

Synthetic studies in the mevinoid field. The total synthesis of ML236A

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Abstract - The sequence of a lactonic Claisen rearrangement and a Lewis acid catalyzed cyclocondensation of an aldehyde with an appropriate diene affords a new route to the title series.

BACKGROUND AND PURPOSE OF THE INVESTIGATION

The discovery of the mevinoids, the recognition of their ability to sharply lower the levels of serum cholesterol and the identification of their mode of action via their inhibition of the enzyme HMG CoA reductase, have been important in cardiovascular medicine (ref. 1, 2). Since the formation of mevalonate from 3-hydroxy-3-methylglutarate is apparently the limiting step in the mammalian biosynthesis of cholesterol (ref. 3), the inhibition of this enzyme is a particularly inviting target for medical intervention.

The studies described herein were formulated not only to reach these compounds, but were seen to have broad applications toward other important targets. After favorable demonstrations in model systems, it was then appropriate to demonstrate the scope of our findings via a total synthesis of the mevinoids (ref. 4).

The second inducement was the opportunity to learn more about the structural specificity for HMG CoA inhibition. Indeed, a great deal of effort has already gone into the study of the impact of molecular modifications of compounds derived from the natural products on biochemical performance (ref. 5). Many compounds which are much simpler than the mevinoids from the standpoint of structural complexity have been evaluated. Our intention was to provide access to targets bearing a close relationship to the naturally occurring inhibitors. *The targets we had in mind could best be made by total synthesis.* The assessment of the impact of these subtle structural changes would provide calibration for the validity of conformational modeling of the natural products and its relevance to HMG CoA inhibition. We have achieved our first goal, i.e., the total synthesis of ML-236A by new chemistry which is described below.

SYNTHETIC PLANNING

The problem was subdivided into its two obvious components - the "hexalin" and "pyranone" issues. The strategies we devised for these two sectors are implicit in Fig. 1. For entry to the hexalin subunit we contemplated a Claisen-like rearrangement of an enolate equivalent, derived from a 6-vinylvalerolactone (see 1 → 2). To reach the pyranone moiety, we proposed a cycloaddition reaction of an aldehyde (3) with a suitable diene (4). The formal cycloadduct 5 might be amenable to transformation to the required substructure, 6.

The prospectus, shown in Fig. 1, deliberately leaves open many crucial particulars. For instance, in structure 1 we have not specified the nature of the substitution at C₅ of the lactone enolate. We defer explanation of the stereochemical assertion implicit in the transformation of 1 → 2. Similarly, we have not dealt with issues of stereochemistry in the pyranone subunit. Also unaddressed here is a protocol for advancement from 5 to 6.

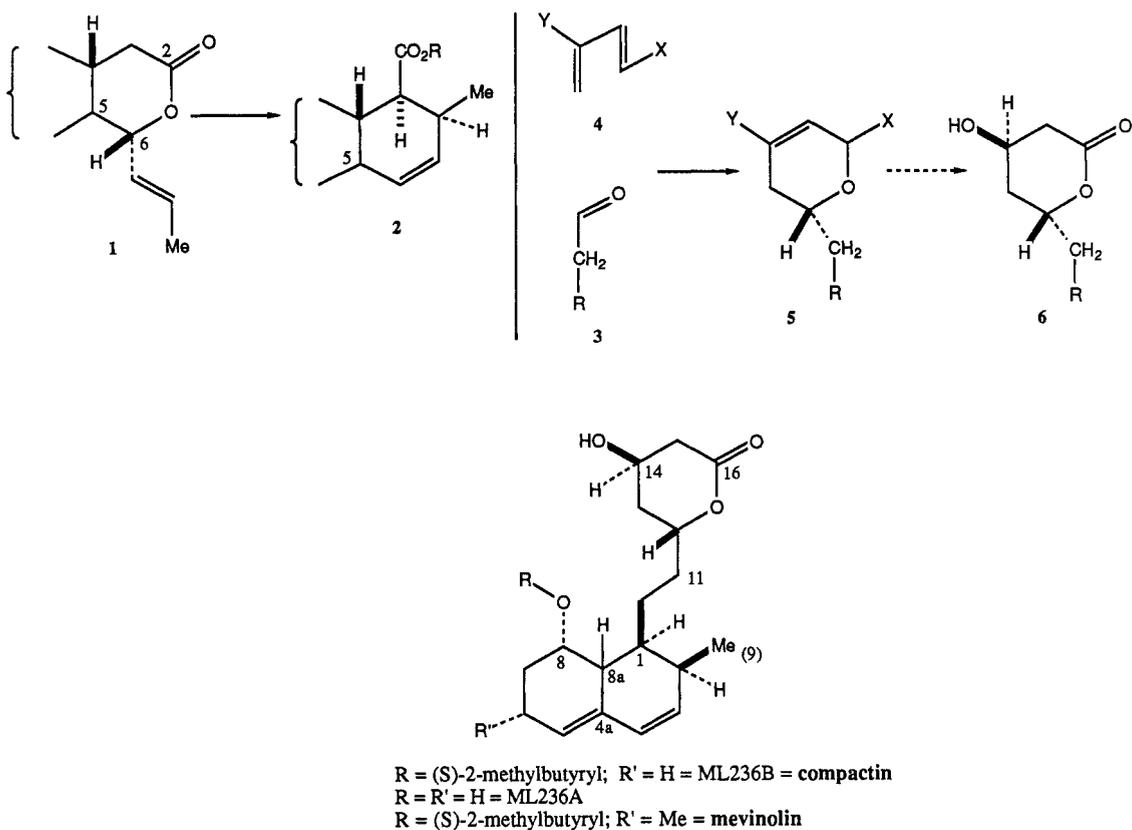


Fig. 1

Two overall possibilities for harmonizing the construction of the subunits were considered. In the "chirality matching" approach, a moiety derived from 2 would be joined to an entity derived from 5 or 6, thus fashioning the "ethano spacer", connecting the two sectors. In an alternative "chirality communication" approach, the R group in 3 would already include the terpene-like residue derived from 2. *This is a more ambitious proposal in that it implies that the resident chirality of the terpenoid aldehyde will determine (in the desired sense) the facial selectivity of the cycloaddition.* These two possibilities are implied in Fig. 2.

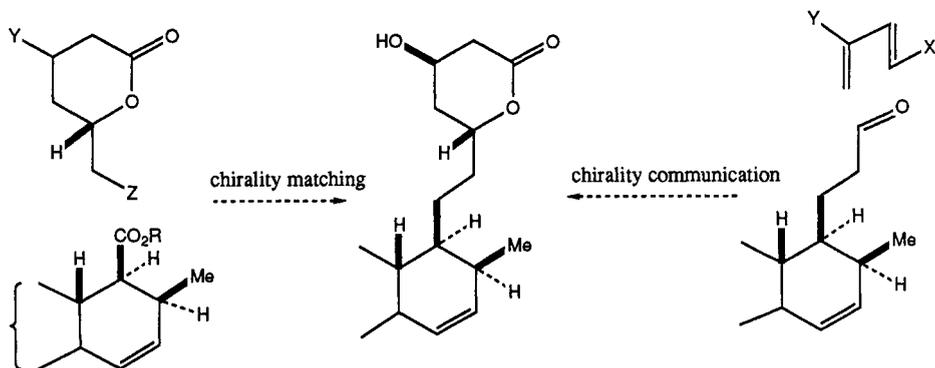


Fig. 2

EARLY FINDINGS

James Kerwin found that with a wide variety of aldehydes and dienes, in the presence of various Lewis acid catalysts, transformations such as $3 + 4 \rightarrow 5$ do indeed occur (ref. 6). At this writing, some six years after our initial disclosures on the process, there seems little need to dwell upon the scope of the reaction which Kerwin developed (ref. 7), its stereochemical patterns (ref. 8), achievements of absolute asymmetric induction (ref. 9), or the applications to a variety of total syntheses (ref. 10). On the matter of the reaction courses (ref. 11), suffice it to say that given the plurality of pathways, we prefer the term "cyclocondensation" (ref. 12), which focuses on gross structural changes rather than "cycloaddition", which is suggestive of a mechanistic commitment.

Even as ideas are offered in the broadest of terms, it is well to recall that one of our early reports in the cyclocondensation field anticipated an application to introduce the required stereochemical pattern (ref. 13). Boron trifluoride etherate catalyzed reaction of benzyloxyacetaldehyde with diene **6** afforded **8**, presumably via **7**. Addition of isopropanol to **8** gave the axial glycoside **9**. Reduction of the ketone with L-Selectride gave quite cleanly the axial alcohol **10**. It was assumed that **10** could be converted to the desired lactone prototype **11** at a suitable stage of the synthesis.

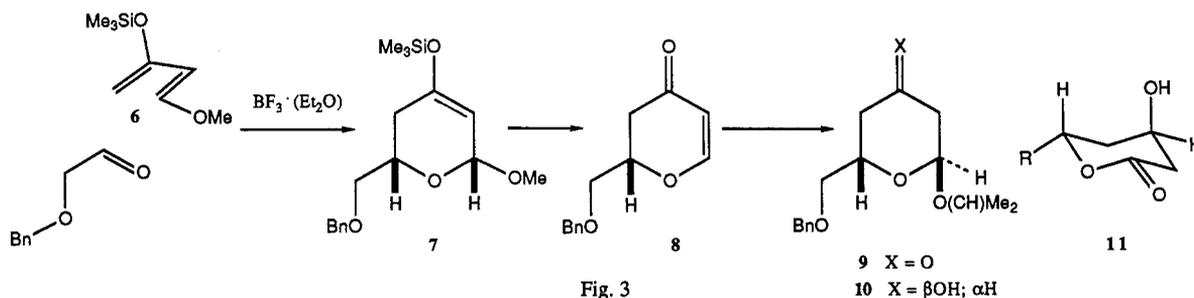


Fig. 3

Even earlier than our observations concerning the cyclocondensation reaction, was our demonstration that the lactone (silyl) enolate Claisen rearrangement was indeed viable and that its stereochemical outcome was amenable to a high degree of definition (ref. 14, 15). The transformation of **12** to **13** demonstrates the consequences of the rigid boat-like transition state imposed by the constraints of the cyclic array. Not the least compelling is the requirement that the final endocyclic double bond be *Z*. The lactonic enolate rearrangement process thus produces a different outcome, with higher specificity than is obtained from the Ireland ester (silyl) enolate rearrangement from which it drew analogy (ref. 16, 17).

The transformation of **14** to **15**, used in a stereospecific total synthesis of widdrol, demonstrates another advantage of conducting the reaction in the cyclic series. The high fidelity of the chirality transmission in the rearrangement can be used to define the relative stereochemistry of the emerging carboxyl group with resident stereogenicity. Thus, the cyclic process has the equivalent of perfect facial selectivity (see Fig. 4).

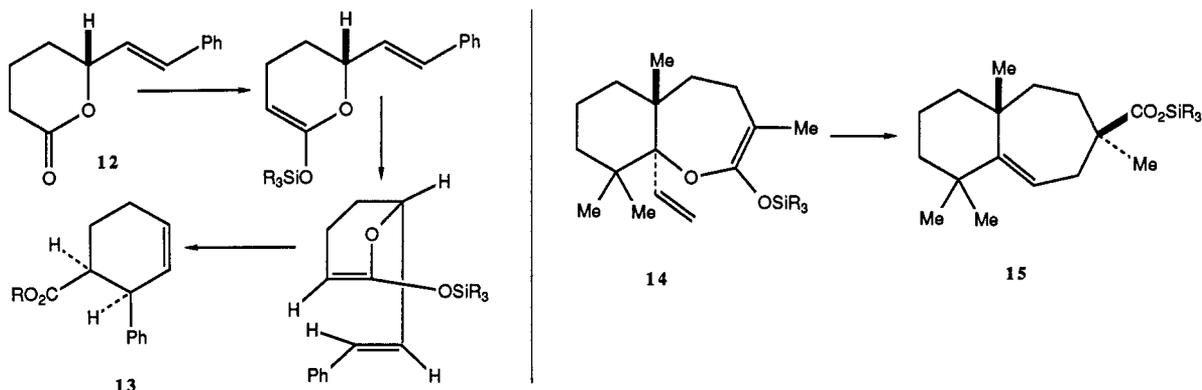


Fig. 4

Given these findings, our initial plan for synthesizing the hexalin portion of compactin envisioned recourse to a vinylic lactone such as **16**. Rearrangement of this compound via a silylketeneacetal would be expected to produce **17**. Unfortunately, we encountered very serious difficulties in our attempts to obtain the required **16**. Thus, reaction of *E*-propenyllithium with enal **18** afforded the epimeric lactone **19** in a highly selective fashion. A variety of attempts to convert **19** to the desired **16** in synthetically useful amounts were unsuccessful. A serious problem in this regard was the rather limited stability of both **16** and **19** (as well as their open hydroxy ester forms) and the difficulties in separating mixtures of these closely related epimers (ref. 18).

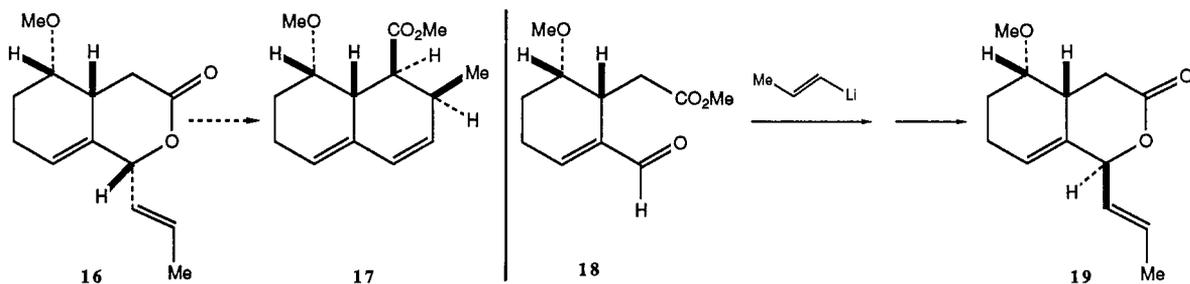


Fig. 5

DISCUSSION OF RESULTS

A recent disclosure by Mukaiyama (ref. 19) provided a lead which encouraged us to take up the hexalin problem anew, though in a context which differed from the scenario indicated in Fig. 5. As we have reported (ref. 20), reaction of cyclohexenone with the OTBS silylketeneacetal derived from methyl propionate afforded **20**. Reaction of **20** with crotonaldehyde (**21**) followed by lactonization gave rise to **22**. The enoxysilane silylketeneacetal **23**, underwent smooth Claisen rearrangement to produce an 80% yield of **24**, with the silyl enol ether in tact. For the moment we have not exploited the enoxysilane functionality. Hydrolysis and esterification of **24** afforded **25** (see Fig. 6).

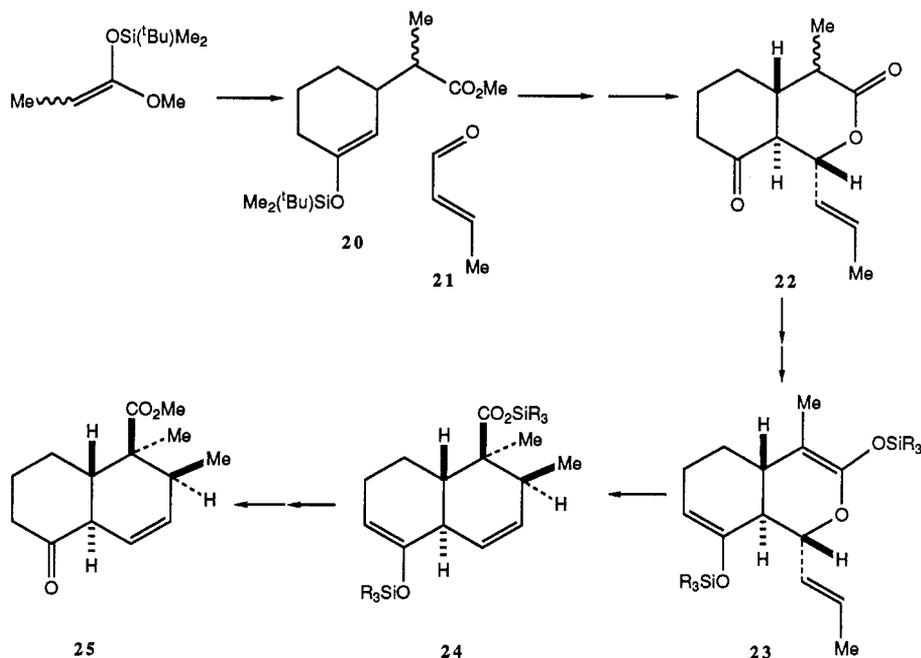


Fig. 6

A similar sequence, employing a 4- functionalized derivative of cyclohexenone could accommodate the oxygen function required for compactin-mevinolin. Of course, the inclusion of such an additional group raised an obvious new stereochemical issue, i.e., the face selectivity of the initial Mukaiyama reaction (ref. 19).

At approximately this time, our laboratory developed a route leading from quinic acid to the *S* enantiomer of 4-TBSO cyclohexenone **26S** (ref. 21, 22). In principle we were prepared to accept the formation of either *trans* **27t** or *cis* **27c** adducts in the "group-transfer" reaction. If, as might be expected from superficial analysis, the former had pertained, it would have been necessary to devise a route to (**26R**) enantiomer and to invert the stereochemistry at the 8 carbon (compactin numbering, ref. 23) at some stage of the synthesis.

In studying the course of nucleophilic additions to **26** rac, an interesting observation was made. Whereas methylation via lithium dimethyl cuprate occurs *trans* to the silyloxy group, several Lewis acid catalyzed processes produce 3,4-*cis* product with high selectivity (ref. 24). We are currently in the process of sorting out the structural and mechanistic features responsible for this very high syn selectivity. For the present we note that this result is extremely convenient for a synthesis of the mevinoids in that it allows us to use the readily available **26S** enantiomer without the need for inversion of C₈.

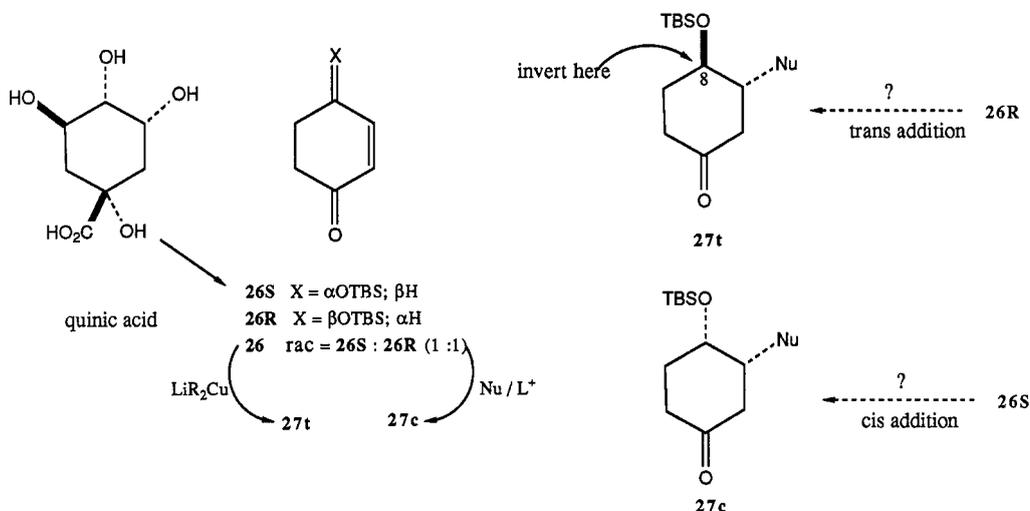


Fig. 7

We preferred, in the first instance, to explore the possibility of "chirality-communication" in the cycloaddition reaction leading to the dihydropyrone (see Fig. 2). Therefore, there was no need for us to work with enantiomerically pure aldehyde type **3**. The issues of facial selectivity and relative stereochemistry could be explored equally well in the racemic series. Accordingly, we could start with racemic **26** for our initial studies. In this spirit we defined as our first goal in this series ML236A, in which the awkwardness of a stereogenic center on the acyl side chain is absent.

Reaction of **26** rac with **28** in the presence of mercuric iodide (ether -78° C) afforded a 90% yield of **29**. The C₃-C₄ *trans* epimer (cyclohexanone numbering), not shown here, could be detected in ca. 4% yield. Boron trifluoride etherate catalyzed reaction of **29** with crotonaldehyde (**21**) at -78° C occurred with a second silyl transfer in a highly stereoselective fashion. The resultant product, when treated with trifluoroacetic acid, afforded the lactone **30**, though only at present in 40% yield. Given the value of this intermediate, the conciseness of its synthesis (three steps from **26**), and its usefulness (vide infra), this yield could be characterized as disappointing rather than fatal to the program.

The stage was set for lactonic Claisen rearrangement. Enol silylation of both the ketonic and ester functions afforded **31** which underwent smooth bond reorganization in toluene at 105° C. Hydrolysis of the carboxy and enol silyloxy functions could be achieved while leaving the secondary silyloxy function in tact. Esterification (diazomethane) afforded the ketoester **32** in an overall yield of 78%. It was a straightforward matter to convert the β,γ -unsaturated ketone to the bicyclic diene using literature precedents (ref. 25, 26). Reduction of **32** with L-Selectride gave axial alcohol **33**. The latter, upon activation with methanesulfonyl chloride gave mesylate **34**.

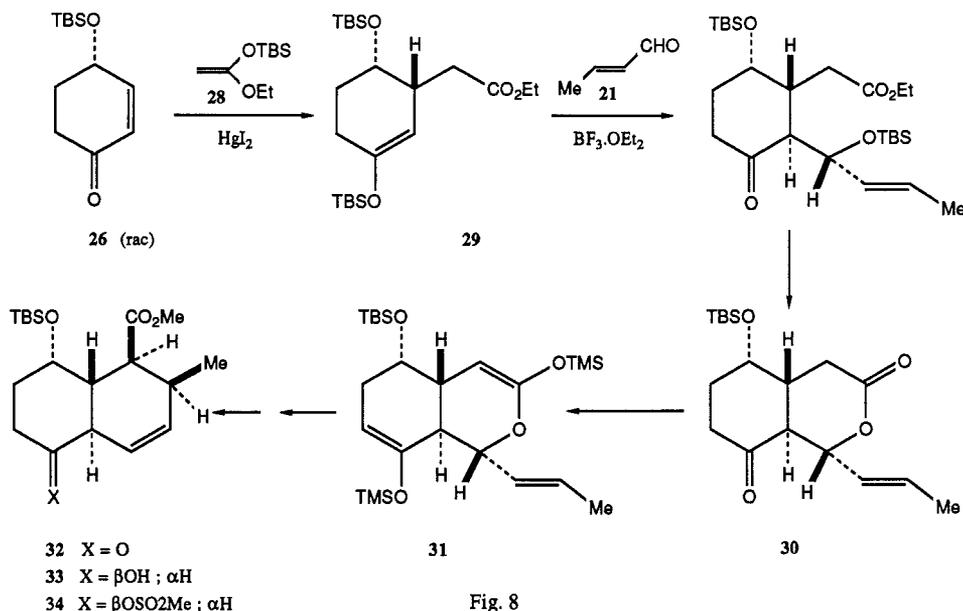


Fig. 8

Trans diaxial elimination of the homoallylic mesylate **34** (DBU pyridine; 105° C) gave rise to **35** (80%). The ester was reduced (diisobutylaluminum hydride) to alcohol **36**. Swern oxidation gave aldehyde **37**. Two-carbon extension was achieved by an Emmons reaction (ref. 27). Conjugate reduction of the resultant **38**, was best accomplished with magnesium in methanol. Reduction of the ester (diisobutylaluminum hydride) afforded alcohol **40** (70% overall from **37**).

Based on precedents from the work of Uskokovic and Wovkulich (ref. 28), it appeared that an acetoxy group at C₈ would be more effective than a silyloxy function for promoting face selectivity in the cyclocondensation reaction. It was thus necessary to go through several steps to achieve the transformation of OTBS to OAc.

De-silylation of **40** with HF in acetonitrile and selective silylation of diol **41** at the primary hydroxyl group gave **42**. Acetylation of the secondary alcohol afforded **43**. De-silylation followed by Swern oxidation gave the required aldehyde **44** (ca. 60% from **40**). We could now test the feasibility of diastereoselection in the cyclocondensation reaction.

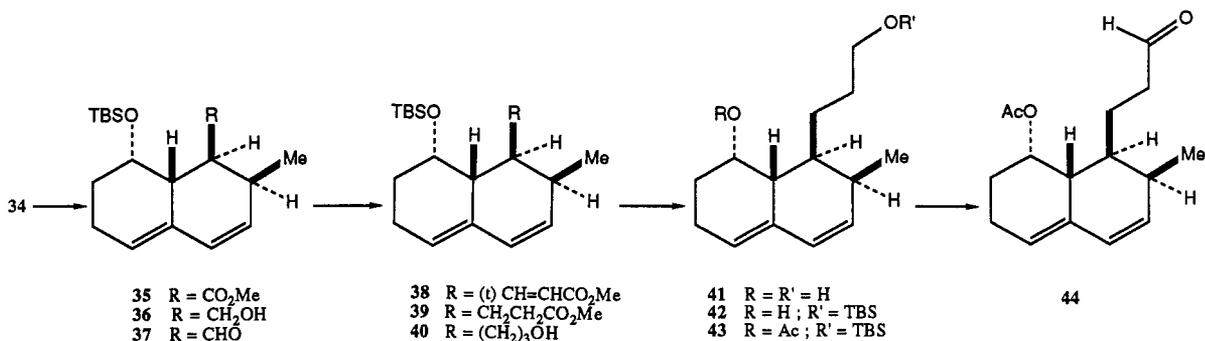


Fig. 9

As alluded to above, we were much guided, in defining the character of our oxygen substituent at C₈ and the experimental conditions, by experiments which were conducted by Wovkulich and Uskokovic (ref. 28) on a different but related substrate. In our case we have resorted to diene **45**, using titanium tetrachloride in methylene chloride. The resultant product consisted of a mixture of dihydropyrone (**46** and **47**) (ref. 29a), as well as aldol-like structures (**48** and **49**) (ref. 29b). The total material was submitted to cyclization with trifluoroacetic acid. Overall there was obtained a 70% yield of **46** and **47** in a 4:1 ratio.

At the time, we could not rigorously assign stereochemistry at C₁₂ to these compounds. That the major one in fact has the desired R configuration was demonstrated by carrying it through to racemic ML-236A. The previously described protocol (ref. 13) was followed. Ethanolysis of **46** afforded the axial glycoside **50**. This set the stage for L-Selectride reduction giving the C₁₄ axial alcohol **51**. Hydrolysis of the ethyl glycoside followed by oxidation with silver carbonate-celite gave the rac ML-236A acetate **52** (41% overall from the dihydropyrone **46**). De-acetylation with lithium hydroxide occurred uneventfully to complete the total synthesis of racemic ML-236A (**53**). In a similar sequence **47** was converted to **54**, wherein the stereochemical relationship of the two chiral sectors is opposite to that of **53**. Indeed, the NMR spectroscopic properties of **54** differ in nuance from those of an authentic sample, while those of fully synthetic **53** are identical.

With the completion of this total synthesis, several goals become accessible. First, we are already using the **26S** enantiomer to reach the targets in their appropriate chiral forms. Also, in the enantiomerically homogeneous series, our program to prepare novel analogs by total synthesis is well under way. Finally, we note that applications of this new chemistry to important targets ranging from prostanoids to the fusarium toxin are already bearing fruit.

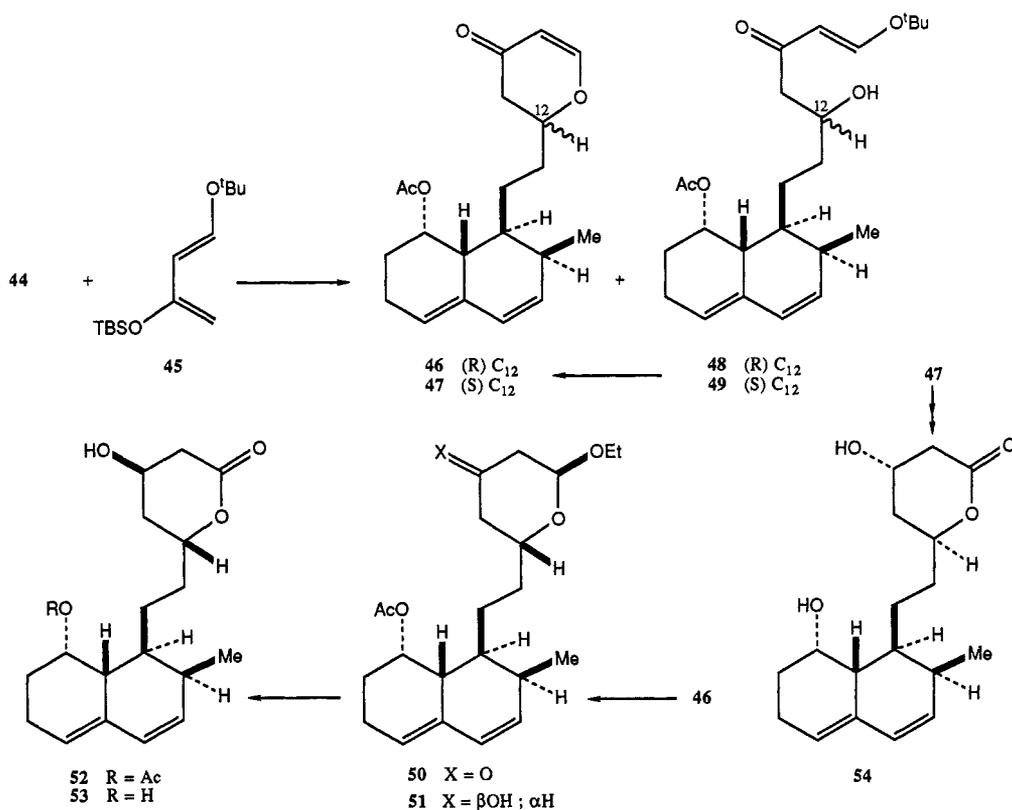


Fig. 10

Acknowledgements

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29. (a) ratio of dihydropyrones **46** and **47**, 3:1. (b) ratio of aldols **48** and **49**, 5:1