protonolyzed aliquots. The combined yields of 2-(*n*-propyl)-1-heptene and 4-decene were 36, 64, 76, and 97% after 1, 3, 6, and 20 h, respectively. The molar ratio of the two products at 20 h was 76:21. No more than a trace, if any, of 1-heptene was present.

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A New Approach to Polypropionates: Routes to Subunits of Monensin and Tirandamycin

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Abstract: Reactions of (*E*,*Z*)-1-methoxy-3-(trialkylsilyloxy)-1,3-pentadiene with various aldehydes under Lewis acid catalysis afford silyloxydihydropyrans. In a few relatively simple operations these products are converted to the title systems, thereby providing the basis for a straightforward and stereoselective route to polypropionates.

Background

It seemed possible that systems of type **1** might be useful for the synthesis of "polypropionates"[1] such as **2**. For such a plan to become a broadly applicable reality, several desiderata must be attained. First, the capacity to assemble the dihydropyran ring (**1**) in an efficient way with various substitution patterns is necessary.[2] Furthermore, a variety of options should be available for exercising stereochemical control in the fashioning of the pyranoid system and throughout the subsequent buildup of functionality as the cycle is being readied for disconnection. Finally, efficient methodology will be necessary for opening of the ring.

Before describing our results in realizing these goals, it is well to place the concept implied above in the broader context of strategies for the synthesis of acyclic arrays bearing stereogenic centers.[3] The classical approach focused on algorithms, wherein the stereochemically determinitive steps were carried out in cyclic systems.[4] It was thought that the rigidity of the ring structure conferred a predictability of behavior which was exploitable for achieving stereochemical control. More recently, significant progress has been realized in attaining high margins of topographic and facial selectivity in acyclic settings.[5] As a consequence of

(1) We use this term broadly to imply systems containing poly(2-alkyl-1,3-diols) or closely related systems. Such units are present in many macrolides and ionophores.

(2) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

(3) For an excellent review of this area see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. In this review Professor Masamune identifies a new strategy, that of reagent control as opposed to the more traditional approach of induction via prior substrate dissymmetry.

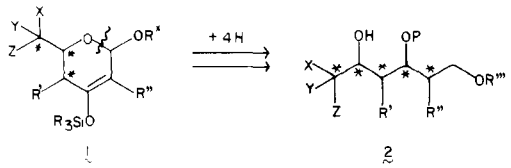
(4) A modern classic which is illustrative of the ring disconnection approach is the Woodward synthesis of erythromycin. This synthesis is critically analyzed in ref 3.

(5) (a) For the use of the Sharpless epoxidation in the solution of this type of problem see: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) For approaches involving aldol strategies see: Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528. Heathcock, C. H. *Science (Washington D.C)* **1981**, *214*, 395. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds., Elsevier: Amsterdam, 1983; Vol. II. (c) For approaches involving acyclic hydroborations see: Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, 807.

0002-7863/85/1507-6647$01.50/0

these dramatic advances, it is no longer necessarily advisable to invest steps in the construction of cyclic intermediates to control acyclic stereochemistry.

From the standpoint of categorization, the approach described herein falls under the domain of stereochemical control through isolable cyclic structures. *However, we register the important proviso that the ring in question is an oxygen heterocycle.* Given the simplicity of pyran ring construction through the applicability of a broad range of dienes and aldehydes to the cyclocondensation process,[2] and given the significant degree of stereochemical control which is available by the simple expedient of manipulating the Lewis acid,[6] the advantages of conciseness and flexibility are apparent. Furthermore, the disconnection phase simply takes advantage of the masked aldehyde character of the hemi-acetal linkage.[7] Hence, both the construction and the disassembly of the cyclic edifice need not add steps to the total program and, therefore, need not be regarded as contrivances.

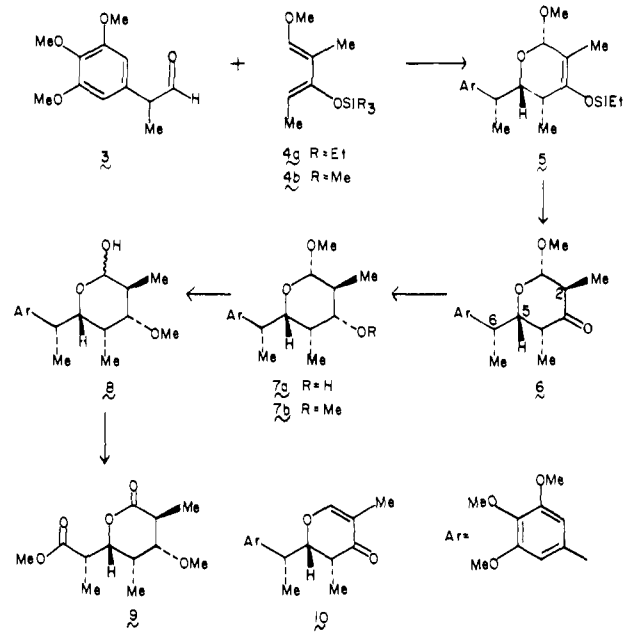


In the opening phase of the inquiry, we sought to develop options for the control of stereochemistry within the pyranoid structure. To focus the effort more sharply, we identified two target systems related to natural products. Lactone **9** is a degradation product of monensin.[8] It also functioned as an intermediate in the Still[9a] and Kishi[9b] total synthesis of this ionophore. As matters transpired, the stereochemical pattern within **9** fell very smoothly within the scope of our methodology. The stereochemical arrangement contained in the acyclic array **19** posed a more difficult but manageable challenge to our method. Depending on the nature of the protecting groups R and R′, such a system can be converted to **20** which is an intermediate in the synthesis of tirandamycin.[10] Our purpose here was not that of achieving a synthesis of tirandamycin. Rather, it was our goal to extend the scope of this new approach to polypropionate targets.

Results

A Synthesis of the Monensin Lactone (9). Compound **3**, prepared in two steps (79% yield) from 3′,4′,5′-trimethoxyacetophenone, was selected as the aldehyde component on the basis of several considerations. First, a related aldehyde, 2-phenylpropanal, had manifested excellent diastereofacial selectivity in the cyclocondensation reaction with the (trimethylsilyl)oxy diene **4b**.[6] The sense of the selectivity was that which was in accord with the Cram[11]–Felkin[12] formulations. If the reaction would

Scheme I



occur in this sense, it would establish the relationship (i.e., C_5(O); C_6(Me) "syn" in the "anti" conformation)[13] required for the monensin lactone (**9**). It was further assumed that the degradation of the 3,4,5-trimethoxyphenyl ring to a carboxyl group would be particularly smooth. This hope was only partially realized.

In previous work from these laboratories, it has been shown that diene **4b** reacts with simple aldehydes under catalysis by soluble lanthanide complexes (e.g., Eu(fod)$_3$ or Yb(fod)$_3$) to afford isolable cycloadducts.[14] Indeed, this capability is one of the particularly useful features of the lanthanide method of catalysis. However, as we began to investigate the use of lanthanide catalysis for the reaction of aldehyde **3** with the (trimethylsilyl)oxy diene **4a**, serious problems emerged. The rate of cycloaddition was quite slow (approximately 50% complete after 24 h with 10 mol % Yb(fod)$_3$). Given the long exposure to even the mild Lewis acid catalyst, it was not surprising to find that the cycloadduct corresponding to the trimethylsilyl version of compound **5** had suffered extensive conversion to dihydropyrone **10**. While one could consider moving forward with this pyrone, a particularly attractive possibility for introducing the required configuration at C_2 would have been lost. Fortunately, this problem was substantially solved through the use of the triethylsilyl enol ether, **4a**. While the rates of cycloaddition of **4b** and **4a** are not obviously different, the stability of the TES adduct was decidedly more favorable.

Reaction of aldehyde **3** with diene **4a** under catalysis by Yb(fod)$_3$ produced the silyl enol ether **5** as the only observed cycloadduct. Though the actual yield of homogeneous **5**, after silica gel chromatography, was only 56%, we could not detect the presence of any significant amounts of stereoisomers of this product. The inability to achieve a higher isolated yield reflected the difficulties of working with the sensitive vinylogous orthoester **5**. Treatment of **5** with HF in pyridine/MeOH afforded an 86% yield of a single ketone **6**. A large (8.8 Hz) coupling between the C_1 and C_2 methines and a small (2.3 Hz) coupling between the C_4 and C_5 methines indicated that the anomeric methoxyl as well as the substituents at C_5 and C_2 were equatorial with only the methyl group at C_4 being axial.

Reduction of ketone **6** with sodium borohydride in methanol–THF afforded equatorial alcohol **7a** (81% after chromatography). This result followed well-established patterns previously demonstrated in our laboratory wherein reductions of 6-substituted 4-pyranones bearing an equatorial alkoxy group at the 2-position

(6) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

(7) This situation has been well-recognized in the application of carbohydrates to the stereoselective synthesis of acyclic systems. See: Hanessian, S. "Total Synthesis of Natural Products: the "Chiron" Approach", Organic Chemistry Series"; Pergamon Press: New York, 1983; Vol. 3. The approach described herein differs in that the pyran is fashioned by total synthesis, thus obviating the need for the extensive manipulations which are often characteristic of the carbohydrate-based syntheses.

(8) Agtarap, A.; Chamberlain, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 5737.

(9) (a) Still, W. C.; Collum, D. B.; McDonald, J. A., III. *J. Am. Chem. Soc.* **1980**, *102*, 2117, 2118, 2120. (b) Kishi, Y. *Lect. Heterocycl. Chem.* **1980**, *5*, 95.

(10) MacKellar, K. L.; Grostic, M. F.; Olson, E. C.; Wnuk, R. J.; Branfman, A. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4943. Dunchamp, D. J.; Brantman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *Ibid.* **1973**, *95*, 4077. For the first total synthesis of tirandamycin A, see ref 26.

(11) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Knight, J. D. *Ibid.* **1952**, *74*, 5855. (c) Cram, D. J.; Abd Elhafez, F. A.; Weingerter, H. *Ibid.* **1953**, *75*, 2293. (d) Cram, D. J.; Greene, F. A. *Ibid.* **1953**, *75*, 6005. (e) Cram, D. J.; Abd Elhafez, F. A.; Nyquist, H. L. *Ibid.* **1954**, *76*, 22. (f) Cram, D. J.; Allinger, J. *Ibid.* **1954**, *76*, 4516. (g) Cram, D. J.; McCarty, J. E. *Ibid.* **1954**, *76*, 5740. (h) Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748. (i) Cram, D. J.; Wilson, D. R. *Ibid.* **1963**, *85*, 1245.

(12) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

(13) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

(14) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(i.e., cis to the 6-substituent) with methyl hydrides, *including L-Selectride* (Aldrich), are highly selective for *axial* hydride delivery.[15] Methylation of **7a** under standard conditions afforded **7b**.

Cleavage of the methyl glycoside linkage of **7b** was accomplished through the action of dilute HCl in THF at 50 °C. Lactol **8** was not fully characterized but rather was treated directly with catalytic ruthenium dioxide in the presence of sodium metaperiodate in a two-phase system (CCl_4–MeCN–H_2O).[16] The crude lactonic acid was esterified with diazomethane to afford the crystalline racemic lactonic methyl ester in an overall yield (from **7b**) of 56%.[17] Racemic **9**, thus obtained, gave infrared, NMR, and mass spectra which were identical with those of an authentic sample of the levorotatory isomer kindly provided by Professor W. Clark Still. Thus, in a total of seven simple and highly stereoselective steps, the monensin lactone containing five stereogenic centers is readily assembled.

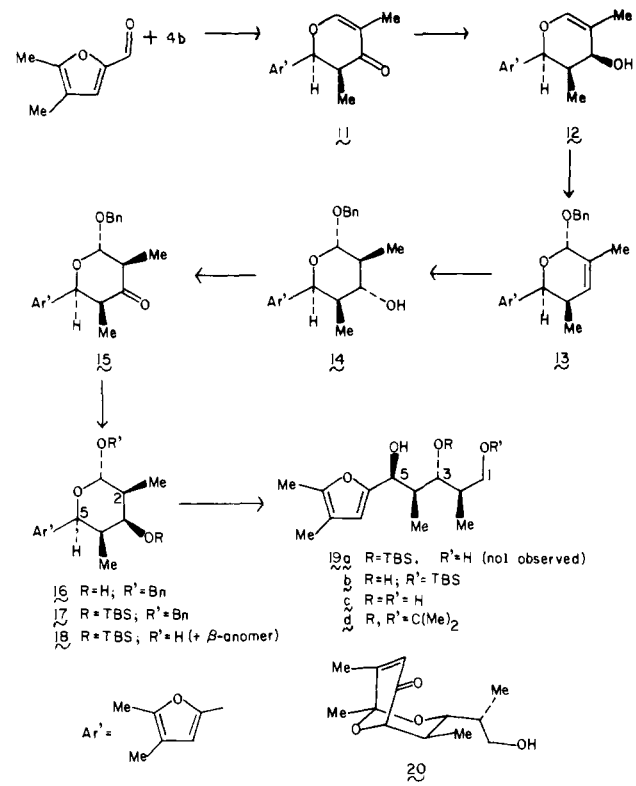
We turn now to a synthesis of the furylpolypropionate system **19**. On the basis of the earlier chemistry of DeShong,[18] Ziegler,[19] and Martin,[20] it was surmised that oxidative (mCPBA) treatment of the 2,3-dimethyl furanoid ring bearing a free hydroxyl at C_5 affords a 2-hydroxypyran-5-one system. Further cyclization with the C_3 alcohol gives the bridged ring system present in the "Ireland alcohol" **20**.[21] Compounds such as **20** can be converted to tirandamycin[10] itself. Accordingly, our goal compound became **19a** with the C_1 hydroxyl group specifically protected with an acid stable blocking group and well differentiated from the C_3 hydroxyl function whose protecting group might well be cleaved in situ during the acid-catalyzed cyclization. It will be recognized that by the pyran strategy envisioned herein, compounds with the stereochemical pattern shown in structures **16–18** (with the particular selection of blocking groups not defined a priori) would be required.

It was expected[14] that endo addition would prevail in the cyclocondensation reaction of diene **4b** with the required furyl aldehyde. Since the aldehyde is achiral, there would be no issue of facial selectivity in the cycloaddition. The challenge lay in adjustment of the stereochemistry within the pyran ring. In this pre-tirandamycin series, the methyl groups at C_2 and C_4 must be cis to one another. To the extent that compounds **16–18** are in the chair conformation, such a configuration would impose a 1,3-diaxial relationship of the two methyl functions. Fortunately, the required system was secured in a highly stereoselective way.

Reaction of 4,5-dimethylfurancarboxaldehyde[20] with diene **4b** in the presence of catalytic Yb(fod)$_3$ in chloroform was followed by brief treatment with trifluoroacetic acid. There was thus obtained the cis-substituted dihydropyrone **11** in 84% yield. In the light of our subsequent designs, it was of no advantage in this series to interdict the process at the stage of the primary cycloadduct. The next step involved the reduction of **11** with lithium aluminum hydride. Pseudoaxial hydride delivery produced alcohol **12** in 89% yield, wherein the configuration of the C_3–OH is appropriate for target systems **16–18**. However, to attain the required configuration at C_2, it was necessary to temporarily forfeit this stereogenic center.

Treatment of **12** with benzyl alcohol in the presence of *p*-toluenesulfonic acid brought about the anticipated Ferrier-like rearrangement,[22] leading to the branched pseudoglycal **13** in 91% yield. Hydroboration of **13** with BH_3–THF followed by oxidation with aqueous alkaline hydrogen peroxide gave a 10:1 ratio of two

Scheme II



secondary alcohols. That the major compound (54% yield) is properly formulated as **14** was established upon completion of the sequence. The minor product (5%) (structure not shown) has the configurations at C_2 and C_3, opposite to those of **14**.

Oxidation of **14** under the conditions of Swern[23] afforded ketone **15** in 88% yield. In our previous study of the reduction of pyranones which are very similar to **15** except that the methyl group at C_2 was α, reduction of the ketone, wherein the anomeric group was axial, with sodium borohydride produced a mixture of C_4 epimers.[15] However, in the C_2 β-methyl substrate, **15**, hydride delivery via sodium borohydride occurred cleanly from the α-face to afford an 84% yield of alcohol **16**, which was smoothly converted to its *tert*-butyldimethylsilyl derivative, **17**.

Under carefully controlled conditions (Na, NH_3, Et_2O, −78 °C, 25 min), compound **17** was converted to anomeric mixture **18** (66%) wherein the lactol ring had survived reductive debenzylation.[24] Under somewhat more severe conditions (Na, NH_3, Et_2O, −33 °C, 1 h), the lactol system **18**, derived from **17**, undergoes further in situ reduction (presumably via its open-chain aldehydo valence tautomer). *In this fashion, the acyclic array corresponding to series 19 is exposed with complete stereochemical definition.* Accompanying this desired result was an unexpected trans silylation. Thus, rather than the simple ring-opened product, **19a**, there was obtained compound **19b** in 62% yield.[25]

That the stereochemistry of our product corresponds to that depicted in **19b** was clear from the NMR spectroscopic properties of its cyclic precursors in conjunction with those related pyranones obtained during the course of our earlier investigations. This unanticipated silyl transfer severely complicated application of

(15) Danishefsky S. J.; Langer, M. *J. Org. Chem.*, in press.
(16) Carlsen, Per H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(17) The low yield for this series of steps appears to be due to incomplete oxidation of the aromatic ring by RuO_4.
(18) (a) DeShong, P.; Ramesh, S.; Perez, J. J.; Bodish, C. *Tetrahedron Lett.* **1982**, *23*, 2243. (b) DeShong, P.; Ramesh, S.; Perez, J. J. *J. Org. Chem.* **1983**, *48*, 2117.
(19) Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617.
(20) Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *J. Org. Chem.* **1984**, *49*, 2512.
(21) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.
(22) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.
(23) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(24) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1984**, *49*, 1462.
(25) The 500-MHz ^{1}H NMR spectrum of compound **19b** shows an ABX pattern [3.91 (dd, J = 10.0, 3.7 Hz, 1 H), 3.62 (dd, J = 10.0, 7.9 Hz, 1 H)] for the C_1 methylene and a broad doublet of triplets (3.66, br dt, J = 7.4, 3.9 Hz, 1 H) for the C_3 methine. In addition, the 250-MHz ^{1}H NMR spectrum of the corresponding crude diacetate (which decomposes during chromatography) shows a doublet (J = 3 Hz, 1 H) at 5.86 ppm for the C_5 methine, a doublet of doublets at 4.92 ppm (J = 8, 5 Hz, 1 H) for the C_3 methine, and an ABX pattern [3.70 (dd, J = 10, 6 Hz, 1 H), 3.36 (dd, J = 10, 7 Hz, 1 H)] for the C_1 methine, indicating that acetylation has occurred at C_3 and C_5 rather than at C_1.

this chemistry to an actual synthesis of tirandamycin, in that it complicated the specific protection of the C_1 alcohol with an acid stable blocking group. It seems to be crucial to have the C_1 alcohol masked as the dimethylfuryl system is subjected to oxidation and acidolysis. In the presence of an unblocked C_1-OH, transformation of compounds of the **19** series to the bridged bicyclic system **20** is beset by difficulties.[18-20]

Indeed, attempted conversion of diol **19b** to the Ireland alcohol **20** through the action of mCPBA, followed by desilylation and cyclization with HF in acetonitrile, afforded alcohol **20** in low yield (<10%). Another low-yielding foray started with desilylation of compound **19b** (n-Bu_4NF–THF). The crude **19c** so generated was subjected to the action of 2-methoxypropene (PPTs, methylene chloride). There was thus generated in low (ca. 10%) yield a sample of the acetonide **19d**.[19] The identity of the spectral properties of synthetic **19d** and synthetic **20** with those of authentic samples served only to corroborate our already secure stereochemical assignments. The quality of these transformations was not such as to encourage the use of compound 19b as an intermediate for a total tirandamycin synthesis.

With the benefit of retrospection, it would be necessary to protect the alcohol function of compound **16** with a blocking group which would not have undergone C_3–O C_1–O migration. While this could undoubtedly be arranged, it became known to us that *a total synthesis* of tirandamycin had been accomplished in an elegant and efficient way by Schlessinger and associates.[26] Accordingly, we closed out this phase of our inquiry with these demonstrations of concise routes to polypropionate structures. Applications to other target systems will be disclosed shortly.

Experimental Section

(*E*,*Z*)-1-Methoxy-2-methyl-3-((triethylsilyl)oxy)-1,3-pentadiene (4a). 1-Methoxy-2-methyl-1-penten-3-one (8.01 g, 626 mmol), triethylamine (12.9 g, 126.9 mmol), and Et_2O (125 mL) were cooled to 0 °C and treated with triethylsilyl triflate (17.2 g, 654 mmol). After 30 min this mixture was diluted with Et_2O (200 mL) and transferred to a separatory funnel from which the lower layer was removed. The organic phase was then washed with saturated $NaHCO_3$ solution (2 × 50 mL) and dried ($MgSO_4$). Concentration in vacuo followed by distillation gave 11.1 g (73%) of diene **4a**: IR ($CHCl_3$) 2960, 2875, 1660, 1635, 1460, 1415, 1380, 1350, 1320, 1220, 1140, 1065, 1015, 940, 860 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.37 (br s, 1 H), 4.70 (q, J = 6.9 Hz, 1 H), 3.65 (s, 3 H), 1.67 (d, J = 1.14, 3 H), 1.64 (d, J = 6.9 Hz, 3 H), 1.01 (br t, J = 7.8 Hz, 9 H), 0.71 (br q, J = 7.8 Hz, 6 H); ^{13}C NMR (62.53 MHz $CDCl_3$) 150.37, 145.42, 113.19, 101.58, 59.84, 11.50, 10.59, 6.93, 5.69; MS, m/e (relative intensity) 243 (3), 242 (M^+, 3), 229 (7), 213 (10), 199 (6), 185 (21), 175 (22), 159 (18), 131 (15), 117 (12), 115 (50), 103 (13), 99 (41), 89 (100), 88 (11), 87 (44), 85 (11), 84 (17), 75 (48), 66 (14), 61 (25).

1-Methoxy-2-(3,4,5-trimethoxyphenyl)propene. NaH (52 g (60% in mineral oil), 130 mmol) was rinsed with pentane (3×), treated with Me_2SO (50 mL), and heated to 40 °C for 10 h under a flow of N_2. After the solution was cooled to 0 °C, THF (20 mL) and Me_2SO (50 mL) were added. (Methoxymethyl)triphenylphosphonium chloride (35 g, ca. 90% pure (Aldrich), ca. 100 mmol) was then carefully added and stirred for 1 h at 0 °C. 3′,4′,5′-Trimethoxyacetophenone (10.6 g, 50.4 mmol) in Me_2SO (50 mL) was then slowly added and stirred for 1.5 h at 0 °C and 1 h at room temperature. The reaction mixture was then poured into 150 mL of H_2O and the aqueous phase extracted with Et_2O (4 × 200 mL). The combined organics were dried (K_2CO_3) and concentrated in vacuo. Silica gel chromatography gave 11.3 g (94%) of 1-methoxy-2-(3,4,5-trimethoxyphenyl)propene (approximately 1.2:1 mixture of isomers): IR ($CHCl_3$) 2995, 2940, 2825, 1650, 1580, 1510, 1465, 1415, 1375, 1355, 1335, 1320 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), major isomer, δ 6.51 (s, 2 H), 6.36 (q, J = 1.4 Hz, 1 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 1.98 (d, J = 1.4 Hz, 3H); ^1H NMR (250 MHz, $CDCl_3$), minor isomer, δ 6.88 (s, 2 H), 6.16 (q, J = 1.3 Hz, 1 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 1.91 (d, J = 1.3 Hz, 3 H); MS, m/e (relative intensity) 239 (13), 238 (M^+, 100), 224 (14), 223 (89), 195 (19), 192 (21), 165 (13).

2-(3,4,5-Trimethoxyphenyl)propionaldehyde (3). 1-Methoxy-2-(3,4,5-trimethoxyphenyl)propene (11.3 g, 47.5 mmol) in acetone (50 mL) and H_2O (12.5 mL) was treated with concentrated HBr (1.5 mL) for 7 h. After neutralization with saturated $NaHCO_3$ solution and extraction with Et_2O (4 × 100 mL) the combined organics were dried (K_2CO_3) and concentrated in vacuo. Silica gel chromatography gave 8.89 g (84%) of aldehyde **3** (mp 56–58 °C): IR ($CHCl_3$) 2960, 2940, 2830, 1730, 1595, 1510, 1465, 1420, 1330, 1220, 1135, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.67 (d, J = 1.3 Hz, 1 H), 6.41 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.58 (br q, J = 7.1 Hz, 1 H), 1.44 (d, J = 7.1 Hz, 3 H); MS, m/e (relative intensity) 224 (M^+, 32), 196 (14), 195 (100), 180 (9), 165 (7), 164 (7), 149 (4), 105 (4), 83 (4), 75 (4).

(2*R,5*S**,6*S**,7*S**)-5,6-Dihydro-3,5-dimethyl-2-methoxy-4-((triethylsilyl)oxy)-6-(1-(3,4,5-trimethoxyphenyl)ethyl)-2*H*-pyran (5).** Aldehyde **3** (3.14 g, 14.0 mmol) and diene **4a** (5.1 g, 21.1 mmol) in $CHCl_3$ (14.0 mL) were treated with YbFOD (1.5 g, 1.4 mmol) for 36 h at room temperature. After the solution was cooled to −78 °C, triethylamine (5.0 mL) was added. Warming to room temperature and rotary evaporation gave an oil which was chromatographed on a cold (~0 °C) column of silica gel with 5% triethylamine in hexane to give 3.65 g (56%) of silyl enol ether **5**: IR ($CHCl_3$) 3000, 2950, 2910, 2875, 2840, 1680, 1590, 1510, 1460, 1420, 1130, 1100, 1060, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.40 (s, 2 H), 5.16 (s, 1 H), 3.85 (s, 6 H), 3.82 (s, 3 H), 3.62 (dd, J = 10.5, 2.3 Hz, 1 H), 3.40 (s, 3 H), 2.82 (dq, J = 10.5, 6.7 Hz, 1 H), 1.64–1.55 (m, 1 H), 1.54 (s, 3 H), 1.36 (d, J = 6.7 Hz, 3 H), 1.05 (d, J = 6.7 Hz, 3 H), 0.86 (br t, J = 8 Hz, 9 H), 0.53 (br q, J = 8 Hz, 6 H); MS, m/e (relative intensity) 467 (3), 466 (M^+, 12), 465 (8), 437 (4), 436 (6), 435 (19), 272 (11), 271 (56), 208 (3), 195 (16), 125 (13), 115 (3), 100 (6), 99 (100), 69 (3).

(2*R,3*S**,5*S**,6*R**,7*S**)-Tetrahydro-3,5-dimethyl-2-methoxy-6-(1-(3,4,5-trimethoxyphenyl)ethyl)-2*H*-pyran-4-one (6).** To a cold (−15 °C) solution of pyridine (45 mL), MeOH (45 mL), and concentrated HF (3.0 mL) was added silyl enol ether **5** (3.65 g, 7.89 mmol) in MeOH (10 mL). After 15 min at −15 °C followed by warming to room temperature for 30 min, the excess acid was quenched with saturated $NaHCO_3$ solution 50 mL). After dilution with H_2O (100 mL), the aqueous phase was extracted with Et_2O (4 × 150 mL) and the combined organics were dried (K_2CO_3). Concentration in vacuo and silica gel chromatography gave ketone **6** (2.35 g, 86%): mp 127.5–128.5 °C; IR ($CHCl_3$) 3000, 2950, 2930, 2840, 1710, 1590, 1510, 1460, 1420, 1330, 1230, 1150, 1130, 1080, 1055, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.35 (s, 2 H), 4.18 (d, J = 8.8 Hz, 1 H), 3.85 (s, 6 H), 3.84 (s, 3 H), 3.64 (s, 3 H), 3.54 (dd, J = 10.2, 2.3 Hz, 1 H), 2.96 (dq, J = 10.2, 6.7 Hz, 1 H), 2.62 (dq, J = 8.7, 6.6 Hz, 1 H), 2.18 (dq, J = 2.2, 7.1 Hz, 1 H), 1.41 (d, J = 6.7 Hz, 3 H), 1.16 (d, J = 7.1 Hz, 3 H), 1.07 (d, J = 6.6 Hz, 3 H); MS, m/e (relative intensity) 353 (2), 352 (M^+, 10), 197 (2), 196 (19), 195 (100), 181 (1), 180 (1), 157 (5), 101 (1), 100 (2), 99 (37), 85 (13), 73 (1), 72 (1). Anal.: ($C_{19}H_{28}O_6$): C, H.

(2*R,3*R**,4*S**,5*R**,6*R*,7*S**)-Tetrahydro-2-methoxy-3,5-dimethyl-6-(1-(3,4,5-trimethoxyphenyl)ethyl)-2*H*-pyran-4-ol (7a).** At −15 °C ketone **6** (49.0 mg, 0.139 mmol) in MeOH (0.5 mL) and THF (0.2 mL) was treated with $NaBH_4$ (8.0 mg, 0.211 mmol) and slowly warmed to room temperature over a 2-h period. Excess $NaBH_4$ was then quenched with saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O (4 × 20 mL) and dried (K_2CO_3). Silica gel chromatography gave alcohol **7a** (40.1 mg, 81%): IR ($CHCl_3$) 3610, 3500 (b), 3000, 2975, 2950, 2910, 2875, 2840, 1590, 1510, 1495, 1465, 1420, 1385, 1335, 1315, 1210, 1135, 1090, 1065, 1040, 1020, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.39 (s, 2 H), 3.97 (d, J = 8.5 Hz, 1 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.57 (s, 3 H), 3.34 (2 H multiplet containing a dd, J = 10.3, 1.4 Hz, 1 H), 2.90 (dq, J = 10.3, 6.8 Hz, 1 H), 1.60 (m, 2 H), 1.43 (d, J = 5.1 Hz, 1 H), 1.36 (d, J = 6.7 Hz, 3 H), 1.03 (d, J = 6.4 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (65.3 MHz, $CDCl_3$) δ 153.45, 139.63, 136.92, 107.22, 104.87, 79.73, 75.96, 60.67, 57.08, 56.35, 42.15, 38.53, 36.09, 20.08, 12.50, 5.89; MS, m/e (relative intensity) 355 (6), 354 (M^+, 32), 236 (2), 197 (3), 196 (18), 195 (59), 181 (12), 160 (4), 159 (48), 142 (8), 141 (100), 129 (3), 127 (18), 113 (7), 109 (2), 103 (13), 101 (22), 99 (3), 97 (2), 87 (19), 85 (6), 74 (3), 73 (76), 59 (3).

(2*R,3*R**,4*S**,5*R**,6*R**,7*S**)-Tetrahydro-2,4-dimethoxy-3,5-dimethyl-6-(1-(3,4,5-trimethoxyphenyl)ethyl)-2*H*-pyran (7b).** NaH (150 mg, 60% in mineral oil (Aldrich), 3.75 mmol) was rinsed with pentane (3×) and suspended in THF (10.0 mL). Alcohol **7a** (508.8 mg, 1.43 mmol) in THF (40 mL) was added slowly. After H_2 evolution had apparently ceased, MeI (1.02 g, 7.23 mmol) and DMF (10 mL) were added. After the solution was stirred for 10 h, the excess NaH was quenched by addition of saturated NH_4Cl solution (5.0 mL) and the reaction mixture was diluted with H_2O (75 mL). The aqueous phase was extracted with Et_2O (4 × 150 mL) and the combined organics were dried ($MgSO_4$). Silica gel chromatography gave methyl ether **7b** (518.3 mg, 98%): mp 137.5–139.0 °C; IR ($CHCl_3$) 2960, 2925, 2830, 1590, 1510, 1490, 1460, 1420, 1385, 1375, 1335, 1320, 1220, 1130, 1160, 1060, 1020, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.40 (s, 2 H), 3.96 (d, J = 8.7 Hz, 1 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.57 (s, 3 H), 3.29 (dd, J = 10.2, 1.7 Hz, 1 H), 3.18 (s, 3 H), 2.93 (dq, J = 10.2, 6.7 Hz, 1 H), 2.81

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(dd, J = 10.7, 4.7 Hz, 1 H), 1.82–1.54 (m, 2 H), 1.36 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H); MS, m/e (relative intensity) 369 (2), 368 (M^+, 11), 196 (**4**), 195, (18), 174 (2), 173 (23), 143 (2), 142 (8), 141 (100), 115 (27), 113 (12), 102 (**4**), 101 (84), 85 (18), 83 (2), 75 (2), 73 (43). Anal. Calcd ($C_{20}H_{32}O_6$): C, H.

Monensin Lactone 9. Pyran **7b** (74.8 mg, 0.203 mmol) in THF (2.0 mL) and H_2O (1.0 mL) was treated with concentrated HCl (0.1 mL) at 50 °C. After 24 h an additional 0.1 mL of concentrated HCl was added. After 48 h the acid was neutralized with saturated $NaHCO_3$ solution. The aqueous phase was extracted with Et_2O (4 × 20 mL) and the combined organics were dried (K_2CO_3) and concentrated in vacuo. The crude lactol **8** was added to a two-phase system of CCl_4 (2.0 mL), CH_3CN (4.0 mL), and H_2O (10.0 mL) containing $NaIO_4$ (850 mg, 3.97 mmol) and catalytic $RuO_2 \cdot H_2O$ (3.0 mg).[16] After 4 h the yellow color (RuO_4) had returned and the reaction mixture was filtered through Celite and diluted with H_2O (50 mL). The aqueous phase was extracted with Et_2O (4 × 30 mL), and the resulting combined organics were concentrated in vacuo. The resulting crude lactonic acid was dissolved in Et_2O and extracted with saturated $NaHCO_3$ solution (4 × 15 mL). The aqueous phase was then cooled to 0 °C, acidified with 6 N HCl, and extracted with Et_2O (4 × 30 mL). After concentration in vacuo, the lactonic acid was treated with excess CH_2N_2 in Et_2O (10.0 mL) for 1 h. Concentration in vacuo followed by silica gel chromatography gave 28.6 mg (58%) of lactonic ester **9** which gave IR, NMR, and mass spectra identical with the spectra obtained from a sample of the levorotatory isomer derived from the natural material kindly provided by Professor W. C. Still. Melting point of racemic material 75.5–76.5 °C; IR ($CHCl_3$) 2980, 2940, 2900, 2820, 1730, 1450, 1430, 1380, 1350, 1330, 1290, 1260, 1190, 1170, 1110, 1070, 990 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.20 (dd, J = 10.3, 2.1 Hz, 1 H), 3.74 (s, 3 H), 3.37 (s, 3 H), 3.28 (dd, J = 10.2, 4.3 Hz, 1 H), 2.84 (dq, J = 10.3, 7.0 Hz, 1 H), 2.47 (dq, J = 10.2, 7.1 Hz, 1 H), 2.39 (ddq, J = 2.5, 4.4, 6 Hz, 1 H), 1.40 (d, J = 6.9 Hz, 3 H), 1.38 (d, J = 7.1 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H); MS, m/e (relative intensity) (no M^+) 213 (0.5), 211 (0.5), 185 (1.0), 184 (1.1), 173 (1.1), 172 (10.1), 171 (100.0), 157 (1.5), 153 (2.7), 144 (7.0), 139 (14.2), 128 (22.4), 125 (10.6), 115 (33.8), 113 (9.3), 101 (8.2), 99 (9.4), 97 (8.4), 85 (16.0), 83 (11.2), 73 (14.0), 72 (64.7), 69 (35).

***cis*-2-(4,5-Dimethyl-2-furyl)-3,5-dimethyl-2,3-dihydro-4*H*-pyrone (11).** A solution of aldehyde **10** (211.6 mg, 1.70 mmol) and diene **4b** (413 mg, 2.06 mmol) in $CDCl_3$ (1.0 mL) was treated with $Yb(fod)_3$ (180 mg, 0.17 mmol) at room temperature for approximately 24 h. CH_2Cl_2 (10.0 mL) was then added and the crude Diels-Alder adduct was cleaved to the 2,3-dihydropyrone by addition of trifluoroacetic acid (100 μL). After 5 min saturated $NaHCO_3$ solution was added (5.0 mL) and the aqueous phase was extracted with Et_2O. The combined organics were dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel to give 314.8 mg (84%) of cis dihydropyrone **11**: mp 57.0–57.5 °C; IR ($CHCl_3$) 3020, 2935, 1670, 1625, 1460, 1390, 1305, 1170 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.17 (d, J = 1.1 Hz, 1 H), 6.10 (s, 1 H), 5.34 (d, J = 4.4 Hz, 1 H), 2.86 (dq J = 4.4, 7.1 Hz, 1 H), 2.20 (s, 3 H), 1.92 (s, 3 H), 1.71 (d, J = 1.1 Hz, 3 H), 1.14 (d, J = 7.1 Hz, 3 H); MS, m/e (relative intensity) 220 (M^+, 5), 164 (1), 137 (9), 136 (100), 135 (6), 122 (2), 121 (8), 109 (4), 93 (3). Exact mass Calcd: 220.1099. Found: 220.1109.

(2*R,3*S**,4*R**)-6-(4,5-Dimethyl-2-furyl)-3,5-dimethyl-4-hydroxy-2,3-dihydro-4*H*-pyran (12).** To a cold (−78 °C) suspension of LAH (6.5 mg, 0.17 mmol) in Et_2O (1.0 mL) was added a solution of dihydropyrone **11** (34.3 mg, 0.156 mmol) in Et_2O (0.5 mL). After 15 min, 2 mL of saturated sodium potassium tartrate solution was added and the mixture warmed to room temperature and stirred for 2 h. Water (5 mL) was added and the aqueous phase extracted with Et_2O (4 × 20 mL). The combined organics were dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel to give alcohol **12** (30.8 mg, 89%): mp 69.0–69.5 °C; IR ($CHCl_3$) 3560, 3020, 2930, 1670, 1460, 1390, 1150 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 6.23 (s, 1 H), 6.09 (s, 1 H), 4.87 (d, J = 3.6 Hz, 1 H), 4.12 (br dd, J = 9.2, 5.6 Hz, 1 H), 2.45–2.39 (m, 1 H), 2.19 (s, 3 H), 1.91 (s, 3 H), 1.87 (d, J = 9.2 Hz, 1 H), 1.69 (s, 3 H), 1.04 (d, J = 7.1 Hz, 3 H); MS, m/e (relative intensity) 222 (M^+, 2), 221 (2), 220 (6), 136 (40), 125 (54), 123 (21), 113 (14), 112 (24), 111 (22), 109 (15), 98 (26), 95 (14), 85 (28), 84 (11), 74 (21), 69 (40), 68 (11), 59 (33), 57 (11), 56 (11), 45 (38), 44 (11), 43 (100).

(2*R,5*S**,6*R**)-6-(4,5-Dimethyl-2-furyl)-3,5-dimethyl-2-(benzyloxy)-5,6-dihydro-2*H*-pyran (13).** The pseudoglycal **12** (48.0 mg, 0.216 mmol) and benzyl alcohol (70.0 mg, 0.647 mmol) in benzene (1.1 mL) were treated with p-toluenesulfonic acid (1.5 mg, 7.87 μmol) for 1.5 h. After quenching with saturated $NaHCO_3$ solution and extraction with Et_2O (4 × 15 mL), the combined organics were dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography gave 61.7 mg (91%) of pyran **13** as a colorless oil: IR ($CHCl_3$) 3010, 2975, 2925, 2880, 1450, 1375, 1125, 1090, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 6.07 (s, 1 H), 5.7 (d, J = 5.4 Hz, 1 H), 5.08 (d, J = 3.3 Hz, 1 H), 4.95 (s, 1 H), 4.83 (d, J = 12.0 Hz, 1 H), 4.61 (d, J = 12.0 Hz, 1 H), 2.30 (m, 1 H), 2.21 (s, 3 H), 1.95 (s, 3 H), 1.74 (s, 3 H), 0.88 (d, J = 7.0 Hz 3 H); MS, m/e (relative intensity) 312 (M^+, 0.9) 205 (1.2), 189 (4.1), 188 (24.0), 159 (2.7) 136 (1.5), 131 (1.2), 130 (1.5), 125 (2.2), 123 (1.7) 118 (1.1), 109 (10.0), 105 (1.2), 97 (6.0), 96 (6.5), 95 (1.4), 93 (1.1), 92 (9.0), 91 (100.0), 79 (1.3), 77 (1.9), 69 (1.1), 67 (1.2), 65 (2.7).

(2*R,3*S**,4*R**,5*S**,6*R**)- and (2*R**,3*R**,4*S**,5*S**,6*R**)-Tetrahydro-2-(benzyloxy)-3,5-dimethyl-6-(4,5-dimethyl-2-furyl)pyran-4-ol (14).** Pyran **13** (89.5 mg, 0.287 mmol), in THF (2.8 mL), was cooled to 0 °C and treated with BH_3·THF solution (0.573 mL of a 1.0 M solution (Aldrich), 0.573 mmol). After 20 min at 0 °C the solution was slowly warmed to room temperature over an 8-h period. The crude borane was oxidized by addition of 30% H_2O_2 solution (300 μL), H_2O (2.0 mL), and NaOH (100 mg). After being stirred for 12 h the reaction mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Careful silica gel chromatography gave approximately 5.0 mg (5.3%) of the minor equatorial alcohol and 50.8 mg (54%) of the major alcohol **14**. Minor alcohol: mp 119–120.5 °C; IR ($CHCl_3$) 3600, 3470 (vbr), 3010, 2985, 2925, 2885, 1455, 1050, 1035, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5 H), 6.04 (s, 1 H), 5.01 (d, J = 2.0 Hz, 1 H), 4.86 (d, J = 3.7 Hz, 1 H), 4.73 (d, J = 12.1 Hz, 1 H), 4.46 (d, J = 12.1 Hz, 1 H), 4.01 (ddd, J = 10.8, 5.5, 5.1 Hz, 1 H), 2.26–2.23 (m, 1 H), 2.20 (s, 3 H), 2.00–1.96 (m, 1 H), 1.94 (s, 3 H), 1.44 (d, J = 5.5 Hz, 1 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H); MS, m/e (relative intensity), minor alcohol, 330 (14), 239 (6), 222 (12), 187 (4), 164 (9), 149 (4), 148 (13), 138 (7), 137 (5), 136 (19) 125 (25), 119 (7), 109 (13), 92 (10), 91 (100), 69 (6), 59 (4), 57 (10); Exact mass Calcd: 330.1831. Found 330.1848. Major alcohol **14**: IR ($CHCl_3$) δ 3600, 3550 (b), 3000, 2975, 2925, 2880, 1455, 1065, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36–7.28 (m, 5 H), 6.04 (s, 1 H), 4.99 (d, J = 5.5 Hz, 1 H), 4.77 (d, J = 11.8 Hz, 1H), 4.56 (d, J = 6.7 Hz, 1 H), 4.46 (d, J = 11.8 Hz, 1 H), 3.64–3.60 (m, 1 H), 2.17 (s, 3 H), 2.09–2.05 (m, 1 H), 1.94 (s, 4 H), 1.75–1.72 (m, 1 H), 1.11 (d, j = 6.83 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H); MS, m/e (relative intensity) 330 (M^+, 9), 315 (5), 239 (9), 222 (31), 187 (9), 182 (5), 165 (5), 164 (22), 148 (27), 143 (8), 138 (14), 137 (13), 136 (54), 125 (64), 119 (19), 109 (22), 91 (100), 85 (10), 71 (9). Exact mass Calcd: 330.1831. Found: 330.1833.

(2*R,3*R**,5*S**,6*S**)-Tetrahydro-2-(benzyloxy)-3,5-dimethyl-6-(4,5-dimethyl-2-furyl)-2*H*-pyran-4-one (15).** By using the procedure of Mancuso and Swern,[23] alcohol **14** (40.8 mg, 0.123 mmol) was oxidized with Me_2SO–oxalyl chloride followed by triethylamine to give pyranone **15** (35.7 mg, 88%) following silica gel chromatography: IR ($CHCl_3$) 2975, 2940, 2880, 1720, 1455, 1375, 1355, 1300, 1130, 1020 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5 H), 5.96 (s, 1 H), 5.22 (d, J = 6.7 Hz, 1 H), 4.82 (d, J = 11.7 Hz, 1 H), 4.503 (d, J = 11.7 Hz, 1 H), 4.499 (d, J = 7.4 Hz, 1 H), 3.01 (dp, J = 1.2, 6.9 Hz, 1 H), 2.60 (dp, J = 1.2, 6.7 Hz, 1 H), 2.14 (s, 3 H), 1.90 (s, 3 H), 1.12 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H); MS, m/e (relative intensity) 328 (M^+, 4), 237 (6), 215 (19), 204 (19), 187 (24), 146 (9), 136 (23), 123 (6), 119 (7), 118 (4), 109 (8), 92 (9), 91 (100). Exact mass Calcd: 328.1675. Found: 328.1673.

(2*R,3*R**,4*R**,5*S**,6*R**)-Tetrahydro-2-(benzyloxy)-3,5-dimethyl-6-(4,5-dimethyl-2-furyl)-2*H*-pyran-4-ol (16).** A solution of ketone **15** (32.3 mg, 0.0984 mmol) in MeOH (1.0 mL) was cooled to −25 °C and treated with $NaBH_4$(s) (38.4 mg, 1.01 mmol). After the solution was slowly warmed to approximately 15 °C over a 3-h period, the excess $NaBH_4$ was quenched with saturated NH_4Cl solution. This mixture was diluted with H_2O (10.0 mL) and extracted with CH_2Cl_2 (4 × 20 mL). Drying ($MgSO_4$), concentration in vacuo, and silica gel chromatography gave 27.3 mg (84%) of alcohol **16**: IR ($CHCl_3$) 3550, 3000, 2920, 1455, 1120, 1070, 1030 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5 H), 6.12 (s, 1 H), 4.96 (d, J = 5.5 Hz, 1 H), 4.77 (d, J = 5.5 Hz, 1 H), 4.75 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 3.97 (ddd, J = 8.1, 4.2, 4.0 Hz, 1 H), 2.35–2.30 (m, 1 H), 2.19 (s, 3 H), 2.11 (d, J = 8.1 Hz, 1 H), 2.00–1.95 (m, 1 H), 1.95 (s, 3 H), 1.10 (d, J = 7.2 Hz, 3 H), 0.93 (d, J = 7.3 Hz, 3 H); MS, m/e (relative intensity) 330 (M^+, 3), 221 (3), 215 (3), 187 (7), 182 (7), 148 (30), 138 (14), 136 (36), 125 (61), 119 (15), 109 (10), 91 (100). Exact mass Calcd: 330.1831. Found: 330.1835.

(2*R,3*R**,4*R**,5*S**,6*R**)-Tetrahydro-2-(benzyloxy)-3,5-dimethyl-6-(4,5-dimethyl-2-furyl)-4*H*-pyran-4-ol (*tert*-Butyldimethylsilyl ether) (17). Alcohol 16** (27.3 mg, 0.0827 mmol) and triethylamine (168 mg, 1.65 mmol) in CH_2Cl_2 (1.0 mL) were cooled to 0 °C and *tert*-butyldimethylsilyl triflate (109.3 mg, 0.414 mmol) was added dropwise. After 1 h, this mixture was treated with saturated $NaHCO_3$ solution (15 mL)

and warmed to room temperature. The aqueous phase was extracted with Et_2O (4 × 20 mL) and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography gave 35.3 mg (96%) of silyl ether **17**: mp 62–63 °C; IR ($CHCl_3$) 2950, 2925, 2880, 2850, 1460, 1360, 1250, 1130, 1090 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5 H), 6.07 (s, 1 H), 5.00 (d, J = 2.6 Hz, 1 H), 4.85 (s, 1 H), 4.72 (d, J = 12.1 Hz, 1 H), 4.48, (d, J = 12.1 Hz, 1 H), 4.28 (t, J = 5.6 Hz, 1 H), 2.20 (s, 3 H), 2.13–2.07 (m, 1 H), 2.07–2.01 (m, 1 H), 1.94 (s, 3 H), 1.07 (d, J = 7.6 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.92 (s, 9 H), 0.08 (s, 6 H); MS, m/e (relative intensity) 444 (M^+, 45), 387 (26), 336 (29), 279 (45), 240 (31), 239 (73), 221 (23), 209 (27), 201 (20), 187 (25), 173 (39), 172 (72), 149 (30), 143 (65), 145 (21), 143 (38), 136 (66), 135 (24), 131 (65), 125 (42), 124 (21), 123 (37), 119 (36), 116 (44), 115 (77), 109 (32), 92 (52), 91 (100), 85 (21), 79 (20), 77 (40), 75 (65), 73 (67), 65 (26). Exact mass Calcd: 444.2696. Found: 444.2689.

(3*R,4*R**,5*S**,6*R**)-Tetrahydro-3,5-dimethyl-4-((*tert*-butyldimethylsilyl)oxy)-6-(4,5-dimethyl-2-furyl)-2*H*-pyran-2-ol (18).** To a cold (−78 °C) solution of pyran **17** (94.8 mg, 0.213 mmol) in Et_2O (5.0 mL) and NH_3 (ca. 10 mL) was added sodium metal (ca. 150 mg, ca. 15 equiv). After 25 min at −78 °C, NH_4Cl(s) was added and the NH_3 was evaporated. After addition of H_2O (20 mL) and extraction with Et_2O (4 × 20 mL) the combined organics were dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography gave lactol **18** (49.5 mg, 66%) as a 2.7:1 mixture of anomers. IR ($CHCl_3$) (of mixture) 3600, 3400 (b), 2960, 2940, 2900, 2860, 1460, 1390, 1255, 1130, 1110, 1090, 1070, 1010, 975, 900, 880, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), major isomer, δ 6.04 (s, 1 H), 5.22 (br s, 1 H), 5.18 (d, J = 3.0 Hz, 1 H), 4.28 (t, J = 5.5 Hz, 1 H), 2.50 (d, J = 3.0 Hz, 1 H), 2.19 (s, 3 H), 2.15–2.05 (m, 1 H), 2.03–1.97 (m, 1H), 1.92 (s, 3 H), 1.08 (d, J = 7.6 Hz, 3 H), 0.94 (d, J = 7.2 Hz, 3 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^1H NMR (500 MHz, $CDCl_3$), minor isomer, δ 6.09 (s, 1 H), 4.89 (dd, J = 7.2, 2.8 Hz, 1 H), 4.53 (dd, J = 2.9 Hz, 1 H), 3.97 (t, J = 5.2 Hz, 1 H), 3.17 (d, J = 7.2 Hz, 1 H), 1.04 (d, J = 7.2 Hz, 3 H), other signals hidden by major isomer.

(1*R,2*S**,3*S**,4*S**)-1-(4,5-Dimethyl-2-furyl)-2,4-dimethylpentan-1,3,5-triol (5-*tert*-Butyldimethylsilyl Ether) (19b).** To a cold (−78 °C solution of pyran **17** (204.5 mg, 0.460 mmol) in Et_2O (10.0 mL) and NH_3 (ca. 15 mL) was added sodium metal (ca. 300 m, (25 to 30 equiv)). After 5 min at −78 °C (solution goes dark blue), the reaction mixture was warmed to reflux (−33 °C) for 1 h. The excess sodium was then quenched with NH_4Cl(s) and the NH_3 was evaporated. After addition of H_2O (20 mL) and extraction with Et_2O (4 × 20 mL), the combined organics were dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography gave diol **19** (101.6 mg, 62%): IR ($CHCl_3$) 3425 (b), 3015, 2965, 2940, 2860, 1470, 1260, 1100, 1075, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (s, 1 H), 5.05 (br s, 1 H), 4.78 (d, J = 2.7 Hz, 1 H), 4.25 (d, J = 2.9 Hz, 1 H), 3.91 (dd, J = 10.0, 3.7 Hz, 1 H), 3.66 (br dt, J = 7.4, 3.9 Hz, 1 H), 3.62 (dd, J = 10.0, 7.9 Hz, 1 H), 2.18 (s, 3 H), 2.14–2.08 (m, 1 H), 2.06–1.99 (m, 1 H), 1.92 (s, 3 H), 1.03 (d, J = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.91 (d, J = 7 Hz, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H); MS, m/e (relative intensity) 356 (M^+, 2.0), 338 (2), 297 (6), 281 (6), 239 (2), 203 (4). Exact mass Calcd: 356.2383. Found: 356.2372.

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Registry No. 3, 98128-00-8; **4a**, 98128-01-9; **4b**, 72486-93-2; **5**, 98128-02-0; **6**, 98128-03-1; **7a**, 98128-04-2; **7b**, 98128-05-3; **8**, 98128-06-4; **9**, 98242-94-5; **9** (acid), 98300-65-3; **10**, 98128-07-5; **11**, 98128-08-6; **12**, 98128-09-7; **13**, 98128-10-0; **14** (major isomer), 98128-11-1; **14** (minor isomer), 98242-95-6; **15**, 98128-12-2; **16**, 98242-96-7; **17**, 98128-13-3; **18** (isomer 1), 98128-14-4; **18** (isomer 2), 98242-97-8; **19b**, 98128-15-5; monensin, 17090-79-8; 1-methoxy-2-methyl-1-penten-3-one, 74074-59-2; triethylsilyl triflate, 79271-56-0; (*E*)-1-methoxy-2-(3,4,5-trimethoxyphenyl)propene, 98128-16-6; (*Z*)-1-methoxy-2-(3,4,5-trimethoxyphenyl)propene, 98169-99-4; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7; 3′,4′,5′-trimethoxyacetophenone, 1136-86-3; *tert*-butyldimethylsilyl triflate, 69739-34-0.

The Role of the Chlorine Substituents in the Antibiotic Vancomycin: Preparation and Characterization of Mono- and Didechlorovancomycin

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Abstract: Mono- and didechlorinated derivatives of the antibiotic vancomycin (**1**) have been prepared by catalytic dehydrogenation with Pd/C (10%) catalyst. Initial dehalogenation occurs on residue **2** to give monochloro derivative **3** (MDCV), followed by a slower removal of the second chlorine to give didechloro derivative **4** (DDCV). Heating of **3** and **4** (pH 4.2, 80 °C) leads to CDP-I type rearrangement products **6** and **7** which were also obtained by catalytic dehalogenation of CDP-I. Rearrangement product **7** failed to show detectable antibiotic activity; the inward-facing chlorine on residue **2** is not, therefore, the sole reason for the lack of activity of CDP-I itself. Binding studies with di- and tripeptides, **8–14**, which are analogues of the natural peptide binding site in bacterial peptidoglycan, indicate that both **3** and **4** bind peptides less effectively than **1**, although **4** is somewhat more tolerant of larger side chains on the C-terminal residue of tripeptides. The role of the chlorines in stabilizing and defining the shape of the peptide binding site is discussed.

Vancomycin, a glycopeptide antibiotic elaborated by *Streptomyces orientalis*,[1a] has been the subject of numerous investigations in recent years.[1b,c,2] Several revisions in its structure have been made, but **1** is now generally accepted to be the correct one.[3] Prior

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