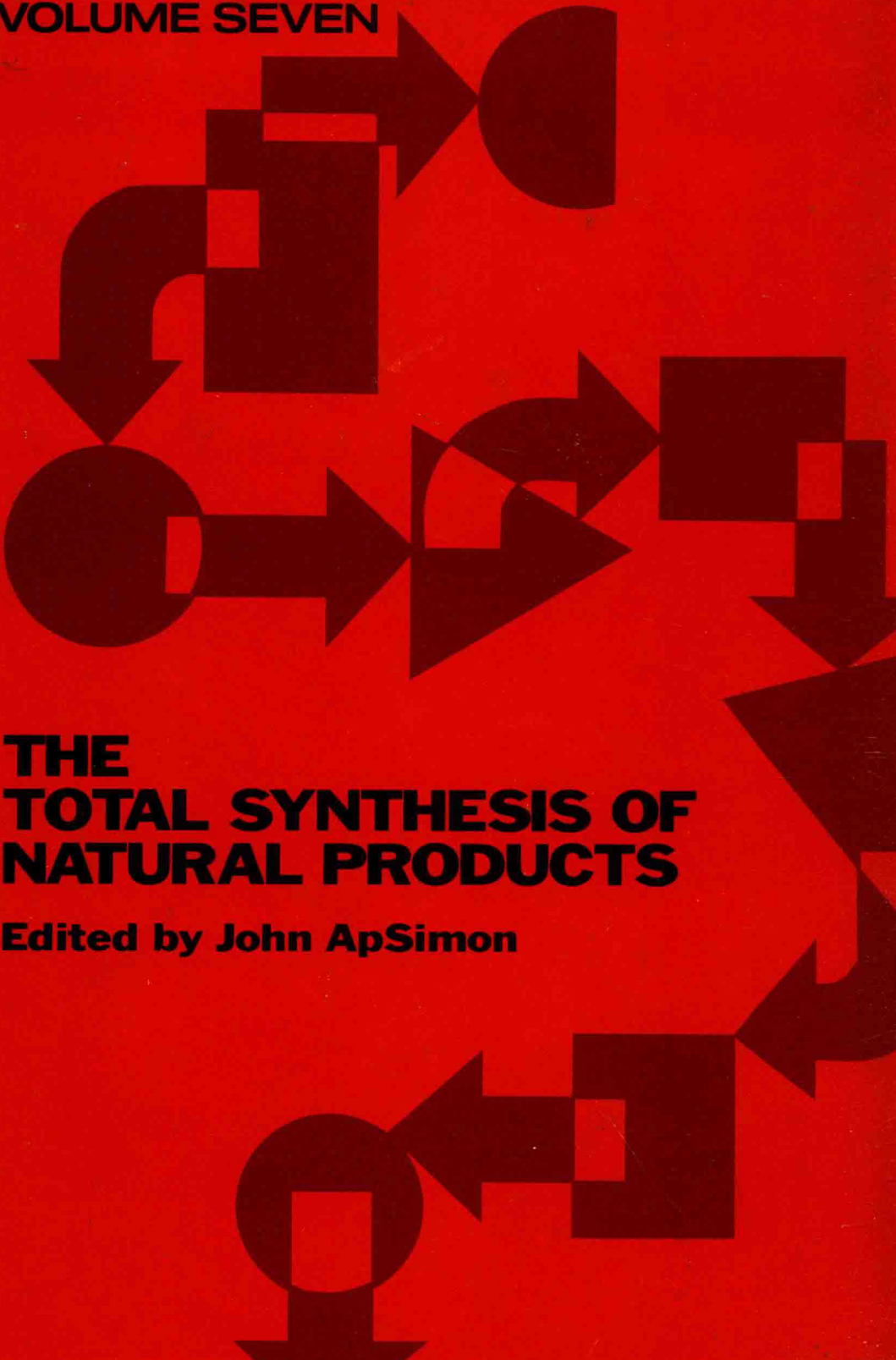
VOLUME SEVEN



THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

Edited by John ApSimon

The Total Synthesis of Natural Products

VOLUME 7

Edited by

John ApSimon

Ottawa—Carleton Chemistry Institute

and

Department of Chemistry
Carleton University, Ottawa

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS

NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

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 0-471-88076-0 (v. 7)

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

Contributors to Volume 7

J. Adams, Merck Frosst Canada Inc., Kirkland, Quebec, Canada

J. G. Atkinson, Merck Frosst Canada Inc., Kirkland, Quebec, Canada

Yvonne Bessière, Borex, Switzerland

R. H. Boeckman, Department of Chemistry, University of Rochester, Rochester, New York

M. Goldstein, Department of Chemistry, University of Rochester, Rochester, New York

Y. Guindon, Merck Frosst Canada, Inc., Kirkland, Quebec, Canada

J. Rokach, Merck Frosst Canada, Inc., Kirkland, Quebec, Canada

Alan F. Thomas, Research Laboratory, Firmenich SA, Geneva, Switzerland

R. N. Young, Merck Frosst Canada, Inc., Kirkland, Quebec, Canada

Preface

It is always a great pleasure to introduce another volume in this series, signalling among other things the health of the art and science of organic synthesis.

This volume contains a chapter updating monoterpene synthesis and reviews the newer areas of leukotrienes and macrocyclic lactones. My grateful thanks are due to the authors of these contributions for their efforts in producing definitive work on their specialty areas.

Future volumes in this series are in the pipeline and I am always prepared to receive suggestions for areas to cover, and offers to help!!

JOHN APSIMON

Ottawa, Canada
January 1988

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The Total Synthesis of Macrocyclic Lactones

R. K. BOECKMAN Jr. and S.W. GOLDSTEIN

Department of Chemistry, University of Rochester, Rochester, New York

INTRODUCTION

This chapter in Volume 7 of *The Total Synthesis of Natural Products* deals almost exclusively with the total synthesis of naturally occurring macrocyclic lactones (macrolides), polylactones (diolides, tetrolides, etc.), and their aglycones. Our use of the term macrolide transcends the original usage where it was restricted to the C_{12}–C_{16} macrocyclic lactone antibiotics. Although several reviews on the synthesis of macrolides have been published,[1–4] these have dealt mainly with the ring-forming lactonization step. We have attempted to chronicle the development of total synthesis in this field from the early efforts directed toward relatively simple targets to the current day assaults on the extremely complex, highly functionalized members of this class.

The chapter is divided into sections that deal with the various target compounds in approximate order of increasing complexity. Section 1 deals with simple monolactones which lack complex substituents such as sugars, esters, and the like attached to the lactone ring. This section includes primarily compounds that exhibit little or no biological activity, such as recifeiolide and diplodialide A. The syntheses in this area are generally quite straightforward and for expedience we have omitted some of the simplest compounds. The omission of some of these early studies is not intended to in any way diminish their value, for these efforts laid the foundations for later advances.

Section 2 deals with the synthesis of the more familiar biologically active macrolides, including the erythronolides, tylosin, and the leucomycin–carbomycin group. These compounds, many of which have important medicinal

uses, possess more highly oxygenated ring systems and are linked, via glycosidic linkages, to one or more sugar units.

Section 3 deals with the polycyclic macrolides such as cytochalasin B and hybridalactone. These compounds also exhibit profound biological activity. Since they are substantially more complicated than the other monolactones, we felt a separate section was warranted.

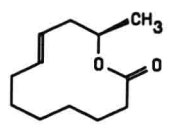
Section 4 deals with the total synthesis of macrolides having more than one lactone linkage in the macrocyclic ring. Compounds included in this group range from the dimeric lactone pyrenophorin and the trichothecanes to the tetrameric lactone nonactin.

Throughout this chapter we have attempted to be as comprehensive as possible in our coverage of the literature through 1984, with selected coverage of early parts of 1985 in the broad area of macrolide total synthesis. However, we have very possibly overlooked some work in the area. We regret the oversight, and we wish to apologize in advance to any workers in the area whose efforts have been inadvertently omitted.

1. SIMPLE MONOCYCLIC MACROLIDES

A. Recifeiolide

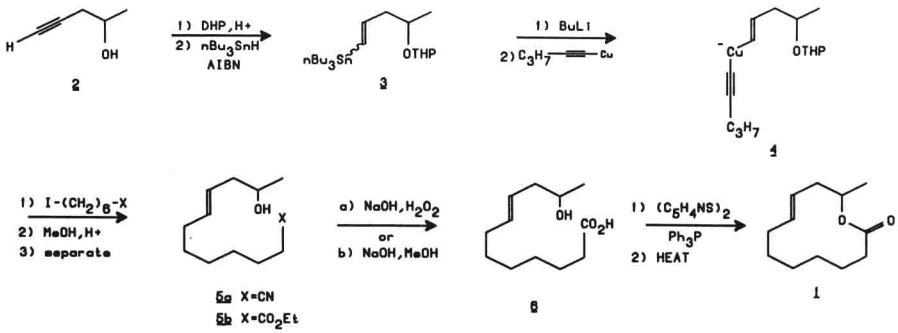
Recifeiolide (**1**), one of the simplest naturally occurring macrocyclic lactones, is isolated from the fungus *Cephalosporium recifie*.[5] Since only one chiral center is present in this molecule, recifeiolide is the common benchmark for macrolide methodology. The first synthesis of this compound, by Corey's group at Harvard, began with 4-hydroxy-1-pentyne (**2**) (Scheme 1.1).[6] Protection of the alcohol as the THP ether followed by hydrostannation afforded a 85:15 mixture of vinyl stannanes **3** with the (*E*)-isomer predominating. The stereospecific conversion of the stannanes **3** to the corresponding vinyl cuprates **4** was achieved by metalation with *n*-butyl lithium followed by quenching into pentynyl copper. The cuprates **4** were then coupled with either 7-iodo-heptanitrile or ethyl 7-iodohepanoate and the alcohol protecting group was removed to afford a 54–56% yield of alkylated products **5a** or **5b**. At this stage, chromatographic separation



1

Figure 1.1. Recifeiolide (**1**).

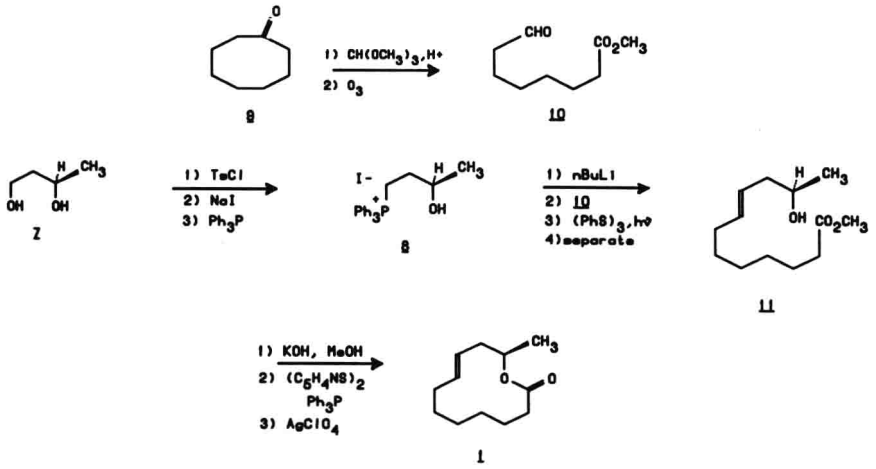
of the olefin isomers yielded (*E*)-**5a** or (*E*)-**5b**, which encompass all the required carbons for conversion to **1**. Alkaline hydrolysis gave the key intermediate seco acid **6** (98%). The final cyclization was accomplished by conversion to the 2-thiopyridyl ester and subsequent thermolysis in dilute xylene to afford recifeiolide (**1**) in 52% overall yield from **6**.



Scheme 1.1. Corey's recifeiolide synthesis.

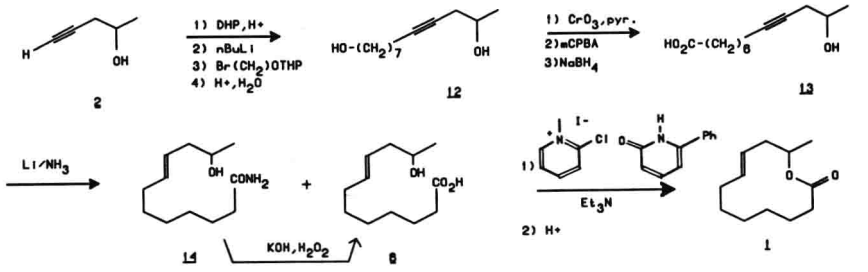
The same year, Gerlach described a synthesis of optically active **1** from (*R*)-1,3-butanediol (**7**) (Scheme 1.2).[7] The diastereomeric esters produced from (−) camphorsulfonyl chloride and racemic 1,3-butanediol were fractionally recrystallized and then hydrolized to afford enantiomerically pure **7**. Tosylation of the primary alcohol, displacement with sodium iodide, and conversion to the phosphonium salt **8** proceeded in 58% yield. Methyl-8-oxo-octanoate (**10**), the ozonolysis product of the enol ether of cyclooctanone (**9**), was subjected to Wittig condensation with the dilithio anion of **8** to give **11** as a mixture of olefin isomers in 32% yield. The ratio, initially 68:32 (*E*:*Z*), was easily enriched further to 83:17 (*E*:*Z*) by photolysis in the presence of diphenyl disulfide. The synthesis was then completed by hydrolysis of the ester to the seco acid, conversion to the 2-thiopyridyl ester, and silver-mediated ring closure to afford **1** (70%). Gerlach's synthesis, while producing the optically active natural product, still did not address the problem posed by the olefin geometry.

A third approach employing lactonization as the final step was published by Mukaiyama in 1977 (Scheme 1.3).[8] Alcohol **2** was protected as the THP acetal and alkylated with a protected 7-bromoheptanol to give diol **12** in 52% yield following acidic deprotection. As **12** contains all of the required carbon atoms for conversion to the target **1**, the remaining steps involve only the manipulation of the oxidation states of the various functional groups and the final lactonization. Accordingly, a series of straightforward oxidations and a reduction then allowed the isolation of hydroxy acid **13** in 50% yield. Lithium metal reduction of the



Scheme 1.2. Gerlach's recifeiolide synthesis.

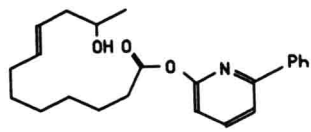
alkyne then furnished the seco acid **6** in 53% along with a small amount of the corresponding amide **14**, which was readily hydrolized back to **6**. Lactonization involving a double activation sequence furnished an 87% yield of **1**.



Scheme 1.3. Mukaiyama's recifeiolide synthesis.

The aforementioned method for carboxyl group activation proceeds via intermediate **6a**, which is then subjected to an intramolecular attack by the secondary alcohol. Among the noteworthy aspects of this synthesis were the rapid entry into the system and the specific formation of the (*E*)-olefin geometry.

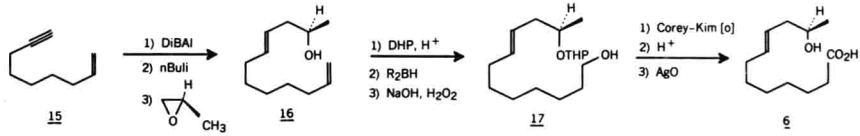
Utimoto and co-workers have successfully achieved a concise synthesis of the optically active seco acid **6** beginning with 1-nonen-8-yne (**15**) (see Scheme 1.4).[9] Hydroalumination of enyne **15** with Dibal and conversion to the alanate with *n*-butyl lithium, followed by treatment with (*R*)-propylene oxide afforded



6a

Figure 1.2.

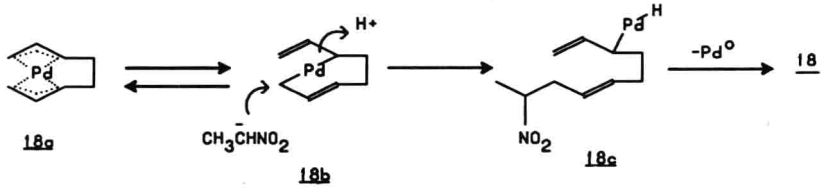
alcohol **16** in 55% yield. Not surprisingly, the syn hydroalumination step produced >99% of the (*E*)-internal olefin. Protection of the alcohol as the THP ether followed by hydroboration and oxidation gave the monoprotected diol **17** (74%). Seco acid **6** was obtained following a Corey–Kim oxidation, acidic hydrolysis of the THP ether (75%), and subsequent silver oxide oxidation (98%). The conversion of **6** to recifeiolide (**1**) then followed the Gerlach procedure.[7]



Scheme 1.4. Utimoto's recifeiolide synthesis.

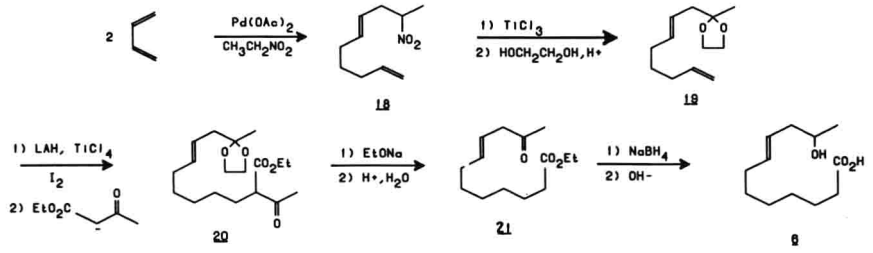
A novel method of stereospecific olefin formation was used by Tsuji for the elaboration of intermediate **18** (Scheme 1.5).[10] Palladium(II)-mediated telomerization of butadiene in nitroethane gave a 56% isolated yield of the (*E*)-nitro olefin **18**. One rationale for the high stereospecificity in the bond-forming steps of this reaction arises from an examination of the mechanism. The addition of Pd^{+2} to butadiene causes initial formation of a dimeric bis π-allyl palladium species. The bis π-allyl species **18a** and the σ-allyl species **18b** (Eq. 1.1) are in rapid equilibrium and the latter intermediate may be intercepted by a nucleophile. Thus the addition of nitroethane to **18b** results in the formation of **18c** with retention of the (*E*)-olefin geometry. Reductive elimination of palladium then produces **18** with retention of the (*E*)-olefin geometry.

After conversion to **19** (70% yield) via Nef reaction and ketalization, selective modification of the terminal olefin by reaction with LAH–$TiCl_4$, quenching with I_2, and displacement of the resulting terminal halogen with ethyl acetoacetate anion afforded **20** in 48% overall yield. Deacetylation with sodium ethoxide followed by deketalization under acidic conditions produced an 88% yield of keto ester **21**. Seco acid **6** was then obtained (in 29% yield from **18**) after reduction of the ketone and ester hydrolysis. Clearly, the significance of this



Telecomerization of butadiene (1.1)

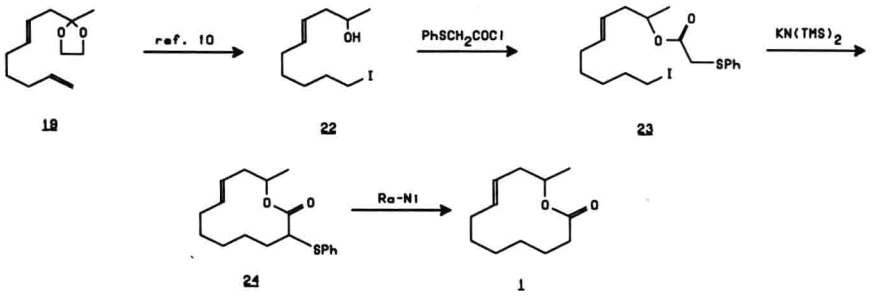
synthesis was the utilization of inexpensive starting materials and the excellent specificity of the olefin-forming reaction. Tsuji has employed this methodology for the synthesis of several other natural products.



Scheme 1.5. Tsuji's first recifeiolide synthesis.

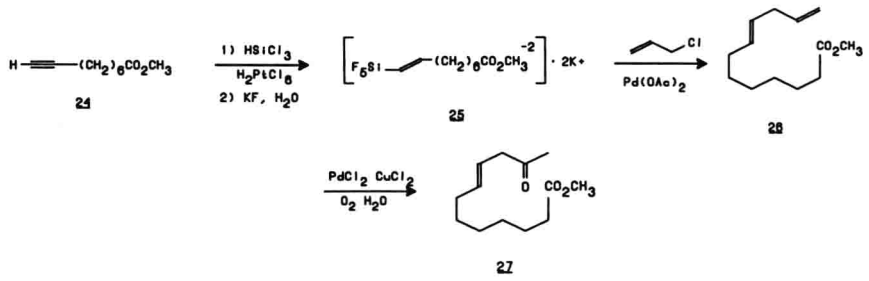
The second Tsuji synthesis, which appeared (see Scheme 1.6) in the latter part of 1978, employed a strategy similar to his earlier work for construction of the basic carbon framework.[11] Ketal diene **19** was transformed to halo alcohol **22** by the use of chemistry established in his previous synthesis.[10] Acylation with phenylthioacetyl chloride readily afforded ester **23**. Intramolecular alkylation resulting in ring closure was brought about by deprotonation with sodium hexamethyldisilazane to give lactone **24** in 71% yield. Synthetic **1** was then obtained in 90% yield following Raney nickel reduction.

Kumada's group at Kyoto installed the (*E*)-olefin required for recifeiolide (**1**) via syn addition to a terminal acetylene (Scheme 1.7).[12] Beginning with methyl 8-nonynoate, chloroplatinic-acid-catalyzed addition of trichlorosilane gave the corresponding (*E*)-silyl olefin. Halogen exchange and formation of the silicate with aqueous KF afforded **25** in 62% yield. Alkylation with allyl chloride mediated by $Pd(OAc)_2$ gave diene **26**, which was transformed by Wacker oxidation to ketone **27** (37%). This completed a formal total synthesis of **1**, as the conversion of **27** to the natural product had previously been achieved by Tsuji.[10] Although somewhat suggestive of Utimoto's approach, the Kumada



Scheme 1.6. Tsuji's second recifeiolide synthesis.

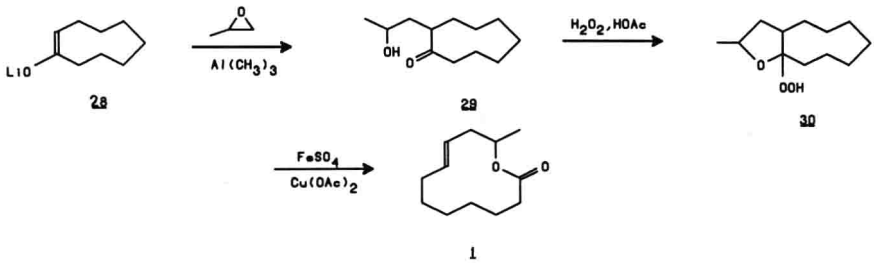
synthesis was less complicated, since fewer oxidation state changes and protecting group manipulations were required.



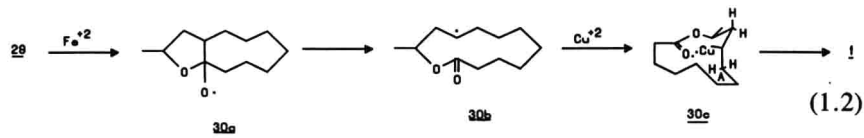
Scheme 1.7. Kumada's recifeiolide synthesis.

By far the most concise synthesis of **1** has arisen from the work of Schreiber in 1980 (see Scheme 1.8).[13] The lithium enolate **28** was monoalkylated with propylene oxide in the presence of trimethyl aluminum to give keto alcohol **29** in 96% yield (based on recovered **28**). The addition of hydrogen peroxide under acidic conditions then made available the hydroperoxide **30** in 99% yield. A ferrous-ion-induced fragmentation then gave the natural product **1** in 96% yield as a single olefin isomer.

The mechanism of the key fragmentation involves initial transfer of an electron to hydroperoxide **30** (Eq. 1.2) from Fe^{+2}, forming intermediate **30a**, which then cleaves homolytically to the carbon radical **30b**. Oxidative coupling with $Cu(OAc)_2$ then forms **30c** in which the ester moiety is in the stable *Z*-configuration, stabilized by internal coordination via a psuedo six-membered ring. From this intermediate, only one hydrogen atom (H_A) is available for syn elimination and, accordingly, only the (*E*)-olefin is produced.

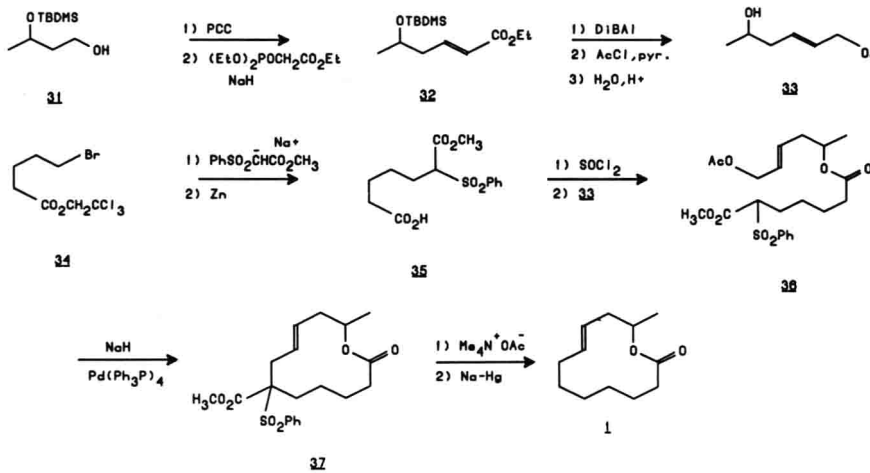


Scheme 1.8. Schreiber's recifeiolide synthesis.



(1.2)

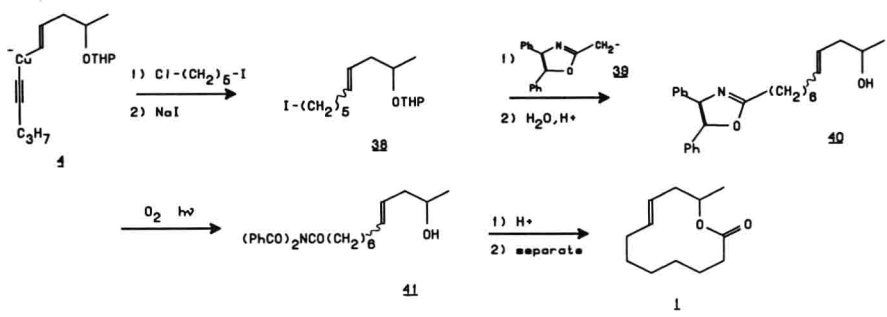
Trost chose to exemplify the utility of organopalladium coupling reactions for carbon–carbon bond formation by use of this process for the ring closure step in a synthesis of **1** (Scheme 1.9).[14] To this end, monoprotected diol **31** was oxidized and chain extended to form the α,β-unsaturated ester **32**. Reduction to the allylic alcohol followed by acetylation and desilylation gave **33** in 53% overall yield from **31**. Carboxylic acid **35** was then obtained via a two-step sequence from bromo ester **34** (84%) by alkylation with methyl



Scheme 1.9. Trost's recifeiolide synthesis.

phenylsulfonylacetate followed by reductive cleavage of the ester. Formation of the analogous acid chloride permitted coupling of **35** and **33** to afford ester **36** in 79% yield. Formation of the 12-membered ring lactone was then achieved by palladium-catalyzed cyclization to afford **37** (78%), with no apparent formation of either any (*Z*)-olefin or 10-membered ring lactone. The stereospecificity of this reaction is quite dramatic when compared with the loss of olefin geometry observed in acyclic cases.[15] The synthesis of **1** was efficiently completed by decarboalkoxylation and reductive desulfonylation to give synthetic **1** in 81% yield. Although this synthesis is somewhat complex for a molecule as structurally simple as **1**, clearly Trost selected recifeiolide as a vehicle to explore methodology useful for the construction of more complex macrolides.

Wasserman has completed two syntheses of recifeiolide, both employing the use of oxazoles as acetic acid dianion equivalents.[16] The first (Scheme 1.10) utilized a route previously developed by Corey[6] for his synthesis of **1**. Cuprate **4** was alkylated and then converted to iodide **38** in a straightforward manner. Alkylation with oxazole anion **39** and removal of the THP with acid then led directly to alcohol **40**. Liberation of the carboximide moiety was achieved by treatment with singlet oxygen to afford **41**, which led to the isolation of synthetic **1** after an acid-mediated lactonization step, and separation of the olefin isomers.



Scheme 1.10. Wasserman's first recifeiolide synthesis.

Wasserman's second synthesis,[16] shown in Scheme 1.11, was similar to a strategy utilized by Gerlach.[7] Anion **39** was alkylated with the acetal of 6-iodohexanal and deprotected to produce aldehyde **42**. A Wittig condensation with the dilithio dianion of racemic **8** afforded the known intermediate **40** as an 8:2 mixture of (*E*)- and (*Z*)-olefin isomers, respectively.

The most recent synthesis of **1** is that of Bestmann.[17] Acetylenic alcohol **2** was converted to the dianion and alkylated with the acetal of 4-bromopentanal to give alkyne **53**. Subsequent reduction of the triple bond with sodium in ammonia generated exclusively the required (*E*)-olefin geometry. *O*-Alkylation