Pure & Appl. Chem., Vol. 59, No. 3, pp. 345–352, 1987.
Printed in Great Britain.

Iterative butenolide construction of polypropionate chains. Application to an efficient synthesis of (+)(9S)-dihydroerythronolide A

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Abstract — A general iterative construction of alternating sequences of carbon atoms bearing methyl and hydroxyl groups, as are found in many naturally occurring polypropionates, has been devised. This consists of the addition to a 5-substituted-2(5H)furanone first of a methyl group at C_4 and then of a hydroxyl at C_3. Since protocols have been devised to achieve this with either R or S configuration at the two new centers, and since the process can be repeated, any polypropionate-derived sequence can, in principle, be made. The new method is illustrated by a description of the most efficient synthesis of Erythronolide A, the aglycone of Erythromycin A.

A contemporary problem of some magnitude deals with the control of the stereochemistry of adjacent centers along a carbon chain. One particular, though not unique example can be found in the polyhydroxy acids which, in the form of their lactones, are the basis of the macrolide antibiotics. In many instances, the sequence of asymmetric centers is made up of alternating secondary methyl and secondary hydroxyl groups. This is a situation which is found, in particular, in those natural products derived from the repeated condensation of propionic acid units. In addition, one sometimes finds that the usual secondary methyl is on a more oxidized carbon which then appears as a tertiary alcohol. Conversely, the secondary hydroxyl center is sometimes present either in a more oxidized form as a ketone or more reduced, as a methylene group. Oleandomycin, the erythromycins and the rifamycins are examples of macrolides which exhibit some or all of those features.

Not surprisingly, the wide occurrence of such structures has prompted a very large amount of work in which a number of imaginative variations on the theme of the aldol condensation have been played[1]. There is no denying the valuable chemical information which has been gained from such endeavors. One can think immediately of the greatly expanded knowledge of the role of chelation control in the aldol and related reactions, and of the extent of applicability of the Cram-Felkin model when chelation is not anticipated[2]. The aldol approach has, in fact, been quite successful in the construction of some macrolide antibiotics, but no entirely general method has emerged which would permit the rational anticipation of the stereochemical outcome in a complex situation, especially when more than one oxygen function might be involved in chelation to a metal center. It became clear that there was a need for a general method which could be used to produce, at will, any specific arrangement of asymmetric centers in a chain consisting of secondary methyl-secondary hydroxyl sequences.

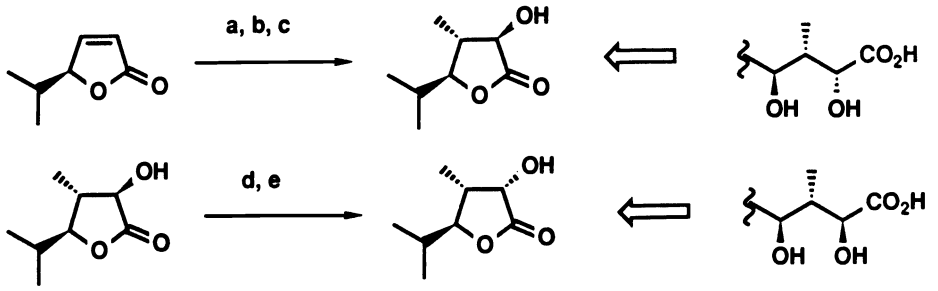
We have worked out a solution which will now be presented, together with its application to an efficient synthesis of erythronolide A[3].

It is probably easiest to think of our approach as one which involves the repetitive construction of a set consisting of two asymmetric carbons, one bearing a methyl and the next bearing a hydroxyl group. Every introduction of a subsequent set of these two carbons can give rise, obviously, to four possible stereoisomers. Any specific one could be made if one had the means of introducing the methyl and the hydroxyl group, at will, in either the R or the S configuration. If this were done on a rigid template, it would only be necessary to transform the template on which the two asymmetric centers had just been established to the next similar template on which to establish again any of the four possible arrangements of the next methyl and hydroxyl set. The problem then requires defining, first, what kind of a template would be particularly suitable to establish the two asymmetric centers in question; and, second, how to proceed from one elaborated template to the next, repetitively. We concluded, at the outset of our work, that a butenolide template should be especially suitable for our purpose. Because of difficulties with the nomenclature of these systems as lactones, and because of the precedent set by Chemical Abstracts, we will mainly refer to these substances as derivatives of 2-furanone.

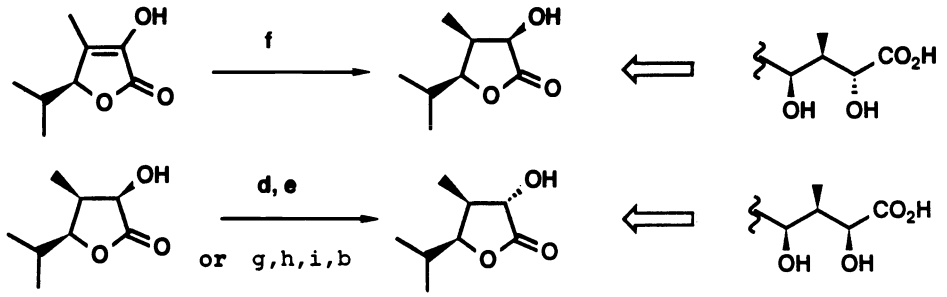
Starting with a 5-subtituted 2-furanone of given absolute configuration (refer to Scheme 1, where an isopropyl group stands for any 5-substituent), the first phase of the problem would be solved by controlling the introduction of a 4-methyl group either trans to the initial 5-substituent or cis to it; and, this accomplished, a secondary hydroxyl would now be inserted, either cis or trans to the just added methyl. The problem is simplified because the effectiveness of the Mitsunobu inversion reaction[4] only makes it necessary to produce stereospecifically one of the two possible configurations of the secondary hydroxyl group. The other one can then be produced by simple inversion.

Other problems, however, turned out to be a great deal more complex. What we may refer to as the "trans methyl" series is easily reached by the conjugate addition of a methyl group to the Δ^3 double bond of a 5-substituted-2-furanone. This takes place cleanly trans to the 5-substituent, but the antagonistic effect of the 5-substituent on one side of the plane to that of the 4-substituent on the other results in loss of control of the stereochemistry of the subsequent hydroxylation at the C3 center. The difficulty was eventually overcome by doing the conjugate addition with a bulky equivalent which would then provide steric control of the hydroxylation at C3. A successful candidate turned out to be the tris thiophenylcarbanion[5]. It readily underwent conjugate addition to the 5-alkylfuranone in the expected trans manner, and hydroxylation could then be performed effectively, for instance with the MoOPH reagent[6], to introduce the hydroxyl group trans to the thiophenyl-substituted carbon, as expected. The high yield Mitsunobu inversion then completed the construction of the two possible members of the "trans methyl" series.

Scheme 1



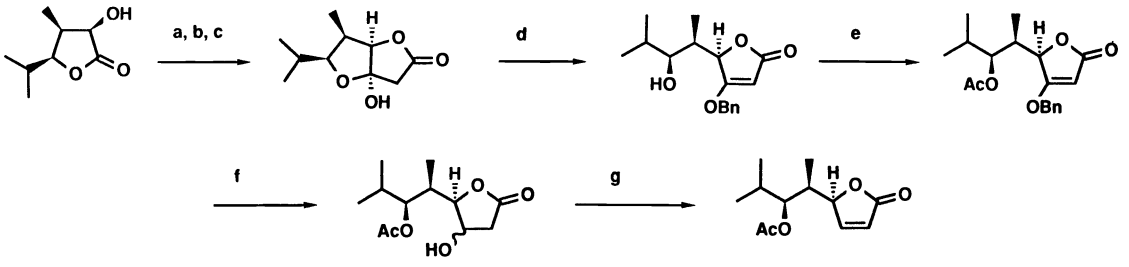
(a) $LiC(SPh)_3$, THF, -78°C; (b) MoOPh, 0°C; (c) Raney Nickel, EtOH; (d) DEAD, PPh_3, $PhCO_2H$, THF; (e) K_2CO_3, MeOH.



(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 "cis methyl" series also posed problems. We had imagined that catalytic hydrogenation of the Δ^3 double bond of a 4-methyl-5-substituted-2-furanone would proceed stereospecifically with the formation of the desired 4,5 cis-disubstituted furanone. In the event, catalytic hydrogenation under a variety of conditions gave variable and sometimes barely acceptable stereoselectivity. We again had to find an alternative to this deceptively simple possibility. The solution we eventually selected consisted of the catalytic hydrogenation not of a simple 4-methyl derivative of a 5 substituted 2-furanone but, rather, of its 3-hydroxy derivative, the stable enol of a 3-keto-2-furanone[7]. There is a bonus to this particular approach in that it not only leads selectively to the 4,5 "cis series" of the furanones, but to a cis 3-hydroxyl group, as well. The other 3-hydroxy member of the "cis series" could then, again, be made by Mitsunobu inversion of the just created secondary hydroxyl. In the "cis series" it was, however, sometimes more effective to produce the trans 3-hydroxyl epimer by removing the hydroxyl entirely from the hydrogenation product, and reintroducing it subsequently by MoOPH oxidation of the C-3 anion. The success of that operation is, of course, due to the fact that, in the "cis methyl" series, both the C-4 and the C-5 substituents block the same face of the furanone ring.

Scheme 2

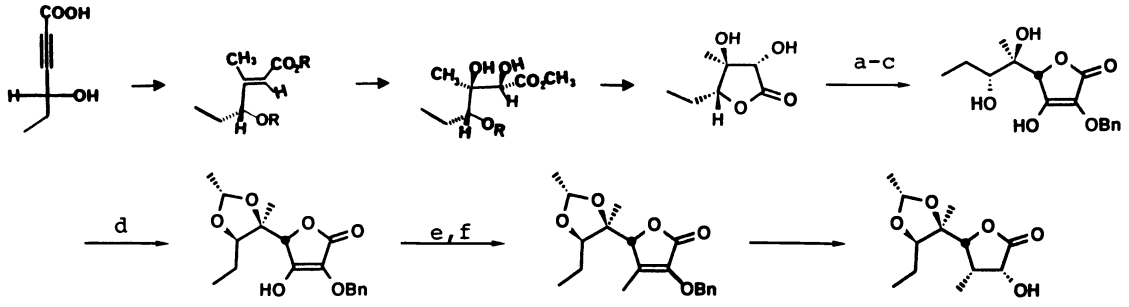


(a) $TMSNMe_2$, THF; (b) $LiOC(OEt)CH_2$, THF, -78°C; (c) K_2CO_3, MeOH;
(d) $PhCH_2Br$, Na_2CO_3, Bu_4NBr, CH_2Cl_2/H_2O; (e) Ac_2O, Et_3N, DMAP;
(f) 5% Rh/Alumina, H_2, MeOH; (g) MsCl, Et_3N.

The successful transformation of a 5-substituted-2-furanone into any one of its four possible 3-hydroxy-4-methyl isomers had been achieved.

We now had to face the problem of transforming the completed furanone into the next butenolide, or hydroxybutenolide, depending on the need to access the next furanone series in the trans- or the cis methyl series. This again proved less simple than we had originally anticipated, but a solution was eventually found. Addition to a completed 3-hydroxy-4-methyl 2-furanone of the anion of ethyl acetate starts the sequence which leads to the next 5-substituted 2-furanone, the precursor of the next "trans methyl" series, as shown in Scheme 2; while addition of the anion of 2-benzyl-oxyacetate leads to the precursor of the next "cis methyl", as illustrated in scheme 3. The process was now truly iterative.

Scheme 3



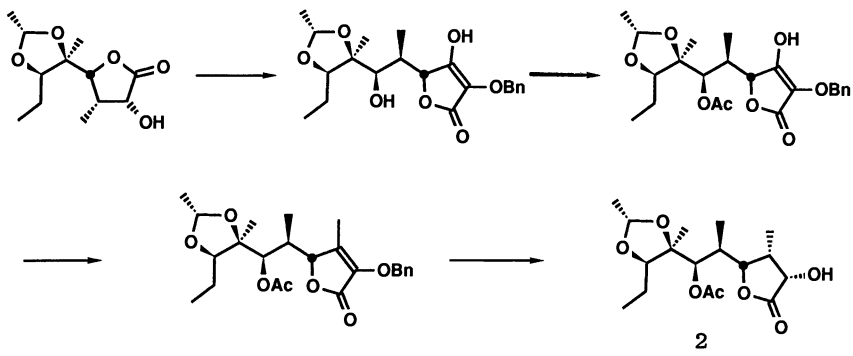
(a) TMSCl, Imidazole, DMF; (b) LIHMDS, $EtOC(O)CH_2OCH_2Ph$, THF, -50°C
(c) K_2CO_3, MeOH ; (d) Acetal, CSA, CH_2Cl_2; (e) $(PhO)_2P(O)Cl$, Na_2CO_3,
CH_2Cl_2/H_2O, Bu_4NBr; (f) Me_2Zn, $Ni(AcAc)_2$, Et_2O.

Not all the problems are solved. There are cases, referred to earlier, in which a methyl-bearing carbon bears a hydroxyl as well; and cases in which the normally secondary hydroxyl appears as either a ketone or a simple hydrogen. The second situation is easily handled: No special difficulties are anticipated in the oxidation of the secondary hydroxyl to a ketone, or in its removal via one of the efficient Barton deoxygenation procedures. The occurrence of a tertiary hydroxyl (at C4 on the 2-furanone template) presents a more serious problem, especially in conjunction with

the required secondary hydroxyl at C3. There are four possible arrangements of such secondary-tertiary glycols. We have devised methods for the controlled construction of three of these[8] and illustrate one of these in the construction of a sequence of the erythronolide A chain to which we now turn our attention.

The construction required that we put together the secoacid corresponding to 9(S)-dihydroerythronolide A, thus using a 9-hydroxyl protected form of the 9-keto group present in erythronolide A itself. The specific choice of the 9(S)dihydro isomer is based on the pioneering work of Woodward and his group[9]. Although they eventually chose to use an amino group as the latent carbonyl at C9, they showed that secoacids of 9(R) dihydroerythronolide are unsuitable precursors of the macrolide, presumably because they lead to conformations that are unfavorable for cyclization.

Scheme 4



2

The specific C_7-C_{13} fragment needed for the dihydroerythronolide synthesis, triol 3, was obtained from hydroxyfuranone 2, the product of two cycles involving the hydroxybutenolide route, as shown in schemes 3 and 4. The successful construction of 3 completes the demonstration of the effectiveness of our iterative scheme.

We now address the problems which had to be solved to complete the erythronolide synthesis. The first had to do with the protecting group to be used for the 9,11-diol: The solution conformation of the C_8-C_{11} portion of 9S-dihydroerythronolide A with a 9,11 cyclic protecting group is shown in figure 1. A 1,3 diaxial interaction is present between R_2 and C_8, so that, when R_2 is an alkyl group, the resulting severe interaction should make cyclization of the seco acid very unfavorable. In accord with this prediction, we found that a seco acid with a 9,11 cyclic ketal (R_1,R_2 = methyl) failed to cyclize. We were similarly unable to cyclize a related 9,11 cyclic acetal in which R_1 = H, R_2 = methyl ("A-methylacetal"). Only those cyclic acetals in which R_1 = aryl, alkyl; R_2 = H ("B-methylacetals") can be expected to cyclize efficiently.

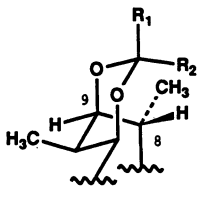
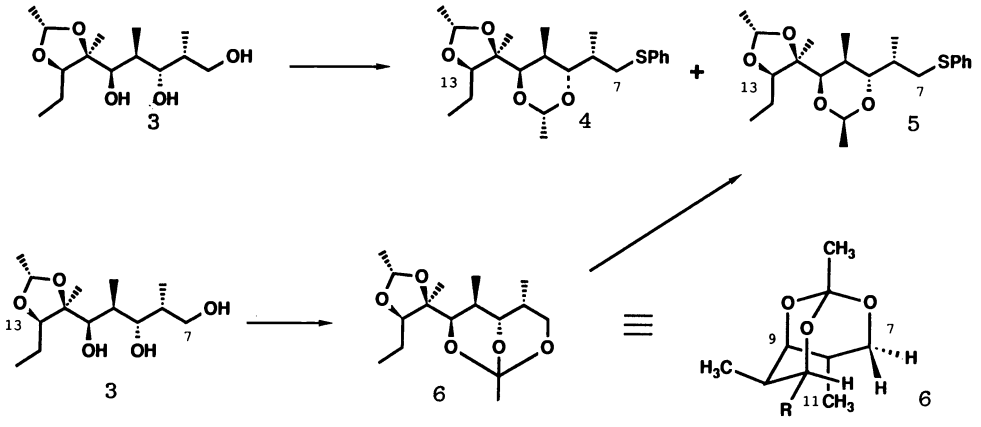


Figure 1

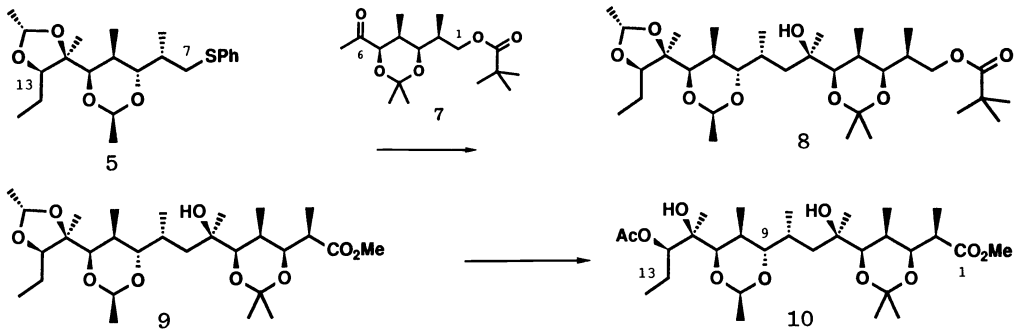
Scheme 5



With these facts in mind, the goal became the conversion of triol 3 to the B-methylacetal (cf 5). Triol 3, prepared via the butenolide template method, was first converted to the the primary alkyl phenyl sulfide which, under acid-catalyzed acetalization conditions (Scheme 5), largely gave, not unexpectedly, the more stable, but undesirable, A-methylacetal 4 (4:5 = 8:1). A stereospecific construction of the required less stable B-methylacetal 5 was, therefore, required. This was achieved via the orthoacetate 6, easily obtained from triol 3. Eliel's demonstration[10] of stereoelectronic control in the reduction of cyclic orthoacetates, suggested that treatment of the orthoacetate 6 with diborane should cleave the less hindered C_7 oxygen-carbon bond with retention of configuration at the orthoester carbon atom. This expectation was realized: Reduction of 6 with diborane now gave the B-methylacetal as a single isomer. Subsequent conversion of the primary alcohol group of the diacetal now led to the phenyl sulfide 5, identical with the minor isomer from direct acetal formation. The necessary B-methylacetal 5 was thus prepared stereospecifically, in three steps and 72% overall yield, from triol 3.

We were now ready to add the C_7-C_{13} fragment represented by the phenyl sulfide 5 to the C_1-C_6 ketone 7 (Scheme 6). We had previously effected a related coupling by adding a C_7 sulfoxide anion to a C_1-C_6 ketone[11]. The anticipated chelation control had indeed favored the desired epimer (5:1) at the newly formed C_6 center. Since there was good reason to expect that better chelation control in the desired direction would result from the reaction of an organometallic reagent rather than of a sulfoxide anion, we devised a method which should be especially useful with the usually troublesome polyoxygenated systems: The phenyl sulfide 5 was converted to the corresponding alkyllithium reagent by addition to three equivalents of LiDBB (lithium 4,4'-di-tert-butylbiphenylide) in THF at -78°C.[12]. Addition of anhydrous magnesium bromide, followed by addition of ketone 7, now gave the required coupled product 8, apparently as a single isomer, in 73% yield.

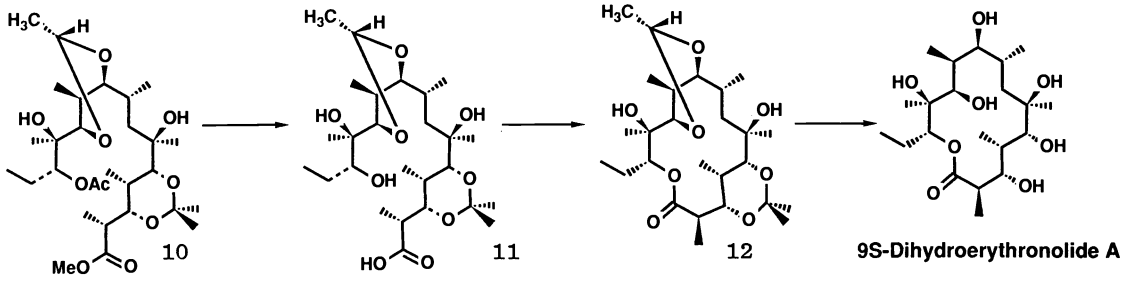
Scheme 6



The coupled product 8 was now elaborated to the seco acid 11. Deprotection of the primary alcohol, PDC oxidation and in situ methylation gave methyl ester 9 in 82% yield. Selective deprotection of the 5-membered acetal was now required to set the stage for the final cyclization. This was accomplished by selective ozonolysis[13] of the methyl ester 9 with ozone which gave the monoacetate 10 in 75% yield. Subsequent hydrolysis gave the seco acid 11 in quantitative yield.

The simple protection and deprotection sequence described here greatly simplified the selective protection problems which had to be solved in the construction of 11 . Cyclization of seco acid 11 was achieved using the conditions recently reported by Keck[14] (Scheme 7). Seco acid 11 was added to a refluxing chloroform solution of dicyclohexylcarbodiimide, 4-dimethylaminopyridine, and its trifluoroacetate salt, via a syringe pump, to give macrocyclic lactone 12 which was isolated in 64% yield. It was shown to be identical with an authentic sample[15] prepared from natural erythromycin A by ^{1}H NMR, IR, MS, TLC in two different solvent systems and optical rotation $(\alpha)_{365}$ + 54° (c = 0.2, methanol). Treatment of macrocyclic lactone 12 with acidic methanol removed the protecting groups to give 9S-dihydroerythronolide A, identical with an authentic sample[15] by ^{1}H NMR, IR, and TLC.

Scheme 7



The synthesis we have just decribed leads in 26 steps and 1.3% overall yield[16] from optically pure 4(R)-hydroxy-2-hexynoate to 9S-dihydroerythronolide A. Since the latter has previously[9] been converted to erythromycin A, this work also constitutes a formal total synthesis of the antibiotic.

Acknowledgement

We with to thank the National Science Foundation and the National Institutes of Health for support of this work.

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