The Total Synthesis of Natural Products

VOLUME 8

Edited by

John ApSimon

Ottawa-Carleton Chemistry Institute

and

Department of Chemistry
Carleton University, Ottawa

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS Inc.

NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The Total Synthesis of Natural Products

VOLUME 8

Edited by

John ApSimon

Ottawa-Carleton Chemistry Institute

and

Department of Chemistry
Carleton University, Ottawa

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS Inc.

NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

A NOTE TO THE READER
This book has been electronically reproduced from digital information stored at John Wiley & Sons, Inc. We are pleased that the use of this new technology will enable us to keep works of enduring scholarly value in print as long as there is a reasonable demand for them. The content of this book is identical to previous printings.

Library of Congress Cataloging in Publication Data:

The Total synthesis of natural products.

"A Wiley-Interscience publication."
Original imprint, v. 1: New York: Wiley-Interscience, 1973.
Includes bibliographical references and indexes.
1. Chemistry, Organic—Synthesis. I. ApSimon, John.
QD262.T655 1973 547'.2 72-4075
ISBN 0-471-03251-4 (v. 1)
ISBN 0-471-54507-4 (v. 8)

10 9 8 7 6 5 4 3 2

Contributors to Volume 8

Kim F. Albizati, Department of Chemistry, College of Liberal Arts, Wayne State University, Detroit, Michigan

David Goldsmith, Department of Chemistry, Emory University, Atlanta, Georgia

N. K. Kochetkov, N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences, Moscow, USSR

Françoise Perron, Department of Chemistry, College of Liberal Arts, Wayne State University, Detroit, Michigan

Norman E. Pratt, Department of Chemistry, College of Liberal Arts, Wayne State University, Detroit, Michigan

Ronald H. Thomson, Department of Chemistry, University of Aberdeen, Aberdeen, Scotland

Valerie Vaillancourt, Department of Chemistry, College of Liberal Arts, Wayne State University, Detroit, Michigan

Preface

The art and science of organic synthesis is alive and well! This volume presents chapters on the synthesis of a variety of natural products.

A long overdue treatment of tri- and tetracyclic diterpenes appears together with an equally important report on naturally occurring quinone synthesis. Recent interests in the biologically important polysaccharides necessitate a consideration of that class of compounds and a background paper on synthetic work to 1985 is provided. Finally a diversion from the traditional treatment of whole biosynthetic classes as synthetic targets provides an overview of strategies and methods derived for those natural products containing the spiroketal functional group.

The announcement of the award of the 1990 Nobel Prize in chemistry to a champion synthetic strategist, Professor E. J. Corey, attests to the scientific importance of organic molecular construction. This volume is dedicated to Professor Corey in honor of his multitudinous contributions to organic synthesis.

JOHN APSIMON

Ottawa, Canada
October 1991

Contents

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The Total Synthesis of Tri- and Tetracyclic Diterpenes

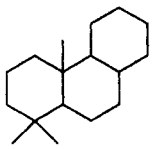
DAVID GOLDSMITH
Department of Chemistry, Emory University, Atlanta, Georgia

INTRODUCTION

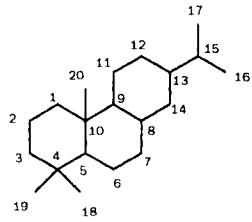
This review covers the synthesis of tri- and tetracarbocyclic diterpenes[1, 2] from the late 1930s until approximately 1987. Some synthetic work from 1988 and 1989 is included. In keeping with the title of the series, the syntheses reviewed here are largely *total* syntheses. Conversions of one natural product into another are, for the most part, not included. The decisions as to which partial syntheses to cover were made on an almost entirely arbitrary basis. Much excellent chemistry has emerged from partial syntheses and conversions, but the general principal has been that if the starting material appears to be more complex and/or more difficult to synthesize than the target molecule, the work is not included. In addition, the field of diterpene synthesis is marked by a myriad of excellent model studies. I have not included, however, preliminary or model study work except when directly applicable to a particular synthesis.

The chapter is organized broadly around skeletal types and these are given in Table 1. Within the general class of abietanes and pimaranes a further

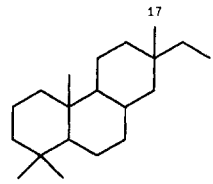
Table 1 Synthesized Diterpene Skeletal Types



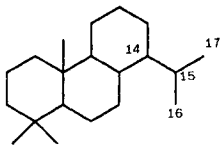
podocarpane



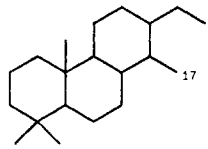
abietane



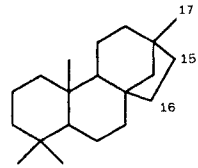
pimarane



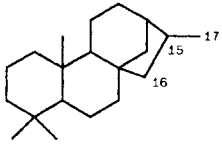
totarane



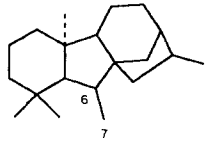
cassane



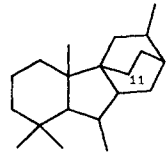
beyerane



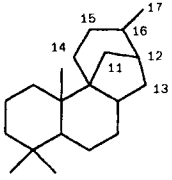
kaurane



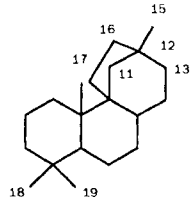
gibbane



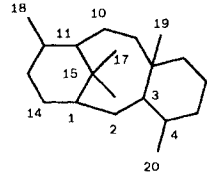
antheridane



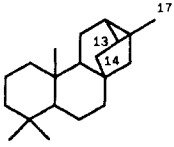
stemodane



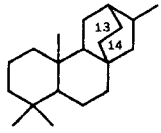
stemarane



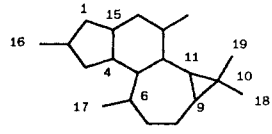
taxane



trachylobane

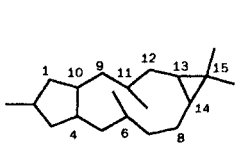


atisane

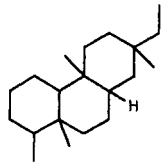


jatrophane

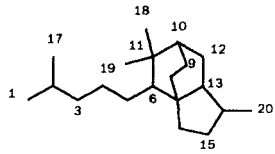
Table 1 Synthesized Diterpene Skeletal Types (*Continued*)



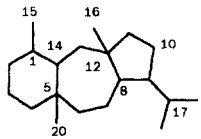
lathyrane



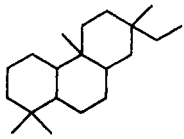
dolabrane



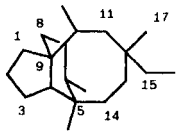
eremane



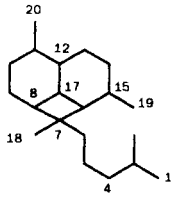
dolastane



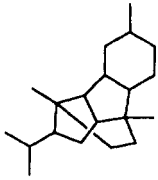
rosane



mutilane



decipiane



ryanodane

division along the lines of major functionality is also made. Abietane C-ring phenols, epoxides, and quinones, for example, are discussed separately from abietic and related acids. The biosynthesis of the diterpenes is not discussed in detail but the the origin of some of the compound types from geranylgeraniol pyrophosphate is outlined to illustrate the structural relationships between members of a general class of substances.

As noted in an earlier volume in this series, the proof of the synthesis review pudding is in the synthetic schemes, and I have attempted to make these as explicit as possible, both with regard to the number of structures in each scheme and in the way that they are presented graphically. In some cases the same molecule may be shown in different structural representations depending on how these may illustrate a particular synthesis. I have also repeated the structures of many of the starting materials and intermediates so that the reader will not have to search for structure **43** when it is used again

for the synthesis of molecule **277**. The discussions of the syntheses in contrast are brief, serving to illustrate some of the more critical points of stereochemistry or strategy or to serve simply as a guide to the structural road map. I apologize in this respect for being unable (and unwilling) to search out and use any additional synonyms for yield, produce, afford, provide, give, and lead to in describing the outcome of a particular transformation. The normal three- and four-letter codes for reagents are used throughout.

Finally, I would like to acknowledge the aid of several graduate students in chemistry at Emory University, in particular Guy Stone, Kevin Swiss, and William Hinkley, for their aid in searching out and gathering the relevant literature.

1. TRICYCLIC DITERPENES

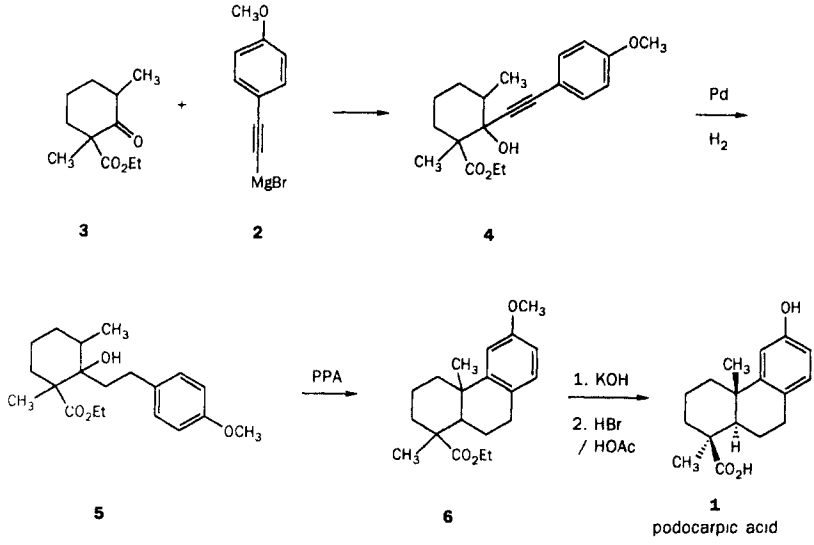
A. Abietanes and Pimaranes

(1) Resin Acids

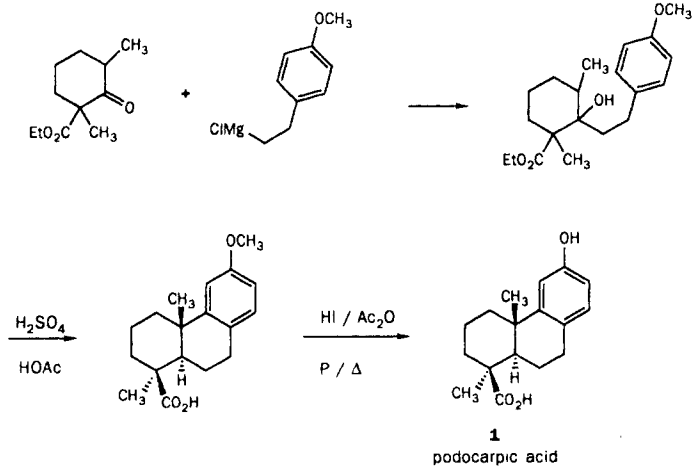
Podocarpic Acid

The first synthesis of podocarpic acid, **1**, in which the product was compared to the natural compound and its constitution verified was carried out by King, King, and Topliss[3] at Nottingham University (Scheme 1). The carbon skeleton is assembled by addition of Grignard reagent **2** to ketone **3**. Catalytic hydrogenation of the acetylene group of **4** affords **5**, which in turn is subjected to acid-catalyzed cyclization with polyphosphoric acid. The product of this unselective reaction is a mixture of several isomers from which **6** is isolated in 30% yield. Hydrolysis of the ester and ether groups of **6** by standard, if drastic, methods affords podocarpic acid. The King group also demonstrated that the compound prepared earlier but not identified by Haworth and Moore[4] (Scheme 2) at Sheffield was podocarpic acid.

The synthesis of podocarpic acid by Wenkert and Tahara[5,6] from Iowa State University (Scheme 3) is based on a Robinson annelation construction of the tricyclic system[7] from 1-methyl 2-naphthol and methyl ethynyl ketone. The highly unsaturated hydroxyketone **7** obtained in 26% yield is subjected to catalytic hydrogenation and acid-catalyzed dehydration to yield enone **8**. Lithium in ammonia affords the *trans*-fused saturated tricyclic ketone **9**. The latter, upon carbonation of the kinetically produced enolate mixture, yields the C-4 keto acid in near equal measure with its C-2 isomer. Both products are isolated as the derived methyl esters and **10**, the appropriate one for podocarpane synthesis, is carried forward. When methylation of **10** is carried

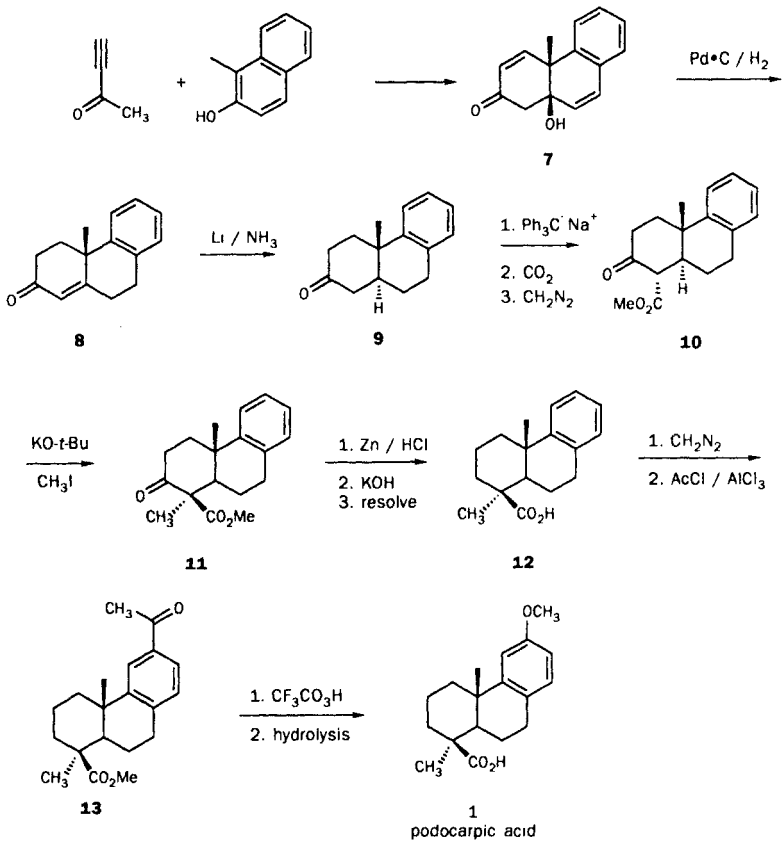


SCHEME 1. King's synthesis of podocarpic acid.



SCHEME 2. Podocarpic acid synthesis of Haworth and Moore.

out with *t*-butoxide and methyl iodide the reaction provides a mixture of products in the ratio of 2.4 to 1 with the desired podocarpane system **11** as the minor isomer. Clemmensen reduction of the ketone function gives desoxypodocarpic acid methyl ester and the derived acid is resolved via its



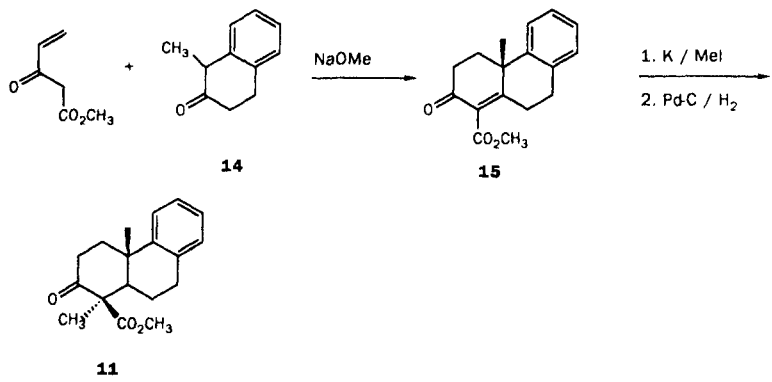
SCHEME 3. Wenkert first synthesis of podocarpic acid.

cinchonine salt to yield the natural series isomer (+)-desoxypodocarpic acid **12**.

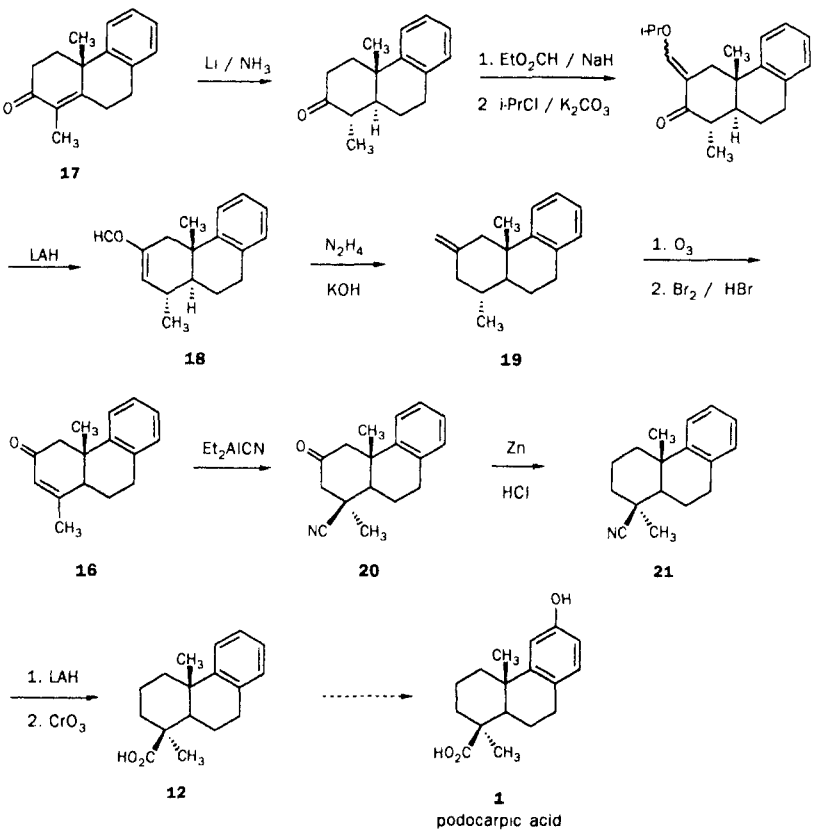
In previous work Wenkert and Jackson[8] showed that desoxypodocarpic acid can be reconverted to the natural product **1** by acetylation of the methyl ester of **12** to give **13** followed by Baeyer–Villiger (Emmons) oxidation and reductive cleavage of the C-4 axial ester group.

The second synthesis of podocarpic acid by Wenkert and co-workers[9] (Scheme 4) features an alternative preparation of keto ester **11** starting from β-tetralone **14**. Alkylation and reduction of Robinson annelation product **15** affords **11** in a more efficient fashion than the original synthetic scheme.

The synthesis of podocarpic acid by Meyer and Maheshwari[10] at the University of Arkansas (Scheme 5) differs from most other approaches to this molecule in the manner in which the stereochemistry at C-4 is introduced.



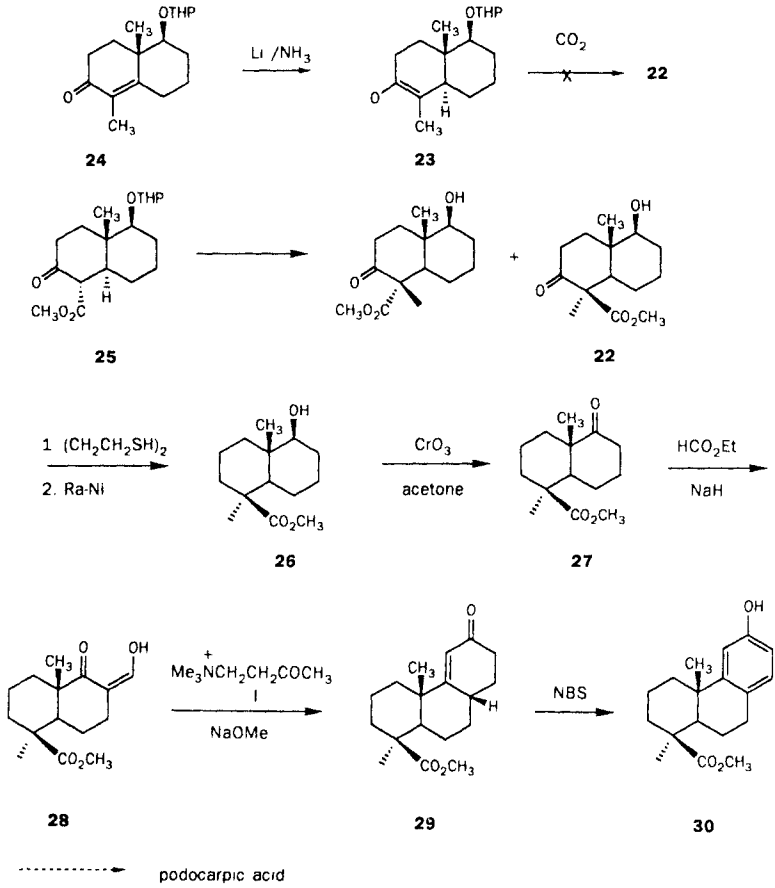
SCHEME 4. Wenkert's alternative synthesis of an intermediate for podocarpic acid.



SCHEME 5. Meyer's synthesis of podocarpic acid.

Rather than introducing a methyl or potential carboxyl group as an electrophile, a one-carbon unit is added by 1,4-nucleophilic addition to a tricyclic enone **16**. Starting from the standard Robinson annelation product **17**, the key intermediate **16** is prepared by an enone transposition sequence. The key step in the transposition is the Wolff–Kishner reduction of **18**, which gives the exocyclic olefin **19** rather than the endocyclic isomer. Addition of the Nagata reagent to enone **16** occurs in an axial sense to produce the podocarpic nitrile stereochemistry of **20**. Subsequent removal of the C-2 keto group to produce nitrile **21** and conversion of the nitrile function to a carboxylic acid one yields an intermediate, **12**, which had been carried through to podocarpic acid.[8]

The approach of Spencer and co-workers[11] at Dartmouth College to podocarpic acid (Scheme 6) is to construct an aromatic C-ring onto a



SCHEME 6. Synthesis of podocarpic acid methyl ester by Spencer.

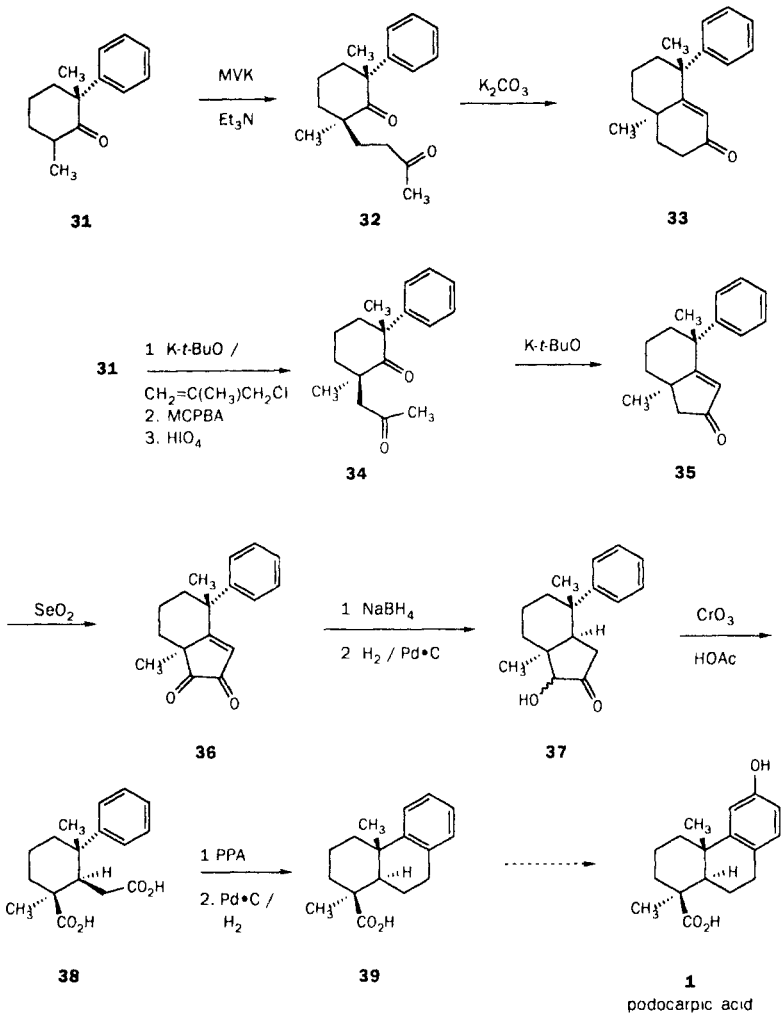
preexisting A/B system. The desired intermediate for the achievement of this plan is ketoester **22**. Initial attempts to produce **22** by carbonation of enolate **23** (generated by lithium–ammonia reduction of **24**) were unsuccessful. Instead **22** is prepared as the minor product from alkylation of saturated ketoester **25**.

To carry **22** forward it is converted into its ethylene thioketal derivative and the latter function is removed by Raney-nickel desulfurization to yield **26**. Oxidation yields **27**, which in turn is condensed with ethyl formate to yield the enolic keto aldehyde **28**. Robinson annelation affords unsaturated ketone **29**, which upon NBS oxidation provides podocarpic acid methyl ester, **30**.

Ireland and Giarrusso[12] at the University of Michigan carried out a synthesis of podocarpic acid (Scheme 7) employing the same general strategy used by Ireland and Kierstead[13, 14] for the synthesis of dehydroabietic acid, **68**. Thus a ring-A unit, **31**, bearing at one α position an aromatic group for ring-C and a methyl group for the angular substituent plus the potential C-4 methyl group at the other α carbon is alkylated first with methyl vinyl ketone to give **32**. In contrast to the epimeric substance used in the synthesis of dehydroabietic acid, the aldol cyclization of **32** to **33** is accompanied by a competing reverse Michael reaction to give substantial amounts of the starting material **31**. Since a 1,4-diketo system would not be subject to the reverse Michael process, **31** is alkylated instead with methallyl chloride and the methallyl group is oxidatively cleaved to yield **34**. The alkylation reaction occurs preferentially from the least-hindered face of the enolate, that is, away from the phenyl group yielding the podocarpic acid stereochemistry. Aldol condensation then produces the fused bicyclic enone **35**.

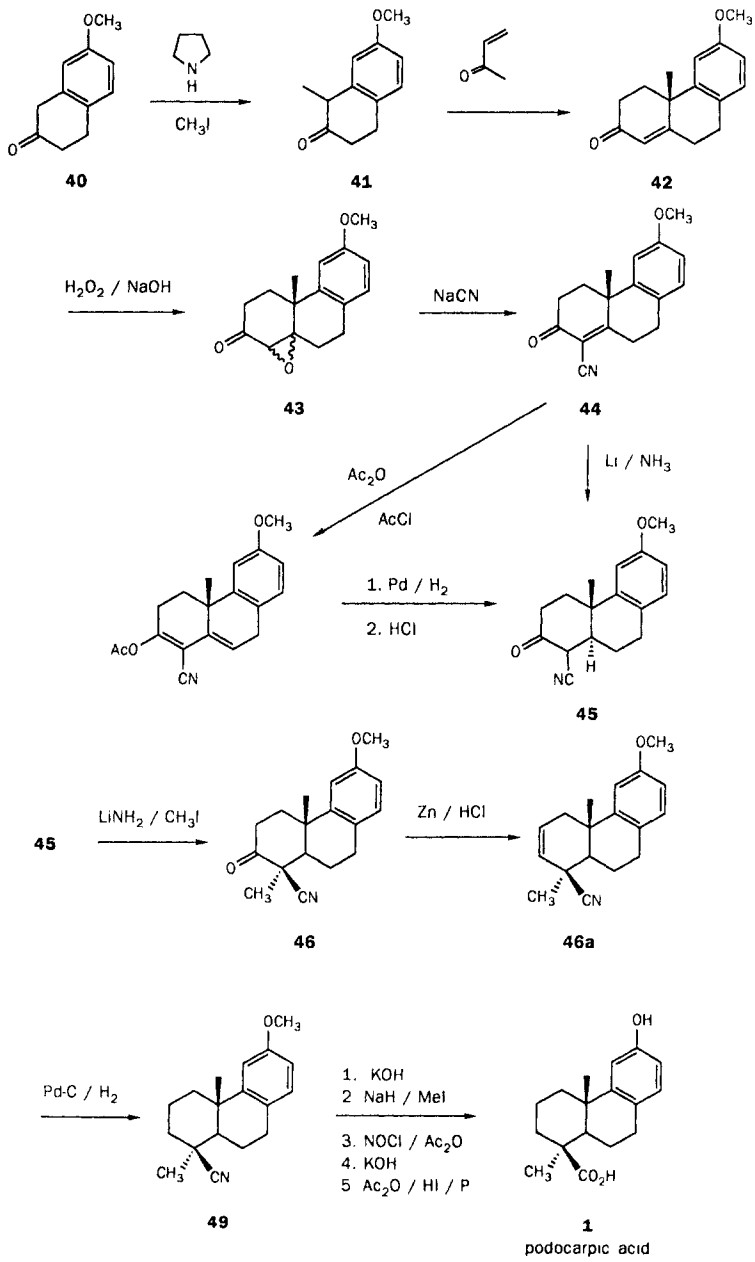
The stereochemistry of the eventual A/B ring junction is established by catalytic reduction after conversion of **35** to α-diketone **36**. Chemical reduction of **35** does not proceed with great stereoselectivity, but the catalytic process produces only the desired geometry. Oxidative cleavage of the five-membered ring of the reduction product **37** then affords a diacid, **38**, which upon cyclization and hydrogenolysis affords desoxypodocarpic acid, **39**. This compound is then carried through to the racemic natural product **1** using the method of Wenkert.[8]

The starting material for the synthesis (Scheme 8) of podocarpic acid by Kuehne and Nelson[15, 16] from the University of Vermont is 7-methoxy-β-tetralone, **40**. Methylation to afford **41** and Robinson annelation leading to tricyclic ketone **42** is followed by base-catalyzed epoxidation affording epoxy ketone **43**. Treatment of **43** with sodium cyanide proceeds via displacement and elimination to form the enone nitrile **44**. Two sequences are employed, both unfortunately going in low yield, to proceed to the saturated cyano-ketone **45**. In each case, however, the desired A/B *trans*-fused product is obtained.

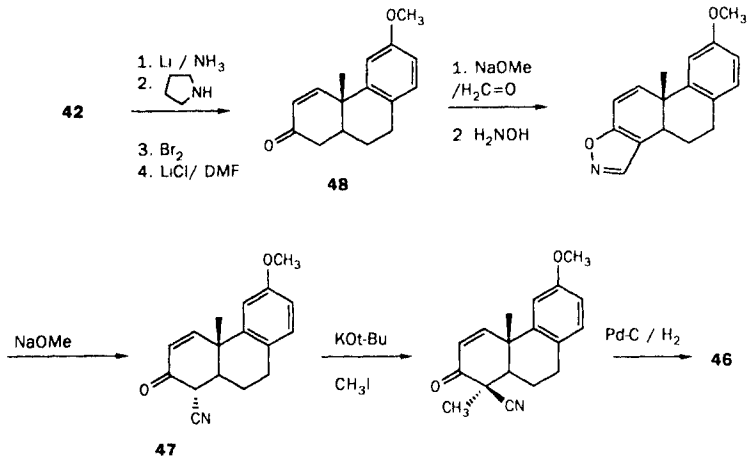


SCHEME 7. Ireland's synthesis of podocarpic acid.

Alkylation of **45** occurs *anti* to the angular methyl group to give **46** with the correct podocarpic acid stereochemistry. Another synthesis (Scheme 9) of this intermediate had been done earlier[15] by conversion of **42** to **47** via the $\Delta^{1,2}$-unsaturated ketone **48**. Alkylation of the unsaturated keto nitrile **47** also yields the podocarpic acid stereochemistry. The saturated alkylation product **46** of Scheme 8 is converted into olefin **46a**, thence to podocarponitrile methyl ether **49** by catalytic reduction. Methods which normally result in reduction



SCHEME 8. Kuehne's synthesis of podocarpic acid.

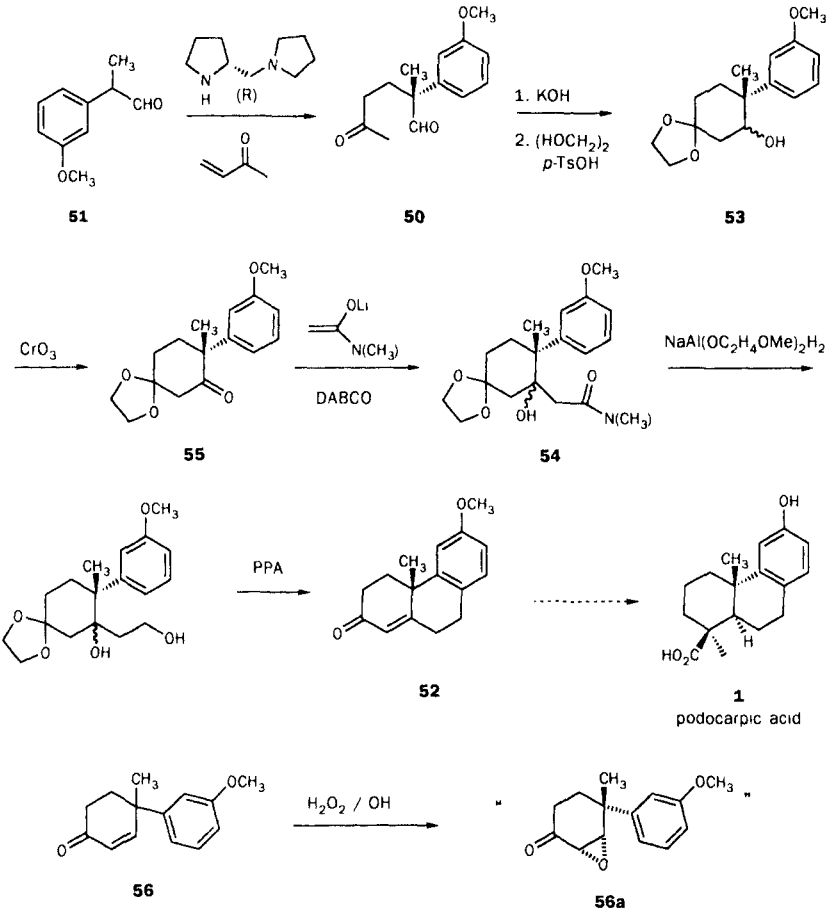


SCHEME 9. Kuehne's alternative synthesis of a podocarpic acid intermediate.

of a carbonyl group to a saturated carbon, for example, the Clemmenson reduction, when applied to ketone **46** yield the partial reduction product **46a**.

To obtain podocarpic acid methyl ether the nitrile, **49**, is subjected to a four-step sequence of partial hydrolysis, methylation, and nitrosation of the resulting amide and hydrolysis of the *N*-nitroso intermediate. Ether cleavage was carried out by the method of Haworth and Moore.[4]

For a chiral synthesis of podocarpic acid, Yamada and co-workers[17-19] at the University of Tokyo first carried out the preparation of keto-aldehyde **50** using (R)-pyrrolidonmethyl pyrrolidine as catalyst for the addition of aldehyde **51** to methyl vinyl ketone (Scheme 10). The product of this asymmetric synthesis, **50**, is chiral but the optical yield is only 42% e.e. For the synthesis of the target molecule only one other stereogenic center, C-5 with its α-disposed hydrogen, must be set. To do so the Yamada group converted **50** to enone **52**, a compound used by Welch[20] in his synthesis of racemic podocarpic acid. In the course of the conversion of **50** into **52** several of the intermediates contain chiral centers other than the one at C-10 established in the initial Michael addition. For example, **53** has a secondary hydroxyl at C-5 and **54**, produced by addition of the lithium enolate of dimethyl acetamide to **55**, has a tertiary hydroxyl and an acetamido chain at the same position. The chirality at C-5 of these compounds is lost in the course of the synthesis, but it is interesting to note that in every case the assignment of the relative configuration at C-5 is most probably incorrect.

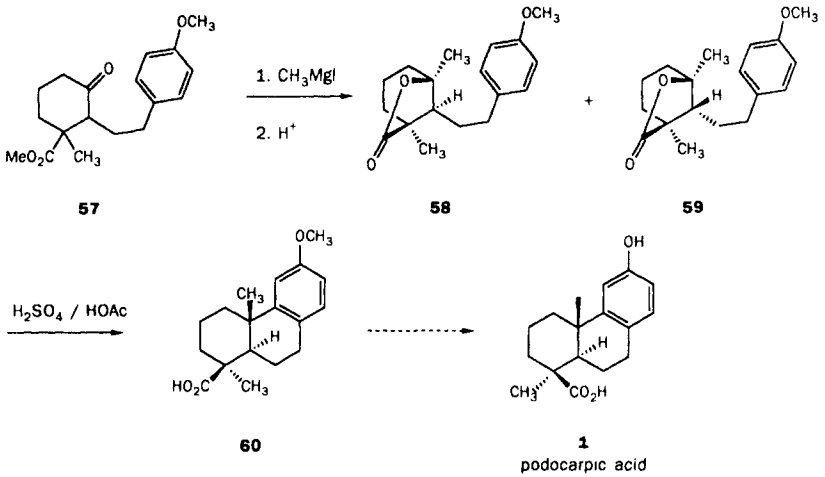


SCHEME 10. Yamada's synthesis of podocarpic acid.

For example, in one series of experiments[17] enone **56** is subjected to base-catalyzed epoxidation. On the basis of the difference in A-value[21] between a phenyl group and a methyl group, the major epoxide product is assigned the stereochemistry shown in **56a**, that is, axial attack of the epoxidizing agent has occurred from the side opposite to the "axial methyl group." In fact, a thorough conformational search[22] of **56** by use of molecular mechanics calculations[23] indicates that the major conformer of **56** (72%) is the one with an axial phenyl group! The minor conformer (28%) is the one with the methyl group in the axial position. Since it is unlikely that major differences in the rate of epoxidation would occur between these two conformers, the ratio of

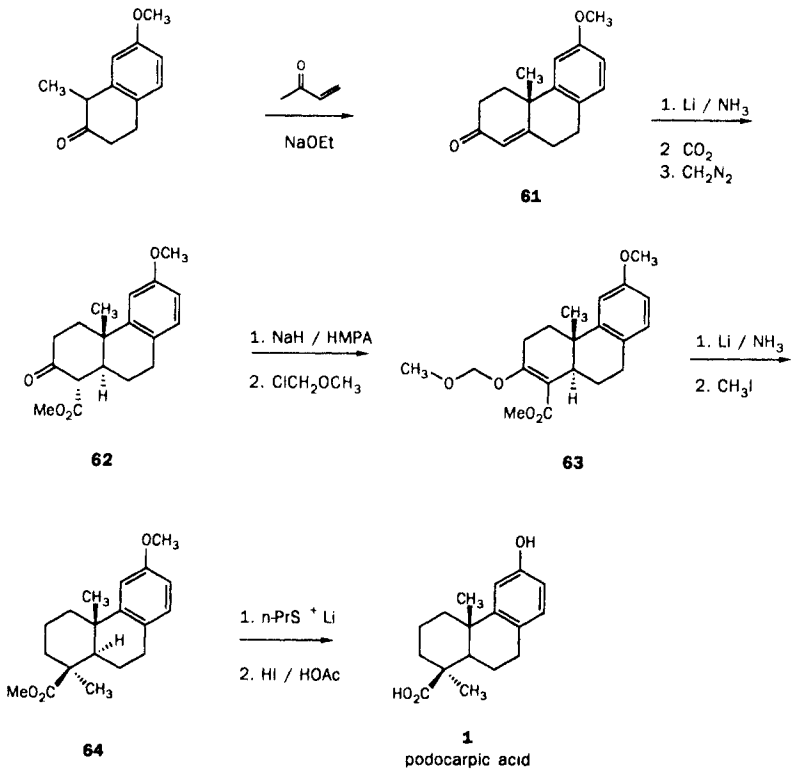
products ought to reflect the initial conformer populations. Indeed the products are obtained in the proportion of 3.5:1 (78–22%), but the assignment of stereochemistry appears to be reversed.

The Ghatak[24] synthesis of podocarpic acid (Scheme 11) from the Indian Association for the Cultivation of Science follows the pattern of the original King approach[3] but is more highly stereoselective. Starting from ketone **57** a mixture of lactones **58** and **59** is produced in a ratio of 9:1. When subjected to acid-catalyzed cyclization, this mixture affords podocarpic acid methyl ether **60** as the sole crystalline product in 41% yield. This material as noted has been carried forward to podocarpic acid.



SCHEME 11. Ghatak's synthesis of podocarpic acid.

In the Welch[20–27] syntheses of podocarpic acid done at the University of Houston, the C-4 methyl group is introduced by alkylation of an exocyclic ester enolate (Scheme 12). This is in contrast to the more general use of the enolate of a C-3 keto group. In accord with the other syntheses in this domain, however, alkylation again occurs from the α face of the nucleophilic carbon. In the approach used by Welch, tricyclic enone **61**, produced by standard means, is converted through dissolving metal reduction, carbonation, and esterification to β-ketoester **62**. O-alkylation then provides enol ether **63**, which in a second lithium in ammonia reaction undergoes reduction, elimination, and then reduction again to provide the enolate ion of the C-4 ester group. Upon addition of methyl iodide, alkylation occurs principally from the least-hindered face of the anion and ester **64** is produced. Cleavage of both ester and ether functions yields podocarpic acid.



SCHEME 12. Welch's synthesis of podocarpic acid.

Callitrisic Acid and Alkylation Stereochemistry

The first synthesis of a resin acid, callitrisic acid, **65**, was carried out in 1939 by Haworth and Baker[28] (Scheme 13). The publication of the work was "desirable in view of the intention of Sterling and Bogert to enter the same field." The synthetic scheme is an extension of the "Bogert–Cook" route to phenanthrene derivatives.[29, 30] The substituted β-keto ester **66** is reacted with a substituted phenylethyl magnesium bromide to afford alcohol **67**. Following dehydration, acid-catalyzed cyclization provides one of the isomers of dehydroabietic acid in approximately 13% yield. At the time of publication this product could not be compared with naturally occurring material short of a resolution. Twenty-four years later, Sharma, Ghatak, and Dutta[31] demonstrated that the product obtained by Haworth and Baker is callitrisic acid, **65**.