A general method for the stereocontrolled synthesis of polypropionate-derived sequences

Gilbert Stork* and Scott D. Rychnovsky

Department of Chemistry, Columbia University, New York, NY 10027

Abstract — We describe a general solution to the problem of synthesizing carbon chains bearing methyls and hydroxyls on alternating carbon atoms. These polypropionate-derived chains, which are common among macrolide antibiotics, are synthesized by repeated use of \(\gamma\)-lactone templates. The scheme is illustrated specifically by the controlled construction of a section of erythronolide A.

There occur, in a large number of natural products, sequences of carbon atoms alternately bearing methyl and hydroxyl groups. These sequences, usually biosynthesized by the condensation of propionate units, are a common occurrence in the macrolide antibiotics. Erythronolide A (1) is a characteristic example. One of the formally simplest possibilities for the elaboration of these polypropionate-derived sequences involves the aldol type of condensation between a growing aldehyde chain and some operational equivalent of a propionaldehyde unit. It is, therefore, not surprising that much effort has been expended over the last several years in the development of methods which would result in better and better control of the stereochemistry of the aldol condensation.

There can be no doubt that organic chemistry has greatly benefited from this massive effort. It is not just synthetic methodology which has been advanced: The role of chelation to a metal center and the conformation of these chelated arrays are now better understood to be major determinants of the stereochemical result of an aldol type of condensation. More and more ingenious ways of controlling transition state conformations, so as to produce one or another diastereoisomer, have further resulted from the rational design of propionaldehyde enolate equivalents, ranging from anions of propionic acid derivatives to those of butene.\(^1\)
Interesting as all this work has been, there is still no general method predictably applicable to the construction of any given alternating sequence of methyls and hydroxyls, especially when the sequences include tertiary\(^2\) as well as secondary alcohols. It is for that reason that we have been engaged for some time in the design of a conceptually different general method for the construction of such chains in any desired stereochemical arrangement.

Consider the problem of adding two carbons, one bearing a methyl the other a hydroxyl, to a carbon chain. There are four possible arrangements from the addition of these two new chiral centers. We, therefore, need a process that will produce specifically any of these four. Note that the problem will be solved for any chain length if the process can be made repetitive. We reached the conclusion some time ago that incorporation of the two carbon atoms in question into a rigid system showing good face selectivity should provide a solution to the problem. We now illustrate our progress with this concept, using the γ-lactone system as the template by means of which any of the four possible arrangements of a secondary methyl and a secondary hydroxyl can be produced. This is shown in schemes 1 and 2.

\[\text{Scheme 1}\]

\[\text{Scheme 2}\]

As we show in scheme 1, we start from an ethynyl carbinol, a starting point which has the advantage of being easily available in chiral form by reduction of the corresponding ethynyl ketone.

A few comments on individual steps follow. The use of tris-thiophenyl methane rather than methyl for conjugate addition to \(\text{Br}^2\) is to ensure high stereoselectivity in the hydroxylation step \(4 \to 5\). We concluded early in the design of our method that it was unnecessary to provide specific introduction of both hydroxyl epimers in a given lactone series. Controlled introduction of just one of these is enough, provided a) that the hydroxyl introduction is essentially stereospecific; b) that inversion
Stereocontrolled synthesis of polypropionate-derived sequences

of that hydroxyl can be carried out efficiently to produce specifically the other hydroxyl epimer. As far as requirement a is concerned, we have already shown (4 + 6) that it can be met via the tris-thiophenylmethane adduct. With respect to the second requirement, we anticipated that the bimolecular displacement of a departing group would be unusually favorable alpha to a lactone carbonyl. In fact, the Mitsunobu reaction leads to stereospecific inversion in good yield, starting with either hydroxyl epimer, thus making possible the construction of either 6 or 7.

As we outline in scheme 2, hydroxylation presents no stereochemical problem in the lactone series in which the methyl and the side chain R are cis to each other (at positions 4 and 5 of what are properly called 3,4-dihydro-2(5H)-furanones). In fact, 11, as expected, hydroxylates cleanly from only one direction to give 12. The other hydroxyl epimer, 13, can again be made by inversion. On the other hand, the seemingly trivial formation of the cis relationship of C5-R and C4-methyl proved more difficult. The problem was solved when we found that the exocyclic methylene lactone 10 could be reduced with good selectivity to the cis disubstituted lactone 11, using the Wilkinson rhodium catalyst. In contrast, the reduction of the more conventionally available conjugated isomer of 10 gave the desired cis product with only modest (6-9 to 1) selectivity at best, under a variety of conditions. It is particularly satisfying that the methylene lactone 10 is readily made, via the same ethynyl carbinol used for the trans series of scheme 1, by the use of the radical cyclization of unsaturated bromoacetalts.

The Fischer projections at the bottom of schemes 1 and 2 emphasize the fact that the four possible arrangements of the two newly added centers shown in the boxed area can now readily be made starting from an ethynyl carbinol of a given absolute configuration. The enantiomeric ethynyl carbinol would obviously lead to the other four possible enantiomers, the mirror images of the Fischer projections shown at the bottom of Schemes 1 and 2.

It now only remained to make the scheme repetitive. This simply requires going from the γ-lactone which has just been elaborated, as shown in the above schemes, to the next lactone template on which to introduce the next two centers. And so on.

Scheme 3

One obvious way to accomplish this entails transforming the lactone which has just served its purpose, so as to produce again the ethynyl carbinol function. This is outlined in scheme 3 (note that the carbonyl carbon of the lactone has to become the first carbon of the required acetylene, as emphasized by the star). Since ethynyl carbinols are
precisely the starting materials for the application of schemes 1 and 2, the problem would be solved. This, indeed, was our first approach. We have temporarily set it aside because we have not been able to effect the conversion of our γ-lactone to the required ethynyl carbinols in acceptable yields.

We have, however, solved the repetitive γ-lactone problem by direct transformation of the last correctly elaborated γ-lactone to the next γ-lactone template. It is again convenient to divide in two sets the four possible arrangements of a 3-hydroxyl and a 4-methyl relative to a particular C-5 epimer (The numbering is based on the 2-furanone system). The first set we consider includes the two hydroxyl epimers at C3 in which the C-4 methyl and the C-5 chain have a trans relationship.

The stereocontrolled construction of that first set is shown in Scheme 4, starting arbitrarily with the hydroxylactone 7.

Reaction of 7 with the lithium anion of ethyl acetate, followed by dehydration of the hemiketal intermediate and hydrogenation of the resulting bicyclic lactone 14 gives 15, the masked equivalent of the intermediate conjugated lactone 3 of scheme 1. A similar sequence to that of scheme 1 is, therefore, all that is necessary to complete the construction of either 17 or 18.

Scheme 5 illustrates the transformation of the other set, in which the required stereochemistry at C4 and C5 correlates with a cis arrangement of the two substituents on the dihydrofuranone ring. The construction again starts with the addition of the anion of an acetic acid derivative, this time bearing an α-benzyloxy group (7'19). Conjugate addition-elimination in the transformation of 20 to 21 was satisfactory with dimethylzinc-nickel acetylacetonate5, but not with cuprates. Catalytic hydrogenation of 21 to 22 on Rhodium/Alumina hydrogenolyzed the benzyl ether and reduced the system to the expected6 all-cis lactone 22. Inversion of the hydroxyl may again be performed, if necessary (23'24).
It is clear that the \( \gamma \)-lactone template approach can produce any desired sequence of secondary hydroxyls and secondary methyls.

Some special cases require further comments. The secondary hydroxyl-bearing carbon is occasionally present in a more oxidized form (carbonyl) or in a more reduced form (methylene). Neither situation presents a real problem because a given secondary hydroxyl can easily be oxidized or removed after it has served its function as a lactone element. Another fairly common situation is not as easily handled. Instead of bearing a hydrogen, a methylated carbon may be present in a more oxidized form, as a tertiary alcohol. Control of such a center within the \( \gamma \)-lactone context requires additional solutions. We illustrate one of these in scheme 6 which shows the application of the repetitive lactone method to a specific case, the construction of a section of an erythronolide A precursor.

Since the construction is a direct application of what we have already discussed, only a few comments are necessary. The lactone 29 was prepared as we have previously described\(^7\), taking advantage of the very high selectivity of the osmylation reaction of \( \gamma \)-alkoxy-(E)\( \alpha,\beta \)-unsaturated esters like 27. The dihydroxylactone 29 was made from the hydroxy ester 26, itself made by chiral reduction of the acetylenic ketone. Simple recrystallization then gave the optically pure dihydroxylactone.

The sequence of steps outlined in schemes 6 and 7 finally leads to 38, also shown in Fischer projection. This sequence of six asymmetric centers, including a tertiary hydroxyl center, has thus been constructed in a completely predictable manner by the proper choice of lactone construction sequence. The process is not inefficient: The overall yield
from 29 to the completed next γ-lactone 34 is 62%. The next cycle, which leads to crystalline 37, has been carried out in 40% yield from 34.8

Some problems remain. We believe, however, that we have evolved a stereorational scheme of considerable value. It is not unlikely that it may prove applicable in a more general context than the repeated aldol sequences we have discussed here.

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

REFERENCES


