13

Multistep Syntheses

Introduction

The reactions discussed in the preceding chapters provide tools for synthesizing new and complex molecules, but a strategy for using these reactions is essential for successful multistep syntheses. The sequence of individual reactions must be planned so that the reactions are mutually compatible with the final synthetic goal. Certain functional groups can interfere with prospective reactions and such problems must be avoided either by a modification of the sequence or by temporarily masking (protecting) the interfering group. *Protective groups* are used to temporarily modify functionality, which is then restored when the protecting group is removed. Another approach is to use a *synthetic equivalent group* in which a particular functionality is introduced as an alternative structure that can subsequently be converted to the desired group.

Protective groups and synthetic equivalent groups are tactical tools of multistep syntheses. They are the means, along with the individual synthetic methods, to reach the goal of a completed synthesis, and these tactical steps must be incorporated into an overall synthetic plan. A synthetic plan is normally created on the basis of a *retrosynthetic analysis*, which involves identification of the particular bonds that can be formed to obtain the desired molecule. Depending on the complexity of the synthetic target, the retrosynthetic analysis may be obvious or intricate. A synthetic plan identifies potential starting materials and reactions that can lead to the desired molecule, and most such plans involve a combination of *linear sequences* and *convergent steps*. Linear sequences construct the target molecule step-by-step by incremental additions and functional group transformations. Convergent steps bring together larger segments of the molecule that have been created by linear sequences. As the overall synthetic yield is the multiplication product of the yield of each of the individual steps in the synthesis, incorporation of a convergent step improves overall yield by reducing the length of the linear sequences. After discussing some general aspects of synthetic analysis and planning, we summarize several syntheses that illustrate application of multistep synthetic methods to representative molecules. In the final sections of the chapter, we consider solid phase synthesis and its application to polypeptide, polynucleotide, and combinatorial syntheses.

13.1. Synthetic Analysis and Planning

13.1.1. Retrosynthetic Analysis

The tools available to the synthetic chemist consist of an extensive catalog of reactions and the associated information on such issues as stereoselectivity and mutual reactivity. This knowledge permits a judgment on the applicability of a particular reaction in a synthetic sequence. Broad mechanistic insight is also crucial to synthetic analysis. The relative position of functional groups in a potential reactant may lead to specific interactions or reactions. The ability to recognize such complications enables appropriate adjustments to the synthetic plan. Mechanistic concepts can guide optimization of reaction conditions. They are as well the basis for developing new reactions that may be necessary in a particular situation.

The planning of a synthesis involves a critical comparative evaluation of alternative reaction sequences that could reasonably be expected to lead to the desired structure from appropriate starting materials. In general, the complexity of a synthetic plan increases with the size of the molecule and with increasing numbers of functional groups and stereogenic centers. The goal of synthetic analysis is to recognize possible pathways to the target compound and to develop a suitable sequence of synthetic steps. In general, a large number of syntheses of any given compound are possible. The objective of synthetic analysis and planning is to develop a reaction sequence that will complete the desired synthesis efficiently within the constraints that apply.

The restrictions that apply depend on the purposes for which the synthesis is being done. A synthesis of a material to be prepared in substantial quantity may impose a limitation on the cost of the starting materials. Syntheses for commercial production must meet such criteria as economic feasibility, acceptability of by-products, and safety. Syntheses of structures having several stereogenic centers must deal with the problem of stereoselectivity. If an enantiomerically pure material is to be synthesized, the means of controlling absolute configuration must be considered. The development of a satisfactory plan is the chemist's intellectual challenge and it puts a premium on creativity and ingenuity. There is no single correct solution. Although there is no established routine by which a synthetic plan can be formulated, general principles that can guide synthetic analysis and planning have been described.[1]

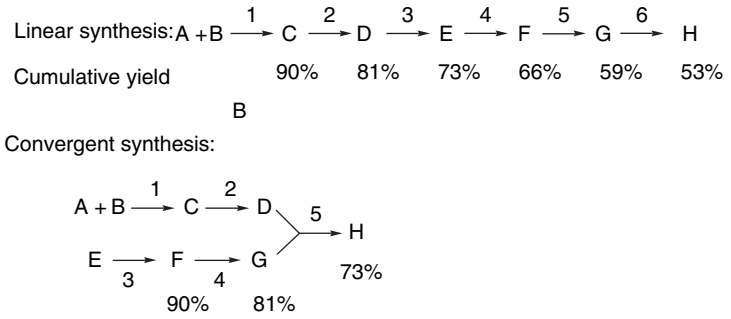
The initial step in creating a synthetic plan involves a *retrosynthetic analysis*. The structure of the molecule is dissected step by step along reasonable pathways to successively simpler compounds until molecules that are acceptable as starting materials are identified. Several factors enter into this process, and all are closely interrelated. The recognition of *bond disconnections* allows the molecule to be broken down into *key intermediates*. Such disconnections must be made in such a way that it is feasible to form the bonds by some synthetic process. The relative placement of potential functionality strongly influences which bond disconnections are preferred. To emphasize that these disconnections must correspond to transformations that can be conducted in the synthetic sense, they are sometimes called *antisynthetic transforms*, i.e., the reverse of synthetic steps. An open arrow symbol, $\Rightarrow$, is used to indicate an antisynthetic transform.

Retrosynthetic analysis can identify component segments of a target molecule that can serve as key intermediates, and the subunits that are assembled to construct

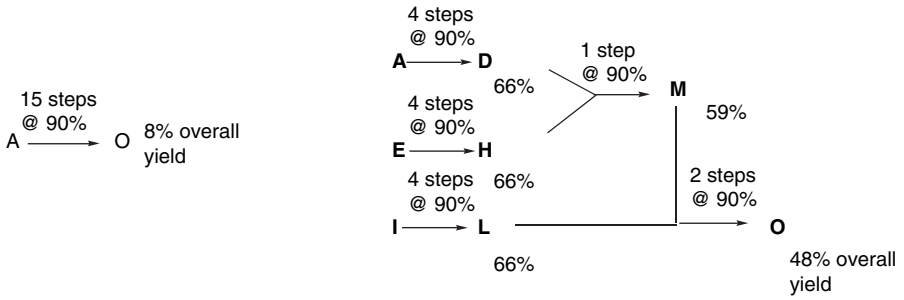
[1] E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989.

them are sometimes called *synthons*. Synthons must not only correspond structurally to the desired subunit, but they must also have appropriate reactivity to allow bond formation with adjacent subunits. For example, in the case of aldol reactions, one reagent must serve as the electrophile and the other as the nucleophile. In a ring construction by a Diels-Alder reaction, the diene and dienophile must have compatible reactivity. Similarly, in bond constructions done using organometallic intermediates, the synthons must possess appropriate mutual reactivity.

The overall synthetic plan consists of a sequence of reactions designed to construct the total molecular framework from the key intermediates. The plan should take into account the advantages of a *convergent synthesis*. The purpose of making a synthesis more convergent is to shorten its overall length. In general, it is desirable to construct the molecule from a few key segments that can be combined late in the synthesis rather than build the molecule step-by-step from a single starting material. The overall yield is the multiplication product of the yields for all the individual steps. Overall yields decrease with the increasing number of steps to which the original starting material is subjected.[2] One of the characteristics of a multistep sequence is the *longest linear sequence*, which is the maximum number of steps from an original starting material to the final product. For example, in the case below, a single convergency that reduces the longest linear sequence from six to three improves the overall yield from 53 to 73% if the yield was 90% in each transformation.



Splitting a 15-step synthesis into three branches of four steps each will improve the yield from 8 to 48% if each step occurs in 90% yield.



After a plan for assembly of the key intermediates into the molecular framework has been developed, the details of incorporation and transformation of functional

[2] A formal analysis of the concept of convergency has been presented by J. B. Hendrickson, *J. Am. Chem. Soc.*, **99**, 5439 (1977).

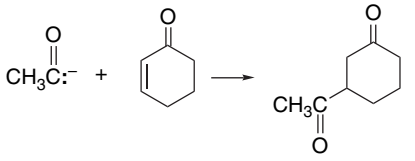
groups are considered. It is frequently necessary to interconvert functional groups, which may be to done to develop a particular kind of reactivity at a center or to avoid interference with a reaction step. Protective groups and synthetic equivalent groups are important for planning of functional group transformations. Owing to the large number of procedures for interconverting the common functional groups, achieving the final array of functionality is often less difficult than establishing the overall molecular skeleton and stereochemistry.

The synthetic plan must also provide for control of stereochemistry. In the case of cyclic compounds, advantage often can be taken of the facial preferences of the rings and the stereoselectivity of reagents to establish the stereochemistry of substituents. For example, the *syn*-directive effect of hydroxy groups in epoxidation (see p. 1093) or the strong preference for *anti* addition in iodolactonization (see p. 311) can be used to determine the configuration of new stereogenic centers. Similarly, the cyclic TS of sigmatropic rearrangements often allows predictable stereoselectivity. Chiral auxiliaries and catalysts provide means of establishing configuration in enantioselective syntheses. A plan for a stereo- or enantioselective synthesis must include the basis for controlling the configuration at each stereocenter.

The care with which a synthesis is analyzed and planned will have a great impact on the likelihood of its success. The investment of material and effort that is made when the synthesis is begun may be lost if the plan is faulty. Even with the best of planning, however, unexpected problems are often encountered. This circumstance again tests the ingenuity of the chemist to devise a modified plan that can overcome the unanticipated obstacle.

13.1.2. Synthetic Equivalent Groups

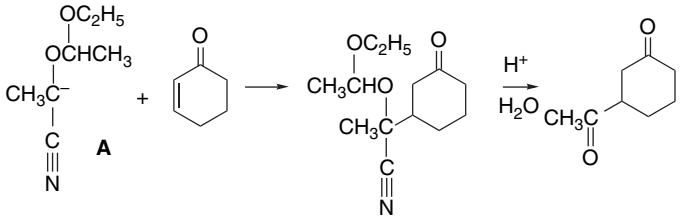
Retrosynthetic analysis may identify a need to use *synthetic equivalent groups*. These groups are synthons that correspond structurally to a subunit of the target structure, but in which the reactivity of the functionality is masked or modified. As an example, suppose the transformation shown below was to be accomplished.



The electrophilic α,β-unsaturated ketone is reactive toward nucleophiles, but the nucleophile that is required, an acyl anion, is not normally an accessible entity. There are several potential reagents that could introduce the desired acyl anion in a masked form. The masked functionality used in place of an inaccessible species is called a synthetically equivalent group. Often the concept of "umpolung" is involved in devising synthetic equivalent groups. The term *umpolung* refers to the formal reversal of the normal polarity of a functional group.[3] Acyl groups are normally *electrophilic*, but a synthetic operation may require the transfer of an acyl group as a *nucleophile*. The *acyl anion* is an umpolung equivalent of the electrophilic acylium cation.

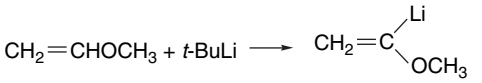
[3] For a general discussion and many examples of the use of the umpolung concept, see D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **18**, 239 (1979).

Owing to the great importance of carbonyl groups in synthesis, a substantial effort has been devoted to developing nucleophilic equivalents for introduction of acyl groups.[4] One successful method involves a three-step sequence in which an aldehyde is converted to an O-protected cyanohydrin. The α-alkoxynitrile is then deprotonated, generating a nucleophilic carbanion **A**.[5] After carbon-carbon bond formation, the carbonyl group can be regenerated by hydrolysis of the cyanohydrin. This sequence has been used to solve the problem of introducing an acetyl group at the β-position of cyclohexenone.[6]

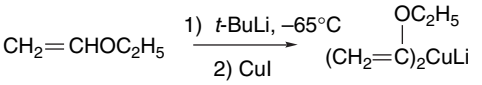


Ref. 5

α-Lithiovinyl ethers and the corresponding cuprates are other examples of acyl anion equivalents.

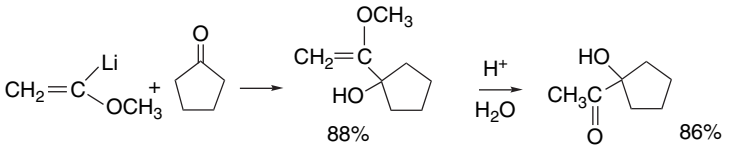


Ref. 7



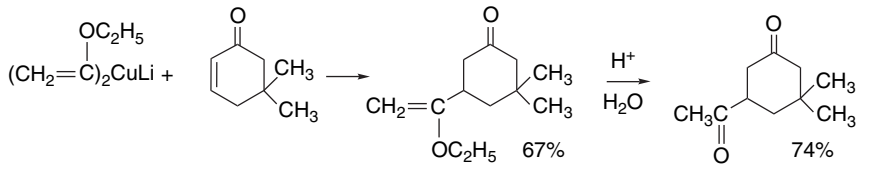
Ref. 8

These reagents are capable of adding the α-alkoxyvinyl group to electrophilic centers. Subsequent hydrolysis can generate the carbonyl group and complete the desired transformation.



Ref. 7

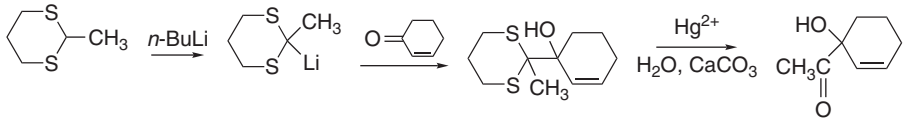
4. For a review of acyl anion synthons, see T. A. Hase and J. K. Koskimies, *Aldrichica Acta*, **15**, 35 (1982).
5. G. Stork and L. Maldonado, *J. Am. Chem. Soc*., **93**, 5286 (1971); *J. Am. Chem. Soc*., **96**, 5272 (1974).
6. For further discussion of synthetic applications of the carbanions of O-protected cyanohydrins, see J. D. Albright, *Tetrahedron*, **39**, 3207 (1983).
7. J. E. Baldwin, G. A. Hoefle, and O. W. Lever, Jr., *J. Am. Chem. Soc*., **96**, 7125 (1974).
8. R. K. Boeckman, Jr., and K. J. Bruza, *J. Org. Chem*., **44**, 4781 (1979).



Ref. 8

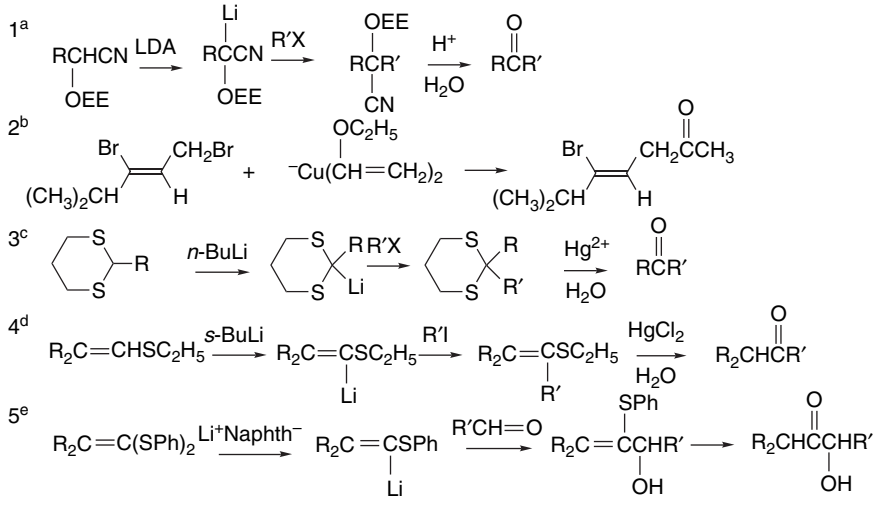
Lithiation of vinyl thioethers[9] and vinyl carbamates[10] also provides acyl anion equivalents.

Sulfur compounds are useful as nucleophilic acyl equivalents. The most common reagents of this type are 1,3-dithianes, which on lithiation provide a nucleophilic acyl equivalent. In dithianes an umpolung is achieved on the basis of the carbanion-stabilizing ability of the sulfur substituents. The lithio derivative is a reactive nucleophile toward alkyl halides and carbonyl compounds.[11]



1,3-Dithianes have found considerable application in multistep syntheses.[12] Scheme 13.1 summarizes some examples of synthetic sequences that employ acyl anion equivalents.

Scheme 13.1. Synthetic Sequences Using Acyl Anion Equivalents



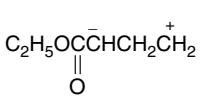
a. G. Stork and L. Maldonado, *J. Am. Chem. Soc*., **93**, 5236 (1971).
b. P. Canonne, R. Boulanger, and P. Angers, *Tetrahedron Lett*., **32**, 5861 (1991).
c. D. Seebach and E. J. Corey, *J. Org. Chem*., **40**, 231 (1975).
d. K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc*., **95**, 2694 (1973).
e. T. Cohen and R. B. Weisenfeld, *J. Org. Chem*., **44**, 3601 (1979).

9. K. Oshima, K. Shimoji, H. Takahashi, and H. Nozaki, *J. Am. Chem. Soc*., **95**, 2694 (1973).
10. S. Sengupta and V. Sniekus, *J. Org. Chem*., **55**, 5680 (1990).
11. D. Seebach and E. J. Corey, *J. Org. Chem*., **40**, 231 (1975); B. H. Lipshutz and E. Garcia, *Tetrahedron Lett*., **31**, 7261 (1990).
12. M. Yus, C. Najera, and F. Foubelo, *Tetrahedron*, **59**, 6147 (2003); A. B. Smith, III, and C. M. Adams, *Acc. Chem. Res*., **37**, 365 (2004).

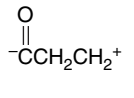
Another synthetic equivalent that has been extensively developed corresponds to the propanal "homoenolate," $^{-}CH_2CH_2CH=O$.[13] This structure is the umpolung equivalent of an important electrophilic reagent, the α,β-unsaturated aldehyde acrolein. Scheme 13.2 illustrates some of the propanal homoenolate equivalents that have been developed. In general, the reagents used for these transformations are reactive toward electrophiles such as alkyl halides and carbonyl compounds. Several general points can be made about the reagents in Scheme 13.2. First, it should be noted that they all deliver the aldehyde functionality in a masked form, such as an acetal or enol ether. The aldehyde is liberated in a final step from the protected precursor. Several of the reagents involve delocalized allylic anions, which gives rise to the possibility of electrophilic attack at either the α- or γ-position of the allylic group. In most cases, the γ-attack that is necessary for the anion to function as a propanal homoenolate is dominant. In Entry 1, the 2-methoxycyclopropyllithium is used to form a cyclopropyl carbinol. The methoxy group serves both to promote fragmentation of the cyclopropyl ring and to establish the aldehyde oxidation level. In Entry 2, the lithiation product of allyl methyl ether serves as a nucleophile and the aldehyde group is liberated by hydrolysis. Entry 3 is similar, but uses a trimethylsilyl ether. In Entry 4, allylic lithiation of an *N*-allylamine provides a nucleophile and can subsequently be hydrolyzed to the aldehyde.

In Entry 5, the carbanion-stabilizing ability of the sulfonyl group enables lithiation and is then reductively removed after alkylation. The reagent in Entry 6 is prepared by dilithiation of allyl hydrosulfide using *n*-butyllithium. After nucleophilic addition and S-alkylation, a masked aldehyde is present in the form of a vinyl thioether. Entry 7 uses the epoxidation of a vinyl silane to form a γ-hydroxy aldehyde masked as a cyclic acetal. Entries 8 and 9 use nucleophilic cuprate reagents to introduce alkyl groups containing aldehydes masked as acetals.

The concept of developing reagents that are the synthetic equivalent of inaccessible species can be taken another step by considering dipolar species. For example, structures **B** and **C** incorporate both electrophilic and nucleophilic centers. Such reagents might be incorporated into ring-forming schemes, since they have the ability, at least formally, of undergoing cycloaddition reactions.

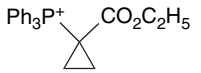


B

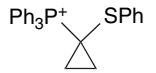


C

Among the real chemical species that have been developed along these lines are the cyclopropyl phosphonium ions **1** and **2**.



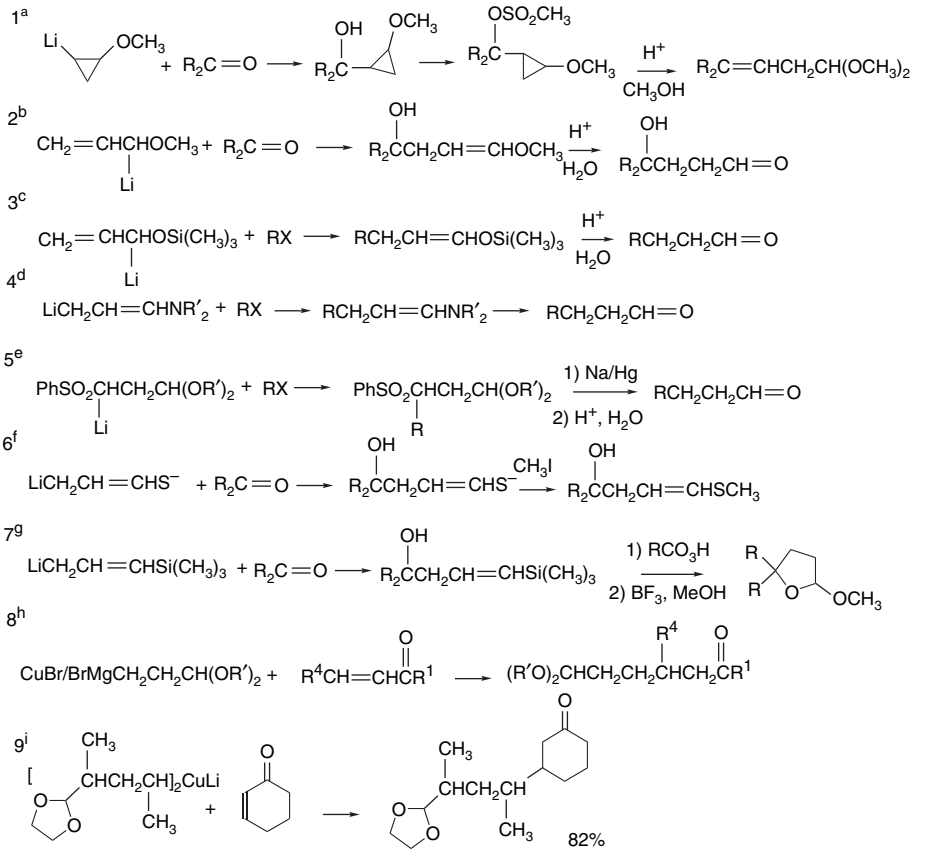
1



2

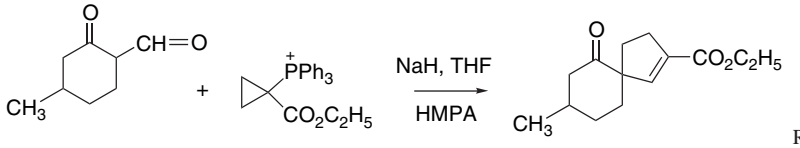
[13] For reviews of homoenolate anions, see J. C. Stowell, *Chem. Rev.*, **84**, 409 (1984); N. H. Werstiuk, *Tetrahedron*, **39**, 205 (1983).

Scheme 13.2. Synthetic Sequences Using Homoenolate Synthetic Equivalents



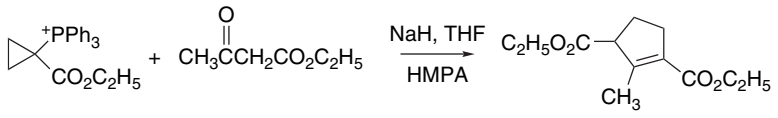
a. E. J. Corey and P. Ulrich, *Tetrahedron Lett*., 3685 (1975).
b. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc*., **96**, 5560 (1974).
c. W. C. Still and T. L. Macdonald, *J. Am. Chem. Soc*., **96**, 5561 (1974).
d. H. Ahlbrecht and J. Eichler, *Synthesis*, 672 (1974); S. F. Martin and M. T. DuPriest, *Tetrahedron Lett*., 3925 (1977); H. Ahlbrecht G. Bonnet, D. Enders, and G. Zimmerman, *Tetrahedron Lett*., **21**, 3175 (1980). e. M. Julia and B. Badet, *Bull. Soc. Chim. Fr*., 1363 (1975); K. Kondo and D. Tunemoto, *Tetrahedron Lett*., 1007 (1975).
f. K.-H. Geiss, B. Seuring, R. Pieter, and D. Seebach, *Angew. Chem. Int. Ed. Engl*., **13**, 479 (1974); K.-H. Geiss, D. Seebach, and B. Seuring, *Chem. Ber*., **110**, 1833 (1977).
g. E. Ehlinger and P. Magnus, *J. Am. Chem. Soc*., **102**, 5004 (1990).
h. A. Marfat and P. Helquist, *Tetrahedron Lett*., 4217 (1978); A. Leone-Bay and L. A. Paquette, *J. Org. Chem*., **47**, 4172 (1982).
i. J. P. Cherkaukas and T. Cohen, *J. Org. Chem*., **57**, 6 (1992).

The phosphonium salt **1** reacts with β-ketoesters and β-ketoaldehydes to give excellent yields of cyclopentenecarboxylate esters.



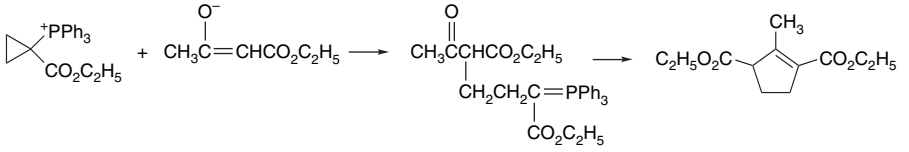
Ref. 14

14. W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc*., **99**, 7307 (1977).

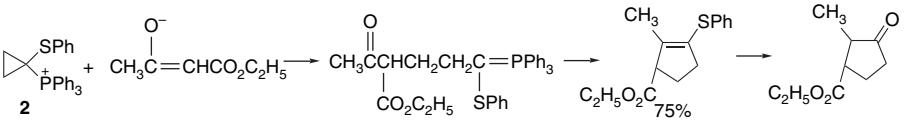


Ref. 15

Several steps are involved in these reactions. First, the enolate of the β-ketoester opens the cyclopropane ring. The polarity of this process corresponds to that in the formal synthon **B** because the cyclopropyl carbons are electrophilic. The product of the ring-opening step is a stabilized Wittig ylide, which can react with the ketone carbonyl to form the carbocyclic ring.

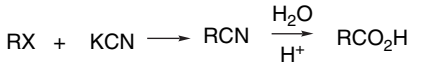


The phosphonium ion **2** reacts similarly with enolates to give vinyl sulfides. The vinyl sulfide group can then be hydrolyzed to a ketone. The overall transformation corresponds to the reactivity of the dipolar synthon **C**.



Ref. 16

Many other examples of synthetic equivalent groups have been developed. For example, in Chapter 6 we discussed the use of diene and dienophiles with masked functionality in the Diels-Alder reaction. It should be recognized that there is no absolute difference between what is termed a "reagent" and a "synthetic equivalent group." For example, we think of potassium cyanide as a reagent, but the cyanide ion is a nucleophilic equivalent of a carboxy group. This reactivity is evident in the classical preparation of carboxylic acids from alkyl halides via nitrile intermediates.



The important point is that synthetic analysis and planning should not be restricted to the specific functionalities that appear in the target molecules. These groups can be incorporated as masked equivalents by methods that would not be possible for the functional group itself.

13.1.3. Control of Stereochemistry

The degree of control of stereochemistry that is necessary during synthesis depends on the nature of the molecule and the objective of the synthesis. The issue

[15.] P. L. Fuchs, *J. Am. Chem. Soc*., **96**, 1607 (1974).
[16.] J. P. Marino and R. C. Landick, *Tetrahedron Lett*., 4531 (1975).

becomes critically important when the target molecule has several stereogenic centers, such as double bonds, ring junctions, and asymmetric carbons. The number of possible stereoisomers is 2^n, where n is the number of stereogenic centers. Failure to control stereochemistry of intermediates in the synthesis of a compound with several centers of stereochemistry leads to a mixture of stereoisomers that will, at best, result in a reduced yield of the desired product and may generate inseparable mixtures. For properties such as biological activity, obtaining the correct stereoisomer is crucial.

We have considered stereoselectivity for many of the reactions that are discussed in the earlier chapters. In ring compounds, for example, stereoselectivity can frequently be predicted on the basis of conformational analysis of the reactant and consideration of the steric and stereoelectronic factors that influence reagent approach. In the *diastereoselective synthesis* of a chiral compound in racemic form, it is necessary to control the *relative configuration* of all stereogenic centers. Thus in planning a synthesis, the stereochemical outcome of all reactions that form new double bonds, ring junctions, or asymmetric carbons must be incorporated into the synthetic plan. In a completely stereoselective synthesis, each successive stereochemical feature is introduced in the proper relationship to existing stereocenters, but this ideal is often difficult to achieve. When a reaction is not completely stereoselective, the product will contain one or more diastereomers of the desired product. This requires either a purification or some manipulation to correct the stereochemistry. Fortunately, diastereomers are usually separable, but the overall efficiency of the synthesis is decreased with each such separation. Thus, high stereoselectivity is an important goal of synthetic planning.

If the compound is to be obtained in enantiomerically pure form, an *enantioselective synthesis* must be developed. As discussed in Section A.2.5, the stereochemical control may be based on chirality in the reactants, auxiliaries, reagents, and/or catalysts. There are several general approaches that are used to obtain enantiomerically pure material by synthesis. One is based on incorporating a *resolution* into the synthetic plan. This approach involves use of racemic or achiral starting materials and resolving some intermediate in the synthesis. In a synthesis based on a resolution, the steps subsequent to the resolution step must meet two criteria: (1) they must not disturb the configuration at existing stereocenters, and (2) new centers of stereochemistry must be introduced with the correct configuration relative to those that already exist. A second general approach is to use an *enantiomerically pure starting material*. Highly enantioselective reactions, such as the Sharpless epoxidation, can be used to prepare enantiomerically pure starting materials. There are a number of naturally occurring materials, or substances derived from them, that are available in enantiomerically pure form.[17]

Enantioselective synthesis can also be based on *chiral reagents*. Examples are hydroboration or reduction using one of the commercial available borane reagents. Again, a completely enantioselective synthesis must be capable of controlling the stereochemistry of all newly introduced stereogenic centers so that they have the proper relationship to the chiral centers that exist in the starting material. When this is not achieved, the desired stereoisomer must be separated and purified. A fourth method for enantioselective synthesis involves the use of a stoichiometric amount of a *chiral auxiliary*. This is an enantiomerically pure material that can control the stereochemistry of one or more reaction steps in such a way as to give product having the desired configuration. When the chiral auxiliary has achieved its purpose, it can be

[17] For a discussion of this approach to enantioselective synthesis, see S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, New York, 1983.

eliminated from the molecule. As in syntheses involving resolution or enantiomerically pure starting materials, subsequent steps must give the correct configuration of newly created stereocenters. Another approach to enantioselective synthesis is to use a *chiral catalyst* in a reaction that creates one or more stereocenters. If the catalyst operates with complete efficiency, an enantiomerically pure material will be obtained. Subsequent steps must control the configuration of newly introduced stereocenters.

In practice, any of these approaches might be the most effective for a given synthesis. If they are judged on the basis of absolute efficiency in the use of a chiral material, the ranking is resolution < chiral reactant < chiral reagent < chiral auxiliary < enantioselective catalyst. A resolution process inherently employs only half of the original racemic material. A chiral starting material can, in principle, be used with 100% efficiency, but it is consumed and cannot be reused. A chiral reagent is also consumed, but in principle it can be regenerated, as is done for certain organoboranes (see p. 350). A chiral auxiliary must be used in a stoichiometric amount but it can be recovered. A chiral catalyst, in principle, can produce an unlimited amount of an enantiomerically pure material.

The key issue for synthesis of pure stereoisomers, in either racemic or enantiomerically pure form, is that the configuration at newly created stereocenters be controlled in some way. This can be accomplished by several different methods. Existing functional groups may exert a steric or stereoelectronic influence on the reaction center. For instance, an existing functional group may control the approach of a reagent by coordination, which occurs, for example, in hydroxy-directed cyclopropanation (see p. 919). An existing chiral center may control reactant conformation and, thereby, the direction of approach of a reagent.

Generally, the closer the reaction occurs to an existing stereogenic center, the more likely the reaction is to exhibit high stereoselectivity. For example, the creation of adjacent stereogenic centers in aldol and organometallic addition reactions is generally strongly influenced by adjacent substituents leading to a preference for a *syn* or *anti* disposition of the new substituent. We also encountered some examples of *1,3-asymmetric induction*, as, for example, the role of chelates in reduction of β-hydroxy ketones (p. 412), in chelation control of Mukaiyama addition reactions (p. 94), and in hydroboration (Section p. 342). More remote chiral centers are less likely to influence stereoselectivity and examples of, e.g., 1,4- and 1,5-asymmetric induction, are less common. Whatever the detailed mechanism, the synthetic plan must include the means by which the required stereochemical control is to be achieved. If this cannot be done, the price to be paid is a separation of stereoisomers and the resulting reduction in overall yield.

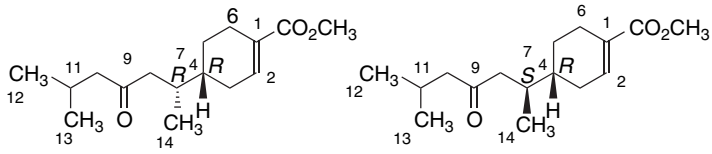
13.2. Illustrative Syntheses

In this section, we consider several syntheses of six illustrative compounds. We examine the retrosynthetic plans and discuss crucial bond-forming steps and the means of stereochemical control. In this discussion, we have the benefit of hindsight in being able to look at successfully completed syntheses. This retrospective analysis can serve to illustrate the issues that arise in planning a synthesis and provide examples of solutions that have been developed. The individual syntheses also provide many examples of the synthetic transformations presented in the previous chapters and of the use of protective groups in the synthesis of complex molecules. The syntheses shown

span a period of several decades and in some cases new reagents and protocols may have been developed since a particular synthesis was completed. Owing to limitations of space, only key steps are discussed although all the steps are shown in the schemes. Usually, only the reagent is shown, although other reaction components such as acids, bases, or solvents may also be of critical importance to the success of the reaction.

13.2.1. Juvabione

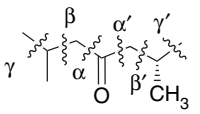
Juvabione is a terpene-derived ketoester that has been isolated from various plant sources. There are two stereoisomers, both of which occur naturally with *R*-configuration at C(4) of the cyclohexene ring and are referred to as *erythro*- and *threo*-juvabione. The 7(*S*)-enantiomer is sometimes called epijuvabione. Juvabione exhibits "juvenile hormone" activity in insects; that is, it can modify the process of metamorphosis.[18]



threo-juvabione *erythro*-juvabione

In considering the retrosynthetic analysis of juvabione, two factors draw special attention to the bond between C(4) and C(7). First, this bond establishes the stereochemistry of the molecule. The C(4) and C(7) carbons are stereogenic centers and their relative configuration determines the diastereomeric structure. In a stereocontrolled synthesis, it is necessary to establish the desired stereochemistry at C(4) and C(7). The C(4)−C(7) bond also connects the side chain to the cyclohexene ring. As a cyclohexane derivative is a logical candidate for one key intermediate, the C(4)−C(7) bond is a potential bond disconnection.

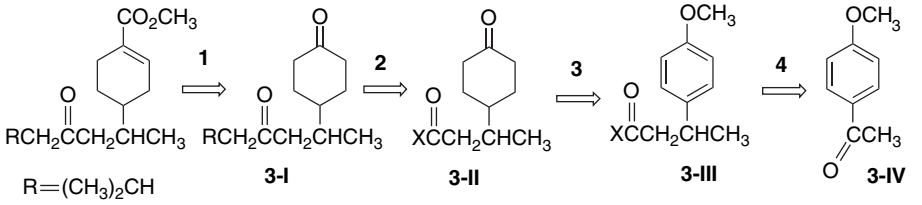
Other bonds that merit attention are those connecting C(7) through C(11). These could be formed by one of the many methods for the synthesis of ketones. Bond disconnections at carbonyl centers can involve the O=C-C(α) (acylation, organometallic addition), the C(α)–C(β) bond (enolate alkylation, aldol addition), or C(β)–C(γ) bond (conjugate addition to enone).



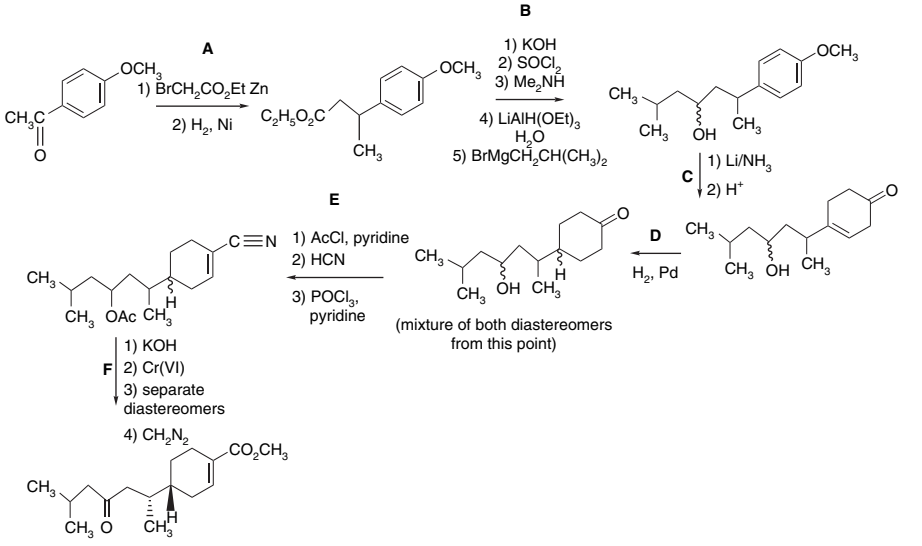
The only other functional group is the conjugated unsaturated ester. This functionality is remote from the stereocenters and the ketone functionality, and does not play a key role in most of the reported syntheses. Most of the syntheses use cyclic starting materials. Those in Schemes 13.4 and 13.5 lead back to a *para*-substituted aromatic ether. The syntheses in Schemes 13.7 and 13.8 begin with an accessible terpene intermediate. The syntheses in Schemes 13.10 and 13.11 start with cyclohexenone. Scheme 13.3 presents a retrosynthetic analysis leading to the key intermediates used for the syntheses in

[18] For a review, see Z. Wimmer and M. Romanuk, *Coll. Czech. Chem. Commun.*, **54**, 2302 (1989).

Scheme 13.3. Retrosynthetic Analysis of Juvabione with Disconnection to 4-Methoxyacetophenone

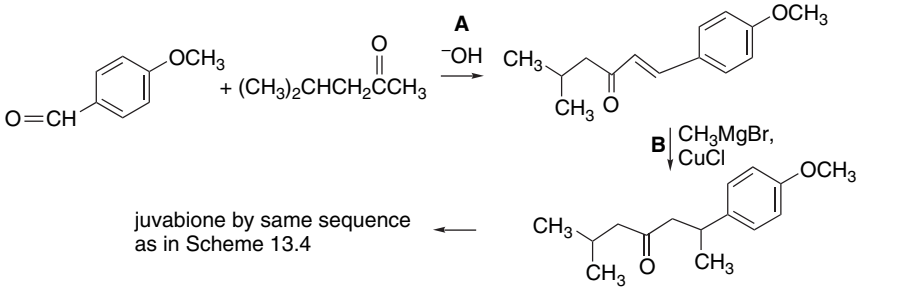


Scheme 13.4. Juvabione Synthesis: K. Mori and M. Matsui[a]



a. K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968).

Scheme 13.5. Juvabione Synthesis: K. S. Ayyar and G. S. K. Rao[a]



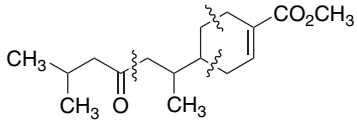
a. K. S. Ayyar and G. S. K. Rao, *Can. J. Chem.*, **46**, 1467 (1968).

Schemes 13.4 and 13.5. These syntheses use achiral reactants and provide mixtures of both stereoisomers. The final products are racemic. The first disconnection is that of the ester functionality, which corresponds to a strategic decision that the ester group can be added late in the synthesis. Disconnection **2** identifies the C(9)−C(10) bond as one that can be formed by addition of some nucleophilic group corresponding to C(10)−C(13) to the carbonyl center at C(9). This corresponds to disconnection α shown above. The third retrosynthetic transform recognizes that the cyclohexanone ring could be obtained by a Birch reduction of an appropriately substituted aromatic ether. The methoxy substituent would provide for correct placement of the cyclic carbonyl group. The final disconnection identifies a simple starting material, 4-methoxyacetophenone.

A synthesis corresponding to this pattern that is shown in Scheme 13.4 relies on well-known reaction types. The C(4)–C(7) bond was formed by a Reformatsky reaction. The adduct was dehydrated during work-up and the product was hydrogenated after purification. The ester group was converted to the corresponding aldehyde by Steps **B**-1 through **B**-4. Step **B**-5 introduced the C(10)–C(13) isobutyl group by Grignard addition to an aldehyde. In this synthesis, the relative configuration at C(4) and C(7) was established by the hydrogenation in Step **D**. In principle, this reaction could be diastereoselective if the adjacent chiral center at C(7) strongly influenced the direction of addition of hydrogen. In practice, the reduction was not very selective and a mixture of isomers was obtained. Steps **E** and **F** introduced the C(1) ester group.

The synthesis in Scheme 13.5 also makes use of an aromatic starting material and follows a retrosynthetic plan similar to that in Scheme 13.3. The starting material was 4-methoxybenzaldehyde. This synthesis was somewhat more convergent in that the entire side chain except for C(14) was introduced as a single unit by a mixed aldol condensation in step **A**. The C(14) methyl was introduced by a copper-catalyzed conjugate addition in Step **B**.

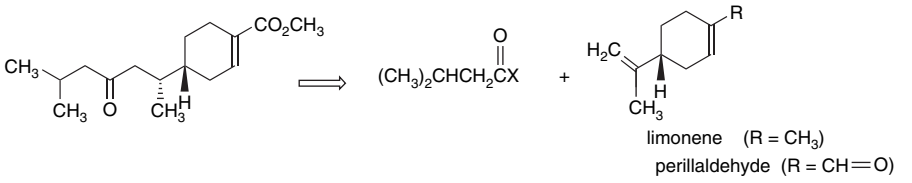
Scheme 13.6 is a retrosynthetic outline of the syntheses in Schemes 13.7 to 13.9. The common feature of these syntheses is the use of terpene-derived starting materials. The use of such a starting material is suggested by the terpenoid structure of juvabione, which can be divided into "isoprene units."



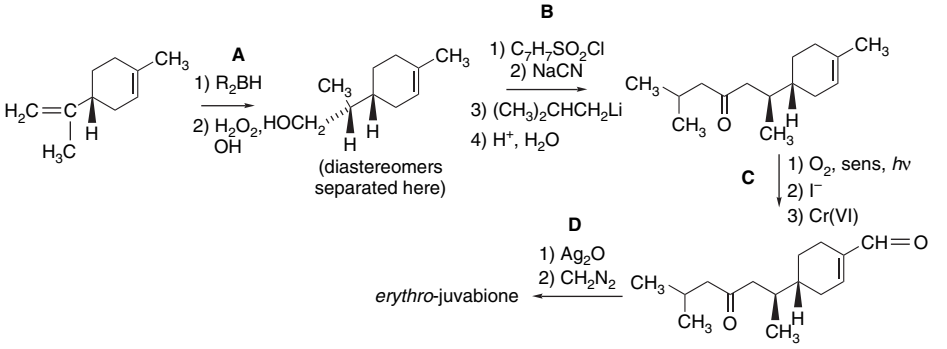
isoprene units in juvabione

The synthesis shown in Scheme 13.7 used limonene as the starting material (R = CH_3 in Scheme 13.6), whereas Schemes 13.8 and 13.9 use the corresponding aldehyde (R = CH=O). The use of these starting materials focuses attention on the means of attaching the C(9)−C(13) side chain. Furthermore, since the starting material is an enantiomerically pure terpene, enantioselectivity controlled by the chiral center at C(4) of the starting material might be feasible. In the synthesis in Scheme 13.7, the C(4)−C(7) stereochemistry was established in the hydroboration that is the first step of the synthesis. This reaction showed only very modest stereoselectivity and a 3:2 mixture of diastereomers was obtained and separated. The subsequent steps do not affect these stereogenic centers. The side chain was elaborated by adding *i*-butyllithium to a nitrile. The synthesis in Scheme 13.7 used a three-step oxidation sequence to oxidize the C(15) methyl group to a carboxy group. The first reaction was oxidation

Scheme 13.6. Retrosynthetic Analysis of Juvabione with Disconnection to the Terpene Limonene

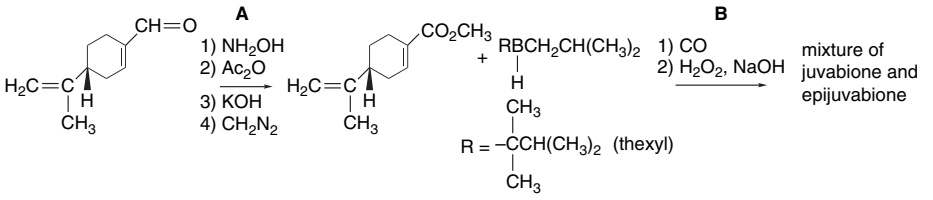


Scheme 13.7. Juvabione Synthesis: B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy[a]



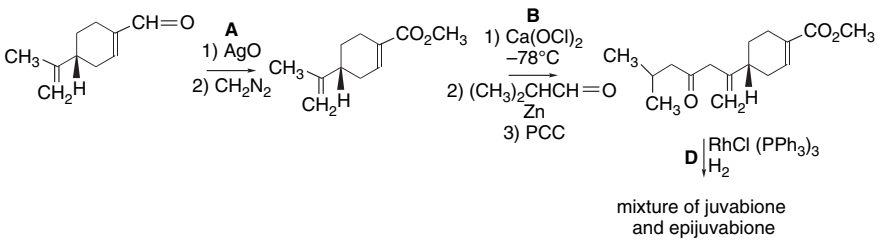
a. B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc*., **92**, 336 (1970).

Scheme 13.8. Juvabione Synthesis: E. Negishi, M. Sabanski, J. J. Katz, and H. C. Brown[a]



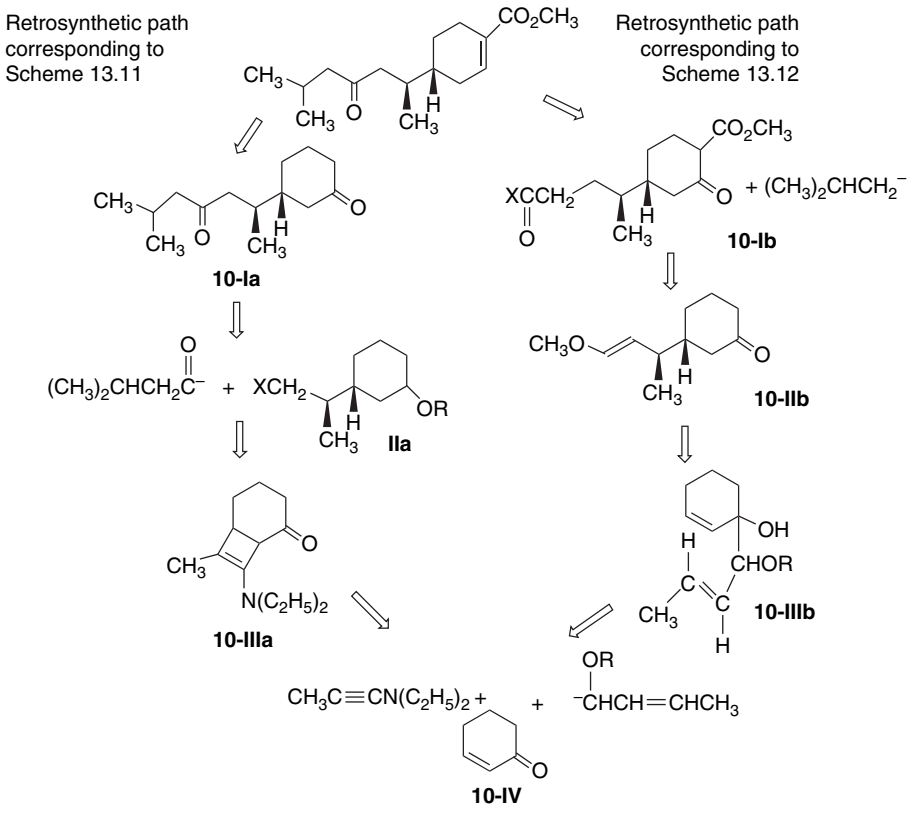
a. E. Negishi, M. Sabanski, J. J. Katz, and H. C. Brown, *Tetrahedron*, **32**, 925 (1976).

Scheme 13.9. Juvabione Synthesis: A. A. Carveiro and I. G. P. Viera[a]

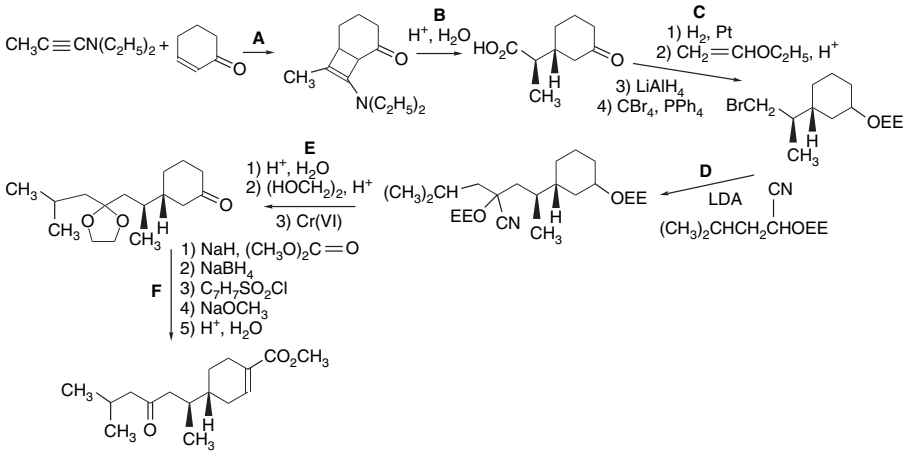


a. A. A. Carveiro and L. G. P. Viera, *J. Braz. Chem. Soc*., **3**, 124 (1992).

Scheme 13.10. Retrosynthetic Analysis of Juvabione with Alternative Disconnections to Cyclohex-2-enone



Scheme 13.11. Juvabione Synthesis: J. Ficini, J. D'Angelo, and J. Noire[a]



a. J. Ficini, J. D'Angelo, and J. Noire, *J. Am. Chem. Soc.*, **96**, 1213 (1974).

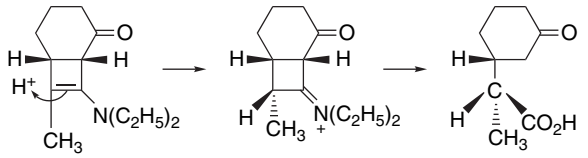
by singlet oxygen to give a mixture of hydroperoxides, with oxygen bound mainly at C(2). The mixture was reduced to the corresponding alcohols, which was then oxidized to the acid via an aldehyde intermediate.

In Scheme 13.8, the side chain was added in one step by a borane carbonylation reaction. This synthesis is very short and the first four steps were used to transform the aldehyde group in the starting material to a methyl ester. The stereochemistry at C(4)–C(7) is established in the hydroboration in Step **B**, in which the C(7)–H bond is formed. A 1:1 mixture of diastereomers resulted, indicating that the configuration at C(4) has little influence on the direction of approach of the borane reagent.

Another synthesis, shown in Scheme 13.9, that starts with the same aldehyde (perillaldehyde) was completed more recently. The C(8)−C(9) bond was established by an allylic chlorination and addition of the corresponding zinc reagent to isobutyraldehyde. In this synthesis, the C(7) stereochemistry was established by a homogeneous hydrogenation of a methylene group, but this reaction also produces both stereoisomers.

The first diastereoselective syntheses of juvabione are described in Schemes 13.11 and 13.12. Scheme 13.10 is a retrosynthetic analysis corresponding to these syntheses, which have certain similarities. Both syntheses started with cyclohexenone, and there is a general similarity in the fragments that were utilized, although the order of construction differs, and both led to (±)-juvabione.

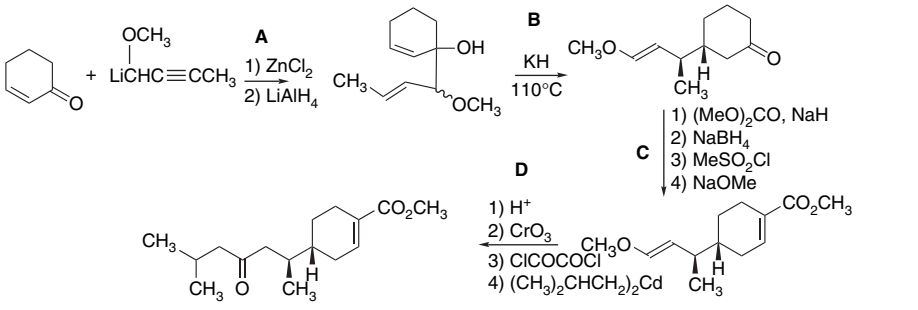
A key step in the synthesis in Scheme 13.11 was a cycloaddition between an electron-rich ynamine and the electron-poor enone. The cyclobutane ring was then opened in a process that corresponds to retrosynthetic step **10-IIa** ⇒ **10-IIIa** in Scheme 13.10. The crucial step for stereochemical control occurs in Step **B**. The stereoselectivity of this step results from preferential protonation of the enamine from the less hindered side of the bicyclic intermediate.



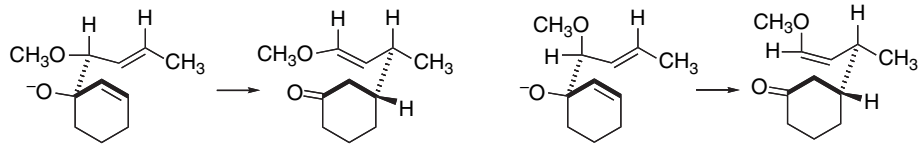
The cyclobutane ring was then cleaved by hydrolysis of the enamine and ring opening of the resulting β-diketone. The relative configuration of the chiral centers is unaffected by subsequent transformations, so the overall sequence is stereoselective. Another key step in this synthesis is Step **D**, which corresponds to the transformation **10-IIa** ⇒ **10-Ia** in the retrosynthesis. A protected cyanohydrin was used as a nucleophilic acyl anion equivalent in this step. The final steps of the synthesis in Scheme 13.11 employed the C(2) carbonyl group to introduce the carboxy group and the C(1)–C(2) double bond.

The stereoselectivity achieved in the synthesis in Scheme 13.12 is the result of a preferred conformation for the base-catalyzed oxy-Cope rearrangement in Step **B**. Although the intermediate used in Step **B** was a mixture of stereoisomers, both gave predominantly the desired relative stereochemistry at C(4) and C(7). The stereoselectivity is based on the preferred chair conformation for the TS of the oxy-Cope rearrangement.

Scheme 13.12. Juvabione Synthesis: D. A. Evans and J. V. Nelson[a]



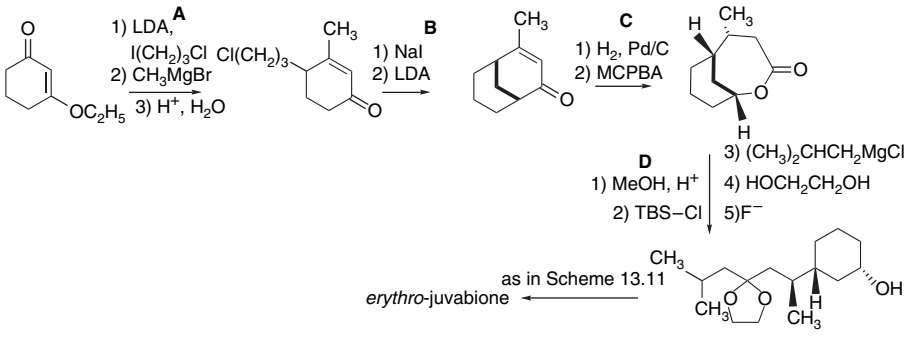
a. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, **102**, 774 (1980).



The synthesis in Scheme 13.13 leads diastereospecifically to the *erythro* stereoisomer. An intramolecular enolate alkylation in Step **B** gave a bicyclic intermediate. The relative configuration of C(4) and C(7) was established by the hydrogenation in Step **C**. The hydrogen is added from the less hindered *exo* face of the bicyclic enone. This reaction is an example of the use of geometric constraints of a ring system to control relative stereochemistry.

The *threo* stereoisomer was the major product obtained by the synthesis in Scheme 13.14. This stereochemistry was established by the conjugate addition in Step **A**, where a significant (4–6:1) diastereoselectivity was observed. The C(4)–C(7) stereochemical relationship was retained through the remainder of the synthesis. The other special features of this synthesis are in Steps **B** and **C**. The mercuric acetate–mediated cyclopropane ring opening was facilitated by the alkoxy substituent.[19] The reduction by $NaBH_4$ accomplished both demercuration and reduction of the aldehyde group.

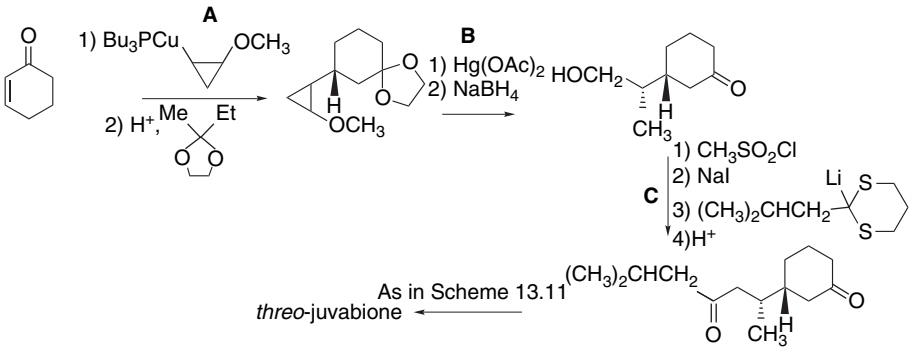
Scheme 13.13. Juvabione Synthesis: A. G. Schultz and J. P. Dittami[a]



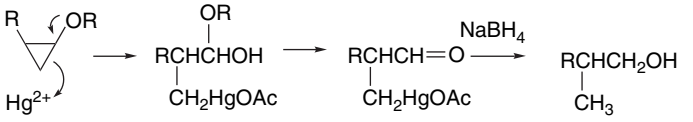
a. A. G. Schultz and J. P. Dittami, *J. Org. Chem.*, **49**, 2615 (1984).

19. A. DeBoer and C. H. DePuy, *J. Am. Chem. Soc.*, **92**, 4008 (1970).

Scheme 13.14. Juvabione Synthesis: D. J. Morgans, Jr., and G. B. Feigelson[a]

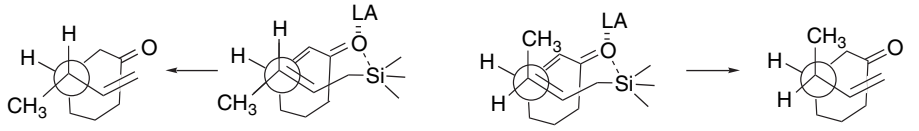


a. D. J. Morgans, Jr., and G. B. Feigelson, *J. Am. Chem. Soc.*, **105**, 5477 (1983).



In Step **C** a dithiane anion was used as a nucleophilic acyl anion equivalent to introduce the C(10)–C(13) isobutyl group.

In the synthesis shown in Scheme 13.15, racemates of both *erythro*- and *threo*-juvabione were synthesized by parallel routes. The isomeric intermediates were obtained in greater than 10:1 selectivity by choice of the *E*- or *Z*-silanes used for conjugate addition to cyclohexenone (Michael-Mukaiyama reaction). Further optimization of the stereoselectivity was achieved by the choice of the silyl substituents. The observed stereoselectivity is consistent with synclinal TSs for the addition of the crotyl silane reagents.

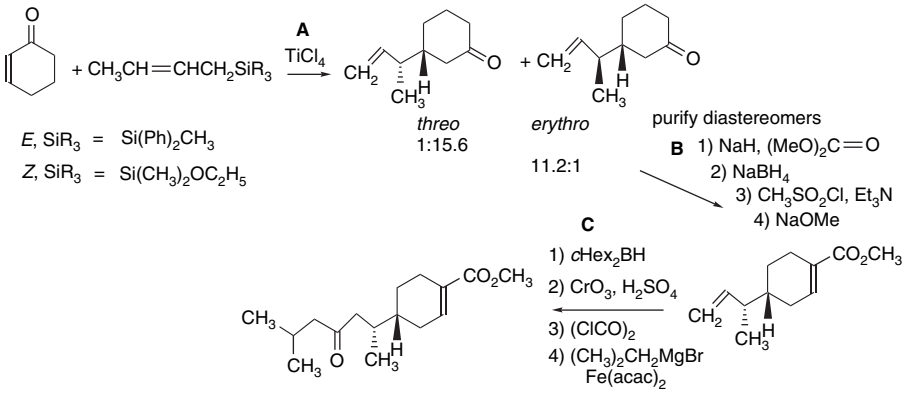


The purified diastereomeric intermediates were then converted to the juvabione stereoisomers.

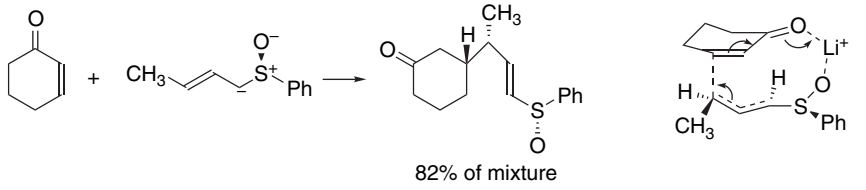
Except for the syntheses using terpene-derived starting materials (Schemes 13.7, 13.8, and 13.9), the previous juvabione syntheses all gave racemic products. Some of the more recent juvabione syntheses are *enantiospecific*. The synthesis in Scheme 13.16 relied on a chiral sulfoxide that undergoes stereoselective addition to cyclohexenone to establish the correct relative and absolute configuration at C(4) and C(7). The origin of the stereoselectivity is a chelated TS that leads to the observed product.[20]

20. M. R. Binns, R. K. Haynes, A. G. Katsifis, P. A. Schober, and S. C. Vonwiller, *J. Am. Chem. Soc.*, **110**, 5411 (1988).

Scheme 13.15. Juvabione Synthesis: T. Tokoroyama and L.-R. Pan[a]



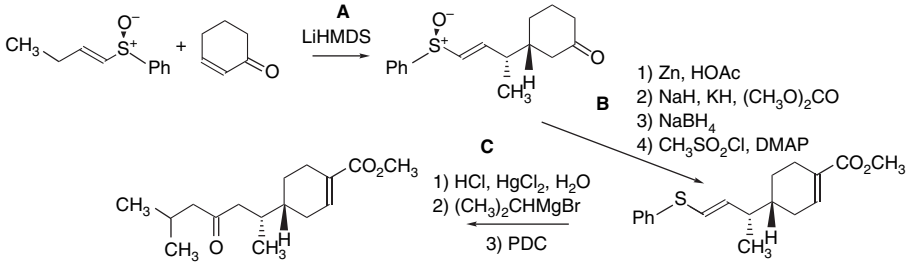
a. T. Tokoroyama and L.-R. Pan, *Tetrahedron Lett.*, **30**, 197 (1989).



The sulfoxide substituent was also used to introduce the C(10)–C(13) fragment and was reduced to a vinyl sulfide in Step **B**-1. In Step **C**-1, the vinyl sulfide was hydrolyzed to an aldehyde, which was elaborated by addition of isobutylmagnesium bromide.

Scheme 13.17 depicts a synthesis based on enantioselective reduction of bicyclo[2.2.2]octane-2,6-dione by Baker's yeast.[21] This is an example of desymmetrization (see Part A, Topic 2.2). The unreduced carbonyl group was converted to an alkene by the Shapiro reaction. The alcohol was then reoxidized to a ketone. The enantiomerically pure intermediate was converted to the lactone by Baeyer-Villiger oxidation and an allylic rearrangement. The methyl group was introduced stereoselectively from the *exo* face of the bicyclic lactone by an enolate alkylation in Step **C**-1.

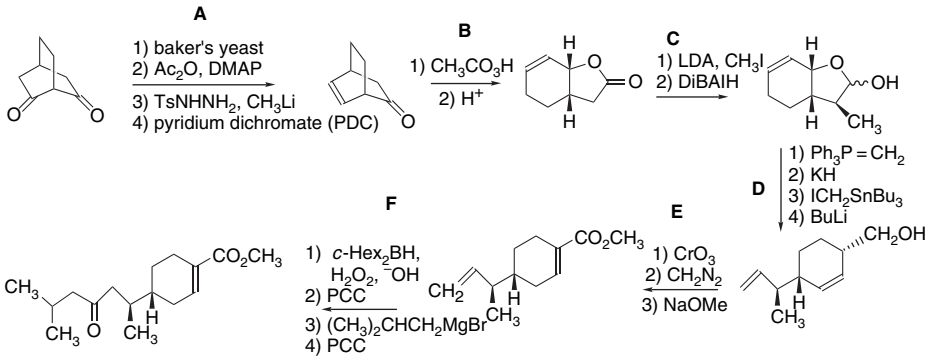
Scheme 13.16. Juvabione Synthesis: H. Watanabe, H. Shimizu, and K. Mori[a]



a. H. Watanabe, H. Shimizu, and K. Mori, *Synthesis*, 1249 (1994).

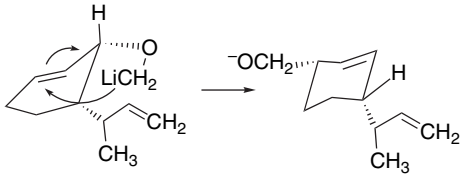
21. K. Mori and F. Nagano, *Biocatalysis*, **3**, 25 (1990).

Scheme 13.17. Juvabione Synthesis: E. Nagano and K. Mori[a]

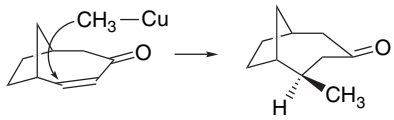


a. E. Nagano and K. Mori, *Biosci. Biotechnol. Biochem.*, **56**, 1589 (1992).

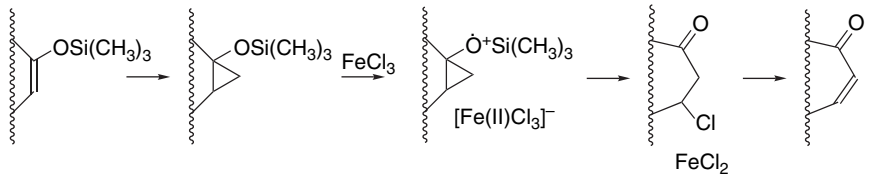
A final crucial step in this synthesis was an anionic [2,3]-sigmatropic rearrangement of an allylic ether in Step **D**-4 to introduce the C(1) carbon.



Another enantioselective synthesis, shown in Scheme 13.18, involves a early kinetic resolution of the alcohol intermediate in Step **B**-2 by lipase PS. The stereochemistry at the C(7) methyl group is controlled by the *exo* selectivity in the conjugate addition (Step **D**-1).

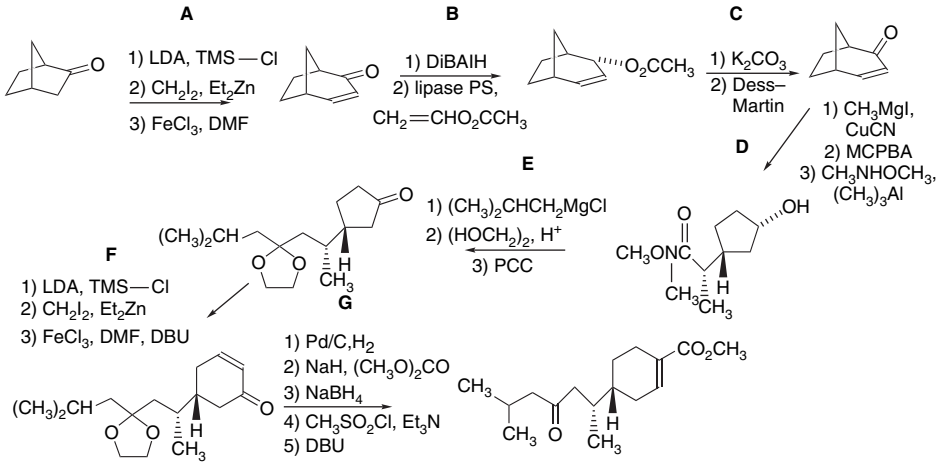


The bicyclic ring is then cleaved by a Baeyer-Villiger reaction in Step **D**-2. Another interesting feature of this synthesis is the ring expansions used in sequences **A** and **F**. Trimethylsilyl enol ethers were treated with Simmons-Smith reagent to form cyclopropyl silyl ethers. These undergo oxidative cleavage and ring expansion when treated with $FeCl_3$ and the α-chloro ketones are then dehydrohalogenated by DBU.[22]



22. V. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976).

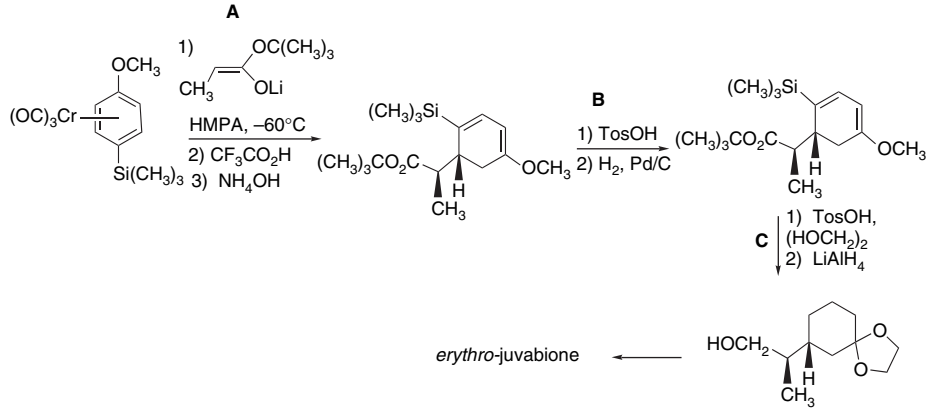
Scheme 13.18. Juvabione Synthesis: K. Ogasawara and Co-workers[a]



a. H. Nagata, T. Taniguchi, M. Kawamura, and K. Ogasawara, *Tetrahedron Lett*., **40**, 4207 (1999).

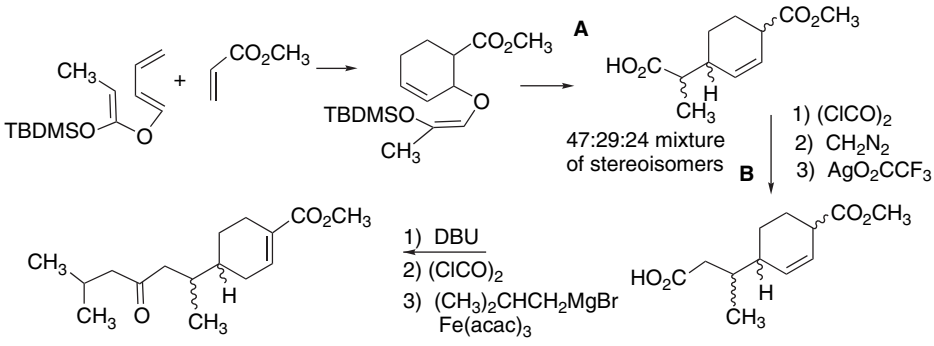
The juvabione synthesis in Scheme 13.19 exploited both the regiochemical and stereochemical features of the starting material, the $Cr(CO)_3$ complex of 4-methoxyphenyltrimethylsilane. The lithium enolate of *t*-butyl propanoate was added, resulting in a 96:4 ratio of *meta:ortho* adducts. The addition was also highly stereoselective, giving a greater than 99:1 preference for the *erythro* stereochemistry. This is consistent with reaction through TS **18-A** in preference to TS **18-B** to avoid a *gauche* interaction between the enolate methyl and the trimethylsilyl substituent.

Scheme 13.19. Juvabione Synthesis: A. J. Pearson, H. Paramahamsan, and J. D. Dudones[a]

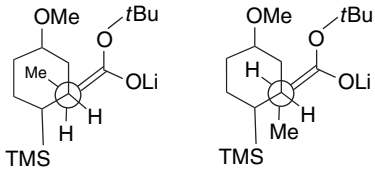


a. A. J. Pearson, H. Paramahamsan, and J. D. Dudones, *Org. Lett*., **6**, 2121 (2004).

Scheme 13.20. Juvabione Synthesis: R. Neier and Co-Workers



a. N. Soldermann, J. Velker, O. Vallat, H. Stoeckli-Evans, and R. Neier, *Helv. Chim. Acta*, **83**, 2266 (2000).



TS **18-A** TS **18-B**

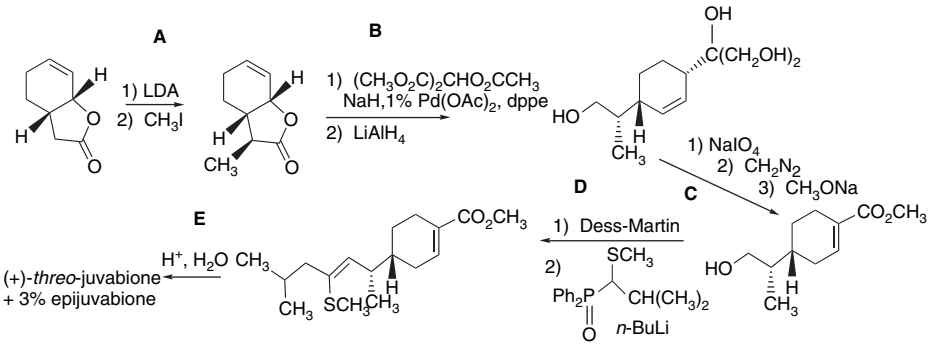
The reaction product was converted to an intermediate that had previously been converted to *erythro*-juvabione.

The synthesis in Scheme 13.20 features a tandem Diels-Alder reaction and Ireland-Claisen [3,3]-sigmatropic shift as the key steps. Although this strategy was very efficient in constructing the carbon structure, it was not very stereoselective. The major isomer results from an *endo* TS for the Diels-Alder reaction and a [3,3]-sigmatropic rearrangement through a boat TS. Three stereoisomers were obtained in the ratio 47:29:24. These were not separated but were converted to a 4:1 mixture of (±)-juvabione and (±)-epijuvabione by Arndt-Eistert homologation, DBU-based conjugation, and addition of the isobutyl group by a $Fe(acac)_3$-catalyzed Grignard addition.

The synthesis in Scheme 13.21 starts with a lactone that is available in enantiomerically pure form. It was first subjected to an enolate alkylation that was stereocontrolled by the convex shape of the *cis* ring junction (Step **A**). A stereospecific Pd-mediated allylic substitution followed by $LiAlH_4$ reduction generated the first key intermediate (Step **B**). This compound was oxidized with $NaIO_4$, converted to the methyl ester, and subjected to a base-catalyzed conjugation. After oxidation of the primary alcohol to an aldehyde, a Wittig-Horner olefination completed the side chain.

The enantioselective synthesis in Scheme 13.22 is based on stereoselective reduction of an α, β-unsaturated aldehyde generated from (−)-(*S*)-limonene (Step **A**). The reduction was done by Baker's yeast and was completely enantioselective. The diastereoselectivity was not complete, generating an 80:20 mixture, but the diastereomeric alcohols were purified at this stage. After oxidation to the aldehyde, the remainder of the side chain was introduced by a Grignard addition. The ester function

Scheme 13.21. Juvabione Synthesis: E. J Bergner and G. Helmchen[a]



a. E. J. Bergner and G. Helmchen, *J. Org. Chem*., **65**, 5072 (2000).

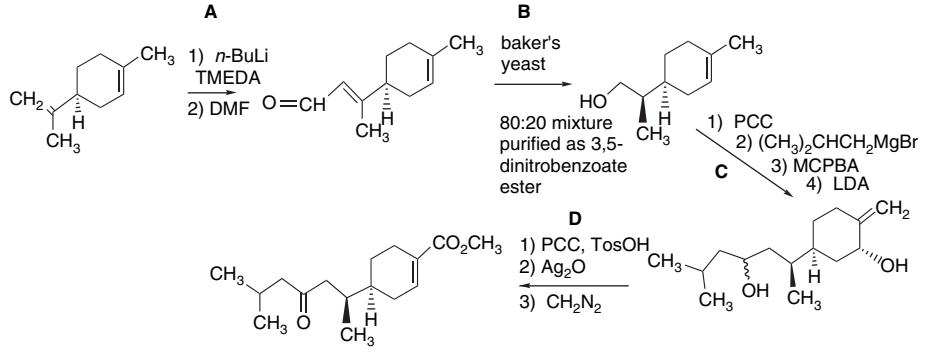
was introduced by a base-catalyzed opening of the epoxide to an allylic alcohol (Step **C**-4), which then underwent oxidation with allylic transposition (Step **D**-1).

Several other syntheses of juvabione have also been completed.[23]

13.2.2. Longifolene

Longifolene is a tricyclic sesquiterpene. It is a typical terpene hydrocarbon in terms of the structural complexity. The synthetic challenge lies in construction of the bicyclic ring system. Schemes 13.24 through 13.33 describe nine separate syntheses of longifolene. We wish to particularly emphasize the methods for carbon-carbon bond formation used in these syntheses. There are four stereogenic centers in longifolene,

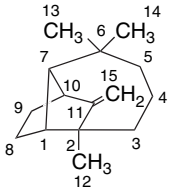
Scheme 13.22. Juvabione Synthesis. C. Fuganti and S. Serra[a]



a. C. Fuganti and S. Serra, *J. Chem. Soc., Perkin Trans. 1*, 97 (2000).

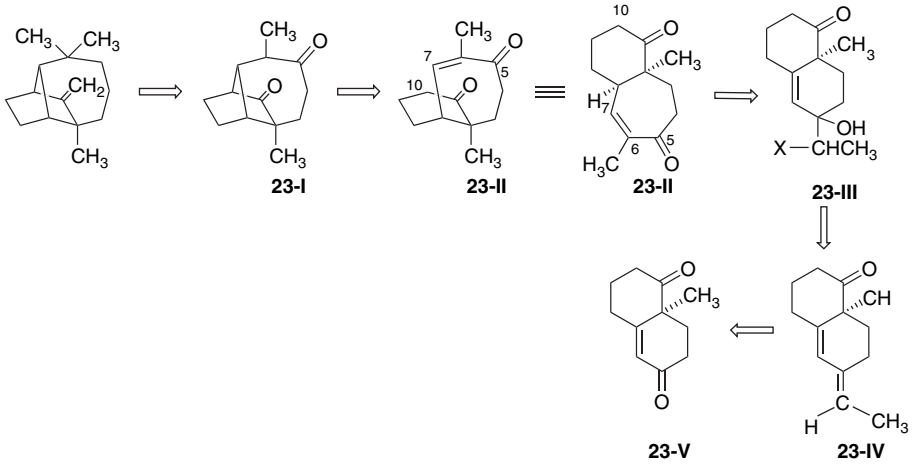
23. A. A. Drabkina and Y. S. Tsizin, *J. Gen. Chem. USSR* (English Transl.), **43**, 422, 691 (1973); R. J. Crawford, U. S. Patent, 3,676,506; *Chem. Abstr*., **77**, 113889e (1972); A. J. Birch, P. L. Macdonald, and V. H. Powell, *J. Chem. Soc. C*, 1469 (1970); B. M. Trost and Y. Tamaru, *Tetrahedron Lett*., 3797 (1975); M. Fujii, T. Aida, M. Yoshihara, and A. Ohno, *Bull. Chem. Soc. Jpn*., **63**, 1255 (1990).

but they are not independent of one another because the geometry of the ring system requires that they have a specific relative relationship. That does not mean stereochemistry can be ignored, however, since the formation of the various rings will fail if the reactants do not have the proper stereochemistry.

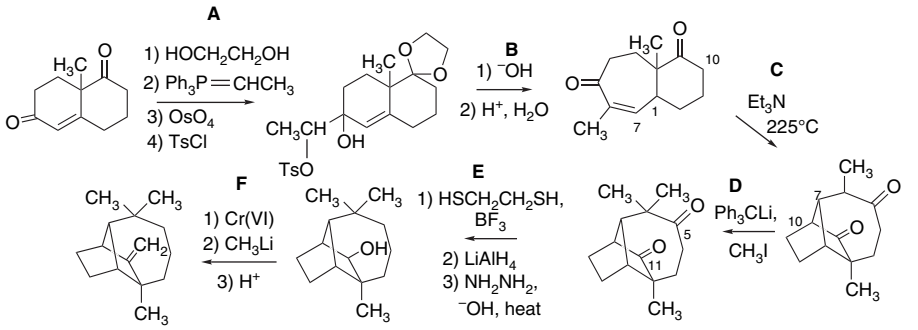


The first successful synthesis of longifolene was described in detail by E. J. Corey and co-workers in 1964. Scheme 13.23 presents a retrosynthetic analysis corresponding to this route. A key disconnection is made on going from **23-I** ⇒ **23-II**. This transformation simplifies the tricyclic to a bicyclic skeleton. For this disconnection to correspond to a reasonable synthetic step, the functionality in the intermediate to be cyclized must engender mutual reactivity between C(7) and C(10). This is achieved in diketone **23-II**, because an enolate generated by deprotonation at C(10) can undergo an intramolecular Michael addition to C(7). The stereochemistry requires that the ring junction be *cis*. Retrosynthetic Step **23-II** ⇒ **23-III** is attractive because it suggests a decalin derivative as a key intermediate. Methods for preparing this type of structure are well developed, since they are useful intermediates in the synthesis of other terpenes as well as steroids. Can a chemical reaction be recognized that would permit **23-III** ⇒ **23-II** to proceed in the synthetic sense? The hydroxy to carbonyl transformation with migration corresponds to the pinacol rearrangement (Section 10.1.2.1). The retrosynthetic transformation **23-II** ⇒ **23-III** corresponds to a workable synthetic step if the group X in **23-III** is a leaving group that could promote the rearrangement. The other transformations in the retrosynthetic plan, **23-III** ⇒ **23-IV** ⇒ **23-V**, are straightforward in concept and lead to identification of **23-V** as a potential starting material.

Scheme 13.23. Retrosynthesis of Longifolene Corresponding to the Synthesis in Scheme 13.24



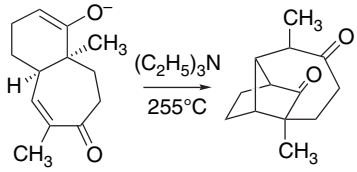
Scheme 13.24. Longifolene Synthesis: E. J. Corey and Co-Workers[a]



a. E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, **86**, 478 (1964).

Compound **23-V** is known as the Wieland-Miescher ketone and can be obtained by Robinson annulation of 2-methylcyclohexane-1,3-dione.

The synthesis was carried out as shown in Scheme 13.24. A diol was formed and selectively tosylated at the secondary hydroxy group (Step **A**-4). Base then promoted the skeletal rearrangement in Step **B**-1 by a pinacol rearrangement corresponding to **23-II** ⇒ **23-III** in the retrosynthesis. The key intramolecular Michael addition was accomplished using triethylamine under high-temperature conditions.

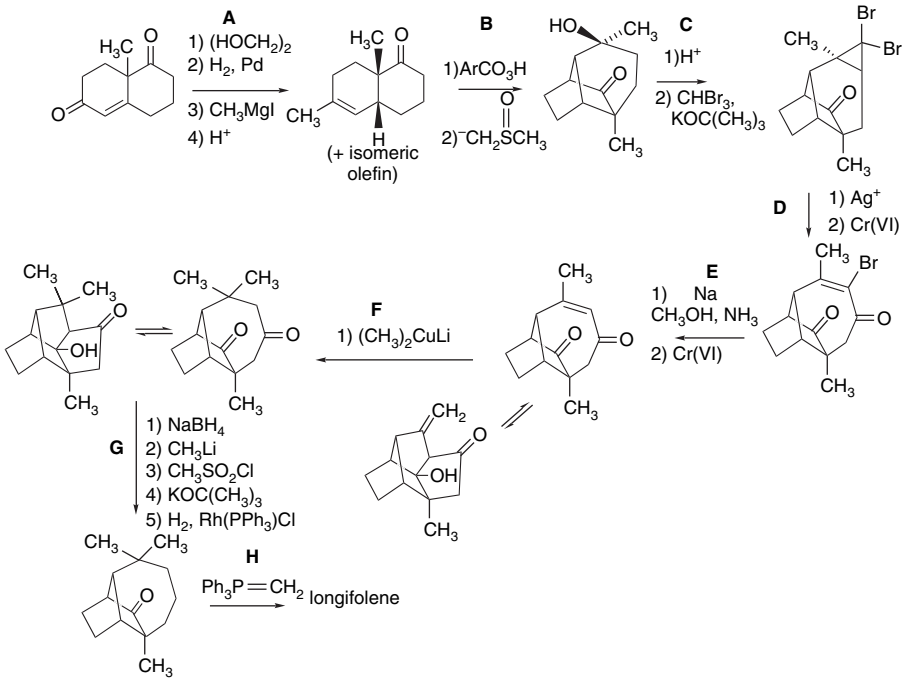


The cyclization requires that the intermediate have a *cis* ring fusion. The stereochemistry of the ring junction was established when the double bond was moved into conjugation in Step **B**-2. The product was not stereochemically characterized, and need not be, because the stereochemically important site at C(1) can be epimerized under the basic cyclization conditions. Thus, the equilibration of the ring junction through a dienol allows the cyclization to proceed to completion from either stereoisomer.

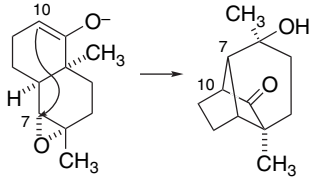
After the crucial cyclization in Step **C**, the subsequent transformations effect the addition of the remaining methyl and methylene groups by well-known methods. Step **E** accomplishes a selective reduction of one of the two carbonyl groups to a methylene by taking advantage of the difference in the steric environment of the two carbonyls. Selective protection of the less hindered C(5) carbonyl was done using a thioketal. The C(11) carbonyl was then reduced to give the alcohol, after which C(5) was reduced to a methylene group under Wolff-Kishner conditions. The hydroxy group at C(11) provided the reactive center necessary to introduce the C(15) methylene group via methyllithium addition and dehydration in Step **F**.

The Wieland-Miescher ketone was also the starting material for the synthesis in Scheme 13.25. The key bond closure was performed on a bicyclo[4.4.0]decane ring system. An enolate was used to open an epoxide ring in Step **B**-2. The ring juncture must be *cis* to permit the intramolecular epoxide ring opening. The required *cis* ring fusion was established during the catalytic hydrogenation in Step **A**.

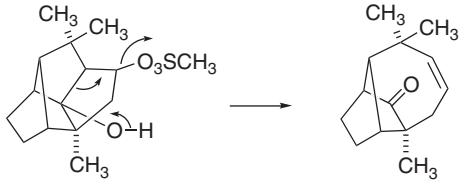
Scheme 13.25. Longifolene Synthesis: J. E. McMurry and S. J. Isser[a]



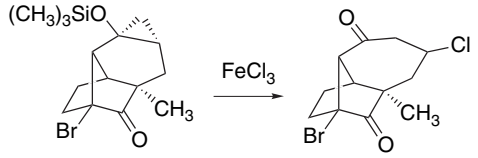
a. J. E. McMurry and S. J. Isser, *J. Am. Chem. Soc*., **94**, 7132 (1972).



The key cyclization in Step **B**-2 was followed by a sequence of steps that effected a ring expansion via a carbene addition and cyclopropyl halide solvolysis. The products of Steps **E** and **F** are interesting in that the tricyclic structures are largely converted to tetracyclic derivatives by intramolecular aldol reactions. The extraneous bond was broken in Step **G**. First a diol was formed by $NaBH_4$ reduction and this was converted via the lithium alkoxide to a monomesylate. The resulting β-hydroxy mesylate is capable of a concerted fragmentation, which occurred on treatment with potassium *t*-butoxide.

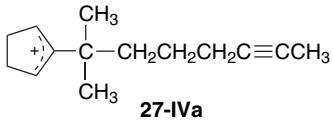


Longifolene has also been synthesized from (±) Wieland-Miescher ketone by a series of reactions that feature an intramolecular enolate alkylation and ring expansion, as shown in Scheme 13.26. The starting material was converted to a dibromo ketone via the *bis*-silyl enol ether in the first sequence of reactions. This intermediate underwent an intramolecular enolate alkylation to form the C(7)−C(10) bond. The ring expansion was then done by conversion of the ketone to a silyl enol ether, cyclopropanation, and treatment of the siloxycyclopropane with $FeCl_3$.



The final stages of the synthesis involved introduction of the final methyl group by Simmons-Smith cyclopropanation and reductive opening of the cyclopropane ring.

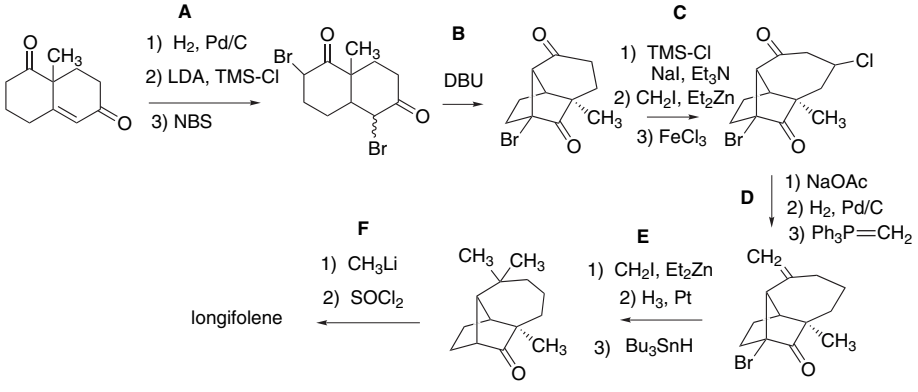
A retrosynthetic analysis corresponding to the synthesis in Scheme 13.28 is given in Scheme 13.27. The striking feature of this synthesis is the structural simplicity of the key intermediate **27-IV**. A synthesis according to this scheme generates the tricyclic skeleton in a single step from a monocyclic intermediate. The disconnection **27-III**–**27-IV** corresponds to a cationic cyclization of the highly symmetric allylic cation **27-IVa**.



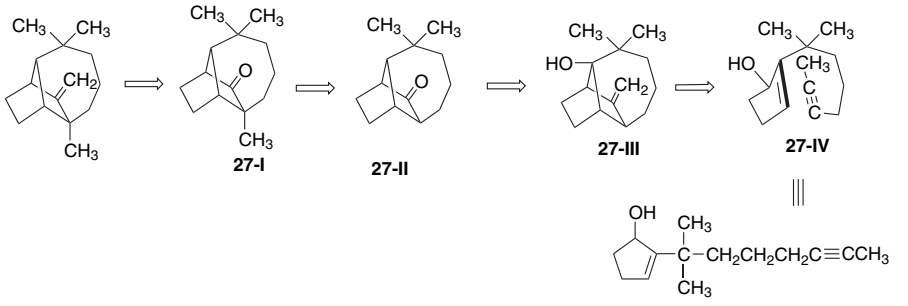
27-IVa

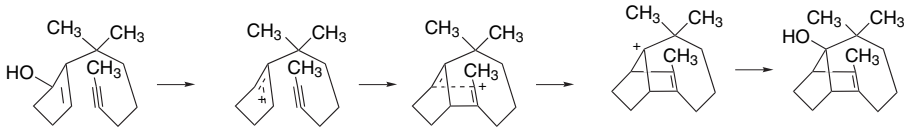
No issues of stereochemistry arise until the carbon skeleton is formed, at which point all of the stereocenters are in the proper relative relationship. The structures of the successive intermediates, assuming a stepwise mechanism for the cationic cyclization, are shown below.

Scheme 13.26. Longifolene Synthesis: S. Karimi and P. Tavares[a]



a. S. Karimi, *J. Nat. Prod.*, **64**, 406 (2001); S. Karimi and P. Tavares, *J. Nat. Prod.*, **66**, 520 (2003).

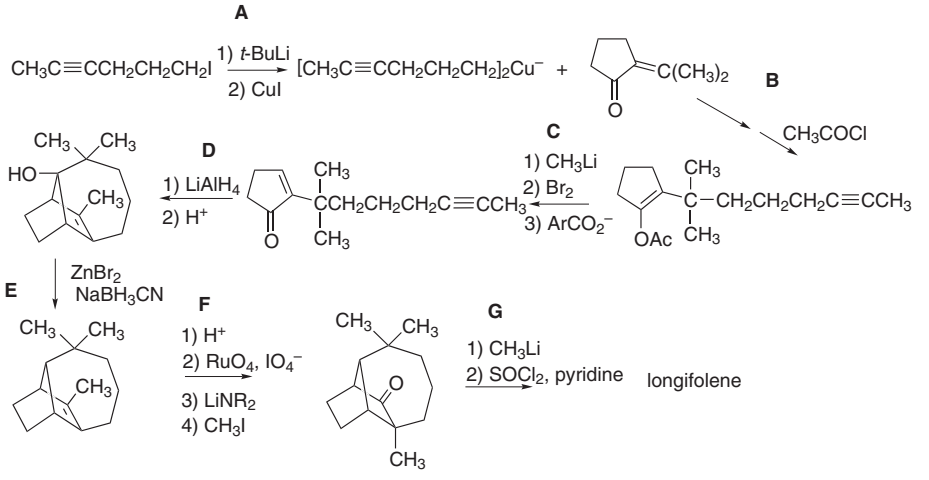




Evidently, these or closely related intermediates are accessible and reactive, since the synthesis was successfully achieved as outlined in Scheme 13.28. In addition to the key cationic cyclization in Step **D**, interesting transformations were carried out in Step **E**, where a bridgehead tertiary alcohol was reductively removed, and in Step **F**, where a methylene group, which was eventually reintroduced, had to be removed. The endocyclic double bond, which is strained because of its bridgehead location, was isomerized to the exocyclic position and then cleaved with RuO_4/IO_4^-. The enolate of the ketone was then used to introduce the C(12) methyl group in Steps **F**-3 and **F**-4.

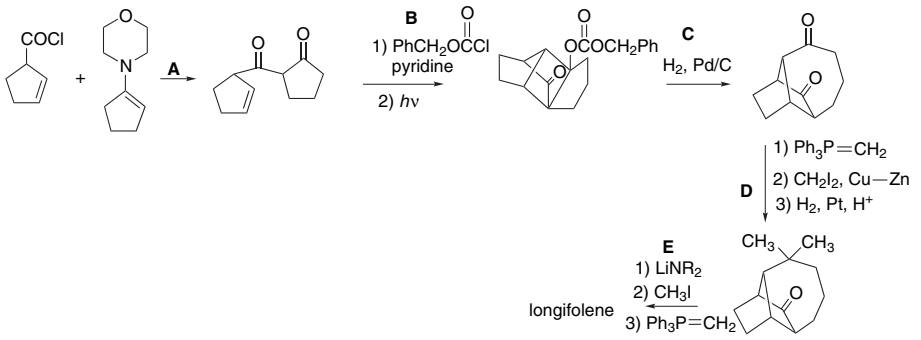
The synthesis in Scheme 13.29 also uses a remarkably simple starting material to achieve the construction of the tricyclic skeleton. A partial retrosynthesis is outlined below.

Scheme 13.28. Longifolene Synthesis: W. S. Johnson and Co-Workers[a]

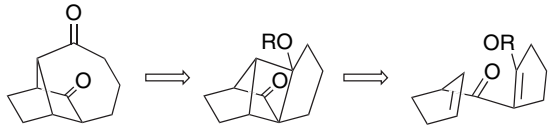


a. R. A. Volkmann, G. C. Anderson, and W. S. Johnson, *J. Am. Chem. Soc.*, **97**, 4777 (1975).

Scheme 13.29. Longifolene Synthesis: W. Oppolzer and T. Godel[a]

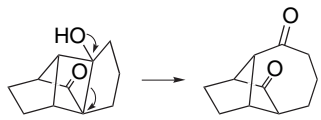


a. W. Oppolzer and T. Godel, *J. Am. Chem. Soc.*, **100**, 2583 (1978); W. Oppolzer and T. Godel, *Helv. Chim. Acta*, **67**, 1154 (1984).



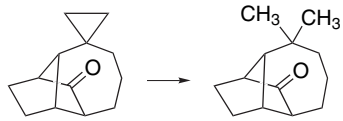
29-I **29-II** **29-III**

Intermediate **29-I** contains the tricyclic skeleton of longifolene, shorn of its substituents, but containing carbonyl groups suitably placed so that the methyl groups at C(2) and C(6) and the C(11) methylene can be introduced. The retrosynthetic Step **29-I** ⇒ **29-II** corresponds to an intramolecular aldol addition. However, **29-II** is clearly strained relative to **29-I**, and so (with OR = OH) should open to **29-I**.

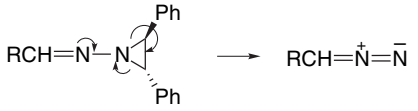


29-II **29-I**

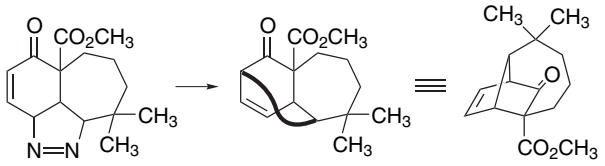
How might **29-II** be obtained? The four-membered ring suggests that a photochemical [2 + 2] cycloaddition might be useful, and this, in fact, was successful (Scheme 13.29, Step **B**). The cyclopentanone intermediate was converted to an enol carbonate. After photolysis, the carbobenzyloxy group was removed by hydrogenolysis, which led to opening of the strained aldol to the diketo intermediate. After liberation of the hydroxy group, the extra carbon-carbon bond between C(2) and C(6) was broken by a spontaneous retro-aldol reaction. Step **D** in this synthesis is an interesting way of introducing the geminal dimethyl groups. It proceeds through a cyclopropane intermediate that is cleaved by hydrogenolysis. In Step **E**, the C(12) methyl group was introduced by enolate alkylation and the C(15) methylene group was installed by a Wittig reaction.



The synthesis of longifolene in Scheme 13.30 commenced with a Birch reduction and tandem alkylation of methyl 2-methoxybenzoate (see Section 5.6.1.2). Step **C** is an intramolecular cycloaddition of a diazoalkane that is generated from an aziridinoimine intermediate.

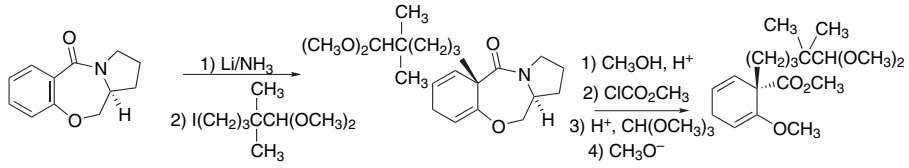


The thermolysis of the adduct generates a diradical (or the corresponding dipolar intermediate), which then closes to the desired carbon skeleton.



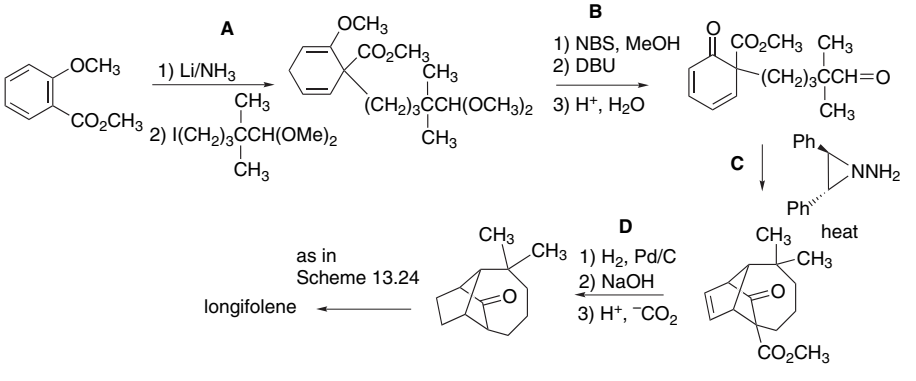
The cyclization product was converted to an intermediate that was used in the longifolene synthesis described in Scheme 12.24.

The synthesis in Scheme 13.30 was also done in such a way as to give enantiomerically pure longifolene. A starting material, whose chirality is derived from the amino acid L-proline, was enantioselectively converted to the product of Step **A** in Scheme 13.30.



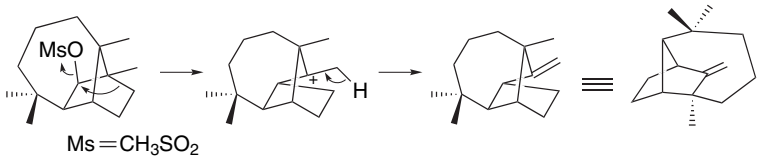
This chiral intermediate, when carried through the reaction sequence in Scheme 13.30, generated the enantiomer of natural longifolene. Thus D-proline would have to be used to generate the natural enantiomer.

Scheme 13.30. Longifolene Synthesis: A. G. Schultz and S. Puig[a]

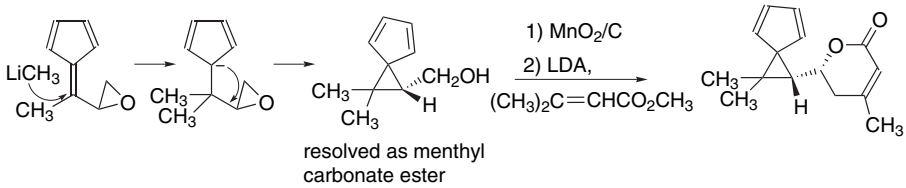


a. A. G. Schultz and S. Puig, *J. Org. Chem.*, **50**, 915 (1985).

An enantiospecific synthesis of longifolene was done starting with camphor, a natural product available in enantiomerically pure form (Scheme 13.31) The tricyclic ring was formed in Step **C** by an intramolecular Mukaiyama reaction. The dimethyl substituents were formed in Step **E-1** by hydrogenolysis of the cyclopropane ring. The final step of the synthesis involved a rearrangement of the tricyclic ring that was induced by solvolysis of the mesylate intermediate.

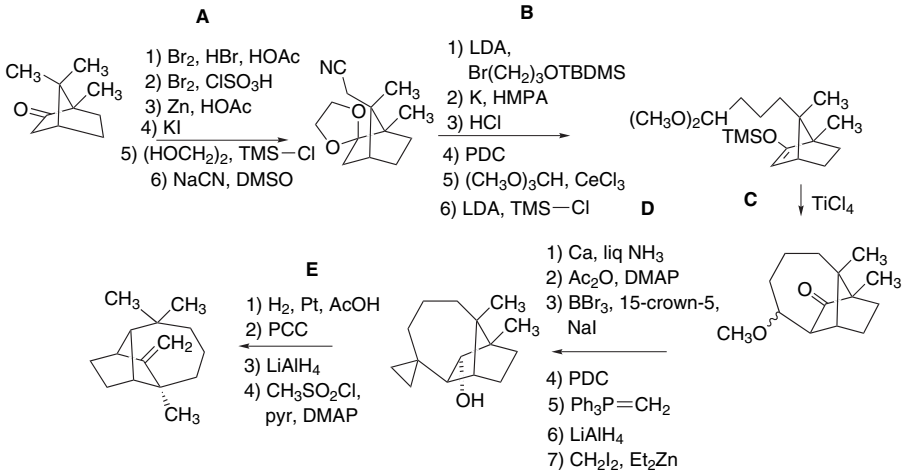


Another enantiospecific synthesis of longifolene shown in Scheme 13.32 used an intramolecular Diels-Alder reaction as a key step. An alcohol intermediate was resolved in sequence **B** by formation and separation of a menthyl carbonate. After oxidation, the dihydropyrone ring was introduced by γ-addition of the ester enolate of methyl 3-methylbutenoate, followed by cyclization.



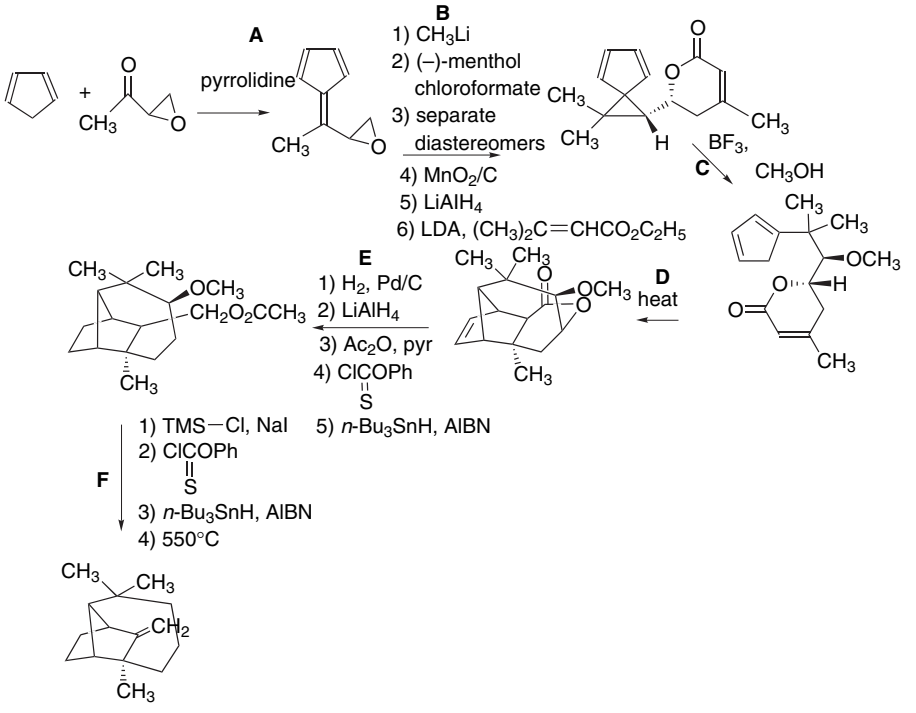
The dihydropyrone ring then served as the dienophile in the intramolecular Diels-Alder (IMDA) cycloaddition that was conducted in a microwave oven. The cyclopentadiene

Scheme 13.31. Longifolene Synthesis: D. L. Kuo and T. Money[a]



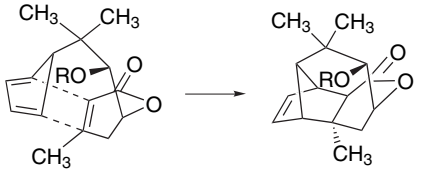
a. D. L. Kuo and T. Money, *Can. J. Chem.*, **66**, 1794 (1988).

Scheme 13.32. Longifolene Synthesis: B. Lei and A. G. Fallis[a]



a. B. Lei and A. G. Fallis, *J. Am. Chem. Soc*., **112**, 4609 (1990); B. Lei and A. G. Fallis, *J. Org. Chem*., **58**, 2186 (1993).

ring permits rapid equilibration of the diene isomers by 1,5-hydrogen shifts and the most stable IMDA TS leads to the desired product.

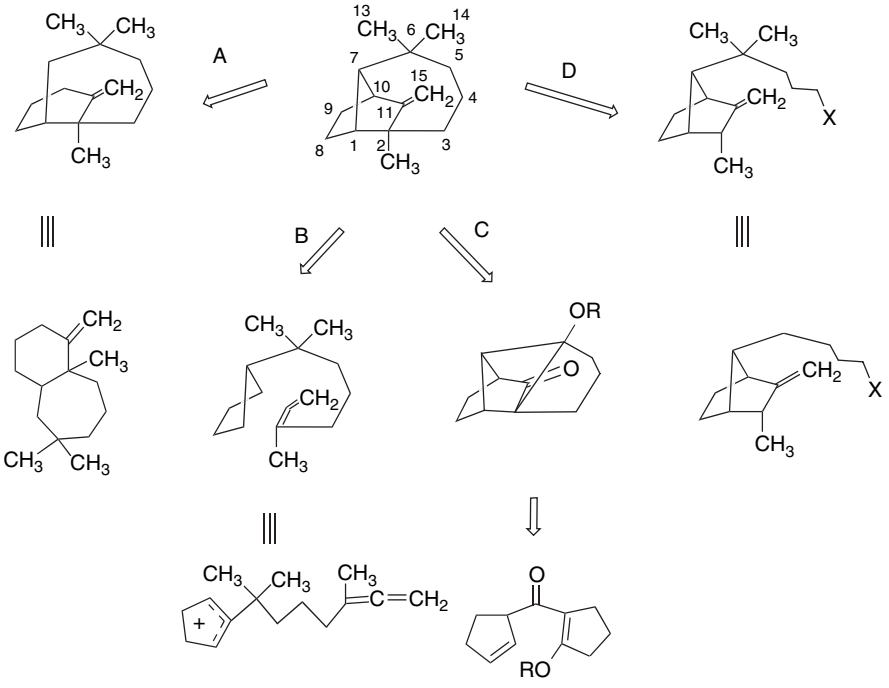


The final step of this synthesis used a high-temperature acetate pyrolysis to introduce the exocyclic double bond of longifolene.

Scheme 13.33 shows broad retrosynthetic formulations of the longifolene syntheses that are discussed in this subsection. Four different patterns of bond formation are represented. In **A**, the C(7)–C(10) bond is formed from a bicyclic intermediate. This pattern corresponds to the syntheses in Schemes 13.24, 13.25, 12.26, and 13.29. In retrosynthesis **B**, there is concurrent formation of the C(1)–C(2) and C(10)–C(11) bonds, as in the synthesis in Scheme 13.28. This is also the pattern found in the synthesis in Scheme 13.32. The synthesis in Scheme 13.29 corresponds to retrosynthesis **C**, in which the C(1)–C(2) and C(6)–C(7) bonds are formed and an extraneous bond between C(2) and C(5) is broken. Finally, retrosynthesis **D**, corresponding to formation of the C(2)–C(3) bond, is represented by the synthesis in Scheme 13.31.

These syntheses of longifolene provide good examples of the approaches that are available for construction of polycyclic ring compounds. In each case, a set of

Scheme 13.33. Summary of Some Retrosynthetic Patterns in Longifolene Syntheses



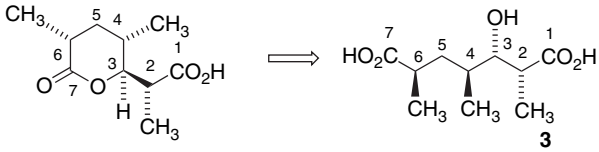
functionalities that have the potential for *intramolecular* reaction was assembled. After assembly of the carbon framework, the final functionality changes were effected. It is the necessity for the formation of the carbon skeleton that determines the functionalities that are present at the ring-closure stage. After the ring structure is established, necessary adjustments of the functionalities are made.

13.2.3. Prelog-Djerassi Lactone

The Prelog-Djerassi lactone (abbreviated here as P-D lactone) was originally isolated as a degradation product during structural investigations of antibiotics. Its open-chain equivalent **3** is typical of the methyl-branched carbon chains that occur frequently in macrolide and polyether antibiotics. The compound serves as a test case for the development of methods of control of stereochemistry in such polymethylated structures. There have been more than 20 different syntheses of P-D lactone.[24] We focus here on some of those that provide enantiomerically pure product, as they illustrate several of the methods for enantioselective synthesis.[25]

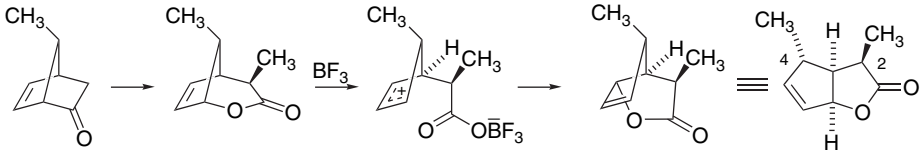
[24] For references to many of these syntheses, see S. F. Martin and D. G. Guinn, *J. Org. Chem*., **52**, 5588 (1987); H. F. Chow and I. Fleming, *Tetrahedron Lett*., **26**, 397 (1985); S. F. Martin and D. E. Guinn, *Synthesis*, 245 (1991).

[25] For other syntheses of enantiomerically pure Prelog-Djerassi lactone, see F. E. Ziegler, A. Kneisley, J. K. Thottathil, and R. T. Wester, *J. Am. Chem. Soc*., **110**, 5434 (1988); A. Nakano, S. Takimoto, J. Inanaga, T. Katsuki, S. Ouchida, K. Inoue, M. Aiga, N. Okukado, and M. Yamaguchi, *Chem. Lett*., 1019 (1979); K. Suzuki, K. Tomooko, T. Matsumoto, E. Katayama, and G. Tsuchihashi, *Tetrahedron*



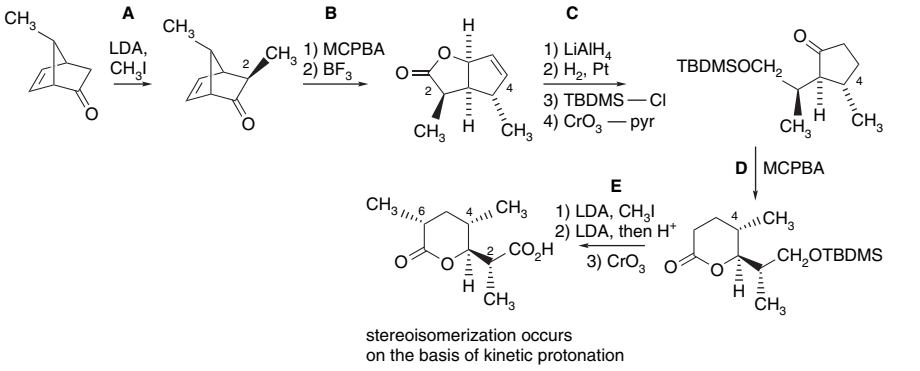
3

The synthesis in Scheme 13.34 is based on a bicyclic starting material that can be prepared in enantiomerically pure form. In the synthesis, C(7) of the norbornenone starting material becomes C(4) of P-D lactone and the methyl group in the starting material becomes the C(4) methyl substituent. The sequence uses the cyclic starting material to control facial selectivity. The configuration of the C(3) hydroxy and C(2) and C(6) methyl groups must be established relative to the C(4) stereocenter. The *exo*-selective alkylation in Step **A** established the configuration at C(2). The Baeyer-Villiger oxidation in Step **B** was followed by a Lewis acid–mediated allylic rearrangement, which is suprafacial. This stereoselectivity is dictated by the preference for maintaining a *cis* ring juncture at the five-membered rings.



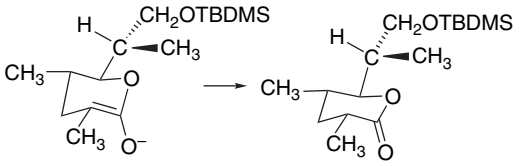
The stereochemistry of the C(3) hydroxy was established in Step **D**. The Baeyer-Villiger oxidation proceeds with retention of configuration of the migrating group (see Section 12.5.2), so the correct stereochemistry is established for the C−O bond. The final stereocenter for which configuration must be established is the methyl group at C(6) that was introduced by an enolate alkylation in Step **E**, but this reaction was not very stereoselective. However, since this center is adjacent to the lactone carbonyl, it can be epimerized through the enolate. The enolate was formed and quenched with acid. The kinetically preferred protonation from the axial direction provides the correct stereochemistry at C(6).

Scheme 13.34. Prelog-Djerassi Lactone Synthesis: P. A. Grieco and Co-Workers[a]

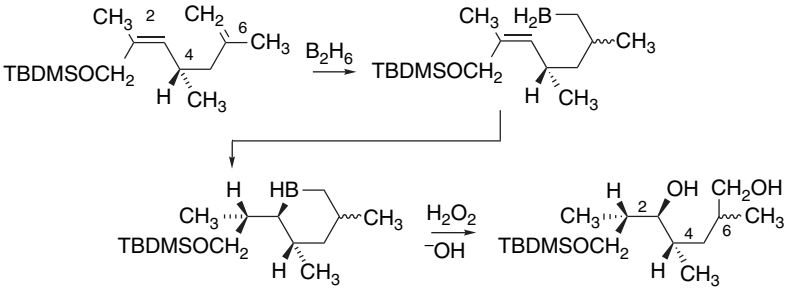


a. P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *J. Am. Chem. Soc*., **101**, 4749 (1979).

Lett., **26**, 3711 (1985); M. Isobo, Y. Ichikawa, and T. Goto, *Tetrahedron Lett*., **22**, 4287 (1981); M. Mori, T. Chuman, and K. Kato, *Carbohydrate Res*., **129**, 73 (1984).



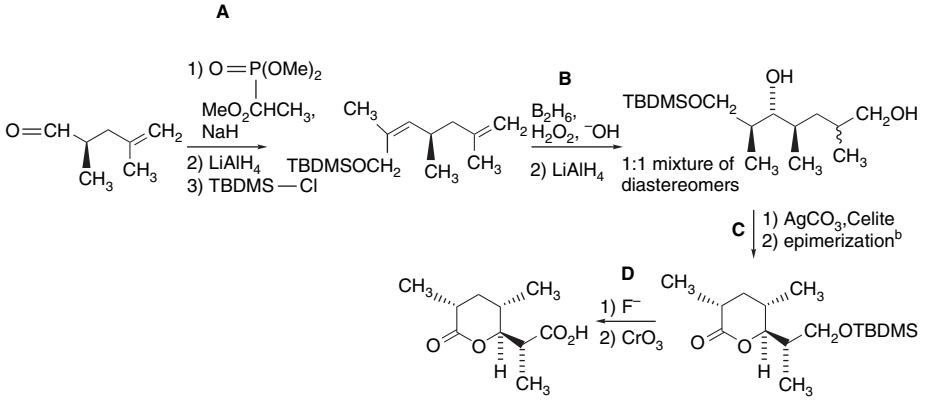
Another synthesis of P-D lactone that is based on an enantiomerically pure starting material is shown in Scheme 13.35. The stereocenter in the starting material is destined to become C(4) in the final product. Steps **A** and **B** served to extend the chain to provide a seven-carbon 1,5-diene. The configuration of two of the three remaining stereocenters is controlled by the hydroboration step, which is a stereospecific *syn* addition (Section 4.5.1). In 1,5-dienes of this type, an intramolecular hydroboration occurs and establishes the configuration of the two newly formed C−B and C−H bonds.



There was, however, no significant selectivity in the initial hydroboration of the terminal double bond. As a result, both configurations are formed at C(6). This problem was overcome using the epimerization process from Scheme 13.34.

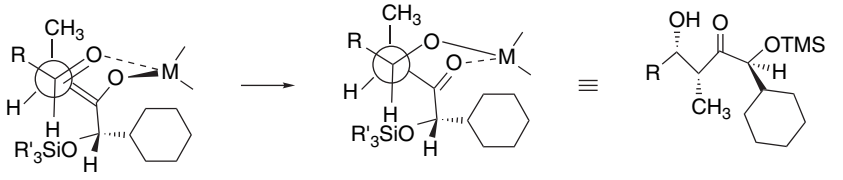
The syntheses in Schemes 13.36 to 13.40 are conceptually related. They begin with symmetric achiral derivatives of *meso*-2,4-dimethylglutaric acid and utilize various approaches to the *desymmetrization* of the *meso* starting material. In Scheme 13.36

Scheme 13.35. Prelog-Djerassi Lactone Synthesis: W. C. Still and K. R. Shaw[a]



a. W. C. Still and K. R. Shaw, *Tetrahedron Lett.*, **22**, 3725 (1981).
b. Epimerization as in Scheme 13.34.

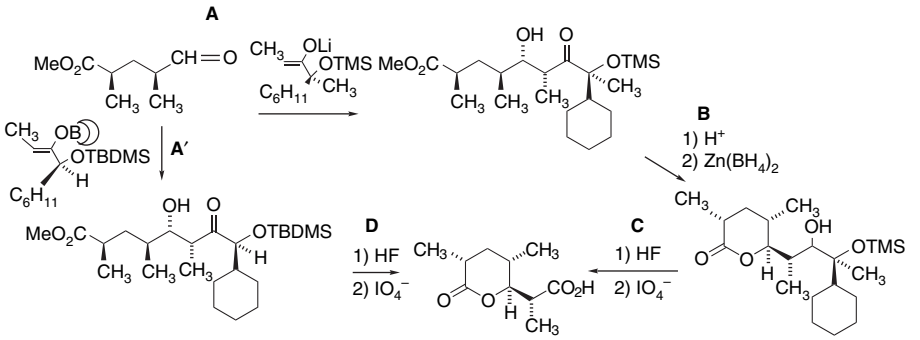
the starting material was prepared by reduction of the half-ester of *meso*-2,4-dimethylglutaric acid. The use of the *meso*-diacid ensures the correct *relative configuration* of the C(4) and C(6) methyl substituents. The half-acid was resolved and the correct enantiomer was reduced to the aldehyde. The stereochemistry at C(2) and C(3) was established by stereoselective aldol condensation methodology. Both the lithium enolate and the boron enolate methods were employed. The use of bulky enolates enhances the stereoselectivity. The enol derivatives were used in enantiomerically pure form so the condensations are examples of *double stereodifferentiation* (Section 2.1.5.3). The stereoselectivity observed in the reactions is that predicted by a cyclic TS for the aldol condensations.



The synthesis in Scheme 13.37 also used a *meso*-3,4-dimethylglutaric acid as the starting material. Both the resolved aldehyde employed in Scheme 13.36 and a resolved half-amide were successfully used as intermediates. The configuration at C(2) and C(3) was controlled by addition of a butenylborane to an aldehyde (see Section 9.1.5). The boronate was used in enantiomerically pure form so that stereoselectivity was enhanced by *double stereodifferentiation*. The allylic additions carried out by the butenylboronates do not appear to have been quite as highly stereoselective as the aldol condensations used in Scheme 13.36, since a minor diastereoisomer was formed in the boronate addition reactions.

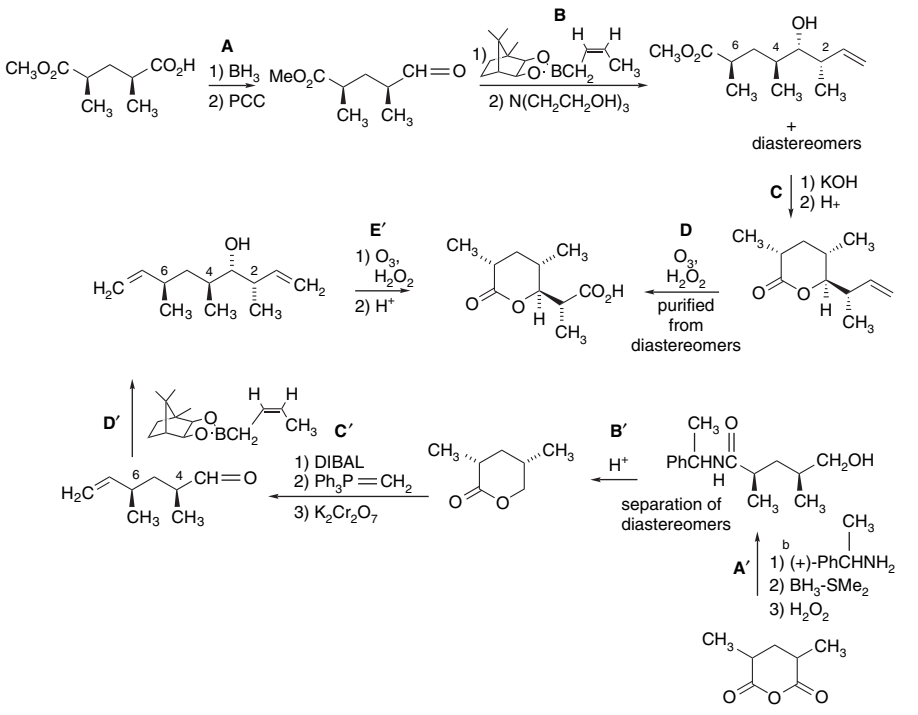
The synthesis in Scheme 13.38 is based on an interesting kinetic differentiation in the reactivity of two centers that are structurally identical, but diastereomeric. A *bis*-amide of *meso*-2,4-dimethylglutaric acid and a chiral thiazoline was formed in Step **A**. The thiazoline is derived from the amino acid cysteine. The two amide carbonyls in this *bis*-amide are nonequivalent by virtue of the diastereomeric relationship established

Scheme 13.36. Prelog-Djerassi Lactone Synthesis: S. Masamune and Co-Workers[a]



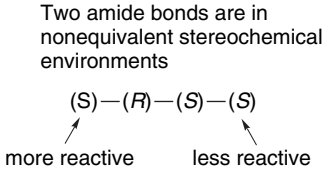
a. S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980); S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, *J. Am. Chem. Soc.*, **103**, 1568 (1981).

Scheme 13.37. Prelog-Djerassi Lactone Synthesis: R. W. Hoffmann and Co-Workers[a]



a. R. W. Hoffmann, H.-J. Zeiss, W. Ladner, and S. Tabche, *Chem. Ber.*, **115**, 2357 (1982).
b. Resolved via α-phenylethylamine salt; S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980).

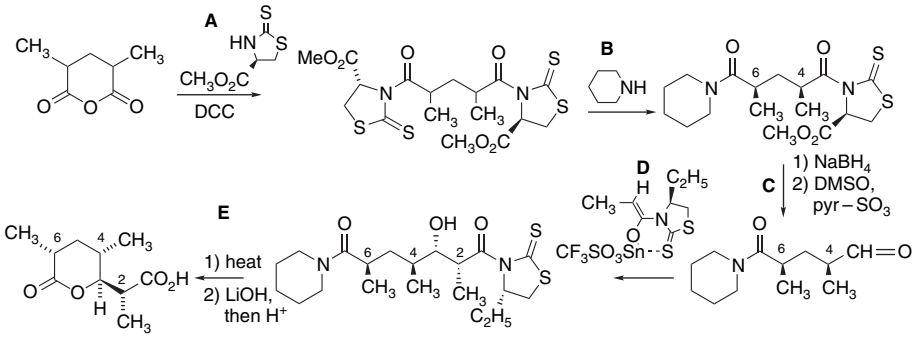
by the stereogenic centers at C(2) and C(4) in the glutaric acid portion of the structure. One of the centers reacted with a 97:3 preference with the achiral amine piperidine.



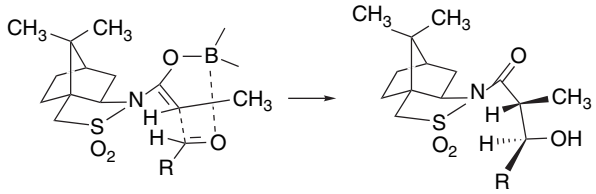
In Step **D** another thiazoline chiral auxiliary, also derived from cysteine, was used to achieve double stereodifferentiation in an aldol addition. A tin enolate was used. The stereoselectivity of this reaction parallels that of aldol reactions carried out with lithium or boron enolates. After the configuration of all the centers was established, the synthesis proceeded to P-D lactone by functional group modifications.

A very short and efficient synthesis based on the desymmetrization principle is shown in Scheme 13.39. *meso*-2,4-Dimethylglutaraldehyde reacted selectively with the diethylboron enolate derived from a bornanesultam chiral auxiliary. This reaction established the stereochemistry at the C(2) and C(3) centers. The dominant aldol product results from an anti-Felkin stereoselectivity with respect to the C(4) center.

Scheme 13.38. Prelog-Djerassi Lactone Synthesis: Y. Nagao and Co-Workers[a]



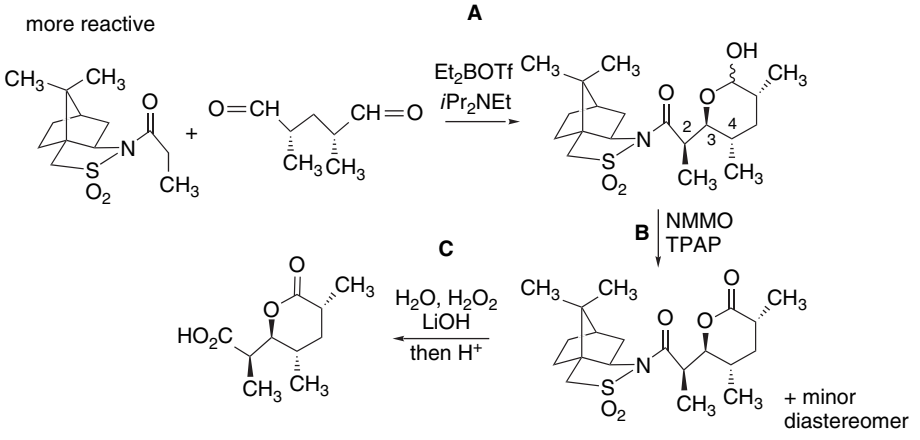
a. Y. Nagao, T. Inoue, K. Hashimoto, Y. Hagiwara, M. Ochai, and E. Fujita, *J. Chem. Soc., Chem. Commun*., 1419 (1985).



The adduct cyclized to a lactol mixture that was oxidized by TPAP-NMMO to give the corresponding lactones in an 8:1 ratio (86% yield). Hydrolysis in the presence of H_2O_2 gave the P-D lactone and recovered chiral auxiliary.

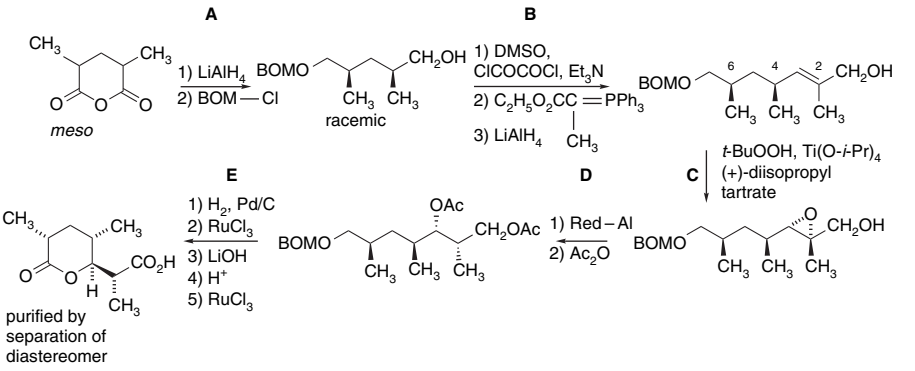
The synthesis in Scheme 13.40 features a catalytic asymmetric epoxidation (see Section 12.2.1.2). By use of *meso*-2,4-dimethylglutaric anhydride as the starting material, the proper relative configuration at C(4) and C(6) is ensured. The epoxidation directed by the (+)-tartrate catalyst controls the configuration established at C(2) and C(3) by the epoxidation. Although the epoxidation is highly selective in

Scheme 13.39. Prelog-Djerassi Lactone Synthesis: W. Oppolzer and Co-Workers[a]



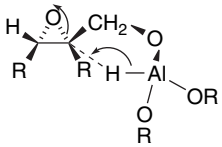
a. W. Oppolzer, E. Walther, C. Perez Balado, and J. De Brabander, *Tetrahedron Lett*., **38**, 809 (1997).

Scheme 13.40. Prelog-Djerassi Lactone Synthesis: M. Yamaguchi and Co-Workers[a]

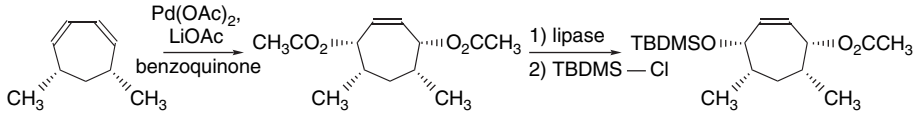


a. M. Honda, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett*., **25**, 3857 (1984).

establishing the configuration at C(2) and C(3), the configuration at C(4) and C(6) does not strongly influence the reaction; a mixture of diastereomeric products was formed and then separated at a later stage in the synthesis. The reductive ring opening in Step **D** occurs with dominant inversion to establish the necessary (*R*)-configuration at C(2). The preference for 1,3-diol formation is characteristic of reductive ring opening by Red-Al of epoxides derived from allylic alcohols.[26] Presumably, initial coordination at the hydroxy group and intramolecular delivery of hydride is responsible for this stereoselectivity.



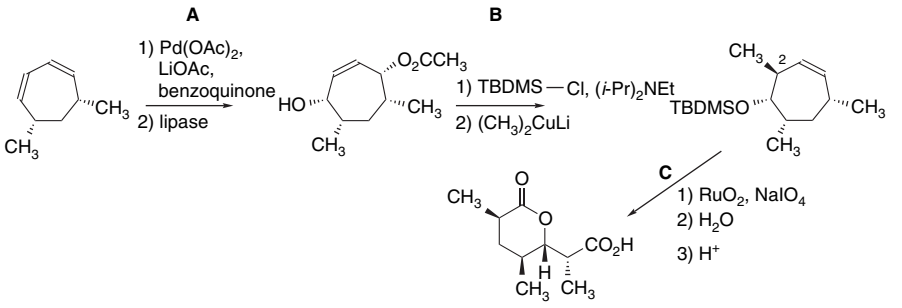
The synthesis in Scheme 13.41 is also built on the desymmetrization concept but uses a very different intermediate. *cis*-5,7-Dimethylcycloheptadiene was acetoxylated with $Pd(OAc)_2$ and the resulting all-*cis*-diacetate intermediate was enantioselectively hydrolyzed with a lipase to give a monoacetate that was protected as the TBDMS ether. An *anti* S_N2' displacement by dimethyl cuprate established the correct configuration of the C(2) methyl substituent. Oxidative ring cleavage and lactonization gave the final product.



There have been several syntheses of P-D lactone that were based on carbohydrate-derived starting materials. The starting material used in Scheme 13.42 was prepared from a carbohydrate produced in earlier work.[27] The relative stereochemistry at C(4)

26. P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, and S. M. Viti, *J. Org. Chem*., **47**, 1378 (1982); S. M. Viti, *Tetrahedron Lett*., **23**, 4541 (1982); J. M. Finan and Y. Kishi, *Tetrahedron Lett*., **23**, 2719 (1982).
27. M. B. Yunker, D. E. Plaumann, and B. Fraser-Reid, *Can. J. Chem*., **55**, 4002 (1977).

Scheme 13.41. Prelog-Djerassi Lactone Synthesis: A. J. Pearson and Y.-S. Lai[a]



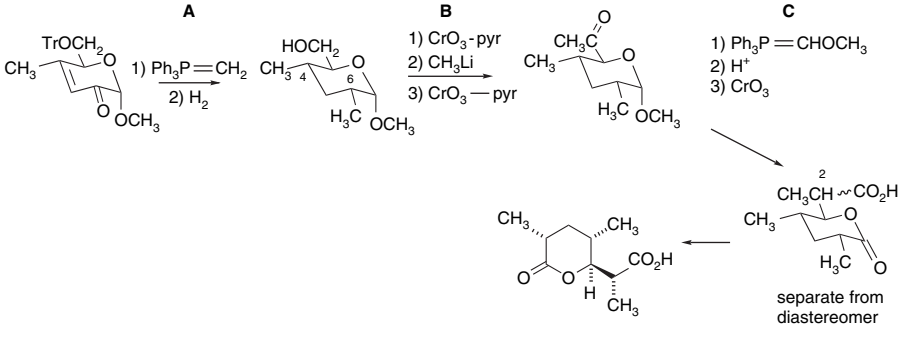
a. A. J. Pearson and Y.-S. Lai, *J. Chem. Soc., Chem. Commun*., 442 (1988).

and C(6) was established by the hydrogenation in Step **A**-2. This *syn* hydrogenation is not completely stereoselective, but provided a 4:1 mixture favoring the desired stereoisomer. The stereoselectivity is presumably the result of preferential absorption from the less hindered β-face of the molecule. The configuration of C(2) was established by protonation during the hydrolysis of the enol ether in Step **C**-2. This step was not stereoselective, so a separation of diastereomers after the oxidation in Step **C**-3 was required.

The synthesis in Scheme 13.43 also began with carbohydrate-derived starting material and uses catalytic hydrogenation in Step **C**-1 to establish the stereochemical relationship between the C(4) and C(6) methyl groups. As was the case in Scheme 13.42, the configuration at C(2) was not controlled in this synthesis and separation of the diastereomeric products was necessary. This synthesis used an organocopper reagent to introduce both the C(4) and C(2) methyl groups. The former was introduced by S_N2' allylic substitution in Step **B** and the latter by conjugate addition to a nitroalkene in Step **D**.

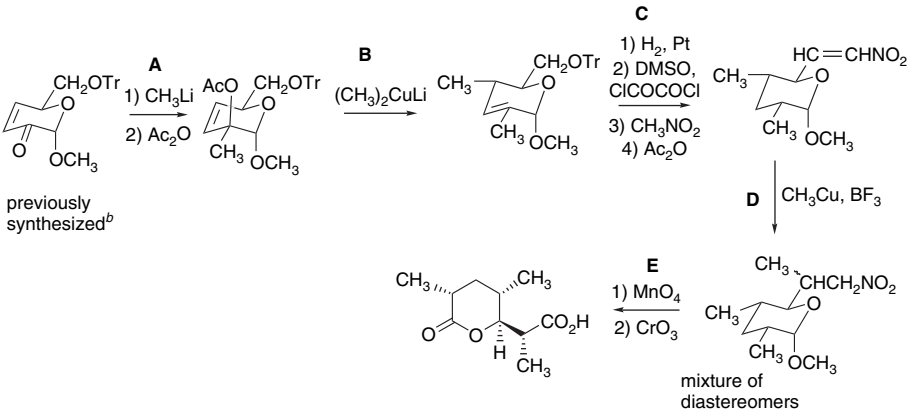
The synthesis in Scheme 13.44 is also based on a carbohydrate-derived starting material. It controlled the stereochemistry at C(2) by means of the stereoselectivity of the Ireland-Claisen rearrangement in Step **A** (see Section 6.4.2.3). The ester enolate was formed under conditions in which the *E*-enolate is expected to predominate. Heating the resulting silyl enol ether gave a 9:1 preference for the expected stereoisomer. The

Scheme 13.42. Prelog-Djerassi Lactone Synthesis: S. Jarosz and B. Fraser-Reid[a]



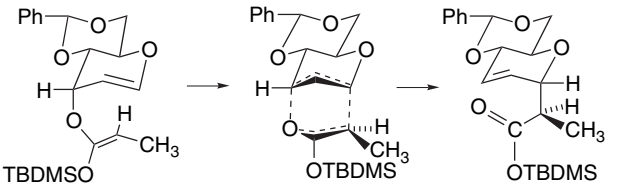
a. S. Jarosz and B. Fraser-Reid, *Tetrahedron Lett*., **22**, 2533 (1981).

Scheme 13.43. Prelog-Djerassi Lactone Synthesis: N. Kawauchi and H. Hashimoto[a]



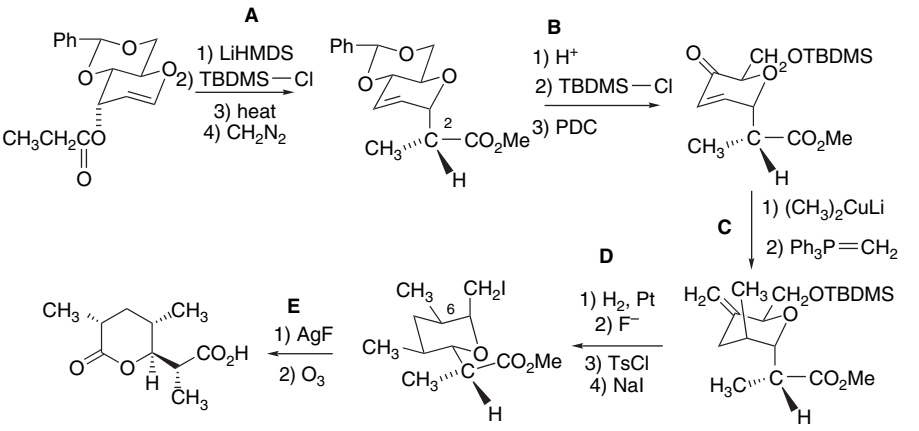
a. N. Kawauchi and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **60**, 1441 (1987).
b. N. L. Holder and B. Fraser-Reid, *Can. J. Chem.*, **51**, 3357 (1973).

preferred TS, which is boatlike, minimizes the steric interaction between the bulky silyl substituent and the ring structure.



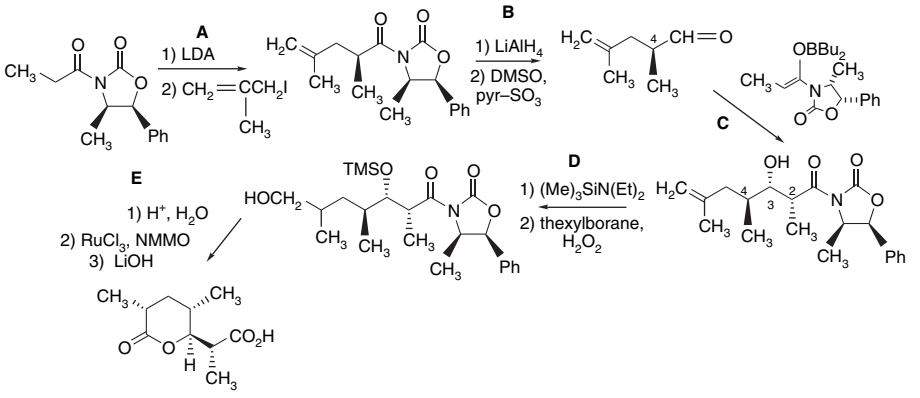
The stereochemistry at C(4) and C(6) was then established. The cuprate addition in Step **C** occurred *anti* to the substituent at C(2) of the pyran ring. After a Wittig

Scheme 13.44. Prelog-Djerassi Lactone Synthesis: R. E. Ireland and J. P. Daub[a]



a. R. E. Ireland and J. P. Daub, *J. Org. Chem.*, **46**, 479 (1981).

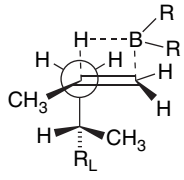
Scheme 13.45. Prelog-Djerassi Lactone Synthesis: D. A. Evans and J. Bartroli[a]



a. D. A. Evans and J. Bartroli, *Tetrahedron Lett*., **23**, 807 (1982).

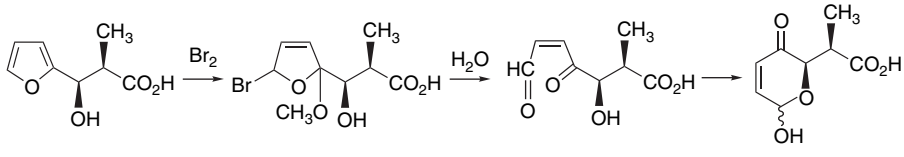
methylenation, the catalytic hydrogenation in Step **D** established the stereochemistry at C(6). The lactone carbonyl was introduced by β-elimination and ozonolysis.

The syntheses in Schemes 13.45 and 13.46 illustrate the use of oxazolidinone chiral auxiliaries in enantioselective synthesis. Step **A** in Scheme 13.45 established the configuration at the carbon that becomes C(4) in the product. This is an enolate alkylation in which the steric effect of the oxazolidinone chiral auxiliary directs the approach of the alkylating group. Step **C** also used the oxazolidinone structure. In this case, the enol borinate is formed and condensed with an aldehyde intermediate. This stereoselective aldol addition established the configuration at C(2) and C(3). The configuration at the final stereocenter at C(6) was established by the hydroboration in Step **D**. The selectivity for the desired stereoisomer was 85:15. Stereoselectivity in the same sense has been observed for a number of other 2-methylalkenes in which the remainder of the alkene constitutes a relatively bulky group.[28] A TS such as **45-A** can rationalize this result.



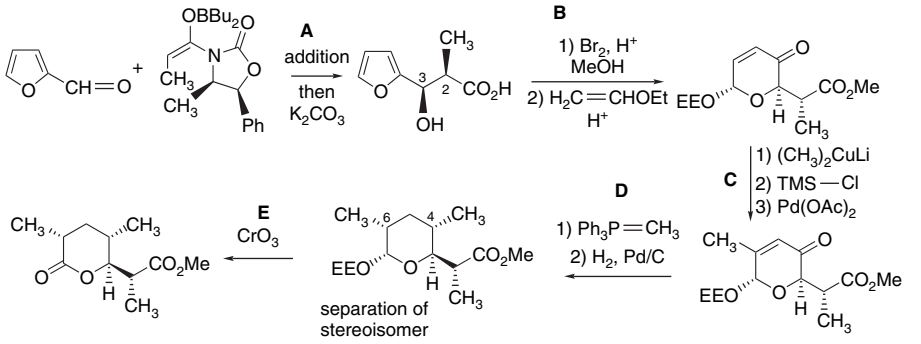
45-A

In the synthesis in Scheme 13.46, a stereoselective aldol addition was used to establish the configuration at C(2) and C(3) in Step **A**. The furan ring was then subjected to an electrophilic addition and solvolytic rearrangement in Step **B**.



28. D. A. Evans, J. Bartroli, and T. Godel, *Tetrahedron Lett*., **23**, 4577 (1982).

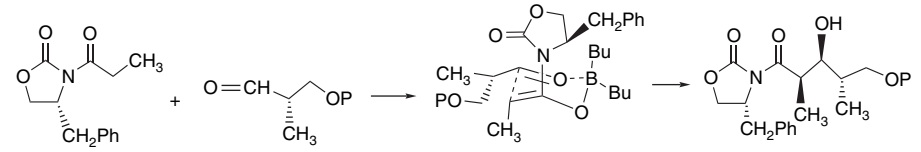
Scheme 13.46. Prelog-Djerassi Lactone Synthesis: S. F. Martin and D. E. Guinn[a]



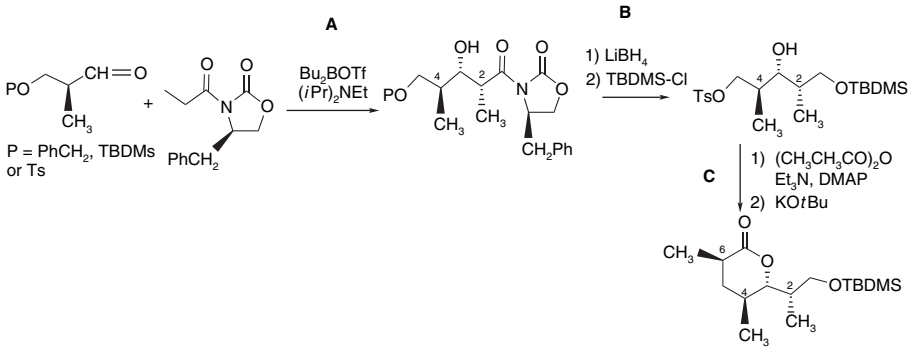
a. S. F. Martin and D. E. Guinn, *J. Org. Chem.*, **52**, 5588 (1987).

The protection of the hemiacetal hydroxyl in Step **B-2** was followed by a purification of the dominant stereoisomer. In Step **C**-1, the addition of the C(6) methyl group gave predominantly the undesired α-stereoisomer. The enolate was trapped as the trimethylsilyl ether and oxidized to the enone by $Pd(OAc)_2$. The enone from sequence **C** was then subjected to a Wittig reaction. As in several of the other syntheses, the hydrogenation in Step **D**-2 was used to establish the configuration at C(4) and C(6).

The synthesis in Scheme 13.47 was also based on use of a chiral auxiliary and provided the TBDMS-protected derivative of P-D lactone in the course of synthesis of the macrolide portion of the antibiotic 10-deoxymethymycin. The relative stereochemistry at C(2)–C(3) was obtained by addition of the dibutylboron enolate of an *N*-propanoyl oxazolidinone. The addition occurs with *syn* anti-Felkin stereochemistry.

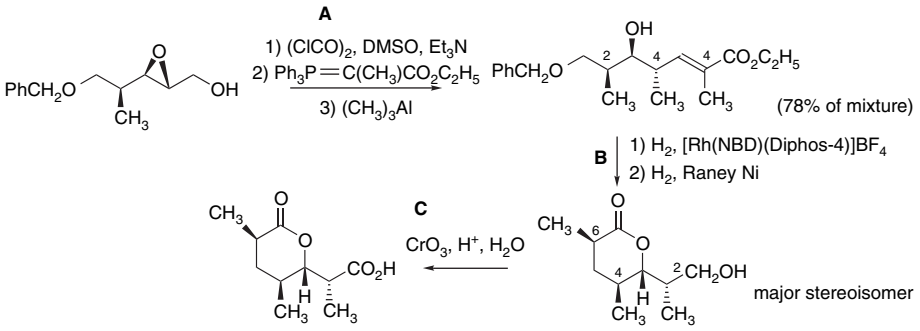


Scheme 13.47. Prelog-Djerassi Lactone Synthesis: R. A. Pilli and Co-Workers[a]



a. R. A. Pilli, C. K. Z. de Andrade, C. R. O. Souto, and A. de Meijere, *J. Org. Chem.*, **63**, 7811 (1998).

Scheme 13.48. Prelog-Djerassi Lactone Synthesis: M. Miyashita and Co-Workers[a]



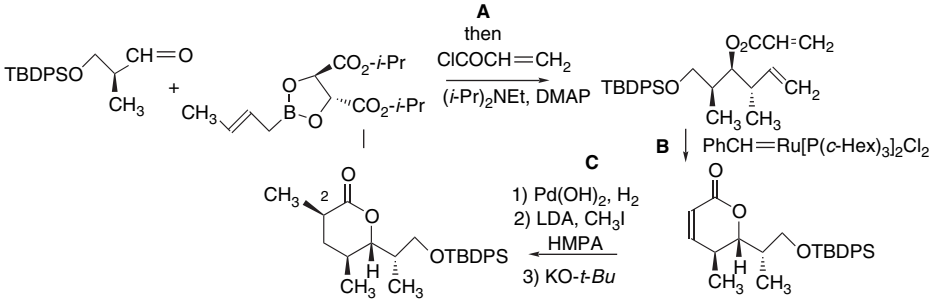
a. M. Miyashita, M. Hoshino, A. Yoshikoshi, K. Kawamine, K. Yoshihara, and H. Irie, *Chem. Lett*., 1101 (1992).

Removal of the chiral auxiliary and reduction gave an intermediate that had differentiated terminal hydroxy groups. Although the sequence was initially carried out on the benzyl or TBDMS-protected aldehyde, with subsequent removal of the protecting group, it was found that the aldol addition could be carried out directly on the tosylate, providing a shorter route. A propanoyl group was added at Step **C**-1 and provided the remainder of the carbon chain. The lactone ring was closed by an intramolecular enolate alkylation. This step is not highly stereoselective, but equilibration (see Scheme 13.34) gave the desired stereoisomer in a 10:1 ratio.

The synthesis in Scheme 13.48 used stereospecific ring opening of an epoxide by trimethylaluminum to establish the stereochemistry of the C(4) methyl group. The starting material was made by enantiospecific epoxidation of the corresponding allylic alcohol.[29] The hydrogenation in Step **B**-1 achieved about 3:1 stereoselectivity at C(2). Removal of the benzyl protecting group by hydrogenolysis then gave the lactone.

The synthesis in Scheme 13.49 features use of an enantioselective allylic boronate reagent derived from diisopropyl tartrate to establish the C(4) and C(5) stereochemistry. The ring is closed by an olefin metathesis reaction. The C(2) methyl group was introduced by alkylation of the lactone enolate. The alkylation is not stereoselective, but base-catalyzed epimerization favors the desired stereoisomer by 4:1.

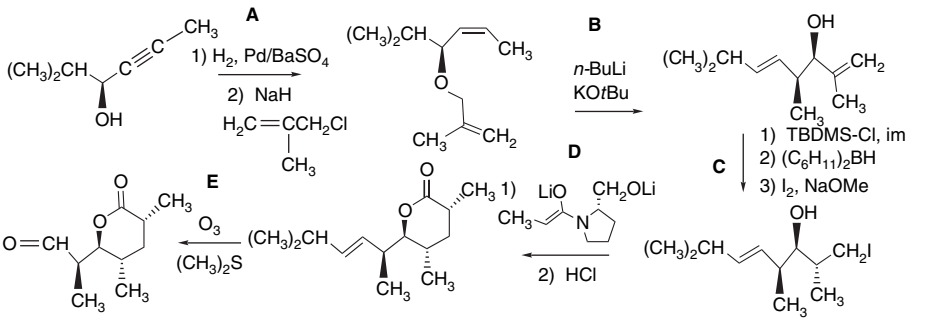
Scheme 13.49. Prelog-Djerassi Lactone Synthesis: J. Cossy, D. Bauer, and V. Bellosta[a]



a. J. Cossy, D. Bauer, and V. Bellosta, *Tetrahedron Lett*., **40**, 4187 (1999).

29. H. Nagaoka and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).

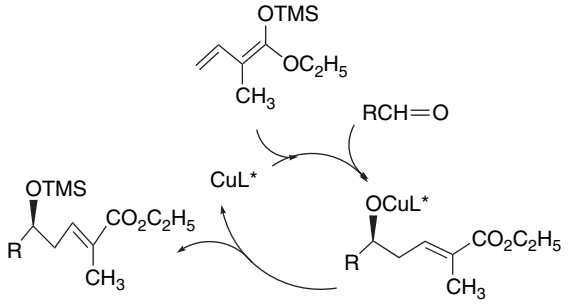
Scheme 13.50. Prelog-Djerrasi Lactone Synthesis: D. J.-S. Tsai and M. M. Midland[a]



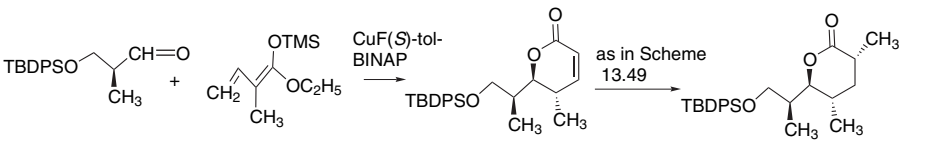
a. D. J.-S. Tsai and M. M. Midland, *J. Am. Chem. Soc.*, **107**, 3915 (1985).

The synthesis in Scheme 13.50 used the stereoselectivity of a [2,3]-sigmatropic rearrangement as the basis of stereochemical control. The starting material was prepared by enantioselective reduction of the corresponding ketone using *S*-Alpine-Borane. The sigmatropic rearrangement of the lithium anion in Step **B** gave 97:3 stereoselectivity for the *syn* isomer (see p. 588). After protection, this intermediate was selectively hydroborated with $(C_6H_{11})_2BH$ and converted to the iodide. The hydroboration in Step **C**-2 establishes the stereochemistry at C(4) with 15:1 stereoselectivity. The iodide was then used in conjunction with a chiral auxiliary to create the C(2)–C(3) bond by alkylation of the amide enolate.

A recent synthesis of P-D lactone (Scheme 13.51) used an enantioselective catalytic approach. A conjugate addition of a silyl ketene acetal derived from an unsaturated ester gave an unsaturated lactone intermediate. The catalyst is CuF-(*S*)-tol-BINAP.[30] The catalytic cycle for the reaction is shown below.



Scheme 13.51. Prelog-Djerassi Lactone Synthesis: J.-M. Campagne and Co-Workers[a]

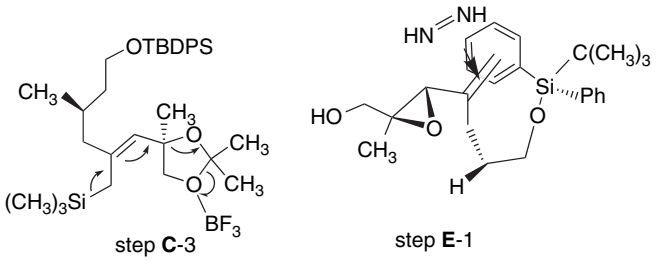


a. G. Bluet, B. Bazan-Tejeda, and J.-M. Campagne, *Org. Lett.*, **3**, 3807 (2001).

30. J. Krueger and E. M. Carreira, *J. Am. Chem. Soc.*, **120**, 837 (1998).

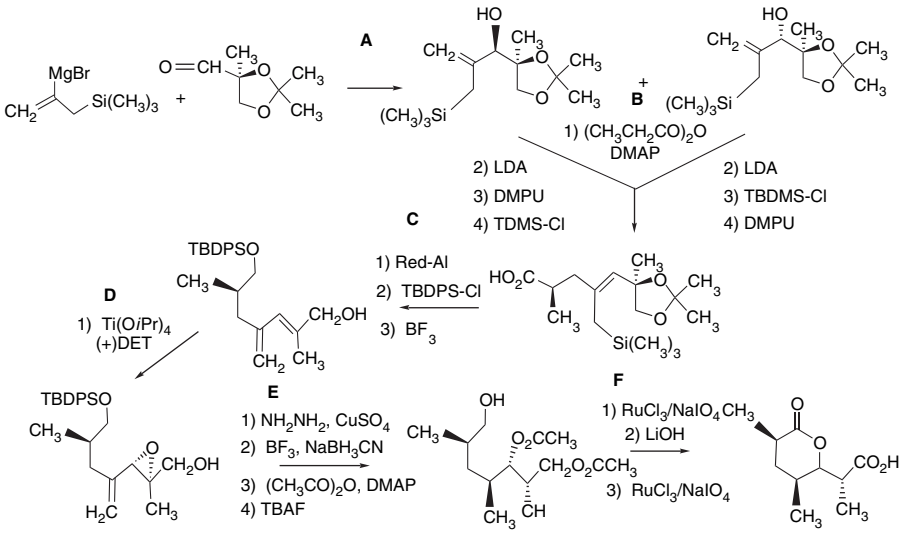
The reaction was very stereoselective for the correct P-D lactone configuration. The synthesis, which is outlined in Scheme 13.51, was completed by the sequence shown in Scheme 13.49.

The synthesis shown in Scheme 13.52 started with an enantiomerically pure protected aldehyde. Reaction with a Grignard reagent installed an allylic silane. This reaction gave a mixture of alcohols, but both were converted to the same intermediate by taking advantage of selective formation of *E*- or *Z*-silyl ketene acetal prior to an Ireland-Claisen rearrangement. These stereoconvergent transformations are described on p. 568. Two subsequent steps are noteworthy. In Step **C**-3, a BF_3-mediated opening of the dioxolane ring triggers a desilylation. In Step **E**-1, the diimide reduction occurs with excellent stereoselectivity. This is attributed to a π-stacking interaction with the TBDPS protecting group, since no similar effect was noted with the TBDMS group.



The final lactonization and oxidation were done as in Scheme 13.40.

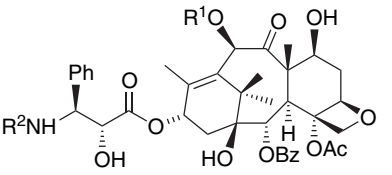
Scheme 13.52. Prelog-Djerassi Lactone Synthesis: P. J. Parsons and Co-Workers[a]



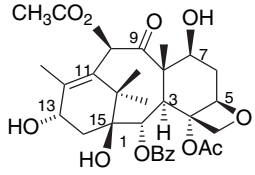
a. S. D. Hiscock, P. B. Hitchcock, and P. J. Parsons, *Tetrahedron*, **54**, 11567 (1998).

13.2.4. Baccatin III and Taxol

Taxol®[31] was first discovered to have anticancer activity during a screening of natural substances,[32] and it is currently an important drug in cancer chemotherapy. Several Taxol analogs differing in the side-chain substitution, such as taxotere, also have good activity.[33] Production of Taxol directly from plant sources presented serious problems because the plants are slow growing and the Taxol content is low. However, the tetracyclic ring system is found in a more available material, Baccatin III, which can be converted to Taxol by introduction of the side chain.[34] The combination of important biological activity, the limited natural sources, and the interesting structure made Taxol a target of synthetic interest during the 1990s. Among the challenging aspects of the structure from a synthetic point of view are the eight-membered ring, the bridgehead double bond, and the large number of oxygen functional groups. Several syntheses of Baccatin III and closely related tetracyclic Taxol precursors have been reported.

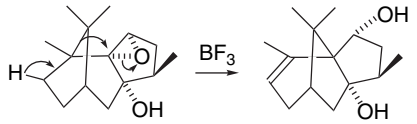


taxol R_1 = Ac, R_2 = PhCO
taxotere R_1 = H, R_2 = $(CH_3)_3CO_2C$



baccatin III

The first synthesis of Taxol was completed by Robert Holton and co-workers and is outlined in Scheme 13.53. One of the key steps occurs early in the synthesis in sequence **A** and effects fragmentation of **4** to **5**. The intermediate epoxide **4** was prepared from a sesquiterpene called "patchino."[35] The epoxide was then converted to **5** by a BF_3-mediated rearrangement.

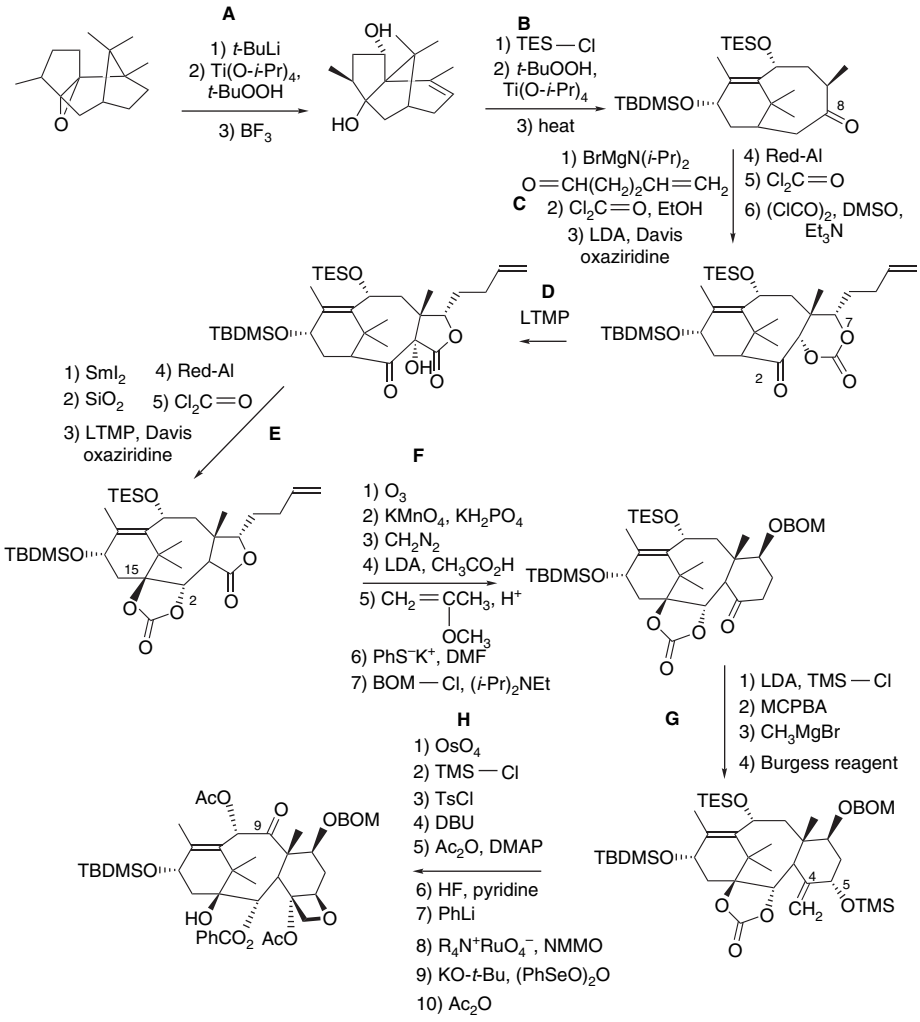


4 **5**

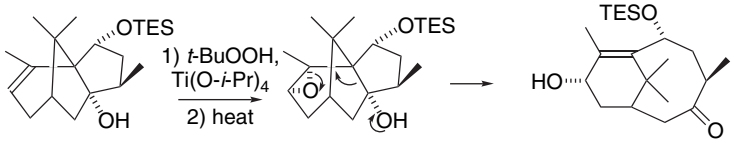
Another epoxidation, followed by fragmentation gave the bicyclic intermediate that contains the eight-membered ring and bridgehead double bond properly positioned for conversion to Taxol (Steps **B**-2 and **B**-3).

31. Taxol is a registered trade name of Bristol-Myers Squibb. The generic name is paclitaxel.
32. M. C. Wani, H. L. Taylor, M. E. Wall, D. Coggon, and A. McPhail, *J. Am. Chem. Soc*., **93**, 2325 (1971); M. E. Wall and M. C. Wani, *Alkaloids*, **50**, 509 (1998).
33. M. Suffness, ed., *Taxol: Science and Applications*, CRC Press, Boca Raton, FL, 1995.
34. J.-N. Denis, A. E. Greene, D. Guenard, F. Gueritte-Vogelein, L. Mangatal, and P. Potier, *J. Am. Chem. Soc*., **110**, 5917 (1988); R. A. Holton, Z. Zhang, P. A. Clarke, H. Nadizadeh, and D. J. Procter, *Tetrahedron Lett*., **39**, 2883 (1998).
35. R. A. Holton, R. R. Juo, H. B. Kim, A. D. Williams, S. Harusawa, R. E. Lowenthal, and S. Yogai, *J. Am. Chem. Soc*., **110**, 6558 (1988).

Scheme 13.53. Baccatin III Synthesis: R. A. Holton and Co-Workers[a]

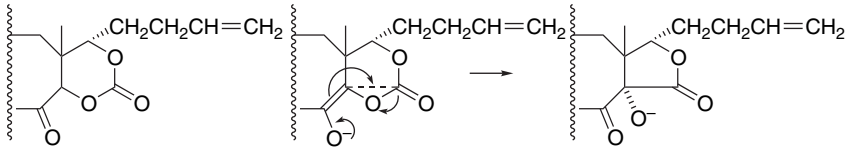


a. R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Lin, *J. Am. Chem. Soc*., **116**, 1597 (1994); R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Liu, *J. Am. Chem. Soc*., **116**, 1599 (1994).



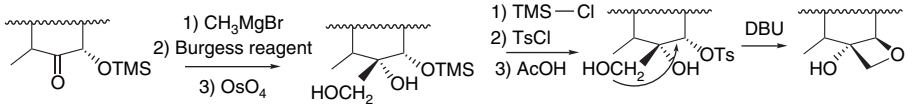
The next phase of the synthesis was construction of the C-ring. An aldol addition was used to introduce a 3-butenyl group at C(8) and the product was trapped as a carbonate ester. The Davis oxaziridine was then used to introduce an oxygen at C(2). After reduction of the C(3) oxygen, a cyclic carbonate was formed, and C(2) was converted

to a carbonyl group by Swern oxidation. In Step **D** this carbonate was rearranged to a lactone.

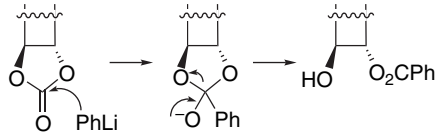


Reaction sequence **E** removed an extraneous oxygen by SmI_2 reduction and installed an oxygen at C(15) by enolate oxidation. The C(1) and C(15) hydroxy groups were protected as a carbonate in Step **E**-5. After oxidation of the terminal vinyl group, the C-ring was constructed by a Dieckmann cyclization in Step **F**-4. After temporary protection of the C(7) hydroxy as the MOP derivative, the β-ketoester was subjected to nucleophilic decarboxylation by phenylthiolate and reprotected as the BOM ether (Steps **F**-5, **F**- 6, and **F**-7).

An oxygen substituent was introduced at C(5) by MCPBA oxidation of a silyl enol ether (Steps **G**-1 and **G**-2). An exocyclic methylene group was introduced at C(4) by a methyl Grignard addition followed by dehydration with Burgess reagent (**G**-3). The oxetane ring was constructed in Steps **H**-1 to **H**-4. The double bond was hydroxylated with OsO_4 and a sequence of selective transformations of the triol provided the hydroxy tosylate, which undergoes intramolecular nucleophilic substitution to form the oxetane ring.

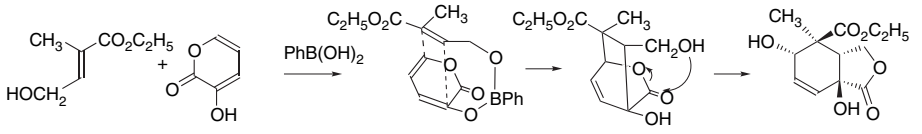


In Step **H**-7 the addition of phenyllithium to the cyclic carbonate group neatly generates the C(2) benzoate group. A similar reaction was used in several other Taxol syntheses.

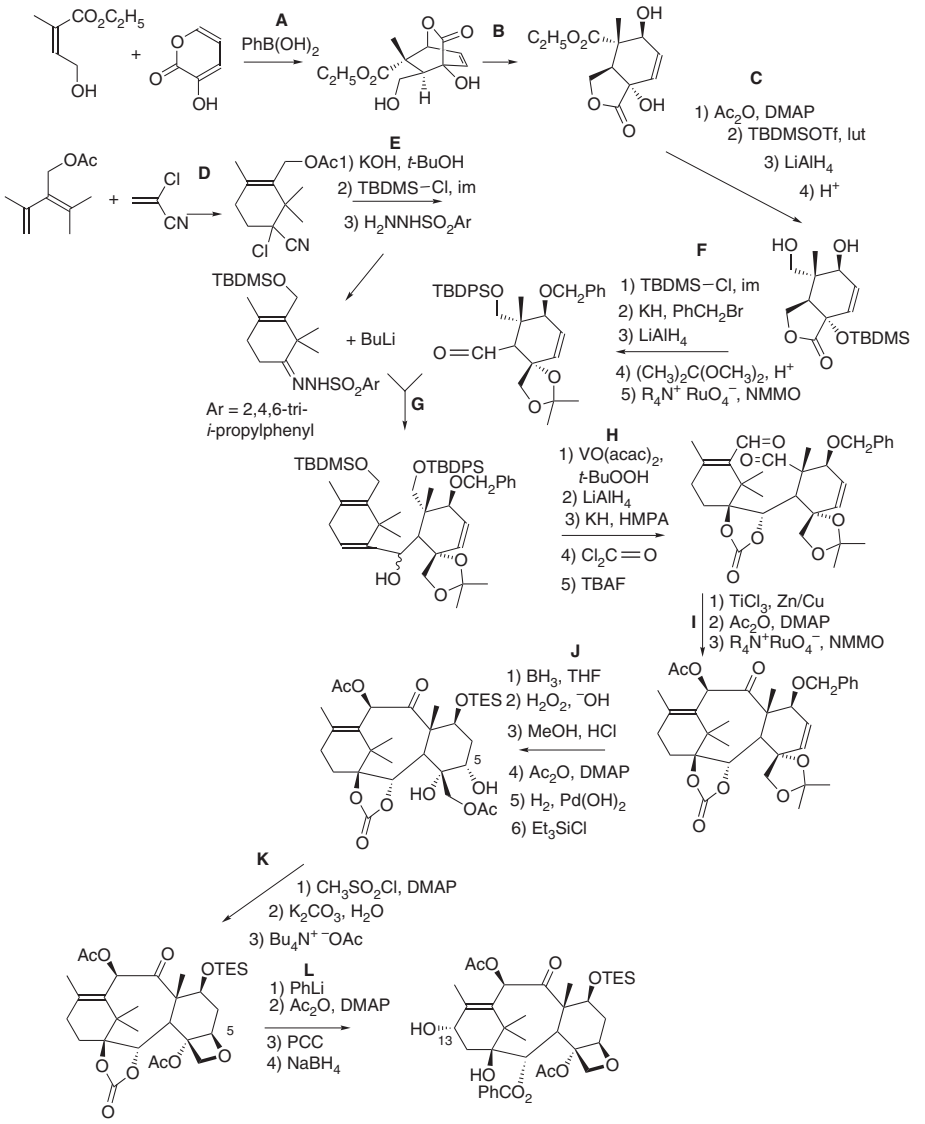


The final phase of the synthesis is introduction of the C(9) oxygen by phenylselenenic anhydride (Step **H**-9) and acetylation.

The Baccatin III synthesis by K. C. Nicolaou and co-workers is summarized in Scheme 13.54. Diels-Alder reactions are prominent in forming the early intermediates. In Step **A** the pyrone ring served as the diene. This reaction was facilitated by phenylboronic acid, which brings the diene and dienophile together as a boronate, permitting an intramolecular reaction.



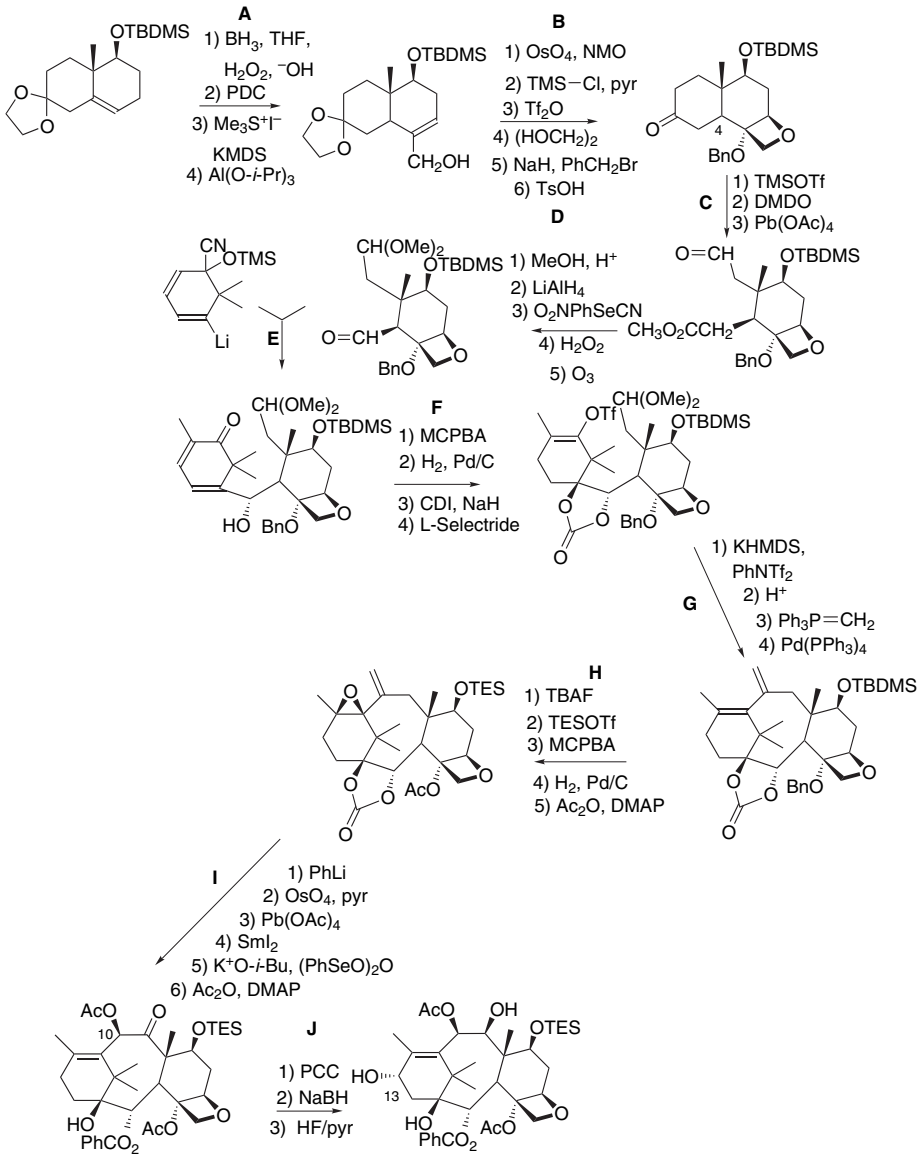
Scheme 13.54. Baccatin III Synthesis: K. C. Nicolaou and Co-Workers[a]



a. K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros, and E. J. Sorenson, *J. Am. Chem. Soc*., **117**, 624 (1995); K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorenson, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada, and P. G. Nantermet, *J. Am. Chem. Soc*., **117**, 634 (1995); K. C. Nicolaou, Z. Zhang, J.-J. Liu, P. G. Nantermet, C. F. Clairborne, J. Renaud, R. K. Guy, and K. S. Shibayama, *J. Am. Chem. Soc*., **117**, 645 (1995); K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, and R. Chadha, *J. Am. Chem. Soc*., **117**, 653 (1995).

The formation of the A-ring in Step **D** used α-chloroacrylonitrile as a ketene synthon. The A-ring and C-ring were brought together in Step **G** by an organolithium addition to the aldehyde. The lithium reagent was generated by a Shapiro reaction. An oxygen was introduced at C(1) by hydroxy-directed epoxidation in Step **H**-1 and reductive ring opening of the epoxide in Step **H**-2. The eight-membered B-ring was then closed by a titanium-mediated reductive coupling of a dialdehyde in Step **I**-1. The oxetane

Scheme 13.55. Baccatin III Synthesis: S. J. Danishefsky and Co-Workers[a]

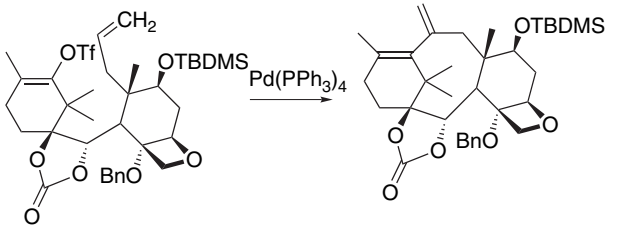


a. S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, and M. J. Di Grandi, *J. Am. Chem. Soc.*, **118**, 2843 (1996).

ring was closed in sequence **K** by an intramolecular O-alkylation with inversion at C(5). The C(13) oxygen was introduced late in the synthesis by an allylic oxidation using PCC (Step **L**-3).

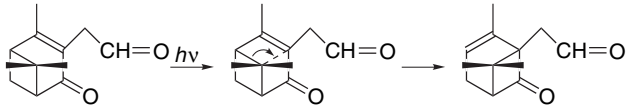
The synthesis of S. J. Danishefsky's group is outlined in Scheme 13.55. The starting material is a protected derivative of the Wieland-Miescher ketone. The oxetane ring is formed early in this synthesis. An epoxide is formed using dimethylsulfonium methylide (Step **A**-3) and opened to an allylic alcohol in Step **A**-4. The double bond

was dihydroxylated using OsO_4. The cyclization occurs via the C(5) triflate and was done in ethylene glycol. After cyclization, the tertiary hydroxy at C(4) was protected by benzylation and the ketal protecting group was removed. The cyclohexanone ring was then cleaved by oxidation of the silyl enol ether. The A-ring was introduced in Step **E** by use of a functionalized lithium reagent. The closure of the B-ring was done by an intramolecular Heck reaction involving a vinyl triflate at Step **G**-4.

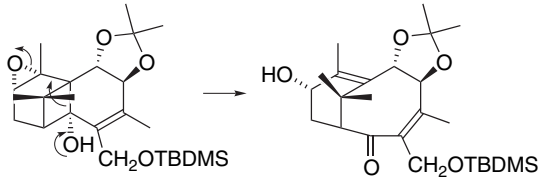


The late functionalization included the introduction of the C(10) and C(13) oxygens, which was done by phenylselenenic anhydride oxidation of the enolate in Step **I**-5 and by allylic oxidation at C(13) in Step **J**-1. These oxidative steps are similar to transformations in the Holton and Nicolaou syntheses.

The synthesis of the Taxol in Scheme 13.56 by P. A. Wender and co-workers at Stanford University began with an oxidation product of the readily available terpene pinene. One of the key early steps was the photochemical rearrangement in Step **B**.



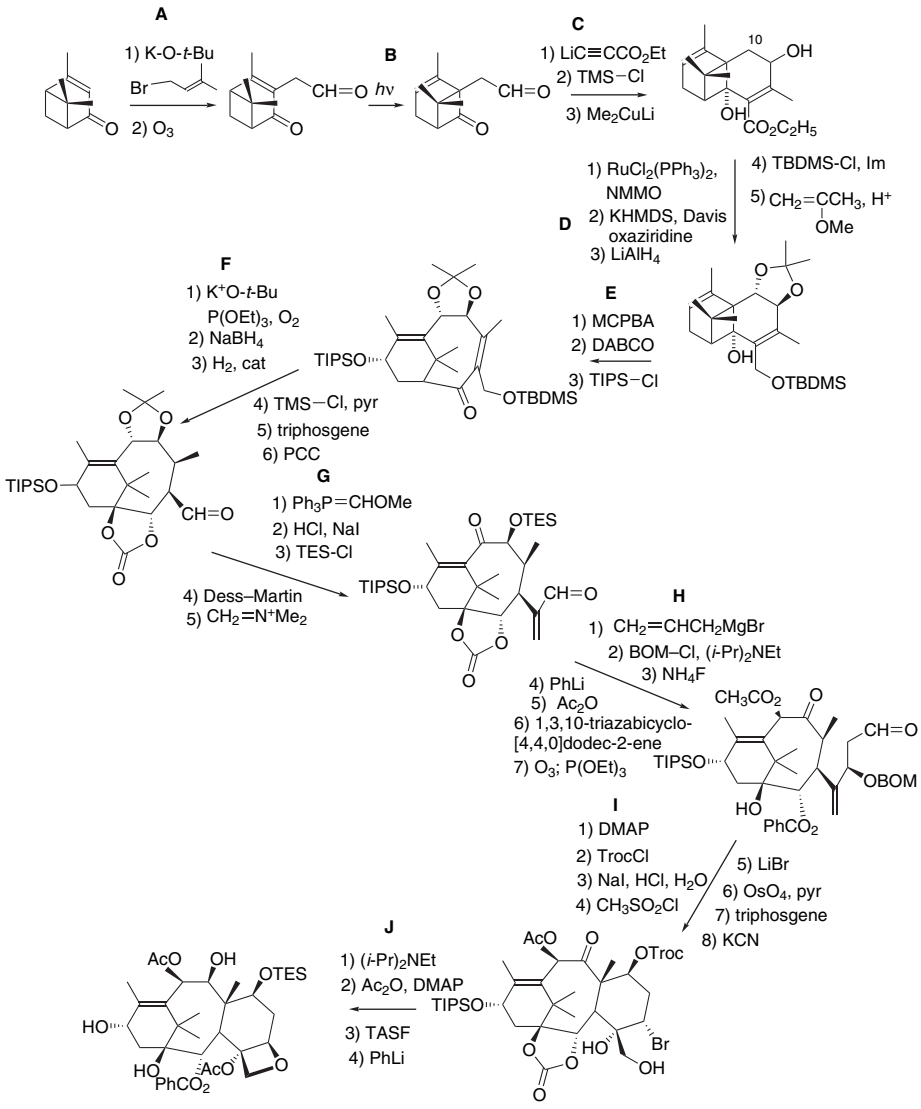
A six-membered ring was then constructed in reaction sequence **C** by addition of lithiated ethyl propynoate and a tandem conjugate addition-cyclization. The C(10) oxygen was introduced by enolate oxidation in Step **D**-2. Another key step is the fragmentation induced by treatment first with MCPBA and then with DABCO (Steps **E**-1 and **E**-2). The four-membered ring is fragmented in the process, forming the eight-membered ring with its bridgehead double bond and providing the C(13) oxygen substituent.



6 **7**

The C(1) oxygen was introduced at Step **F**-1 by enolate oxidation. The **C**-ring was constructed by building up a substituent at C(16) (Steps **G** and **H**). After forming the benzoate at C(2) in Step **H**-4, the C(9) acetoxy ketone undergoes transposition. This is an equilibrium process that goes to about 55% completion. An aldehyde was generated by ozonolysis of the terminal allylic double bond. This group was used to close the **C**-ring by an aldol cyclization in Step **I**-1. This step completed the construction of the

Scheme 13.56. Baccatin III Synthesis: P. A. Wender and Co-Workers[a]

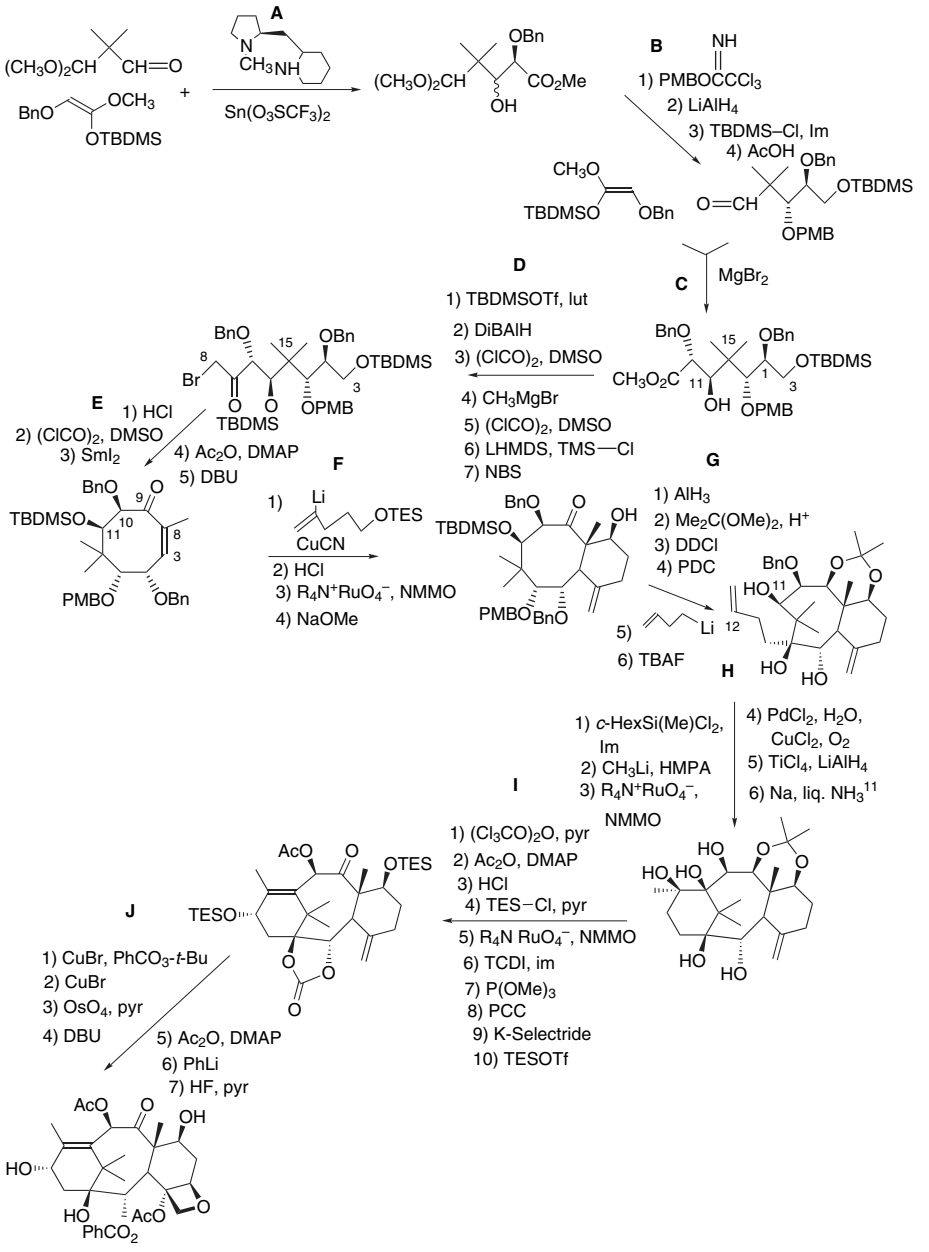


a. P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Granicher, J. B. Houze, J. Janichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Muhlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, and K. Tomooka, *J. Am. Chem. Soc*., **119**, 2755 (1997); P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, and R. E. Taylor, *J. Am. Chem. Soc*., **119**, 2757 (1997).

carbon framework. The synthesis was completed by formation of the oxetane ring by the sequence **I**-3 to **I**-8, followed by the cyclization in Step **J**-1.

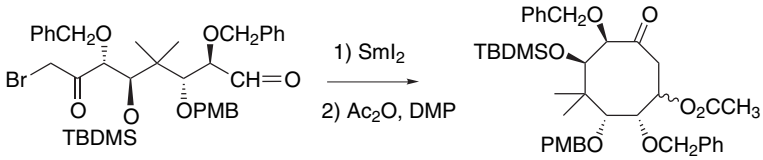
The synthesis of Baccatin III shown in Scheme 13.57, which was completed by a group led by the Japanese chemist Teruaki Mukaiyama, takes a different approach for the previous syntheses. Much of the stereochemistry was built into the B-ring by a series of acyclic aldol additions in Steps **A** through **D**. A silyl ketene acetal derivative

Scheme 13.57. Baccatin III Synthesis: T. Mukaiyama and Co-Workers[a]

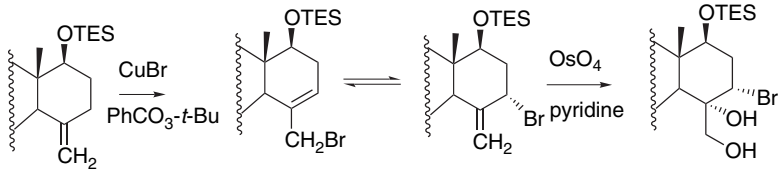


a. T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, and K. Saitoh, *Chem. Eur. J.*, **5**, 121 (1999).

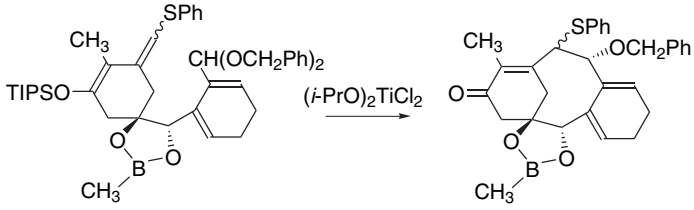
of methyl α-benzyloxyacetate served as the nucleophile in Steps **A** and **C**. The C(10)–C(11) bond is formed in Step **C** using $MgBr_2$ to promote the Mukaiyama addition, which forms the correct stereoisomer with 4:1 diastereoselectivity. The B-ring was closed in Step **E**-3 by a samarium-mediated cyclization, forming the C(3)–C(8) bond.



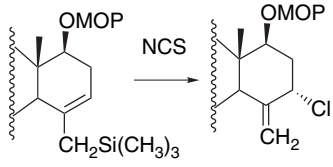
The C(4)–C(7) segment was added by a cuprate conjugate addition in Step **F**-1. The C-ring was then closed using an intramolecular aldol addition in Step **F**-4. The A-ring was closed by a Ti-mediated reductive coupling between carbonyl groups at C(11) and C(12) in Step **H**-5. The C(11)–C(12) double bond was introduced from the diol by deoxygenation of the thiocarbonate (Steps **I**-6 and **I**-7). The final sequence for conversion to Baccatin III, which began with a copper-mediated allylic oxidation at C(5), also involves an allylic rearrangement of the halide that is catalyzed by CuBr. The exocyclic double bond was then used to introduce the final oxygens needed to perform the oxetane ring closure.



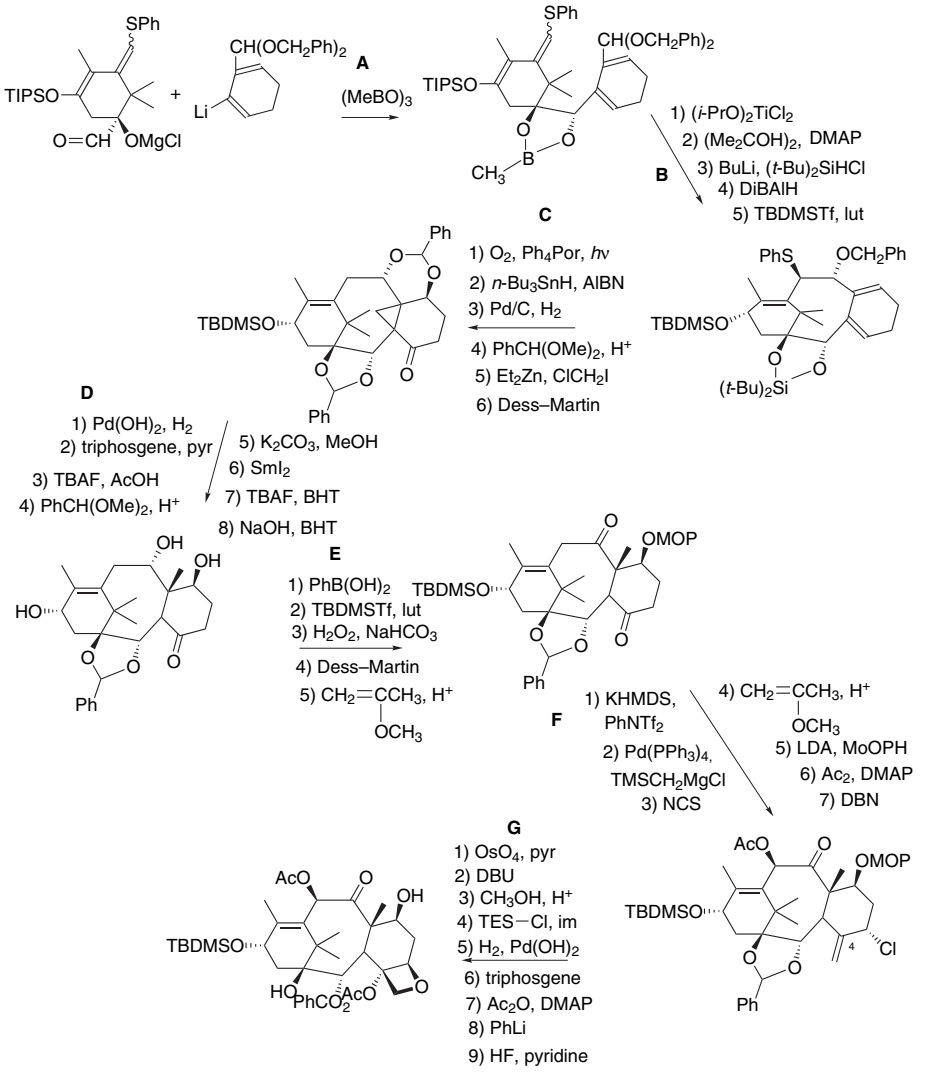
Another Japanese group developed the Baccatin III synthesis shown in Scheme 13.58. The eight-membered B-ring was closed early in the synthesis using a Lewis acid–induced Mukaiyama reaction (Step **B**-1), in which a trimethylsilyl dienol ether served as the nucleophile.



Oxygen was introduced at C(4) and C(7) by a singlet O_2 cycloaddition in Step **C**-1. The peroxide bond was cleaved and the phenylthio group removed by Bu_3SnH in Step **C**-2. The C(19) methyl group was introduced via a cyclopropanation in Step **C**-5, followed by a reduction in Step **D**-1. A Pd-catalyzed cross-coupling reaction was used to introduce a trimethylsilylmethyl group at C(4) via an enol triflate in Step **F**-2. The vinyl silane was then subjected to chlorination in Step **F**-3. The chlorine eventually serves as the leaving group for oxetane ring formation in Step **G**-2.



Scheme 13.58. Baccatin III Synthesis: H. Kusama, I. Kuwajima, and Co-Workers[a]



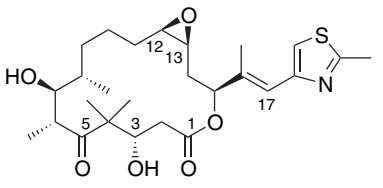
a. K. Morihara, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, and I. Kuwajima, *J. Am. Chem. Soc*., **120**, 12980 (1998); H. Kusama, R. Hara, S. Kawahara, T. Nishimori, H. Kashima, N. Nakamura, K. Morihara, and I. Kuwajima, *J. Am. Chem. Soc*., **122**, 3811 (2000).

These syntheses of Baccatin III illustrate the versatility of current methodology for ring closure and functional group interconversions. The Holton, Nicolaou, Danishefsky, and Wender syntheses of Baccatin III employ various cyclic intermediates and take advantage of stereochemical features built into these rings to control subsequent reaction stereochemistry. As a reflection of the numerous oxygens in Baccatin III, each of the syntheses makes use of enolate oxidation, alkene hydroxylation, and related oxidation reactions. These syntheses also provide numerous examples of the selective use of protective groups to achieve distinction between the several hydroxy groups that are present in the intermediates. The Mukaiyama synthesis in Scheme 13.57 is somewhat different in approach in that it uses acyclic intermediates to introduce

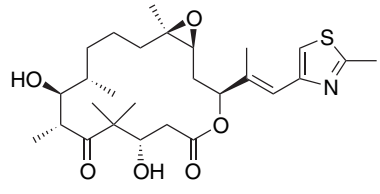
several of the stereocenters. Perhaps because of the structure, none of these syntheses is particularly convergent. The Nicolaou, Danishefsky, and Kusama syntheses achieve some convergence by coupling the A-ring and the C-ring and then forming the B-ring. The Holton and Wender syntheses take advantage of available natural substances as starting materials.

13.2.5. Epothilone A

The epothilones are natural products containing a 16-membered lactone ring that are isolated from mycobacteria. Epothilones A–D differ in the presence of the C(12)–C(13) epoxide and in the C(12) methyl group. Although structurally very different from Taxol, they have a similar mechanism of anticancer action and epothilone A and its analogs are of substantial current interest as chemotherapeutic agents.[36] Schemes 13.59 to 13.66 summarize eight syntheses of epothilone A. Several syntheses of epothilone B have also been completed.[37]



epothilone A
epothilone C(12-13) = CH=CH



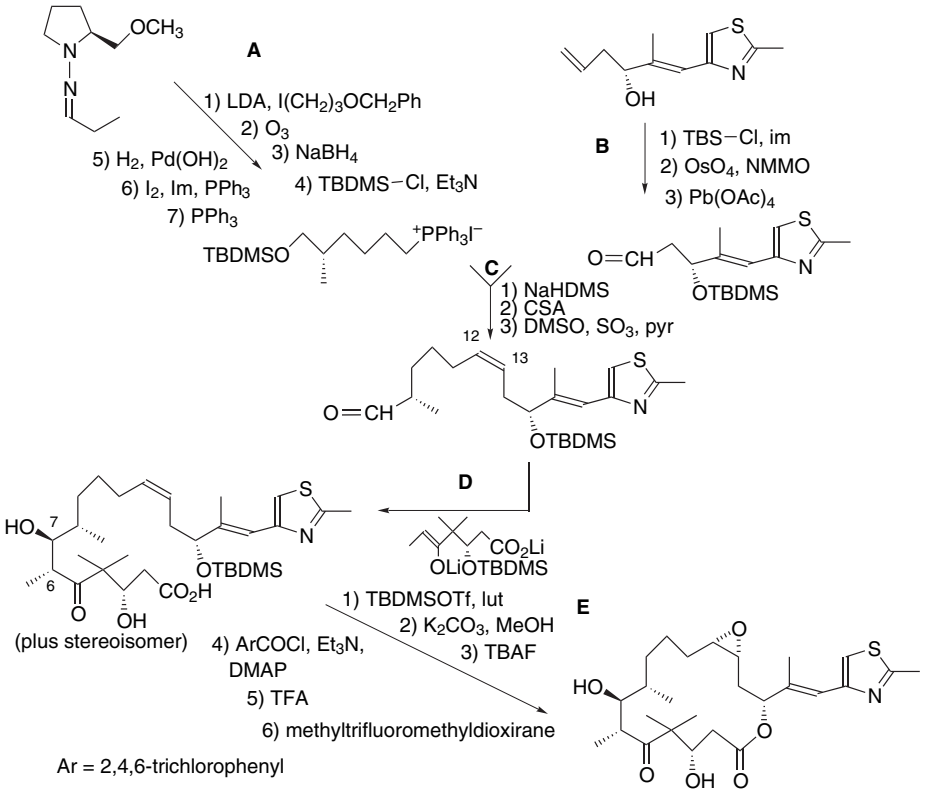
epothilone B
epothilone C(12-13) = CH=CH

Two critical objectives for planning the synthesis of epothilone A are the control of the configuration of the stereocenters and the closure of the 16-membered ring. There are eight stereocenters, including the C(16)–C(17) double bond. As the 16-membered lactone ring is quite flexible, it does not impose strong facial stereoselectivity. Instead, the stereoselective synthesis of epothilone A requires building the correct stereochemistry into acyclic precursors that are cyclized later in the synthesis. The stereocenters at C(3), C(6), C(7), and C(8) are adjacent to a potential aldol connection

36. T. C. Chou, X. G. Zhang, C. R. Harris, S. D. Kuduk, A. Balog, K. A. Savin, J. R. Bertino, and S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA*, **95**, 15978 (1998).

37. J. Mulzer, A. Mantoulidis, and E. Ohler, *Tetrahedron Lett*., **39**, 8633 (1998); D. S. Sa. D. F. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T.-C. Chou, L. He, and S. B. Horowitz, *Angew. Chem. Int. Ed. Engl*., **36**, 757 (1997); A. Balog, C. Harris, K. Savin, S. G. Zhang, T. C. Chou, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl*., **37**, 2675 (1998); D. Shinzer, A. Bauer, and J. Schieber, *Synlett*, 861 (1998); S. A. May and P. A. Grieco, *J. Chem. Soc., Chem. Commun*., 1597 (1998); K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, and Z. Yang, *J. Am. Chem. Soc*., **119**, 7974 (1997); K. C. Nicolaou, D. Hepworth, M. R. V. Finlay, B. Wershkun, and A. Bigot, *J. Chem. Soc., Chem. Commun*., 519 (1999); D. Schinzer, A. Bauer, and J. Schieber, *Chem. Eur. J*., **5**, 2492 (1999); J. D. White, R. G. Carter, and K. F. Sundermann, *J. Org. Chem*., **64**, 684 (1999); J. Mulzer, A. Moantoulidis, and E. Oehler, *J. Org. Chem*., **65**, 7456 (2000); J. Mulzer, G. Karig, and P. Pojarliev, *Tetrahedron Lett*., **41**, 7635 (2000); D. Sawada, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc*., **122**, 10521 (2000); S. C. Sinha, J. Sun, G. P. Miller, M. Wartmann, and R. A. Lerner, *Chem. Eur. J*., **7**, 1691 (2001); J. D. White, R. G. Carter, K. F. Sundermann, and M. Wartmann, *J. Am. Chem. Soc*., **123**, 5407 (2001); H. J. Martin, P. Pojarliev, H. Kahlig, and J. Mulzer, *Chem. Eur. J*., **7**, 2261 (2001); R. E. Taylor and Y. Chen, *Org. Lett*., **3**, 2221 (2001); M. Valluri, R. M. Hindupur, P. Bijoy, G. Labadie, J.-C. Jung, and M. A. Avery, *Org. Lett*., **3**, 3607 (2001); N. Martin and E. J. Thomas, *Tetrahedron Lett*., **42**, 8373 (2001); M. S. Ermolenko and P. Potier, *Tetrahedron Lett*., **43**, 2895 (2002); J. Sun and S. C. Sinha, *Angew. Chem. Int. Ed. Engl*., **41**, 1381 (2002); J.-C. Jung, R. Kache, K. K. Vines, Y.-S. Zheng, P. Bijoy, M. Valluri, and M. A. Avery, *J. Org. Chem*., **69**, 9269 (2004).

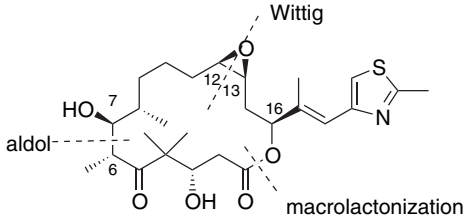
Scheme 13.59. Epothilone A Synthesis by Macrolactonization: K. C. Nicolaou and Co-Workers[a]



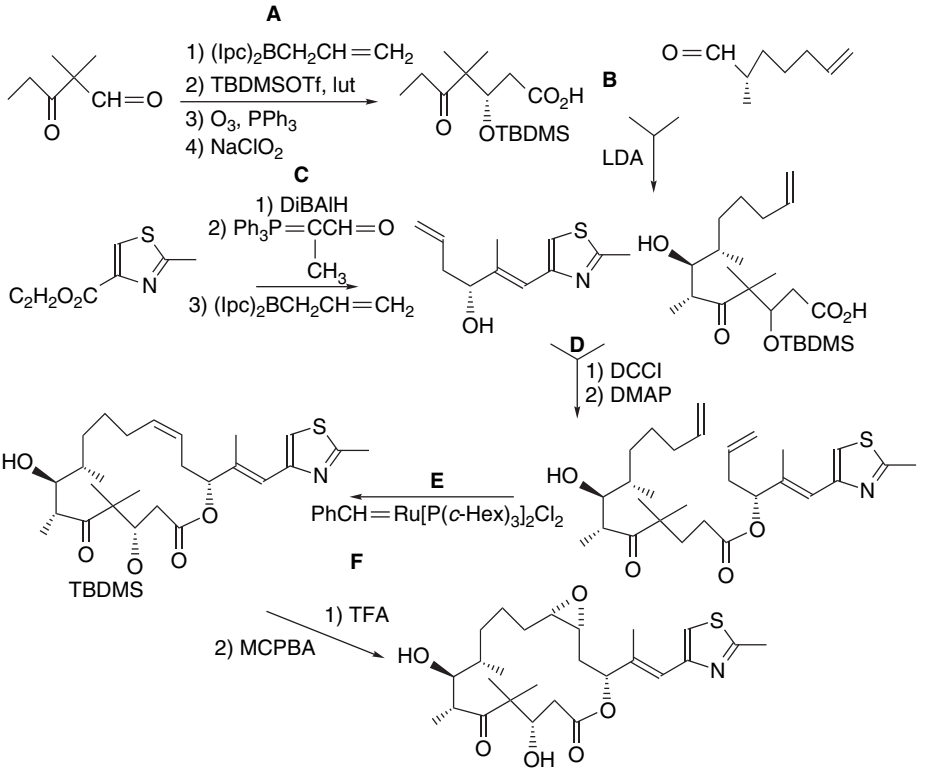
a. K. C. Nicolaou, F. Sarabia, S. Ninkovic, and Z. Yang, *Angew. Chem. Int. Ed. Engl*., **36**, 525 (1997); K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, and Z. Yang, *J. Am. Chem. Soc*., **119**, 7974 (1997).

between C(6) and C(7) and are amenable to control by aldol methodology. Introduction of the epoxide by epoxidation requires a *Z*-double bond. Several methods for ring closure have been used, but the two most frequently employed are macrolactonization (see Section 3.4) and alkene metathesis (see Section 8.4).

K. C. Nicolaou's group at Scripps Research Institute developed two synthetic routes to epothilone A. One of the syntheses involves closure of the lactone ring as a late step. Three major fragments were synthesized. The bond connection at C(6)–C(7) was made by an aldol reaction. The C(12)–C(13) bond was formed by a Wittig reaction and later epoxidized. The ring was closed by macrolactonization.



Scheme 13.60. Epothilone A Synthesis by Olefin Metathesis: K. C. Nicolaou and Co-Workers[a]



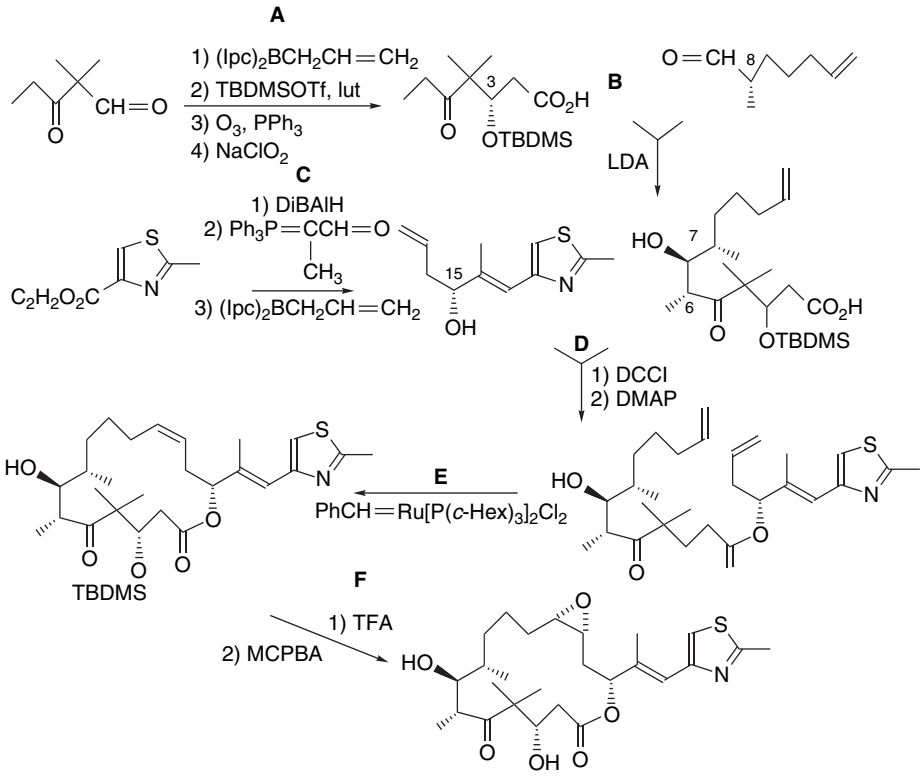
a. Z. Yang, Y. He, D. Vourloumis, H. Vallberg, and K. C. Nicolaou, *Angew. Chem. Int. Ed. Engl.*, **36**, 166 (1997).

This synthesis is shown in Scheme 13.59. Two enantiomerically pure starting materials were brought together by a Wittig reaction in Step **C**. The aldol addition in Step **D** was diastereoselective for the *anti* configuration, but gave a 1:1 mixture with the 6*S*, 7*R*-diastereomer. The stereoisomers were separated after Step **E**-2. The macrolactonization (Step **E**-4) was accomplished by a mixed anhydride (see Section 3.4.1). The final epoxidation was done using 3-methyl-3-trifluoromethyl dioxirane.

The second synthesis from the Nicolaou group is shown in Scheme 13.60. The disconnections were made at the same bonds as in the synthesis in Scheme 13.59. The C(1)–C(6) segment contains a single stereogenic center, which was established in Step **A-**1 by enantioselective allylboration. The C(6)–C(7) configuration was established by the aldol addition in Step **B**. The aldolization was done with the dianion and gave a 2:1 mixture with the 6S, 7R diastereomer. The two fragments were brought together by esterification in Step **D**. The synthesis used an olefin metathesis reaction to construct the 16-membered ring (Step **E**). This reaction gave a 1.4:1 ratio of *Z:E* product, which was separated by chromatography.

The olefin metathesis reaction was also a key feature of the synthesis of epothilone A completed by a group at the Technical University in Braunschweig, Germany (Scheme 13.61). This synthesis employs a series of stereoselective additions to create the correct substituent stereochemistry. Two enantiomerically pure starting materials

Scheme 13.61. Epothilone A Synthesis: D. Schinzer and Co-Workers[a]



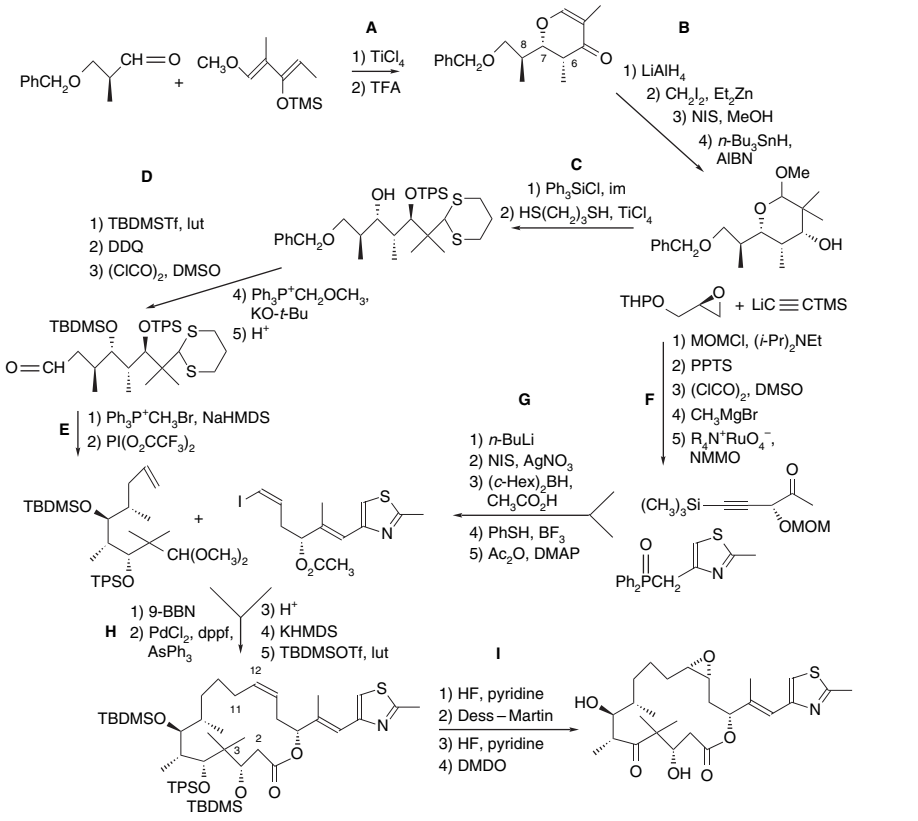
a. D. Schinzer, A. Limberg, A. Bauer, O. M. Bohm, and M. Cordes, *Angew. Chem. Int. Ed. Engl.*, **36**, 523 (1997); D. Schinzer, A. Bauer, O. M. Bohm, A. Limberg, and M. Cordes, *Chem. Eur. J.*, **5**, 2483 (1999).

were used, containing the C(3) and C(8) stereocenters. Step **B** used a stereoselective aldol addition to bring these two fragments together and to create the stereocenters at C(6) and C(7). The thiazole ring and the C(13)–C(15) fragment were constructed in sequence **C**. The configuration at C(15) was established by enantioselective allylboration in Step **C**-3. The two segments were coupled by esterification at Step **D**, and the ring was closed by olefin metathesis (Step **E**). The metathesis reaction gave a 1.7:1 ratio favoring the *Z*-isomer. The synthesis was completed by deprotection and epoxidation, after which the stereoisomers were separated by chromatography. This group has also completed a synthesis based on a macrolactonization approach.[38]

Samuel Danishefsky's group at the Sloan Kettering Institute for Cancer Research in New York has also been active in the synthesis of the natural epothilones and biologically active analogs. One of their syntheses also used the olefin metathesis reaction (not shown). The synthesis in Scheme 13.62 used an alternative approach to create the macrocycle, as indicated in the retrosynthetic scheme. The stereochemistry at C(6), C(7), and C(8) was established by a $TiCl_4$-mediated cyclocondensation (Step **A**). The thiazole-containing side chain was created by reaction sequences **F** and **G**. The

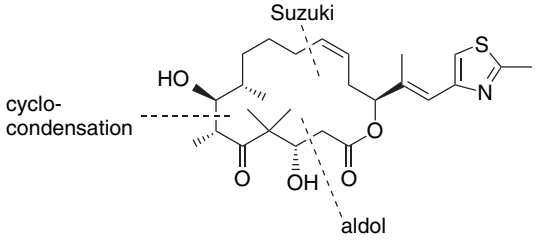
38. D. Schinzer, A. Bauer, and J. Schieber, *Chem. Eur. J.*, **5**, 2483 (1999).

Scheme 13.62. Epothilone A Synthesis by Macroaldol Cyclization: S. J. Danishefsky and Co-Workers[a]

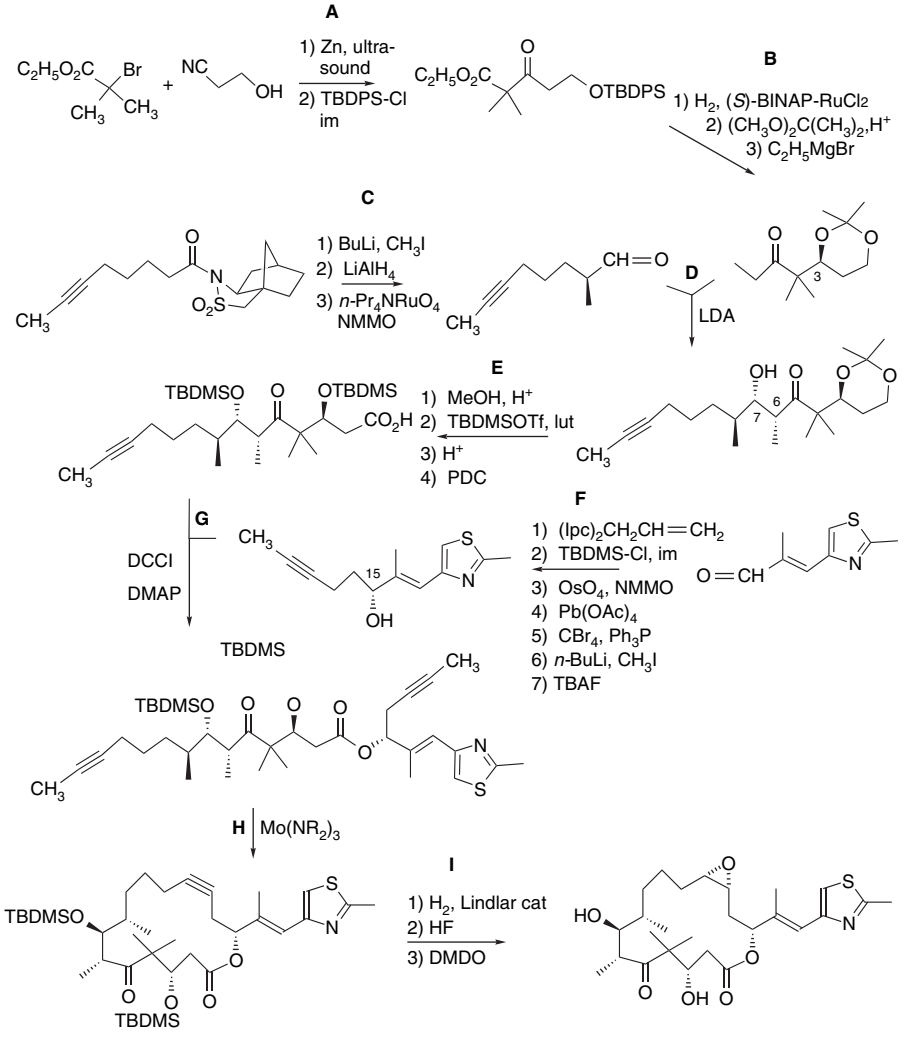


a. A. Balog, D. Meng, T. K. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **35**, 2801 (1996); D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **119**, 10073 (1997).

Z-vinyl iodide was obtained by hydroboration and protonolysis of an iodoalkyne. The two major fragments were coupled by a Suzuki reaction at Steps **H**-1 and **H**-2 between a vinylborane and vinyl iodide to form the C(11)–C(12) bond. The macrocyclization was done by an aldol addition reaction at Step **H**-4. The enolate of the C(2) acetate adds to the C(3) aldehyde, creating the C(2)–C(3) bond and also establishing the configuration at C(3). The final steps involve selective deprotonation and oxidation at C(5), deprotection at C(3) and C(7), and epoxidation.



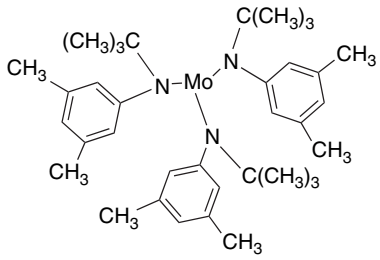
Scheme 13.63. Epothilone A Synthesis: A. Furstner, C. Mathes, and C. W. Lehmann[a]



a. A. Furstner, C. Mathes, and C. W. Lehmann, *Chem. Eur. J.*, **7**, 5299 (2001).

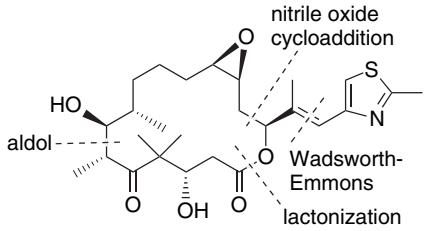
The epothilone A synthesis shown in Scheme 13.63 involves an *alkyne metathesis reaction*. The first subunit was constructed using a Reformatsky-type addition to 3-hydroxypropanonitrile. The configuration at C(3) was established by an enantioselective hydrogenation using (*S*)-(BINAP)RuCl[2] under acidic conditions. A bornanesultam chiral auxiliary was used to establish the stereochemistry at C(8) by alkylation (Step **C**-1). The stereochemistry at the C(6)–C(7) bond was established by an aldol addition at Step **D**. The thiazole segment was constructed from a conjugated enal, which was subjected to enantioselective allylboration using (+)-$Ipc_2BCH_2CH{=}CH_2$ in Step **F**-1. This reaction established the configuration at C(5) A terminal alkyne was then installed by the Corey-Fuchs procedure (see p. 835). The lithium acetylide was methylated in situ using CH_3I. A DMAP-DCCI esterification was then used to couple the two major fragments and set the stage for the alkyne metathesis at Step **H**. The

catalyst is a molybdenum amide, which is one of a family of catalysts that show good activity in alkyne metathesis. The use of alkyne metathesis avoids the complication of formation of both *Z*- and *E*-isomers, which sometimes occurs in olefin metathesis.

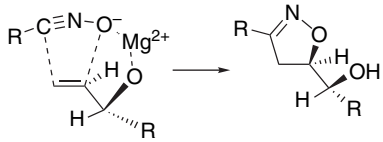


The yield in the metathesis reaction was 80% and was followed by a Lindlar reduction. The synthesis was completed by epoxidation with DMDO.

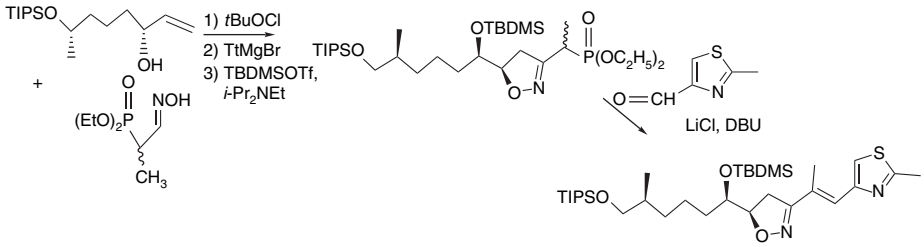
The synthesis in Scheme 13.64 was carried out by E. Carreira and co-workers at ETH in Zurich, Switzerland. A key step in the synthesis in Scheme 13.64 is a stereoselective cycloaddition using a phosphonyl-substituted nitrile oxide, which was used to form the C(16)–C(17) bond and install the C(15) oxygen.



The C(6)–C(15) segment was synthesized by Steps **C**-1 and **C**-2. The stereoselectivity of the cycloaddition reaction between the nitrile oxide and allylic alcohol is the result of a chelated TS involving the Mg alkoxide.[39]

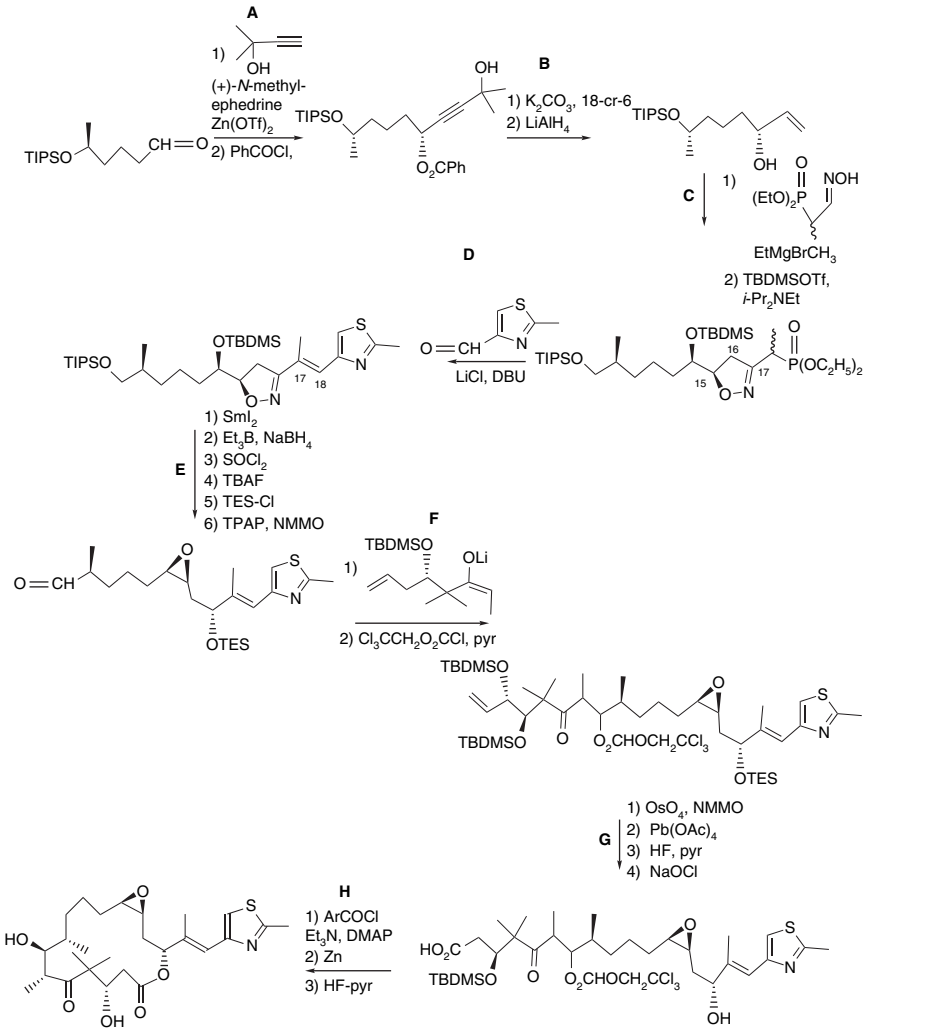


After the cycloaddition, the thiazole ring was introduced via a Wadsworth-Emmons reaction at Step **D**, forming the C(17)–C(18) bond.



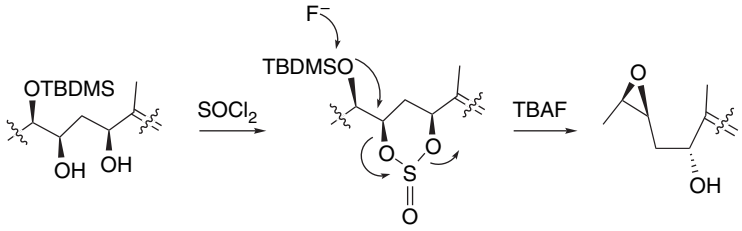
[39] S. Kanemasa, M. Nishiuchi, A. Kamimura, and K. Hori, *J. Am. Chem. Soc*., **116**, 2324 (1994); S. Fukuda, A. Kanimura, S. Kanemasa, and K. Hori, *Tetrahedron*, **56**, 1637 (2000).

Scheme 13.64. Epolthilone A Synthesis: J. W. Bode and E. M. Carreira[a]



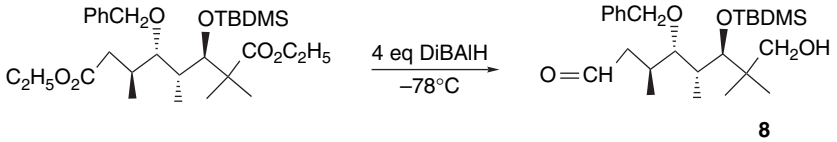
a. J. W. Bode and E. M. Carreira, *J. Am. Chem. Soc.*, **123**, 3611 (2001); *J. Org. Chem.*, **66**, 6410 (2001).

The reduction of the isoxazoline ring after the cycloaddition was not successful with the usual reagents (see p. 532), but SmI_2 accomplished the reaction. In contrast to the epoxidation used as the final step in most of the other epothilone A syntheses, the epoxide was introduced through a sulfite intermediate. Deprotection of C(15) leads to intramolecular displacement at the sulfite with formation of the epoxide (Steps **E**-3 and **E**-4).



The C(1)–C(6) and C(7)–C(17) fragments were joined by an aldol addition via a lithium enolate (Step **F**-1), and the ring was closed by a macrolactonization.

The synthesis of epothilone A in Scheme 13.65 features the use of chiral allylic silanes that were obtained by kinetic resolution using *Pseudomonas* AK lipase. The C(5)–C(8) fragment was synthesized by condensing the enantiomerically pure silane with a TBDPS-protected aldehyde in the presence of BF_3. The adduct was then subjected to a chelation-controlled aldol addition using $TiCl_4$, adding C(3) and C(4). After protecting group manipulation and oxidation, the chain was extended by two carbons using a Wittig reaction in Step **C**-3. The methyl group at C(8) was added by a stereoselective cuprate conjugate addition in Step **C**-4. The intermediate was then converted to **8** using a DiBAlH reduction under conditions that discriminated between the two ester groups (Step **D**-1). The more hindered group was reduced to the primary alcohol, leaving the less hindered one at the aldehyde level. This selectivity probably arises as a result of the lesser stability of the more hindered partially reduced intermediate. (See p. 401 to review the mechanism of DiBAlH reduction.)



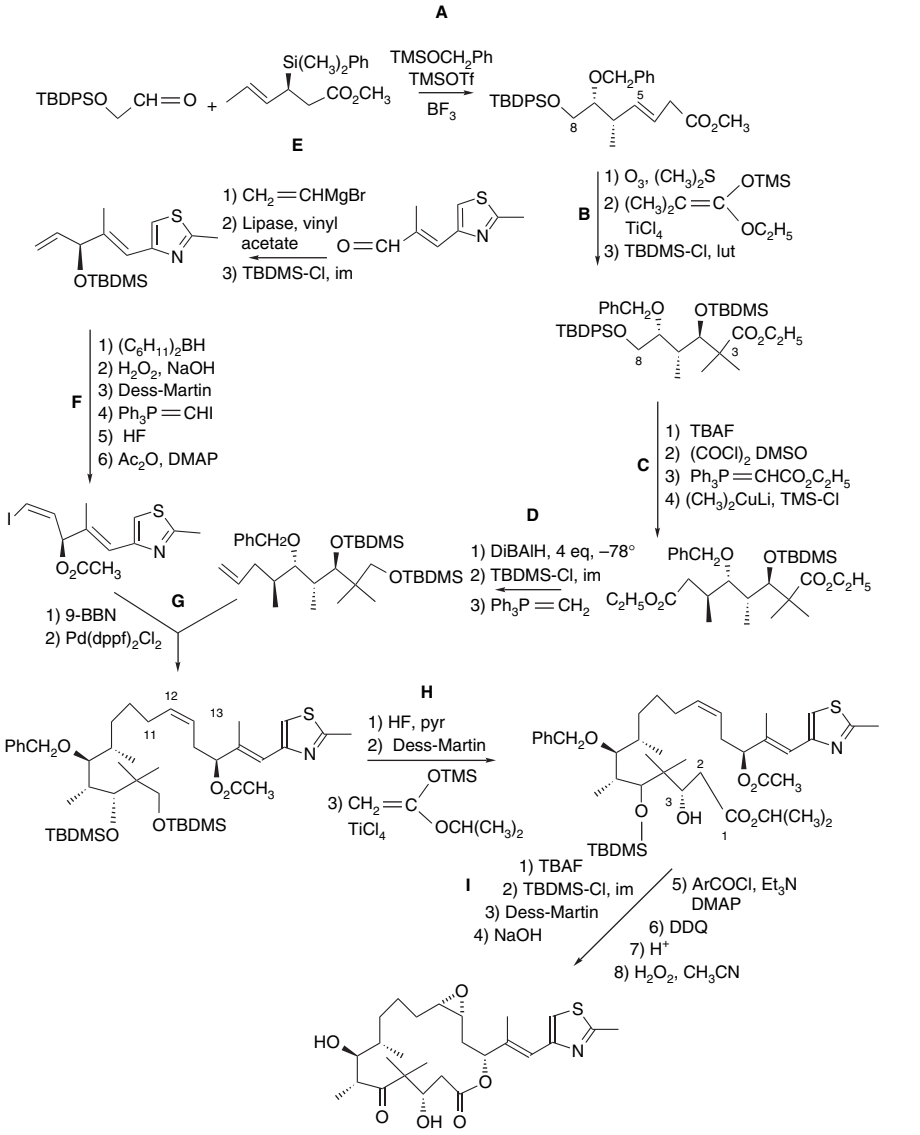
8

The aldehyde was then converted to the terminal alkene via a Wittig reaction (Step **D**-3).

A kinetic resolution was also used to establish the configuration of the thiazole portion. An allylic aldehyde was subjected to kinetic resolution by ester exchange with vinyl acetate in Step **E**-2 (see Topic 2.2, Part A). The resolved alcohol was protected and subjected to hydroboration, oxidation, and a Wittig reaction to introduce the *Z*-vinyl iodide. The two fragments were coupled using the Suzuki reaction and the final two carbons were installed by another $TiCl_4$-mediated silyl ketene acetal addition in sequence **H**. The stereochemistry at C(3) presented some problems, but use of the silyl ketene acetal of the isopropyl ester provided an 8:1 mixture favoring the desired diastereomer. The isopropyl ester was used to slow competing lactonization of the intermediate. The macrolactonization was done under the Yamaguchi conditions. The synthesis was completed by epoxidation using the peroxyimidic acid generated in situ from acetonitrile and hydrogen peroxide.

The synthesis shown in Scheme 13.66 starts with the Sharpless asymmetric epoxidation product of geraniol. The epoxide was opened with inversion of configuration by $NaBH_3CN$-BF_3. The double bond was cleaved by ozonolysis and converted to the corresponding primary bromide. The terminal alkyne was introduced by alkylation of

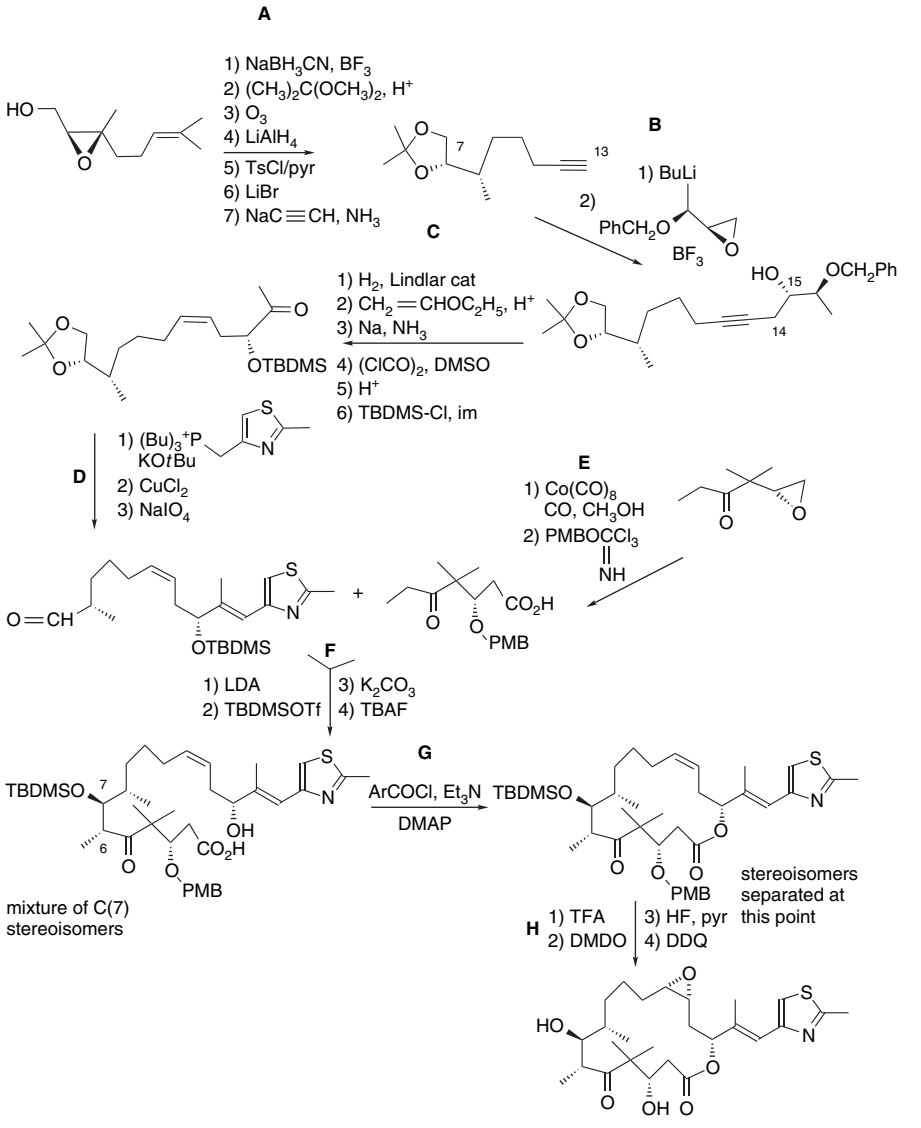
Scheme 13.65. Epothilone A Synthesis: B. Zhu and J. S. Panek[a]



a. B. Zhu and J. S. Panek, *Eur. J. Org. Chem.*, 1701 (2001).

sodium acetylide, completing the synthesis of the C(7)–C(13) segment (Steps **A**-4 to **A**7). The BF_3-mediated epoxide ring opening in Step **B**-2 occurred with inversion of configuration, establishing the configuration at C(15). The *Z*-stereochemistry at the C(12)–C(13) double bond was established by reduction over a Lindlar catalyst. An EE protecting group was used during the Swern oxidation (Step **C**-4) but then replaced by a TBDMS group for the Wittig reaction and beyond. The chirality of the C(1)–C(6) segment was established by a kinetic resolution of an epoxide by selective ring opening

Scheme 13.66. Epothilone A Synthesis: Z.-Y. Liu and Co-Workers[a]



a. Z.-Y. Liu, Z.-C. Chen, C.-Z. Yu, R.-F. Wang, R.-Z. Zhang, C.-S. Huang, Z. Yan, D.-R. Cao, J.-B Sun, and G. Li, *Chem. Eur. J.*, **8**, 3747 (2002).

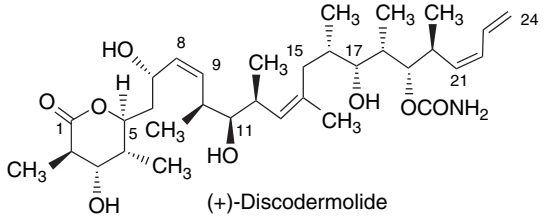
catalyzed by a chiral salen-Co(III) complex.[40] The resolved epoxide was converted to an ester by a $Co_2(CO)_8$-catalyzed carbonylation in Step **E**-1. The C(6)–C(7) bond was formed by an aldol reaction of a *dianion* of the intermediate. The product was a 1:1 mixture of diastereomers. After protecting group manipulations, this adduct was cyclized by macrolactonization. The two diastereomers were separated prior to completion of the synthesis by deprotection and epoxidation.

40. M. Tokunaga, J. F. Larrow, F. Kakiuchi, and E. N. Jacobsen, *Science*, **277**, 936 (1997).

Although each of the epothilone syntheses has its unique features, there are several recurring themes. Each synthesis uses one or more enantiopure compound as a starting material. All except the Danishefsky synthesis in Scheme 13.62 utilize the ester bond as a major disconnection. Most also use the C(12)–C(13) double bond as a second major disconnection, and several make the synthetic connection by the alkene (or alkyne) metathesis reaction. Others make the C(11)–C(12) disconnection and use a Suzuki coupling reaction in the synthetic sense to form the C(10)–C(11) bond. Wittig reactions figure prominently in the assembly of the thiazole-containing side chain. The configuration of the isolated stereocenter at C(15) is established by use of an enantiopure starting material (Schemes 13–59, 13–62, 13–64, and 13–66), an enantioselective reagent (Schemes 13–60, 13–61, and 13–63), or a kinetic resolution (Scheme 13–65). The stereochemical issues present are in the C(3)–C(8) segment and are addressed mainly by aldol reaction stereoselectivity.

13.2.6. Discodermolide

(+)-Discodermolide is a natural product isolated from a deep-water sponge found in the Caribbean Sea. The compound is probably produced by a symbiotic microorganism and isolation is not currently a practical source of the material. Like Taxol and epothilone A, (+)-discodermolide is a microtubule stabilizing agent with a promising profile of antitumor activity. A significant feature of the discodermolide structure is the three CH_3-OH-CH_3 triads that establish the configuration of nine stereogenic centers. The C(2)–C(4) and C(18)–C(20) triads are *syn, anti*, whereas the C(10)–C(12) triad is *anti, syn*. Seven syntheses are described here. Recently, major elements of two of these syntheses have been combined to provide sufficient material for Phase I clinical trials of (+)-discodermolide.

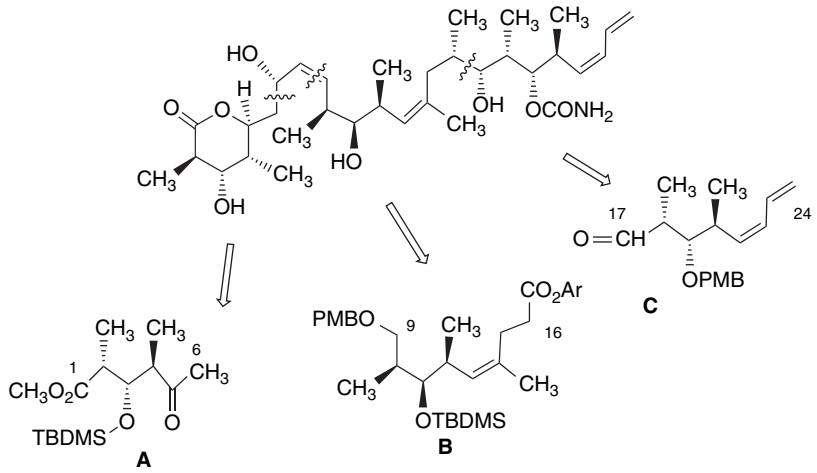


(+)-Discodermolide

The first (+)-discodermolide synthesis was completed by Stuart Schreiber's group at Harvard University and is outlined in Scheme 13.68. This synthesis was carried through for both enantiomers and established the absolute configuration of the natural material. The retrosynthetic plan outlined in Scheme 13.67 emphasizes the stereochemical triads found at C(2)–C(4), C(10)–C(12) and C(18)–C(20) and was designed to use a common chiral starting material. Each of the segments contains one of the stereochemical triads.

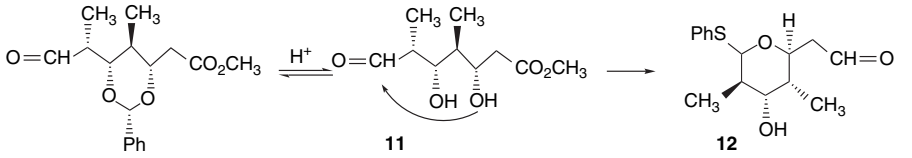
The starting material for the synthesis, methyl (*S*)-3-hydroxy-2-methylpropanoate, was converted to the corresponding aldehyde by reduction. The aldehyde was then converted to the diastereomeric homoallylic alcohols **9** and **10** using a chiral crotonylboronate (Scheme 13.68). The stereochemistry at C(5) was established by formation of the phenyldioxane ring by conjugate addition of a hemiacetal intermediate in Step **A**-3. After oxidation of C(1) to the aldehyde level the compound was rearranged to **11**, which eventually furnished the lactone terminus. The aldehyde group was introduced

Scheme 13.67. Retrosynthetic Analysis of (+)-Discodermolide to Fragments containing Stereotriads[a]



a. D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996).

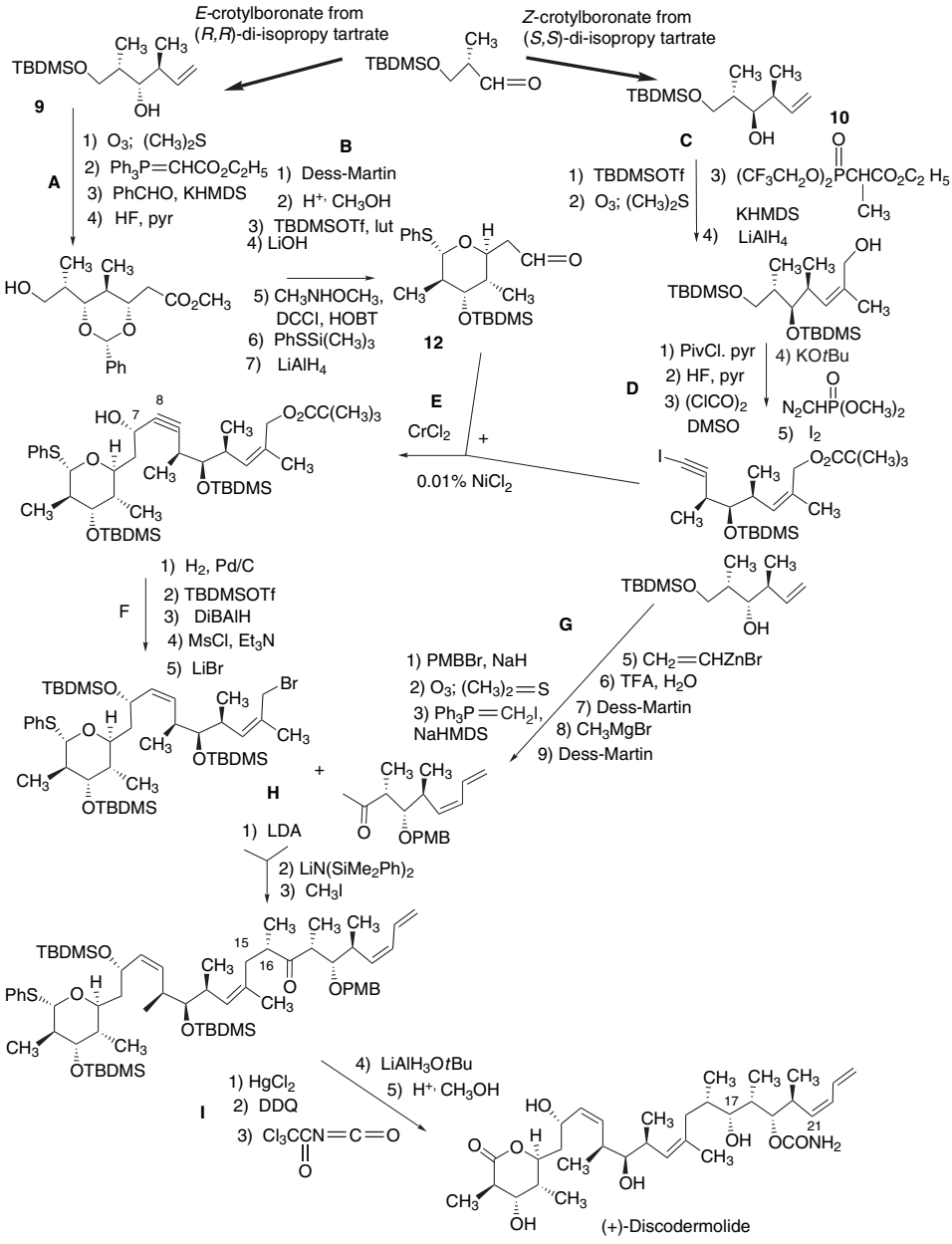
prior to coupling by reductions of the *N*-methyl-*N*-methyl amide by $LiAlH_4$ (Steps **B**-5 to **B**-7). This fragment was carried through most of the synthesis as the corresponding phenylthio acetal.



The stereoisomeric alcohol **10** was converted to the C(9)−C(15) fragment by a *Z*-selective Wadsworth-Emmons reaction, followed by reduction of the ester group in Steps **C**-1 to **C**-4. The alcohol was protected as the pivalate ester and then converted to a terminal alkyne using dimethyl diazomethylphosphonate. The C(1)–C(7) and C(8)–C(15) fragments were coupled by a Ni-catalyzed Cr(II) reaction in Step **E**. After reduction to the *Z*-alkene, the allylic alcohol was converted to the bromide via a mesylate. This set the stage for coupling with the C(16)–C(24) segment by enolate alkylation. The C(16) methyl group was installed at this point by a second alkylation (Step **H**-2). When the alkylation was carried out with this methyl group already in place, the C(16) epimer of (+)-discodermolide was obtained. The final conversion to (+)-discodermolide was achieved after carbamoylation of the C(19) hydroxy group. This group promoted stereoselective reduction at C(17) using a bulky hydride reducing agent. Deprotection then gave (+)-discodermolide.

The synthesis of (+)-discodermolide in Scheme 13.69 was completed in James Marshall's laboratory at the University of Virginia and applies allenylmetal methodology at key stages. The starting material was O-protected (*S*)-3-hydroxy-2-methylpropanal. An enantiopure butynyl mesylate was the other starting material. The CH_3-OH-CH_3 stereochemical triad was established by addition to the aldehyde using Pd-catalyzed reaction with an allenyl zinc reagent generated from a butenyl

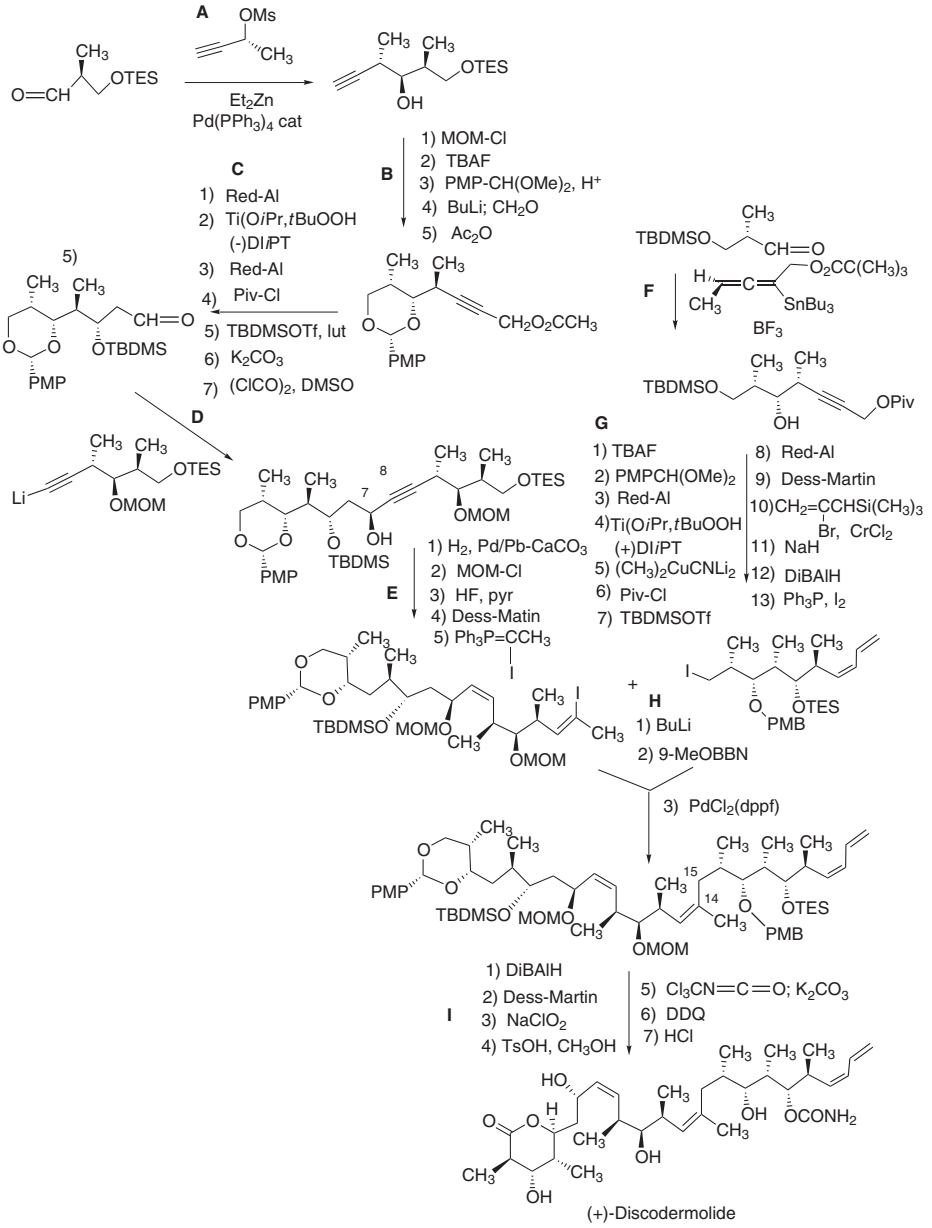
Scheme 13.68. Synthesis of Discodermolide: S. L. Schreiber and Co-Workers[a]



a. D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996).

mesylate (Step **A**). The adduct was cyclized as a 1,3-dioxane and further elaborated to an aldehyde intermediate. Reduction to an allylic alcohol by Red-Al was followed by Sharpless epoxidation. The epoxide was opened by a second Red-Al reduction. After protecting group manipulation, the aldehyde functional group was obtained by Swern oxidation. (Steps **C**-1 to **C**-7). This aldehyde was coupled

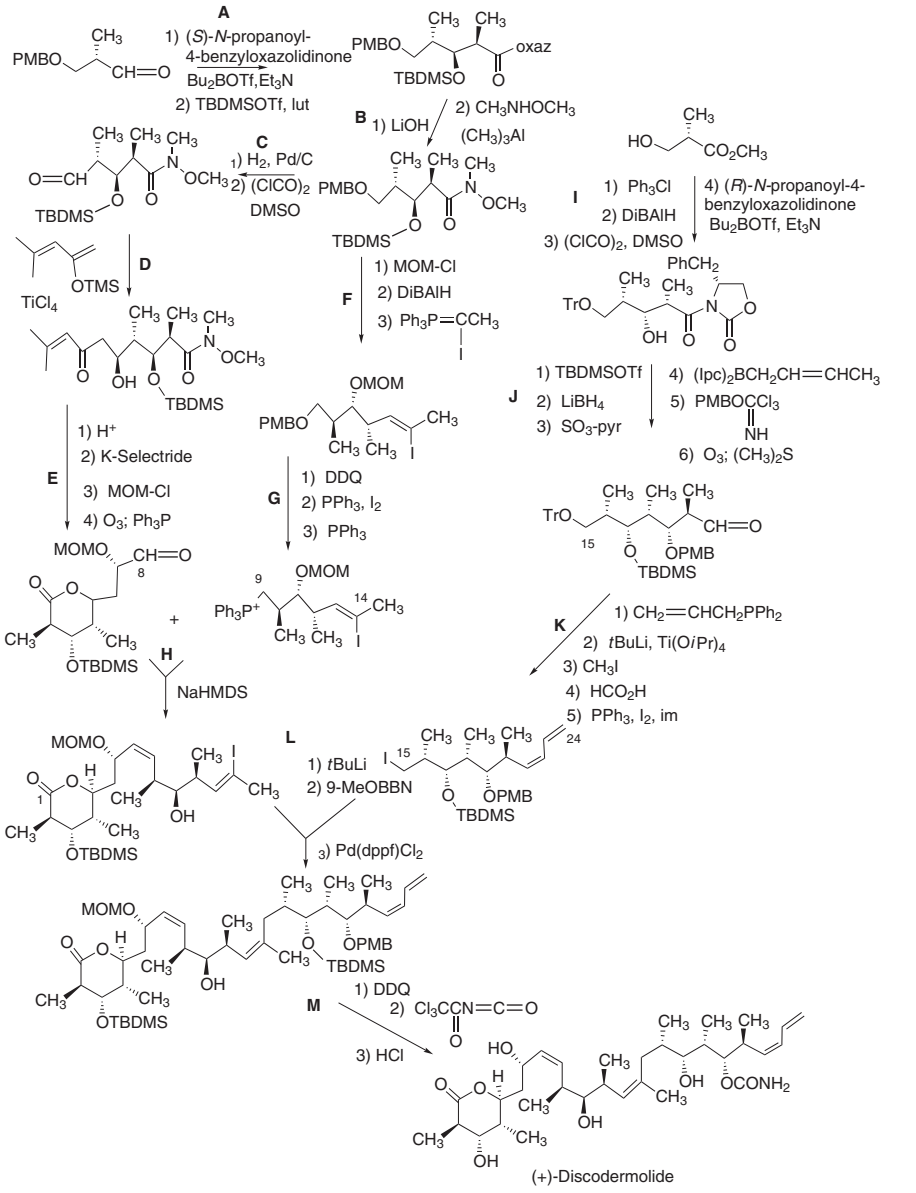
Scheme 13.69. Discodermolide Synthesis: J. A. Marshall and Co-Workers[a]



a. J. A. Marshall, Z.-H. Lu, and B. A. Johns, *J. Org. Chem.*, **63**, 817 (1998); J. A. Marshall and B. A. Johns, *J. Org. Chem.*, **63**, 7885 (1998).

with a protected alkyne, forming the C(7)–C(8) bond (Step **D**). Reduction with a Lindlar catalyst gave the *Z*-double bond, which provided C(1)–C(13) of the discodermolide skeleton with the correct stereochemistry. A terminal vinyl iodide including C(14) and its methyl substituent was introduced by a Wittig reaction using 1-iodoethylidenetriphenylphosphorane.

Scheme 13.70. Discodermolide Synthesis: A. B. Smith, III and Co-Workers[a]



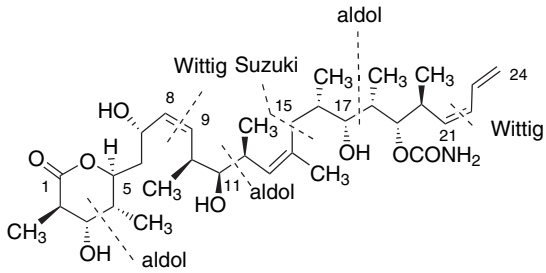
a. A. B. Smith, III, B. S. Freeze, M. Xian, and T. Hirose, *Org. Lett.*, **7**, 1825 (2005).

The C(15)–C(24) segment was constructed by addition of a chiral allenylstannane reagent to the starting aldehyde in Step **F**. The propargyl acetate terminus was reduced by DiBAlH, giving an allylic alcohol that was subjected to Sharpless asymmetric epoxidation. The methyl substituent at C(20) was added by nucleophilic opening of the epoxide with dimethylcyanocuprate. This segment was extended to include the terminal diene unit in **G**-9 and **G**-10. The terminal diene unit was

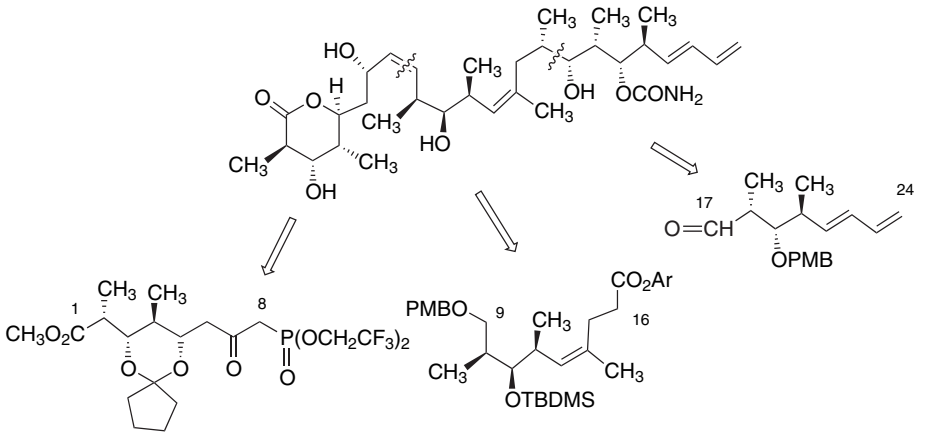
introduced by $CrCl_2$-mediated addition in Step **G**-10, followed by base-induced elimination from the β-hydroxysilane.

The two major subunits were coupled by a Suzuki reaction in Step **H**-3. The synthesis was then completed by reductive opening of the 1,3-dioxane ring, oxidation of the terminal alcohol to the carboxylic acid, carbamoylation, deprotection, and lactonization.

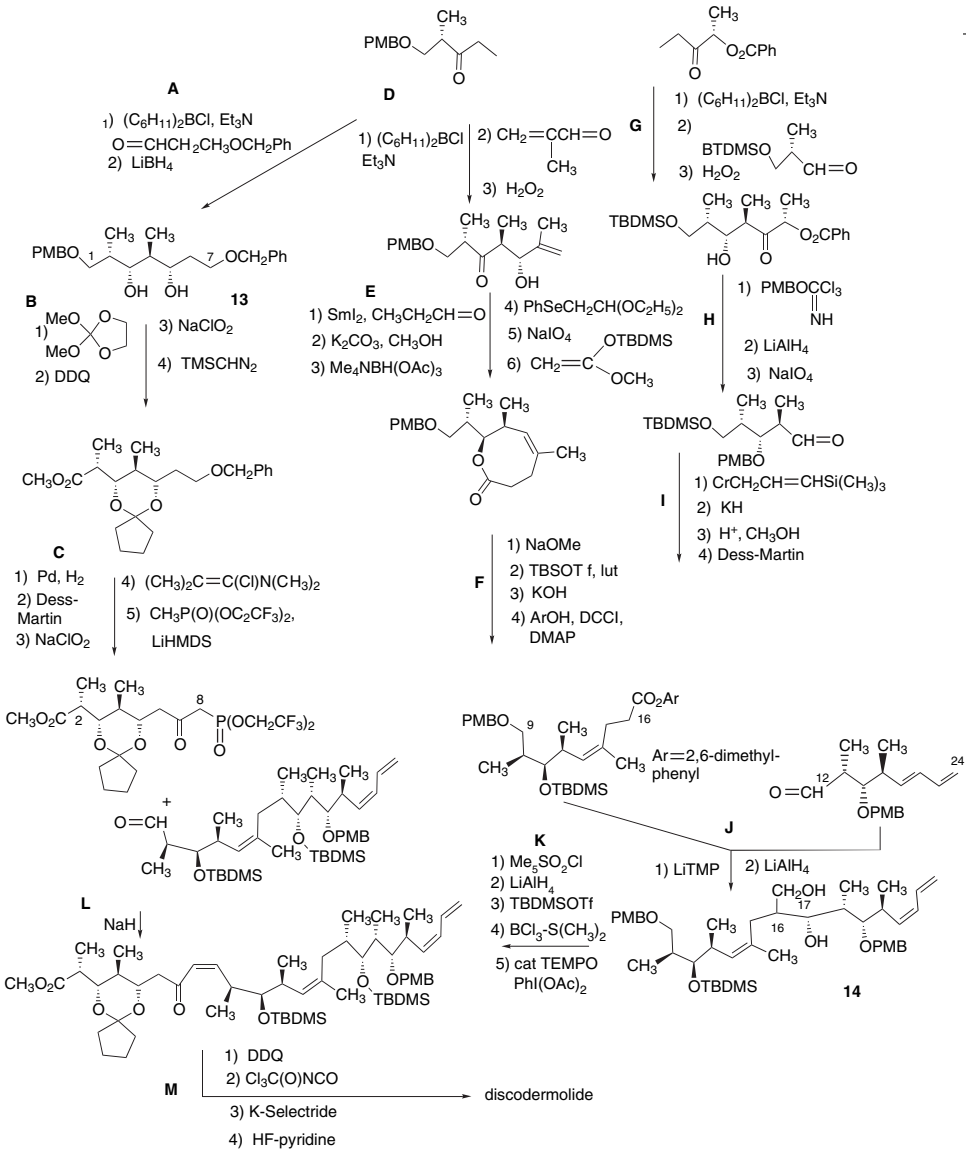
The synthesis of discodermolide in Scheme 13.70 was developed by A. B. Smith, III, and co-workers at the University of Pennsylvania. The synthesis shown in the scheme, which is the result of refinement of several previous syntheses from this laboratory, used a common precursor prepared in Steps **A** and **B**. The stereochemistry of the fragments was established by use of oxazolidinone chiral auxiliaries. The boron enolate of *N*-propanoyl-4-benzyloxazolidinone was added to PMP-protected (*S*)-3-hydroxy-2-methylpropanal in Step **A**. The chiral auxiliary was then replaced by an *N*-methoxy-*N*-methylamide in Step **B**. This intermediate was used for the construction of the C(1)−C(8) and C(9)−C(14) segments. The connection between these two fragments was made by a Wittig reaction at Step **H**. The C(15)−C(21) segment was also derived from an oxazolidinone chiral auxiliary, in this case the (*R*)-enantiomer. The configuration at C(20) was established by allylboration (Step **J**-4). The terminal diene was introduced by a Wittig reaction in Step **K**-1. The two major segments were then coupled at the C(14)–C(15) bond by using the Suzuki reaction in Step **L**. The final steps involve deprotection and installation of the carbamoyl group. The overall yield for this version is 9% with a longest linear sequence of 17 steps.



Scheme 13.71 shows the most recent version of a synthesis of (+)-discodermolide developed by Ian Paterson's group at Cambridge University. The synthesis was based on three major subunits and used boron enolate aldol addition reactions to establish the stereochemistry.

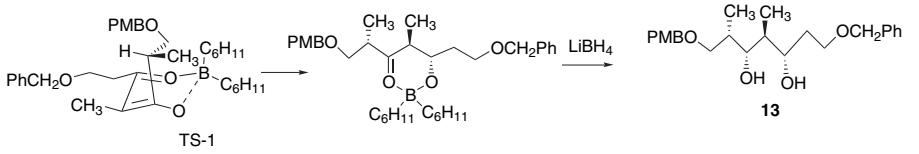


Scheme 13.71. Discodermolide Synthesis: I. Paterson and Co-Workers[a]



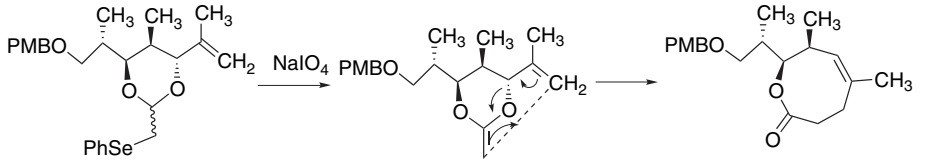
a. I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, and N. Sereinig, *J. Am. Chem. Soc.*, **123**, 9535 (2001); I. Paterson, O. Delgado, G. J. Florence, I. Lyothier, J. P. Scott, and N. Sereinig, *Org. Lett.*, **5**, 35 (2003); I. Paterson and I. Lyothier, *J. Org. Chem.*, **70**, 5494 (2005).

The synthesis of the C(1)–C(6) subunit was based on addition of an enol boronate to 3-benzyloxypropanal through TS-1. Immediate reduction of the chelate is also stereoselective and provides the intermediate **13**. These steps establish the configuration at C(2)–C(5).



The diol was protected and the C-terminal group converted to a methyl ester in sequence **B**. A phosphonate group was installed at C(7) via an acylation reaction in Step **C**-5. Successive oxidations of the primary and deprotected secondary alcohol gave the C(1)–C(8) intermediate.

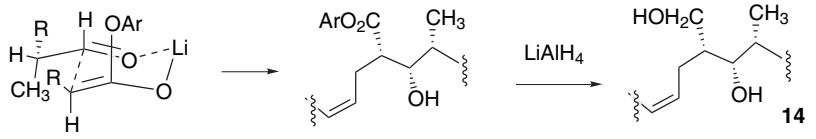
The C(9)−C(16) subunit was synthesized from the same starting material. The chain was extended by a boron enolate addition to 2-methylpropenal (Step **D**-2). After introduction of a double bond by selenoxide elimination in Step **E**-4, a Claisen rearrangement was used to generate an eight-membered lactone ring (Step **E**-6).



The lactone ring was then opened and the carboxy group converted to a hindered phenolic ester (Step **F**-4), providing the C(9)–C(16) intermediate.

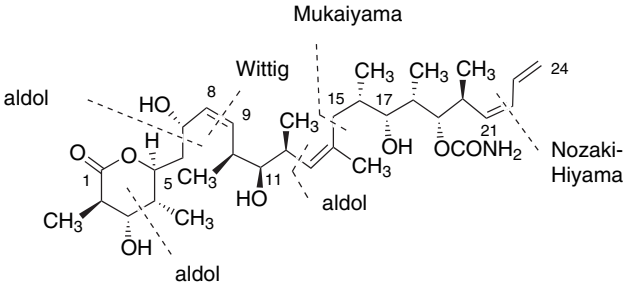
The synthesis of the C(17)−C(24) segment also began with a diastereoselective boron enolate aldol addition. The adduct was protected and converted to an aldehyde in sequence **H**. The terminal diene unit was installed using a γ-silylallyl chromium reagent, which generates a β-hydroxysilane. Peterson elimination using KH then gave the *Z*-diene.

The three fragments were then coupled. The C(16)−C(17) bond was established by addition of the lithium enolate of the aryl ester in the C(9)−C(16) fragment with the aldehyde group of the C(17)–C(24) fragment. The stereochemistry is consistent with the cyclic aldol addition TS. The adduct was immediately reduced to the diol **14** by $LiAlH_4$.

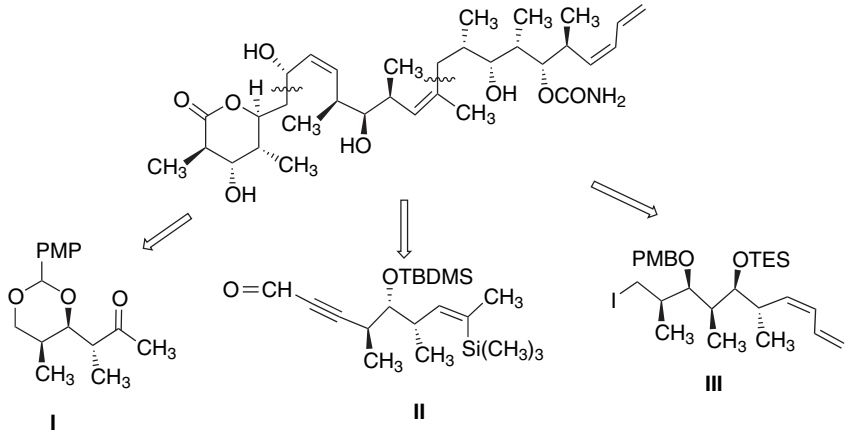


The primary hydroxymethyl group at C(16) was deoxygenated via the mesitylenesulfonate. After removal of the PMP protecting group, a sterically demanding oxidant, TEMPO-PhI$(OAc)_2$ was used to selectively oxidize the primary alcohol group to an aldehyde. The Still-Gennari version of the Wadsworth-Emmons reaction was used to couple with the C(1)−C(8) fragment in Step **L**. This reaction proceeded with 5:1 *Z* : *E* selectivity and led to isolation of the *Z*-product in 73% yield. The PMB protecting group was then removed and the carbamate group introduced at C(19). The remaining protecting groups were then removed and the lactonization completed the synthesis.

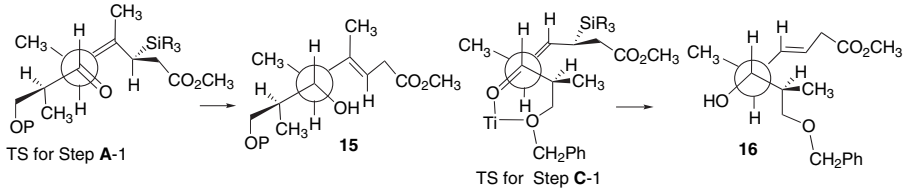
The overall yield was about 12% over a longest linear sequence of 23 steps and about 40 steps total. The major disconnections are illustrated below.



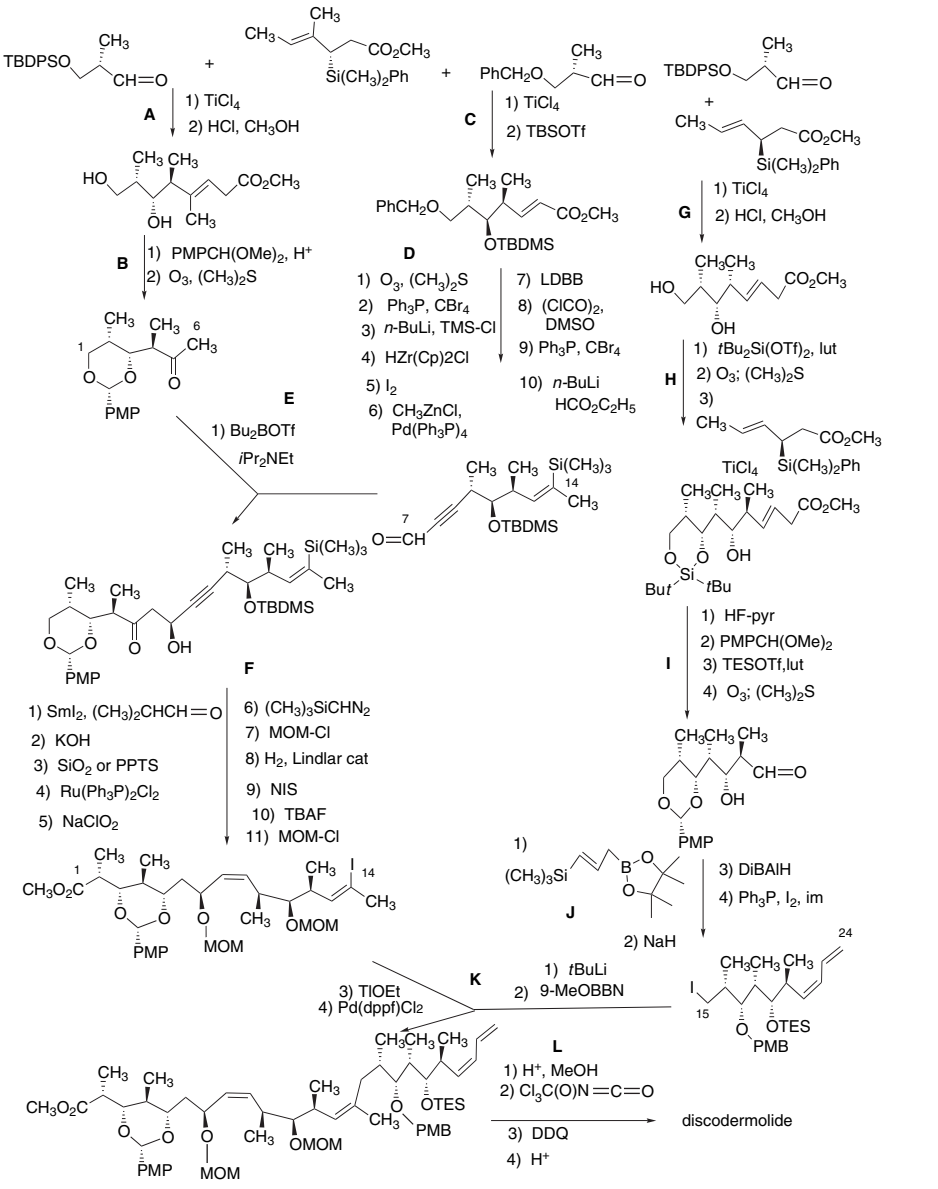
The synthesis outlined in Scheme 13.72 was carried out by James Panek's group at Boston University and is based on three key intermediates that were synthesized from two closely related methyl 3-(dimethylphenylsilyl)hex-4-enoates.



The stereochemistry was controlled by Lewis acid–induced addition of the allylic silanes to aldehydes. The reaction of the silane with O-protected (*S*)-3-hydroxy-2-methylpropanal provides **15**. The silane reacted with the benzyl-protected analog to provide **16**.



Scheme 13.72. Discodermolide Synthesis: J. S. Panek and A. Arefolov[a]



a. A. Arefolov and J. S. Panek, *J. Am. Chem. Soc*., **127**, 5596 (2005).

These intermediates were then converted to the fragments **I** and **II**, respectively. Intermediate **15** was protected as a cyclic acetal and then ozonized to give segment **I**. In the synthesis of the **II** fragment the adduct was extended by two Corey-Fuchs sequences with in situ functionalization to provide the alkyne intermediate **II** (Steps **D**-2 and **D**-9). Trimethylsilyl and methyl groups were introduced at C(14) and a formyl groups was added at C(8). The fragments **I** and **II** were coupled by boron enolate methodology and a single stereoisomer was obtained in 88% yield (Step **E**).

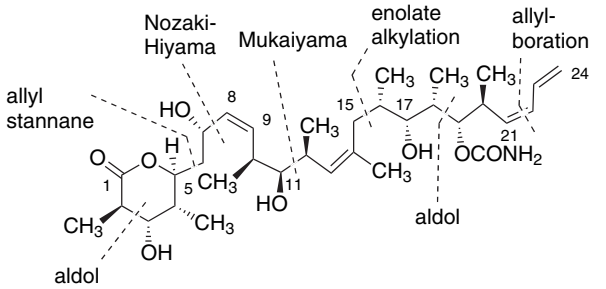
The coupled fragments were then converted to a vinyl iodide. The key steps were a *Z*-selective Lindlar reduction and iodinolysis of the vinyl silane, which was done using NIS in acetonitrile (sequence **F**-1 to **F**-11).

The C(15)–C(24) segment **C** was created by two successive additions of the allylic silane synthons (Steps **G**-1 and **H**-3). The unsaturated esters resulting from the additions were subjected to ozonolysis. The terminal diene unit was added using a silyl-substituted allylic boronate and then subjected to base-mediated elimination. The coupling of the **I**-**II** and **III** segments was done by Suzuki methodology. It was also carried out in somewhat lower yield using a zinc reagent prepared from the vinyl iodide. The synthesis was completed by deprotection and lactonization. There are a total of 42 steps, with the longest linear sequence being 27 steps, in overall 21% yield.

The synthesis of discodermolide in Scheme 13.73 was completed at the University of California, Berkeley by D. C. Myles and co-workers. The synthesis began with a $TiCl_4$-mediated cycloaddition that gave a dihydropyrone intermediate that contains the stereochemistry at C(10)−C(12) and the *Z*-configuration at the C(13)−C(14) double bond. Reduction and H^+-promoted Ferrier rearrangement gave a lactol containing C(9)−C(15) (Steps **B-**1 and **B-**2). This lactol was converted to an allylic iodide, providing one of the key intermediates, **II**.

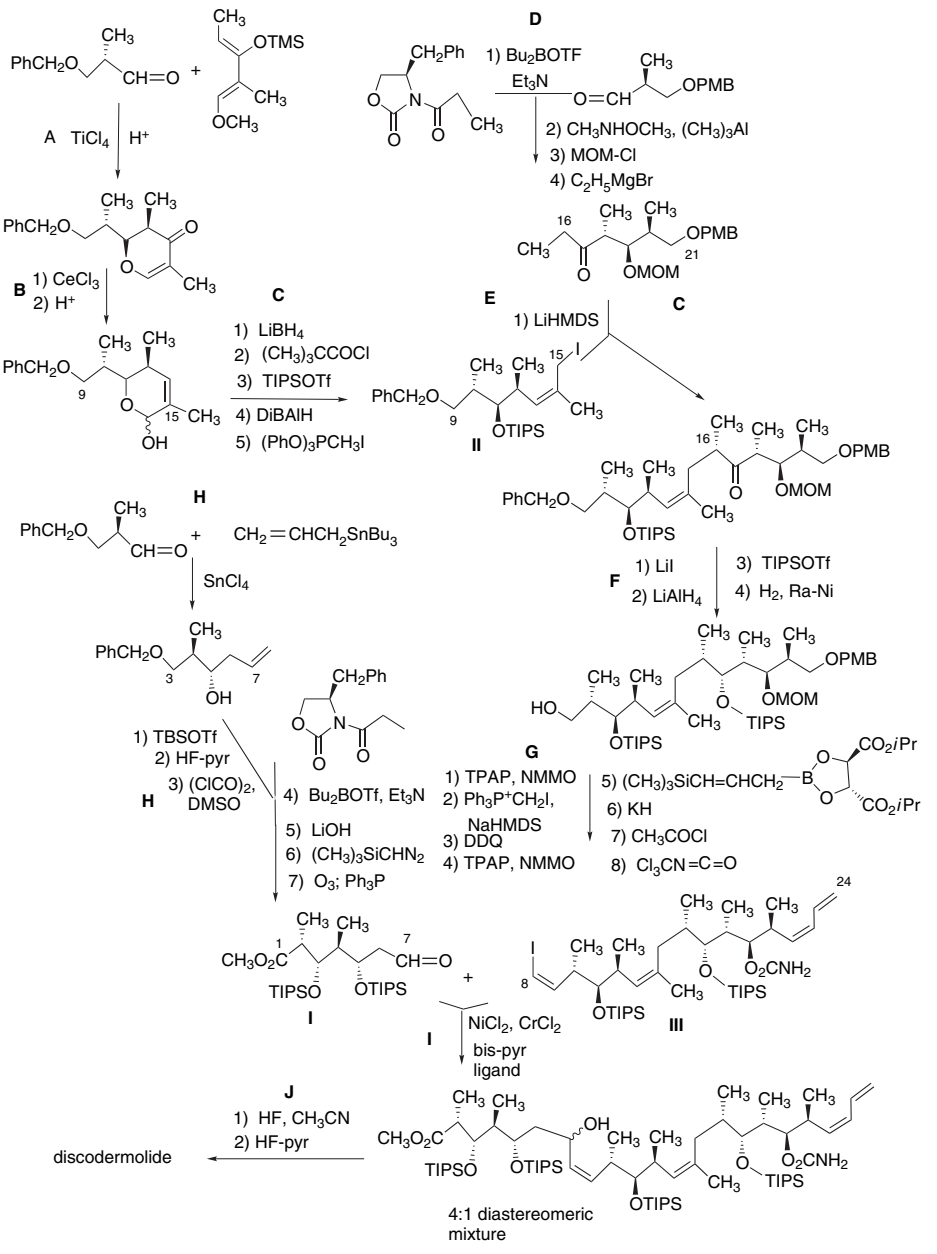
The stereochemistry at C(18)−C(20) was established using an oxazolidinone chiral auxiliary (Step **D**-1). Carbon-16 and its methyl substituent were added by a Grignard addition in Step **D**-4. The C(9)−C(15) and C(16)−C(21) segments were joined by enolate alkylation (Step **E**). Under optimum conditions, a 6:1 preference for the desired stereoisomer at C(16) was achieved. The stereochemistry at C(17) was established by $LiAlH_4$ reduction in the presence of LiI, with 8:1 stereoselectivity. An iodovinyl group containing C(8) was installed using iodomethylenetriphenylphosphorane, giving a $Z:E$ isomer ratio of 20:1 (Step **G**-2). The terminal diene unit was installed using a γ-silylallylboronate, followed by base-mediated *syn* elimination (Steps **G**-5 and **G**-6). The carbamate group was then installed, completing the synthesis of intermediate **III**.

The synthesis of the C(1)–C(7) fragment began with allylstannylation (Step **H**). The C(1)–C(2) terminus was introduced using the dibutylboron enolate of an oxazolidinone chiral auxiliary. The C(8)–C(24) fragment was added via a $NiCl_2$-$CrCl_2$ coupling. This reaction was improved by inclusion of a chiral *bis*-pyridine ligand. Sequential deprotection and lactonization afforded discodermolide. The overall yield was 1.5% based on a 22-step longest linear sequence.



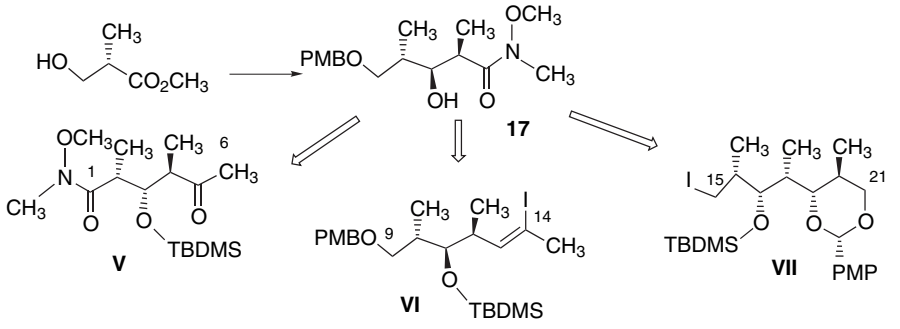
The synthesis of (+)-discodermolide shown in Scheme 13.74 was developed in the laboratories of the Novartis Pharmaceutical Company and was designed to provide sufficient material for initial clinical trials. The synthesis is largely based on the one

Scheme 13.73. Discodermolide Synthesis: D. C. Myles Co-workers[a]



a. S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, and D. C. Myles, *J. Org. Chem.*, **68**, 6646 (2003).

by A. B. Smith, III, and co-workers (Scheme 13.70), with the final stages being based on the synthesis in Scheme 13.71. The synthesis begins with a single starting material having one stereogenic center and proceeds through Smith's common intermediate **17** to three segments containing the stereochemical triads.

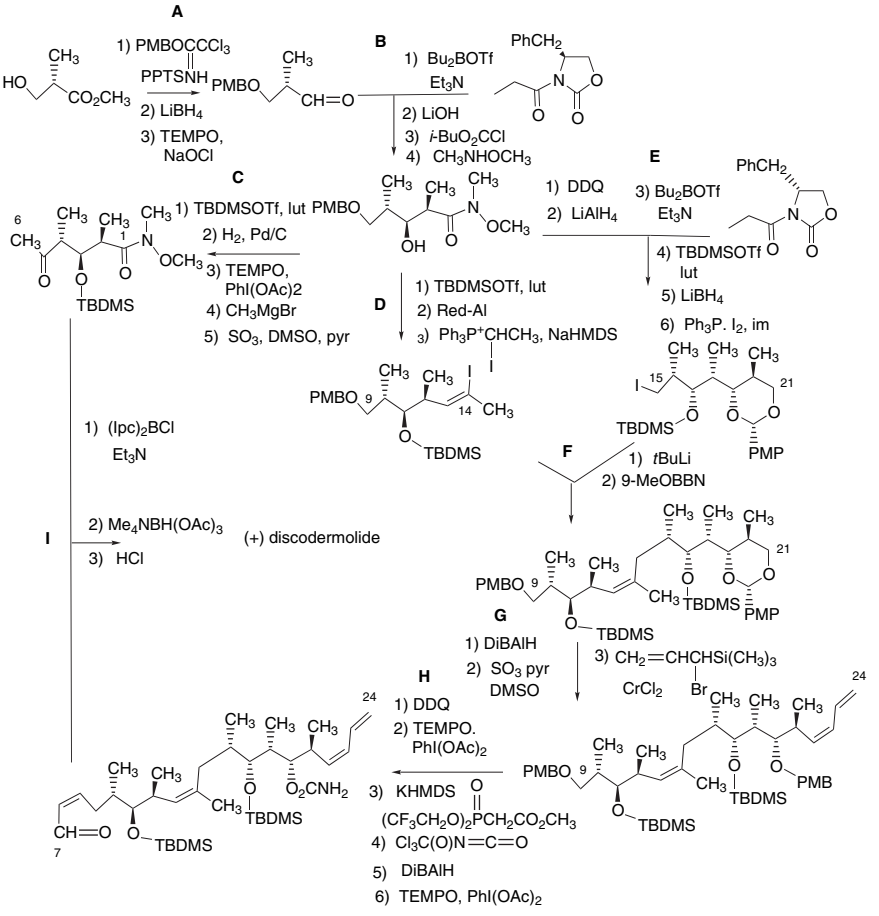


A number of modifications were made to meet scale-up requirements. In the preparation of the common intermediate, $LiBH_4$ was used in place of $LiAlH_4$ in Step **A**-2 and a TEMPO-NaOCl oxidation was used in place of Swern oxidation in Step **A**-3. Some reactions presented difficulty in the scale-up. For example, the boron enolate aldolization in Step **B**-1 gave about 50% yield on the 20- to 25-kg scale as opposed to greater than 75% on a 50-g scale. The amide formation in Step **B**-3 was modified to eliminate the use of trimethylaluminum, and the common intermediate **17** could be prepared on a 30-kg scale using this modified sequence. The synthesis of the C(1)–C(6) segment **V** was done by Steps **C**-1 to **C**-5 in 66% yield on the scale of several kg.

The C(9)−C(14) segment **VI** was prepared by Steps **D**-1 to **D**-3. The formation of the vinyl iodide in Step **D**-3 was difficult and proceeded in only 25–30% yield. The C(15)−C(21) segment **VII** was synthesized from the common intermediate **17** by Steps **E**-1 to **E**-6. A DDQ oxidation led to formation of a 1,3-dioxane ring in Step **E**-1. The *N*-methoxy amide was converted to an aldehyde by $LiAlH_4$ reduction and the chain was extended to include C(14) and C(15) using a boron enolate of an oxazolidinone chiral auxiliary. After reductive removal of the chiral auxiliary, the primary alcohol group was converted to a primary iodide. The overall yield for these steps was about 25%.

The C(9)−C(14) and C(15)−C(21) segments were then coupled using Suzuki methodology (Step **F**). The terminal diene unit was then introduced in Steps **G**-1 to **G**-3. The cyclic acetal was reduced with DiBAlH, restoring the PMB protecting group and deprotecting the C(21) hydroxy. This primary alcohol was oxidized to the aldehyde and coupled with an allylic silane using $CrCl_2$, as in Scheme 13.69. The chain was then extended by adding C(7) and C(8) using the *Z*-selective Still-Gennari modification of the Wadsworth-Emmons reaction (Step **H**-3) and the ester was converted to an aldehyde. This permitted the final coupling with the C(1)−C(6) fragment using a boron enolate prepared from $(Ipc)_2BCl$. The optimized procedure gave the product in 50–55% yield with stereoselectivity of about 4:1. A process for converting the minor diastereomer to the desired product was developed. The final reduction was done with $[(CH_3)_4N]^+[BH(OAc)_3]^-$. Removal of the final silyl protecting group and lactonization gave (+)-discodermolide. The overall synthesis involved 39 steps.

Scheme 13.74. Discodermolide Synthesis: Novartis Group[a]



a. S. J. Mickel, G. H. Sedelmeier, D. Niederer, R. Daeffler, A. Osmani, K. Shreiner, M. Seeger-Weibel, B. Berod, K. Schaer, R. Gamboni, S. Chen, W. Chen, C. T. Jagoe, F. R. Kinder, Jr., M. Loo, K. Prasad, O. Repic, W.-C. Shieh, R.-M. Wang, L. Waykole, D. D. Xu, and S. Xue, *Org. Proc. Res. Dev.*, **8**, 92 (2004); S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, D. Grimler, G. Koch, R. Daeffler, A. Osmani, A. Hirni, K. Schaer, R. Gamboni, A. Bach, A. Chaudhary, S. Chen, W. Chen, B. Hu, C. T. Jagoe, H.-Y. Kim, F. R. Kinder, Jr., Y. Liu, Y. Lu, J. McKenna, M. Prasad, T. M. Ramsey, O. Repic, L. Rogersk, W.-C. Shieh, R.-M. Wang, and L. Waykole, *Org. Proc. Res. Dev.*, **8**, 101 (2004); S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, G. Koch, E. Kuesters, R. Daeffler, A. Osmani, M. Seeger-Weibel, E. Schmid, A. Hirni, K. Schaer, R. Gamboni, A. Bach, S. Chen, W. Chen, P. Geng, C. T. Jagoe, F. R. Kinder, Jr., G. T. Lee, J. McKenna, T. M. Ramsey, O. Repic, L. Rogers, W.-C. Shieh, R.-M. Wang, and L. Waykole, *Org. Proc. Res. Dev.*, **8**, 107 (2004); S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, M. Seger, K. Schreiner, R. Daeffler, A. Osmani, D. Bixel, O. Loiseleur, J. Cercus, H. Stettler, K. Schaer, R. Gamboni, A. Bach, G.-P. Chen, W. Chen, P. Geng, G. T. Lee, E. Loesser, J. McKenna, F. R. Kinder, Jr., K. Konigberger, K. Prasad, T. M. Ramsey, N. Reel, O. Repic, L. Rogers, W.-C. Shieh, R.-M. Wang, L. Waykole, S. Xue, G. Florence, and I. Paterson, *Org. Proc. Res. Dev.*, **8**, 113 (2004); S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Shaer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder, Jr., K. Koningberger, K. Prasad, T. M. Ramsey, O. Repic, R.-M. Wang, G. Florence, I. Lyothier, and I. Paterson, *Org. Proc. Res. Dev.*, **8**, 122 (2004).

These syntheses of (+)-discodermolide provide examples of the application of several current methods for control of acyclic stereochemistry. They illustrate the use of allylic boronates, allenyl stannanes, oxazolidinone auxiliaries, boron enolates, and allylic silanes to achieve enantioselective formation of key intermediates. Wittig and Suzuki reactions figure prominently in the coupling of key intermediates. Several of the syntheses use β-hydroxy silane elimination to introduce the terminal diene. The discodermolide structure lends itself to a high degree of convergency, and the relationship among the three stereochemical triads permits utilization of common starting materials, which contributes to overall synthetic efficiency. The composite synthesis completed by the Novartis group provides an insight into the logistics of scale-up of a synthesis of this complexity. The synthesis described in Scheme 13.74 produced 60 g of pure (+)-discodermolide. The effort involved about 40 chemists and was carried out over a period of 20 months.

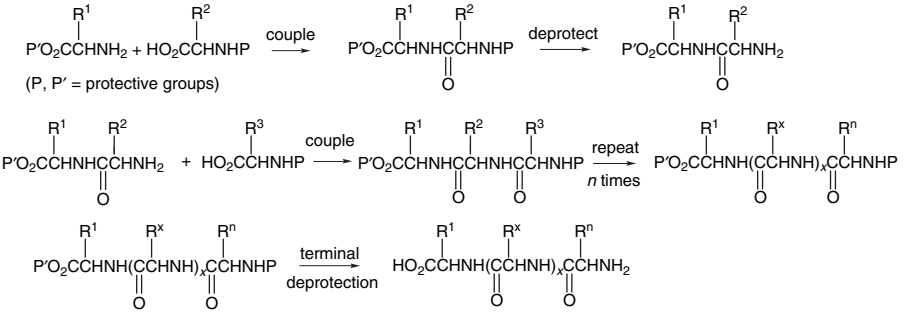
13.3. Solid Phase Synthesis

The syntheses discussed in the previous sections were all carried out in *solution phase* and intermediates were isolated and purified. There is another general approach to multistep synthesis in which the starting material is attached to a solid support. The sequence of synthetic steps is then carried out with the various intermediates remaining attached to the solid support. Called *solid phase synthesis*, this approach has a potential advantage in that excess reagents and by-products can simply be washed away after each step. When the synthesis is complete, the product can be detached from the support. Another potential advantage of solid phase synthesis is that the operations can be automated. A particular sequence for addition of reactants, reagents, and solvents for removal of soluble material can be established. Instruments can then be programmed to carry out these operations.

The most highly developed applications of solid phase methods are in the syntheses of polypeptides and oligonucleotides. These molecules consist of linear sequences of individual amino acids or nucleotides. The connecting bonds are the same for each subunit: amides for polypeptides and phosphate esters for the polynucleotides. The synthesis can be carried out by sequentially adding the amino acids or nucleotides and coupling reagents. The ability to synthesize polypeptides and oligonucleotides of known sequence is of great importance in a number of biological applications. Although these molecules can be synthesized by synthetic manipulations in solution, they are now usually synthesized by solid phase methods, using automated repetitive cycles of deprotection and coupling. Another important application of solid phase synthesis is in combinatorial synthesis, where the goal is to make a large number of related molecules by systematic variation of the individual components.

13.3.1. Solid Phase Polypeptide Synthesis

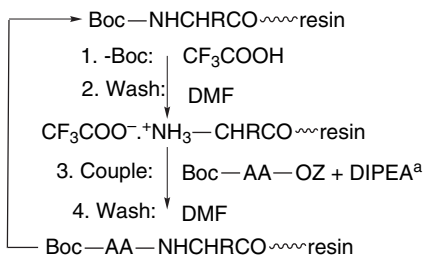
The techniques for automated solid phase synthesis were first highly developed for polypeptides and the method is abbreviated as *SPPS*. Polypeptide synthesis requires the sequential coupling of the individual amino acids. After each unit is added, it must be deprotected for use in the next coupling step.



Excellent solution methods involving alternative cycles of deprotection and coupling are available for peptide synthesis,[41] and the techniques have been adapted to solid phase synthesis.[42] The N-protected carboxy terminal amino acid is linked to the solid support, which is usually polystyrene with divinylbenzene cross-linking. The amino group is then deprotected and the second N-protected amino acid is introduced and coupled. The sequence of deprotection and coupling is then continued until the synthesis is complete. Each deprotection and coupling step must go in very high yield. Because of the iterative nature of solid phase synthesis, errors accumulate throughout the process. For the polypeptide to be of high purity, the conversion must be very efficient at each step.

The first version of SPPS to be developed used the *t*-Boc group as the amino-protecting group. *t*-Boc can be cleaved with relatively mild acidic treatment and TFA is usually used. The original coupling reagents utilized for SPPS were carbodiimides. In addition to dicyclohexylcarbodiimide (DCCI), *N*, *N*′-diisopropylcarbodiimide (DIPCDI) is often used. The mechanism of peptide coupling by carbodiimides was

Scheme 13.75. *t*-Boc Protocol for Solid Phase Peptide Synthesis

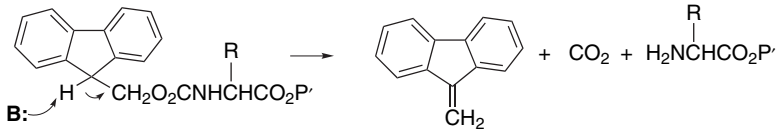


a. OZ = active ester; DIPEA = diisopropylethylamine

41. M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, 2nd Edition, Springer Verlag, Berlin, 1994; V. J. Hruby, and J.-P. Mayer, in *Bioorganic Chemistry: Peptides and Proteins*, S. Hecht, ed. Oxford University Press, Oxford, 1998, pp. 27–64.
42. R. B. Merrifield, *Meth. Enzymol.*, **289**, 3 (1997); R. B. Merrifield, in *Peptides: Synthesis, Structure, and Applications*, B. Gutte, ed., Academic Press, San Diego, CA, p. 93; E. Atherton and R. C. Sheppard, *Solid Phase Peptide Synthesis*, IRL Press, Oxford, 1989; P. Lloyd-Williams, F. Albericio, and E. Giralt, *Chemical Synthesis of Peptides and Proteins*, CRC Press, Boca Raton, FL, 1997.

discussed in Section 3.4. Currently, the optimized versions of the *t*-Boc protocol can provide polypeptides of 60–80 residues in high purity.[43] The protocol for using *t*-Boc protection is outlined in Scheme 13.75

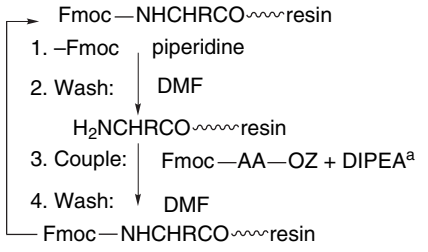
A second method that uses the fluorenylmethoxycarboxy (Fmoc) protecting group has been developed.[44] The Fmoc group is stable to mild acid and to hydrogenation, but it is cleaved by basic reagents via fragmentation triggered by deprotonation at the acidic 9-position of the fluorene ring. The protocol for SPPS using the Fmoc group is shown in Scheme 13.76.



In both the *t*-Boc and Fmoc versions of SPPS, the amino acids with functional groups in the side chain also require protecting groups. These protecting groups are designed to stay in place throughout the synthesis and then are removed when the synthesis is complete. The serine and threonine hydroxyl groups can be protected as benzyl ethers. The ε-amino group of lysine can be protected as the trifluoroacetyl derivative or as a sulfonamide derivative. The imidazole nitrogen of histidine can also be protected as a sulfonamide. The indole nitrogen of tryptophan is frequently protected as a formyl derivative. The exact choice of protecting group depends upon the deprotection-coupling sequence being used.

The original version of SPPS attached the carboxy terminal residue directly to the resin as a benzylic ester using chloromethyl groups attached to the polymer. At the present time the attachment is done using "linking groups." Two of the more common linking groups are shown. These groups have the advantage of permitting

Scheme 13.76. Fmoc Protocol for Solid Phase Peptide Synthesis

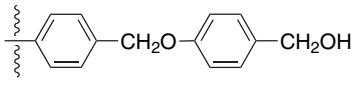


a. OZ = active ester; DIPEA = diisopropylethylamine

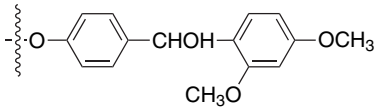
[43] M. Schnolzer, P. Alewood, A. Jones, D. Alewood, and S. B. H. Kent, *Int. J. Peptide Protein Res*., **40**, 180 (1992); M. Schnolzer and S. B. H. Kent, *Science*, **256**, 221 (1992).

[44] L. A. Carpino and G. Y. Han, *J. Org. Chem*., **37**, 3404 (1972); G. B. Fields and R. L. Noble, *Int. J. Peptide Protein Res*., **35**, 161 (1990); D. A. Wellings and E. Atherton, *Meth. Enzymol*., **289**, 44 (1997); W. C. Chan and P. D. White, ed., *Fmoc Solid Phase Peptide Synthesis: A Practical Approach*, Oxford University Press, Oxford, 2000.

milder conditions for the final removal of the polypeptide from the solid support. The C-terminal amino acid is attached to the hydroxy group of the linker.



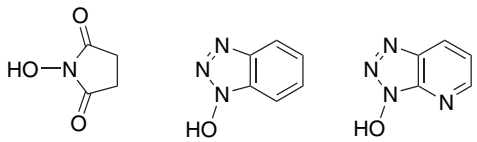
Wang linker[45]



Rink linker[46]

In the *t*-Boc protocol, the most common reagent for final removal of the peptide from the solid support is anhydrous hydrogen fluoride. Although this is a hazardous reagent, commercial systems designed for safe handling are available. In the Fmoc protocol milder acidic reagents can be used for cleavage from the resin. The alkoxybenzyl group at the linker can be cleaved by TFA. Often, a scavenger, such as thioanisole, is used to capture the cations formed by cleavage of *t*-Boc protecting groups from side-chain substituents.

At the present time, the coupling is usually done via an activated ester (see Section 3.4). The coupling reagent and one of several *N*-hydroxy heterocycles are first allowed to react to form the activated ester, followed by coupling with the deprotected amino group. The most frequently used compounds are *N*-hydroxysuccinimide, 1-hydroxybenzotriazole (HOBt), and 1-hydroxy-7-azabenzotriazole (HOAt).[47]

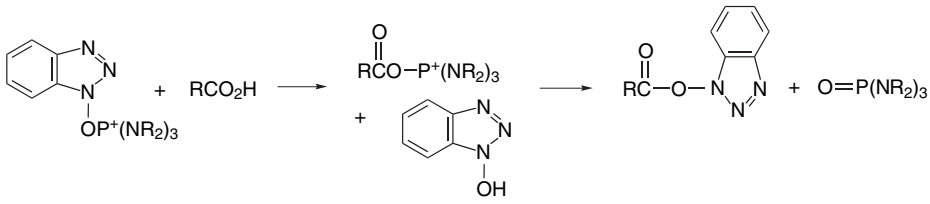


N-hydroxysuccinimide HOBt HOAt

Another family of coupling reagents frequently used with the Fmoc method is related to *N*-hydroxybenzotriazole and *N*-hydroxy 7-azabenzotriazole but also incorporates phosphonium or amidinium groups. The latter can exist in either the O-(uronium) or *N*-(guanidinium) forms.[48] Both can effect coupling. The former are more reactive but isomerize to the latter. Which form is present depends on the protocol of preparation, including the amine used and the time before addition of the carboxylic acid.[49] The

45. S. Wang, *J. Am. Chem. Soc*., **95**, 1328 (1993).
46. H. Rink, *Tetrahedron Lett*., **28**, 3787 (1987); M. S. Bernatowicz, S. B. Daniels, and H. Koster, *Tetrahedron Lett*., **30**, 4645 (1989); R. S. Garigipati, *Tetrahedron Lett*., **38**, 6807 (1997).
47. F. Albericio and L. A. Carpino, *Meth. Enzymol*., **289**, 104 (1997).
48. L. A. Carpino, H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Muegge, H. Wenschuh, J. Klose, M. Beyermann, and M. Beinert, *Angew. Chem. Int. Ed. Engl*., **41**, 441 (2002); T. K. Srivastava, W. Haq, S. Bhanumati, D. Velmurugan, U. Sharma, N. R. Jagannathan, and S. B. Katti, *Protein and Peptide Lett*., **8**, 39 (2001).
49. L. A. Carpino and A. El-Faham, *Tetrahedron*, **55**, 6813 (1999); L. A. Carpino and F. J. Ferrer, *Org. Lett*., **3**, 2793 (2001); F. Albericio, J. M. Bofill, A. El-Faham, and S. A. Kates, *J. Org. Chem*., **63**, 9678 (1998).

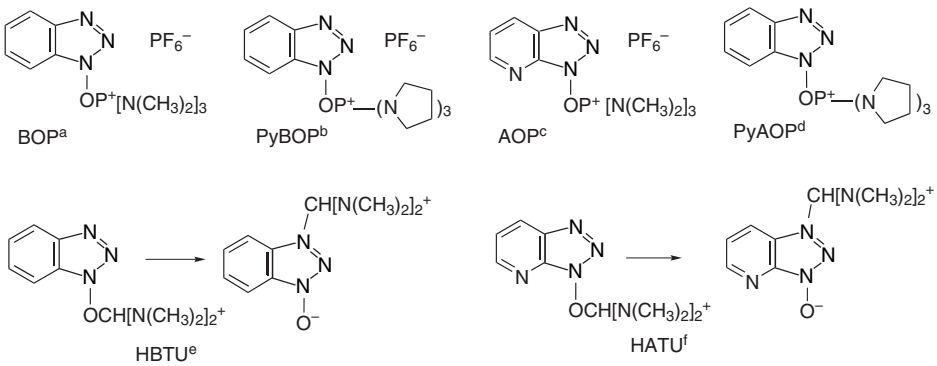
phosphonium coupling reagents are believed to form acyloxyphosphonium species that can then be converted to the active ester incorporating the *N*-hydroxy heterocycle.[50]



The structures and abbreviations of these reagents are given in Scheme 13.77.

The development of highly efficient protection-deprotection and coupling schemes has made the synthesis of polypeptides derived from the standard amino acids a highly efficient process. Additional challenges can come into play when other amino acids are involved. The HATU reagent, for example, has been applied to *N*-methyl amino acids, as in the case of cyclosporin A, an undecapeptide that is important in preventing transplant rejection. Seven of eleven amino acids are *N*-methylated. The synthesis of cyclosporin analogs has been completed by both solution and solid phase methods. Scheme 13.78 summarizes this synthesis. Fmoc protecting groups were used. Unlike the case of normal amino acids, quantitative coupling was not achieved, even when the coupling cycle was repeated twice for each step. Therefore, after each coupling cycle, a *capping step* using acetic anhydride was done to prevent carrying unextended material to the next phase. The final macrocyclization was done using propylphosphonic anhydride and DMAP, a reaction that presumably proceeds through a mixed phosphonic anhydride.[51]

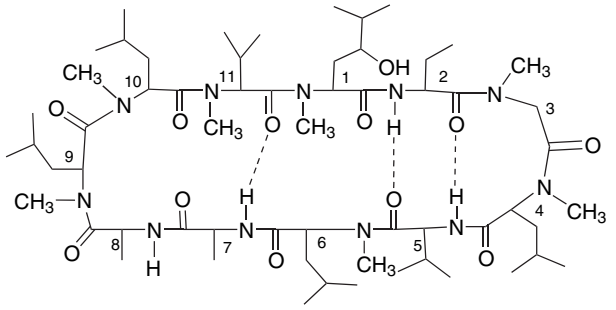
Scheme 13.77. Phosphonium, Uronium, and Guanidinium Coupling Reagents



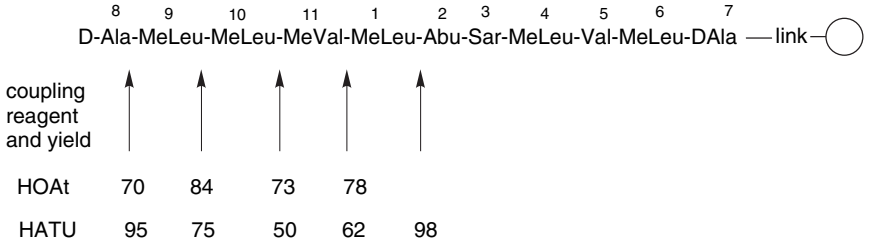
a. B. Castro, J. R. Dormoy, G. Evin, and C. Selve, *Tetrahedron Lett*., 1219 (1975).
b. J. Coste, D. Le-Nguyen, and B. Castro, *Tetrahedron Lett*., **31**, 205 (1990).
c. L. A. Carpino, A. El-Faban, C. A. Minor, and F. Albericio, *J. Chem. Soc., Chem. Commun*., 201 (1994).
d. F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino, and S. A. Kates, *Tetrahedron Lett*., **38**, 4853 (1997).
e. R. Knorr, A. Trezciak, W. Barnwarth, and D. Gillessen, *Tetrahedron Lett*., **30**, 1927 (1989).
f. L. A. Carpino, *J. Am. Chem. Soc*., **115**, 4397 (1993).

50. J. Coste, E. Frerot, and P. Jouin, *J. Org. Chem*., **59**, 2437 (1994).
51. R. M. Wegner, *Helv. Chim. Acta*, **67**, 502 (1984); W. J. Colucci, R. D. Tung, J. A. Petri, and D. H. Rich, *J. Org. Chem*., **55**, 2895 (1990).

Scheme 13.78. Synthesis of a Cyclosporin Analog by Solid Phase Peptide Synthesis[a]



Cyclosporin A



a. Y. M. Angell, C. Garcia-Echeverria, and D. H. Rich, *Tetrahedron Lett*., **35**, 5981 (1994); Y. M. Angell, T. L. Thomas, G. R. Flentke, and D. H. Rich, *J. Am. Chem. Soc*., **117**, 7279 (1995). The analog contains *N*-methylleucine at position 1.

13.3.2. Solid Phase Synthesis of Oligonucleotides

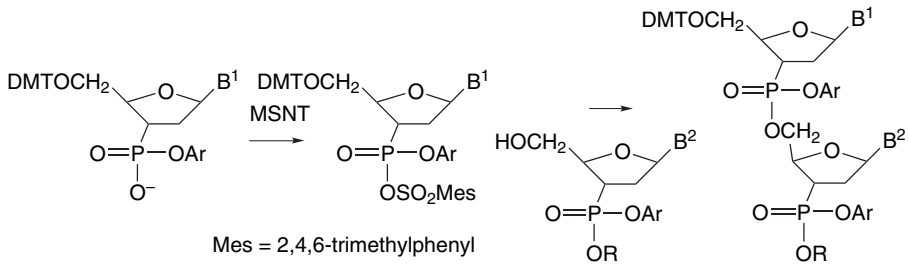
Synthetic oligonucleotides are very important tools in the study and manipulation of DNA, including such techniques as site-directed mutagenesis and DNA amplification by the polymerase chain reaction. The techniques for chemical synthesis of oligonucleotides are highly developed. Very efficient automated methodologies based on solid phase synthesis are used extensively in fields that depend on the availability of defined DNA sequences.[52]

The construction of oligonucleotides proceeds from the four nucleotides by formation of a new phosphorus oxygen bond. The potentially interfering nucleophilic sites on the nucleotide bases are protected. The benzoyl group is usually used for the 6-amino group of adenosine and the 4-amino group of cytidine, whereas the *i*-butyroyl group is used for the 2-amino group of guanosine. These amides are cleaved by ammonia after the synthesis is completed. The nucleotides are protected at the 5′-hydroxy group as ethers, usually with the 4,4′-dimethoxytrityl (DMT) group.

In the early solution phase syntheses of oligonucleotides, coupling of phosphate diesters was used. A mixed 3′-ester with one aryl substituent, usually *o*-chlorophenyl, was coupled with a deprotected 5′-OH nucleotide. The coupling reagents were sulfonyl halides, particularly 2,4,6-tri-*i*-propylbenzenesulfonyl chloride,[53] and the reactions proceeded by formation of reactive sulfonate esters. Coupling conditions

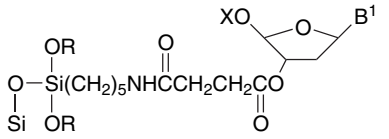
52. S. L. Beaucage and M. H. Caruthers, in *Bioorganic Chemistry: Nucleic Acids*, S. M. Hecht, ed., Oxford University Press, Oxford, 1996, pp. 36–74.
53. C. B. Reese, *Tetrahedron*, **34**, 3143 (1978).

have subsequently been improved and a particularly effective coupling reagent is 1-mesitylenesulfonyl-3-nitrotriazole (MSNT).[54]



Current solid phase synthesis of oligonucleotides relies on coupling at the phosphite oxidation level. The individual nucleotides are introduced as phosphoramidites and the technique is called the *phosphoramidite method*.[55] The *N,N*-diisopropyl phosphoramidites are usually used. The third phosphorus substituent is methoxy or 2-cyanoethoxy. The cyanoethyl group is easily removed by mild base (β-elimination) after completion of the synthesis. The coupling is accomplished by tetrazole, which displaces the amine substituent to form a reactive phosphite that undergoes coupling. After coupling, the phosphorus is oxidized to the phosphoryl level by iodine or another oxidant. The most commonly used protecting group for the 5′-OH is the 4,4′-dimethoxytrityl group (DMT), which is removed by mild acid. The typical cycle of deprotection, coupling, and oxidation is outlined in Scheme 13.79. One feature of oligonucleotide synthesis is the use of a *capping step*, an acetylation that follows coupling, the purpose of which is to permanently block any 5′-OH groups that were not successfully coupled. This prevents the addition of a nucleotide at the site in the succeeding cycle, terminates the further growth of this particular oligonucleotide, and avoids the synthesis of oligonucleotides with single-base deletions. The capped oligomers are removed in the final purification.

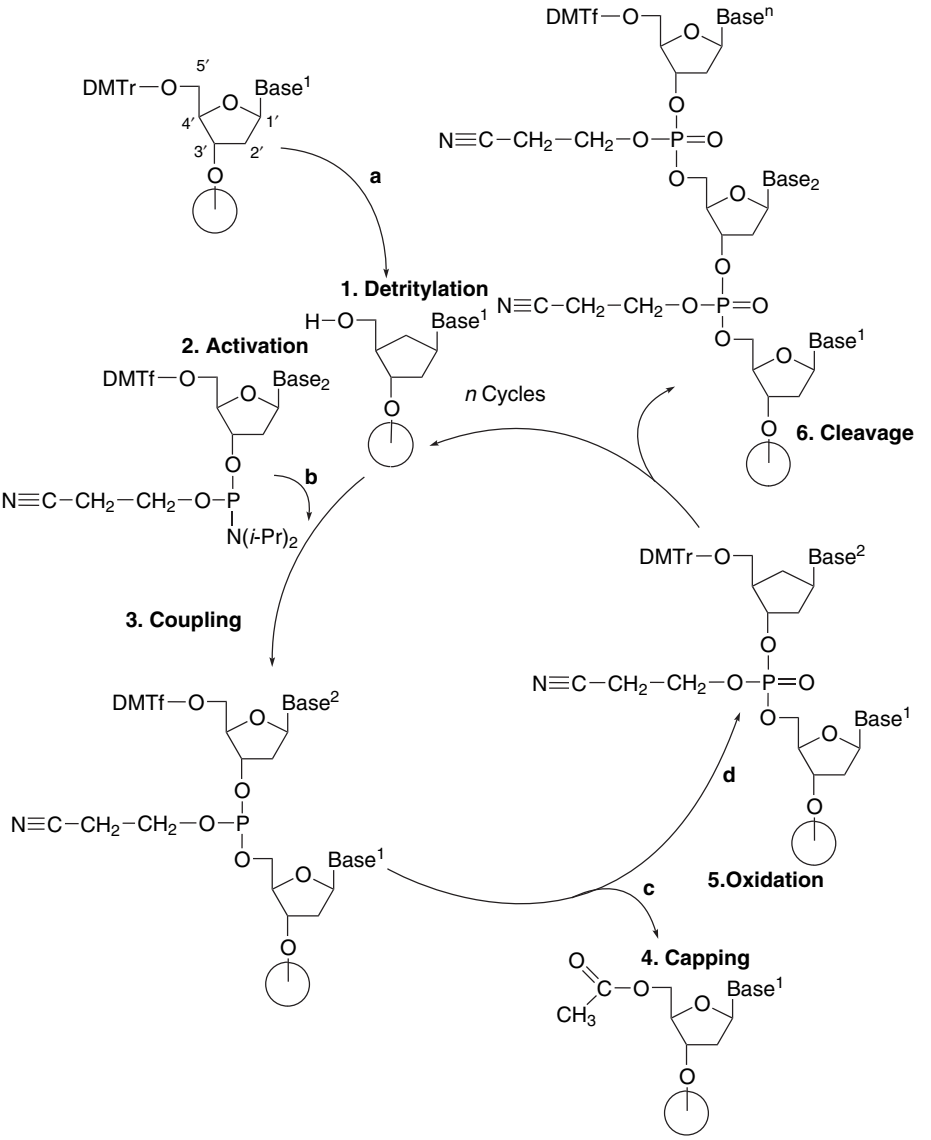
Silica or porous glass is usually used as the solid phase in oligonucleotide synthesis. The support is functionalized through an amino group attached to the silica surface. There is a secondary linkage through a succinate ester to the terminal 3′-OH group.



Although use of automated oligonucleotide synthesis is widespread, work continues on the optimization of protecting groups, coupling conditions, and deprotection methods, as well as on the automated devices.[56]

54. J. B. Chattapadyaya and C. B. Reese, *Tetrahedron Lett*., **20**, 5059 (1979).
55. R. L. Letsinger and W. B. Lunsford, *J. Am. Chem. Soc*., **98**, 3655 (1976); S. L. Beaucage and M. H. Caruthers, *Tetrahedron Lett*., **22**, 1859 (1981); M. H. Caruthers, *J. Chem. Ed*., **66**, 577 (1989); S. L. Beaucage and R. P. Iyer, *Tetrahedron*, **48**, 2223 (1992).
56. G. A. Urbina, G. Grubler, A. Weiber, H. Echner, S. Stoeva, J. Schernthaner, W. Gross, and W. Voelter, *Z. Naturforsch*., **B53**, 1051 (1998); S. Rayner, S. Brignac, R. Bumeiester, Y. Belosludtsev, T. Ward, O. Grant, K. O'Brien, G. A. Evans, and H. R. Garner, *Genome Res*., **8**, 741 (1998).

Scheme 13.79. Protocol for Automated Solid-Phase Synthesis of Oligonucleotides[a]



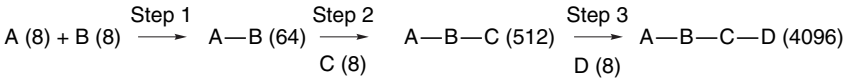
Reagents: **a**: 3% Cl_3CCO_2H in CH_2Cl_2; **b**: 3% tetrazole in CH_3CN; $\mathbf{c}_1$: 10% Ac_2O and 10% 2,6-lutidine in THF; $\mathbf{c}_2$: 7% 1-methylimidazole in THF; **d**: 3% I_2, 2 % H_2O, 2% pyridine in THF.

a. G. A. Urbina, G. Gruebler, A. Weiler, H. Echner, S. Stoeva, J. Schernthaler, W. Grass, and W. Voelter, *Z. Naturforsch.* **B53**, 1051 (1998).

13.4. Combinatorial Synthesis

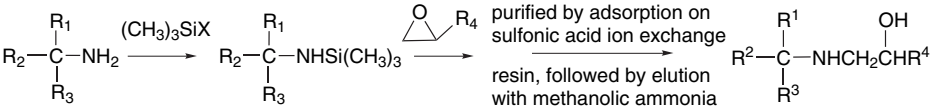
Over the past decade the techniques of *combinatorial synthesis* have received much attention. Solid phase synthesis of polypeptides and oligonucleotides are especially adaptable to combinatorial synthesis, but the method is not limited to these fields. The goal of combinatorial synthesis is to prepare a large number of related

molecules by carrying out a synthetic sequence with several closely related starting materials and reactants. For example, if a linear three-step sequence is done with eight related reactants at each step, a total of 4096 different products are obtained. The product of each step is split into equal portions for the next series of reactions.



The objective of traditional multistep synthesis is the preparation of a single pure compound, but combinatorial synthesis is designed to make many related molecules.[57] The purpose is often to have a large collection (library) of compounds for evaluation of biological activity. A goal of combinatorial synthesis is *structural diversity*, that is, systematic variation in subunits and substituents so as to explore the effect of a range of structural entities. In this section, we consider examples of the application of combinatorial methods to several kinds of compounds.

One approach to combinatorial synthesis is to carry out a series of conventional reactions in parallel with one another. For example, a matrix of six starting materials, each treated with eight different reactants will generate 48 reaction products. Splitting each reaction mixture and using a different reactant for each portion can further expand the number of final compounds. However, relatively little savings in effort is achieved by running the reactions in parallel, since each product must be separately isolated and purified. The reaction sequence below was used to create a 48-component library by reacting six amines with each of eight epoxides. Several specific approaches were used to improve the purity of the product and maximize the efficiency of the process. First, the amines were monosilylated to minimize the potential for interference from dialkylation of the amine. The purification process was also chosen to improve efficiency. Since the desired products are basic, they are retained by acidic ion exchange resins. The products were absorbed on the resin and nonbasic impurities were washed out, followed by elution of the products by methanolic ammonia.[58]



A considerable improvement in efficiency can be achieved by solid phase synthesis.[59] The first reactant is attached to a solid support through a linker group, as was described for polypeptide and oligonucleotide synthesis. The individual reaction steps are then conducted on the polymer-bound material. Use of solid phase methodology has several advantages. Excess reagents can be used to drive individual steps to completion and obtain high yields. The purification after each step is also simplified, since excess reagents and by-products are simply rinsed from the solid support. The process can be automated, greatly reducing the manual effort required.

When solid phase synthesis is combined with sample splitting, there is a particularly useful outcome.[60] The solid support can be used in the form of small beads, and

57. A. Furka, *Drug Dev. Res*., **36**, 1 (1995).
58. A. J. Shuker, M. G. Siegel, D. P. Matthews, and L. O. Weigel, *Tetrahedron Lett*., **38**, 6149 (1997).
59. A. R. Brown, P. H. H. Hermkens, H. C. J. Ottenheijm, and D. C. Rees, *Synlett*, 817 (1998).
60. A. Furka, F. Sebestyen, M. Asgedon, and G. Dibo, *Int. J. Peptide Protein Res*., **37**, 487 (1991); K. S. Lam, M. Lebl, and V. Krchnak, *Chem. Rev*., **97**, 411 (1997).

the starting point is a collection of beads, each with one initial starting material. After each reaction step the beads are recombined and divided again. As the collection of beads is split and recombined during the combinatorial synthesis, each bead acquires a particular compound, depending on its history of exposure to the reagents, *but every bead in a particular split has the same compound, since their reaction histories are identical*. Figure 13.1 illustrates this approach for three steps, each using three different reactants. However, in the end all of the beads are together and there must be some means of establishing the identity of the compound attached to any particular bead. In some cases it is possible to detect compounds with the desired property while they are still attached to the bead. This is true for some assays of biological or catalytic activity that can be performed under heterogeneous conditions.

Another approach is to tag the beads with identifying markers that encode the sequence of reactants and thus the structure of the product attached to a particular bead.[61] One method of coding involves attachment of a chemically identifiable tag,

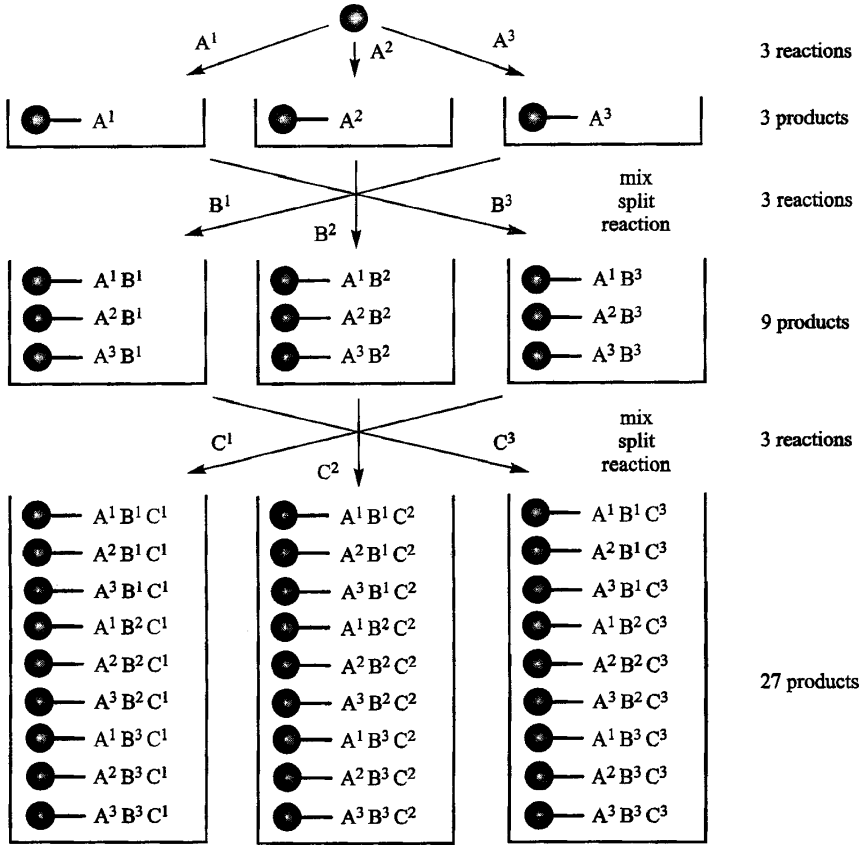


Fig. 13.1. Splitting method for combinatorial synthesis on solid support. Reproduced from F. Balkenhohl, C. von dem Bussche-Huennefeld, A. Lansky, and C. Zechel, *Angew. Chem. Int. Ed. Engl.*, **35**, 2288 (1996), by permission of Wiley-VCH.

[61] S. Brenner and R. A. Lerner, *Proc. Natl. Acad. Sci. USA*, **89**, 5381 (1993).

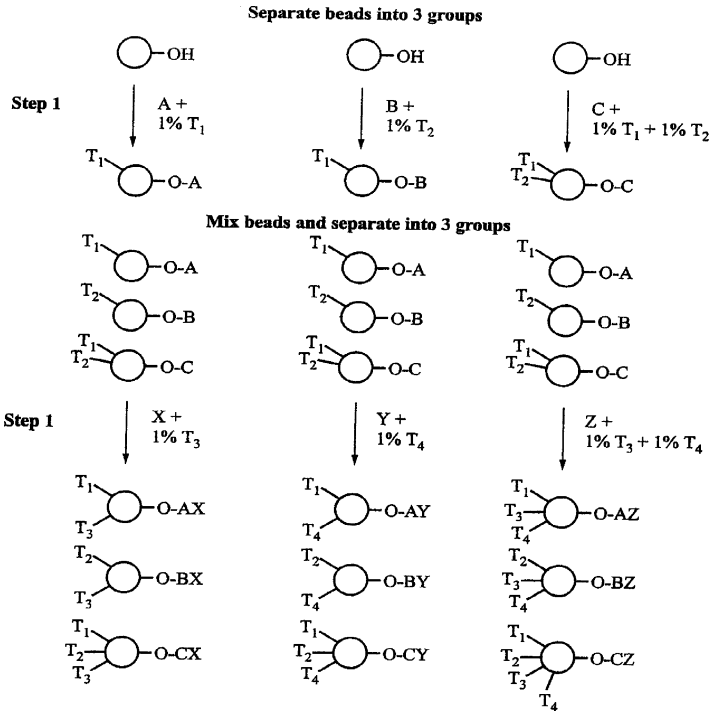
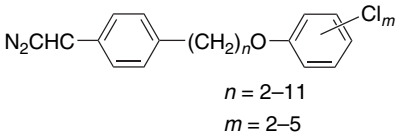


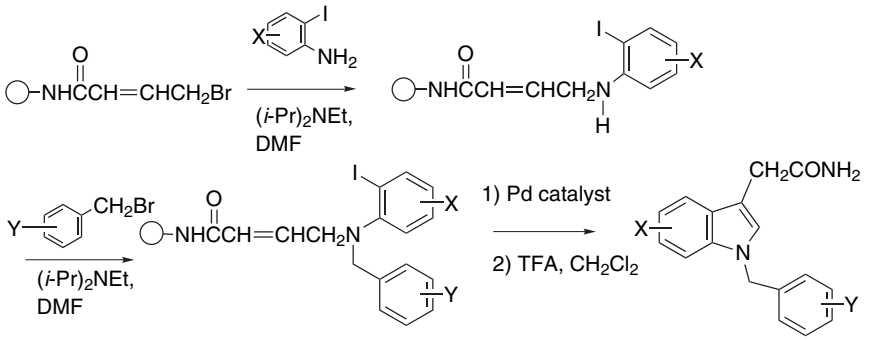
Fig. 13.2. Use of chemical tags to encode the sequence in a combinatorial synthesis on a solid support. Reproduced from W. C. Still, *Acc. Chem. Res*., **29**, 155 (1996), by permission of the American Chemical Society.

as illustrated in Figure 13.2.[62] After each combinatorial step, a different chemical tag is applied to each of the splits before they are recombined. The tags used for this approach are a series of chlorinated aromatic ethers that can be detected and identified by mass spectrometry. The tags are attached to the polymer support by a Rh-catalyzed carbenoid insertion reaction. Detachment is done by oxidizing the methoxyphenyl linker with CAN. Any bead that shows interesting biological activity can then be identified by analyzing the code provided by the chemical tags for that particular bead.



Combinatorial approaches can be applied to the synthesis of any type of molecule that can be built up from a sequence of individual components, for example, in reactions forming heterocyclic rings.[63] The equations below represent an approach to preparing differentially substituted indoles.

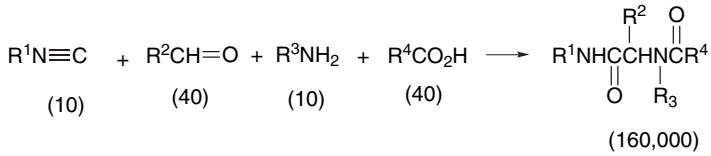
62. H. P. Nestler, P. A. Bartlett, and W. C. Still, *J. Org. Chem*., **59**, 4723 (1994); C. Barnes, R. H. Scott, and S. Babasubramanian, *Recent Res. Develop. Org. Chem*., **2**, 367 (1998).
63. A. Netzi, J. M. Ostresh, and R. A. Houghten, *Chem. Rev*., **97**, 449 (1997).



Ref. 64

There is nothing to prevent incorporation of additional diversity by continuing to build on a side chain at one of the substituent sites.

Another kind of combinatorial synthesis can be applied to reactions that assemble the product from several components in a single step, a *multicomponent reaction*. A particularly interesting four-component reaction is the *Ugi reaction*, which generates dipeptides from an isocyanide, an aldehyde, an amine, and a carboxylic acid.

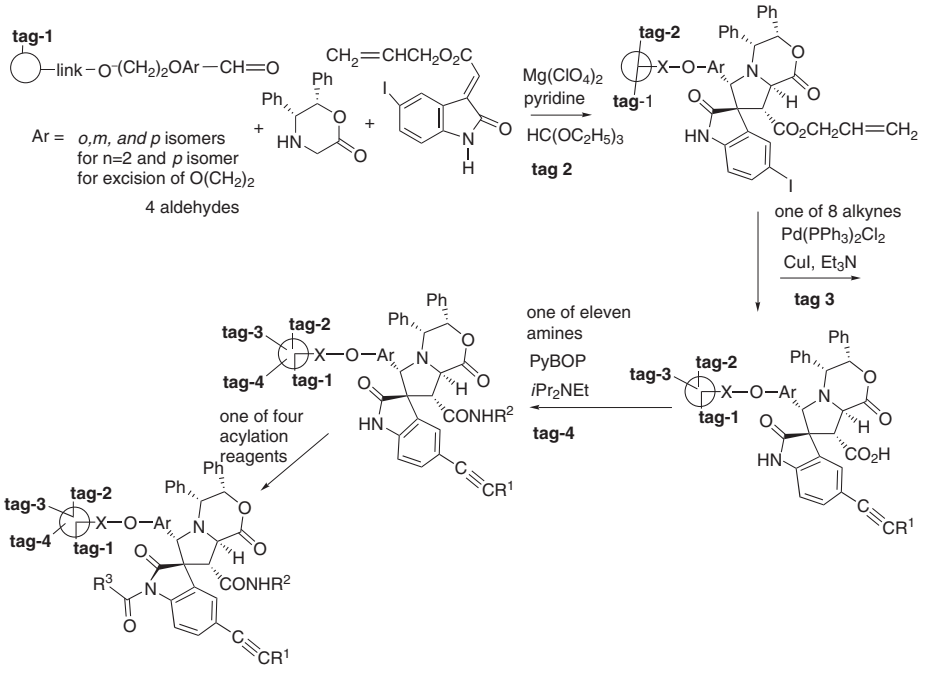


For example, use of 10 different isocyanides and amines, along with 40 different aldehydes and carboxylic acids has the potential to generate 160,000 different dipeptide analogs.[65] This system was explored by synthesizing arbitrarily chosen sets of 20 compounds that were synthesized in parallel. The biological assay data from these 20 combinations were then used to select the next 20 combinations for synthesis. The synthesis-assay-selection process was repeated 20 times. At the end of this process the average inhibitory concentration of the set of 20 products had been decreased from 1 mM to less than 1 μM.

A library of over 3000 spirooxindoles was created based on a sequence of four reactions.[66] The synthetic sequence is based on the total synthesis of a natural product called (–)-spirotryprostatin B.[67] A morpholinone chiral auxiliary, aldehyde, and an oxindole condense to give the ring system. Substituents were then added by replacement of the iodine by one of several terminal alkynes. Simultaneous deprotection occurred at the allyl ester. These carboxylic acids were converted to amides using a variety of amines and coupling with PyBOP. The final reaction in the sequence was acylation of the oxindole nitrogen. At each stage in the library creation, certain alkynes or amines reacted poorly and were excluded from the library, which was eventually derived from eight alkynes, twelve amines, and four acylation reagents. As outlined in Scheme 13.80, this synthesis has the potential to prepare 3104 different

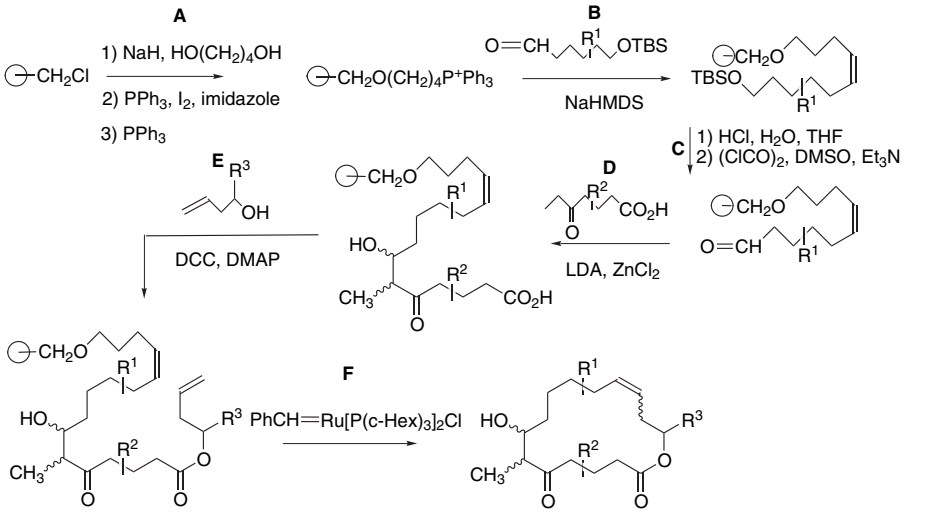
64. H.-C. Zhang and B. E. Maryanoff, *J. Org. Chem.*, **62**, 1804 (1997).
65. L. Weber, S. Walbaum, C. Broger, and K. Gubernator, *Angew. Chem. Int. Ed. Engl.*, **34**, 2280 (1995).
66. M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, and S. L. Schreiber, *J. Am. Chem. Soc.*, **126**, 16077 (2004).
67. P. R. Sebahar, H. Osada, T. Usui, and R. M. Williams, *Tetrahedron*, **58**, 6311 (2002).

Scheme 13.80. Creation of a Combinatorial Library of Spirooxindoles[a]



a. M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, and S. L. Schreiber, *J. Am. Chem. Soc*., **126**, 16077 (2004).

Scheme 13.81. Combinatorial Synthesis of Epothilone Analogs Using Microreactors[a]



a. K. C. Nicolaou, D. Vorloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschanger, N. P. King, M. R. V. Finlay, P. Giannakakou, D. Verdier-Pinard, and E. Hamel, *Angew. Chem. Int. Ed. Engl*., **36**, 2097 (1997).

compounds, including those lacking a particular substituent (skip) (4 aldehydes $\times 2$ morpholines $\times 1$ oxindole)$= 8$ core structures $\times$ $(1 + 8 \times 12) \times 4 = 3104$ different compounds. A version of the chemical tagging method was used for coding the beads.[68] Analysis of a sample of the beads indicated that at least 82% of them contained the desired compound in greater than 80% purity.

The epothilone synthesis in Scheme 13.59 (p. 1221) has been used as the basis for a combinatorial approach to epothilone analogs.[69] The acyclic precursors were

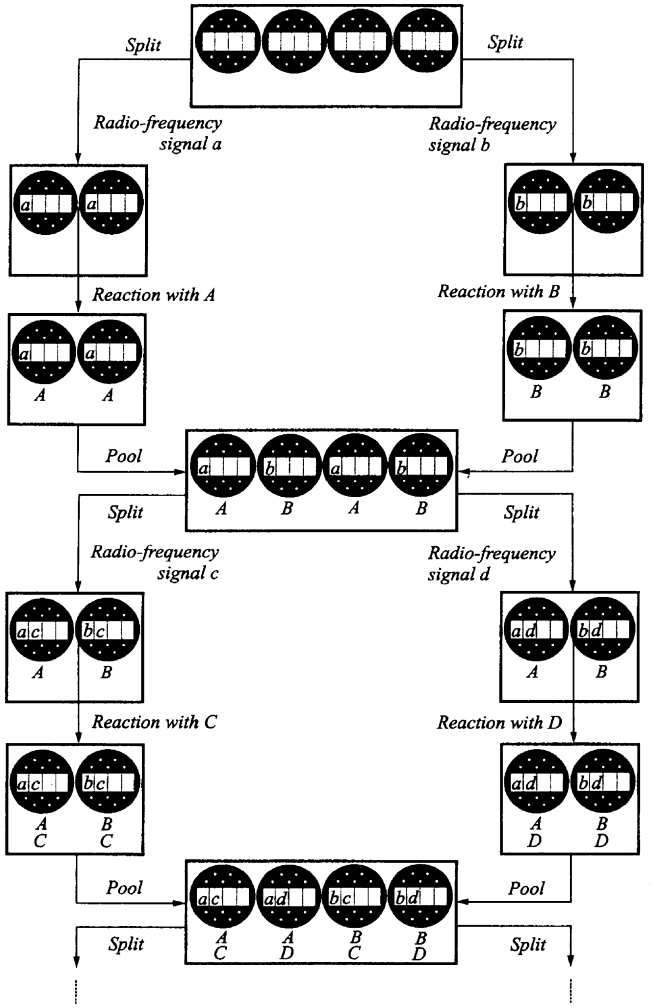


Fig. 13.3. Radio-frequency tagging of microreactors for combinatorial synthesis on a solid support. Reproduced from K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, and M. P. Nova, *Angew. Chem. Int. Ed. Engl.*, **34**, 2289 (1995), by permission of Wiley-VCH.

68. H. B. Blackwell, L. Perez, R. A. Stavenger, J. A. Tallarico, E. Cope-Etough, M. A. Foley, and S. L. Schreiber, *Chem. Biol.*, **8**, 1167 (2001).
69. K. C. Nicolaou, N. Wissinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, S. Yang, T. Li, P. Giannakakou, and E. Hamel, *Nature*, **387**, 268 (1997); K. C. Nicolaou, D. Vourloumis, T.

synthesized and attached to a solid support resin by Steps **A** and **B** in Scheme 13.81. The cyclization and disconnection from the resin was then done by the olefin metathesis reaction in Step **F**. The aldol condensation in Step **D** was not highly stereoselective. Similarly, olefin metathesis gave a mixture of *E*- and *Z*-stereoisomers, so the product of each combinatorial sequence was a mixture of four isomers. These were separated by thin-layer chromatography prior to bioassay. In this project, reactants **A** (three variations), **B** (three variations), and **C** (five variations) were used, generating 45 possible combinations. The stereoisomeric products increase this to 180 (45×4).

In this study a nonchemical means of encoding the identity of each compound was used. The original polymer-bound reagent was placed in a porous microreactor that is equipped with a radiofrequency device that can be used for identification.[70] The porous microreactors permit reagents to diffuse into the polymer-bound reactants, but the polymer cannot diffuse out. At each split, the individual microreactors are coded to identify the reagent that is used. When the synthesis is complete, the sequence of signals recorded in the radiofrequency device identifies the product that has been assembled in that particular reactor. Figure 13.3 illustrates the principle of this coding method.

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70. K. C. Nicolaou, Y.-Y. Xiao, Z. Parandoosh, A. Senyei, and M. P. Nova, *Angew. Chem. Int. Ed. Engl*., **34**, 2289 (1995); E. J. Moran, S. Sarshar, J. F. Cargill, M. M. Shahbaz, A. Lio, A. M. M. Mjalli, and R. W. Armstrong, *J. Am. Chem. Soc*., **117**, 10787 (1995).

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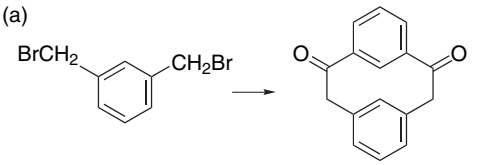
Problems

(*References for these problems will be found on page 1292.*)

13.1. Show how synthetic equivalent groups could be used to carry out each of the following transformations:

(a)



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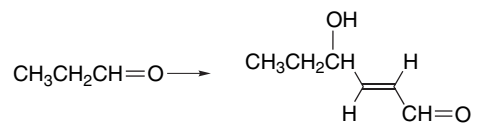

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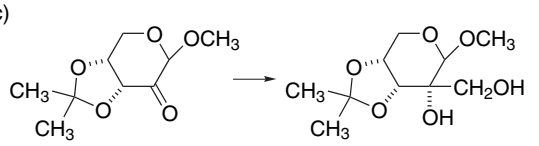

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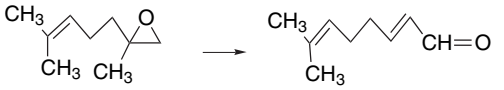

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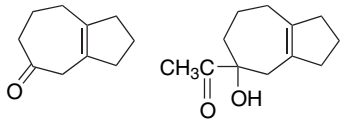

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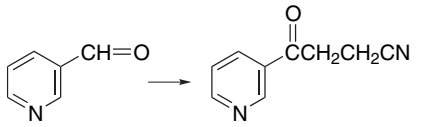

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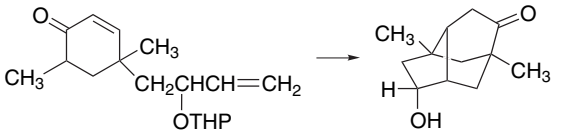

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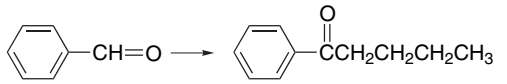

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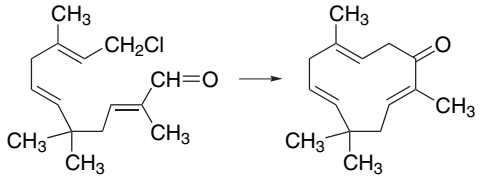

13.2. Indicate a reagent or short synthetic sequence that would accomplish each of the following transformations:

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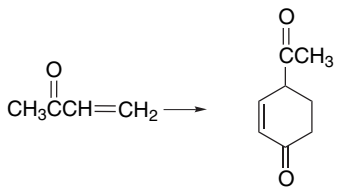

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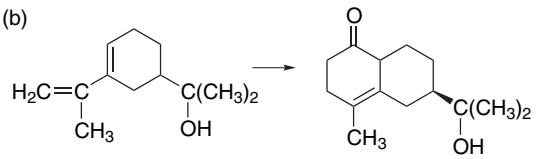

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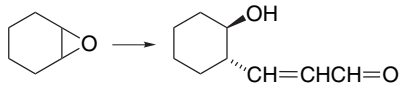

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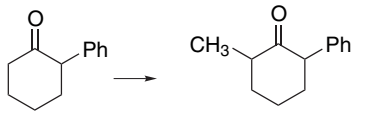

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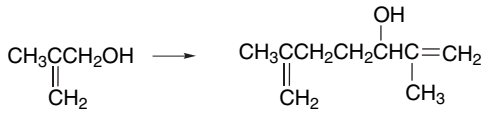

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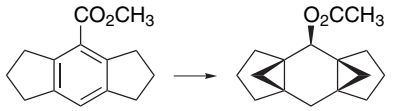

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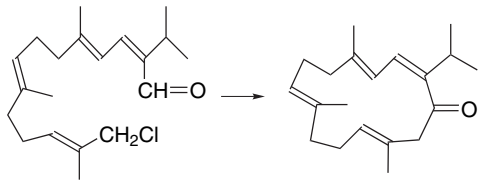
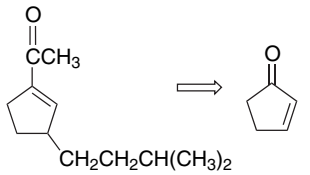


13.3. Indicate reagents or short reaction sequences that could accomplish the synthesis of the target on the left from the starting material on the right.

(a)



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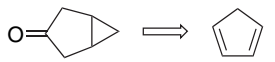

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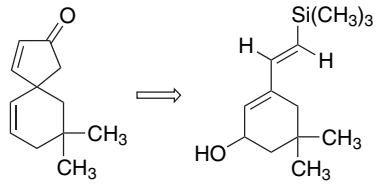

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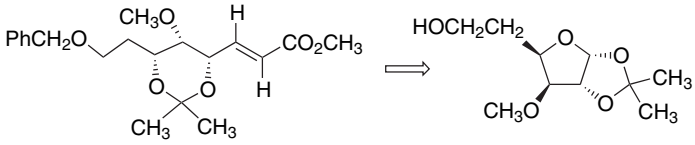

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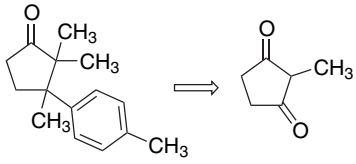
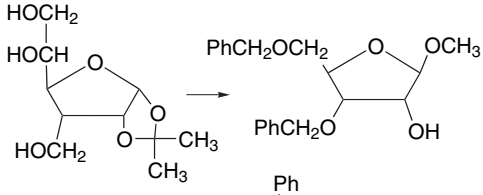


13.4. As they are available from natural sources in enantiomerically pure form, carbohydrates are useful starting materials for syntheses of enantiomerically pure compounds. However, the multiple hydroxy groups require versatile methods for selective protection, reaction, and deprotection. Show how appropriate manipulation of protecting groups and/or selective reagents could be used to effect the following transformations.

(a)



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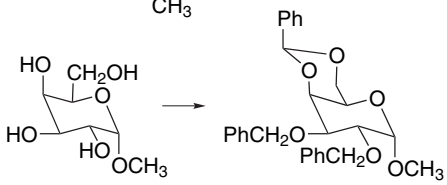

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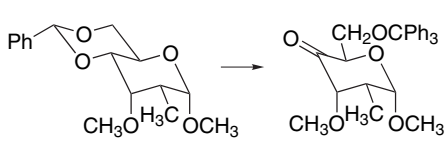

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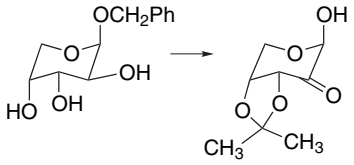
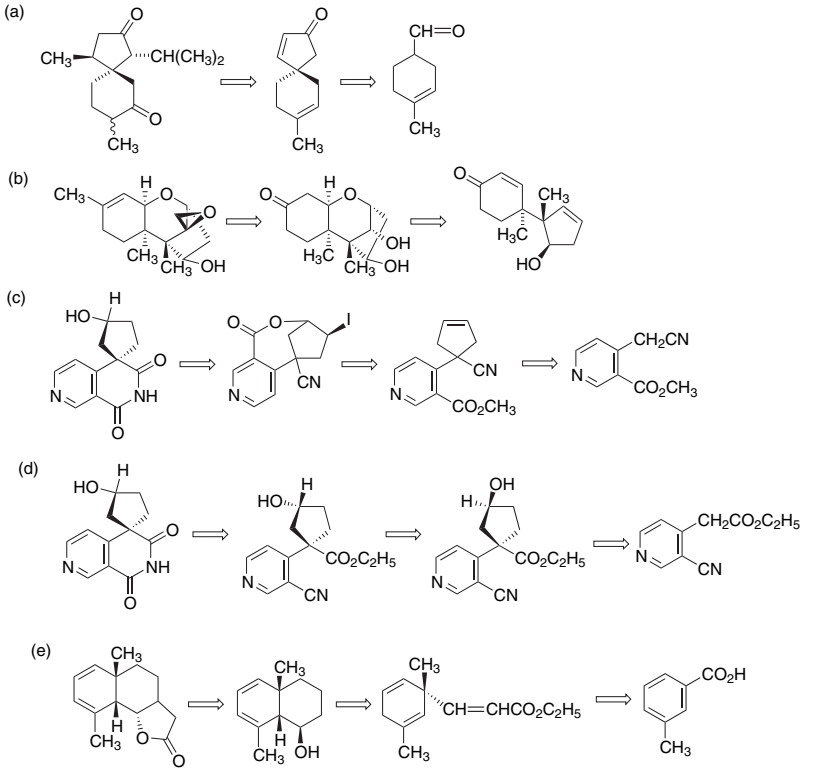


13.5. Several synthetic transformations that are parts of total syntheses of natural products are summarized by retrosynthetic outlines. For each retrosynthetic transform suggest a reagent or short reaction sequence that could accomplish the forward synthetic conversion. The proposed route should be diastereoselective but need not be enantioselective.



13.6. Diels-Alder reactions are attractive for synthetic application because of the predictable regio- and stereochemistry. There are, however, limitations on the types of compounds that can serve as dienophiles or dienes. As a result, the idea of synthetic equivalence has been exploited by development of dienophiles and dienes that meet the reactivity requirements of the Diels-Alder reaction and can then be converted to the desired structure. For each of the dienophiles and dienes given below, suggest a Diels-Alder reaction and subsequent transformation(s) that would give a product not directly attainable by a Diels-Alder reaction. Give the structure of the diene or dienophile "synthetic equivalent" and indicate why the direct Diels-Alder reaction is not possible.

Dienophiles

(a) $CH_2{=}CHP^+Ph_3$

(b) $CH_2{=}CHS(C{=}O)Ph$

(c) $CH_2{=}C(CO_2C_2H_5)(O_2CCH_3)$

(d) $CH_2{=}C(C{=}O)C(O_2CAr)CH_3$ Ar = 4-nitrophenyl

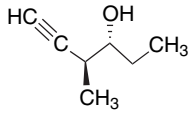
Dienes

(e) $CH_2{=}C(OSi(CH_3)_3)CH{=}CHOCH_3$

(f) $CH_2{=}C(SPh)C(O_2CCH_3){=}CH_2$

13.7. One approach to the synthesis of enantiomerically pure compounds is to start with an available enantiomerically pure substance and effect the synthesis by a series of enantiospecific reactions. Devise a sequence of reactions that would be appropriate for the following syntheses based on enantiomerically pure starting materials.

(a)



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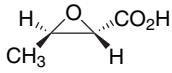

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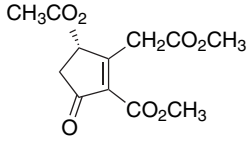

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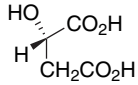

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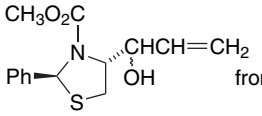

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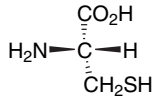

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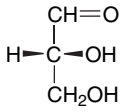

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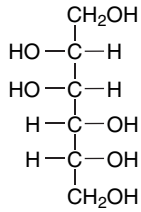

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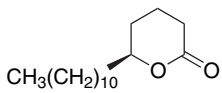

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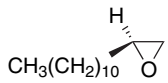

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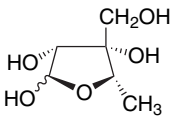

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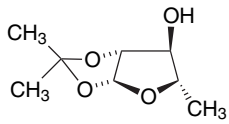

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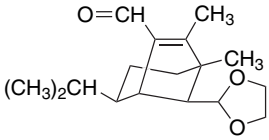

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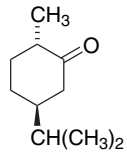

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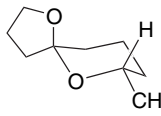

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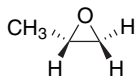
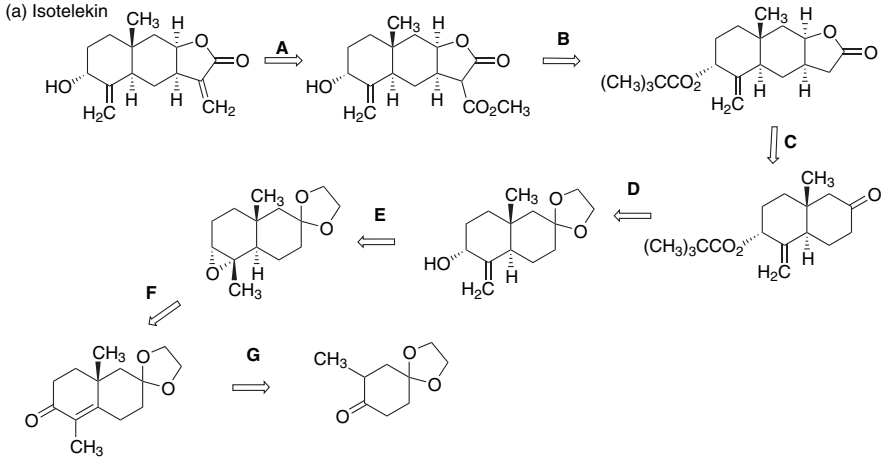
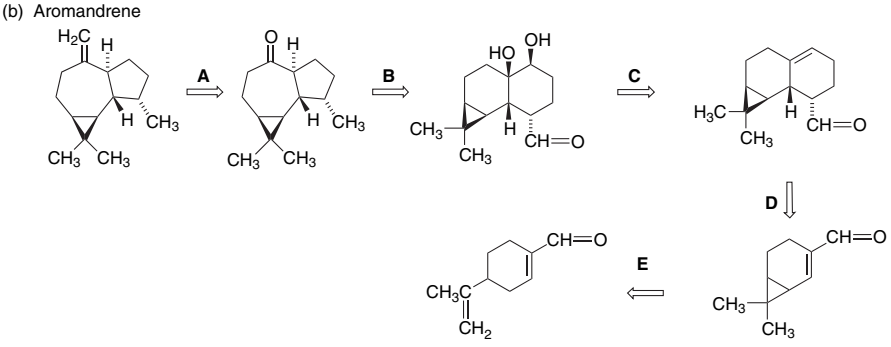


13.8. Several syntheses of terpenoids are outlined in retrosynthetic form. Suggest a reagent or short reaction sequence that could accomplish each lettered transformation in the synthetic direction. The structures refer to racemic material.

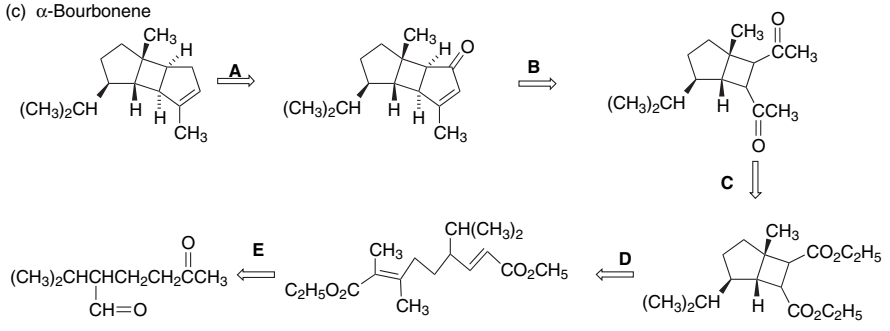
(a) Isotelekin



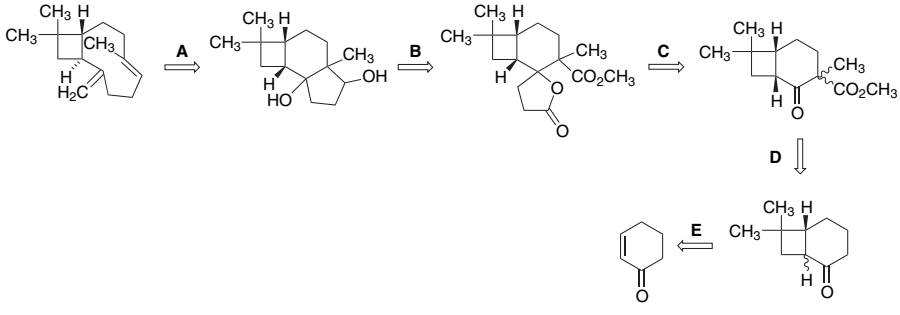
(b) Aromandrene



(c) α-Bourbonene

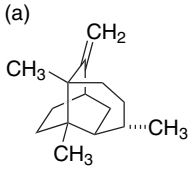


(d) Caryophyllene



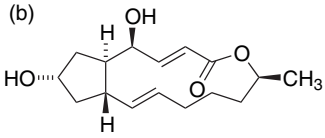
13.9 Use retrosynthetic analysis to suggest syntheses of the following compounds. Develop at least three outline schemes. Discuss the relative merits of the schemes and develop a fully elaborated synthetic plan for the most promising retrosynthetic scheme.

(a)



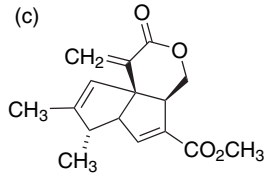
seychellene

(b)



brefeldin A

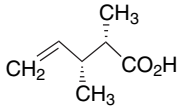
(c)



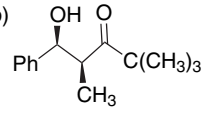
pentalenolactone E

13.10. Suggest a method for diastereoselective synthesis of the following compounds:

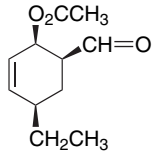
(a)



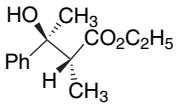
(b)



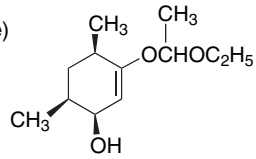
(c)



(d)

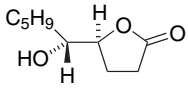


(e)



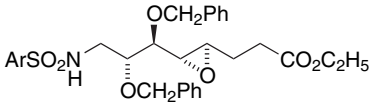
13.11. Devise a route that could be used for synthesis of the desired compound in high enantiomeric purity from the suggested starting material.

(a)

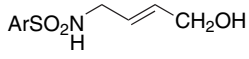


from D-ribose

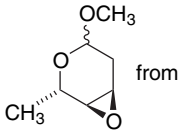
(b)



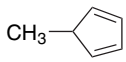
from



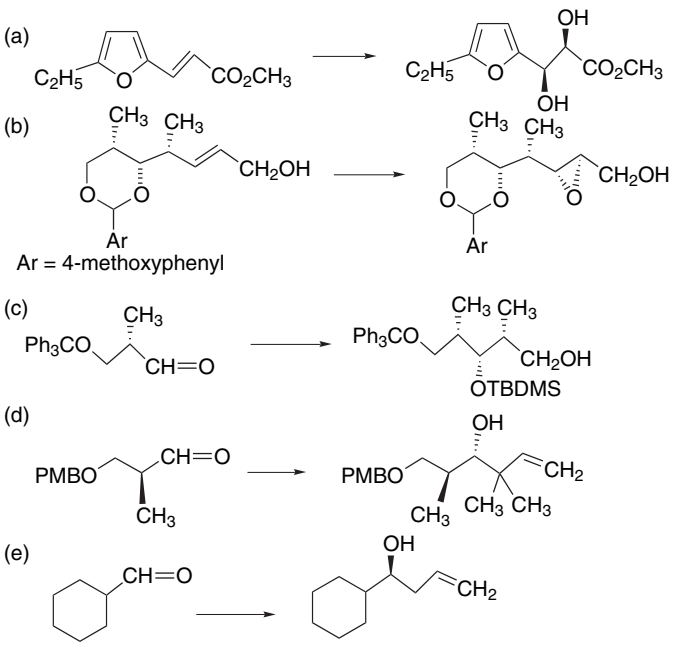
(c)



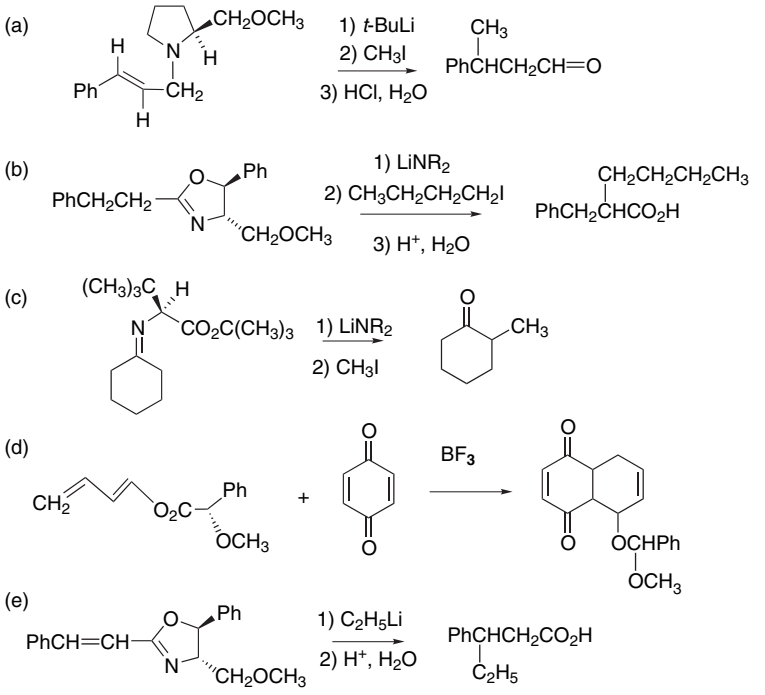
from

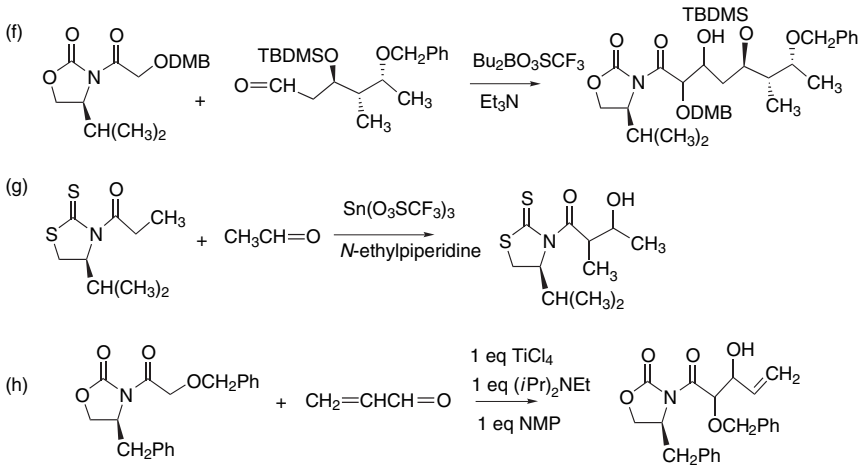


13.12. Select a reagent that will achieve the following syntheses with high enantioselectivity.

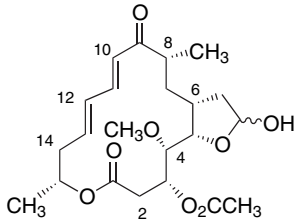


13.13. The following reactions use chiral auxiliaries to achieve enantioselectivity. By consideration of possible TSs, predict the absolute configuration of the major product of each reaction.



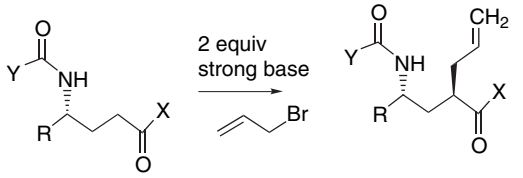


13.14. The macrolide carbonolide B contains six stereogenic centers at sp^3 carbons. Devise a strategy for synthesis of cabonolide B and in particular for establishing the stereochemistry of the C(1)–C(8) segment of the molecule.



carbonolide B

13.15. 4-(Acylamino)-substituted carboxylate esters and amides can be alkylated with good *anti*-2,4 stereoselectivity using two equivalents of a strong base. The stereoselectivity is independent of the steric bulk of the remainder of the carboxylate structure. Propose a TS that is consistent with these observations.



R	Y	X
CH_3	CF_3	OCH_3
$(CH_3)_2CHCH_2$	CF_3	OCH_3
$PhCH_2$	CF_3	OCH_3
$PhCH_2$	CF_3	$N(CH_3)_2$
$PhCH_2$	CF_3	$N(CH_3)OCH_3$
CH_3	$(CH_3)_3CO$	OCH_3
$(CH_3)_2CH$	$(CH_3)_3CO$	OCH_3

13.16. Using as a designation of a "step" each numbered reagent or reagent combination in Schemes 13.54 to 13.59 for the synthesis of the Taxol precursors shown there, outline the syntheses in terms of convergence and determine the longest linear sequence (as on p. 1166). In general, these Taxol syntheses are quite linear in character. Is there a structural reason for this tendency toward linearity?