Total Synthesis of Bioactive Marine Macrolides†

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Received March 17, 1995 (Revised Manuscript Received June 12, 1995)

Contents

I. Introduction

Nature has stocked the seas with a seemingly limitless range of diverse and often highly complex secondary metabolites, which exhibit one or more of a variety of biological properties including cytotoxicity, neurotoxicity, antiviral, and antifungal activity.[1] This review focuses on chemical efforts directed toward the total synthesis of a specific subset of biologically active marine natural products—namely those compounds which possess a macrocyclic lactone moiety, *i.e.* the marine macrolides.[2,3] The literature is surveyed from the onset of the subject, in the early 1980s, until the close of 1994.

The topical nature of this field of chemical research may be illustrated by reference to the spongistatins, a group of nine extremely potent cytotoxic marine macrolides which have recently been isolated from an Eastern Indian Ocean sponge of the genus *Spongia* (spongistatins 1–3 (**1**–**3** in Figure 1)), and from the Southwest African marine sponge *Spirastrella spinispirulifera* (spongistatins 4–9 (**4**–**9**)).[4] In addition, some presumably identical compounds, the altohyrtins A–C (**1**, **2**, and **10**) and 5-desacetylaltohyrtin A (**3**), have been isolated from the Okinawan marine sponge *Hyrtios altum*,[5] and a compound named cinachyrolide A (assumed to be identical to spongistatin 4) has been isolated from a marine sponge of the genus *Cinachyra*.[6] The spongistatins represent some of the most potent substances presently known against a subset of highly chemoresistant tumor types in the US NCI panel of 60 human cancer cell lines. They show especially powerful growth inhibitory activity against human melanoma, lung, colon, and brain cancers. Indeed, spongistatins 1 (mean panel $GI_{50} = (2.5–3.5) \times 10^{-11}$ M) and 9 (mean panel $GI_{50} = 4 \times 10^{-11}$ M) are the most potent members of the spongistatin family and are claimed to be the most cancer cell growth inhibitory antimitotic substances discovered to date.[4]

Synthetic interest in the marine macrolides stems mainly from their biological activities, and, in particular, their potential as chemotherapeutic agents. Most of these natural products are available in only microscopic quantities from their biological source: spongistatin 1 (**1**), for example, is obtained in only 3.4×10^{-7}% isolated yield from the whole sponge, and spongistatin 9 (**9**) is isolated in 2.2×10^{-7}% yield. Large-scale harvesting of marine organisms, such as sponges, is neither practical nor ecologically acceptable, but total synthesis has, in principle, the potential for supplying sufficient quantities of natural product for biological and pharmaceutical testing. The fact that closely related chemical structures have been found in several disparate marine sources, as in the case of the spongistatins, suggests that these natural products may in fact be produced by symbiotic organisms living in association with the different marine hosts.[7] Potentially, in such cases, fermentation cultures of the symbiotic organisms provide a means of obtaining significant quantities of the marine macrolides. To date, however, this appproach has met with only partial success, and total synthesis remains the only viable alternative. In addition, *de novo* chemical synthesis provides the possibility for preparation of nonnatural analogues, which may be used as probes to determine the mechanism of action of the natural product, as well as being useful for therapeutic evaluation.

Total synthesis is also a valuable tool for confirming, and in some cases determining, the stereochemistry of marine macrolides, which may not always be possible by spectroscopic or crystallographic means alone. For instance, although a complete absolute configuration for spongistatin 1 (≡ altohyrtin A) has been volunteered by Kitagawa and co-workers on the basis of spectroscopic studies on the natural product,[5b] this stereochemical assignment is partially in conflict with relative stereochemistry proposed by Pettit *et al.*[4d,e] and by Fusetani *et al.*[6] Thus, at the time of writing, there is uncertainty about the absolute configuration of portions of the spongistatin stucture, and therefore a need for unambiguous determination of stereochemical configuration via total synthesis. In recent years, the combination of chemical synthesis and conformational analysis using NMR methods and computational molecular modeling has proved

† We dedicate this review to Professor David A. Evans.
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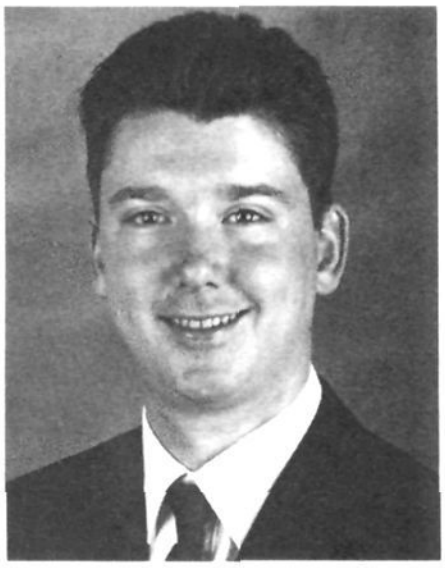
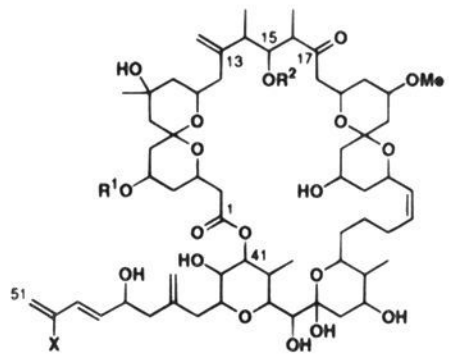


Roger Norcross was born in Manchester, England, in 1967. He studied for a B.A. degree in Natural Sciences at Cambridge University, and it was during this time that his interest in organic synthesis, and asymmetric synthesis in particular, was kindled. He received his Ph.D. degree from Cambridge University in 1992, under the supervision of Dr. Ian Paterson, on the subject of new stereoselective aldol methodology and its application in the total synthesis of macrolide antiobiotics. From 1992 to 1994 he was a NATO Postdoctoral Fellow in the laboratories of Professor David A. Evans, at Harvard University. During these immensely stimulating two years he concentrated upon the search for new asymmetric catalysts. Upon returning to Cambridge University in 1994, he reentered the field of total synthesis, focusing upon the development of new stereoselective methods for application in the synthesis of marine macrolides. He is currently working at the Corporate Research Laboratories of Ciba-Geigy in Basel, Switzerland.

Ian Paterson was born in Dundee, Scotland, in 1954. He received a B.Sc. degree in Chemistry from St. Andrews University in 1976. In 1979 he obtained his Ph.D. from Cambridge University, working under the supervision of Ian Fleming, on the development of new synthetic methods using allylsilanes and silyl enol ethers. After spending a highly rewarding and enjoyable year with Gilbert Stork at Columbia University as a NATO Postdoctoral Fellow, working on the total synthesis of erythromycin A, he joined the faculty at University College, London, in 1980. In 1983 he moved to his present position as a Lecturer at Cambridge University and Fellow of Jesus College. His research interests are centered on the design and development of new synthetic methods for the control of stereochemistry and their application to the total synthesis of a range of biologically active compounds, which currently include several marine macrolides.

valuable as a tool in determining the stereochemistry of marine macrolides, most notably in the case of the halichondrins and aplyronines (*vide infra*).

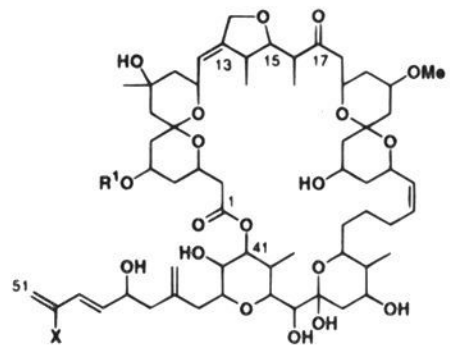
The exquisitely complex structures of many of the marine macrolides serve as inspiration for the development of new methodology in organic synthesis, and as an elegant platform for exhibiting the creativity of the modern organic chemist, which seems to be limited only by the structures themselves. The



spongistatin 1 (**1**) : X = Cl, $R^1 = R^2$ = Ac
2 (**2**) : X = H, $R^1 = R^2$ = Ac
3 (**3**) : X = Cl, R^1 = H, R^2 = Ac
4 (**4**) : X = Cl, R^1 = Ac, R^2 = H
6 (**6**) : X = H, R^1 = Ac, R^2 = H

altohyrtin B (**10**): X = Br, $R^1 = R^2$ =Ac
A ≡ spongistatin 1
C ≡ spongistatin 2
5-desacetylaltohyrtin A ≡ spongistatin 3

cinachyrolide A ≡ spongistatin 4



spongistatin 5 (**5**) : X = Cl, R^1 = H
7 (**7**) : X = R^1 = H
8 (**8**) : X = H, R^1 = Ac
9 (**9**) : X = Cl, R^1 = Ac

Figure 1. Structures of the spongistatins.

marine macrolides present a 5-fold synthetic challenge to the organic chemist: (i) The stereochemical challenge provided by target structures possessing, in some cases, in excess of 30 stereogenic centers. Historically, many marine macrolide syntheses have relied on the use of starting materials from the chiral pool, such as carbohydrates, to supply most of the stereogenic centers.[8] Increasingly, concomitant with the appearance of new methods for achieving acyclic stereocontrol, alternative strategies have been employed relying on either reagent- or substrate-based asymmetric induction.[9]

(ii) Formation of the macrocycle. This has generally been achieved by using macrolactonization reactions, which are increasingly becoming routine procedures in organic synthesis,[10] but carbon–carbon bond-forming reactions have occasionally been employed. Thus far, the largest ring constructed has been that of the 44-membered macrodiolide swinholide A (*vide infra*).

(iii) The need for efficient processes for coupling complex, often highly oxygenated, fragments, suitable for use in the latter stages of a synthesis.

(iv) The judicious choice of protecting group arrangements for polyoxygenated structures. In several cases, the success or failure of a synthetic route has depended entirely on the selection of a protecting group for a single hydroxyl-bearing center (*vide infra*).

(v) The requirement of many of the marine macrolides for the stereocontrolled formation of di- or trisubstituted double bonds.

In this review, the marine macrolides are presented in order of decreasing ring size (as determined by counting along a contiguous carbon skeleton wherever possible), except that closely related structures are considered in succession in order to aid comparison. After giving a brief description of the natural source and biological properties, a summary of the associated synthetic work then follows. Where total syntheses have been achieved, details for all transformations in the route are to be found in the accompanying diagrams. Discussion in the text concentrates on those key reactions which establish stereochemistry, close rings, or couple complex segments. Wherever possible, an approximate indication of the overall yield and total number of steps is given. As a guide to synthetic efficiency, the approximate number of steps per stereogenic center of the target structure is also provided.

II. Survey of Syntheses of Marine Macrolides

A. The Swinholides

The swinholides (**11**–**17** in Figure 2) are a series of complex macrodiolides, isolated from the marine sponge *Theonella swinhoei*,[11,12] which display potent cytotoxicity against a variety of human tumor cell lines.[13d] Swinholide A (**11**) was originally misassigned as a monomeric 22-membered[14] macrolide,[11] but more recent mass spectroscopic[13a] and X-ray crystallographic[13b-d] studies have elucidated the true C_2-symmetrical, 44-membered,[14] macrodiolide structure depicted in Figure 2. Isoswinholide A (**18**), a minor congener of swinholide A, having an unsymmetrical 46-membered macrodiolide structure, has also been isolated from *Theonella*,[12a] along with the monomeric seco-acid preswinholide A (**19**), which is believed to be the biosynthetic precursor of swinholide A.[12b,c] Other cytotoxic macrodiolides isolated from *Theonella* sp. include the bistheonellides (**20**–**22**), which lack two of the swinholide double bonds and are thus 40-membered macrocycles.[15b-d] Note that the structures of the monomeric units of both swinholide A (**11**) and bistheonellide A (**20**) (also called misakinolide A[15a,c]) are very similar[13c] to that of scytophycin C (**23**),[16a] one of a class of cytotoxic macrolides (**23**–**27**) isolated from the terrestial blue-green alga *Scytonema pseudohofmanni* (*vide infra*).[16] This structural homology implies a genetic link between the producing organisms, lending support to the assumption that the swinholides and bistheonellides are actually metabolites of symbiotic microorganisms associated with *Theonella* sp.[7,13c] Indeed, the presence of a symbiotic blue-green alga in the marine sponge *Theonella swinhoei* has been detected using electron microscopy.[13c]

The first total synthesis of swinholide A (and also of its minor congener isoswinholide A) was reported by Paterson *et al.* in 1994,[17g] following syntheses of preswinholide A earlier that year.[17e,f] Two significant segments of swinholide A have been prepared by Nicolaou and co-workers,[18] and Nakata *et al.* have also synthesized a swinholide A segment.[19]

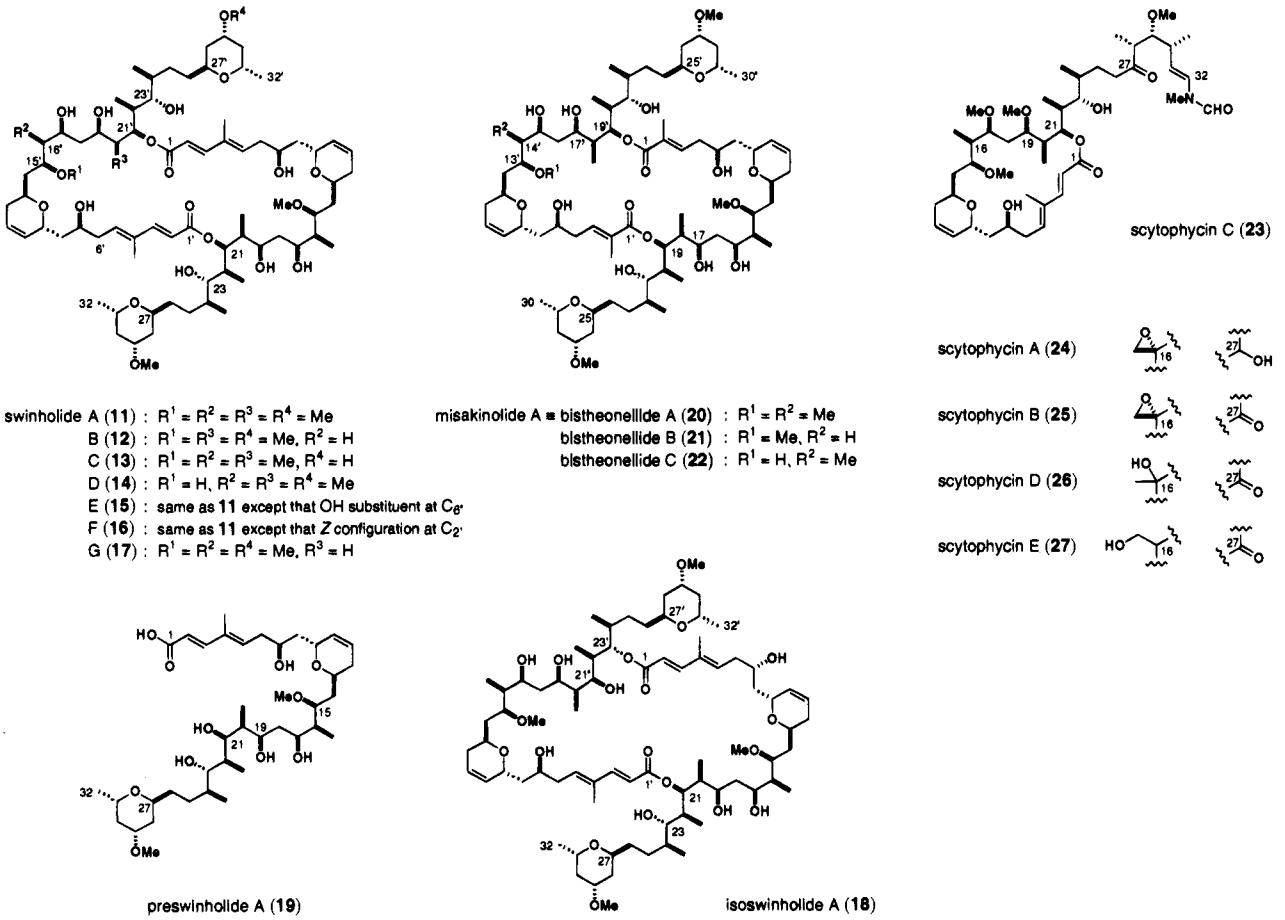
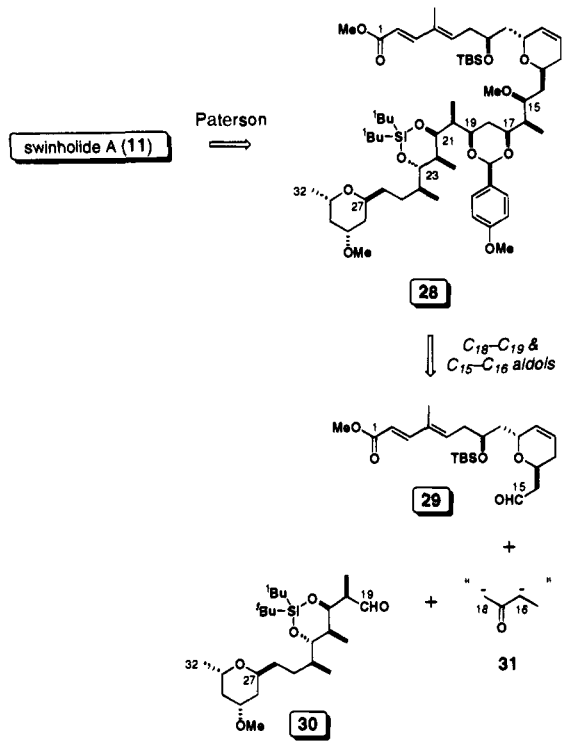


Figure 2. Structures of the swinholides, misakinolides, and scytophycins.

Scheme 1



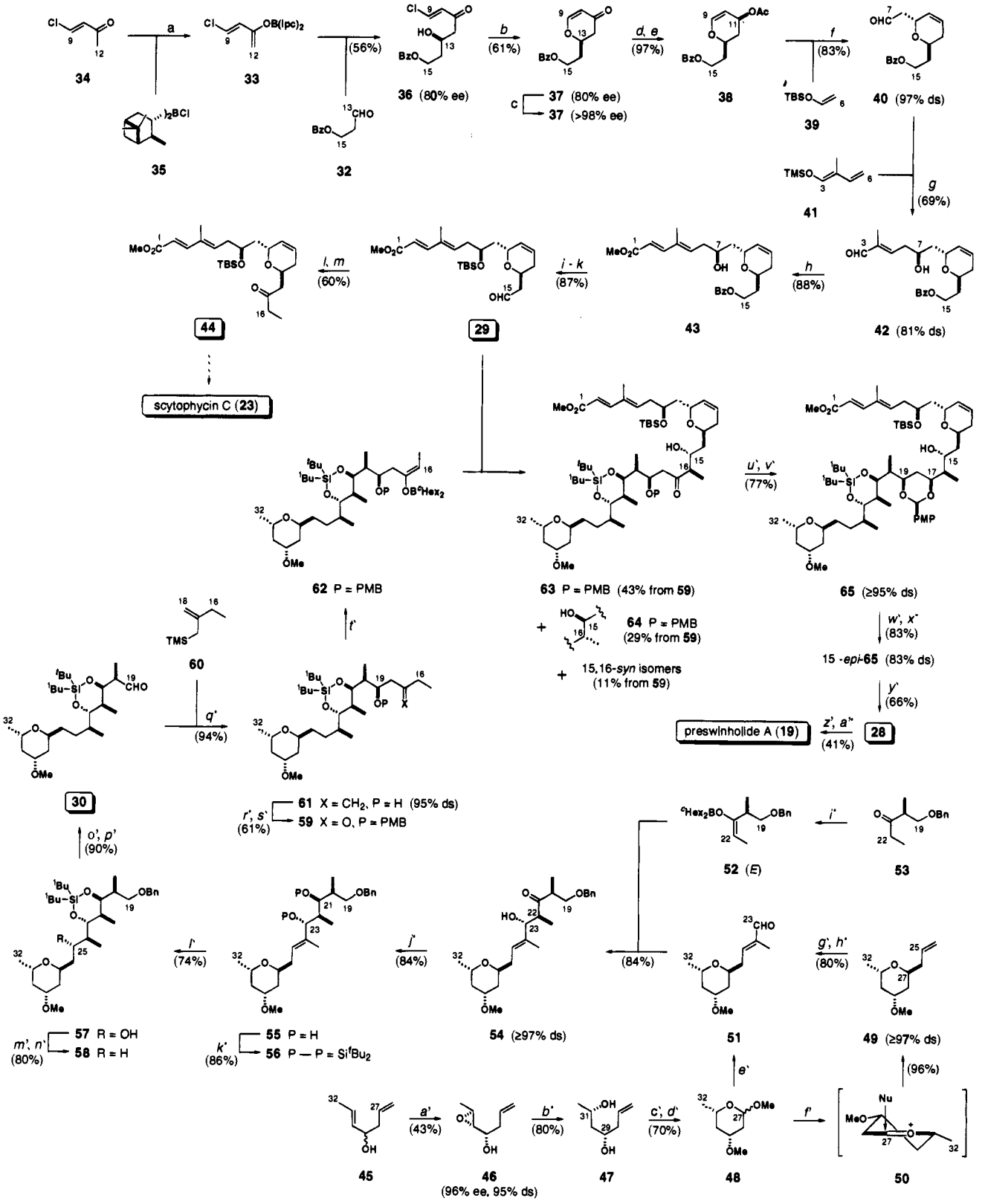
1. Paterson Total Synthesis[17]

The synthesis of swinholide A (**11**) by Paterson *et al.* was based on the selective deprotection and regiocontrolled dimerization of **28**, a fully protected version of the monomeric seco-acid preswinholide A (Scheme 1). The monomeric unit **28** was constructed by the union of the C_1-C_{15} aldehyde segment **29** and the $C_{19}-C_{32}$ aldehyde segment **30** employing a butanone synthon (**31**) as a linking unit.[20] By varying the order of the $C_{15}-C_{16}$ and $C_{18}-C_{19}$ aldol bond constructions, the stereochemically most efficient sequence for this key segment coupling was determined. The stereocontrolled syntheses of **29** and **30**, in turn, relied heavily on various types of asymmetric aldol reactions, which were used to form the C_6-C_7, $C_{12}-C_{13}$, and $C_{22}-C_{23}$ bonds.

a. C_1-C_{15} Segment Synthesis.[17b,c] Preparation of the C_1-C_{15} segment **29** began by employing methodology developed by Paterson for the enantioselective synthesis of dihydropyrones.[21] Thus, reagent-controlled asymmetric aldol reaction of aldehyde **32** with the bis(isopinocampheyl) enol borinate **33**, derived from enolization of ketone **34**[22] by (+)-bis(isopinocampheyl)boron chloride **35**, gave the aldol adduct **36** in 80% ee (Scheme 2). Cyclization of **36** to the dihydropyrone **37** was then accomplished by treatment with TMSOTf/^{i}Pr$_2$NEt and recrystallization provided **37** in enantiomerically pure form. Stereoselective Luche reduction[23] of **37** to the corresponding allylic alcohol (α-face attack), followed by acetylation, then supplied the glycal **38**. Stereoselective introduction of the aldehydic side chain at C_9, with concomitant allylic transposition, was achieved by employing a variant of the Ferrier rearrangement.[24] Thus, Ti(O^{i}Pr)$_2$Cl$_2$-mediated reaction of **38** with silyl enol ether **39**[25] afforded aldehyde **40** with 97% diastereoselectivity (ds). Chain extension at C_7 was effected by means of a novel vinylogous Mukaiyama aldol reaction between **40** and the silyl dienol ether **41**[26] promoted by BF_3·OEt_2, which provided **42** with 81% ds in favor of the required stereochemistry at C_7 and with the correct (*E*)-enal terminus. Note that this reaction results in exclusive γ-attack on **41** and proceeds without chelate participation from the dihydropyran oxygen of **40**. The second (*E*)-double bond of the diene ester moiety was cleanly introduced by Horner–Emmons olefination of **42** to afford **43**. Protection of the C_7 hydroxyl, followed by deprotection and Dess–Martin oxidation[27] at C_{15}, then gave the C_1-C_{15} segment **29** of swinholide A. Thus, in this segment synthesis, introduction of the C_{13} stereogenic center was achieved by a reagent-controlled boron aldol reaction, **32** + **33** → **36**, while the remaining two stereogenic centers were set up by the sequence **38** → **40** → **42** using substrate control. Note that addition of ethylmagnesium bromide to aldehyde **29**, followed by oxidation, gave **44**, a C_1-C_{16} segment of scytophycin C. [C_1-C_{15} segment **29**: 11% overall yield from **34**; 10 steps; ~3 steps per stereogenic center.]

b. $C_{19}-C_{32}$ Segment Synthesis.[17a] Synthesis of the $C_{19}-C_{32}$ segment **30** began with kinetic resolution of racemic allylic alcohol **45** using Sharpless asymmetric epoxidation,[28a,b] which provided epoxide **46** with high diastereo- and enantiomeric purity (95% ds, 96% ee, Scheme 2).[28c] Directed reductive opening[29] of **46** then afforded diol **47**, with the correct configuration at both C_{29} and C_{31}. Ozonolysis of **47** followed by acidic workup and O-methylation furnished the acetal **48** as a mixture of anomers; and highly diastereoselective TMSOTf-catalyzed allylsilane addition[30] to **48** then gave the tetrahydropyran **49** with the correct configuration at C_{27}, via kinetically controlled axial attack on the oxonium ion **50**. After ozonolysis of **49** to give the C_{25} aldehyde, stereoselective Wittig homologation[31] afforded the (*E*)-enal **51**. Alternatively, **51** could be obtained from acetal **48** in a single transformation, *viz.* TMSOTf-catalyzed addition of the silyl dienol ether **41**. Construction of the $C_{22}-C_{23}$ bond by a highly diastereoselective *anti* aldol reaction[32] between aldehyde **51** and the (*E*)-dicyclohexyl enol borinate **52**, derived[33] from ketone **53** which was in turn prepared from (*S*)-methyl 3-hydroxy-2-methylpropionate (*vide infra*),[34] then gave the β-hydroxy ketone **54** with the required configuration at C_{22} and C_{23}. Stereoselective reduction of **54** using the Saksena–Evans reagent[35] provided the C_{21},C_{23}-*anti* diol **55**, which was protected as its di-*tert*-butylsilylene derivative **56**. Note that Paterson *et al.* did not opt for differential protection of the C_{21} and C_{23} hydroxyls, and thus a regioselective lactonization would be required later in the synthesis (*vide infra*). The remaining stereogenic center at C_{24} was installed by a substrate-controlled[36] hydroboration of **56**, to give alcohol **57** with ≥97% ds, followed by Barton deoxygenation[37] of the surplus hydroxyl at C_{25} to afford **58**. Finally, deprotection at C_{19} and subsequent Swern oxidation[38] then supplied the $C_{19}-C_{32}$ segment **30** of swinholide A. Note that this also corresponds to the $C_{17}-C_{30}$ segment of bistheonellide A. Thus, in the synthesis of segment **30**, introduction of the C_{29} and C_{31} stereogenic centers was achieved by reagent-control (Sharpless epoxidation of **45** →

Scheme 2. Paterson Preswinholide A Synthesis[17a-c,e] [a]



[a] (a) **34**, (+)-Ipc$_2$BCl, ^{i}Pr$_2$NEt; **32**; H_2O_2; (b) TMSOTf, ^{i}Pr$_2$NEt; (c) recrystallize; (d) $NaBH_4$, $CeCl_3$; (e) Ac_2O, ^{i}Pr$_2$NEt; (f) **38** + **39**, Ti(O^{i}Pr)$_2$Cl$_2$; (g) **40** + **41**, BF_3·OEt_2; (h) $(MeO)_2P(=O)CH_2CO_2Me$, ^{n}BuLi; (i) TBSOTf, 2,6-lutidine; (j) K_2CO_3, MeOH; (k) Dess–Martin periodinane; (l) EtMgBr; (m) Dess–Martin periodinane; (a') (+)-DIPT, Ti(O^{i}Pr)$_4$, ^{t}BuOOH; (b') Red-Al; (c') O_3, MeOH; Me_2S; 1 M HCl; (d') NaH, MeI; (e') **48** + **41**, TMSOTf; (f') $H_2C{=}CHCH_2TMS$, TMSOTf; (g') O_3; Me_2S; (h') $Ph_3P{=}C(Me)CHO$; (i') **53**, (^{c}Hex)$_2$BCl, Et_3N; **51**; H_2O_2; (j') $Me_4NBH(OAc)_3$; (k') ^{t}Bu$_2$Si(OTf)$_2$, 2,6-lutidine; (l') thexylborane; H_2O_2, NaOH; (m') (imid)$_2C{=}S$; (n') ^{n}Bu$_3$SnH; (o') H_2, 10% Pd–C; (p') Swern oxidation; (q') **30** + **60**, $TiCl_4$; (r') O_3; Me_2S; (s') $Cl_3CC(=NH)OPMB$, TfOH; (t') **59**, (^{c}Hex)$_2$BCl, Et_3N; **29**; H_2O_2; (u') catecholborane; (v') DDQ; (w') Dess–Martin periodinane; (x') LiAl(O^{t}Bu)$_3$H; (y') MeOTf, 2,6-di-*tert*-butylpyridine; (z') HF; (a'') NaOH.

46), while the remaining stereogenic centers were set up by a series of substrate-controlled reactions: **48** → **49**, **51** + **52** → **54** → **55**, and **56** → **57**. [C_{19}–C_{32} segment **30**: 5.7% overall yield from **45**; 15 steps

longest linear sequence; 18 steps total; ~2 steps per stereogenic center.]

c. The Synthesis of Preswinholide A.[17e,f] By varying the order of the $C_{15}-C_{16}$ and $C_{18}-C_{19}$ bond constructions in the segment coupling sequence, two different syntheses of the fully protected monomeric seco-acid preswinholide A (**28**) were achieved by Paterson *et al.* The first route (Scheme 2) was based on formation of the $C_{18}-C_{19}$ bond before the $C_{15}-C_{16}$ bond.[17e] Thus, addition of a butanone equivalent to the $C_{19}-C_{32}$ aldehyde **30** gave the ethyl ketone **59** which was then aldol coupled to the C_1-C_{15} aldehyde **29**.

$TiCl_4$-promoted addition of allylsilane **60**[39] to aldehyde **30**, under Felkin–Anh control, gave the adduct **61** with 95% ds in favor of the desired configuration at C_{19}. Ozonolysis of the alkene and protection of the C_{19} hydroxyl then gave **59**. Note that model studies[17d] indicated that, in contrast, enol borinate addition to **30** would give the undesired anti-Felkin epimer 19-*epi*-**59**. The model studies also indicated that for a *syn* aldol coupling of aldehyde **29** with the (*Z*)-enol borinate derived from ketone **59**, the intrinsic diastereofacial selectivities of the two chiral components were matched in the wrong stereochemical sense for swinholide A. Unfortunately, attempts to confer reagent control in this reaction by using isopinocampheyl enol borinates[40] proved unsuccessful. Hence, a boron-mediated *anti* aldol reaction was used instead for the coupling of **29** and **59**, which meant that a stereochemical inversion was required later in the synthesis. Thus, substrate-controlled aldol reaction of aldehyde **29** with the (*E*)-dicyclohexyl enol borinate **62** derived[33] from ketone **59** gave the two *anti* aldol isomers **63** and **64** in 60:40 ratio, together with a small amount of *syn* aldol isomers (*anti*/*syn* = 87:13). Compound **63** had the correct configuration of the C_{16} methyl, but required inversion of the hydroxyl at C_{15}. Catecholborane reduction[41] of **63** gave the corresponding C_{17},C_{19}-*syn* diol with >95% ds, and treatment with DDQ then induced cyclization of the C_{19} PMB ether[42a] onto the C_{17} hydroxyl to afford acetal **65**. Inversion of configuration at C_{15} was then accomplished by oxidation, followed by selective reduction, to supply 15-*epi*-**65** with 83% ds. Note that the aldol adduct **64** could also be used productively in the synthesis of preswinholide A by conversion into the ketone precursor of 15-*epi*-**65** by a four-step sequence involving epimerization at C_{16}. With all the stereogenic centers required for preswinholide A installed, methylation of the C_{15} hydroxyl of 15-*epi*-**65** gave the fully protected seco-acid **28** in 10% overall yield over the nine steps from **30**. Total deprotection of **28** afforded preswinholide A (**19**), which served to confirm the complete stereostructure.

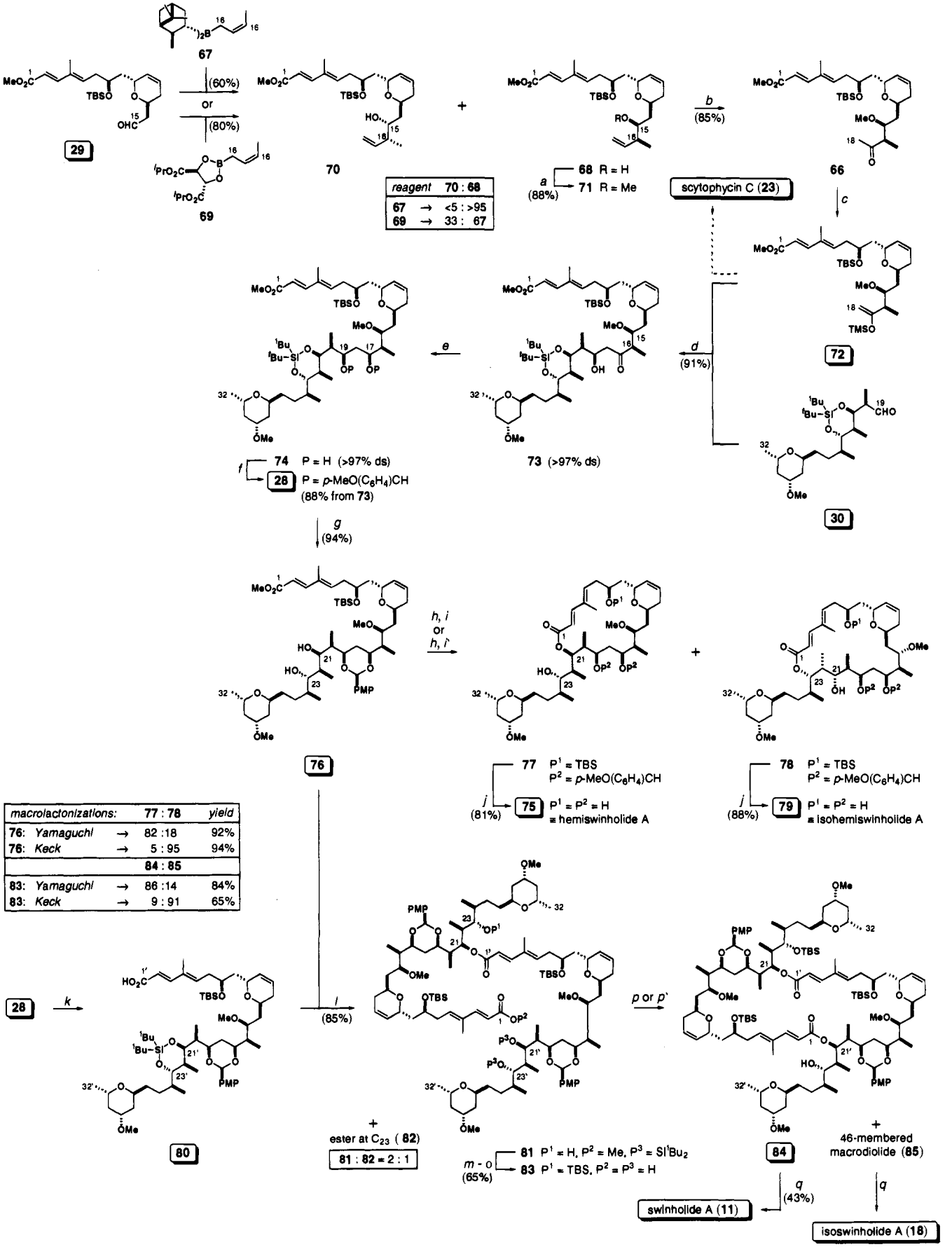
The second, and more efficient, route to preswinholide A developed by Paterson *et al.* (Scheme 3) was based on the opposite order for the segment coupling sequence: *i.e.* $C_{15}-C_{16}$ bond construction prior to $C_{18}-C_{19}$ bond construction.[17f] Model studies[17d] had indicated that the greatest stereochemical efficiency would be expected from reagent-controlled addition of a butanone equivalent to the C_1-C_{15} aldehyde **29** to give the methyl ketone **66**, followed by substrate-controlled Mukaiyama aldol coupling[25] with the $C_{19}-C_{32}$ aldehyde **30**.

Thus, $C_{15}-C_{16}$ bond construction by *syn* crotylboration of **29** using the Brown chiral crotylboron reagent **67**[43] furnished the desired homoallylic alcohol **68** with >95% ds. The corresponding Roush reagent **69**[44] proved less selective in this mismatched situation, generating a 2:1 ratio of **68** and **70**. After O-methylation of **68** to give **71**, Wacker oxidation[45] of the terminal alkene supplied the methyl ketone **66**. $C_{18}-C_{19}$ bond construction by Mukaiyama aldol coupling of aldehyde **30** with the silyl enol ether **72**, derived from kinetic enolization of ketone **66**, then afforded the Felkin–Anh aldol adduct **73** as the sole product. Note that the silyl enol ether **72** is also a C_1-C_{18} segment for scytophycin C. A modified Narasaka–Prasad[46] *syn* reduction of β-hydroxy ketone **73**, via the preformed boron chelate, then gave the C_{17},C_{19}-*syn* diol **74**. Thus, the four stereogenic centers spanning $C_{15}-C_{19}$ of preswinholide A had been introduced with an overall diastereoselectivity of approximately 95%. Protection of diol **74** as its *p*-methoxybenzylidene acetal then supplied the fully protected derivative **28** of preswinholide A in 36% overall yield over the seven steps from **29**. [Preswinholide A (**19**): first route—0.2% overall yield from **45**; 26 steps longest linear sequence; 39 steps total; ~2–3 steps per stereogenic center; second route—1.6% overall yield from **34**; 20 steps longest linear sequence; 37 steps total; ~2–3 steps per stereogenic center.]

d. Completion of the Total Syntheses of Hemiswinholide A, Isohemiswinholide A, Swinholide A, and Isoswinholide A.[17g] In order to complete a synthesis of swinholide A, Paterson *et al.* required selective deprotection and regiocontrolled dimerization of **28**. Note that by using the cyclic di-*tert*-butylsilylene group, these researchers had forgone the opportunity for selective protection of the C_{21} and C_{23} hydroxyls. This strategy was bold, but ultimately proved to be successful.

The synthesis of the 22-membered[14] macrolide **75**, designated hemiswinholide A, corresponding to the erroneous monomeric structure initially proposed for swinholide A,[11] is outlined in Scheme 3. Selective removal of the silylene group of **28** gave the C_{21},C_{23} diol **76**. After base-catalyzed hydrolysis of the terminal methyl ester of **76**, macrolactonization was attempted. By employing the Yamaguchi protocol (formation of the mixed anhydride by treatment with $2,4,6\text{-}Cl_3(C_6H_2)COCl/Et_3N$, followed by DMAP-promoted cyclization in toluene),[47] an 82:18 mixture of the 22- and 24-membered macrolides **77** and **78** was obtained. In contrast, use of the Keck conditions (DCC, DMAP, DMAP·HCl in chloroform)[48] led to a reversal of selectivity, furnishing a 5:95 ratio of **77** and **78**. Note that performing the Keck macrolactonization in toluene, as in the Yamaguchi procedure, gave a 40:60 mixture of **77** and **78**. Thus the regioselectivity of macrolactonization appears to be sensitive to solvent polarity, which presumably alters the conformational preferences of the activated seco-acid. Note also that only monomeric lactones were obtained. Deprotection of the acetal and silyl protecting groups of **77** supplied hemiswinholide A (**75**).

Scheme 3. Paterson Swinholide A and Isoswinholide A Synthesis[17f,g a]



[a] (a) MeOTf, 2,6-di-*tert*-butylpyridine; (b) $PdCl_2$, CuCl, O_2; (c) LiHMDS, TMSCl, Et_3N; (d) **30** + **72**, $BF_3{\cdot}OEt_2$; (e) $^nBu_2BOMe$; $LiBH_4$; H_2O_2; (f) *p*-MeO(C_6H_4)CH($OMe)_2$, CSA; (g) HF·py; (h) NaOH; (i) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N; DMAP; (i') DCC, DMAP, DMAP·HCl; (j) HF; (k) NaOH; (l) **80**, 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N; **76**, DMAP; (m) TBSCl, Et_3N, DMAP; (n) HF·py; (o) $Ba(OH)_2$; (p) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N; DMAP; (p') DCC, DMAP, DMAP·HCl; (q) HF.

Similarly, **78** was converted to isohemiswinholide A (**79**).

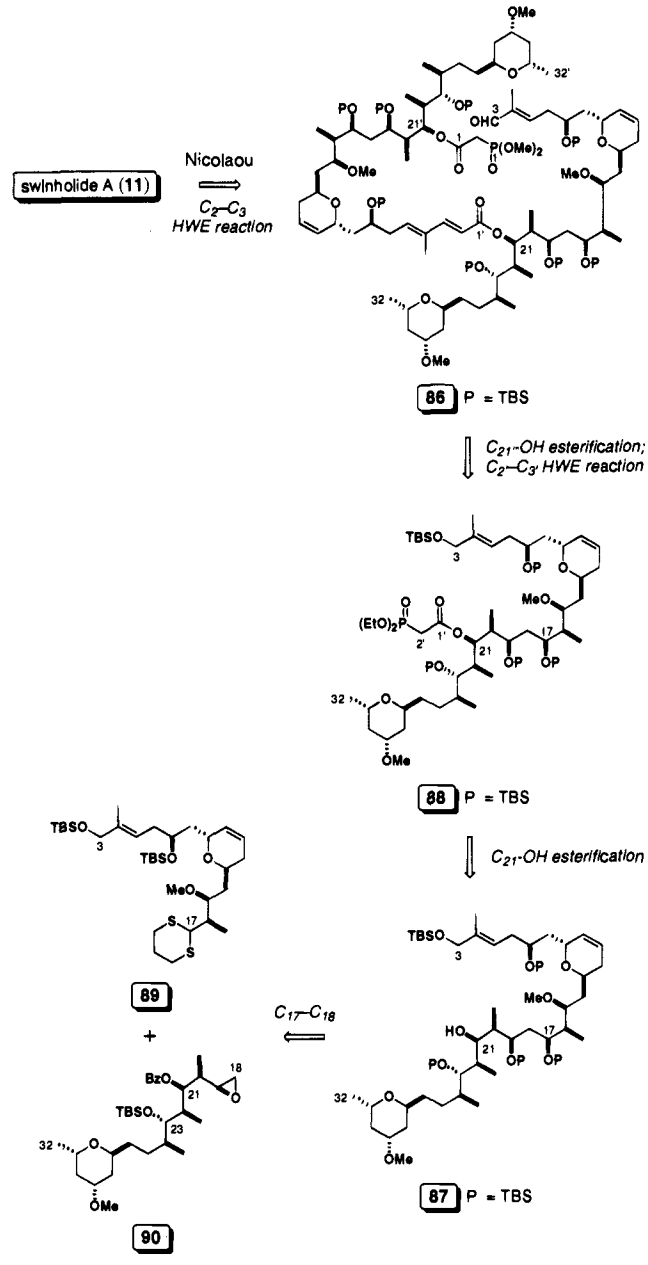
The synthesis of swinholide A itself exploited the differentiation of the C_{21} and C_{23} hydroxyls uncovered above. Thus, hydrolysis of the C_1 ester in **28** gave the acid **80**, which was used to selectively esterify the C_{21} hydroxyl of diol **76** (Scheme 3). Activation of **80** using the Yamaguchi conditions[47] followed by DMAP-promoted addition of **76** afforded a 2:1 mixture of the desired C_{21} ester **81** and its C_{23} regioisomer **82**. After chromatographic separation, **82** could be recycled by methanolysis to give back **76** and **28**. Meanwhile, silyl protection of the C_{23} hydroxyl of **81**, followed by silylene removal and selective hydrolysis of the terminal methyl ester, then afforded the dimeric seco-acid **83**. Note that without silyl protection of the C_{23} hydroxyl, competing cleavage of the C_{21} ester, and/or transesterification to the C_{23} position was observed during the final hydrolysis step. Cyclization of **83** was facile and high yielding (60–84%): subjection of **83** to the Yamaguchi macrolactonization conditions[47] at room temperature, and without the need for high dilution, afforded an 86:14 mixture in favor of the desired **84** (acylation of the C_{21}- hydroxyl) over the larger macrodiolide **85** (acylation of the C_{23}- hydroxyl). As with **76** → **77** + **78**, the selectivity in ring size was sensitive to the macrolactonization conditions: use of the Keck protocol[48] gave a 9:91 mixture of **84** and **85**, permitting selective formation of the isoswinholide ring. Finally, total deprotection of **84** completed the first total synthesis of swinholide A (**11**). Similarly, isoswinholide A (**18**) was obtained upon deprotection of **85**. Of particular note in these syntheses is the fact that the regioselectivity of macrolactonization was controlled without the need for differential hydroxyl protection. [Swinholide A (**11**): 0.4% overall yield from **34**; 25 steps longest linear sequence; 43 steps total; ~3 steps per stereogenic center, allowing for C_2 symmetry].

2. Nicolaou Segment Syntheses[18]

The strategy proposed by Nicolaou and co-workers for achieving a synthesis of swinholide A is outlined in Scheme 4. Ring closure by Horner–Emmons reaction of the ketophosphonate–aldehyde **86** is planned,[49] in contrast to the macrolactonization approach adopted by Paterson *et al.* The dimer **86** is expected to be obtained from the monomer **87** by a sequence of (i) esterification of the C_{21} hydroxyl of **87** to give ketophosphonate **88**;[50] (ii) Horner–Emmons coupling of **88** with another monomer unit corresponding to the $C_{3'}$ aldehyde derived from **87**; and, finally, (iii) esterification of the $C_{21'}$ hydroxyl. Formation of the C_3–C_{32} segment **87** by coupling of the C_3–C_{17} segment **89** and the C_{18}–C_{32} segment **90** is envisaged. At the time of writing, the preparation of **89** and **90** has been reported.

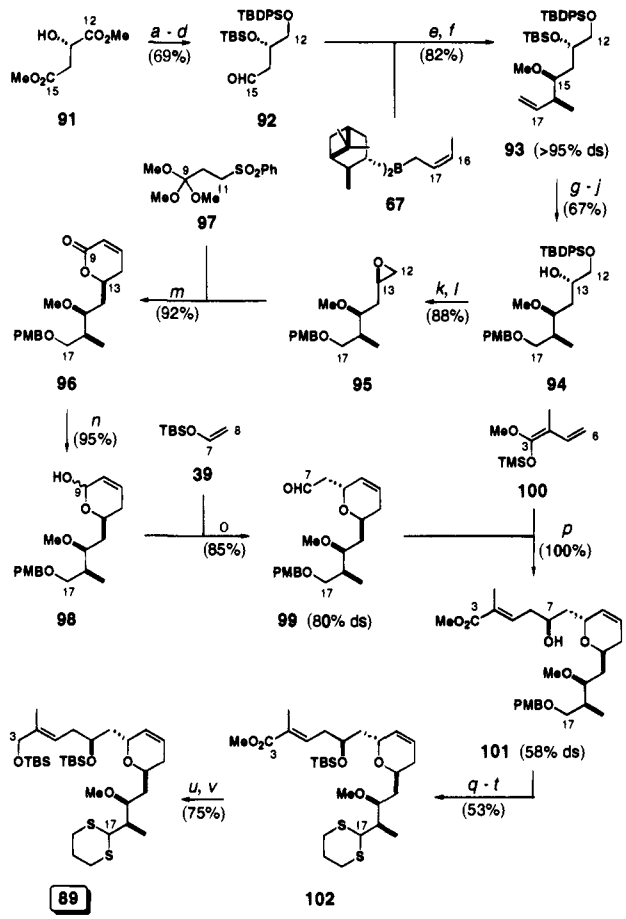
a. C_3–C_{17} Segment Synthesis.[18a] The C_3–C_{17} segment **89** was prepared from (*S*)-dimethyl malate (**91**) as outlined in Scheme 5. Thus, directed reduction of **91** to give the C_{12},C_{13} diol[51] was followed by sequential silylation with TBDPSCl and TBSOTf; DIBAL reduction at C_{15} then supplied the aldehyde **92**. C_{15}–C_{16} bond construction by *syn*-crotylboration

Scheme 4



of **92** using the Brown chiral crotylboron reagent **67**,[43] followed by O-methylation, furnished the desired homoallylic ether **93** with >95% ds (*cf.* similar diastereoselectivity was obtained by Paterson *et al.* for the transformation **29** → **68** → **71**: Scheme 3). Ozonolysis of **93** followed by a reductive workup gave the corresponding C_{17} alcohol which was protected as its PMB ether. Complete desilylation followed by regioselective reprotection at C_{12} then afforded alcohol **94**. After mesylation of the C_{13} hydroxyl of **94**, treatment with TBAF effected cyclization to give the epoxide **95** with inversion of configuration at C_{13}. The α,β-unsaturated-δ-lactone **96** was prepared by using Ghosez's methodology,[52] involving reaction of epoxide **95** with the lithio derivative of methyl 3-(phenylsulfonyl)orthopropionate (**97**) and subsequent acid hydrolysis and DBU-induced elimination. Lactone **96** was reduced to the corresponding lactol **98**, and $ZnCl_2$-catalyzed C-glycosidation using silyl enol ether **39**[25] then supplied the aldehyde **99** with 80% ds. Chain extension at C_7 was effected by means of a

Scheme 5. Nicolaou Swinholide A C_3–C_{17} Synthesis[18a] a



[a] (a) BH_3·Me_2S; cat. $NaBH_4$; (b) TBDPSCl, Et_3N, DMAP; (c) TBSOTf, 2,6-lutidine; (d) DIBAL; (e) **67** + **92**; H_2O_2, NaOH; (f) NaH, MeI; (g) O_3; $NaBH_4$; (h) $Cl_3CC(=NH)OPMB$, CSA; (i) TBAF; (j) TBDPSCl, Et_3N, DMAP; (k) MsCl, Et_3N; (l) TBAF; (m) **97**, DMPU, ^{n}BuLi; **95**; H_2SO_4; *p*-TsOH; Et_3N, DBU; (n) DIBAL; (o) **39** + **98**, $ZnCl_2$; (p) **99** + **100**, BF_3·OEt_2; (q) TBSOTf, 2,6-lutidine; (r) DDQ, H_2O; (s) Swern oxidation; (t) $HS(CH_2)_3SH$, $TiCl_4$; (u) DIBAL; (v) TBSOTf, 2,6-lutidine.

BF_3·OEt_2-promoted vinylogous Mukaiyama aldol reaction between **99** and the silyl ketene acetal **100**,[53] which provided **101** with 58% ds in favor of the required stereochemistry at C_7 and with the correct (*E*)-α,β-unsaturated ester terminus. Note that a similar aldol reaction utilized in the Paterson synthesis (**40** → **42** in Scheme 2) proceeded with higher diastereoselectivity (81% ds).[17a,b] The degree of stereoinduction arising in these aldol reactions appears to be highly sensitive to subtle changes in substrate structure. With all of the stereogenic centers present in the C_3–C_{17} segment of swinholide A now installed, **101** was converted to a derivative suitable for coupling to the C_{18}–C_{32} segment **90**. Thus, protection of the C_7 hydroxyl of **101** was followed by deprotection at C_{17} and oxidation to give the C_{17} aldehyde; dithiane formation then afforded **102**. Reduction of the ester at C_3 followed by protection of the resulting hydroxyl then gave the desired C_3–C_{17} segment **89**. Of the four newly created stereogenic centers in **89**, two were set up in a single reagent-controlled reaction (**92** → **93**), and the remaining two arose from two substrate-controlled reactions (**98** → **99** → **101**). [C_3–C_{17} segment **89**: 3.3% overall yield from **91**; 22 steps; ~4 steps per stereogenic center.]

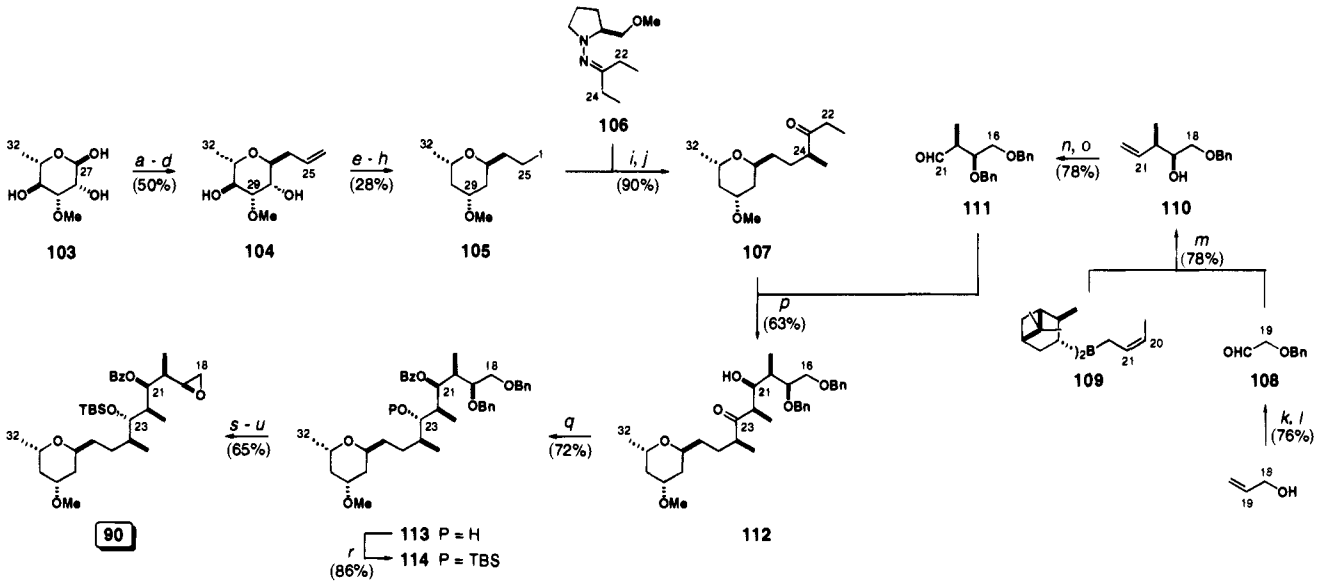
b. C_{18}–C_{32} Segment Synthesis.[18b] The C_{18}–C_{32} segment **90** was prepared from L-rhamnose (**103**) as outlined in Scheme 6. Thus, peracetylation of **103** was followed by C-glycosidation[54] with allyltrimethylsilane to give exclusively the α-glycoside. Complete deacetylation and subsequent regioselective methylation of the C_{29} hydroxyl, using ^{n}Bu_2SnO and methyl iodide in the presence of cesium fluoride,[55] then supplied **104**. Barton deoxygenation[37] at C_{28} and C_{30} of **104** was followed by reductive ozonolysis to give the C_{25} primary alcohol, which was then transformed into iodide **105**. Enders alkylation[56] using iodide **105** and the SAMP hydrazone **106**, followed by ozonolytic removal of the chiral auxiliary, then furnished the ketone **107** with high diastereoselectivity at the newly formed stereogenic center at C_{24}. Meanwhile *syn* crotylboration of aldehyde **108**, using the Brown chiral crotylboron reagent **109**,[43] gave the homoallylic ether **110** with the correct configurations at C_{19} and C_{20}. Benzylation and ozonolysis then provided the aldehyde **111**, which, using the Evans protocol,[57] underwent a stereoselective aldol reaction with the chlorotitanium enolate derived from ketone **107** to give the *syn*-aldol adduct **112**. A samarium-catalyzed, intramolecular Tischenko–Evans[58] reduction of β-hydroxy ketone **112** then furnished the corresponding monoprotected C_{21},C_{23}-*anti*-diol **113**. Silylation of the C_{23} hydroxyl of **113** then gave **114**. Note that use of the Tischenko–Evans reduction enabled differential protection of the C_{21} and C_{23} hydroxyls, which should permit esterification of the C_{21} hydroxyl later in the synthesis of swinholide A, as required. This is in marked contrast to the route of Paterson *et al.*, wherein such differential protection was not employed. With all of the stereogenic centers present in the C_{18}–C_{32} segment of swinholide A now installed, **114** was converted to a derivative suitable for coupling to the C_3–C_{17} segment **89**. Thus hydrogenolysis of the benzyl ethers at C_{18} and C_{19} of **114** was followed by selective monotosylation of the resulting diol, and treatment with base then gave the C_{18}–C_{32} epoxide segment **90**. Thus, three of the nine stereogenic centers present in **90** originated from a carbohydrate, while the other six stereogenic centers were installed using a combination of reagent-controlled (**108** + **109** → **110**), auxiliary-controlled (**105** + **106** → **107**), and substrate-controlled (**107** + **111** → **112** → **113**) reactions. [C_{18}–C_{32} segment **90**: 3.2% overall yield from **103**; 16 steps longest linear sequence; 21 steps total; ~2 steps per stereogenic center.]

3. Nakata Segment Syntheses[19]

Nakata *et al.* have recently completed the synthesis of a C_{11}–C_{32} segment (**115**) corresponding to the polyol portion of swinholide A via stereoselective, auxiliary-controlled aldol coupling of the C_{11}–C_{23} and C_{24}–C_{32} segments **116** and **117** (Scheme 7).

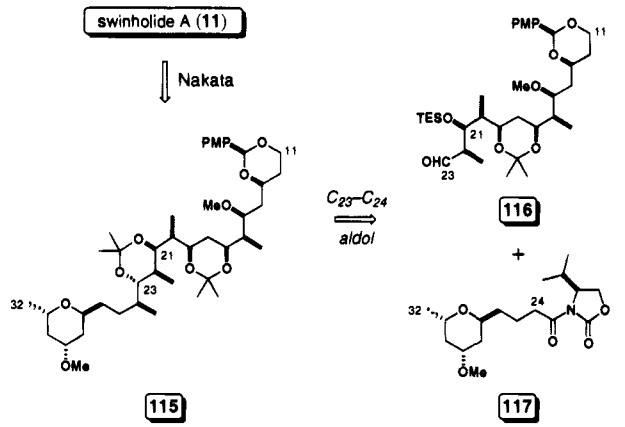
a. C_{11}–C_{23} Segment Synthesis.[19a] The C_{11}–C_{23} segment **116** was obtained via desymmetrization of the C_2 symmetric ketone **118**, which was prepared according to the method of Nakata and Oishi for the stereocontrolled synthesis of 1,3-polyols (Scheme 8).[59] Thus, (*S*)-malic acid (**119**) was converted into alcohol **120**.[60] After protection of the C_{11} hydroxyl of **120**, cleavage of the acetonide gave the C_{13},C_{14} diol;

Scheme 6. Nicolaou Swinholide A C_{18}–C_{32} Synthesis[18b] [a]



[a] (a) Ac_2O, Et_3N, DMAP; (b) $H_2C{=}CHCH_2TMS$, $BF_3{\cdot}OEt_2$, TMSOTf; (c) NaOMe, MeOH; (d) $^nBu_2SnO$; CsF, MeI; (e) NaH, imidazole; CS_2; MeI; (f) $^nBu_3SnH$, AIBN; (g) O_3; $NaBH_4$; (h) I_2, PPh_3, imidazole; (i) **106**, LDA; **105**; (j) O_3; (k) NaH, BnBr, $^nBu_4NI$, imidazole; (l) O_3; Me_2S; (m) **108** + **109**; H_2O_2, NaOH; (n) KH, BnBr; (o) O_3; PPh_3; (p) $TiCl_4$, **107**, Et_3N; **111**; (q) PhCHO, SmI_2; (r) TBSOTf, 2,6-lutidine; (s) H_2, 10% Pd–C; (t) TsCl, Et_3N, DMAP; (u) K_2CO_3, MeOH.

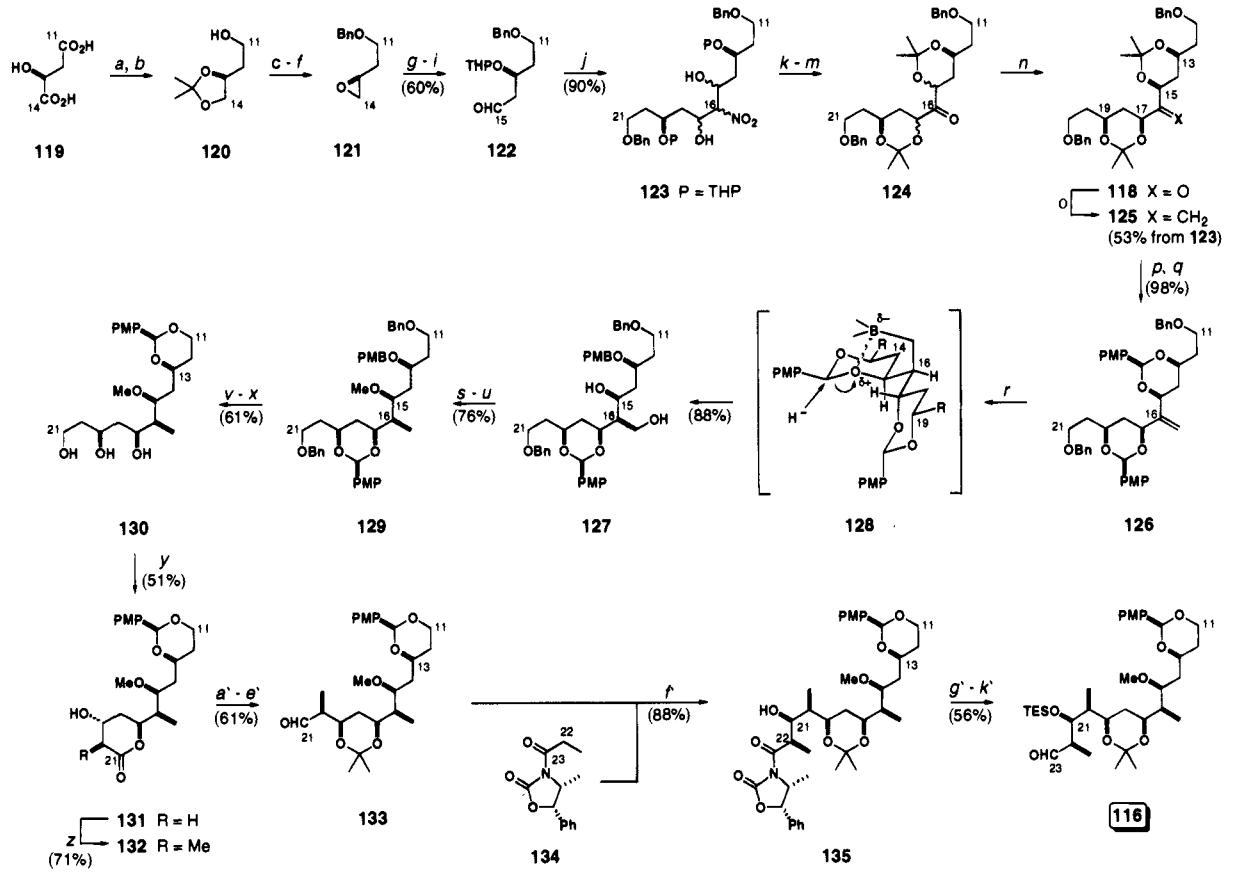
Scheme 7



selective tosylation of the C_{14} primary hydroxyl and treatment with base then furnished the epoxide **121**. Regioselective opening of epoxide **121** by attack of lithiated 1,3-dithiane at C_{14}, followed by protection of the resulting C_{13} hydroxyl and subsequent dithiane hydrolysis, afforded the aldehyde **122**. Double nitroaldol reaction between nitromethane and 2 equiv of aldehyde **122** then gave the mixture of diols **123**. Protecting group exchange, followed by hydrolysis of the nitro group,[61] supplied a mixture of diastereomeric ketones **124**. By analogy with the earlier work of Stork on erythronolide A,[62] treatment of this mixture with potassium carbonate in methanol effected epimerization to give exclusively the C_{13},C_{15}-*syn*-C_{17},C_{19}-*syn* C_2 symmetrical ketone **118**. This was predicted to be the thermodynamically most favorable epimer, since the acetonide rings both adopt chair conformations with the alkyl side chains at C_{13}, C_{15}, C_{17}, and C_{19} all equatorially disposed.

Introduction of a methyl group at C_{16} and desymmetrization was now required. Thus, Wittig methylenation at C_{16} of **118** supplied **125**, and replacement of the acetonide protecting groups by *p*-methoxybenzylidene acetals then afforded **126**. Reaction of **126** with excess $BH_3{\cdot}Me_2S$ led to hydroboration of the C_{16} exomethylene group and concomitant differential reductive cleavage[63] of one of the *p*-methoxybenzylidene acetals, furnishing the fully differentiated diol **127** as a single diastereomer. Note that attempts to perform the same reaction on **125** resulted in lower yields due to the diminished reduction potential of the acetonide moiety compared to the *p*-methoxybenzylidene acetal. The authors have proposed that, after hydroboration, the reaction proceeds via the transition state **128** in which the boron atom can coordinate with only one oxygen atom of the two acetals (that at C_{15}), thus activating the corresponding acetal C–O bond to reductive cleavage. Regioselective deoxygenation of **127** was accomplished by selective tosylation of the primary alcohol and subsequent $LiAlH_4$ reduction. Methylation of the remaining C_{15} hydroxyl then afforded **129**. After deprotection of the benzyl groups in **129** with Raney nickel and acid hydrolysis of the *p*-methoxybenzylidene acetal, treatment with DDQ led to cyclization[42a] of the C_{13} PMB ether onto the hydroxyl revealed at C_{11} to supply triol **130**. Selective oxidation of the primary alcohol of **130** with Ag_2CO_3 on celite gave the β-hydroxy δ-lactone **131**, and stereoselective methylation[64] at the C_{20} α carbon then afforded **132**. This completed the introduction of the stereogenic centers spanning C_{13}–C_{20} of swinholide A. A five-step sequence of protecting group exchange and adjustment of oxidation level at C_{21} transformed **132** into aldehyde **133**, and a diastereoselective Evans *syn* aldol reaction of **133** with the (*Z*)-enol borinate derived from chiral oxazolidinone **134**[65] correctly installed the remaining stereogenic centers at C_{21} and C_{22}. Removal of the chiral auxiliary from the aldol adduct **135** and transformation into the C_{23} aldehyde, along with protection of the C_{21} hydroxyl, then furnished the C_{11}–C_{23} segment **116** of swinholide A, in readiness for aldol coupling to the C_{24}–C_{32} segment **117**. [C_{11}–C_{23} segment **116**: 1.2%

Scheme 8. Nakata Swinholide A C_{11}–C_{23} Synthesis[19a] [a]



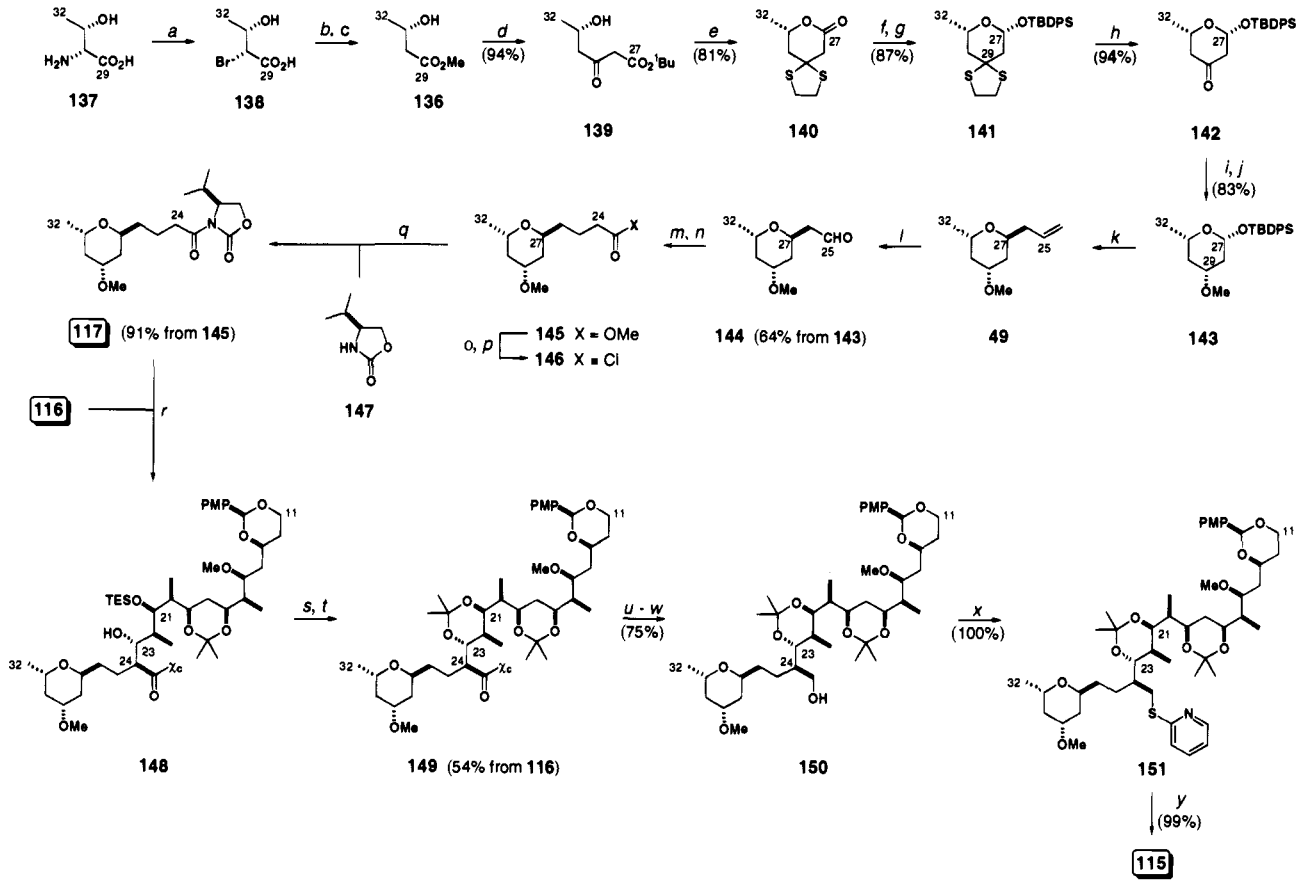
[a] (a) BH_3·Me_2S; (b) Me_2CO, H^+; (c) BnBr, NaH, $^nBu_4NI$; (d) H_2SO_4; (e) TsCl, py; (f) K_2CO_3, MeOH; (g) ^{n}BuLi, 1,3-dithiane; (h) DHP, *p*-TsOH; (i) HgO, $HgCl_2$, H_2O; (j) **122** (2 equiv), $MeNO_2$ (1 equiv), Et_3N, 5.5 kbar; (k) AcOH, H_2O; (l) $(MeO)_2CMe_2$, CSA; (m) ^{t}BuONa, $KMnO_4$, $MgSO_4$, H_2O; (n) K_2CO_3, MeOH; (o) $Ph_3P^+MeI^-$, ^{n}BuLi; (p) AcOH, H_2O; (q) *p*-$MeO(C_6H_4)CH(OMe)_2$, CSA; (r) BH_3·Me_2S (3 equiv); H_2O_2, NaOH; (s) TsCl, py; (t) LAH; (u) KH, MeI; (v) H_2, Raney Ni; (w) AcOH, H_2O; (x) DDQ; (y) Ag_2CO_3–celite; (z) LDA, MeI, HMPA; (a') $LiBH_4$; (b') TBDPSCl, imidazole; (c') $(MeO)_2CMe_2$, PPTS; (d') TBAF; (e') Swern oxidation; (f') **134**, $^nBu_2BOTf$, $^iPr_2NEt$; **133**; H_2O_2; (g') LiOH, H_2O_2; (h') CH_2N_2; (i') TESOTf, 2,6-lutidine; (j') DIBAL; (k') PDC.

overall yield from **121**; 37 steps; ~5 steps per stereogenic center.]

b. C_{24}–C_{32} Segment Synthesis.[19b] The route to the C_{24}–C_{32} segment **117** began with (*S*)-methyl 3-hydroxybutyrate (**136**), which was prepared from D-threonine (**137**) according to the method of Larchevêque (Scheme 9).[66] Thus, deamination of **137** in the presence of bromide ion gave **138**, and esterification followed by reduction then supplied **136**. A Claisen reaction between ester **136** and the lithium enolate of *tert*-butyl acetate afforded β-keto ester **139**, and subsequent lactonization and simultaneous protection of the C_{29} carbonyl furnished **140**. Reduction of **140** delivered the corresponding lactol as a 4:1 mixture of α- and β-anomers, which upon silylation gave a single isomer **141** having the C_{27} silyloxy group equatorial. This fixing of the anomeric group in the equatorial position was essential in order to achieve complete stereoselectivity in the subsequent introduction of the C_{29} stereogenic center, which was achieved by means of ketone reduction.[67] Thus, after deprotection of the thioacetal to give ketone **142**, reduction with $LiAlH_4$ took place on the less-hindered β-face, resulting in exclusive formation of the corresponding C_{29}-α alcohol;[67] methylation then afforded **143**. Stereoselective introduction of the C_{27} side chain was accomplished by BF_3·OEt_2-mediated allylsilane addition to **143**, which gave exclusively the allyl glycoside **49**, having the allyl group axially disposed.[54] Note that a similarly stereoselective transformation was used in the Paterson synthesis (**48** → **49** in Scheme 2).[17a] After ozonolysis of **49**, to afford aldehyde **144**, extension of the side chain by Wittig olefination, followed by hydrogenation, then furnished the C_{32}–C_{24} segment **145**. Finally, conversion to acyl chloride **146** and treatment with the lithium salt of **147**[65] gave the imide **117**.

c. C_{11}–C_{32} Segment Synthesis.[19b] Coupling of the C_{11}–C_{23} and C_{24}–C_{32} segments was achieved by an Evans *syn* aldol reaction[65] between aldehyde **116** and the (*Z*)-enol borinate derived from imide **117**. This supplied the β-hydroxy imide **148**, having the correct configurations at C_{23} and C_{24} (Scheme 9). After an exchange of protecting groups to give **149**, removal of the chiral auxiliary[68] and adjustment of oxidation state afforded the alcohol **150**. In order to complete the synthesis of the C_{11}–C_{32} segment, conversion of the C_{24} hydroxymethyl group of **150** into a methyl group was now required. Procedures for effecting this transformation via the coresponding mesylate, tosylate, xanthate, or iodide were found to be unsatisfactory. However, conversion to the 2-pyridyl sulfide **151**,[69] followed by reductive cleavage of the carbon–sulfur bond upon treatment with Raney nickel,[70] furnished the C_{11}–C_{32} segment **115** of swinholide A. In this synthesis, three of the stereogenic centers in **115** (those at C_{13}, C_{19}, and C_{31}) originated from the chiral pool, the four stereogenic centers

Scheme 9. Nakata Swinholide A $C_{11}-C_{32}$ Synthesis[19b a]



[a] (a) $NaNO_2$, HBr, KBr; (b) MeOH, H^+; (c) H_2, Pd–C; (d) $MeCO_2{}^tBu$, LDA; **136**; (e) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$; (f) DIBAL; (g) TBDPSCl, imidazole; (h) NBS, $AgNO_3$, Na_2CO_3, H_2O; (i) LAH; (j) KH, MeI; (k) $H_2C{=}CHCH_2TMS$, $BF_3{\cdot}OEt_2$; (l) O_3; Me_2S; (m) $Ph_3P{=}CHCO_2Me$; (n) H_2, 10% Pd–C; (o) LiOH, H_2O; (p) $(COCl)_2$; (q) **147**, ^{n}BuLi; **146**; (r) **117**, $^nBu_2BOTf$, $^iPr_2NEt$; **116**; H_2O_2; (s) HF·py, py; (t) $(MeO)_2CMe_2$, PPTS; (u) LiOH, H_2O_2, H_2O; (v) CH_2N_2; (w) LAH; (x) 2,2'-dipyridyl disulfide, $^nBu_3P$; (y) Raney Ni.

spanning $C_{21}-C_{24}$ were introduced by two auxiliary-controlled reactions (**133** + **134** → **135** and **116** + **117** → **149**), and the remaining six stereogenic centers were set up by reactions relying on substrate control of asymmetric induction. [$C_{11}-C_{32}$ segment **115**: 0.5% overall yield from **121**; 45 steps longest linear sequence; 62 steps total; ~5 steps per stereogenic center.]

B. The Halichondrins

The halichondrins (**152**–**160** in Figure 3) are a series of complex polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* Kadota,[71] which show potent *in vitro* and *in vivo* antitumor activity.[71-73] Halichondrin B (**152**) has been selected by the NCI for development as an anticancer drug, and most synthetic efforts have focused on this member of the class. Due to the scarcity of the halichondrins obtained from sponge extracts, total synthesis is highly desirable to augment the natural supply. In 1992, Kishi and co-workers reported the first total synthesis of halichondrin B (and also of norhalichondrin B (**155**)).[74e] Significant segments have also been prepared by the groups of Salomon[75] and Horita and Yonemitsu.[76a-d] Burke *et al.* have also reported the synthesis of two halichondrin B segments.[77]

1. Kishi Total Synthesis[74]

The landmark synthesis of halichondrin B (**152**) by Kishi and co-workers was based on the assembly of

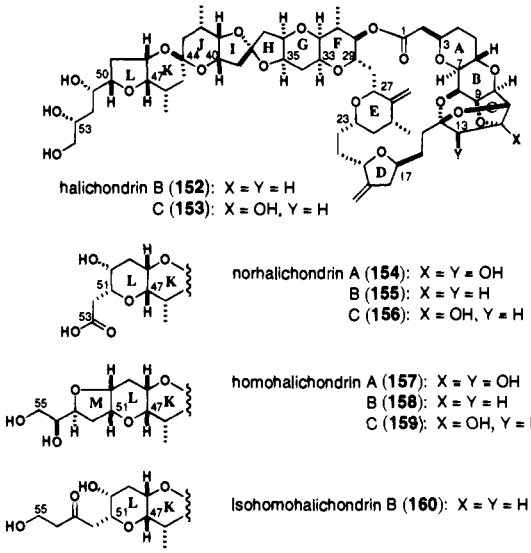
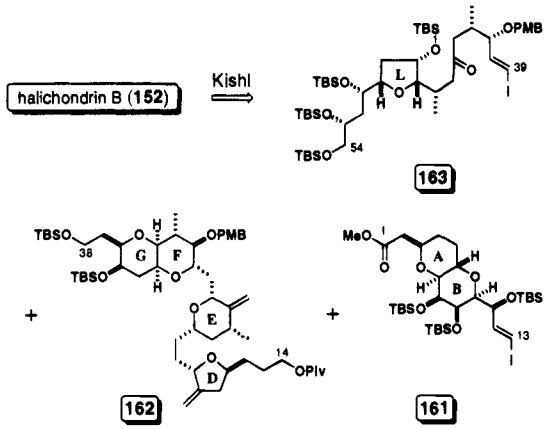


Figure 3. Structures of the halichondrins.

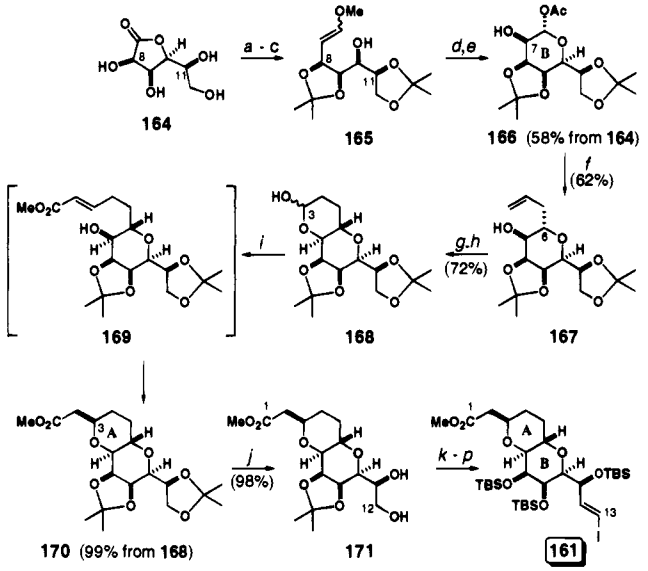
three segments: a C_1-C_{13} segment (**161**), a $C_{14}-C_{38}$ segment (**162**), and a $C_{39}-C_{54}$ segment (**163**) (Scheme 10). Kishi–Nozaki Ni(II)/Cr(II)-mediated coupling reactions[78] were used to construct the $C_{13}-C_{14}$ and $C_{38}-C_{39}$ bonds, and a macrolactonization reaction was used to close the macrocycle.

a. C_1-C_{13} Segment Synthesis.[74f] The most efficient and most recent synthesis of the C_1-C_{13} segment **161** is outlined in Scheme 11. The route began with

Scheme 10



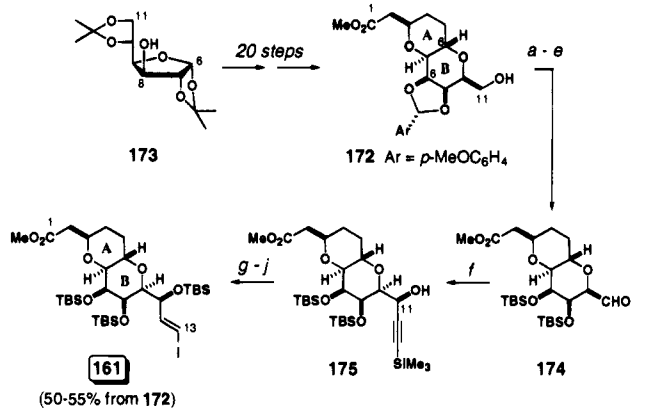
Scheme 11. Kishi Halichondrin C_1–C_{13} Synthesis[74f] [a]



[a] (a) Acetonide protection; (b) DIBAL; (c) ^{t}BuOK, $MeOCH_2PPh_3^+Cl^-$; (d) OsO_4, $(^i PrNHCH_2)_2$; (e) Ac_2O, DMAP, py; (f) $H_2C{=}CHCH_2TMS$, TMSOTf; (g) catecholborane, $RhCl(PPh_3)_3$; (h) PCC/alumina; (i) $Ph_3P{=}CHCO_2Me$; Triton B methoxide; (j) *p*-TsOH; (k) $NaIO_4$; (l) *trans*-^{n}BuCH=CHI, $NiCl_2$ (1.1%)–$CrCl_2$; (m) $FeCl_3$, SiO_2; (n) TBSOTf, 2,6-lutidine; (o) O_3; (p) CHI_3, $CrCl_2$.

L-mannonic γ-lactone (**164**), whose four stereocenters match those at C_8–C_{11} of halichondrin. Acetonide protection, reduction to the C_7 aldehyde and Wittig olefination converted **164** to **165**. Osmylation of enol ether **165** then introduced the correct hydroxyl stereochemistry at C_7 (16:1 in favor of the desired), in accordance with the Kishi empirical rule.[79] After acetalization to give **166**, C-allylation provided exclusively the expected[54a] axial allyl glycoside **167** with the desired configuration at C_6. Following conversion to **168** and Wittig olefination at C_3 to give **169**, an *in situ* intramolecular hetero-Michael reaction then provided **170** and its C_3 epimer in 1:1 ratio. Upon treatment of the mixture with Triton B methoxide, however, complete equilibration to the thermodynamically more stable desired epimer **170** occurred. Thus the transformation **168** → **170** was achieved in one pot. Selective hydrolysis of one of the two acetonide groups in **170** furnished the C_1–C_{12} segment **171**. A six-step sequence involving Ni(II)/Cr(II)-mediated vinyl addition to the C_{11} aldehyde (*vide infra*)[78] then provided the C_1–C_{13} segment **161** used in the total synthesis. Thus, in the synthesis of **161**, the four stereogenic centers spanning C_8–C_{11} originated in the chiral pool, and the other three stereogenic centers were installed using reactions relying on substrate control of asymmetric induction.

Scheme 12. Kishi Halichondrin C_1–C_{13} Synthesis[80] [a]

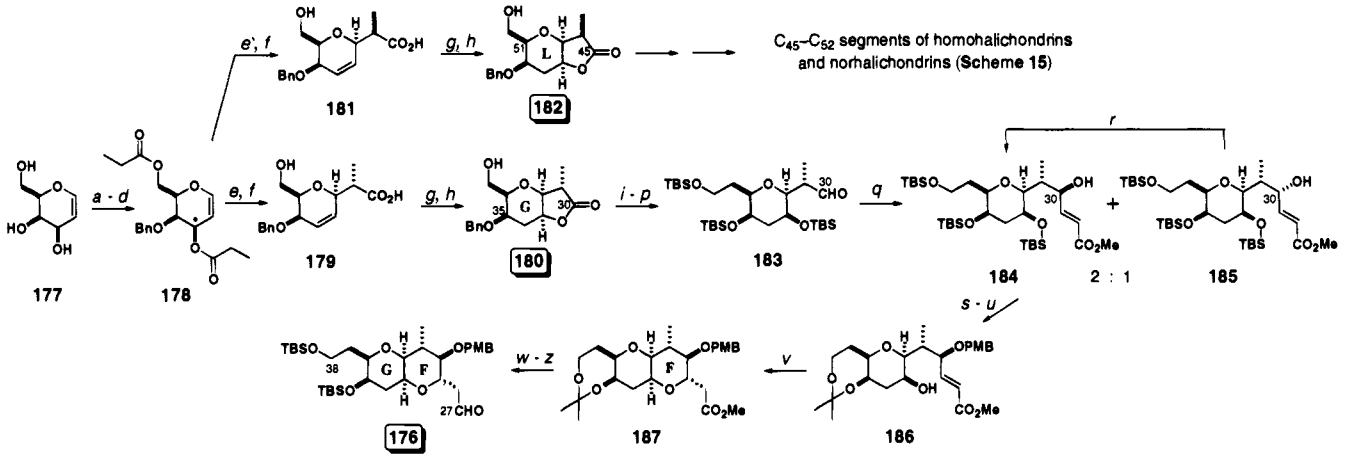


[a] (a) BzCl, py; (b) *p*-TsOH, MeOH; (c) TBSOTf, Et_3N; (d) MeONa; (e) Swern oxidation; (f) IC≡CTMS, $NiCl_2$ (0.01%)–$CrCl_2$; (g) $AgNO_3$; (h) $^n Bu_3SnH$, AIBN; (i) I_2; (j) TBSOTf, Et_3N.

An earlier, and longer, synthesis[80] of C_1–C_{13} segment **161** is summarized in Scheme 12. Alcohol **172** was synthesized from D-glucose diacetonide (**173**) in 20 steps.[81] This involved transformation to L-talofuranoside to provide the B ring,[82] allyl glycoside formation at C_6, and formation of the A ring by an intramolecular hetero-Michael reaction (analogous to **169** → **170** in Scheme 11). After a sequence of protecting group exchange and oxidation to provide the C_{11} aldehyde **174**, a Ni(II)/Cr(II)-mediated coupling[78] with an alkynyl iodide then gave the propargylic alcohol **175** with a selectivity of ~8:1 in favor of the desired, and anticipated,[78c] configuration at C_{11}. Alcohol **175** was then converted into the vinyl iodide **161** in a further four steps. Note that the coupling methodology is well suited for labile aldehydes such as **174**: in this case, no complications due to enolization, such as epimerization or dehydration, were observed. A similar stereoselective Ni(II)/Cr(II)-mediated coupling reaction, this time involving a vinyl iodide, was used during the transformation **171** → **161** (Scheme 11). [C_1–C_{13} segment **161**: improved route—16 steps from **164**; ~2 steps per stereogenic center; original route—30 steps from **173**; ~4 steps per stereogenic center.]

b. C_{27}–C_{38} Segment Synthesis.[74b] Synthesis of the C_{27}–C_{38} segment **176** was accomplished using the Ireland–Claisen rearrangement,[83] Ni(II)/Cr(II)-mediated coupling[78] and intramolecular hetero-Michael reactions as key steps (Scheme 13). The synthesis began with D-galactose glycal (**177**), which was converted into its 4-*O*-benzyl-3,6-*O*-dipropionate derivative (**178**). Ireland–Claisen rearrangement of **178** under appropriate conditions (LiHMDS, TBSCl, HMPA/THF to generate the ketene silyl acetal; then reflux) gave the expected[84] product **179** with ~8:1 stereoselectivity. Iodolactonization of this mixture, followed by reductive removal of the iodine, then afforded the γ-lactone **180**; the minor diastereomer was removed by chromatography or recrystallization at this stage. In contrast, Ireland–Claisen rearrang-

Scheme 13. Kishi Halichondrin C_{27}–C_{38} Synthesis[74b] [a]



[a] (a) TBSCl, imidazole; (b) BnBr, NaH; (c) TBAF; (d) $(EtCO)_2O$, Et_3N; (e) LiHMDS, TBSCl, HMPA; Δ; (e') LDA; TBSCl; Δ; (f) NaOH; (g) I_2, KI, $NaHCO_3$; (h) $^nBu_3SnH$, AIBN; (i) DIBAL; (j) *p*-TsOH, MeOH; (k) Tf_2O, py; NaCN; (l) DIBAL; $NaBH_4$; (m) $H_2/Pd(OH)_2$–C; (n) EtSH, $BF_3{\cdot}OEt_2$; (o) TBSOTf, Et_3N; (p) I_2, $NaHCO_3$, H_2O; (q) *trans*-$MeO_2CCH{=}CHI$, $NiCl_2$ (1.0%)–$CrCl_2$; (r) PPh_3, *p*-$O_2NC_6H_4CO_2H$; $EtO_2CN{=}NCO_2Et$; K_2CO_3, MeOH; (s) $Cl_3CC(=NH)OPMB$, $BF_3{\cdot}OEt_2$; (t) HF·Py; (u) $Me_2C(OMe)_2$, PPTS; (v) TBAF; (w) PPTS, MeOH; (x) TBSOTf, Et_3N; (y) LAH; (z) Dess–Martin periodinane.

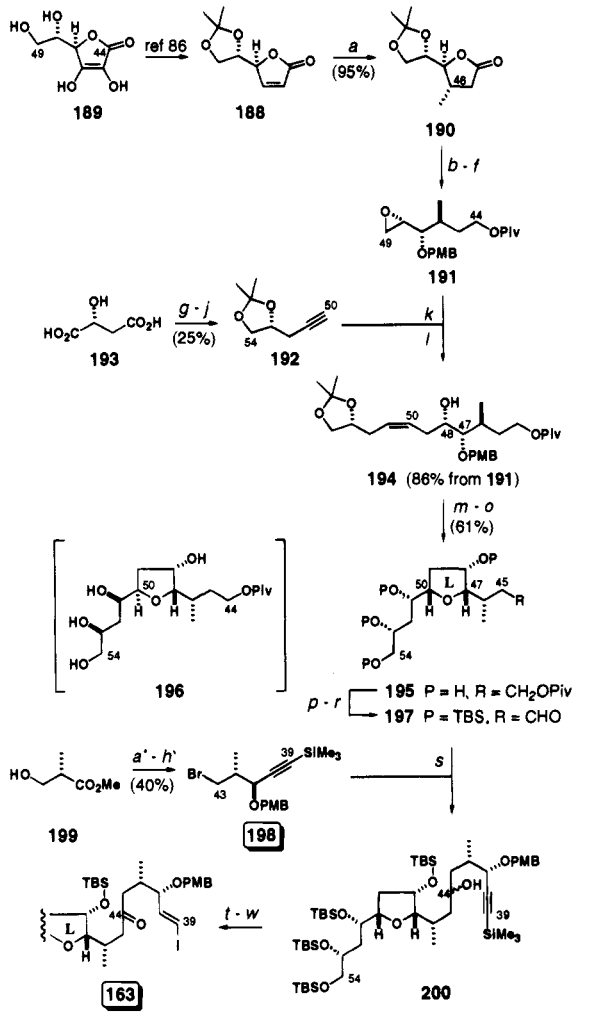
ment of the isomeric ketene silyl acetal generated from **178** in the absence of HMPA gave the epimeric **181** as the major product with 5:1 stereoselectivity; this was converted to γ-lactone **182**. Whereas the stereochemistry of **180** matches the C_{31}–C_{36} portion of the halichondrins, that of **182** matches the C_{46}–C_{51} portions of the norhalichondrins and homohalichondrins. Thus the configuration at C_3 (galactose numbering) of **178** (indicated *) sets up the C_{32} (or C_{47}) stereocenter, and the stereochemistry of the ester enolate determines the C_{31} (or C_{46}) configuration. Note that use of 3,4,6-tripropionate-D-galactose glycal could eliminate three steps needed for differential protection of the hydroxyls. Experimentally, however, the rates of the Ireland–Claisen rearrangements of the C_3 and C_4 propionates were found to be similar, and selective protection of the C_4 hydroxyl was required, as in **178**.

γ-Lactone **180** was converted into the C_{30} aldehyde **183**, and then a Ni(II)/Cr(II)-mediated coupling reaction[78] was used to construct the C_{29}–C_{30} bond. Unfortunately, a 2:1 mixture of the two possible diastereomers **184** and **185** was formed, favoring the desired **184**. The minor undesired **185** could be converted to **184** by using the Mitsunobu inversion procedure.[85] A sequence of protecting group interconversions transformed **184** into **186**, and then a fluoride ion-mediated intramolecular hetero-Michael reaction was used to close the F ring with greater than 20:1 stereoselectivity at C_{25}, in favor of the desired **187**. Note that Michael reaction of the corresponding triol initially yielded the desired diastereomer as the major product, but it rapidly isomerized to the undesired diastereomer. Protecting group exchange and partial reduction at C_{27} then gave the C_{27}–C_{38} segment **176**. Thus, in this synthesis, two of the seven stereogenic centers in **176** originated in the chiral pool (C_{35} and C_{36}), and the remaining five stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. Compound **176** was also synthesized from methyl L-glucopyranoside, by a longer route, which served to confirm the stereochemistry.[74b] [C_{27}–C_{38} segment **176**: 25 steps from **177**; ~3–4 steps per stereogenic center.]

c. C_{39}–C_{54} Segment Synthesis.[74c] Scheme 14 outlines the synthesis of the C_{39}–C_{54} segment **163**. Conjugate addition of methyl cuprate to the α,β-unsaturated lactone **188**, prepared from L-ascorbic acid (**189**),[86] afforded the single C_{46} stereoisomer **190**, which was then transformed into epoxide **191**. Construction of the C_{49}–C_{50} bond by Yamaguchi coupling[87] of **191** with alkyne **192**, obtained from (*R*)-malic acid (**193**), followed by Lindlar reduction of the coupled product, gave the *cis*-alkene **194**. $VO(acac)_2$-catalyzed[88] epoxidation of **194** (employing aromatic solvents for optimum stereoselectivity) and subsequent acid treatment then gave the tetrahydrofuran **195** with 7–8:1 stereoselectivity. The stereochemistry of the epoxidation was assigned on the basis of literature precedents.[89] Note that at this time there was still ambiguity concerning the C_{50}, C_{51}, and C_{53} configurations of halichondrin B. By using both alkyne **192** and its antipode, by generating either *cis* or *trans* alkenes at C_{50}–C_{51}, and by employing either $VO(acac)_2$[88] or *m*-CPBA[90] epoxidation, the Kishi route allowed the preparation of all the stereoisomers at the C_{50}, C_{51}, and C_{53} centers. These were prepared and their ^1H NMR spectra compared with the reported[71] spectrum for halichondrin B. The data for **195** and **196** matched well with the reported values, and so these two diastereomers were separately taken on to halichondrin B (and its diastereomer). In this way the stereochemistry of **195** was established as that of the natural product. This study elegantly illustrates the use of total synthesis to probe the stereochemical configuration of structurally complex natural products, as well as revealing the powerful advantage offered by using acyclic methods of stereocontrol, whereby the preparation of stereochemical analogs is made synthetically viable by simple changes of reagent.

Coupling of the C_{44} aldehyde **197** (derived from **195**) with the C_{43} alkyllithium derived from bromide **198** (in turn obtained from methyl (*S*)-3-hydroxy-2-methylpropionate (**199**)) provided the C_{39}–C_{54} seg-

Scheme 14. Kishi Halichondrin C_{39}–C_{54} Synthesis[74c a]



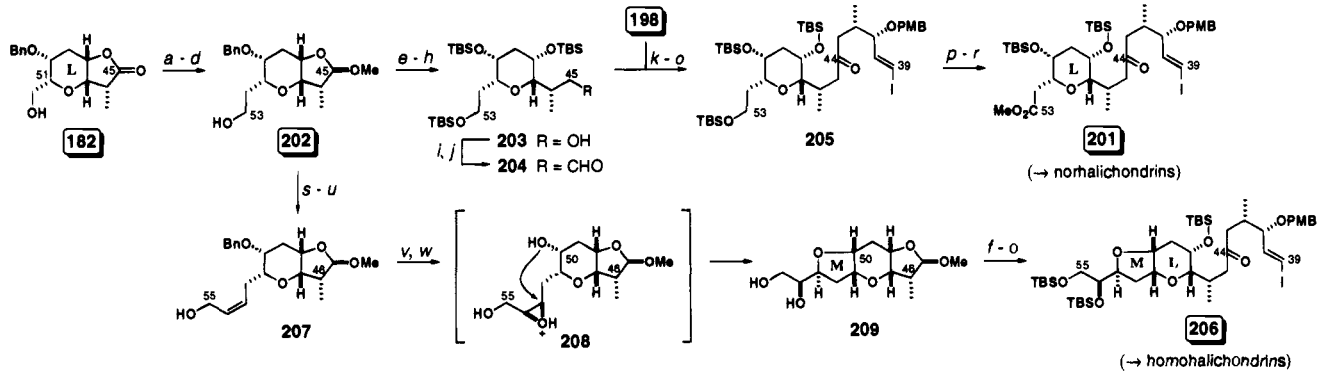
[a] (a) Me_2CuLi, TMSCl; (b) LAH; (c) PivCl, py; (d) PMBBr, KH; (e) AcOH, H_2O; (f) NaH; *N*-tosylimidazole; (g) BH_3·SMe_2, $B(OMe)_3$; (h) Me_2CO, *p*-TsOH; (i) Swern oxidation; (j) $(MeO)_2P(=O)CHN_2$, ^{t}BuOK; (k) **192**, ^{n}BuLi; **191**, BF_3·OEt_2; (l) H_2, Lindlar catalyst, quinoline; (m) ^{t}BuOOH, $VO(acac)_2$; (n) TFA; (o) AcOH, H_2O; (p)TBSOTf, Et_3N; (q) LAH; (r) Dess–Martin periodinane; (s) **198**, ^{t}BuLi; **197**; (t) $AgNO_3$, HMDS; (u) ^{n}Bu_3SnH, AIBN; (v) I_2; (w) Dess–Martin periodinane; (a') DHP, H^+; (b') LAH; (c') Swern oxidation; (d') LiC≡CTMS; (e') $Cl_3CC(=NH)OPMB$, BF_3·OEt_2; (f') CSA, MeOH; (g') MsCl, Et_3N; (h') LiBr.

ment **200**. Oxidation at C_{44}, and transformation of the alkynylsilane functionality to the vinyl iodide then provided segment **163**. Thus, in this synthesis, four of the eight stereogenic centers in **163** originated in the chiral pool (C_{42}, C_{47}, C_{48}, and C_{53}), and the other four stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. [C_{39}–C_{54} segment **163**: 19 steps from **188** longest linear sequence; 31 steps total; ~4 steps per stereogenic center.]

d. C_{39}–C_{53} Norhalichondrin and C_{39}–C_{55} Homohalichondrin Segment Syntheses.[74d] Synthesis of the C_{39}–C_{53} segment **201** of the norhalichondrins began with the previously prepared γ-lactone **182** which bore the correct stereochemical configuration at C_{46}–C_{51} (Scheme 15). Compound **182** was converted into acetal **202** using the transformations already performed on the epimeric γ-lactone **180** (Scheme 13), and then the protecting groups changed and the oxidation level at C_{45} adjusted to give alcohol **203**, which was subsequently homologated to the C_{44} aldehyde **204**. The same five-step sequence that was used to complete the C_{39}–C_{54} halichondrin segment (*i.e.* **197** → **163** in Scheme 14) was employed to provide **205**, and finally conversion to the C_{53} methyl ester gave the C_{39}–C_{53} norhalichondrin segment **201**.

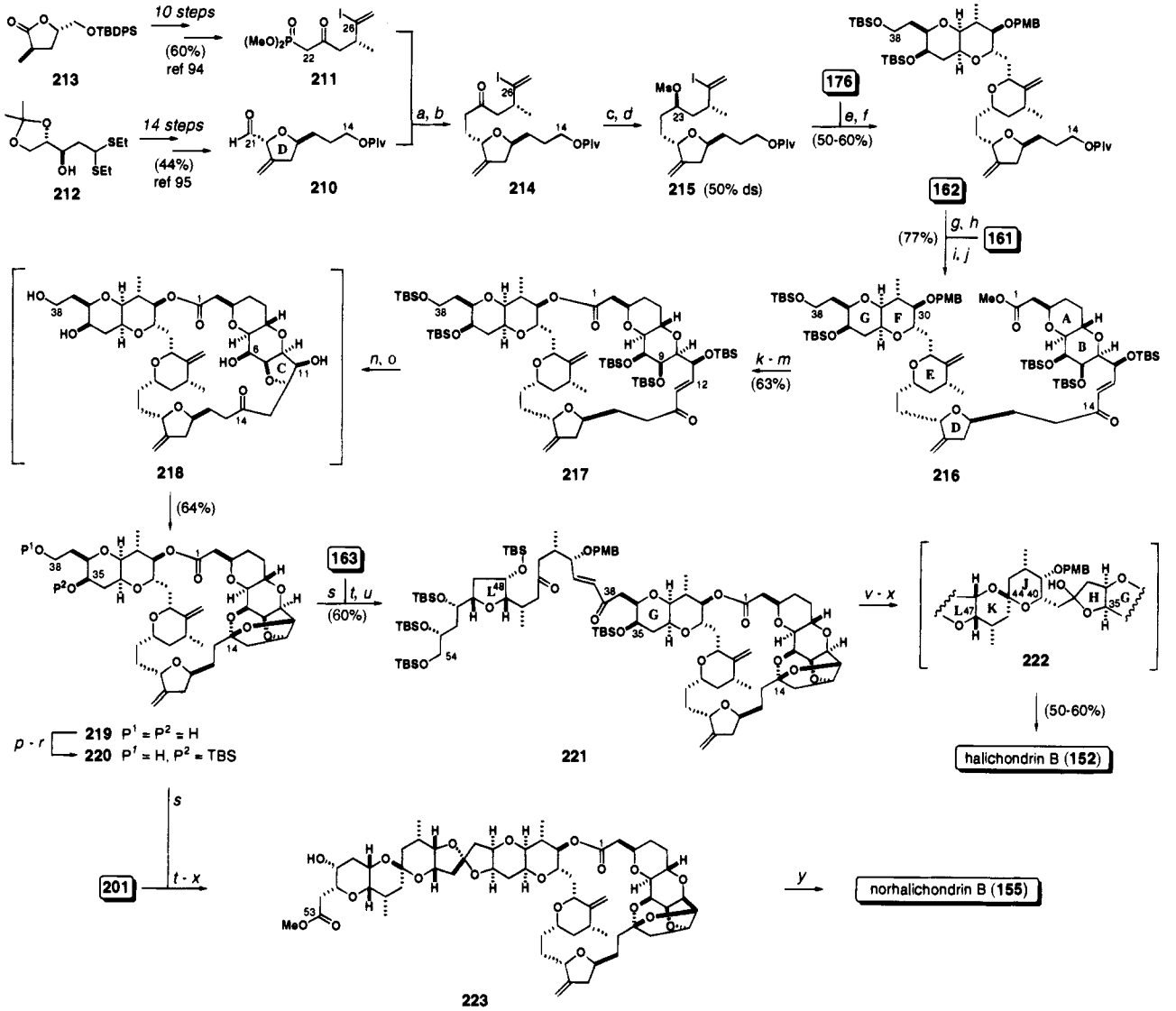
Acetal **202** was also converted into the C_{39}–C_{55} homohalichondrin segment **206**. Oxidation at C_{53} of **202**, followed by Still Horner–Emmons homologation[91] and subsequent reduction, gave the C_{45}–C_{55} segment **207**, which was then submitted to Sharpless asymmetric epoxidation.[92] *In situ* acid-catalyzed cyclization of the epoxide **208** then provided the completed M-ring compound **209**. Note that the C_{53} and C_{54} configurations of the homohalichondrins were unknown at the time. Thus, preparation of both alkene **207** and its *trans* isomer and use of both enantiomers of diethyltartrate ligand in the Sharpless epoxidation allowed all possible stereoisomers to be made.[93] Comparison of ^{1}H NMR data with that reported for homohalichondrin A[71b] identified tetrahydrofuran **209** as having the natural configuration. Elaboration of **209** to the complete C_{39}–C_{55} homohalichondrin segment **206** was accomplished as for the norhalichondrin segment (*cf.* **202** → **205**).

Scheme 15. Kishi Norhalichondrin C_{39}–C_{53} and Homohalichondrin C_{39}–C_{55} Syntheses[74d a]



[a] (a) DIBAL; (b) *p*-TsOH, MeOH; (c) Tf_2O, py; NaCN; (d) DIBAL; $NaBH_4$; (e) H_2, $Pd(OH)_2$–C; (f) EtSH, BF_3·OEt_2; (g) TBSOTf, Et_3N; (h) I_2, $NaHCO_3$; $NaBH_4$; (i) MsCl, Et_3N; NaCN; (j) DIBAL; (k) **198**, ^{t}BuLi; the C44 aldehyde for norhalichondrin or for homohalichondrin; (l) $AgNO_3$, HMDS; (m) ^{n}Bu_3SnH, AIBN; (n) I_2; (o) Dess–Martin periodinane; (p) CSA; (q) Dess–Martin periodinane; (r) $NaClO_2$, NaH_2PO_4, CH_2N_2; (s) Dess–Martin periodinane; (t) $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, KHMDS, 18-crown-6; the aldehyde from step(s); (u) DIBAL; (v) ^{t}BuOOH, (+)-DET, $Ti(O^iPr)_4$; (w) *p*-TsOH, wet $CHCl_3$.

Scheme 16. Kishi Halichondrin B and Norhalichondrin B Syntheses[74e a]



[a] (a) **211**, NaH; **210**; (b) $[(Ph_3P)CuH]_6$, H_2; (c) $NaBH_4$; (d) the more polar alcohol, Ms_2O, Et_3N; (e) **176** + **215**, $NiCl_2$ (0.5%)–$CrCl_2$; (f) KH; (g) **162**, LAH; (h) Dess–Martin periodinane; (i) the aldehyde from previous step + **161**, $NiCl_2$ (0.1%)–$CrCl_2$; (j) Dess–Martin periodinane; (k) DDQ; (l) LiOH, H_2O; (m) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N; DMAP, Δ; (n) TBAF; (o) PPTS; (p) *p*-$O_2NC_6H_4COCl$, py; (q) TBSOTf, Et_3N; (r) K_2CO_3, MeOH; (s) **220**, Dess–Martin periodinane; (t) the aldehyde from the previous step + **163** (for halichondrin B) or **201** (for norhalichondrin B), $NiCl_2$ (0.1%)–$CrCl_2$; (u) Dess–Martin periodinane; (v) TBAF; (w) DDQ; (x) CSA; (y) LiOH, H_2O.

Thus, in the synthesis of **201**, three of the seven stereogenic centers in the target molecule originated in the chiral pool (C_{42}, C_{50}, and C_{51}), and the other four stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. In the synthesis of **201**, the two additional stereogenic centers in the target molecule, at C_{53} and C_{54}, were constructed using a chiral reagent. [C_{39}–C_{53} norhalichondrin segment **201**: 26 steps from **177** longest linear sequence; 34 steps total; ~5 steps per stereogenic center; C_{39}–C_{55} homohalichondrin segment **206**: 27 steps from **177** longest linear sequence; 35 steps total; ~4 steps per stereogenic center.]

e. Completion of the Total Syntheses of Halichondrin B and Norhalichondrin B.[74e] Assembly of the segments and completion of the total synthesis of halichondrin B (**152**) and norhalichondrin B (**155**) is outlined in Scheme 16. The C_{14}–C_{21} and C_{22}–C_{26} segments **210**[94] and **211**[95] were prepared from the precursors **212** and **213**, respectively. The C_{21}–C_{22} bond construction was accomplished by a Horner–Emmons reaction between **210** and **211**, under carefully controlled conditions, followed by conjugate reduction using the Stryker reagent ($[(Ph_3P)CuH]_6/H_2$),[96] to afford **214**. Note that no double-bond isomerization from the C_{19} exocyclic to the C_{19}–C_{20} endocyclic position was observed during these transformations. Unfortunately, hydride reduction of **214** gave a 1:1 ratio of C_{23} alcohol epimers. These were interconvertible via Mitsunobu inversion,[85] but because their stereochemistry could not be firmly established, both were transformed separately into the corresponding mesylates and used in the next coupling reaction. A Ni(II)/Cr(II)-mediated coupling[78] of **215** and the C_{27}–C_{38} segment **176** yielded a 6:1 mixture of the two possible allylic alcohols, which were immediately subjected to base-catalyzed E-ring cyclization to give **162** (and the undesired minor diastereomer). The C_{23} and C_{27} configurations were now established by nOe experiments.

A Ni(II)/Cr(II) coupling[78] of the C_{14} aldehyde derived from **162** with the C_1–C_{13} segment **161**, fol-

lowed by Dess–Martin oxidation,[27] gave the enone **216**. After removal of the C_{30} PMB ether[42b,c] and hydrolysis of the C_1 methyl ester, a Yamaguchi macrolactonization[47] provided the macrocycle **217**. TBAF-mediated deprotection of **217** led to hetero-Michael cyclization of exclusively the C_9 hydroxyl onto C_{12} with 5–6:1 stereoselectivity in the desired sense to generate saturated ketone **218**, bearing the C ring, which was then cyclized using PPTS to give the complete C_1–C_{38} portion **219** of halichondrin B. At this stage, the undesired diastereomer from the hetero-Michael cyclization could be separated and recycled under TBAF conditions. Selective protection of the C_{35} hydroxyl via temporary protection of the C_{38} hydroxyl then gave **220**. A Ni(II)/Cr(II)-mediated coupling[78] of the C_{38} aldehyde derived from **220** with the C_{39}–C_{54} halichondrin segment **163** and subsequent Dess–Martin oxidation[27] gave the enone **221**. A three-step sequence, without isolation of intermediates, finally converted **221** into halichondrin B (**152**). ^{1}H NMR analysis after the first step (TBAF) indicated the partial structure **222**, suggesting initial deprotection of the C_{48} TBS ether, hemiacetal formation with the C_{44} ketone (→ K ring), and hetero-Michael addition of the hemiacetal hydroxyl onto C_{40} (→ J ring). Simultaneously, deprotection of the C_{35} TBS ether led to hemiacetal formation with the C_{38} ketone (→ H ring). Deprotection of the C_{41} PMB ether (DDQ)[42b,c] and acid-catalyzed spiroacetalization with the C_{38} hemiacetal then completed the I ring. Note that the differential protection of the C_{48} hydroxyl prevents formation of the alternative 5,5-spiroacetal between the C_{44} ketone and C_{41} and C_{48} hydroxyls.

The synthesis of norhalichondrin B (**155**) was carried out in an analagous manner using the C_{39}–C_{53} norhalichondrin segment **201**, except that an additional final step was required, *viz.* hydrolysis of the C_{53} methyl ester of **223**.

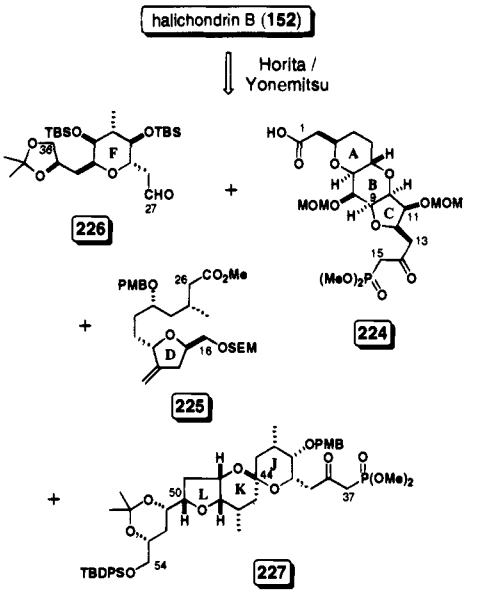
The masterful Kishi total syntheses of **152** and **155** are noteworthy for their repeated use of Ni(II)/Cr-(II)-mediated coupling reactions[78] to assemble complex structures, and for the several examples of hetero-Michael intramolecular ring closures. Carbohydrate-based stereocontrol strategies[8] supplied many of the stereogenic centers in the target molecules. Improvements to the route are now being explored by Kishi and co-workers in an attempt to enhance the synthetic supply of halichondrin B. [Halichondrin B (**152**): 45 steps from **177** longest linear sequence; 120 steps total; ~4 steps per stereogenic center; norhalichondrin B (**155**): 46 steps from **177** longest linear sequence; 124 steps total; 4 steps per stereogenic center.]

2. Horita/Yonemitsu Segment Syntheses[76]

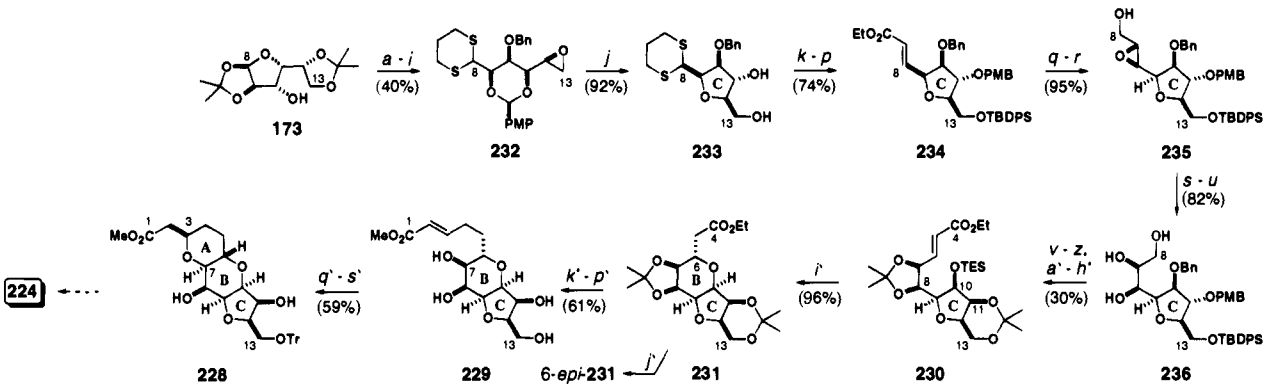
Horita, Yonemitsu, and co-workers have synthesized the four halichondrin B segments depicted in Scheme 17: C_1–C_{15} segment **224**, C_{16}–C_{26} segment **225**, C_{27}–C_{36} segment **226**, and C_{37}–C_{54} segment **227**. The total synthesis has not yet been reported, but assembly of the segments in the order [(**225** + **226**) + **227**] + **224** or [(**226** + **227**) + **225**] + **224** and final macrolactonization has been proposed.[76a]

a. C_1–C_{13} Segment Synthesis.[76a] The Horita/Yonemitsu synthesis of a C_1–C_{13} halichondrin B segment (**228**) involved the construction of the A and B rings by intramolecular hetero-Michael reactions under thermodynamic and kinetic conditions, respectively (**229** → **228** and **230** → **231** in Scheme 18). Treatment of epoxide **232**, obtained in nine steps from D-glucose diacetonide (**173**), with acetic acid led to a 5-*exo*[97] C-ring cyclization to afford tetrahydrofuran **233**. Differential protection of the C_{13} and C_{11} hydroxyls of **233**, dithiane hydrolysis[98] to reveal the C_8 aldehyde, and a Horner–Emmons reaction then gave α,β-unsaturated ester **234**. After reduction at C_6, a Sharpless asymmetric epoxidation[92] gave epoxide **235**, whose ring opening into triol **236** via a carbamate was attained only by employing Roush's method.[99] A 13-step sequence involving protecting group exchange, inversion at C_{11} and extension by two carbon units at C_6 then gave the B ring precursor **230**. The C_7,C_8 diol acetonide in **230** fixes the α,β-unsaturated side chain in a favorable conformation for cyclization to the B ring, and so TBAF-mediated C_{10} deprotection of **230** and subsequent *kinetically controlled* cyclization led to the desired C_6,C_{10}-*trans* tetrahydropyran **231**. Note that on treatment with alkali, **231** isomerized to the thermodynamically more stable tetrahydropyran 6-*epi*-**231**.[100] A six-step sequence converted **231** to the A-ring precursor **229**. Cyclization under *thermodynamic conditions* was expected to provide the desired C_3,C_7-*cis* tetrahydropyran. Brief treatment of **229** with TBAF, followed by trityl protection of the C_{13} primary hydroxyl, gave a 2:1 mixture of the C_3,C_7-*cis* tetrahydropyran **228** and its C_3 epimer. Prolonged exposure of this mixture to TBAF increased the ratio to 19:1, in favor of the desired **228**. Elaboration of **228** to the C_1–C_{15} segment **224** requires a two-carbon extension at C_{13}, but has not yet been reported. Thus, in the synthesis of **228**, two stereogenic centers originated in the chiral pool (C_9 and C_{10}), one stereogenic centers was constructed using a chiral reagent (C_8), and the remaining five stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. [C_1–C_{13} segment **228**: 2.2% overall yield from **173**; 44 steps; ~5–6 steps per stereogenic center.]

Scheme 17

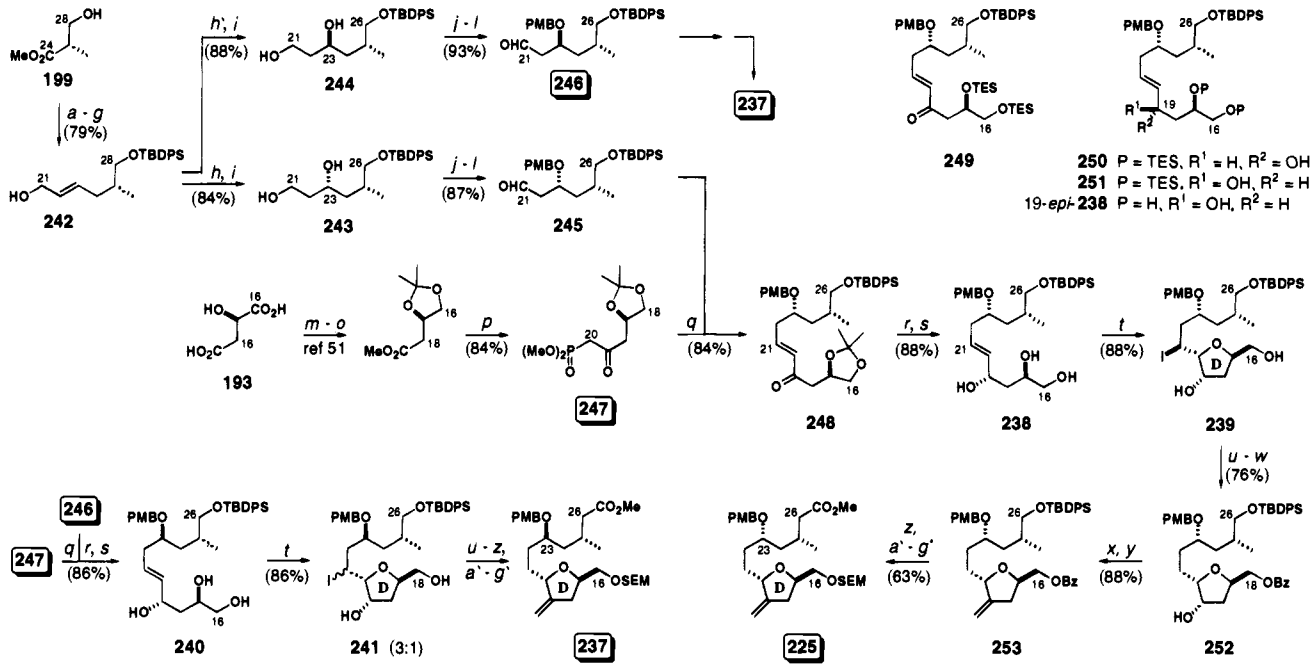


Scheme 18. Horita/Yonemitsu Halichondrin B C_1–C_{13} Synthesis[76a] a



a (a) BnCl, NaH; (b) 0.8 N H_2SO_4, MeOH; (c) BzCl, py; (d) 6 N HCl; (e) $HS(CH_2)_3SH$, $ZnCl_2$; (f) $PMPCH(OMe)_2$, CSA; (g) MsCl, Et_3N; (h) K_2CO_3; (i) ^{t}BuOK; (j) 80% AcOH; (k) TrCl, DMAP, Et_3N; (l) PMBCl, NaH; (m) CSA; (n) TBDPSCl, imidazole; (o) HgO, $BF_3{\cdot}OEt_2$; (p) $(^i PrO)_2P(=O)CH_2CO_2Et$, ^{t}BuOK; (q) DIBAL; (r) (−)-DET, $Ti(^iOPr)_4$, ^{t}BuOOH, molecular sieves; (s) PhNCO, Et_3N; (t) $BF_3{\cdot}OEt_2$; (u) K_2CO_3; (v) PivCl, DMAP, Et_3N; (w) $H_2C{=}C(OMe)Me$, PPTS; (x) DDQ; (y) Swern oxidation; (z) $NaBH_4$; (a') TBAF; (b') $H_2C{=}C(OMe)Me$, *p*-TsOH; (c') Na, liquid NH_3; (d') PivCl, DMAP, py; (e') TESCl, imidazole, DMAP; (f') DIBAL; (g') Swern oxidation; (h') $(^iPrO)_2P(=O)CH_2CO_2Et$, ^{t}BuOK; (i') TBAF; (j') ^{t}BuOK; (k') LAH; (l') TsCl, DMAP, Et_3N; (m') NaCN; (n') DIBAL; (o') $Ph_3P{=}CHCO_2Me$; (p') CSA; (q') TBAF; (r') TrCl, DMAP, Et_3N; (s') TBAF.

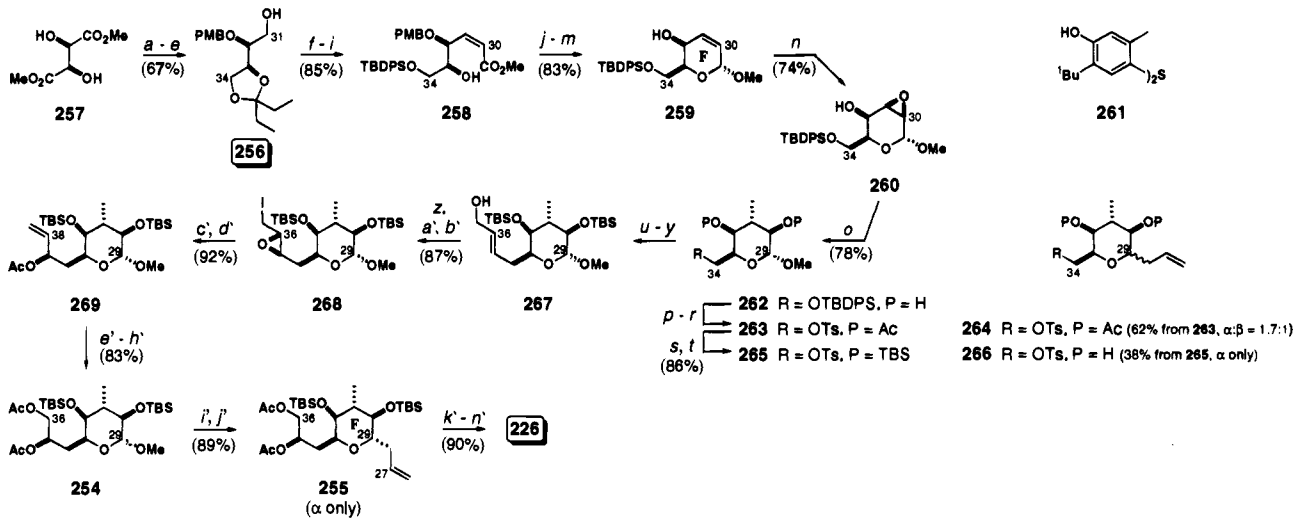
Scheme 19. Horita/Yonemitsu Halichondrin B C_{16}–C_{26} Synthesis[76b] a



a (a) TBDPSCl, Et_3N; (b) $Ca(BH_4)_2$; (c) TsCl, Et_3N; (d) NaCN; (e) DIBAL; H^+; (f) $Ph_3P{=}CHCO_2Me$; (g) DIBAL; (h) (−)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (h') (+)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (i) Red-Al; (j) $PMPCH(OMe)_2$, *p*-TsOH; (k) DIBAL; (l) Swern oxidation; (m) MeOH, H^+; (n) $BH_3{\cdot}Me_2S$; cat. $NaBH_4$; (o) $H_2C{=}C(Me)OMe$, PPTS; (p) $(MeO)_2P(=O)Me$, ^{n}BuLi; (q) **247**, ^{n}BuLi; **245** or **246**; (r) LiI, LAH; (s) AcOH, MeOH; (t) I_2, $NaHCO_3$; (u) NaH; (v) Raney Ni, H_2; (w) BzCl, py; (x) Swern oxidation; (y) $Ph_3P{=}CH_2$; (z) TBAF; (a') TsCl, Et_3N, DMAP; (b') NaCN; (c') K_2CO_3, MeOH; (d') SEMCl, $^iPr_2NEt$; (e') DIBAL; 1 N HCl; (f') Jones oxidation; (g') CH_2N_2.

b. C_{16}–C_{26} Segment Syntheses.[76b] Scheme 19 outlines the syntheses of two C_{16}–C_{26} segments **225** and **237**, epimeric at C_{23}, in which the D ring was constructed by iodoetherification (**238** → **239** and **240** → **241**, respectively). Horita and Yonemitsu envisage coupling of C_{16}–C_{26} and C_{27}–C_{36} segments by aldol construction of the C_{26}–C_{27} bond, followed by cyclization to form ring E. Cyclization with inversion at C_{23} would require **225** as the choice of C_{16}–C_{26} segment, cyclization with retention would require **237**. The syntheses of **225** and **237** both began with the allylic alcohol **242**, obtained from methyl (*S*)-3-hydroxy-2-methylpropionate (**199**) in seven steps. Sharpless epoxidation[92] of **242**, using the (−)-diethyl tartrate ligand, and subsequent Red-Al reduction[29] gave the 23*R* diol **243**. Likewise, use of the antipodal Sharpless catalyst afforded the 23*S* epimer **244**. Formation of the *p*-methoxybenzylidene acetal, regioselective reductive cleavage to the C_{21} alcohol, and oxidation then provided the C_{21} aldehydes **245** (from **243**) and **246** (from **244**). Next, construction of the C_{20}–C_{21} bond by Horner–Emmons reaction of aldehyde **245** and β-keto phosphonate **247**, derived from (*R*)-malic acid (**193**), gave the C_{16}–C_{26} segment **248**. Stereoselective reduction of **248** at C_{23} under chelation-controlled conditions[102] and removal of the acetonide then provided the D-ring precursor **238**. Iodoetherification (I_2, $NaHCO_3$) of **238** gave exclusively the desired C_{17},C_{20}-*trans* tetrahydrofuran **239**. Note that, in preliminary studies, the TES-protected ana-

Scheme 20. Horita/Yonemitsu Halichondrin B C_{27}–C_{36} Synthesis[76c] [a]



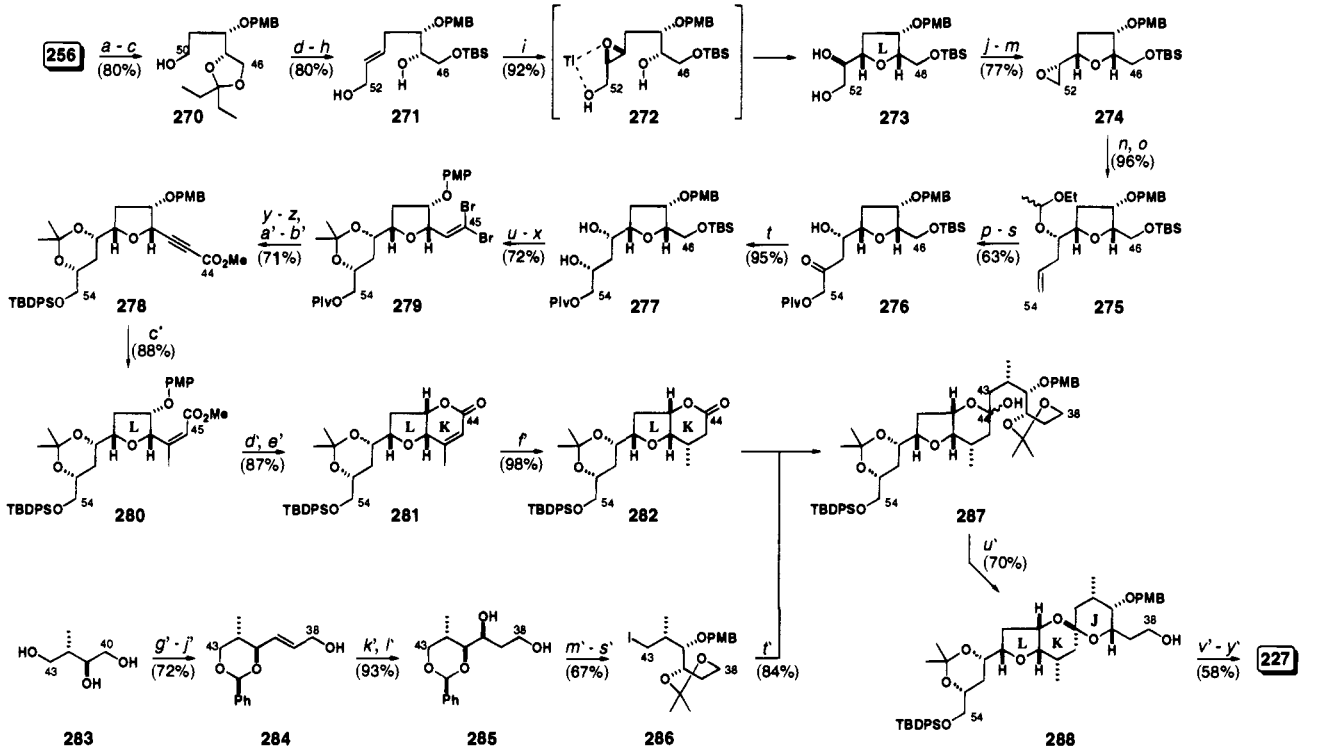
[a] (a) *p*-MeO(C_6H_4)CH(OMe)$_2$, *p*-TsOH; (b) LAH; (c) TBSCl, imidazole; (d) DIBAL; (e) CSA, MeOH; $(MeO)_2CMe_2$, *p*-TsOH; (f) Swern oxidation; (g) $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, 18-crown-6, KHMDS; (h) 1 N HCl, MeOH; (i) TBDPSCl, imidazole; (j) *p*-TsOH; (k) DIBAL; (l) CSA, MeOH; (m) DDQ; (n) *m*-CPBA, **261**; (o) MeMgCl, MeLi; (p) Ac_2O, Et_3N, DMAP; (q) TBAF; (r) TsCl, Et_3N; (s) K_2CO_3, MeOH; (t) TBSOTf, Et_3N; (u) NaCN; (v) DIBAL; (w) 1 N HCl; (x) $Ph_3P{=}CHCO_2Me$; (y) DIBAL; (z) (−)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (a') TsCl, Et_3N, DMAP; (b') NaI, $NaHCO_3$; (c') ^{t}BuLi; (d') Ac_2O, Et_3N, DMAP; (e') OsO_4, NMO; (f') $NaIO_4$; (g') $NaBH_4$; (h') Ac_2O, Et_3N, DMAP; (i') $H_2C{=}CHCH_2TMS$, $BF_3{\cdot}OEt_2$, TMSOTf; (j') TBSOTf, Et_3N; (k') K_2CO_3, MeOH; (l') $Me_2C(OMe)_2$, CSA; (m') OsO_4, NMO; (n') $NaIO_4$.

logue (**249**) of **248** was prepared. Unfortunately, reduction of **249** (using $NaBH_4$-$CeCl_3$) gave a 1.8:1 mixture of C_{19} epimers **250** and **251**. Whereas iodoetherification of **250** gave exclusively **239**, iodoetherification of **251** (or the derived triol 19-*epi*-**238**) gave the unwanted C_{17},C_{20}-*cis* tetrahydrofuran isomer (~2:1 mixture at C_{21}) as the major product.[103] With **239** in hand, from **248**, reduction of the iodide via an olefin and protection of the primary hydroxyl afforded **252**. Swern oxidation[38] at C_{19} and Wittig methylenation then gave **253**, which was converted into the C_{16}–C_{26} segment **225** in a further eight steps. In the same manner, Horner–Emmons coupling of **247** and the aldehyde **246** gave **240** which was transformed, via iodoetherification to **241**, into the C_{23}-epimeric, C_{16}–C_{26} segment **237**. Thus, in the synthesis of **225**, two stereogenic centers originated in the chiral pool (C_{17} and C_{25}), one stereogenic center was constructed using a chiral reagent (C_{23}), and the remaining stereogenic center was installed using substrate control of asymmetric induction (C_{20}). [C_{16}–C_{26} segment **225**: 16% overall yield from **199**; 29 steps longest linear sequence; 33 steps total; ~8 steps per stereogenic center.]

c. C_{27}–C_{36} Segment Syntheses.[76c] The route to the C_{27}–C_{36} segment **226**, in which the F ring is constructed by a stereoselective C-glycosidation (**254** → **255**), is outlined in Scheme 20. Alcohol **256**, prepared in five steps from dimethyl L-tartrate (**257**),[104] was converted to the F-ring precursor **258** by a four-step sequence including a *Z*-selective Horner–Emmons reaction using the procedure of Still.[91] Sequential lactonization, reduction to the lactol, methylation, and, finally, oxidative removal of the C_{32} PMB ether,[42b,c] then gave allylic alcohol **259**. An *m*-CPBA epoxidation of **259**, directed by the C_{32} hydroxyl, exclusively afforded the β-epoxide **260**.[105] Note that no reaction occurred unless the radical scavenger phenol **261** was also present.[106] Trans-diaxial opening of epoxide **260** with "Me_2Mg" (obtained from the supernatant of a mixture of MeMgCl and salt-free MeLi in ether and THF) gave **262** exclusively. Compound **262** was then converted into bis(acetate) **263**. Unfortunately, C-glycosidation of **263** using allyltrimethylsilane, in the presence of boron trifluoride etherate,[54] gave a mixture of α and β epimers (**264**). Replacement of the acetyl groups with larger TBS groups, however, as in **265**, led to exclusive α-allylation (with *in situ* loss of the TBS groups) to give **266**, but only in low yield. The selective α-glycosidation of **265** prompted a search for a substrate that would give higher yields. Thus **265** was transformed into allylic alcohol **267**; Sharpless epoxidation[92] and iodination then gave **268**. After lithium–halogen exchange on **268**, *in situ* epoxide opening and acetylation of the product gave **269**, which was converted into **254**. C_{29}-Allylation of **254** was now completely α-selective, and high yielding (89% *cf.* 38% for **265**), and the resulting diol was reprotected with TBS groups to give **255**. Finally, protecting group exchange at C_{35} and C_{36} and oxidative cleavage of the double bond then gave the C_{27}–C_{36} segment **226**. Thus, in this synthesis, two stereogenic centers originated in the chiral pool (C_{32} and C_{33}), one stereogenic center was constructed using a chiral reagent (C_{35}), and the remaining three stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. [C_{27}–C_{36} segment **226**: 40 steps from **257**; ~7 steps per stereogenic center.]

d. C_{37}–C_{54} Segment Syntheses.[76d] Scheme 21 outlines the synthesis of the C_{37}–C_{54} segment **227** involving construction of the three consecutive JKL rings. Alcohol **256**, derived from dimethyl L-tartrate[104] and used as a starting material in the C_{27}–C_{36} segment synthesis (Scheme 20), was converted into its homologue **270** and thence to the L-ring precursor **271**. Sharpless epoxidation[92] of **271** was accompanied by an *in situ* 5-*exo*[97] cyclization of epoxide **272** to give the tetrahydrofuran **273** directly. Inversion at C_{51} and two-carbon extension to provide C_{53} and C_{54} was now required. Conversion to epoxide

Scheme 21. Horita/Yonemitsu Halichondrin B $C_{37}-C_{54}$ Synthesis[76d] [a]



[a] (a) Swern oxidation; (b) $Ph_3PMe^+Br^-$, ^{t}BuOK; (c) $(Sia)_2BH$; H_2O_2, NaOH; (d) Swern oxidation; (e) $(EtO)_2P(=O)CH_2CO_2Me$, NaH; (f) 1 N HCl, MeOH; (g) TBSCl, imidazole; (h) DIBAL; (i) (−)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (j) BzCl, py; (k) MsCl, Et_3N, DMAP; (l) K_2CO_3, MeOH; (m) ^{t}BuOK; (n) $H_2C{=}CHMgBr$, CuI; (o) $H_2C{=}CH(OEt)$, PPTS; (p) OsO_4, NMO; (q) PivCl, py; (r) Swern oxidation; (s) PPTS, MeOH; (t) Et_2BOMe, $NaBH_4$; (u) $H_2C{=}CH(OMe)$, PPTS; (v) TBAF; (w) Swern oxidation; (x) Ph_3P, CBr_4; (y) LDA; (z) K_2CO_3, MeOH; (a') TBDPSCl, imidazole; (b') ^{n}BuLi; $ClCO_2Me$; (c') MeMgCl, CuI; (d') DDQ; (e') NaI; (f') H_2, 10% Pd−C; (g') $PhCH(OMe)_2$, CSA; (h') Swern oxidation; (i') $(EtO)_2P(=O)CH_2CO_2Me$, NaH; (j') DIBAL; (k') (−)-DET, ^{t}BuOOH, $Ti(O^iPr)_4$; (l') Red-Al; (m') $H_2C{=}C(OMe)Me$, PPTS; (n') Na, liquid NH_3; (o') TBDPSCl, imidazole; (p') PMBCl, KHMDS; (q') TBAF; (r') TsCl, Et_3N, DMAP; (s') NaI, $NaHCO_3$; (t') **286**, ^{t}BuLi, $CeCl_3$; **282**; (u') *p*-TsOH; (v') Swern oxidation; (w') $NaClO_2$, NaH_2PO_4; (x') $TMSCHN_2$; (y') $(MeO)_2P(=O)Me$, ^{n}BuLi.

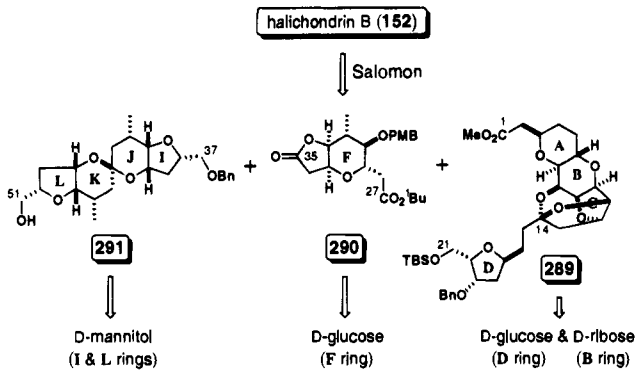
274 followed by a regioselective cuprous iodide-catalyzed addition of vinylmagnesium bromide achieved both these aims, and protection of the homoallylic alcohol product then gave **275**. Osmylation of alkene **275** afforded a diastereomeric mixture that was converted via oxidation and protecting group exchange to the single β-hydroxy ketone **276**. A Narasaka[46a,b] reduction of **276** then correctly set up the C_{53} stereogenic center with 20:1 diastereoselectivity, to afford diol **277**. Introduction of the C_{46} methyl substituent was achieved via alkyne **278**. Thus **277** was transformed into dibromoalkene **279**, followed by reaction with LDA to generate an alkyne, which was then methoxycarbonylated to provide **278**. Reaction with dimethylcopper resulted in a *cis* carbocupration[107] which furnished alkene **280**. After transformation of **280** to the α,β-unsaturated lactone **281**, heterogeneous hydrogenation exclusively on the convex face delivered the $C_{44}-C_{54}$ coupling segment **282** with the correct configuration at C_{46}, thus completing construction of the K ring. Meanwhile, the known triol **283**, derived from D-tartaric acid,[108] was converted into allylic alcohol **284**. Sharpless epoxidation[92] and Red-Al reduction[29] then gave the 1,3-diol **285** selectively. A sequence of acetonide protection at C_{38} and C_{40}, protecting group exchange at C_{41} and C_{43}, and conversion to the C_{43} iodide then gave the $C_{38}-C_{43}$ coupling segment **286**. Lithium−halogen exchange in **286** and addition to lactone **282**, in the presence of cerium trichloride,[109] then provided the $C_{38}-C_{54}$ segment **287**. Acid-catalyzed acetonide deprotection of **287** and *in situ* stereoselective spiroacetalization at C_{44} afforded **288**, which completed the construction of the JKL ring system. Finally, conversion of **288** to the β-keto phosphonate **227** provided the desired $C_{37}-C_{54}$ segment. Thus, in this synthesis, three stereogenic centers originated in the chiral pool (C_{41}, C_{47}, and C_{48}), three stereogenic centers were constructed using chiral reagents (C_{40}, C_{50}, and C_{51}), and the remaining four stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. Coupling of all the halichondrin segments **224**−**227** to complete a total synthesis is currently in progress by Horita, Yonemitsu, and co-workers. [$C_{37}-C_{54}$ segment **227**: 2.7% overall yield from **257**; 43 steps longest linear sequence; 56 steps total; ~6 steps per stereogenic center.]

3. Salomon Segment Syntheses[75]

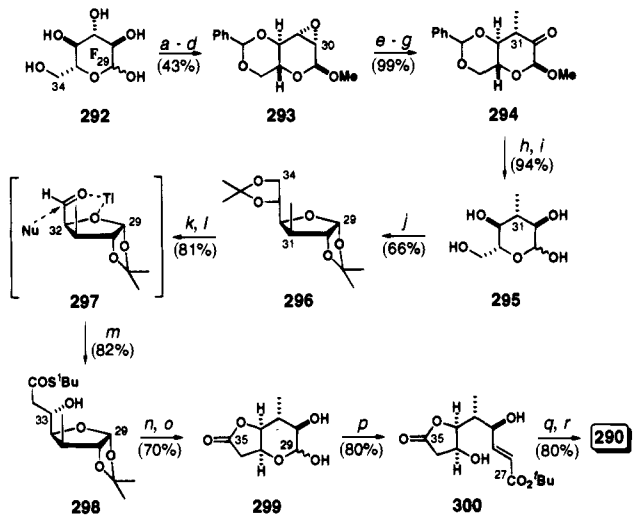
The stereogenic centers in the halichondrins are located in several discrete regions of the molecule, and this can be exploited in the synthetic plan. Salomon and co-workers have synthesized each stereochemically isolated segment of halichondrin B starting from a variety of inexpensive commercially available carbohydrates: a C_1-C_{15} segment from D-ribose, a C_1-C21 segment **289** from D-ribose and D-glucose, a $C_{27}-C_{35}$ segment **290** from D-glucose, and a $C_{37}-C_{51}$ segment **291** from D-mannitol (Scheme 22).

a. $C_{27}-C_{35}$ Segment Syntheses.[75a] Scheme 23 outlines the route to the $C_{27}-C_{35}$ segment **290**, in

Scheme 22



Scheme 23. Salomon Halichondrin B $C_{27}-C_{35}$ Synthesis[75a] [a]



[a] (a) MeOH; (b) PhCHO, $ZnCl_2$; (c) *N*-tosylimidazole, NaOMe; (d) NaH; (e) MeMgCl; (f) TFAA, DMSO; Et_3N; (g) Et_3N; (h) LAH; (i) H_2SO_4, H_2O; (j) MeCOMe, $ZnCl_2$, H_3PO_4; (k) AcOH, H_2O; (l) $NaIO_4$; (m) $H_2C{=}C(OTBS)S^tBu$, $TiCl_4$; (n) 0.2 N NaOH; (o) TFA, H_2O; (p) $Ph_3P{=}CHCO_2{}^tBu$; (q) Na; (r) $Cl_3CC(=NH)OPMB$, TfOH.

which D-glucose was used to provide the F ring. This necessitated replacement of hydroxyl with methyl at C_{31}, homologation at C_{34} and C_{29}, and epimerization at C_{33}. Initial selective protection of all but the *trans* hydroxyls at C_{30} and C_{31} of D-glucose (**292**)[110] was followed by selective tosylation of the C_{30} hydroxyl and formation of epoxide **293**.[111] Regioselective opening of this epoxide at C_{31} with MeMgCl (axial attack) introduced the methyl group with the incorrect configuration. Oxidation to the ketone at C_{30} and base-catalyzed epimerization of the C_{31} methyl to the thermodynamically preferred equatorial position, however, afforded **294**. Stereoselective reduction at C_{30} (axial attack) and protecting group hydrolysis then gave tetrol **295**.[112] Inversion of the stereochemistry at C_{33} and extension of the side chain was achieved by a C–C bond cleavage sequence exploiting the pyranose to furanose interconversion which occurred on acetonide protection of **295**.[113] Thus selective mono deacetalization at $C_{33}-C_{34}$ of **296** and oxidative cleavage of the resulting diol gave the C_{33} aldehyde **297**, so destroying the incorrect stereogenic center. Entirely stereoselective (>99:1) generation of the correct C_{33} configuration then ensued from chelation-controlled addition of a silyl ketene thioacetal,[114] which supplied carbon atoms 34 and 35, to

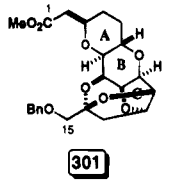
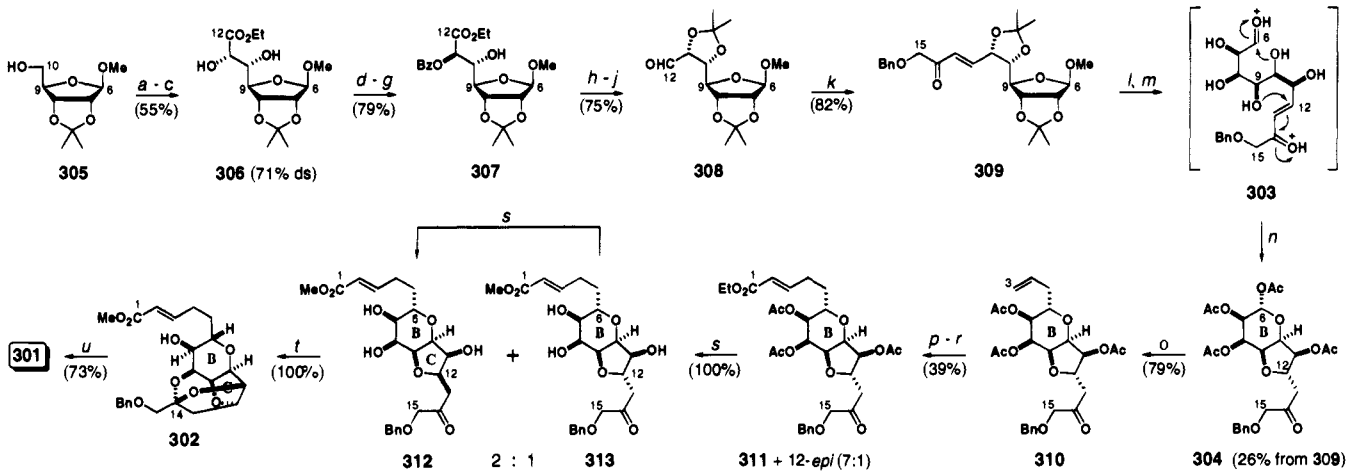


Figure 4. Halichondrin C_1-C_{15} subunit.

afford thioester **298**. After base-catalyzed thioester hydrolysis, acid-catalyzed acetonide cleavage led to interconversion of furanose back to pyranose. *In situ* lactonization then provided **299**. Finally, homologation at C_{29} by Wittig olefination of **299** and intramolecular hetero-Michael reaction of the intermediate α,β-unsaturated ester **300** was followed by PMB protection of the C_{30} hydroxyl to supply the $C_{27}-C_{35}$ segment **290**. Note that the hetero-Michael cyclization to form ring F occurred with 97% ds, under the thermodynamic conditions employed, in favor of the desired C_{29},C_{33}-*trans* tetrahydropyran which adopts a chair conformation with the C_{29} side chain equatorial. Thus, in the synthesis of **290**, one stereogenic center originated in the chiral pool (C_{32}), and the other four stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. [$C_{27}-C_{35}$ segment **290**: 7.9% overall yield from **292**; 18 steps; ~4 steps per stereogenic center.]

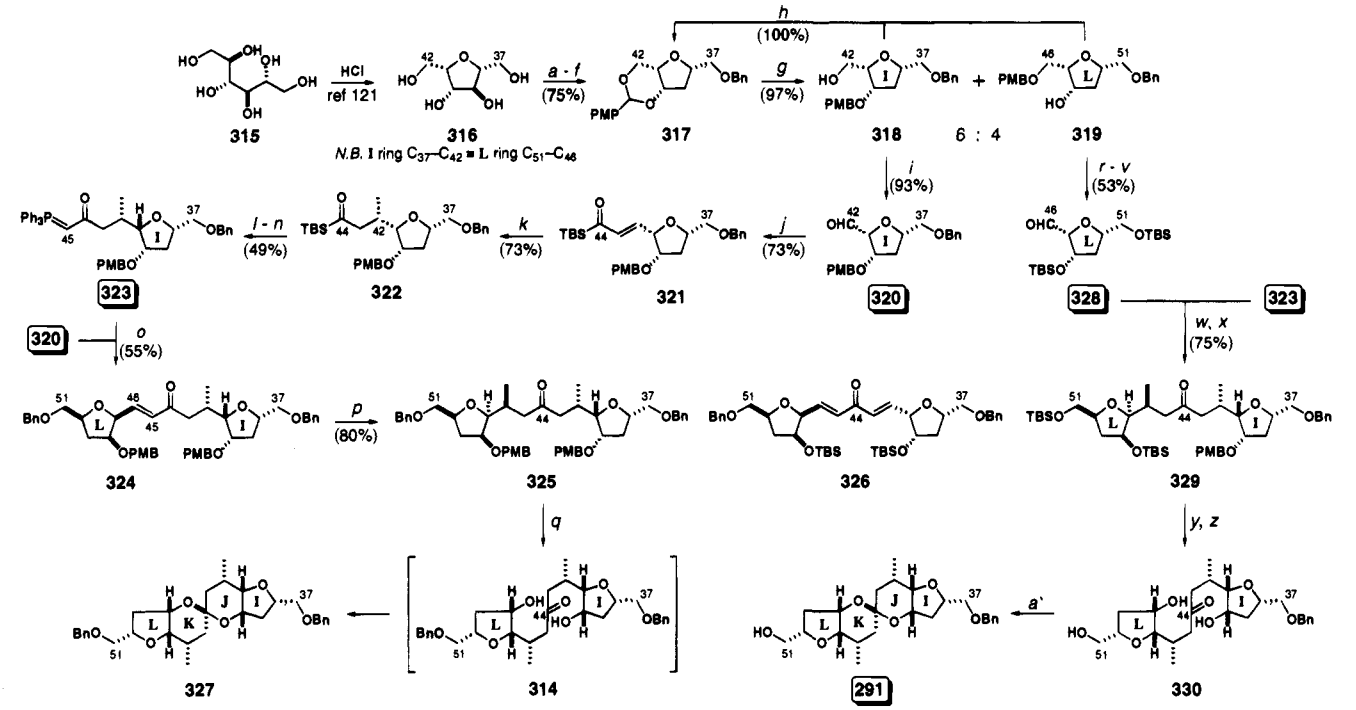
b. C_1-C_{15} Segment Syntheses.[75b] The synthesis of a C_1-C_{15} segment (**301** in Figure 4) is depicted in Scheme 24. D-Ribose was used to provide the B ring carbons, and intramolecular hetero-Michael reactions were employed to construct both the A (**302** → **301**) and C (**303** → **304**) rings. Oxidation of the commercially available ribofuranoside **305** to the C_{10} aldehyde[115] was followed by Wittig olefination. An early variant of the Sharpless asymmetric dihydroxylation[116] then afforded diol **306** with 71% ds. The configuration at C_{11} needed to be inverted, and this was accomplished by conversion to the cyclic sulfate and regioselective nucleophilic substitution[117] at C_{11} to provide **307**. A three-step sequence of debenzoylation, acetonide formation, and DIBAL reduction then afforded the C_{12} aldehyde **308** which underwent Wittig olefination to supply enone **309**. TFA-mediated acetonide hydrolysis of **309** produced a tetrol and stronger acid (Dowex 50W) opened the furanoside to generate intermediate **303**. *In situ* intramolecular hetero-Michael reaction, to close the C ring, and hemiacetal formation, to close the B ring, then took place; acetylation provided the product **304**. Note that the wrong configuration resulted at C_{12}, and all attempts to epimerize this center at this stage led to decomposition. Allylation of **304** with allyltrimethylsilane using a trityl perchlorate-catalyzed reaction[118] stereoselectively gave **310** (axial attack). Compound **310** was then converted into α,β-unsaturated ester **311** in three steps. Epimerization at C_{12} was now feasible. Methoxide-catalyzed transesterification of **311** and hydroxyl deprotection led to partial epimerization to the desired C_{12} epimer **312** (2:1 mixture of **312** and **313**). Treatment of this mixture with PPTS then effected spiroacetalization at C_{14} of **312** to generate the desired tetracycle **302**. This acetal proved separable from the unreacted **313**, which upon treatment with sodium methoxide provided more **312** by epimerization. Finally, methox-

Scheme 24. Salomon Halichondrin B C_1–C_{15} Synthesis[75b] a



[a] (a) DMSO, TFAA, Et_3N; (b) $Ph_3P{=}CHCO_2Et$; (c) OsO_4, NMO, dihydroquinidine *p*-chlorobenzoate; (d) $SOCl_2$, Et_3N; (e) $RuCl_3$, $NaIO_4$; (f) $^nBu_4NOCOPh$; (g) H_2SO_4, H_2O; (h) $Ba(OMe)_2$; (i) $Me_2C(OMe)_2$, PPTS; (j) DIBAL; (k) $Ph_3P{=}CHCOCH_2OBn$; (l) TFA, H_2O; (m) Dowex 50W, H_2O; (n) Ac_2O, py, DMAP; (o) $H_2C{=}CHCH_2SiMe_3$, Ph_3CClO_4; (p) $(Sia)_2BH$; H_2O_2, NaOH; (q) py·SO_3, DMSO; Et_3N; (r) $Ph_3P{=}CHCO_2Me$; (s) NaOMe, MeOH; (t) PPTS; (u) $Me_3BnNOMe$.

Scheme 25. Salomon Halichondrin B C_{37}–C_{51} Synthesis[75c] a

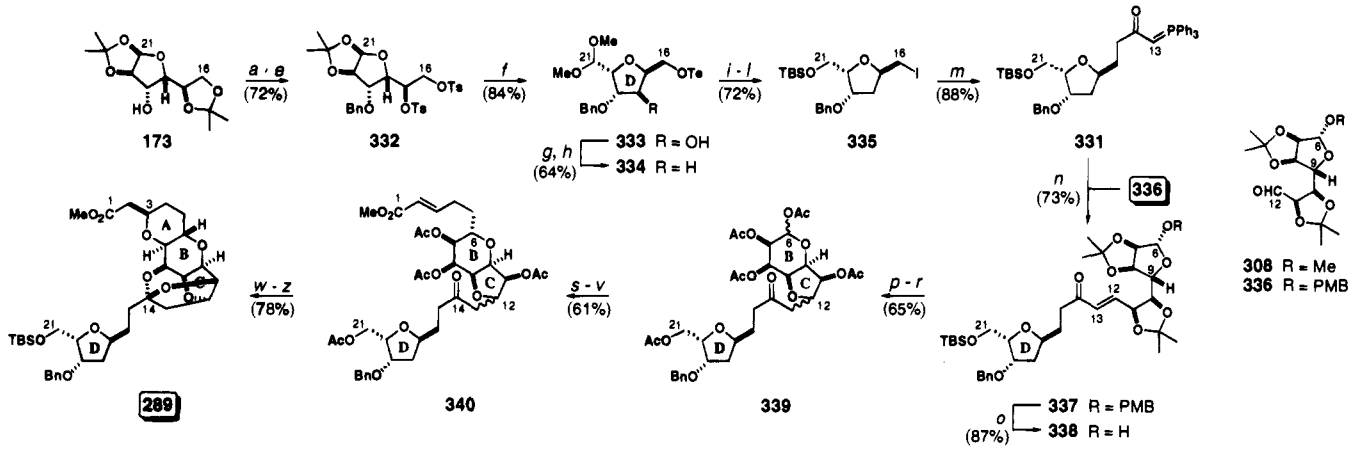


[a] (a) *p*-MeO(C_6H_4)CHO, molecular sieves; (b) TBSCl, imidazole; (c) NaH, imidazole; CS_2; MeI; (d) $^nBu_3SnH$, AIBN; (e) TBAF; (f) BnBr, NaH; (g) DIBAL; (h) DDQ, anhydrous; (i) Swern oxidation; (j) $(MeO)_2P(=O)CH_2COTBS$, NaH; (k) $Me_2Cu(CN)Li_2$, TMSCl; (l) NaOH, 30% H_2O_2; HCl; (m) $PhOP(=O)Cl_2$; PhSH; (n) $Ph_3P{=}CH_2$; (o) **320** + **323**, Δ; (p) $Me_2Cu(CN)Li_2$, TMSCl; (q) $(NH_4)_2Ce(NO_3)_6$; (r) TBSOTf, Et_3N; (s) Raney Ni, H_2; (t) TBSCl, imidazole; (u) DDQ; (v) Swern oxidation; (w) **323** + **328**, Δ; (x) $Me_2Cu(CN)Li_2$, TMSCl; (y) DDQ; (z) TBAF; (a') 1% HCl.

ide-induced intramolecular hetero-Michael reaction of **302** (thermodynamic conditions) closed the A ring and completed the synthesis of the C_1–C_{15} segment **301**. The correct configuration of the C_3 stereogenic center was generated in the cyclization reaction, with the carbomethoxymethyl substituent adopting an equatorial orientation in the chair conformation of tetrahydropyran A. Thus, in the synthesis of **301**, three stereogenic centers originated in the chiral pool (C_7–C_9), one stereogenic center was installed using a chiral reagent (C_{10}), and the other five stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. [C_1–C_{15} segment **301**: 0.7% overall yield from **305**; 21 steps; ~2 steps per stereogenic center.]

c. C_{37}–C_{51} Segment Synthesis.[75c] The C_{37}–C_{51} segment **291**, containing the IJKL tetracyclic array, was synthesized as outlined in Scheme 25. Owing to the double anomeric effect[119] and the preference for diequatorial disposition of the C_{42} and C_{46} methyl substituents on the J and K rings, Salomon and coworkers reasoned that the required IJKL array might be obtained by diastereoselective spiroacetalization, under thermodynamic control, at C_{44} of ketodiol intermediates such as **314**. Diastereoselective conjugate addition of two methyl nucleophiles to a

Scheme 26. Salomon Halichondrin B C_1–C_{21} Synthesis[75d] [a]



[a] (a) BnBr, NaH; (b) AcOH; (c) Ac_2O, py; (d) $Ba(OH)_2$, MeOH; (e) TsCl, py; (f) HCl, MeOH, (g) PhOC(=S)Cl, DMAP; (h) $^nBu_3SnH$, AIBN; (i) TFA, H_2O; (j) $NaBH_4$; (k) NaI; (l) TBSCl, imidazole; (m) $Ph_3P{=}CHCOCH_2Li$; (n) **331** + **336**; (o) $(NH_4)_2Ce(NO_3)_6$, H_2O; (p) AcOH, H_2O; (q) Triton B; (r) Ac_2O, py, DMAP; (s) $H_2C{=}CHCH_2TMS$, $HClO_4$; (t) $(Sia)_2BH$; H_2O_2, NaOH; (u) Swern oxidation; (v) $Ph_3P{=}CHCO_2Me$; (w) NaOMe, MeOH; (x) NaOMe, MeCN; PPTS; (y) TBSCl, imidazole; (z) Triton B methoxide.

dienone was envisaged to construct **314**.[120] Due to the C_2 symmetry of the IJKL portion of halichondrin B, the rings I and L are identical, as are J and K. The route pursued cleverly exploits this symmetry feature.

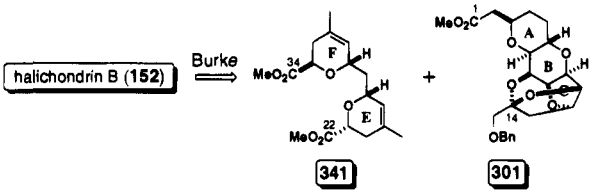
Using known chemistry, acid-catalyzed cyclization of D-mannitol (**315**) gave tetrol **316**.[121] A sequence of (i) selective formation of the monoacetal at C_{40} and C_{42} of **316**; (ii) selective silylation of the C_{37} primary hydroxyl; (iii) Barton deoxygenation[37] at C_{39}; and finally, (iv) protecting group exchange at C_{37}, then gave **317** which bears all the stereogenic centers of both the I and L rings. Reductive cleavage of **317** with DIBAL[122] generated a 6:4 ratio of the differentially protected regioisomers **318** and **319**. Either could be quantitatively recycled to **317** by oxidation with DDQ under anhydrous conditions.[42a] Swern oxidation[38] of **318** provided the C_{42} aldehyde **320**. A Horner–Emmons reaction then provided the α,β-unsaturated acyl silane **321**, which underwent diastereoselective 1,4-addition with $Me_2Cu(CN)Li_2$,[123] in the presence of TMSCl,[124] to provide **322**. A sequence of (i) oxidative desilylation, (ii) conversion of the resulting acid to the thioester, (iii) acylation of methylenetriphenylphosphorane, and (iv) condensation of the resulting ylid **323** with aldehyde **320** then gave enone **324**. A second diastereoselective 1,4-methyl addition gave the key C_2-symmetric ketone **325**. Note that use of the α,β-unsaturated acyl silane **321** was required, since the corresponding α,β-unsaturated ester was completely unreactive with methyl cuprates, even in the presence of TMSCl;[124] and although the corresponding α,β-unsaturated methyl ketone underwent conjugate addition, aldol addition of the product with aldehyde **320** did not generate enone **324**. Note also that this stepwise approach for construction of the IJKL-ring carbon skeleton **325** (*i.e.* **320** → **321** → **322** → **324** → **325**) proved to be necessary since dienones such as **326** proved to be unreactive toward Me_2CuLi, and the use of TMSCl to promote the conjugate addition[124] led to undesired side reactions such as Nazarov cyclizations.[125] Upon treatment of **325** with ceric ammonium nitrate, oxidative removal of the PMB ethers[42b,c] gave dihydroxy ketone **314**, which was followed by spiroacetalization to afford the C_2-symmetric IJKL segment **327**.

Since the symmetry of the IJKL segment must be broken upon incorporation into halichondrin B, a nonsymmetric analogue of **327** was required. This was obtained by employing both the regioisomers **318** and **319**. Thus **319** was converted to aldehyde **328**, which involved selective hydrogenolysis with Raney nickel of a benzyl in the presence of a *p*-methoxybenzyl ether.[126] Wittig coupling of **328** with phosphorus ylide **323**, already obtained from **320**, generated an enone and then diastereoselective conjugate methyl addition provided the unsymmetrical ketone **329**. Deprotection of **329** with DDQ[42b,c] and then TBAF gave triol **330**, which afforded the IJKL C_{37}–C_{51} segment **291** upon treatment with dilute hydrochloric acid. Thus, in this synthesis, six stereogenic centers originated in the chiral pool, and the other three stereogenic centers (C_{42}, C_{44}, and C_{46}) were installed using reactions relying on substrate control of asymmetric induction. [C_{37}–C_{51} segment **291**: 19 steps longest linear sequence from **315**; 24 steps total; ~3 steps per stereogenic center.]

d. C_1–C_{21} Segment Synthesis.[75d] The synthesis of the C_1–C_{21} segment **289** is outlined in Scheme 26. A D-ring segment **331** was obtained from D-glucose, the B ring was derived from D-ribose, and intramolecular hetero-Michael reactions were employed to construct the A and C rings.

Benzyl protection[127] of the C_{19} hydroxyl of D-glucose diacetonide (**173**) followed by selective cleavage of the C_{16}–C_{17} acetonide and tosylation of the resulting diol gave **332**. After acid-catalyzed transacetalization and intramolecular O-alkylation to afford **333**, Barton deoxygenation[37] at C_{16} then provided the D-ring segment **334**. Adjustment of oxidation level at C_{21} followed by protection at C_{21} and iodine introduction at C_{16} gave **335**, which was elaborated into the C_{13}–C_{21} segment **331**. Wittig olefination of **331** with the C_{12} aldehyde **336** (obtained in an analogous manner to the preparation of **308** from D-ribose outlined in Scheme 24) then gave C_6–C_{21} segment **337**. Selective removal of the C_6 PMB group was accomplished using ceric amonium nitrate to give **338**, followed by mild acid hydrolysis of the acetonides and silyl group.

Scheme 27



Treatment with Triton B, followed by acetylation of the crude product, gave the BC-ring segment **339**. It appears that after acetonide hydrolysis, the furanoside (as in **338**) to pyranoside (as in the B ring of **339**) interconversion is essentially complete, and the intramolecular hetero-Michael reaction of the revealed C_9 hydroxyl onto C_{12} is facile under the basic conditions of Triton B. Note that a similar transformation of the methyl furanoside **309** → **304** (Scheme 24) was much lower yielding, due to side reactions occurring under the more strongly acidic conditions needed to hydrolyse the methyl furanoside of **309** compared to the *p*-methoxybenzyl furanoside of **337**.

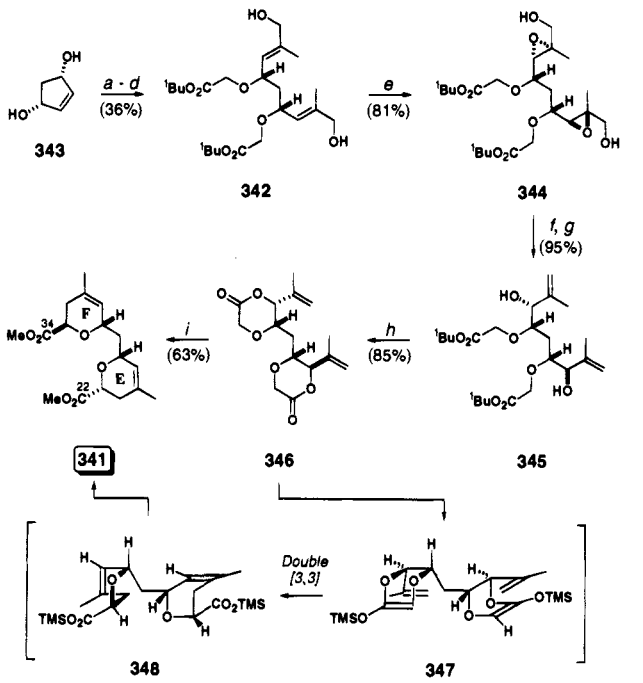
Conversion of **339** to **340** was carried out as for the analogous conversion of **304** → **311** (Scheme 24), involving axial allylation at C_6 of **339**; reaction of **340** with sodium methoxide in methanol then afforded a tetrol (*cf.* **312**, Scheme 24). Completion of the C_1–C_{21} segment **289** required a modified procedure in which base-catalyzed intramolecular hetero-Michael cyclization to form the A ring was effected *prior to* spiroacetalization at C_{14} (*cf.* these reactions were performed in the opposite order in the transformation **312** → **302** → **301**, Scheme 24). After silylation of the remaining hydroxyl, a C_3 epimer was converted to the natural isomer by treatment with Triton B methoxide to deliver the desired C_1–C_{21} segment **289**. Thus, in this synthesis, six stereogenic centers originated in the chiral pool, two stereogenic centers were constructed using a chiral reagent (C_{10} and C_{11}), and the remaining four stereogenic centers were installed using reactions relying on substrate control of asymmetric induction. At the time of writing, coupling of the segments **289**, **290**, and **291** to complete a synthesis of halichondrin B had not been reported by Salomon and co-workers. [C_1–C_{21} segment **289**: 4.8% overall yield from **174**; 26 steps longest linear sequence; >36 steps total; ~3 steps per stereogenic center.]

4. Burke Segment Syntheses[77]

Burke *et al.* have reported syntheses of two halichondrin segments: a shorter route to the C_1–C_{15} segment **301** of Salomon, and an ingenious synthesis of a C_{22}–C_{34} segment **341** (Scheme 27).

a. C_{22}–C_{34} Segment Synthesis.[77a] Burke *et al.* noticed that the target C_{22}–C_{34} segment **341** was a single epimerization away from being a meso compound. Hence, the strategy they adopted involved the asymmetric desymmetrization[128] of the meso bis(allylic alcohol) **342** (Scheme 28). A four-step sequence of (i) bis(O-alkylation) of *meso*-2-cyclopentene-1,4-diol (**343**)[129] with *tert*-butyl bromoacetate under phase-transfer conditions,[130] (ii) ozonolytic ring cleavage, (iii) Wittig homologation,[131] and, finally, (iv) borohydride reduction, provided the bis(allylic alcohol) **342**. Desymmetrization of **342** was achieved by using the Sharpless asymmetric epoxidation[92] to provide the bis(epoxy alcohol) **344** with high diastereo- and enantiomeric purity.[128,132,133] Dimesylation of **344** followed by displacement with NaI, wherein excess iodide effected reductive opening of the epoxide, then afforded **345** in high yield; TFA-mediated lactonization subsequently gave the bis(dioxonone) **346**. Finally, kinetic enolization of **346** using LHMDS and trapping with TMSCl provided the bis(silylketene acetal) **347**, which on heating underwent two stepwise Ireland–Claisen [3,3] sigmatropic rearrangements,[83,134] thus forming **348**. On work up and esterification, **348** provided the C_{22}–C_{34} segment **341**. Thus, in the synthesis of **341**, the two newly created stereogenic centers at C_{23} and C_{33} were installed using a combination of reagent control of asymmetric induction (Sharpless asymmetric epoxidation) and substrate-controlled transfer of chirality (Claisen rearrangement). At the time of writing, the elaboration of segment **341** into a completely functionalized C_{22}–C_{34} halichiondrin intermediate had not yet been reported by Burke *et al.* [C_{22}–C_{34} segment **341**: 15% overall yield from **343**; 9 steps; ~2 steps per stereogenic center].

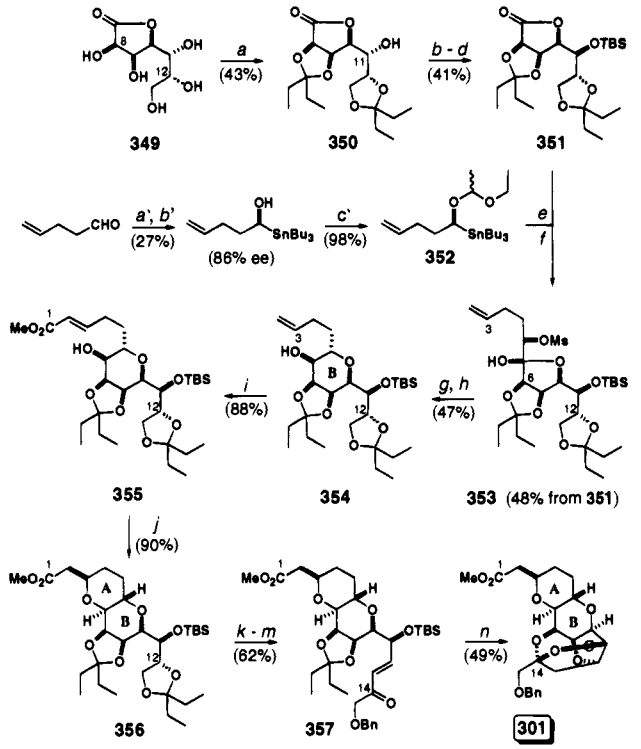
Scheme 28. Burke Halichondrin B C_{22}–C_{34} Synthesis[77a] *a*



a (a) $BrCH_2CO_2{}^tBu$, NaOH, $^nBu_4NHSO_4$; (b) O_3, Ph_3P; (c) $Ph_3P{=}C(Me)CHO$, K_2CO_3; (d) $NaBH_4$; (e) (+)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (f) MsCl, Et_3N; (g) NaI; (h) TFA; (i) LHMDS; TMSCl–Et_3N; Δ; H^+; CH_2N_2.

b. C_1–C_{15} Segment Synthesis.[77b] Burke *et al.* have reported a shorter route to the Salomon[75b] C_1–C_{15} segment **301** (Scheme 29). The synthesis began with the the commercially available carbohydrate **349** (D-glycero-D-*gluco*-hepto-γ-lactone) which requires inversion at C_{11}, but which has the correct configuration for C_8–C_{10} of halichondrin B. In this latter respect, it is similar to the Kishi synthesis of a C_1–C_{13} segment **162** from **165**, depicted in Scheme 11. Regioselective bis(acetalization)[135] of **349** with 3-pentanone gave **350**. Note that bis(acetonide) formation

Scheme 29. Burke Halichondrin B C_1–C_{14} Synthesis[77b] [a]



[a] (a) EtCOEt, H_2SO_4; (b) PDC, AcOH; (c) $Zn(BH_4)_2$; (d) TBSOTf, 2,6-lutidine; (e) **352**, ^{n}BuLi, **351**, 1.8 N HCl; (f) MsCl, Et_3N, DMAP; (g) EtMgBr, Δ; (h) DIBAL; (i) O_3, PPh_3, $Ph_3P{=}CHCO_2Me$; (j) $BnMe_3NOMe$; (k) 80% AcOH; (l) $NaIO_4$; (m) $Ph_3P{=}CHCOCH_2OBn$; (n) 52% aqueous HF; (a') ^{i}PrMgCl, ^{n}Bu$_3$SnH, Galvinoxyl; (b') (*R*)-BINAL; (c') $CH_3CH(OEt)Cl$, Me_2NPh.

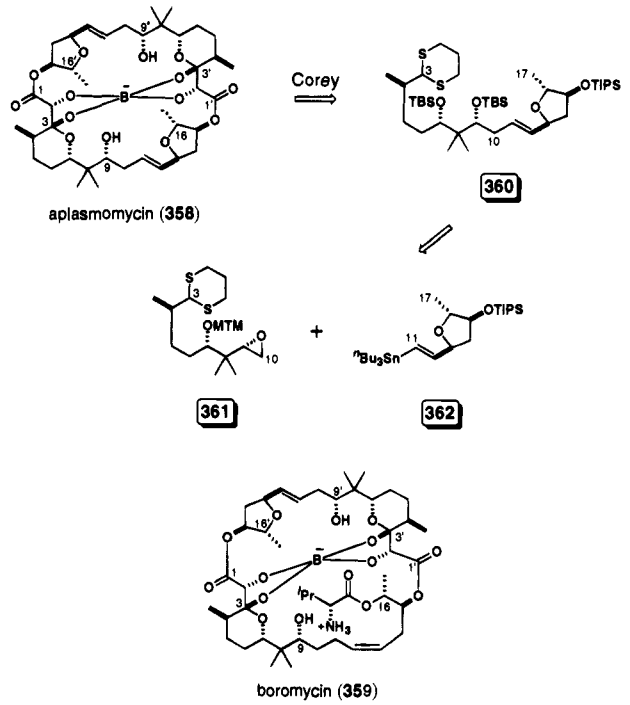
is known to proceed with a different regioselectivity.[135b,c] Oxidation of **350** to the C_{11} ketone and chelation-controlled reduction[136] with $Zn(BH_4)_2$ afforded the epimerized C_{11} alcohol which was then protected as its TBS ether to provide **351**. Meanwhile, stannane **352** was prepared via asymmetric reduction of the acyl stannane derived from 4-pentenal.[137] Transmetalation of **352**, to afford the corresponding α-alkoxyorganolithium reagent,[138] followed by reaction with ketone **351** and subsequent mesylation then supplied the indicated diastereomer of C_3–C_{12} segment **353**. Treatment of this with ethylmagnesium bromide initiated a pinacol rearrangement[139] to form the pyranone, which was subsequently stereoselectively reduced at C_7 to afford the B-ring product **354**. Ozonolysis of the double bond of **354**, followed by a reductive work up and *in situ* Wittig olefination, then provided the A-ring precursor **355**. The now standard intramolecular hetero-Michael reaction, mediated by methoxide ion, closed the A ring to supply **356** with the correct (thermodynamic) configuration at C_3. Selective hydrolysis[135b-d] of the C_{12},C_{13} acetonide of **356** and periodate cleavage of the ensuing vicinal diol was then followed by Wittig homologation[65b] to afford enone **357**. Finally, HF-mediated acetonide and TBS ether cleavage was followed by *in situ* intramolecular hetero-Michael addition of the C_9 hydroxyl onto C_{12}, to close the C ring, and spiroacetalization of the C_8 and C_{11} hydroxyls at C_{14} then furnished the C_1–C_{15} segment **301**. Thus, in this synthesis, four of the nine stereogenic centers in the target molecule originated from the chiral pool (C_8–C_{11}), one was created using a chiral reagent (→ **352**), and the remaining four stereogenic centers were introduced using substrate-controlled reactions. [C_1–C_{15} segment **301**: 1.0% overall yield from **349**; 14 steps longest linear sequence; 17 steps total; ~2 steps per stereogenic center.]

In surveying the various synthetic approaches to the halichondrins, it is clear that carbohydrate-based strategies[8] have proved overwhelmingly popular, despite the large number of protecting group manipulations that are frequently required when adopting this approach, and the ensuing length of some of the resulting syntheses. Besides the construction of many stereogenic centers, the other major synthetic challenge associated with the halichondrins has been the formation of spiroacetal,[140] tetrahydropyran,[141] and tetrahydrofuran[141] ring systems. While the spiroacetal rings have generally been synthesized using acid-catalyzed acetalization reactions of hydroxy ketones, intramolecular hetero-Michael reactions have been repeatedly used to construct the tetrahydropyran and tetrahydrofuran rings.

C. Aplasmomycin

Aplasmomycin (**358** in Scheme 30), isolated from a strain of *Streptomyces griseus* found in shallow sea mud, is a boron-containing ionophoric antibiotic that exhibits activity against Gram-positive bacteria *in vitro* and *Plasmodia berghei in vivo*.[142a] It has a completely symmetrical C_2 structure[142b] and belongs to the family of borate-bridged macrodiolides of which boromycin (**359**), produced by the terrestrial actinomycete *Streptomyces antibioticus*, was the first known member.[143,144] The first total synthesis of aplasmomycin was reported by Corey *et al.* in 1982.[145] White *et al.* have also completed a total synthesis,[146a] and Nakata, Oishi and co-workers[147] and Matsuda *et al.*[148] have each achieved a formal total synthesis of aplas-

Scheme 30



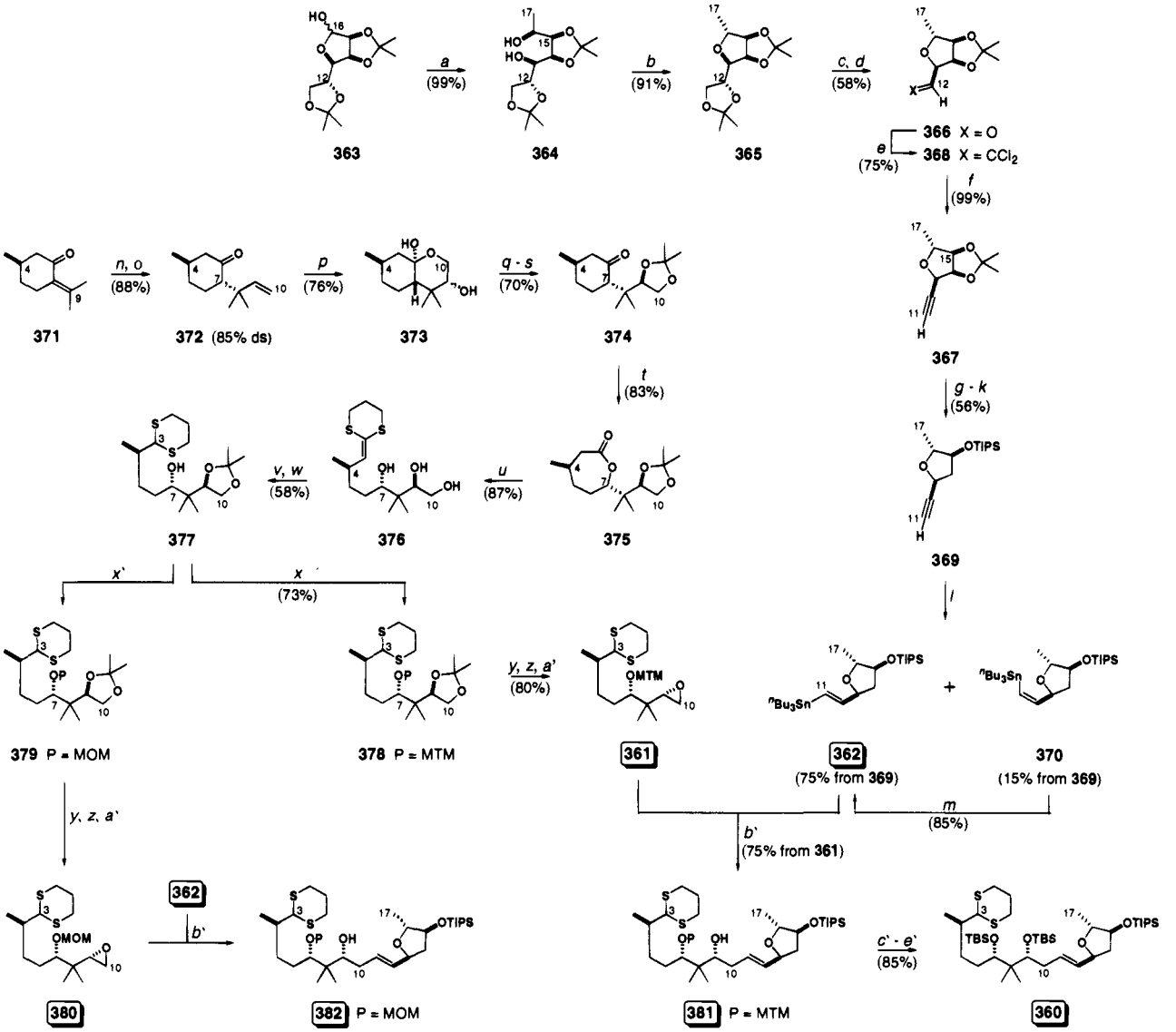
momycin by preparation of a key intermediate (**360**) used in Corey's synthesis.

1. Corey Total Synthesis[145]

The synthesis of aplasmomycin (**358**) by Corey *et al.* was based on the construction of a C_3-C_{17} segment (**360** in Scheme 30) from C_3-C_{10} and $C_{11}-C_{17}$ segments (**361** and **362**). Chain extension of **360** with dimethyl oxalate then provided the entire C_1-C_{17} sequence of aplasmomycin. Direct dimerization to form the macrodiolide, or, alternatively, sequential coupling and macrolactonization, was followed by introduction of the borate to furnish the natural product.

a. C_3-C_{17} Segment Synthesis.[145a] The $C_{11}-C_{17}$ segment **362** was prepared from D-mannose (Scheme 31). Thus, reaction of D-mannose diacetonide (**363**)[149] with methyllithium afforded exclusively the diol **364** resulting from chelation control by the C_{15} oxygen. Selective tosylation of the less-hindered C_{16} hydroxyl of **364** and *in situ* S_N2 displacement by the C_{13} hydroxyl, with inversion of configuration at C_{16}, provided the tetrahydrofuran **365**. The side chain acetonide of **365** was selectively hydrolyzed, and oxidative cleavage of the resulting diol then supplied the C_{12} aldehyde **366**, which was converted into the alkyne **367** via the dichloroolefin **368**.[150] A five-step sequence involving acetonide cleavage, selective silylation of the C_{15} hydroxyl, and deoxygenation at C_{14} (via triflate ester formation, displacement by iodide,[151] and reduction with tributyltin hydride[152]) then provided alkyne **369**. Radical-mediated reaction of **369** with tributylstannane gave the desired *trans* vinylstannane $C_{11}-C_{17}$ segment **362**, together with a smaller amount of the undesired *cis* isomer **370** (*trans/cis* = 5:1) which could be thermally equilibrated to provide more of **362** (*trans/cis* = 85:15).

Scheme 31. Corey Aplasmomycin C_3-C_{17} Synthesis[145a] [a]



[a] (a) MeLi; (b) TsCl, py; (c) HCl, H_2O; (d) $NaIO_4$, $NaHCO_3$; (e) $CBrCl_3$, $(Me_2N)_3P$; (f) ^nBuLi; (g) HCl, MeOH; (h) TIPSCl, DMAP; (i) Tf_2O, py; (j) $^nBu_4NI$; (k) $NaBH_4$, $^nBu_3SnCl$, $h\nu$; (l) $^nBu_3SnH$, AIBN; (m) Δ; (n) $H_2C{=}CHMgBr$, CuI; (o) NaOMe, MeOH; (p) OsO_4, NMO; (q) LAH; (r) Me_2CO, *p*-TsOH; (s) PCC, 3 Å molecular sieves; (t) *m*-CPBA; (u) Me_3Al, $HS(CH_2)_3SH$; (v) O_3; DMS; $BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$; (w) $(MeO)_2CMe_2$, *p*-TsOH; (x) DMSO, Ac_2O, AcOH; (x') MOMCl, Et_3N, DMAP; (y) AcOH, H_2O; (z) PhCOCN, Et_3N; MsCl, Et_3N; (a') $^nBu_4NOH$, MeOH; (b') **362**, ^{n}BuLi; CuCN; **361** or **380**; (c') TBSOTf, 2,6-lutidine; (d') $AgNO_3$, 2,6-lutidine, H_2O; (e') TBSOTf, 2,6-lutidine.

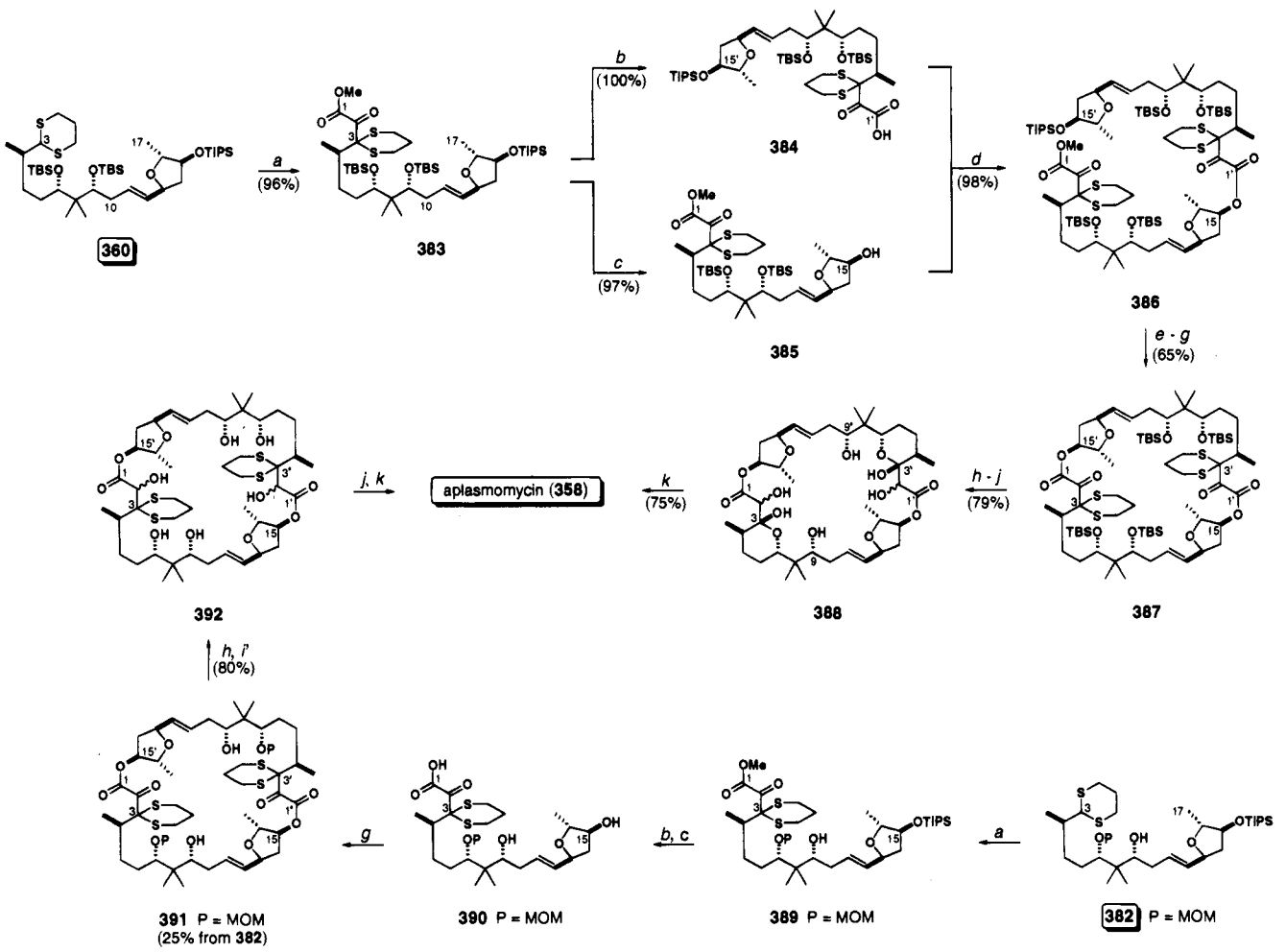
The C_3-C_{10} segment **361** was prepared from (*R*)-pulegone (**371**). Conjugate addition of a vinylmagnesiocuprate to **371** gave a 1:1 mixture of *trans*- and *cis*-cyclohexanones, which was equilibrated using sodium methoxide to provide an 85:15 mixture in favor of the *trans* isomer **372** having the required configuration at C_7. Osmylation of **372** occurred stereoselectively on the more accessible *si* face of the olefin to set up the C_9 stereogenic center with unnatural configuration, and *in situ* hemiacetal formation then afforded **373**. Reduction of **373** to generate a triol and selective acetonide protection of the C_9 and C_{10} hydroxyls was followed by reoxidation to give ketone **374**, which underwent Baeyer–Villiger oxidation to supply lactone **375**. Reaction of **375** with trimethylaluminum/propane-1,3-dithiol[153] then gave the ketenethioacetal triol **376**. Ozonolysis of **376** and subsequent thioacetalization at C_3, followed by selective acetonide protection of the C_7 and C_9 hydroxyls, then gave **377** which bore the complete C_3-C_{10} chain for incorporation into aplasmomycin. The C_7 hydroxyl of **377** was protected in two alternative ways: as the (methylthio)methyl (MTM) ether (**378**),[154] and as the methoxymethyl (MOM) ether (**379**). Compound **378** was transformed into the epoxide C_3-C_{10} segment **361** by a three-step sequence of (i) selective hydrolysis of the acetonide of **378** to give a 1,2-diol, (ii) selective benzoylation of the primary hydroxyl followed by mesylation of the secondary hydroxyl, and (iii) benzoate cleavage and *in situ* epoxide closure with inversion to provide the natural configuration at C_9. In a similar manner, **379** was converted into the alternative C_3-C_{10} segment **380**.

Coupling of the C_3-C_{10} and $C_{11}-C_{17}$ segments **361** and **362** was accomplished via transmetalation of stannane **362** to generate the corresponding organocuprate[155] and addition of epoxide **361**. Exchange of protecting groups in the resulting **381** then provided the C_3-C_{17} segment **360**. Likewise, coupling of **380** with the organocuprate derived from **362** gave the alternative C_3-C_{17} segment **382**. [C_3-C_{17} segment **360**: 6.2% overall yield from **371**; 18 steps longest linear sequence; 30 steps total; 5 steps per stereogenic center; C_3-C_{17} segment **382**: 15 steps longest linear sequence; 27 steps total; ~4–5 steps per stereogenic center.]

b. Completion of the Total Synthesis of Aplasmomycin.[145b] Two complementary routes were developed by Corey *et al.* for the completion of the synthesis of aplasmomycin. In one route, coupling of two C_1-C_{17} segments and subsequent macrolactonization generated the macrodiolide; in the other approach, the coupling and cyclization were accomplished in a single step (Scheme 32).

In the first route, lithiation of the dithiane moiety of the C_3-C_{17} segment **360** and reaction with di-

Scheme 32. Corey Aplasmomycin Synthesis[145b] a



[a] (a) ^{n}BuLi, TMEDA; HMPA, $(CO_2Me)_2$; (b) LiI, 2,6-lutidine; (c) TBAF; (d) **384** + **385**, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), Et_3N; (e) LiI, 2,6-lutidine; (f) TBAF; (g) BOPCl, Et_3N; (h) $NaBH_4$; (i) HF; (i') $(^iPrS)_2BBr$; (j) $HgCl_2$, $CaCO_3$, H_2O; (k) $B(OMe)_3$.

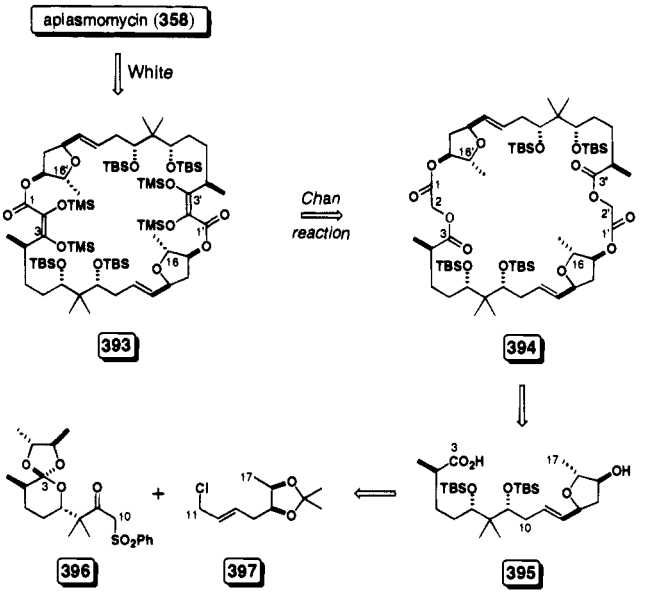
methyl oxalate provided the complete C_1-C_{17} segment **383** with both its carboxyl (C_1) and hydroxyl (C_{15}) termini protected. Ester cleavage at C_1 then afforded acid **384**, whereas selective desilylation at C_{15} gave alcohol **385**. Coupling of **384** and **385** was then accomplished by esterificaton using the Palomo-Coll protocol (BOP chloride/triethylamine)[156] to afford **386**. Cleavage of both the C_1 ester and $C_{15'}$ silyl ether of **386** gave a seco-acid, which was macrolactonized using the Palomo-Coll procedure[156] to supply the macrodiolide **387** in good yield (64% from the two C_1-C_{17} segments). Reduction of the α-keto groups of **387** and subsequent desilylation, followed by dithiane cleavage and *in situ* hemiacetal formation at C_3 and $C_{3'}$ then gave deboraplasmomycin **388**, as a mixture of diastereomers differing in configuration at C_2 and $C_{2'}$. Treatment of this mixture with trimethyl borate afforded diastereomerically pure aplasmomycin (**358**). Note that borate bridging is accompanied by equilibration at C_2 and $C_{2'}$ via enolization, and the natural configuration at these centers must be the thermodynamically most favorable stereochemistry.

For the second approach, the alternatively protected C_3-C_{17} segment **382** was employed. Two-carbon homologation at C_3 to provide **389** was performed in exactly the same way as for **360** → **383**. Cleavage of both the C_1 ester and $C_{15'}$ silyl ether of **389** then supplied the ω-hydroxy acid C_1-C_{17} segment **390**. Subjection of **390** to the Palomo-Coll esterification protocol[156] then gave directly the desired macrodiolide **391**. Although the yield of **391** was only moderate (25%), the various byproducts underwent saponification with base to regenerate **390**, making this one-step coupling-cyclization procedure highly effective due to its extreme economy of steps. Cleavage of the MOM ethers of **391** by use of diisopropylthioboron bromide[157] was followed by ketone reduction at C_2 and $C_{2'}$ to give **392**, again as a mixture of diastereomers at these centers. Note that the cleavage of the C_7 MOM ethers could not be achieved by conventional acid-catalyzed hydrolysis since participation of the C_9 hydroxyl resulted in formation of a six-membered cyclic methylene acetal. In the case of diisopropylthioboron bromide, the C_9 hydroxyl forms a diisopropylthioborate ester which facilitates MOM ether cleavage by coordination to the C_7 oxygen.[158] After dithiane hydrolysis and *in situ* hemiacetal formation as for the first route, borate complexation then afforded the natural product in diastereomerically pure form. Thus, in this synthesis, three stereogenic centers in the target molecule originated from the chiral pool (C_4, C_{13}, and C_{15}), and the remaining five stereogenic centers were introduced using substrate-controlled reactions. [Aplasmomycin (**358**): first route—2.2% overall yield from **371**; 28 steps longest linear sequence; 41 steps total; ~5 steps per stereogenic center, allowing for C_2 symmetry; second route—23 steps longest linear sequence; 35 steps total; ~4 steps per stereogenic center, allowing for C_2 symmetry.]

2. White Total Synthesis[146a]

In the synthesis of aplasmomycin by White *et al.*, the macrodiolide **393** was constructed by ring contraction of the key intermediate **394** in a novel

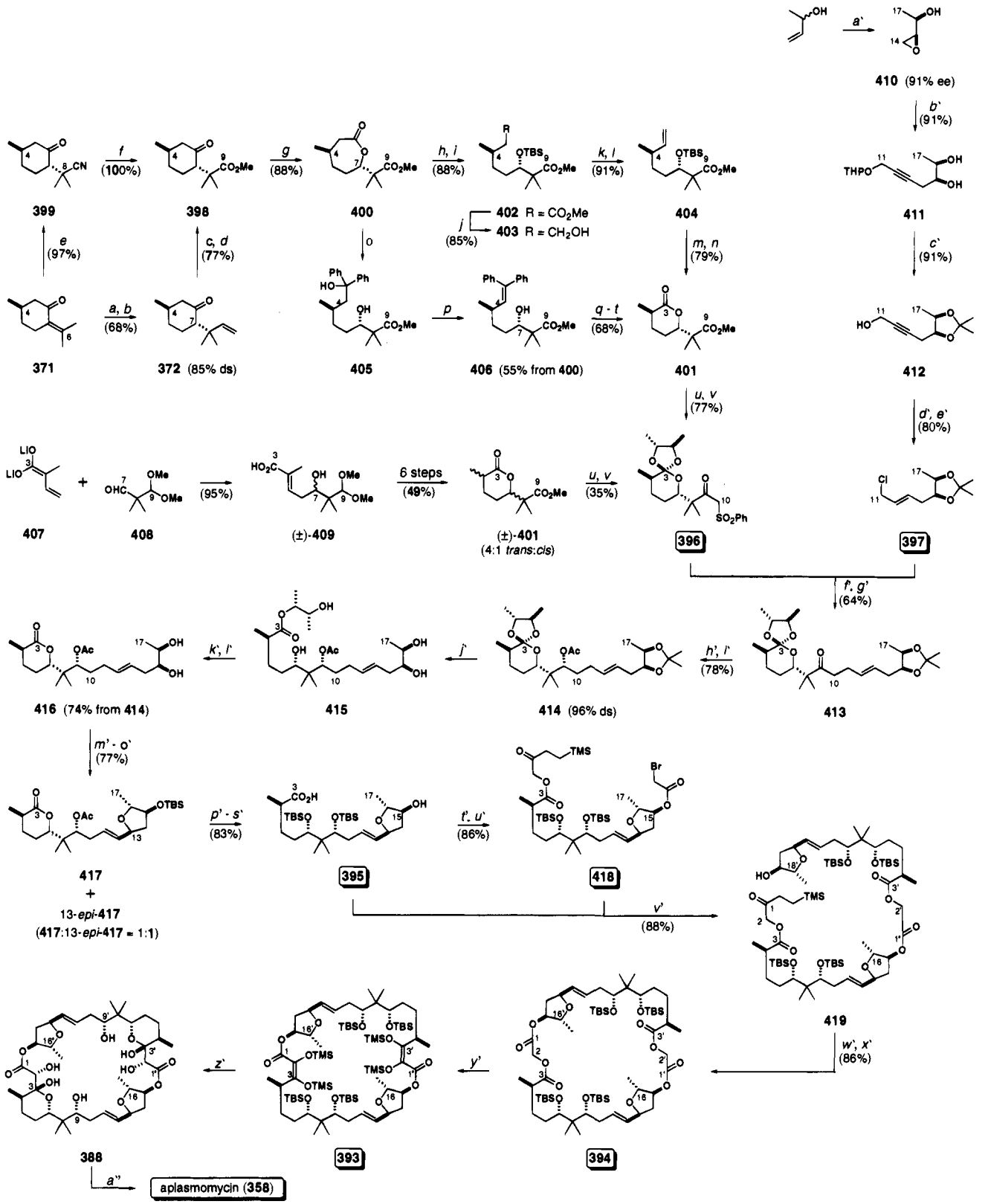
Scheme 33



application of the Chan reaction[159] (Scheme 33). Compound **394** was obtained from the C_3-C_{17} segment **395**, which was in turn constructed from C_3-C_{10} and $C_{11}-C_{17}$ segments (**396** and **397**).

The most recent, and most efficient, route[146b] to the C_3-C_{10} segment **396** began with (*R*)-pulegone (**371** in Scheme 34). As in the Corey synthesis,[145a] conjugate addition of a vinylmagnesiocuprate to **371** followed by base-catalyzed equilibration gave ketone **372** with 85% ds at C_7. Oxidative cleavage[160] of the vinyl group of **372** and esterification of the resulting carboxylic acid then gave **398**. More expediently, hydrocyanation of (*R*)-pulegone gave **399** with >97% ds at C_7,[161] and methanolysis then supplied **398**. In common with the Corey synthesis, a Baeyer–Villiger reaction was used to introduce an oxygen atom at C_7. Accordingly, lactone **400** was obtained from ketone **398** with high regioselectivity. Two sequences were then developed to transform **400** into its lower homologue, the C_3-C_9 segment **401**. Thus, methanolysis of **400** and silylation of the resulting C_7 hydroxyl gave diester **402**. Selective reduction of the less-hindered ester then afforded primary alcohol **403**, and elimination of the derived *o*-nitrophenyl selenoxide[162] supplied olefin **404**. Oxidative cleavage[160] of the double bond of **404** to give the C_3 carboxylic acid was followed by HF-mediated desilylation at C_7 and *in situ* lactonization to provide **401**. Alternatively, a variant of the Barbier–Wieland degradation[163] was used to convert **400** to **401**. Thus, reaction of lactone **400** with phenylmagnesium bromide gave diol **405**, together with some of the ketone resulting from only monoaddition of Grignard reagent, and acid-catalyzed dehydration of **405** then supplied alkene **406**. Temporary protection of the C_7 hydroxyl of **406** was followed by oxidative cleavage[160] of the double bond to give the C_3 carboxylic acid. Deprotection at C_7 and lactonization then afforded **401**. Note that both routes provided **401** in diastereo- and enantiomerically pure form. Reaction of **401** with (2*R*,3*R*)-2,3-butanediol furnished the corresponding ortholactone and condensation with the lithio anion of methyl phenyl sulfone then gave the C_3-C_{10} segment **396**.

Scheme 34. White Aplasmomycin Synthesis[146] [a]



[a] (a) $H_2C{=}CHMgBr$, CuBr; (b) KOH, EtOH; (c) $RuCl_3$, $NaIO_4$; (d) CH_2N_2; (e) NaCN, NH_4Cl; (f) MeOH, H_2SO_4; (g) CF_3CO_3H; (h) K_2CO_3, MeOH; (i) TBSOTf, 2,6-lutidine; (j) LAH; (k) o-$O_2NC_6H_4SeCN$, $^nBu_3P$; (l) H_2O_2; (m) $RuCl_3$, $NaIO_4$; (n) HF; (o) PhMgBr; (p) PPTS; (q) Ac_2O, py, DMAP; (r) $RuCl_3$, $NaIO_4$; (s) K_2CO_3, MeOH; (t) 1 N HCl; (u) (2*R*,3*R*)-butanediol, p-TsOH; (v) $MeSO_2Ph$, ^{n}BuLi; (a') $Ti(O^iPr)_4$, (−)-DIPT, ^{t}BuOOH; (b') $THPOCH_2C{\equiv}CH$, ^{n}BuLi; (c') $(MeO)_2CMe_2$, p-TsOH, MeOH; (d') LAH, $AlCl_3$; (e') NCS, DMS; (f') **396**, ^{n}BuLi, KI; **397**; (g') Al-Hg; (h') LAH; (i') Ac_2O, DMAP; (j') p-TsOH, H_2O; (k') NaOH, H_2O; (l') 5% HCl; (m') PhSeCl; (n') H_2O_2; (o') TBSOTf, 2,6-lutidine; (p') NaOH, H_2O; (q') TBSOTf, 2,6-lutidine; (r') K_2CO_3, H_2O; (s') TBAF; (t') $BrCH_2CO_2(CH_2)_2TMS$, K_2CO_3; (u') $BrCH_2COCl$, py, DMAP; (v') **395** + **418**, K_2CO_3; (w') TBAF; (x') 2-chloropyridinium methiodide, Et_3N; (y') LDA; TMSOTf; (z') HF; (a'') $B(OMe)_3$.

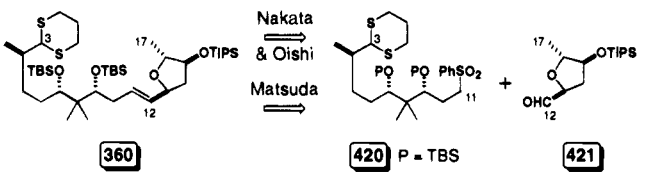
Note that the preparation of **396** from (*R*)-pulegone (11 steps, 25% overall yield) is more stereochemically efficient than the original route,[144e] which began with the aldol reaction[164] between the lithio dianion (**407**)

of tiglic acid and aldehyde **408** (prepared in three steps from isobutyraldehyde and formaldehyde) and which generated **409** in racemic form. Transformation of **409** to **401** (obtained as a 4:1 mixture of racemic *trans* and *cis* isomers) was then followed by resolution with (2*R*,3*R*)-2,3-butanediol, chromatographic separation, and sulfone introduction to provide enantiomerically pure **396** (12 steps, <11% overall yield).[144e]

The $C_{11}-C_{17}$ segment **397** was prepared[144f] by kinetic resolution of racemic 3-buten-2-ol via Sharpless asymmetric epoxidation.[28a] The resulting epoxide **410** (91% ee) underwent regioselective ring opening with an alkynyllithium to provide diol **411**, and an exchange of protecting groups then gave the propargylic alcohol **412**. After reduction of **412** with $LiAlH_4/AlCl_3$ to provide the *trans* allylic alcohol,[165] transformation into the allylic chloride[166] furnished the $C_{11}-C_{17}$ segment **397**.

Construction of the $C_{10}-C_{11}$ bond was achieved[144f] via alkylation of the lithium enolate of keto sulfone **396** with chloride **397**. Reductive removal of the sulfone moiety then afforded ketone **413**, which underwent highly stereoselective reduction (96% ds)[146a] due to chelation control by the pyran oxygen at C_7. Acetylation of the resulting alcohol then provided **414**, and acid-catalyzed hydrolysis effected acetonide cleavage at C_{15} and C_{16} and simultaneous opening of the ortholactone at C_3 to provide ester **415**. Saponification of **415** gave a carboxylic acid at C_3 and acid-catalyzed lactonization then afforded **416**. Regioselective intramolecular oxyselenation[167] of alkene **416**, involving 5-*exo*-trig[97] attack of the C_{16} hydroxyl at the C_{13} terminus of the double bond, followed by oxidative elimination of the resulting selenide provided, after silylation of the C_{15} hydroxyl, the tetrahydrofuran **417** together with its C_{13} epimer in a 1:1 ratio. Saponification of **417**, silylation of the resulting dihydroxy acid, and subsequent selective cleavage of the C_{15} silyl ether then furnished the ω-hydroxy acid C_3-C_{17} segment **395**. Reaction of the potassium salt of **395** with 2-(trimethylsilyl)ethyl α-bromoacetate was followed by esterification with α-bromoacetyl chloride to give **418**, which was then coupled with the potassium salt of carboxylic acid **395** to give the cyclization precursor **419**. After removal of the (trimethylsilyl)ethyl ester protecting group at C_1 of **419**, macrolactonization according to the Mukaiyama protocol[168] provided **394** in excellent yield. Treatment of **394** with LDA followed by TMSOTf then initiated the key "double-Chan" reaction,[159] providing the macrodiolide **393** in good yield. HF-mediated desilylation of **393** and *in situ* hemiacetalization then supplied deboraplasmomycin **388**. Finally, reaction of **388** with trimethyl borate,[144c,145] furnished the natural product. Thus, in this synthesis, one stereogenic center in the target molecule originated from the chiral pool (C_4), two stereogenic centers were installed using asymmetric induction from a chiral catalytic reagent (C_{15} and C_{16}), and the remaining five stereogenic centers were introduced using substrate-controlled reactions. [Chan reaction precursor **394**: 2.6% overall yield from **371**; aplasmomycin (**358**): 34 steps longest linear sequence; 39 steps total; ~5 steps per stereogenic center, allowing for C_2 symmetry.]

Scheme 35



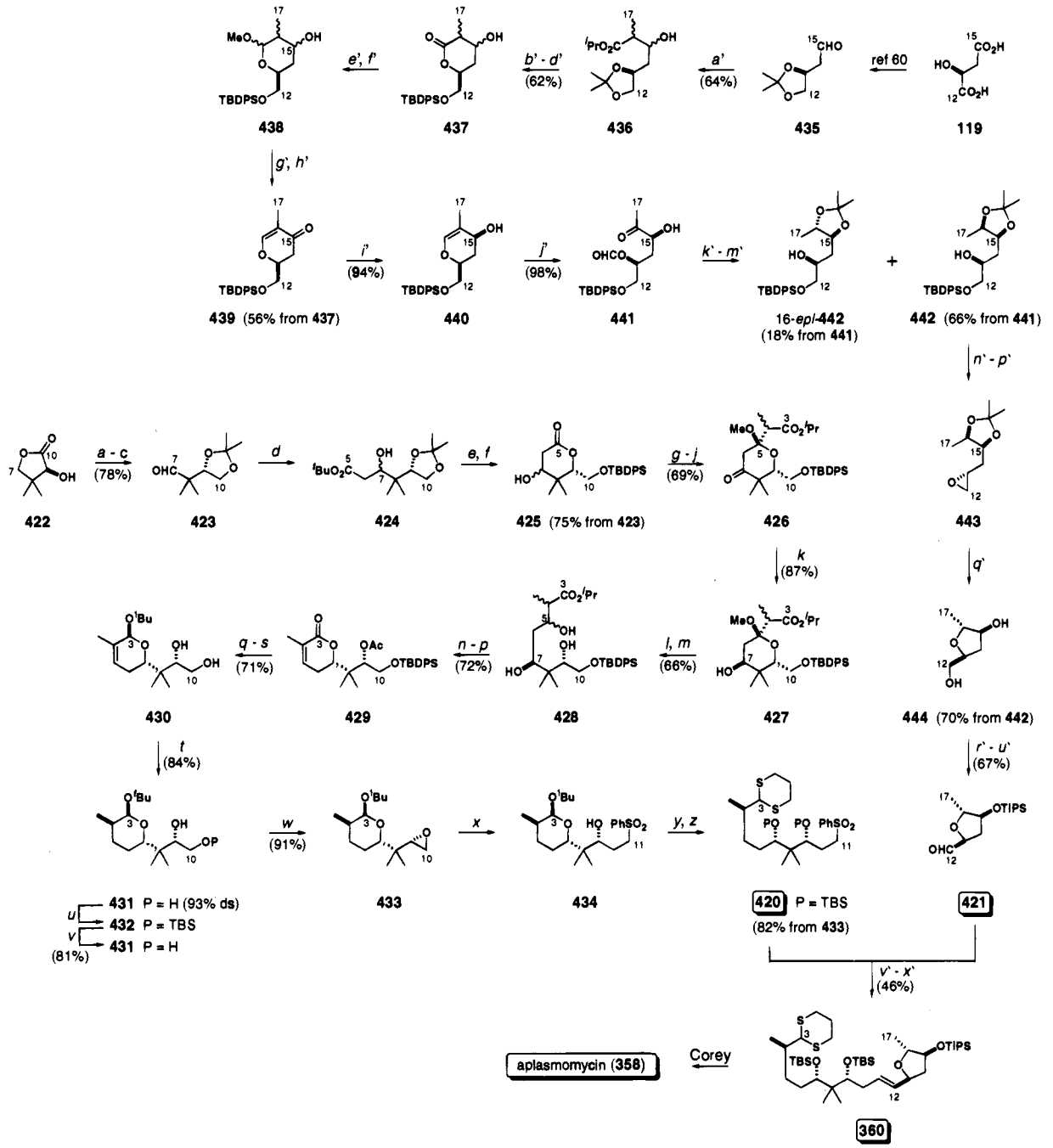
3. Nakata and Oishi Formal Total Synthesis[147]

Nakata, Oishi, and co-workers have achieved a formal total synthesis of aplasmomycin by preparation of the C_3-C_{17} segment **360**, which was an intermediate in Corey's earlier total synthesis. Compound **360** was constructed by a Julia olefination reaction between the C_3-C_{11} and $C_{12}-C_{17}$ segments **420** and **421** (Scheme 35). Stereoselective ketone reductions were used several times to set up key stereogenic centers.

The C_3-C_{11} segment **420** was prepared from commercially available (*S*)-pantolactone (**422**), which supplied the C_9 stereogenic center (Scheme 36). Thus a three-step sequence of reduction, acetonide protection, and oxidation provided aldehyde **423** from **422**.[169] Aldol reaction of **423** with the lithium enolate of *tert*-butyl acetate then gave β-hydroxy ester **424** as a mixture of C_7 epimers. Acetonide deprotection and *in situ* lactonization followed by selective silylation of the C_{10} primary hydroxyl then led to lactone **425**. After temporary protection of the C_7 hydroxyl of **425**, sequential aldol addition of the lithium enolate of isopropyl propionate to C_5, methoxylation of the resulting hemiacetal, and simultaneous deprotection at C_7 followed by oxidation at C_7 then gave ketone **426**. Stereoselective reduction at C_7 of **426** by L-selectride then furnished exclusively the axial alcohol **427**.[170b] Acid-catalyzed hydrolysis of **427** was followed by $NaBH_4$ reduction at C_5 to provide **428**, as a mixture of diastereomers at C_4 and C_5. Acid-mediated lactonization of the C_7 hydroxyl of **428** and subsequent acetylation of the remaining hydroxyls was followed by DBU-induced elimination across C_4-C_5 to afford the α,β-unsaturated lactone **429**. After DIBAL reduction of **429**, acetalization at C_3 and desilylation then gave diol **430**. Heterogeneous hydrogenation of **430** proceeded stereoselectively from the less-hindered α face to generate **431** with 93% ds at C_4.[171] After silylation of the primary hydroxyl at C_{10}, chromatographic removal of the minor C_4-α epimer afforded **432**; desilylation then provided diastereomerically pure **431**. On treatment with NaH and TsCl, or simply excess KH, **431** was converted into epoxide **433**, which underwent regioselective $BF_3{\cdot}OEt_2$-mediated addition[87] of the lithio anion of methyl phenyl sulfone to afford **434**. Transacetalization with 1,3-propanedithiol provided the C_3 thioacetal and silylation of the resulting diol then supplied the C_3-C_{11} segment **420**.

The $C_{12}-C_{17}$ segment **421** was derived from (*S*)-malic acid (**119**), which supplied the C_{13} stereogenic center. Thus **119** was converted into aldehyde **435**,[60] and aldol addition of the lithium enolate of isopropyl propionate then gave β-hydroxy ester **436**, as a

Scheme 36. Nakata/Oishi Aplasmomycin C_3–C_{17} Synthesis[147] [a]



[a] (a) LAH; (b) Me_2CO, *p*-TsOH; (c) PCC; (d) $MeCO_2{}^tBu$, LDA; **423**; (e) HCl, MeOH; (f) TBDPSCl, imidazole; (g) $H_2C{=}CHOEt$, PPTS; (h) $EtCO_2{}^iPr$, LDA; (i) CSA, MeOH; (j) PCC; (k) L-selectride; (l) HCl; (m) $NaBH_4$; (n) CSA; (o) Ac_2O, py, DMAP; (p) DBU; (q) DIBAL; (r) PPTS, ^tBuOH; (s) TBAF; (t) H_2, 5% Rh–Al_2O_3; (u) TBDPSCl, imidazole; (v) TBAF; (w) KH or NaH, TsCl; (x) $MeSO_2Ph$, ^nBuLi, HMPA, $BF_3{\cdot}OEt_2$; (y) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$; (z) TBSOTf, 2,6-lutidine; (a') $EtCO_2{}^iPr$, LDA; **435**; (b') HCl, MeOH; (c') TBDPSCl, imidazole; (d') CSA; (e') DIBAL; (f') CSA, $CH(OMe)_3$; (g') PCC; (h') NaOMe; (i') $NaBH_4$, $CeCl_3$; (j') O_3; DMS; (k') $Zn(BH_4)_2$; (l') K_2CO_3, MeOH; (m') Me_2CO, *p*-TsOH; (n') MsCl, py; (o') TBAF; (p') NaOMe; (q') AcOH, H_2O; (r') BzCl, py; (s') TIPSCl, imidazole; (t') K_2CO_3, MeOH; (u') PCC; (v') **420**, ^nBuLi, HMPA; **421**; (w') BzCl, py, DMAP; (x') 6% Na–Hg.

mixture of C_{15} and C_{16} epimers. Protecting group exchange and lactonization then furnished **437** which, after reduction to the lactol and acetalization with methanol, provided **438**. Oxidation at C_{15} of **438** and subsequent base-induced elimination then gave the enone **439** which underwent a highly stereoselective Luche reduction[23] to correctly set the C_{15} stereogenic center. Ozonolysis of **440** gave α-hydroxy ketone **441**, which underwent a moderately selective chelation-controlled reduction[170a] with $Zn(BH_4)_2$. After deformylation at C_{13} and selective acetonide protection of the C_{15} and C_{16} hydroxyls, the desired diastereomer **442** was obtained, together with its C_{16} epimer, in a ratio of 79:21. Mesylation of the C_{13} hydroxyl of **442** was followed by cleavage of the C_{12} silyl ether. Treatment with base then generated the epoxide **443** with inversion of configuration at C_{13}. Exposure of **443** to acid then led to cleavage of the acetonide, and cyclization of the resulting C_{16} hydroxyl onto the epoxide, with inversion at C_{13} again, to give tetrahydrofuran **444**. Protecting group exchange and oxidation then afforded the C_{12}–C_{17} segment **421**.

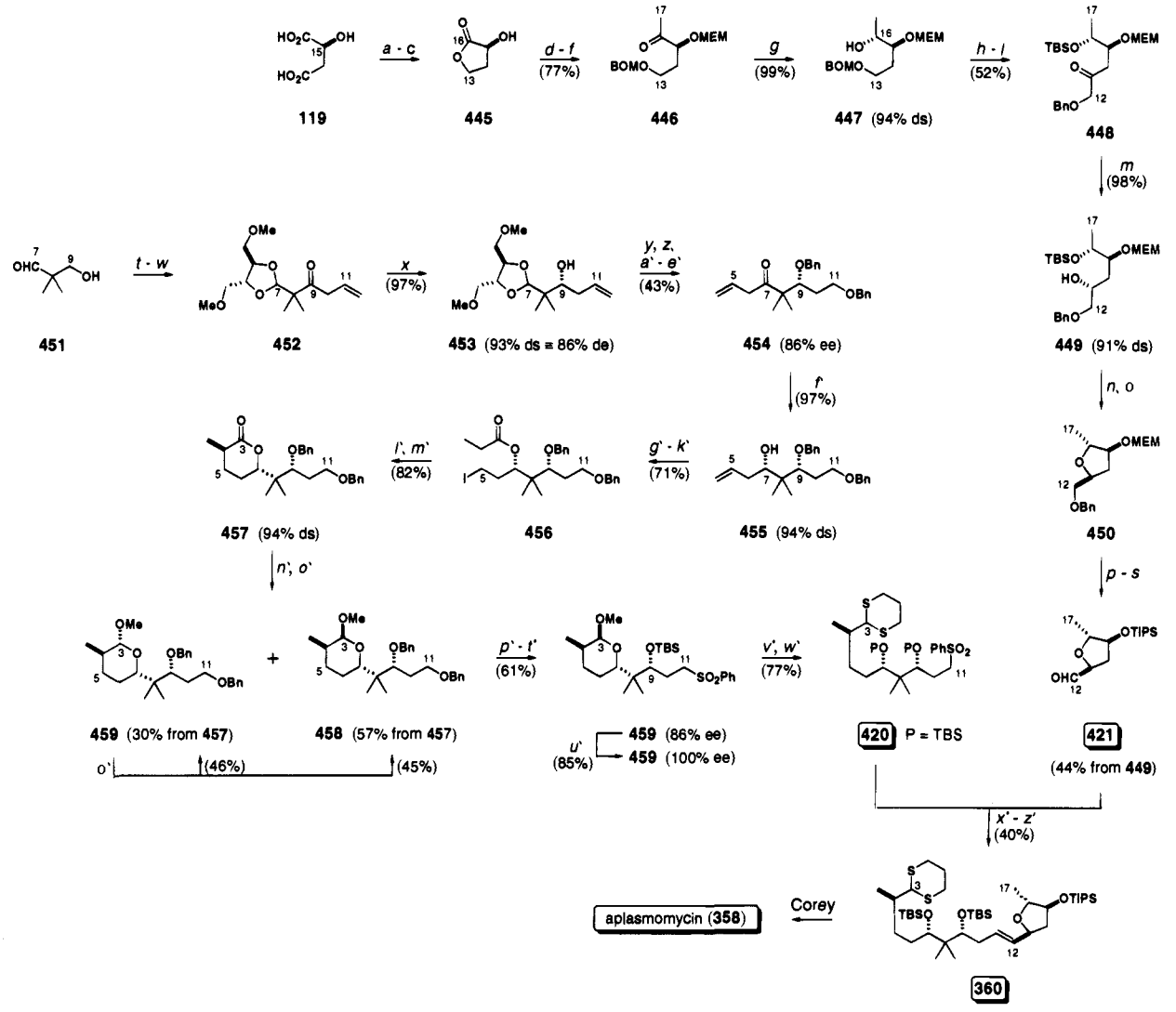
A Julia olefination reaction between the lithio anion of sulfone **420** and aldehyde **421** gave the C_3–C_{17} segment **360**, the Corey intermediate, and so completed a formal total synthesis of aplasmomycin. Thus, in this synthesis of **360**, two of the five stereogenic centers in the target molecule originated from the chiral pool (C_9 and C_{13}); the remaining three stereogenic centers were introduced using substrate-controlled reactions (**429** → **430** → **431** for C_4, **425** → **426** → **427** for C_7, **439** → **440** for C_{15}, and **441** → **442** for C_{16}). [C_3–C_{17} segment **360**: 2.8% overall yield from **422**; 29 steps longest linear sequence; 51 steps total; ~8–9 steps per stereogenic center.]

4. Matsuda Formal Total Synthesis[148]

Matsuda *et al.* have also achieved a formal total synthesis of aplasmomycin by preparation of the Corey intermediate **360**. In common with the earlier work of Nakata, Oishi, and co-workers,[147] **360** was constructed from the C_3–C_{11} and C_{12}–C_{17} segments **420** and **421** (Scheme 35), and many of the key stereogenic centers were again set up by means of stereoselective ketone reductions.

The C_{12}–C_{17} segment **421** was derived from (*S*)-malic acid (**119**), which supplied the C_{15} stereogenic center (Scheme 37). Note that Nakata, Oishi, and co-workers also used (*S*)-malic acid to prepare **421**, but in that case the acid supplied the C_{13} stereogenic center. By using Still's procedure,[172] Matsuda *et al.* converted **119** into 2-hydroxybutanolide (**445**). After protection of the hydroxyl, reaction with methyllithium and subsequent protection of the resulting C_{13} hydroxyl furnished ketone **446**. Chelation-controlled reduction[170a] of **446** using $Zn(BH_4)_2$ then set up the C_{16} stereogenic center with high diastereoselectivity (94% ds). After silylation of the C_{16} hydroxyl of **447**, deprotection at C_{13} was followed by oxidation to the C_{13} aldehyde. Reaction with [(benzyloxy)methyl]lithium,[173] followed by oxidation, then gave ketone **448**. Stereoselective reduction[174] at C_{13}

Scheme 37. Matsuda Aplasmomycin C_3–C_{17} Synthesis[148] a



[a] (a) $(MeO)_2CMe_2$, *p*-TsOH; (b) BH_3; (c) H^+; (d) MEMCl, $^iPr_2NEt$; (e) MeLi; (f) BOMCl, $^iPr_2NEt$; (g) $Zn(BH_4)_2$; (h) TBSCl, imidazole; (i) Li, liquid NH_3; (j) CrO_3·2py; (k) $BnOCH_2Li$; (l) CrO_3·2py; (m) $LiAlH(O^tBu)_3$; (n) MeLi; TsCl; (o) TBAF; (p) HCl, MeOH; (q) TIPSCl, DMAP; (r) Na, liquid NH_3; (s) Swern oxidation; (t) (2*R*,3*R*)-1,4-dimethoxy-2,3-butanediol, *p*-TsOH; (u) PCC, NaOAc; (v) $H_2C{=}CHCH_2MgBr$; (w) Jones oxidation; (x) LAH, LiBr; (y) BnCl, NaO^tAm; (z) OsO_4, $NaIO_4$; (a') $NaBH_4$; (b') BnCl, NaO^tAm; (c') HCl, Me_2CO; (d') $H_2C{=}CHCH_2MgBr$; (e') Jones oxidation; (f') LAH; (g') $(EtCO)_2O$, py, DMAP; (h') OsO_4, $NaIO_4$; (i') $NaBH_4$; (j') TsCl, Et_3N, DMAP; (k') KI; (l') LDA; (m') KOMe, MeOH; *p*-TsOH; (n') DIBAL; (o') CSA, MeOH; (p') Na, liquid NH_3; (q') TsCl, Et_3N; (r') LiSPh; (s') TBSOTf, 2,6-lutidine; (t') *m*-CPBA; (u') recrystallize; (v') $HS(CH_2)_3SH$, BF_3·OEt_2; (w') TBSOTf, 2,6-lutidine; (x') **420**, ^{n}BuLi, HMPA; **421**; (y') BzCl, py, DMAP; (z') 6% Na–Hg.

of **448** using $LiAl(O^tBu)_3H$ then gave **449** with 91% ds. Note that the reduction of ketone **446** apparently involves 1,2-asymmetric induction from an α-alkoxy group, *viz.* the C_{15} MEM ether, whereas reduction of **448** relies on 1,3-asymmetric induction from a β-alkoxy group, namely the same C_{15} MEM ether. The C_{15} hydroxyl stereochemistry originating from (*S*)-malic acid is thus used to direct the introduction of the stereogenic centers at both C_{13} and C_{16}. After tosylation of the C_{13} hydroxyl of **449**, silyl ether cleavage at C_{16} led to *in situ* cyclization, with inversion of configuration at C_{13}, to give the tetrahydrofuran **450**. Protecting group exchange and oxidation at C_{12} then gave aldehyde **421**.

The C_3-C_{11} segment **420** was derived from 3-hydroxy-2,2-dimethylpropanal (**451**). Acetalization of **451** with (2*R*,3*R*)-1,4-dimethoxy-2,3-butanediol[175] was followed by oxidation to the aldehyde at C_9, addition of allylmagnesium bromide, and reoxidation at C_9 to give the ketone **452** bearing a C_2-symmetric chiral auxiliary.[174] $LiAlH_4$ reduction of **452** in the presence of LiBr under carefully controlled conditions furnished **453** and introduced the C_9 stereogenic center with 93% ds. Note that the stereocontrol imparted on the reduction by chelation of the chiral auxiliary is an example of 1,5-asymmetric induction. After protection of the C_9 hydroxyl of the diastereomeric mixture **453**, oxidative cleavage of the alkene was followed by reduction to the C_{11} primary alcohol and subsequent protection of the hydroxyl. Acid-catalyzed removal of the chiral auxiliary then supplied the C_7 aldehyde; reaction with allylmagnesium bromide, followed by oxidation, then afforded the ketone **454**. This was accordingly obtained in 86% ee, since **453** was of 86% de. Chelation-controlled reduction[174] of **454** → **455** then set up the C_7 stereogenic center with 94% ds. After protection of the C_7 hydroxyl of **455** as its propionate, oxidative cleavage of the double bond was followed by a three-step conversion to C_5 iodide **456**. Treatment of **456** with excess LDA effected ring closure, and kinetically controlled protonation of the resulting lithium enolate furnished a 1:1 mixture of C_4 epimers. Upon exposure to methanolic potassium methoxide, this mixture was equilibrated to provide **457** with 94% ds in favor of the desired C_4 stereochemistry. DIBAL reduction of **457** to give the lactol, followed by acid-catalyzed methoxylation, gave a 66:34 mixture of acetal epimers **458** and **459**. Only **458** was taken on to sulfone **420**, but **459** could be equilibrated under acidic conditions to provide more of **458**. Cleavage of the benzyl ethers of **458**; selective monotosylation of the resulting diol at C_{11}; and subsequent thiophenolate displacement, silylation at C_{13}, and subsequent oxidation then afforded the sulfone **459**. This was obtained in 86% ee, but recrystallization allowed the isolation of **459** in enantiomerically pure form. Transacetalization with 1,3-propanedithiol and protection of the resulting C_7 hydroxyl then furnished the C_3-C_{11} segment **420**.

Finally, Julia olefination of aldehyde **421** and sulfone **420**, according to the procedure of Nakata, Oishi, and co-workers,[147b] supplied the Corey intermediate **360** and completed a formal total synthesis of aplasmomycin. Thus, in this synthesis of **360**, one

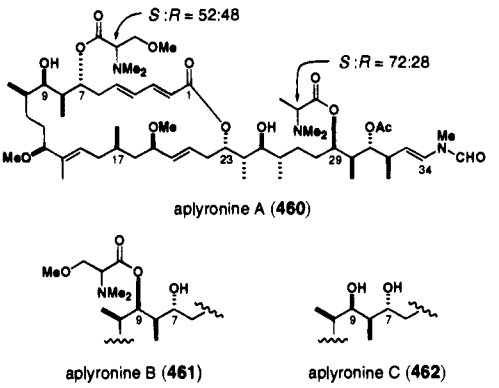


Figure 5. Structures of the aplyronines.

of the five stereogenic centers in the target molecule originated from the chiral pool (C_{15}), one stereogenic center was installed using asymmetric induction from a chiral auxiliary (**452** → **453** for C_9), and the remaining four stereogenic centers were introduced using substrate-controlled reactions (**456** → **457** for C_4, **454** → **455** for C_7, **448** → **449** → **450** for C_{13}, and **446** → **447** for C_{16}). [C_3-C_{17} segment **360**: 1.4% overall yield from **452**; 33 steps longest linear sequence; 52 steps total; ~9 steps per stereogenic center.]

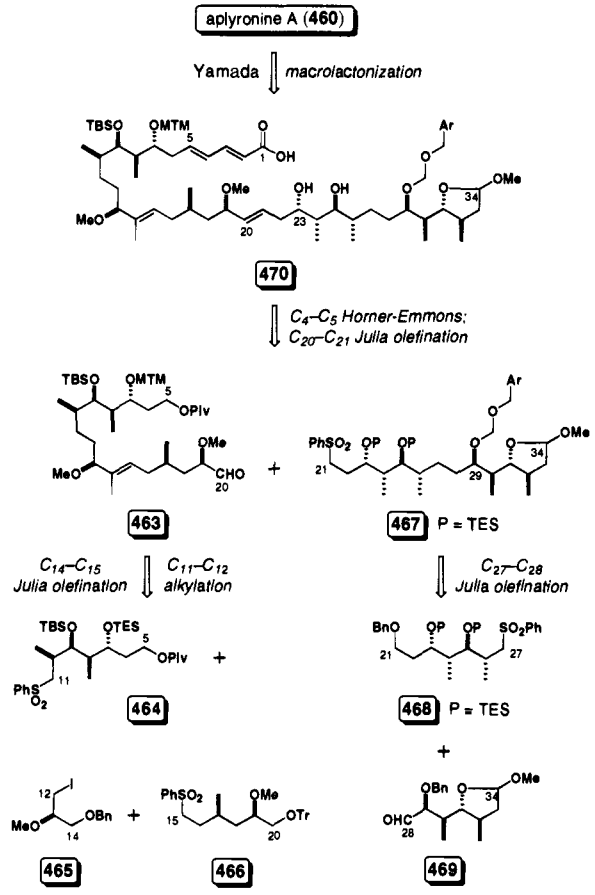
D. The Aplyronines

Aplyronine A (**460** in Figure 5) and its congeners aplyronines B (**461**) and C (**462**) are potent antitumor macrolides, isolated from the Japanese sea hare *Aplysia kurodai*, which were reported by Yamada and co-workers in 1993.[176a-d] In addition to the 24-membered macrocycle, the structures are interesting due to the presence of a terminal *N*-methyl-*N*-vinylformamide unit, as found in several other antitumor marine macrolides,[177] and, in particular, because of the presence of two scalemic[178] amino acid residues. Note that the *N*,*N*,*O*-trimethylserine moiety on C_7 exists as a 2-1.1:1 mixture of *S* and *R* configurations, whereas the *N*,*N*-dimethylalanine moiety on C_{29} exists as a 6-3:1 mixture of *S* and *R* configurations.[176a] Since these isomer ratios vary slightly according to the animal sample employed, it is possible that partial epimerization of the amino acid residues occurs during isolation from the sponge extracts. Yamada and co-workers established the absolute stereochemistry of aplyronine A by enantioselective synthesis of degradation products,[176c,d] and in 1994 completed the total synthesis of alpyronine A itself.[176e,f]

1. Yamada Total Synthesis[176e,f]

Yamada and co-workers designed a highly convergent route to aplyronine A (Scheme 38). Thus a C_5-C_{20} segment (**463**) was constructed by the sequential connection of three segments (**464**-**466**), and a $C_{21}-C_{34}$ segment (**467**) was assembled from two segments (**468** and **469**). Julia coupling[179] of **463** and **467** followed by addition of the C_1-C_4 portion by a Horner-Emmons reaction[180] gave the seco-acid **470**, which was then macrolactonized. The extensive use of sulfone additions in the synthesis is noteworthy, as is the use of acyclic methods of stereocontrol. Evans aldol reactions[65] and Sharpless asymmetric

Scheme 38



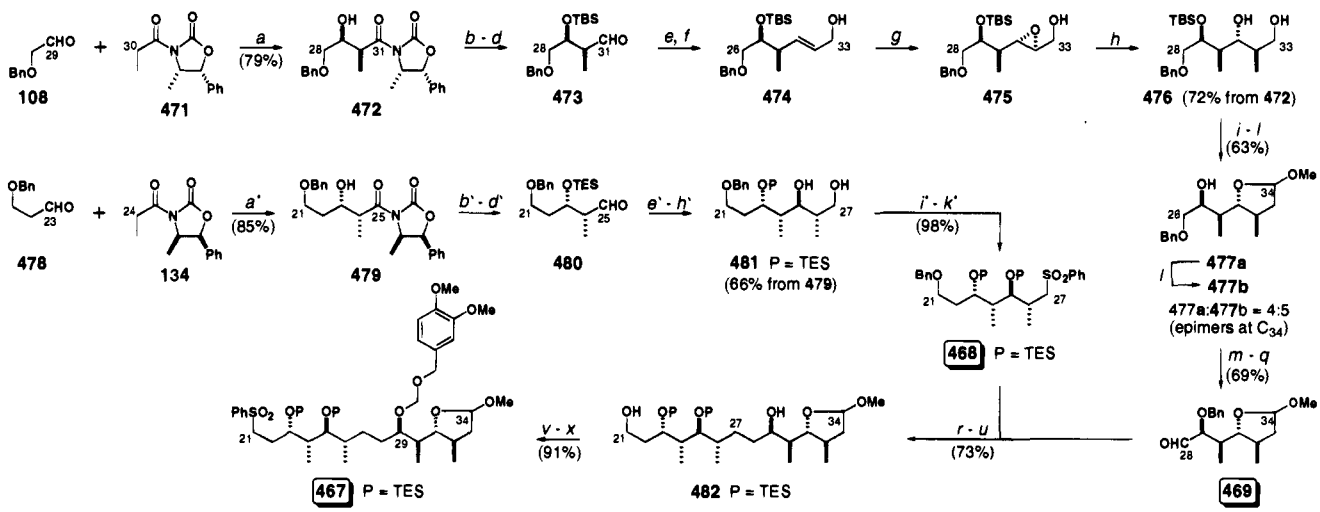
epoxidations[92] were used to construct the three sets of four contiguous stereogenic centers at C_7-C_{10} (as in **464**), $C_{23}-C_{26}$ (as in **468**), and $C_{29}-C_{32}$ (as in **469**).

a. $C_{21}-C_{34}$ Segment Synthesis.[176e] Yamada and coworkers observed that the relative stereochemistry of the two sets of four contiguous stereogenic centers spanning $C_{23}-C_{26}$ and $C_{29}-C_{32}$ of aplyronine A is the same, *i.e. syn-anti-anti*. However, the absolute stereochemistry of one set is opposite to that of the other. Accordingly, the introduction of the stereogenic centers for the $C_{21}-C_{27}$ segment **468** and the $C_{28}-C_{34}$ segment **469** was accomplished using identical methodology, but starting from antipodal starting materials (Scheme 39).

The synthesis of **469** began with the Evans aldol reaction[65] between imide **471** and aldehyde **108** to give **472** with extremely high diastereoselectivity. Transamidation to the Weinreb (*N*-methyl-*N*-methoxy) amide,[181a] protection of the C_{29} hydroxyl, and reduction[181b] at C_{31} then provided the aldehyde **473**, which was homologated at C_{31} by means of a Horner–Emmons reaction and subsequently reduced at C_{33} to give the allylic alcohol **474**. Sharpless asymmetric epoxidation[92] of **474** afforded **475**, which underwent stereo- and regioselective (10:1) opening[182] at C_{32} upon treatment with Me_2CuLi to give diol **476**, which bore the complete *syn-anti-syn* stereorelationship. Transformation of the C_{33} primary hydroxyl of **476** to a cyano group was followed by reduction to give the C_{34} aldehyde and spontaneous formation of a hemiacetal with the C_{31} hydroxyl. Acetalization with acidic methanol and simultaneous deprotection at C_{29} then afforded a separable 4:5 mixture of epimeric acetals **477a** and **477b**. Equilibration of the minor acetal **477a** provided more of **477b**. Protecting group exchange and subsequent oxidation at C_{28} then furnished the $C_{28}-C_{34}$ segment **469**.

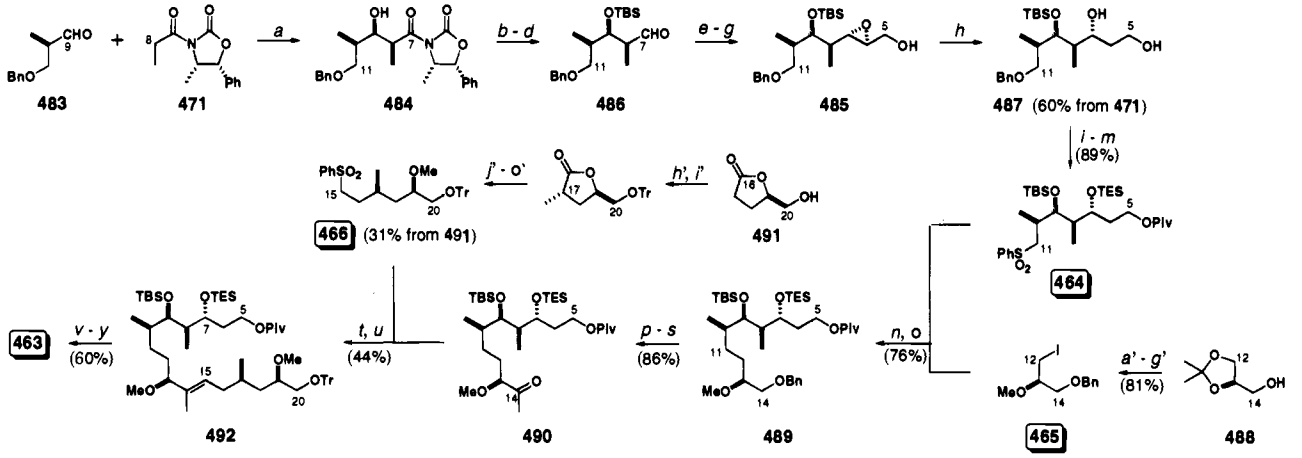
The synthesis of **468** employed the same synthetic strategy as that used for **469**. Thus, an Evans aldol reaction[65] between imide **134** and aldehyde **478** afforded **479**, which was led onto aldehyde **480** in the standard manner. Compound **480** was converted into diol **481** using the same sequence of reactions used to obtain diol **476** from **473**, except that the antipodal Sharpless epoxidation catalyst was now used. Note that the regioselectivity of epoxide opening was only 3:1 in this case. Transformation of the C_{27} primary hydroxyl of **481** to a sulfide group,

Scheme 39. Yamada Aplyronine A $C_{21}-C_{34}$ Synthesis[176e] *a*



[a] (a) **471**, $^nBu_2BOTf$, Et_3N; **108**; (b) $Me_2AlN(Me)OMe$; (c) TBSCl, imidazole; (d) DIBAL; (e) $(^iPrO)_2P(=O)CH_2CO_2Et$, ^{t}BuOK; (f) DIBAL; (g) $Ti(O^iPr)_4$, (+)-DET, ^{t}BuOOH; (h) Me_2CuLi; (i) *p*-TsCl, py; (j) NaCN; (k) DIBAL; (l) CSA, MeOH; (m) Na, liquid NH_3; (n) TBDPSCl, imidazole; (o) BnBr, NaH; (p) TBAF; (q) Swern oxidation; (r) **468**, ^{n}BuLi; **469**; (s) 6% Na–Hg; (t) Ca, liquid NH_3; (u) H_2, 5% $Rh-Al_2O_3$; (v) PhSSPh, $^nBu_3P$; (w) *m*-CPBA; (x) *m,p*-$(MeO)_2C_6H_3CH_2OCH_2Cl$, $^iPr_2NEt$; (a') **134**, $^nBu_2BOTf$, Et_3N; **478**; (b') $Me_2AlN(Me)OMe$; (c') TESCl, imidazole; (d') DIBAL; (e') $(^iPrO)_2P(=O)CH_2CO_2Et$, ^{t}BuOK; (f') DIBAL; (g') $Ti(O^iPr)_4$, (−)-DET, ^{t}BuOOH; (h') Me_2CuLi; (i') PhSSPh, $^nBu_3P$; (j') TESCl, imidazole; (k') *m*-CPBA.

Scheme 40. Yamada Alplyronine A C_5–C_{20} Synthesis[176f a]



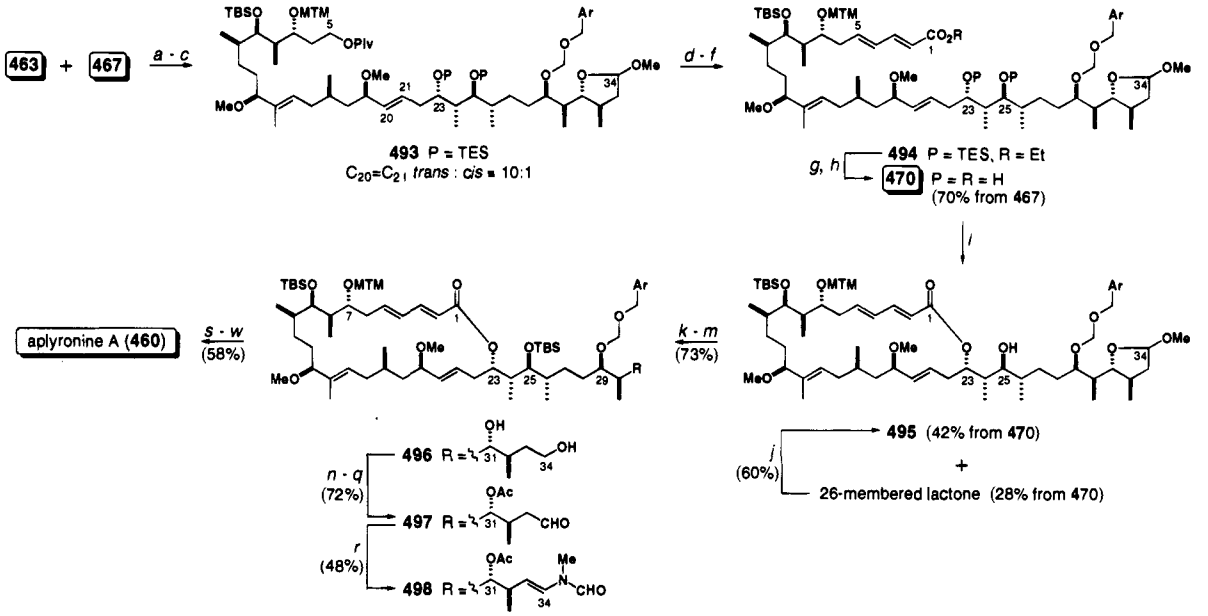
protection of the C_{23} secondary hydroxyl, and subsequent oxidation to the C_{27} sulfone then furnished the C_{21}–C_{27} segment **468**. Note that Yamada and coworkers did not opt for differential protection of the C_{23} and C_{25} hydroxyls, and thus a regioselective lactonization was required later in the synthesis of aplyronine A.

A Julia olefination reaction[179] between the carbanion of sulfone **468** and aldehyde **469**, followed by reductive cleavage of the C_{21} and C_{29} benzyl ethers and hydrogenation of the C_{27}–C_{28} double bond, provided the C_{21}–C_{34} segment **482**. Protection of the C_{29} hydroxyl and transformation to the sulfone at C_{21} then gave **467** [16% overall yield from **471**; 24 steps longest linear sequence; 35 steps total; ~4 steps per stereogenic center].

b. C_5–C_{20} Segment Synthesis.[176f] The construction of the set of four contiguous stereogenic centers spanning C_7–C_{10} of **464** (Scheme 40) was accomplished using methodology similar to that used to set up the stereochemistry of **468** and **469**. Aldehyde **483** was prepared from commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate,[44b] and its Evans aldol reaction[65] with imide **471** then provided **484**. Transformation of **484** to epoxide **485** was accomplished via aldehyde **486**, as for **472** → **473** → **475** (Scheme 39), and regioselective reduction[29] at C_6 of **485** afforded diol **487**. Protection of the C_5 and C_7 hydroxyls and conversion into the sulfone at C_{11} then gave **464**. Alkylation[183] of the carbanion of sulfone **464** with iodide **465** (prepared in seven steps from the glycerol derivative **488**) and subsequent reductive removal of the sulfonyl group furnished the C_5–C_{14} segment **489**, which was then transformed into the C_{14} ketone **490** in a further four steps. The Julia olefination reaction[179] between ketone **490** and sulfone **466** (obtained in eight steps from lactone **491**) provided the desired *trans* olefin **492** (44% yield) along with the undesired *cis* isomer (20%) and the C_{14} tertiary alcohol (23%). Protecting group exchange at C_7 of **492** and deprotection and oxidation at C_{20} then gave the C_5–C_{20} segment **463** [9.0% overall yield from **471**; 25 steps longest linear sequence; 40 steps total; ~6 steps per stereogenic center].

c. Completion of the Total Synthesis of Aplyronine A.[176f] The union of the C_5–C_{20} segment **463** with the C_{21}–C_{34} segment **467** and the completion of the total synthesis of aplyronine A (**460**) by Yamada and coworkers is summarized in Scheme 41. Once again, a Julia olefination reaction[179] was employed, this time to join **463** and **467** to give alkene **493** with high stereoselectivity (C_{20}–C_{21} *trans/cis* = 10:1). Deprotection and Dess–Martin oxidation[27] at C_5 of **493**, followed by installation of the C_1–C_4 section by a Horner–Emmons reaction,[180] then gave **494**. Silyl ether cleavage at C_{23} and C_{25} of **494** and hydrolysis at the C_1 terminus provided seco-acid **470**; Yamaguchi macrolactonization[47] using the modified conditions of Yonemitsu[184] then afforded the desired 24-membered macrolide **495** (42% yield) and a 26-membered lactone (28%).[185] The latter could be isomerized to **495** (2.5:1 equilibrium ratio in favor of **495**, 60–65% isolated yield of **495**) in the presence of $Ti(O^iPr)_4$. After silylation of the C_{25} hydroxyl of **495**, hydrolysis and reduction at C_{34} gave diol **496**, which was converted into aldehyde **497** in a further four steps. Reaction of **497** with *N*-methylformamide in the presence of PPTS and DDQ introduced the terminal *trans*-*N*-methyl-*N*-vinylformamide moiety to give **498**. After oxidative cleavage of the [(*m*,*p*-dimethoxybenzyl)oxy]methyl ether at C_{29} of **498** (note that a [(*p*-methoxybenzyl)oxy]methyl ether at C_{29} could not be cleaved without decomposition of the conjugated lactone), the resulting hydroxyl was acylated[48] with *N*,*N*-dimethylalanine (*S*/*R* = 3:2) to give a diastereomeric mixture of dimethylalanine esters (*S*/*R* = 4:1). Similarly, deprotection at C_7 and acylation[48] with *N*,*N*,*O*-trimethylserine (*S*/*R* = 5:2) afforded a diastereomeric mixture of trimethylserine esters (*S*/*R* = 4:3). Note that the use of optically pure amino acids also afforded diastereomeric mixtures, implying that partial epimerization occurs during introduction of the amino acid residues. It is possible that some kinetic resolution also takes place when

Scheme 41. Yamada Aplyronine A Synthesis[176f] a



[a] (a) **467**, ^{n}BuLi; **463**; (b) Ac_2O, DMAP, py; (c) 5% Na–Hg; (d) DIBAL; (e) Dess–Martin periodinane; (f) $(EtO)_2P(=O)CH_2CH=CHCO_2Et$, LDA; (g) HF·py, py; (h) LiOH; (i) $Cl_3C_6H_2COCl$, Et_3N, DMAP; (j) $Ti(O^iPr)_4$; (k) TBSCl, imidazole; (l) HCl, H_2O; (m) $NaBH(OMe)_3$; (n) TrCl, py; (o) Ac_2O, DMAP, py; (p) HCO_2H; (q) Dess–Martin periodinane; (r) MeNHCHO, PPTS, hydroquinone; (s) DDQ; (t) *N,N*-dimethylalanine (*S*/*R* = 3:2), DCC, DMAP, CSA; (u) $AgNO_3$, 2,6-lutidine, H_2O; (v) *N,N,O*-trimethylserine (*S*/*R* = 5:2), DCC, DMAP, CSA; (w) HF·py, py.

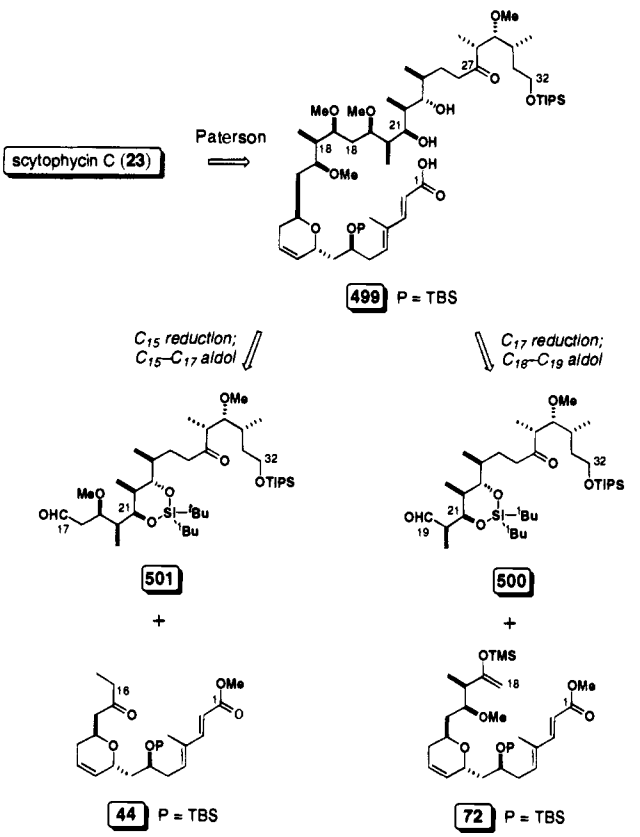
using the scalemic amino acid samples. Finally, silyl ether cleavage at C_9 and C_{25} furnished aplyronine A (**460**). Thus, in this synthesis, five of the stereogenic centers in the target molecule originated from the chiral pool (→ C_{10}, C_{13}, C_{19}, and the two amino acid stereogenic centers), six stereogenic centers were constructed in three auxiliary-controlled Evans aldol reactions (→ C_8, C_9, C_{23}, C_{24}, C_{29}, and C_{30}), three stereogenic centers were installed using chiral reagents via three Sharpless epoxidation reactions (→ C_7, C_{25}, and C_{31}), and the remaining three stereogenic centers (C_{17}, C_{26}, and C_{32}) were set up by reactions relying on substrate control of asymmetric induction. [Aplyronine A (**460**): 0.5% overall yield from **471**; 47 steps longest linear sequence; 98 steps total; ~6–7 steps per stereogenic center.]

E. The Scytophycins

The scytophycins (**23**–**27** in Figure 2) are a class of macrolides which exhibit potent cytotoxicity against human tumor cell lines, as well as displaying broad spectrum antifungal activity.[16] They are isolated from the terrestial blue-green alga *Scytonema pseudohofmanni* and are therefore not marine natural products, and thus, strictly speaking, lie outside the scope of this review. However, in view of the close structural homology[13c] between the C_1–C_{26} portions of swinholide A (**11**) and scytophycin C (**23**), this latter congener does merit some discussion here. Indeed, this structural homology implies a genetic link between the organisms producing the scytophycins and the swinholides (*vide supra*).[186]

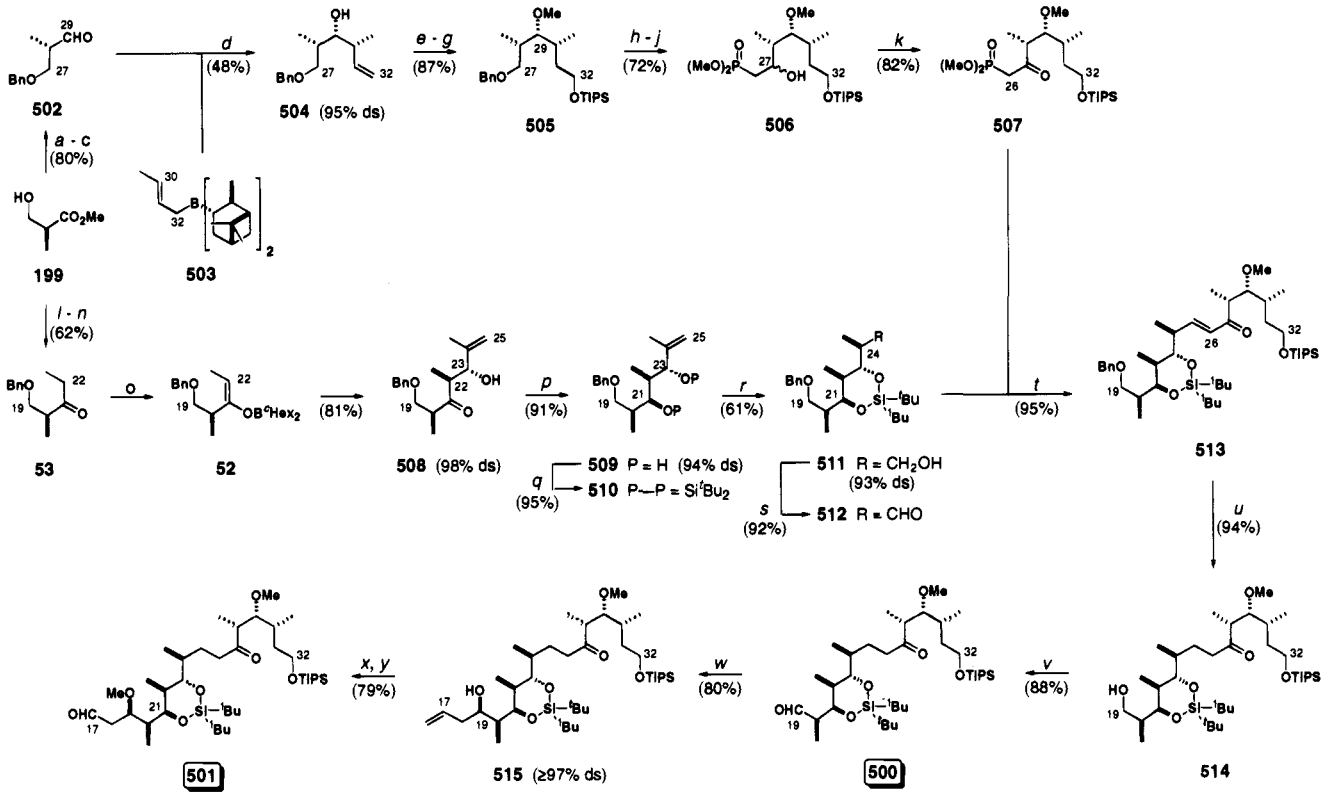
At the time of writing, the total synthesis of scytophycin C has not been reported. Paterson *et al.* have proposed a synthesis involving regioselective macrolactonization of the seco-acid **499**, followed by addition of the vinyl formamide moiety at C_{32} (Scheme 42).[187,188] Two routes to **499** have been outlined.

Scheme 42



Thus, construction of the C_{18}–C_{19} bond by stereoselective aldol union of the silyl enol ether **72** and aldehyde **500**, followed by stereoselective ketone reduction at C_{17} is analogous to the transformation **30** + **72** → **73** → **74** used in the synthesis of swinholide A (Scheme 3).[17f] Alternatively, the C_{16}–C_{17} bond might be constructed by stereoselective aldol union of the ethyl ketone **44** and aldehyde **501**, followed by stereoselective ketone reduction at C_{15}.[187]

Scheme 43. Paterson Scytophycin C C_{17}–C_{32} Synthesis[187] [a]



[a] (a) $Cl_3CC(=NH)OBn$, TfOH; (b) LAH; (c) Swern oxidation; (d) **502** + **503**; H_2O_2, NaOH; (e) MeI, NaH; (f) 9-BBN; H_2O_2, NaOH; (g) TIPSCl, imidazole; (h) H_2, Pd–C; (i) Swern oxidation; (j) $(MeO)_2P(=O)Me$, ^{n}BuLi; (k) PDC; (l) $Cl_3CC(=NH)OBn$, TfOH; (m) Me(MeO)NH·AlMe$_3$; (n) EtMgBr; (o) ^{c}Hex$_2$BCl, Et$_3$N; $H_2C=C(Me)CHO$; H_2O_2; (p) Me$_4$NBH(OAc)$_3$; (q) ^{t}Bu$_2$Si(OTf)$_2$, 2,6-lutidine; (r) 9-BBN; H_2O_2, NaOH; (s) Swern oxidation; (t) **507** + **512**, Ba(OH)$_2$; (u) H_2, Pd–C; (v) Dess–Martin periodinane; (w) $H_2C=CHCH_2TMS$, BF_3·OEt_2; (x) MeOTf, 2,6-di-*tert*-butylpyridine; (y) O_3, $NaHCO_3$; Me_2S.

The syntheses of **44** and **72** have already been described (Schemes 2 and 3, respectively). The preparation of aldehydes **500** and **501** is outlined in Scheme 43.

Anti crotylboration of aldehyde **502**, obtained in three steps from (*S*)-methyl 3-hydroxy-2-methylpropionate (**199**),[44b] using the Brown chiral crotylboron reagent **503**,[43b] afforded homoallylic alcohol **504** with 95% ds, thus setting up the three contiguous stereogenic centers spanning C_{28}–C_{30} of scytophycin C (Scheme 43). After methylation of the C_{29} hydroxyl, hydroboration of the alkene and subsequent protection of the resulting alcohol gave **505**. Debenzylation and oxidation to the C_{27} aldehyde was followed by addition of lithiated methyl dimethylphosphonate to provide β-hydroxy phosphonates **506**, as a 2:1 mixture of C_{27} epimers. Oxidation of this mixture then supplied the β-keto phosphonate **507**. Meanwhile, substrate-controlled aldol addition of methacrolein to the (*E*)-dicyclohexyl enol borinate **52** derived[33] from ethyl ketone **53**, itself obtained from (*S*)-methyl 3-hydroxy-2-methylpropionate (**199**),[34] gave β-hydroxy ketone **508**, having the desired configuration at C_{22} and C_{23}, with 98% ds.[32] Stereoselective reduction of **508** using the Saksena–Evans reagent[35] gave the C_{21},C_{23}-*anti* diol **509** with 94% ds, which was protected as its di-*tert*-butylsilylene derivative **510**. Note that, as was the case in the synthesis of swinholide A,[17a] Paterson *et al.* did not opt for differential protection of the C_{21} and C_{23} hydroxyls, and thus a regioselective lactonization will be required later in the synthesis of scytophycin C. Introduction of the C_{24} stereogenic center was effected by hydroboration of **510** to give **511** with 93% ds. This completed the synthesis of the stereopentad spanning C_{20}–C_{24}. Oxidation of alcohol **511** then afforded the aldehyde **512** and C_{25}–C_{26} bond construction was accomplished by a Horner–Emmons coupling[180] of **507** and **512** to give exclusively the (*E*)-enone **513**. Note the rare use of barium hydroxide as the base in this reaction,[189,190] which proceeded cleanly without β-elimination in the aldehyde **512** or epimerization of either **507** or **512** occurring.[191] Use of the existing Masamune–Roush (LiCl, ^{i}Pr$_2$NEt or DBU)[192a] or Rathke (LiBr or $MgBr_2$, Et_3N)[192b] protocols was unsuccessful in this case. Catalytic heterogeneous hydrogenation of **513** led to debenzylation and 1,4-reduction of the enone to give the alcohol **514**. Dess–Martin[27] oxidation then supplied the C_{19}–C_{32} aldehyde segment **500**. The C_{19} stereogenic center was set up by BF_3·OEt_2-promoted addition of allyltrimethylsilane to **500**, which afforded the desired Felkin–Anh diastereomer **515** with ≥97% ds. Note that use of $TiCl_4$ in this reaction led to much lower diastereoselectivity, providing a 2:1 mixture of C_{19} epimers. Finally, O-methylation[193] of **515** and ozonolysis then furnished the C_{17}–C_{32} aldehyde segment **501**. In this synthesis, five of the seven newly created stereogenic centers were installed by a series of four substrate-controlled reactions (**53** → **508**, **508** → **509**, **510** → **511**, and **500** → **515**); the remaining two were set up in a single reagent-controlled reaction (**502** + **503** → **504**). [C_{17}–C_{32} segment **501**: 9.3% overall yield from **199**; 17 steps longest linear se-

quence; 25 steps total; ~3 steps per stereogenic center.]

F. The Ulapualides and Halichondramides

The ulapualides, *e.g.* ulapualide A (**516** in Figure 6), are a class of tris(oxazole)-containing macrolides which were first isolated from egg masses of the marine nudibranch *Hexabranchus sanguineas*.[194] Similar structurally related macrolides, which have variously been called kabiramides,[195] mycalolides,[196] and halichondramides,[195b,197] *e.g.* **517**, have been isolated from other nudibranches and also from marine sponges.[198] This family of marine metabolites exhibits a wide variety of biological activities, including antifungal, antileukemic, and ichthyotoxic properties. Such a biological profile may in part be associated with the capacity of the metabolites to sequester and transport metal ions *in vivo* using the several oxygen and nitrogen ligand binding sites in their structures.[199]

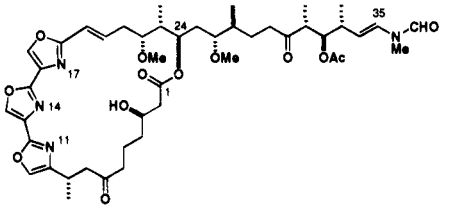
The relative stereochemistries of the ulapualides and halichondramides have not yet been unequivocally established. However, Pattenden and co-workers have remarked[200c,d] that both classes of molecules bear side chains terminating in formyl enamine residues which are very similar to side chains found in the scytophycins, *e.g.* **23**,[16,201] and the aplyronines, *e.g.* **460**.[176a-d] Since the absolute and relative stereochemistries of **23** and **460** have been secured by partial synthesis and/or X-ray crystallography, Pattenden and co-workers have suggested identical configurations for the side chains of ulapualide A (**516**)[200b,d] and halichondramide (**517**)[200c] at the coincident stereogenic centers, as indicated in Figure 6. In addition, Pattenden and co-workers have also proposed a complete stereochemical assignment for ulapualide A (**516**) based on computer modeling studies.[200d] They speculated that if ulapualide A is indeed an ionophore, then the natural stereoisomer will be the one best able to form a metal chelate, *i.e.* that stereoisomer which shows the lowest strain energy for a ulapualide–metal complex. On the basis of molecular mechanics calculations on a ulapualide A–Co(III) complex, the stereochemistry indicated in Figure 6 was predicted. Note that the stereochemical prediction for the side chain so obtained matched exactly that expected by comparison with the side chain of scytophycin C.

At the time of writing, no total syntheses of either ulapualide A or halichondramide have been reported. However, both Yoo[202] and Pattenden and co-workers[200a] have prepared tris(oxazole) segments.[203] In addition, Pattenden and co-workers have come extremely close to synthesizing the ulapualide A macrocycle,[200b] and the side chain of halichondramide has also been prepared by the same research group.[200c]

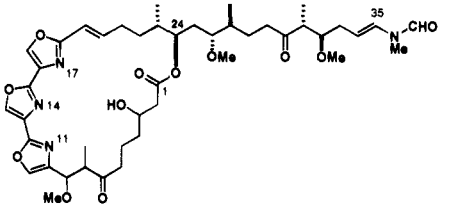
The first synthetic work performed on the ulapualides concerned the preparation of the unprecedented tris(oxazole) segment. The probable biosynthetic pathway to the tris(oxazole) moiety involves cyclization and oxidation of a substituted tris(serine) tripeptide intermediate, and the first synthesis of a contiguous tris(oxazole) (**518** in Scheme 44), by Pattenden and co-workers,[200a] employed three molecules of serine in three sequential oxazoline cyclization–oxidation sequences (the first cyclization being **519** → **520**), according to the method of Meyers and co-workers.[204] Later, Yoo prepared the segment **521**, using three sequential [3 + 2]-cycloaddition reactions of nitriles with dimethyl diazomalonate (the first cycloaddition being **522** + **523** → **524**),[202] following precedent from the work of Helquist and co-workers.[205]

1. Yoo Tris(oxazole) Segment Synthesis[202]

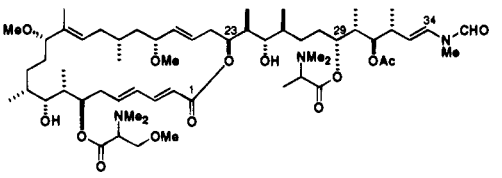
The Yoo tris(oxazole) segment synthesis began with the $Rh_2(OAc)_4$-mediated cycloaddition reaction between dimethyl diazomalonate (**523**) and cyanohydrin **522**, obtained from pivaldehyde (**525**), which afforded oxazole **526** (Scheme 45).[205] Reductive removal of the 5-methoxy group and simultaneous reduction of the 4-methoxycarbonyl moiety then supplied oxazole **527**, and a three-step sequence converted **527** into the nitrile **524**. Repetition of the cycloaddition–reduction–nitrile formation sequence provided the bis(oxazole) **528**. After a third cycloaddition and reduction to give alcohol **529**, adjustment of hydroxyl-protecting groups then furnished the tris-



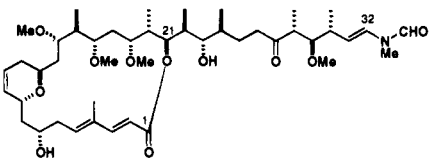
ulapualide A (**516**)



halichondramide (**517**)



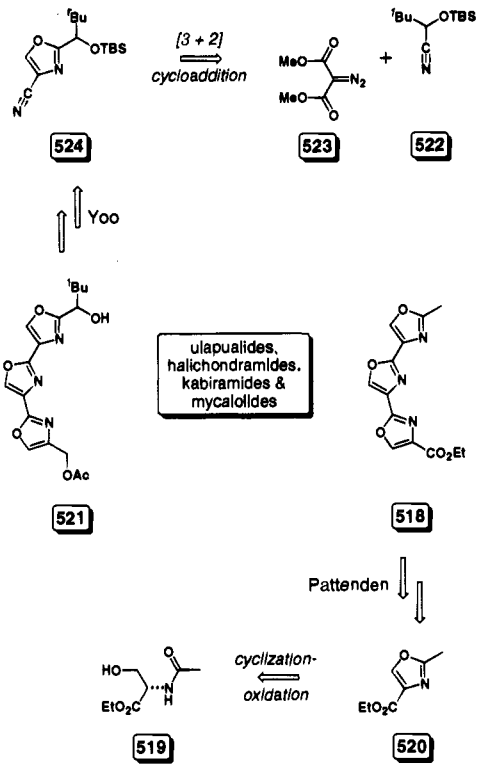
aplyronine A (**460**)



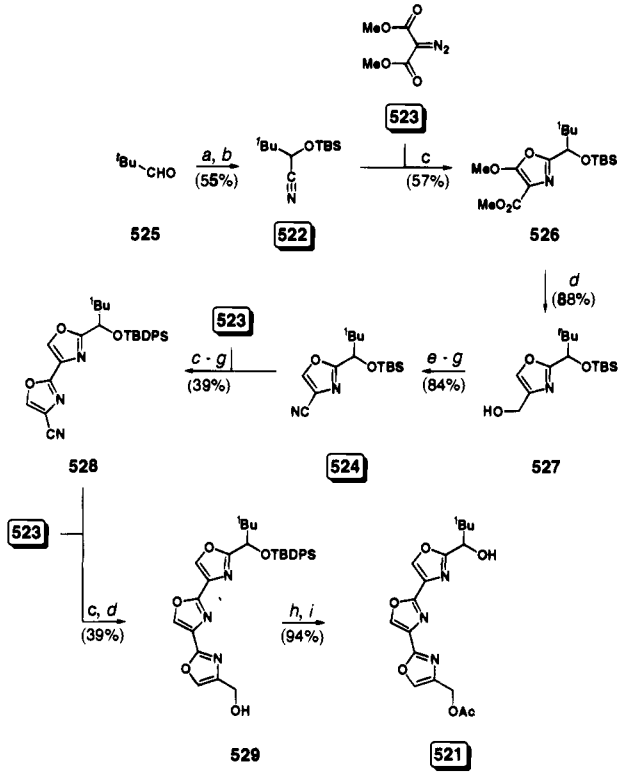
scytophycin C (**23**)

Figure 6. Proposed structures for ulapualide A and halichondramide in comparison with known structures of aplyronine A and scytophycin C.

Scheme 44



Scheme 45. Yoo Halichondramide/Ulapualide A Tris(oxazole) Synthesis[202] a



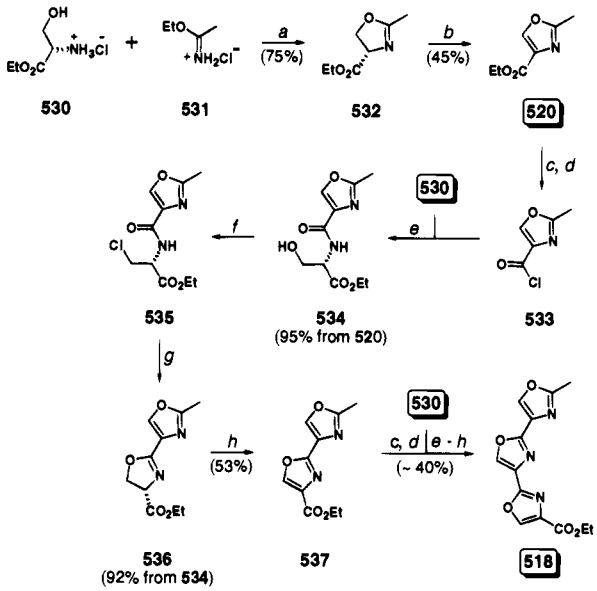
[a] (a) KCN; (b) TBSCl, imidazole; (c) **523**, $Rh_2(OAc)_4$; (d) LAH; (e) Swern oxidation; (f) $NH_2OH{\cdot}HCl$, K_2CO_3; (g) Tf_2O, Et_3N; (h) Ac_2O, Et_3N; (i) TBAF.

(oxazole) segment **521** [3.3% overall yield from **525**; 16 steps].

2. Pattenden Tris(oxazole) Segment Synthesis[200a]

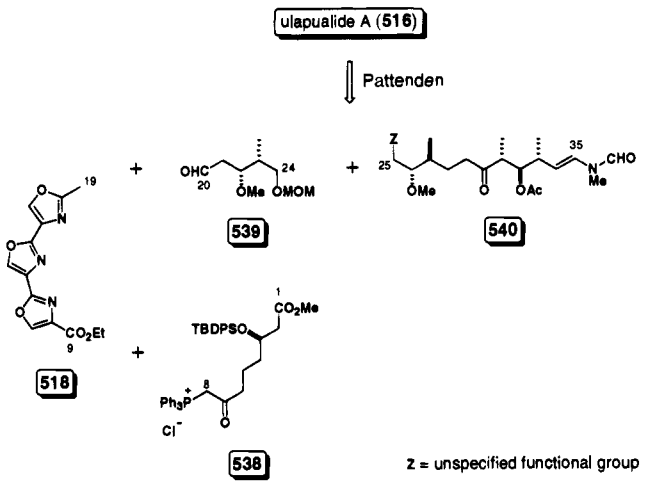
The synthesis of a tris(oxazole) segment by Pattenden and co-workers began with the condensation

Scheme 46. Pattenden Halichondramide/ Ulapualide A Tris(oxazole) Synthesis[200a] a



[a] (a) **530** + **531**, Et_3N; (b) NiO_2, Δ; (c) KOH, H_2O; (d) $SOCl_2$; (e) **530**, Et_3N; (f) $SOCl_2$; (g) AgOTf; (h) NiO_2, Δ.

Scheme 47

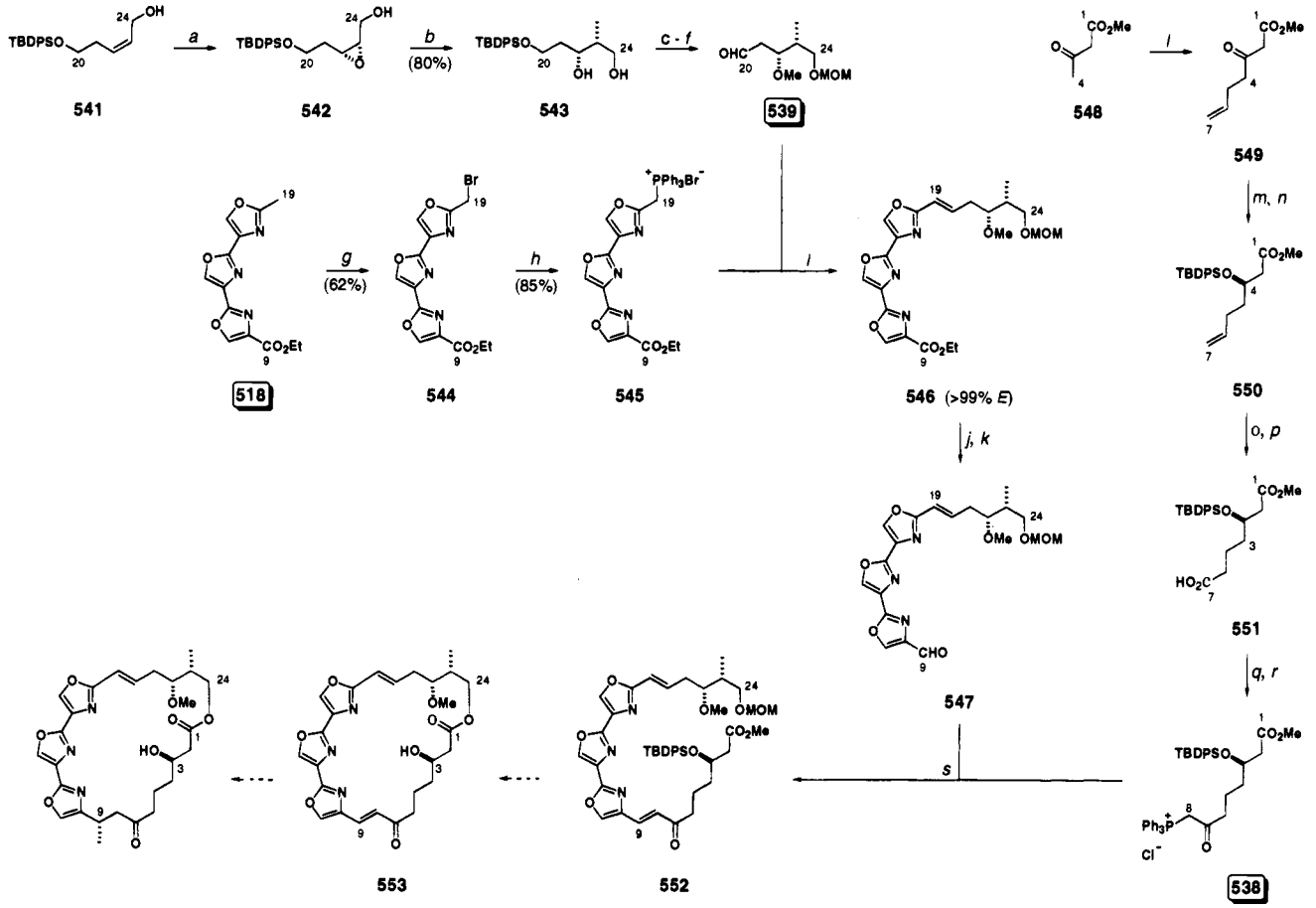


between L-serine ethyl ester hydrochloride (**530**) and ethyl acetimidate hydrochloride (**531**) in the presence of base, which afforded oxazoline **532** (Scheme 46). Oxidation of **532** using nickel peroxide, according to the procedure of Meyers,[204] then gave the oxazole **520**. Saponification of **520** and subsequent formation of the acid chloride **533** was followed by amide formation using a second molecule of **530** to supply **534**. After reaction of **534** with thionyl chloride to provide **535**, AgOTf-induced cyclization[206] furnished **536** and oxidation then gave the bis(oxazole) **537**. Repetition of the sequence of reactions used to transform **520** into **537** then afforded the tris(oxazole) segment **518** [~6% overall yield from **531**; 14 steps].

3. Pattenden C_1–C_{24} Segment Synthesis[200b]

Besides the synthesis of the tris(oxazole) segment **518** spanning C_9–C_{19} of ulapualide A (*vide supra*),[200a] Pattenden and co-workers have also prepared the C_1–C_8 and C_{20}–C_{24} segments **538** and **539** (Scheme 47). Sequential coupling of the segments **518**, **539**, and **538** has been achieved,[200b] to provide a C_1–C_{24}

Scheme 48. Pattenden Ulapualide A C_1–C_{24} Synthesis[200b] [a]



[a] (a) (+)-DET, $Ti(O^iPr)_4$, ^tBuOOH; (b) Me_2CuLi; (c) MOMCl, $^iPr_2NEt$; (d) NaH, MeI; (e) TBAF; (f) Swern oxidation; (g) NBS, AIBN, $h\nu$; (h) PPh_3; (i) **545**, ^tBuOK; **539**; (j) DIBAL; (k) Dess–Martin periodinane; (l) **548**, LDA; $H_2C{=}CHCH_2Br$; (m) Bakers' yeast; (n) TBDPSCl, imidazole; (o) BH_3; H_2O_2; (p) Jones oxidation; (q) $(COCl)_2$; (r) $Ph_3P{=}CH_2$; (s) **538**, base; **547**.

segment of ulapualide A. Cyclization of this segment has not yet been reported; neither has the synthesis of the C_{25}–C_{37} side-chain segment **540**. However, the side chain of halichondramide has been prepared by the same research group (*vide infra*).[200c]

Synthesis of the C_{20}–C_{24} segment **539** began with Sharpless asymmetric epoxidation[92] of the allylic alcohol **541**, which afforded epoxide **542** (Scheme 48). Directed ring opening with lithium dimethylcuprate[182] then supplied the diol **543** with the required configurations at both C_{22} and C_{23}. Protecting group manipulations and adjustment of oxidation state then gave the aldehyde **539**. Meanwhile, bromination of the tris(oxazole) segment **518** at the carbon α to the terminal oxazole furnished the bromide **544**, which was transformed into the phosphonium salt **545**. After an *E*-selective Wittig coupling of **539** and **545**, adjustment of oxidation state in the resulting **546** provided the C_9 aldehyde **547**.

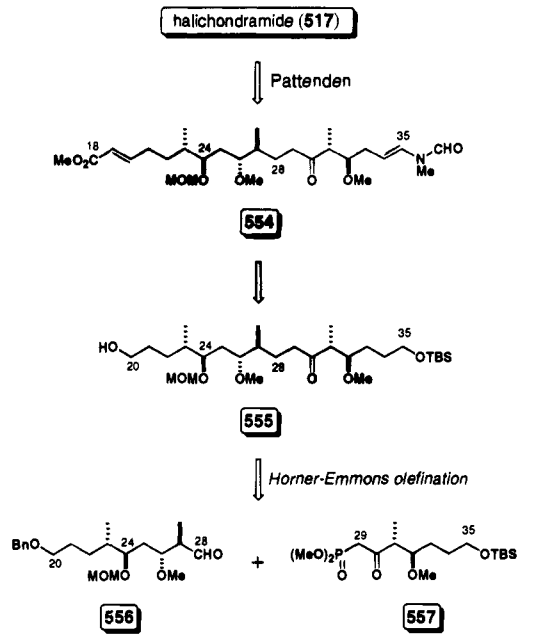
Synthesis of the C_1–C_8 segment **538** began with monoalkylation of the dianion of methyl acetoactetate (**548**) to afford the ketone **549**. Incubation with Bakers' yeast then supplied the corresponding C_3 alcohol with the configuration required for ulapualide A, and protection of the hydroxyl provided **550**. After regioselective hydroboration of **550**, oxidation of the resulting primary alcohol gave the carboxylic acid **551**. This was converted to the corresponding acid chloride, and then to the β-keto phosphonium salt **538**. Wittig coupling of **547** and the ylide derived from **538** furnished the C_1–C_{24} enone segment **552**. Deprotection at both C_1 and C_{24} of **552** to afford the seco-acid, followed by macrolactonization to supply the truncated macrolide **553**, has not yet been reported. Stereoselective introduction of the C_9 methyl group is envisaged via Michael addition of lithium dimethylcuprate to enone **553**, which is expected to proceed in the required stereochemical sense as a consequence of macrocyclic stereocontrol.[207] Pattenden and co-workers have not specified whether the C_{25}–C_{37} side chain is to be introduced before or after macrolactonization.

Thus, in the synthesis of **552**, one of the three stereogenic centers (C_{22}) was installed using a reagent-controlled reaction (**541** → **542**); a second stereogenic center (C_3) was set up using an enzyme-mediated reaction (**549** → **550**); and the third stereogenic center (C_{23}) was introduced via a reaction relying on substrate-controlled asymmetric induction (**542** → **543**). Introduction of a fourth stereogenic center, at C_9 of **553**, is envisaged using macrocyclic stereocontrol. [C_1–C_{24} segment **552**: 20 steps longest linear sequence; 33 steps total.]

4. Pattenden Halichondramide Side Chain Synthesis[200c]

Pattenden and co-workers have synthesized the C_{18}–C_{37} side chain **554** of halichondramide (Scheme 49).[200c] Compound **554** was obtained via elaboration

Scheme 49



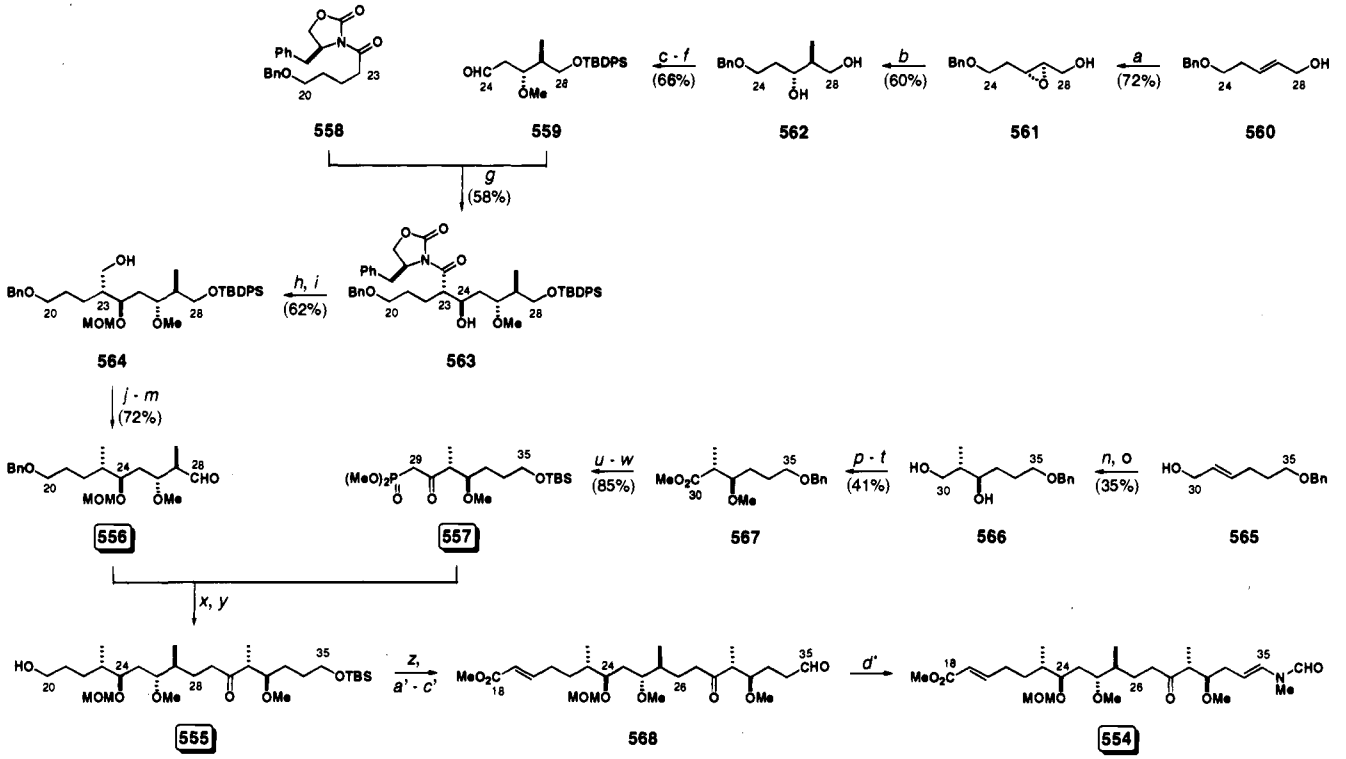
of the $C_{20}-C_{35}$ segment **555**, which was prepared by Horner–Emmons coupling of the $C_{20}-C_{28}$ and $C_{29}-C_{35}$ segments **556** and **557**.

The key step in the synthesis of the $C_{20}-C_{28}$ segment **556** involved an Evans aldol reaction[65] between the chiral oxazolidinone **558** and the $C_{24}-C_{28}$ aldehyde segment **559** (Scheme 50). Synthesis of **559** began with Sharpless asymmetric epoxidation[92] of the allylic alcohol **560**, which afforded epoxide **561**.[208] Directed ring-opening[208] with methylmagnesium bromide in the presence of catalytic CuI then supplied the diol **562** with the required configurations at both C_{26} and C_{27}. Protecting group manipulations and adjustment of oxidation state gave the aldehyde **559**, and addition to the (*Z*)-enol dibutylborinate derived from imide **558** delivered the aldol adduct **563** having the required configurations at both C_{23} and C_{24}. After protection of the C_{24} hydroxyl of **563**, reductive removal[209] of the chiral auxiliary gave **564**. Conversion to the corresponding C_{23}-methyl compound was effected via sequential mesylation followed by hydride displacement; deprotection at C_{28} followed by oxidation then furnished the aldehyde **556** [7.4% overall yield from **560**; 13 steps; ~3 steps per stereogenic center].

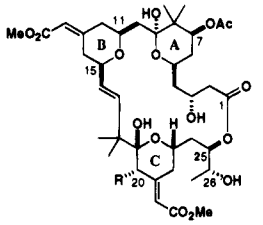
Meanwhile, the $C_{29}-C_{35}$ segment **557** was prepared from allylic alcohol **565**. Thus, **565**[29b] was converted into diol **566**, having the required configurations at C_{31} and C_{32}, via a two-step sequence already used in the transformation of **560** into **562**. Protecting group manipulations and adjustment of oxidation state then gave the ester **567**, which, following a further protecting group interconversion, was used to acylate the anion derived from diethyl methylphosphonate, thus providing **557** [12% overall yield from **565**; 10 steps; 5 steps per stereogenic center].

Horner–Emmons coupling of aldehyde **556** and the β-keto phosphonate **557** proceeded smoothly to afford the (*E*)-alkene; hydrogenation then effected simultaneous reduction of the double bond and hydrogenolysis of the C_{20} ether to supply alcohol **555**. After

Scheme 50. Pattenden Halichondramide $C_{18}-C_{37}$ Synthesis[200c a]



[a] (a) (−)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (b) MeMgBr, CuI; (c) TBDPSCl, imidazole; (d) NaH, MeI; (e) H_2, $Pd(OH)_2$–C; (f) Swern oxidation; (g) **558**, ^{n}Bu_2BOTf, Et_3N; **559**; H_2O_2; (h) MOMCl, ^{i}Pr_2NEt; (i) $LiBH_3$(OMe); (j) MsCl, ^{i}Pr_2NEt; (k) $LiBH_3$(OMe), Δ; (l) TBAF; (m) Swern oxidation; (n) (−)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH; (o) MeMgBr, CuI; (p) TBDPSCl, imidazole; (q) NaH, MeI; (r) TBAF; (s) PDC; (t) AcCl, MeOH; (u) H_2, $Pd(OH)_2$–C; (v) TBSOTf, 2,6-lutidine; (w) $(EtO)_2P(=O)Me$, ^{n}BuLi; (x) **557**, KHMDS; **556**; (y) H_2, $Pd(OH)_2$–C; (z) Swern oxidation; (a') $Ph_3P{=}CHCO_2Me$; (b') TBAF; (c') oxidize; (d') HCONHMe, H^+.



bryostatin 1 (**570**): R = $O_2C(CH)_4(CH_2)_2Me$
7 (**571**): R = OAc
11 (**569**): R = H

Figure 7. Structures of the bryostatins.

oxidation to the C_{20} aldehyde, Wittig reaction with methyl (triphenylphosphoranylidene)acetate led to the (*E*)-α,β-unsaturated ester. Deprotection at C_{35} and oxidation then afforded aldehyde **568**. Finally, reaction with *N*-methylformamide under mild acid catalysis (conditions not specified) furnished the halichondramide $C_{18}-C_{35}$ side-chain segment **554**. In this synthesis, two of the six stereogenic centers were introduced in two reagent-controlled reactions (**560** → **561** and the analogous transformation of **565**), two were installed using substrate-controlled asymmetric induction (**561** → **562** and the analogous preparation of **566**), and two were constructed in a single auxiliary-controlled reaction (**558** + **559** → **563**). [$C_{18}-C_{37}$ segment **554**: 20 steps longest linear sequence from **560**; 30 steps total; 5 steps per stereogenic center.]

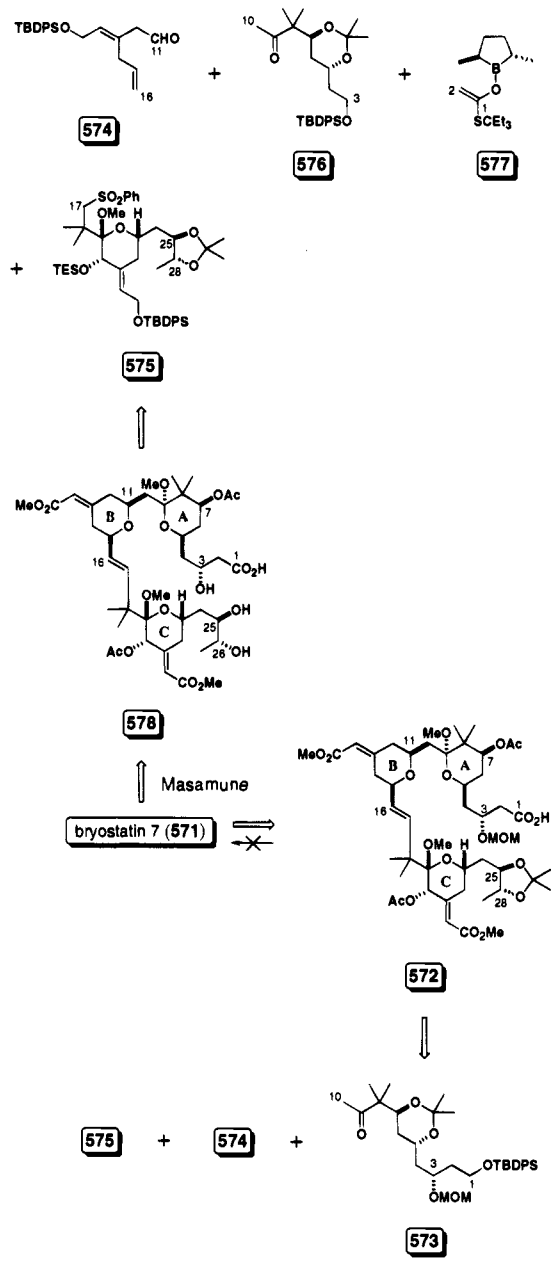
G. The Bryostatins

The bryostatins constitute a class of 17 macrolides, isolated from the marine bryozoans *Bugula neritina* Linnaeus and *Amanthia convoluta*, which exhibit exceptionally high levels of antineoplastic activity against lymphocytic leukemia and ovarian carcinoma,[210] and which have recently reached phase 2 clinical trials.[211] Except for the C_{20}-deoxy analogues, such as bryostatin 11 (**569** in Figure 7),[210h] they differ only in the nature of the ester functions at C_7 and C_{20}. Bryostatins 1 (**570**)[210a] and 7 (**571**),[210e] in particular, have attracted synthetic interest, and the first total synthesis of bryostatin 7 was completed by Masamune and co-workers in 1990.[212e] No other total syntheses have been completed, but several groups[213-218] have reported the synthesis of segments, including significant contributions from the groups of Vandewalle,[213] Roy,[214] Hale,[215] Evans,[216] and Nishiyama and Yamamura.[217]

1. Masamune Total Synthesis[212]

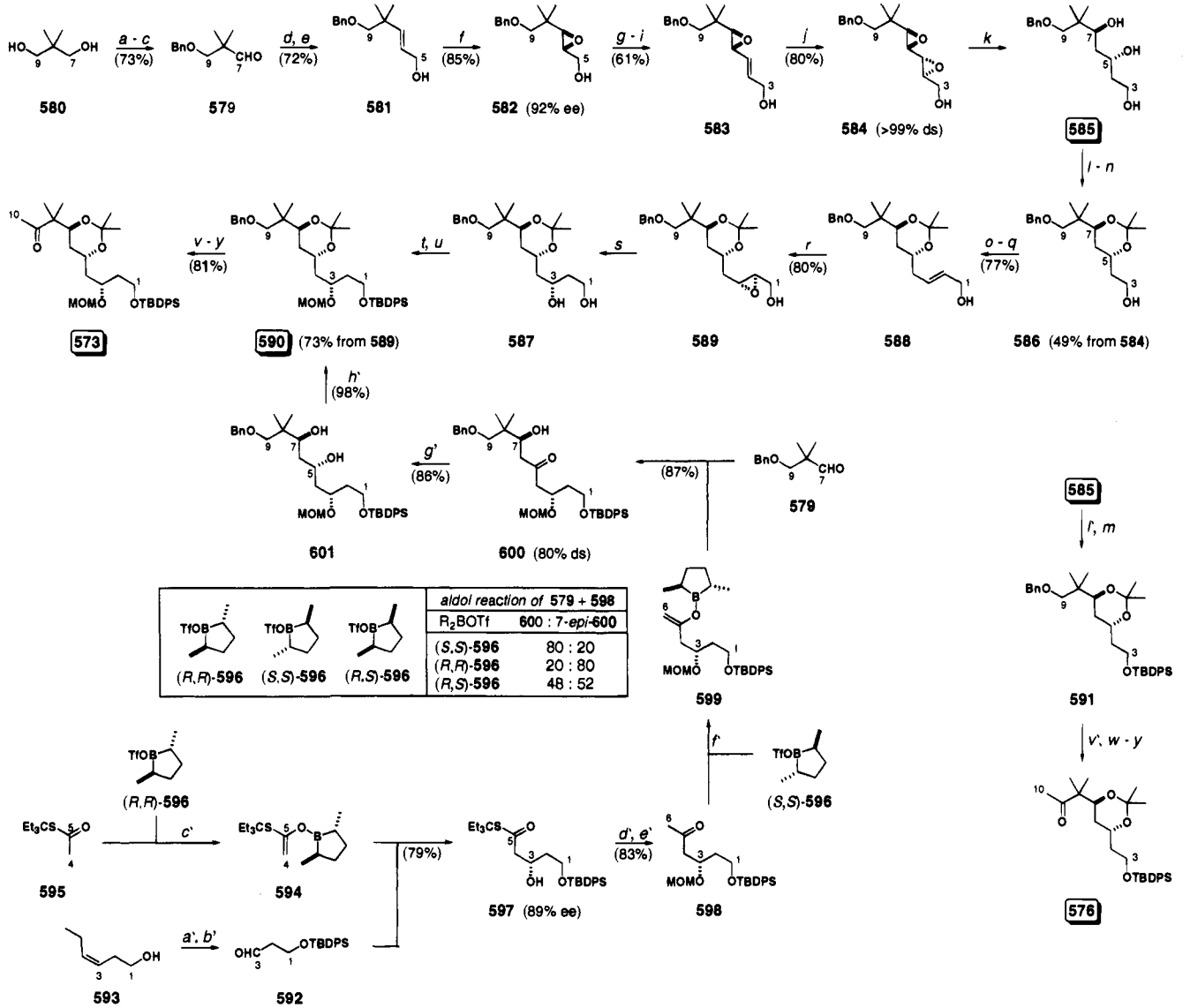
Initial efforts by Masamune and co-workers to synthesize bryostatin 7 culminated in the preparation of the seco-acid derivative **572**, which was obtained via coupling of C_1-C_{10}, $C_{11}-C_{16}$, and $C_{17}-C_{27}$ segments **573**, **574**, and **575**, respectively (Scheme 51).[212a-c] Unfortunately, cleavage of the C_3 MOM ether of **572**, which had been introduced at an early stage, was problematic. Thus the original synthetic route was revised such that creation of the C_3 stereogenic center was postponed until the end of the seco-acid synthesis.[219] Accordingly, sequential connection of the C_3-C_{10} segment **576** (instead of the C_1-C_{10} segment **573**), segments **574** and **575**, and finally the C_1-C_2 segment **577**, followed by deprotection, afforded seco-acid **578**. Macrolactonization then completed the synthesis of bryostatin 7.[212e]

Scheme 51



a. C_1-C_{10} and C_3-C_{10} Segment Syntheses.[212b-d,220] The original route designed by Masamune and co-workers for preparation of the C_1-C_{10} segment **573** exploited methodology developed by Masamune and Sharpless for achieving stereoselective synthesis of 1,3-diols via directed reduction of chiral epoxides.[29a] Thus, Horner–Emmons reaction of aldehyde **579**, obtained from diol **580**, followed by reduction gave the allylic alcohol **581** (Scheme 52). Sharpless asymmetric epoxidation[92] then afforded epoxide **582** with 92% ee. A three-step sequence of oxidation to the C_5 aldehyde, formylolefination, and reduction supplied the allylic alcohol **583**, and Sharpless asymmetric epoxidation[92] then afforded the bis(epoxide) **584** with >99% ds. Note that this second epoxidation using a chiral substrate and a chiral catalyst leads to product **584** of enhanced enantiomeric purity as a result of diastereomer formation. Directed double

Scheme 52. Masamune Bryostatin 7 C_1–C_{10} and C_3–C_{10} Syntheses[212b-d,220] *a*

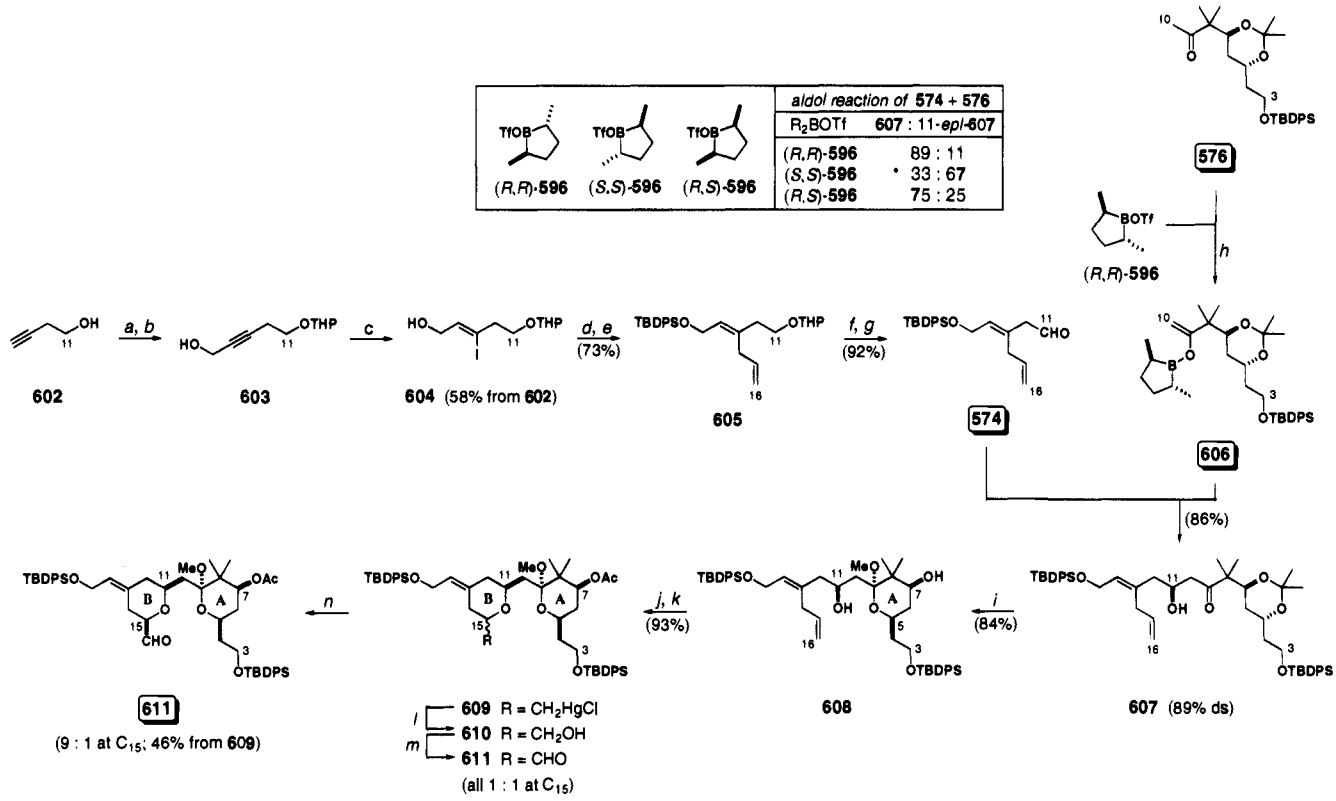


a (a) PhCHO, H^+; (b) $BH_3{\cdot}Me_2S$; (c) PCC; (d) $(EtO)_2P(=O)CH_2CO_2Et$, NaH; (e) DIBAL; (f) (−)-DET, $Ti(O^iPr)_4$, ^tBuOOH; (g) Swern oxidation; (h) $Ph_3P{=}CHCHO$; (i) $NaBH_4$; (j) (+)-DET, $Ti(O^iPr)_4$, ^tBuOOH; (k) Red-Al; (l) ^tBuCOCl, py; (l') TBDPSCl, imidazole; (m) $(MeO)_2CMe_2$, PPTS; (n) DIBAL; (o) Swern oxidation; (p) $(EtO)_2P(=O)CH_2CO_2Et$, NaH; (q) DIBAL; (r) (−)-DET, $Ti(O^iPr)_4$, ^tBuOOH; (s) Red-Al; (t) TBDPSCl, imidazole; (u) MOMBr, $^iPr_2NEt$; (v) Raney Ni; (v') Na, liquid NH_3; (w) Swern oxidation; (x) MeLi; (y) Swern oxidation; (a') TBDPSCl, imidazole; (b') O_3; Me_2S; (c') **595** + (*R,R*)-**596**, $^iPr_2NEt$; **592**; H_2O_2; (d') $(MeO)_2CH_2$, P_2O_5; (e') $LiCuMe_2$; (f') **598** + (*S,S*)-**596**, $^iPr_2NEt$; **579**; H_2O_2; (g') $Me_4NBH(OAc)_3$; (h') $(MeO)_2CMe_2$, PPTS.

reduction[29] of **584** using Red-Al gave the C_5,C_7-*anti* diol **585**. A series of protecting group manipulations then furnished **586**, and a second sequence of Swern oxidation,[38] Horner–Emmons olefination, reduction, Sharpless epoxidation,[92] and Red-Al reduction[29] then afforded diol **587** (*i.e.* **586** → **588** → **589** → **587**, *cf.* **582** → **583** → **584** → **585**). After differential protection of the C_1 and C_3 hydroxyls of **587** to give **590**,[221] a four-step sequence of (i) deprotection at C_9, (ii) oxidation to the C_9 aldehyde, (iii) methyllithium addition, and (iv) reoxidation at C_9 provided the C_1–C_{10} segment **573**.

Due to the number of functional group transformations and protecting group manipulations, the above linear route to **573** involved 25 steps [3.9% overall yield from **580**], which was considered too many for a target containing only three stereogenic centers. However, by applying Masamune's asymmetric aldol methodology using chiral boron reagents,[222] a shorter and more efficient convergent synthesis of **573** was developed. Thus, aldehyde **592**, which was obtained from *cis*-3-hexen-1-ol (**593**), underwent an enantioselective aldol reaction with the chiral enol borinate **594** derived from thioacetate **595** and the chiral boron triflate reagent (*R,R*)-**596**,[222] to provide the aldol adduct **597** with 89% ee (Scheme 52). Compound **594** thus served as a chiral acetate equivalent. After protection of the C_3 hydroxyl of **597**, treatment with lithium dimethylcuprate[223] supplied the methyl ketone **598**. Regioselective kinetic enolization of **598** in the presence of the chiral boron triflate reagent (*S,S*)-**596** afforded the enol borinate **599**, and aldol addition to aldehyde **579** then delivered the aldol adduct **600** with 80% ds in favor of the required configuration at C_7. Note that aldol reaction using the antipodal chiral reagent (*R,R*)-**596** proceeded with equal and opposite diasteroselectivity, furnishing the epimeric adduct 7-*epi*-**600** with 80% ds. Note

Scheme 53. Masamune Bryostatin 7 C_3–C_{16} Synthesis[212c-e a]



[a] (a) DHP, PPTS; (b) ^{n}BuLi, HCHO; (c) Red-Al; I_2; (d) TBDPSCl, imidazole; (e) $H_2C{=}CHCH_2MgBr$, CuI; (f) PPTS, EtOH; (g) $(py)_2CrO_3$; (h) **576** + (*R,R*)-**596**, ^{i}Pr$_2$NEt; **574**; H_2O_2; (i) $(MeO)_3CH$, MeOH, PPTS, (j) $Hg(OAc)_2$; KCl; (k) Ac_2O, py, DMAP; (l) $NaBH_4$, O_2; (m) Swern oxidation; (n) Al_2O_3, H_2O.

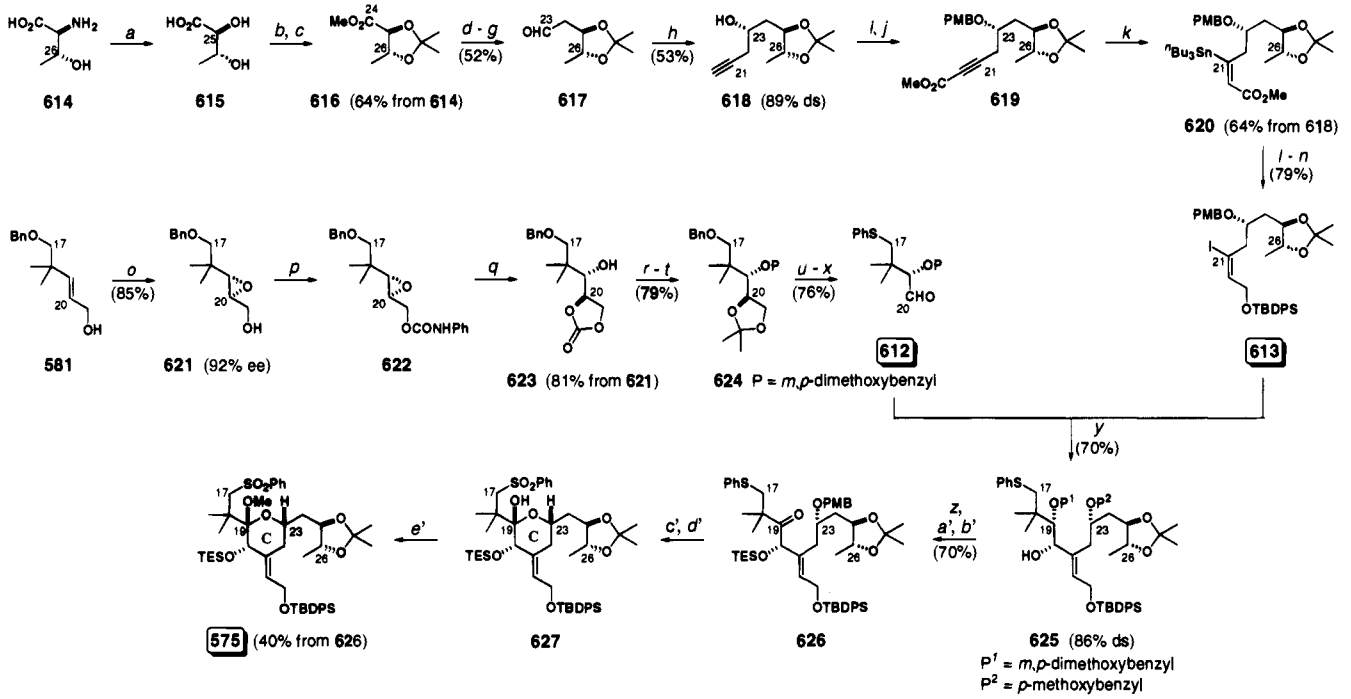
also that use of the achiral meso reagent (*R,S*)-**596** resulted in an approximately 1:1 ratio of **600** and 7-*epi*-**600**. Hence, there is negligible substrate control of asymmetric induction in this reaction, and control comes almost entirely from the chiral reagents employed. In addition, by using a chiral boron reagent, the aldol reaction of ketone **598** leads to product **600** of enhanced enantiomeric purity as a result of diastereomer formation. Reduction of β-hydroxy ketone **600** using the Saksena–Evans reagent[35] gave the C_5,C_7-*anti* diol **601** which was then protected as its acetonide **590**. Compound **590** was converted into the C_1–C_{10} segment **573** as before. In this revised synthetic route, **573** was obtained in approximately half the previous number of steps [12 steps longest linear route; 15 steps total; 5 steps per stereogenic center] and in 31% overall yield from **592**. In the initial route to **573**, all three stereogenic centers were installed using chiral reagents via three Sharpless epoxidation reactions. In this latter approach, two of the stereogenic centers were constructed using reagent control (**592** + **595** → **597** and **579** + **598** → **600**) and the third was set up using substrate control (**600** → **601**).

The C_1–C_{10} segment **573** was used in the synthesis of protected seco-acid **572** in the initial approach to bryostatin 7 (*vide supra*).[212a-c,219] However, in the revised synthetic route, the C_3–C_{10} segment **576** was required. This was obtained via a modification of the initial route to **573**.[220] Thus, selective silylation[221] of the primary hydroxyl of **585** and subsequent acetonide protection of the secondary hydroxyls provided **591**, which was transformed into the methyl ketone **576** in an analogous manner to the conversion of **590** into **573**. Accordingly, the C_3–C_{10} segment **576** was prepared in 17 steps from **580** [*i.e.* 8–9 steps per stereogenic center].

b. C_{11}–C_{16} Segment Synthesis and Coupling to C_3–C_{10} Segment.[212c-e] Preparation of the C_{11}–C_{16} segment **574** required stereoselective construction of the C_{13} exocyclic double bond. This was achieved by application of Corey's methodology for the synthesis of trisubstituted olefins.[224a] Thus, after protection of the hydroxyl of **602**, alkynyllithium formation, and addition to formaldehyde provided propargylic alcohol **603** (Scheme 53). Reduction with Red-Al[224b] followed by iodination then gave selectively the (*Z*) iodoolefin **604**, and hydroxyl protection followed by copper-catalyzed allyl Grignard addition afforded **605** with the required configuration of the C_{13} exocyclic double bond. Deprotection at C_{11} followed by oxidation then gave the C_{11}–C_{16} segment **574**.

Stereoselective construction of the C_{10}–C_{11} bond was accomplished by means of an aldol reaction between aldehyde **574** and the enol borinate **606** derived from enolization of ketone **576** using the chiral boron reagent (*R,R*)-**596**.[212d,222] Accordingly, the β-hydroxy ketone **607** was obtained with 89% ds in favor of the required configuration at C_{11}. Note that this is a *matched* double-diastereodifferentiating reaction:[9b] use of the achiral *meso* reagent (*R,S*)-**596** still afforded **607** as the major adduct, but with diminished diastereoselectivity (75% ds), indicating the degree of substrate control of asymmetric induction. In the *mismatched* case using the antipodal chiral reagent (*S,S*)-**596**, reagent control dominated substrate control and the epimeric product 11-*epi*-

Scheme 54. Masamune Bryostatin 7 C_{17}–C_{27} Synthesis[212b a]



[a] (a) $NaNO_2$, H_2SO_4, H_2O; (b) MeOH, AcCl; (c) $(MeO)_2CMe_2$, *p*-TsOH; (d) DIBAL; (e) $Ph_3P{=}CH_2$; (f) Sia_2BH; H_2O_2; (g) PCC; (h) allenylZnBr; (i) NaH, PMBCl; (j) ^{t}BuLi; $ClCO_2Me$; (k) ^{n}Bu$_3$SnCu·LiBr·Me_2S, MeOH; (l) DIBAL; (m) TBDPSCl, imidazole; (n) I_2; (o) (+)-DET, Ti(O^iPr)$_4$, ^{t}BuOOH; (p) PhNCO, Et_3N; (q) BF_3·OEt_2, H_2SO_4, H_2O; (r) K_2CO_3, MeOH; (s) $(MeO)_2CMe_2$, PPTS or $(MeO)_3CH$, *p*-TsOH; (t) NaH, *m,p*-dimethoxybenzyl chloride; (u) Raney Ni; (v) MsCl, Et_3N; PhSNa; (w) HCl, MeOH; (x) $NaIO_4$; (y) **613**, ^{n}BuLi; **612**; (z) TESOTf, 2,6-lutidine; (a') DDQ (1 equiv); (b') DMSO, Ac_2O; Et_3N; (c') MoO_5·HMPA·H_2O; (d') DDQ; SiO_2; (e') TMSOTf, TMSOMe or BF_3·OEt_2, MeOH.

607 was produced as the major diastereomer with 67% ds.[212d]

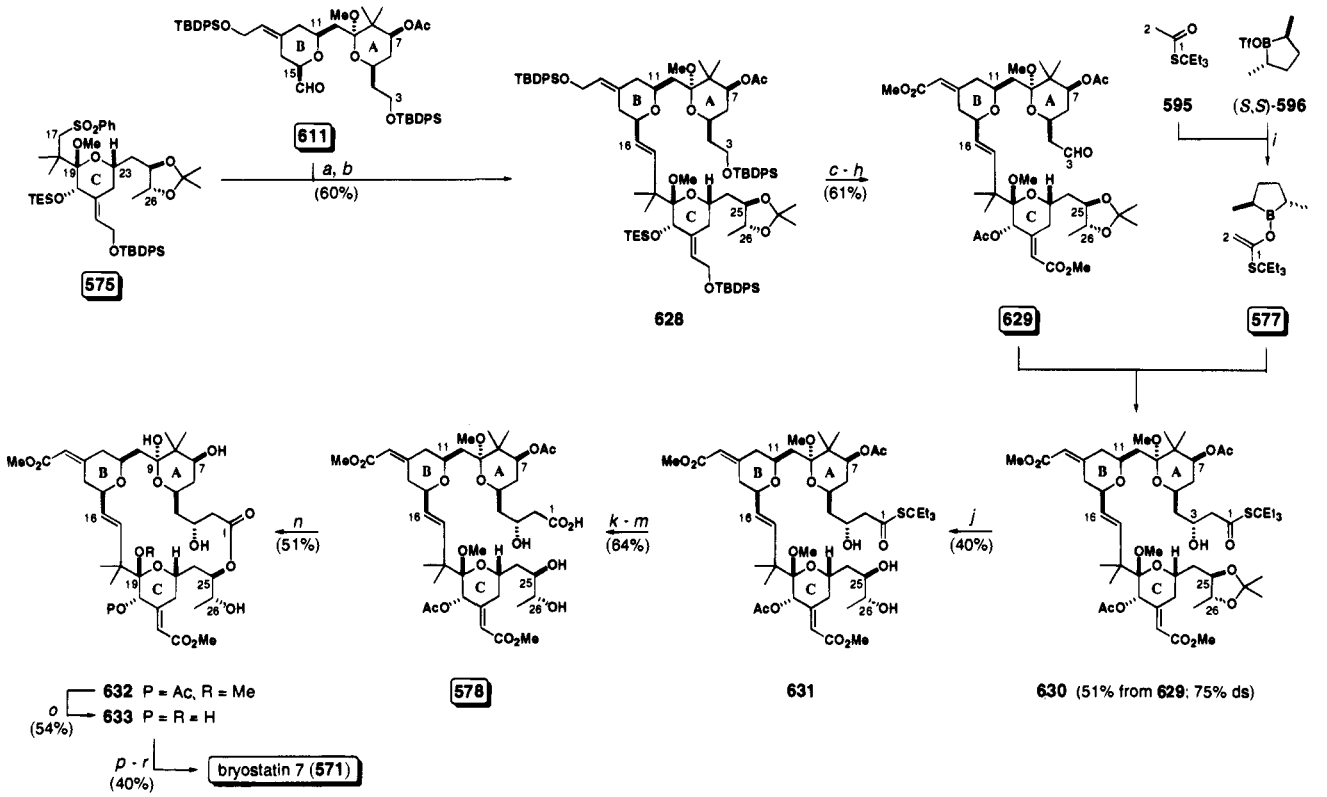
Acid-catalyzed cleavage of the C_5,C_7 acetonide in **607** triggered simultaneous acetalization at C_9 to provide **608** with the correctly assembled A ring. Formation of the B ring was achieved by oxymercuration of the terminal double bond of **608**; acetylation of the C_7 hydroxyl then furnished **609** as a mixture of C_{15} epimers. After oxidative demercuration[225] to give alcohol **610**, Swern oxidation[38] afforded aldehyde **611** as a 1:1 mixture of C_{15} epimers. Upon exposure to alumina, however, equilibration was effected to afford a 9:1 ratio in favor of the desired equatorially disposed aldehyde **611**. Thus, in the synthesis of the C_3–C_{16} segment **611**, one of the three newly created stereogenic centers was constructed using reagent control of asymmetric induction (**574** + **606** → **607** for C_{11}); the other two were installed by substrate-controlled reactions (**607** → **608** for C_9, and thermodynamic equilibration of aldehyde **611** for C_{15}). [C_3–C_{16} segment **611**: <5% overall yield from **580**; 24 steps longest linear sequence; 31 steps total; ~6 steps per stereogenic center.]

c. C_{17}–C_{27} Segment Synthesis.[212b] The C_{17}–C_{27} segment **575** was constructed via the coupling of C_{17}–C_{20} and C_{21}–C_{27} segments **612** and **613** (Scheme 54). Compound **613** was prepared from L-threonine (**614**). Thus, deamination of **614** gave **615**, with retention of configuration at C_{25},[225] and esterification followed by acetonide formation then supplied **616**.[226] After reduction to the corresponding C_{24} aldehyde, homologation to provide **617** was effected by a three-step sequence of Wittig olefination, hydroboration, and oxidation. Chelation-controlled addition of allenylzinc bromide to **617** then furnished alkyne **618** with 89% ds in favor of the required configuration at C_{23}. After protection of the C_{23} hydroxyl, alkynyllithium formation, and addition to methyl chloroformate afforded the acetylenic ester **619**. Stereoselective introduction of the exocyclic double bond at C_{21} was accomplished by using Piers' method.[228] Thus conjugate addition of a (tributylstannyl)cuprate to **619** gave **620**. After reduction of the ester and protection of the resulting alcohol, replacement of the tributylstannyl group with iodine then afforded **613**.

Meanwhile, aldehyde **612** was prepared from allylic alcohol **581**, which was used in the synthesis of the C_3–C_{10} segment **576**, via a sequence of reactions developed by Masamune and Sharpless for saccharide synthesis.[229] Thus, Sharpless epoxidation[92] of **581** afforded **621** with 92% ee; **621** was then converted into the phenylurethane **622** and exposure to BF_3·OEt_2 led to formation of the carbonate **623** with inversion of configuration at C_{20}.[229] After a sequence of protecting group manipulations to give **624**, deprotection at C_{17} was followed by mesylation and thiophenolate displacement. Acetonide removal followed by oxidative glycol cleavage then furnished the C_{17}–C_{20} segment **612**.

The stereogenic center at C_{19} of **612** was used to direct the introduction of stereochemistry at C_{20}, and, having served its purpose, was then destroyed through oxidation. Thus, chelation-controlled coupling of aldehyde **612** with the lithio anion derived from iodide **613** afforded the C_{17}–C_{27} segment **625** with 86% ds in favor of the required configuration at C_{20}. After protection of the C_{20} hydroxyl, selective cleavage of the C_{19} *m,p*-dimethoxybenzyl ether in the presence of the C_{23} *p*-methoxybenzyl ether[42b,230] was followed by oxidation at C_{19} to supply ketone **626**.

Scheme 55. Masamune Bryostatin 7 Synthesis[212e] [a]



[a] (a) **575**, PhLi; **611**; BzCl, DMAP; (b) Na–Hg, Na_2HPO_4; (c) TBAF; (d) TBSCl, imidazole; (e) Ac_2O, py, DMAP; (f) TBAF; (g) MnO_2; MeOH, NaCN, AcOH; (h) Swern oxidation; (i) **595** + (*S*,*S*)-**596**, $^iPr_2NEt$; **629**; H_2O_2; (j) CSA, MeOH; (k) TESOTf, 2,6-lutidine; (l) $Hg(O_2CCF_3)_2$, Na_2HPO_4; (m) HF·py; (n) DCC, PPTS, py; (o) K_2CO_3, MeOH; 5% HCl, H_2O; (p) TBSCl, Et_3N, DMAP; (q) Ac_2O, py; (r) HF.

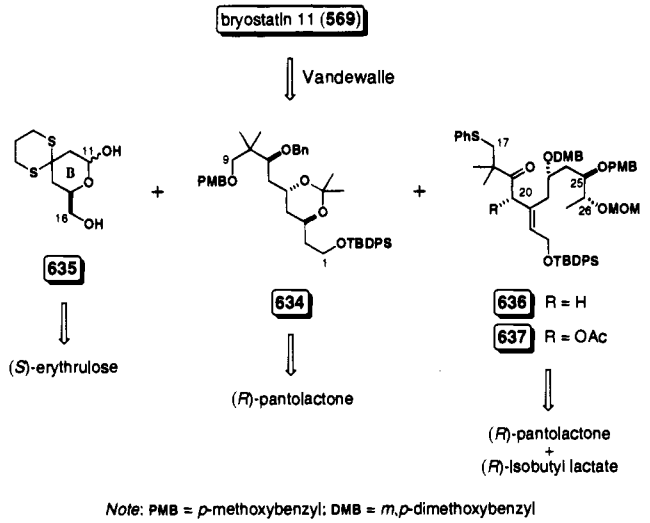
Deprotection at C_{23} and subsequent intramolecular hemiacetal formation then furnished **627**. Finally, methoxylation of **627** under forcing conditions[231] gave the C_{17}–C_{27} segment **575** having all stereogenic centers in the C ring correctly installed. Thus, in the synthesis of **575**, two stereogenic centers originated in the chiral pool, and the remaining three were installed by substrate-controlled reactions. One of the substrate-controlled reactions (**612** + **613** → **625**) relied on asymmetric induction from a stereogenic center, created using reagent control, which was later destroyed. Note that in **575**, Masamune and co-workers opted to forego the possibility of differential protection of the C_{26} and C_{25} hydroxyls. Hence a regioselective macrolactonization would be required later in the synthesis. [C_{17}–C_{27} segment **575**: 1.3% overall yield from **614**; 22 steps longest linear sequence; 36 steps total; ~7 steps per stereogenic center.]

d. Completion of the Total Synthesis of Bryostatin 7.[212e] The C_3–C_{16} and C_{17}–C_{27} segments **611** and **575** were coupled by means of a Julia–Lythgoe reaction[179] using phenyllithium as base (Scheme 55). Note that the choice of base was critical: because of the steric congestion around C_{17}, weaker bases such as lithium amide bases (LDA, $LiNEt_2$) were ineffective; stronger carbon bases (^{n}BuLi, ^{t}BuLi) led to concomitant formation of arylic anions. A reductive elimination reaction, performed in the presence of Na_2HPO_4 in order to retain the C_7 acetate group,[232] then furnished **628** with the required *trans* double bond at C_{16}–C_{17}. After a series of protecting group manipulations and adjustment of oxidation state to afford **629**, introduction of the C_1–C_2 unit was effected by means of a reagent-controlled[222] double diastereodifferentiating aldol reaction. Thus addition of the chiral enol borinate **577** to aldehyde **629** provided β-hydroxy thioester **630** with 75% ds in favor of the required configuration at C_3. Note that **577** and **629** constitute a mismatched pair,[9b] and hence reagent control from **577** is required to overturn the intrinsic diastereofacial preference of **629**. With the carbon skeleton of bryostatin 7 now intact, selective cleavage of the acetonide of **630** gave the seco-acid derivative **631**. All attempts to achieve direct macrolactonization of **631** using a thiophilic metal cation[233] failed, and hence **631** was converted into the seco-acid **578**. Macrolactonization of **578** was effected by employing a modification of the procedure of Boden and Keck[48] (DCC, with pyridine and PPTS in place of DMAP). Note that cyclization occurred selectively at C_{25}, without the need for protection of the C_{26} hydroxyl. The C_9 methyl acetal and C_7 acetate were hydrolyzed under the reaction conditions, affording macrolide **632**. The C_{19} methyl acetal could not be hydrolyzed (note that forcing conditions[231] were required for its creation: **627** → **575** in Scheme 54) unless the electron-withdrawing acetate group at C_{20} was first removed. Selective silylation of the C_{26} hydroxyl of **633** followed by reacetylation and desilylation then furnished bryostatin 7 (**571**) [5×10^{-3}% overall yield from **614**; 42 steps longest linear sequence; 80 steps total; ~7 steps per stereogenic center].

2. Vandewalle Segment Syntheses[213]

Vandewalle and co-workers have synthesized the three bryostatin 11 segments depicted in Scheme 56: C_1–C_9 segment **634**, C_{11}–C_{16} segment **635**, and

Scheme 56

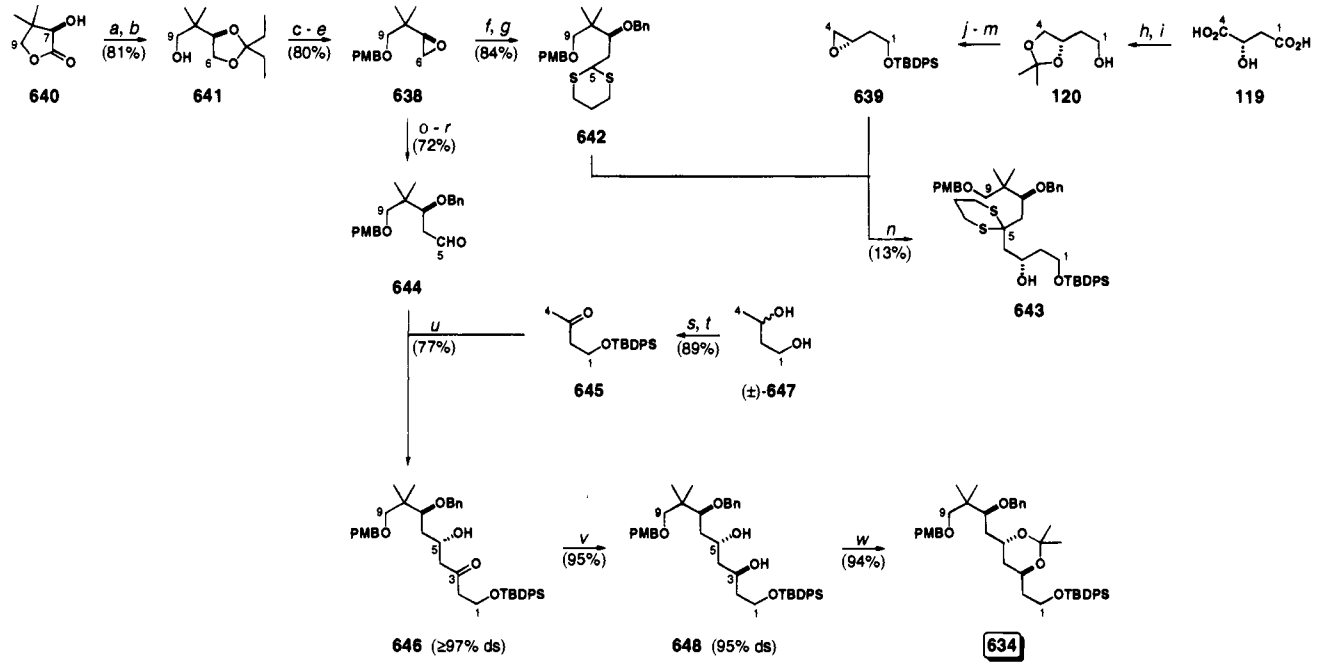


C_{17}–C_{27} segment **636**. Preparation of a C_{17}–C_{27} segment **637**, suitable for bryostatin 7, was also attempted. The total synthesis has not yet been reported, but assembly of segments **634** and **635** using a β-keto phosphonate to introduce C_{10}, subsequent construction of the C_{16}–C_{17} bond by a Julia–Lythgoe olefination reaction,[179] and final macrolactonization has been proposed.[213c] Vandewalle and co-workers adopted the "chiron" approach,[8] whereby **634**–**636** were all prepared from starting materials available from the chiral pool, as indicated in Scheme 56.

a. C_1–C_9 Segment Synthesis.[213a,c] Vandewalle and co-workers investigated two different routes to the C_1–C_9 segment **634**, both starting from epoxide **638** (Scheme 57). The first, abortive, approach centered on the successive coupling of epoxides **638** and **639** to dithiane, which provided C_5. After dithiane cleavage, the stereogenic center at C_5 was to be installed by a 1,3-*anti* selective reduction of a β-hydroxy ketone. Epoxide **639** was available from (*S*)-malic acid (**119**) via alcohol **120**[60] (*cf.* **119** → **120** → **121** in Scheme 8). Epoxide **638**, meanwhile, was derived from (*R*)-pantolactone (**640**) following the route of Lavallée *et al.*[234] Thus, reduction of **640** followed by acetalization provided exclusively the C_6,C_7-pentylidene acetal **641**; protection of the C_9 hydroxyl, acetal hydrolysis, and subsequent tosylimidazole-mediated epoxide formation then supplied **638**. Reaction of **638** with 2-lithiodithiane followed by protection of the resulting C_7 hydroxyl furnished **642**. Unfortunately, coupling of the lithio anion of **642** with epoxide **639** afforded only very low yields of **643**, even under optimized conditions. Accordingly, the first synthetic strategy was abandoned.

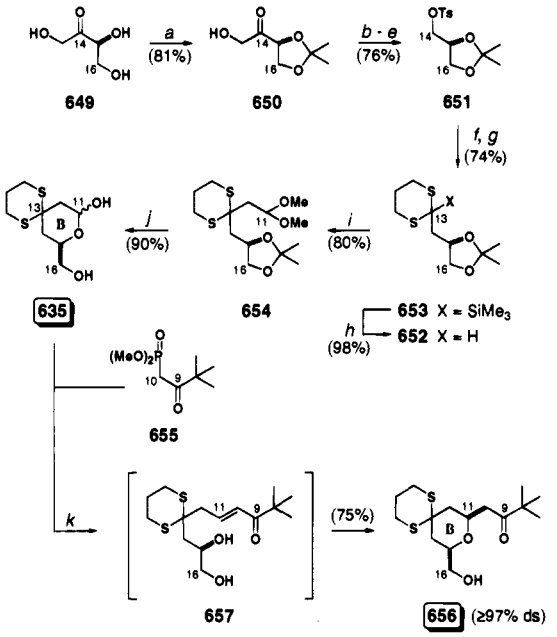
In the second approach, only the C_7 stereogenic center originated in the chiral pool. Construction of the C_5 stereogenic center was accomplished by a chelation-controlled aldol reaction between **644** and **645**; a 1,3-*anti* selective reduction of β-hydroxy ketone **646** then set up the C_3 stereogenic center. Production of aldehyde **644** by cleavage of dithiane **642** proved troublesome. Instead, **644** was obtained by vinylcuprate addition to epoxide **638** followed by hydroxyl protection and subsequent two-step oxidative alkene cleavage. The chelation-controlled aldol reaction between aldehyde **644** and ketone **645**, obtained from 1,3-butanediol (**647**), afforded exclusively the β-hydroxy ketone **646** with the required configuration at C_5. However, stereoselective reduction to provide **648** was accomplished only by using $LiAl(O^tBu)_3H$ in the presence of lithium iodide.[235] Note that the Saksena–Evans reagent[35] proved completely unselective in this case. Finally, ac-

Scheme 57. Vandewalle Bryostatin 11 C_1–C_9 Synthesis[213a,c] *a*



[a] (a) LAH; (b) Et_2CO, *p*-TsOH; (c) ^{t}BuOK, PMBCl; (d) HCl; (e) NaH; *N*-tosylimidazole; (f) 1,3-dithiane, ^{n}BuLi; (g) ^{t}BuOK, BnBr; (h) BH_3·Me_2S; (i) Me_2CO, H^+; (j) TBDPSCl, imidazole; (k) H^+; (l) TsCl, py; (m) K_2CO_3, MeOH; (n) **642**, ^{n}BuLi, TMEDA; **639**, DMPU; (o) $(H_2C{=}CH)_2Cu(CN)Li$; (p) ^{t}BuOK, BnBr; (q) OsO_4, NMO, H_2O; (r) $Pb(OAc)_4$, py; (s) TBDPSCl, imidazole; (t) CrO_3·py_2; (u) **645**, LDA; **644**; (v) $LiAl(O^tBu)_3H$, LiI; (w) $(MeO)_2CMe_2$, Amberlyst-15.

Scheme 58. Vandewalle Bryostatin 11 C_{11}–C_{16} Synthesis[213a a]



[a] (a) Me_2CO, $ZnCl_2$, Na_2SO_4; (b) $NaBH_4$; (c) $NaIO_4$; (d) $NaBH_4$; (e) TsCl, Et_3N; (f) NaI; (g) 2-(trimethylsilyl)-1,3-dithiane, ^{n}BuLi; (h) TBAF; (i) **652**, ^{n}BuLi, HMPA; $BrCH_2CH(OMe)_2$; (j) HCl; (k) **655**, ^{n}BuLi; **635**.

etonide protection gave the C_1–C_9 segment **634** [30% overall yield from **640**; 12 steps longest linear sequence; 14 steps total; ~5 steps per stereogenic center].

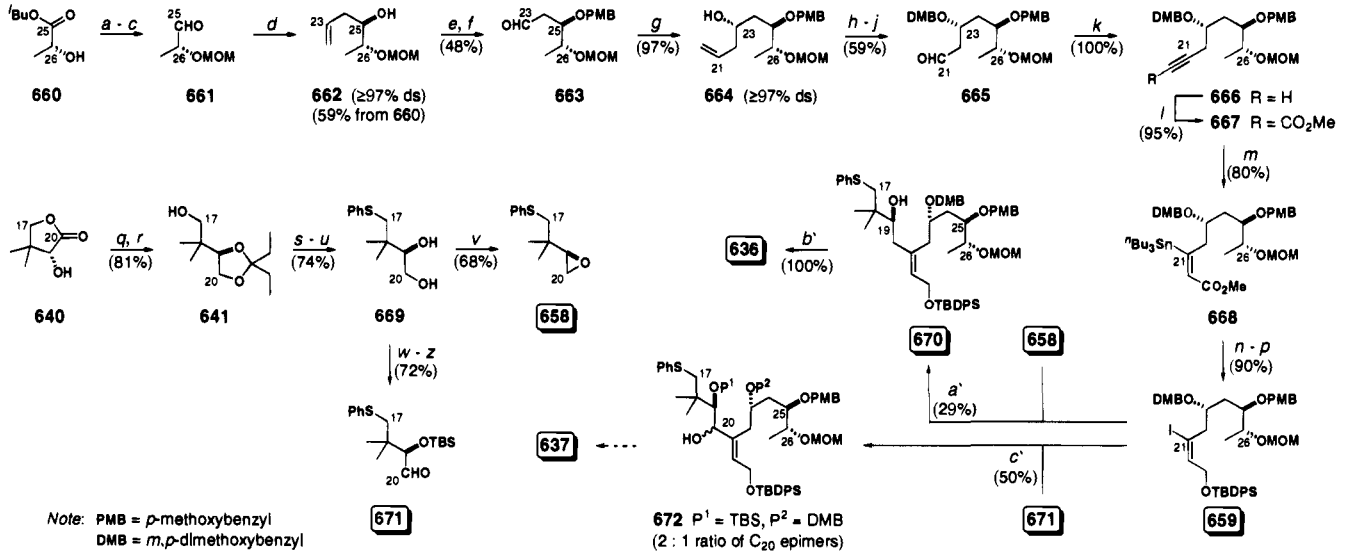
b. C_{11}–C_{16} Segment Synthesis.[213a] The C_{11}–C_{16} segment **635** was obtained from L-erythrulose (**649**), which provided the C_{15} stereogenic center (Scheme 58). Thus, conversion of **649** into the C_{15},C_{16} acetonide **650** was followed by reduction at C_{14} and cleavage of the resulting glycol to afford the corresponding C_{14} aldehyde.[236] Reduction and subsequent tosylation then furnished **651**, which was transformed into dithiane **652** via **653**.[237] Note that direct formation of **652** from **651** was low yielding. Alkylation of the C_{13} lithio anion of **652** supplied **654**, and acid-catalyzed transacetalization provided the C_{11}–C_{16} segment **635** as an anomeric mixture. Note that **635** has a protected carbonyl group at C_{13}. Vandewalle and co-workers envisage formation of the C_{13} exocyclic α,β-unsaturated ester via a stereoselective Horner–Emmons reaction[238,239] later in the synthesis. [C_{11}–C_{16} segment **635**: 32% overall yield from **649**; 10 steps.]

Vandewalle and co-workers have proposed union of the C_1–C_9 and C_{11}–C_{16} segments **634** and **635** using a β-keto phosphonate to introduce C_{10}. Model studies have been performed using β-keto phosphonate **635**. Thus, deprotonation of **655** and addition to **635** afforded **656** as the sole product. The stereoselective construction of the B ring in **656** occurs via the *in situ* intramolecular hetero-Michael reaction of intermediate **657**, in which formation of the new C_{11} stereogenic center is controlled by the existing C_{15} stereogenic center.

c. C_{17}–C_{27} Segment Synthesis.[213b,c] The bryostatin 11 C_{17}–C_{27} segment **636** was constructed from C_{17}–C_{20} and C_{21}–C_{27} segments **658** and **659** (Scheme 59). Compound **659** was prepared from (*R*)-isobutyl lactate (**660**), which supplied the C_{26} stereogenic center. Two chelation-controlled allylation reactions were then used to install the C_{25} and C_{23} stereogenic centers. Compound **658**, meanwhile, was obtained from (*R*)-pantolactone (**640**). Although the C_{19} stereogenic center in **640** was destroyed in the synthesis of **636**, it has the potential for controlling the installation of a stereogenic center at C_{20} in a synthesis of the bryostatin 7 C_{17}–C_{27} segment **637**.

Thus, after protection of the hydroxyl of **660**, adjustment of oxidation state led to aldehyde **661**. α-Chelation-controlled allylstannane addition[240] to **661** then afforded exclusively **662** having the required configuration at C_{25}. Oxidative cleavage of the

Scheme 59. Vandewalle Bryostatin 11 C_{17}–C_{27} Synthesis[213b,c a]



[a] (a) MOMCl, ^{i}Pr$_2$NEt; (b) LAH; (c) Swern oxidation; (d) $H_2C{=}CHCH_2Sn^nBu_3$, $MgBr_2{\cdot}OEt_2$; (e) ^{t}BuOK, PMBCl; (f) OsO_4, $NaIO_4$; (g) $H_2C{=}CHCH_2Sn^nBu_3$, $MgBr_2{\cdot}OEt_2$; (h) ^{t}BuOK, *m*,*p*-dimethoxybenzyl chloride; (i) OsO_4, NMO; (j) $NaIO_4$, ^{n}Bu$_4$NBr, H_2O; (k) $(MeO)_2P(=O)CHN_2$, ^{t}BuOK; (l) ^{n}BuLi; $ClCO_2Me$; (m) ^{n}Bu$_3$SnCu·Me$_2$S·LiBr, MeOH; (n) DIBAL; (o) TBDPSCl, imidazole, DMAP; (p) I_2; (q) LAH; (r) Et_2CO, *p*-TsOH; (s) TsCl, py, DMAP; (t) ^{t}BuOK, PhSH; (u) H_2SO_4, MeOH; (v) NaH, TsCl; (w) ^{t}BuPh(MeO)SiBr, Et_3N; (x) TBSOTf, 2,6-lutidine; (y) HF·py; (z) TPAP, NMO; (a') **659**, ^{t}BuLi; 2-thienyl-CuCNLi; **658**, $BF_3{\cdot}OEt_2$; (b') DMSO, $SO_3{\cdot}$py; Et_3N; (c') **659**, ^{t}BuLi; **671**.

double bond of **662** provided aldehyde **663**, and a β-chelation-controlled allylstannane addition provided **664** as the sole product. Note the much lower level of diastereoselectivity (71% ds) observed for the corresponding reaction of the C_{25},C_{26} acetonide-protected analogue of **663**, wherein each acetal oxygen could be involved in chelation. After protection of the C_{23} hydroxyl of **664**, oxidative double-bond cleavage supplied the aldehyde **665**. Conversion to the alkyne **666** was best effected by employing the Seyferth reagent (dimethyl diazomethylphosphonate).[241] Lithiation of **666** and addition to methyl chloroformate then gave **667**. As in the Masamune synthesis (*vide supra*),[212b] stereoselective introduction of the exocyclic double bond at C_{21} was accomplished by using Piers' method.[228] Thus, conjugate organostannylcuprate addition to **667** gave the (*E*)-vinylstannane **668**. After reduction of the ester and protection of the resulting alcohol, replacement of the tributylstannyl group with iodine then afforded **659** (*cf.* **619** → **620** → **613** in Scheme 54).

Meanwhile, tosylation of alcohol **641**, derived from (*R*)-pantolactone (**640**), followed by thiophenolate displacement and acetal cleavage supplied diol **669**. Conversion to epoxide **658** was then effected via the primary tosylate. Reaction of **658** with the mixed higher order cuprate derived from iodide **659** led to the C_{17}–C_{27} segment **670**, albeit in low yield, together with substantial amounts of dehalogenated **659**. Although oxidation at C_{19} was envisaged after C_{16}–C_{17} coupling, Vandewalle and co-workers sought to confirm that oxidation could be performed without concomitant migration of the C_{21} exocyclic double bond. In fact, oxidation of **670** led smoothly to **636** [3.2% overall yield from **660**; 18 steps longest linear sequence; 24 steps total; 8 steps per stereogenic center].

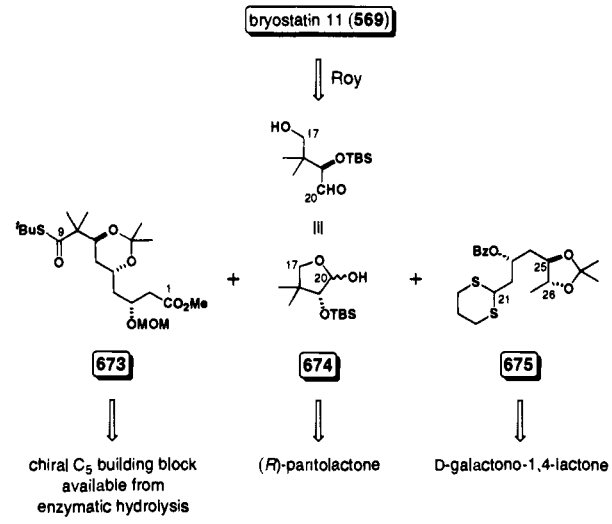
The potential for controlled installation of a stereogenic center at C_{20} via the coupling of **659** with aldehyde **671** was also investigated. Unfortunately, reaction of **671**, prepared from diol **669**, with the lithio anion derived from iodide **659** furnished the C_{17}–C_{27} segment **672** as a 2:1 ratio of C_{20} epimers. The degree of Cram control in this reaction was lower than expected, and better stereocontrol is required for efficient synthesis of the bryostatin 7 segment **637**. Note that Masamune and co-workers were able to achieve much higher diastereoselectivity (86% ds) in the C_{20}–C_{21} bond construction by employing the antipode of aldehyde **671** and by using a dimethoxybenzyl ether rather than a silyl ether as the protecting group at C_{19}, such that chelation control could be used effectively in the coupling reaction (**612** + **613** → **625** in Scheme 54).[212b]

3. Roy Segment Syntheses[214]

Roy *et al.* have synthesized the three bryostatin 11 segments depicted in Scheme 60: C_1–C_9 segment **673**, C_{17}–C_{20} segment **674**, and C_{21}–C_{27} segment **675**. These segments were all prepared according to the "chiron" approach,[8] *i.e.* using starting materials available from the chiral pool, as indicated in the scheme.

a. C_1–C_9 Segment Synthesis.[214b] In the synthesis of the C_1–C_9 segment **673**, the C_5 stereogenic center

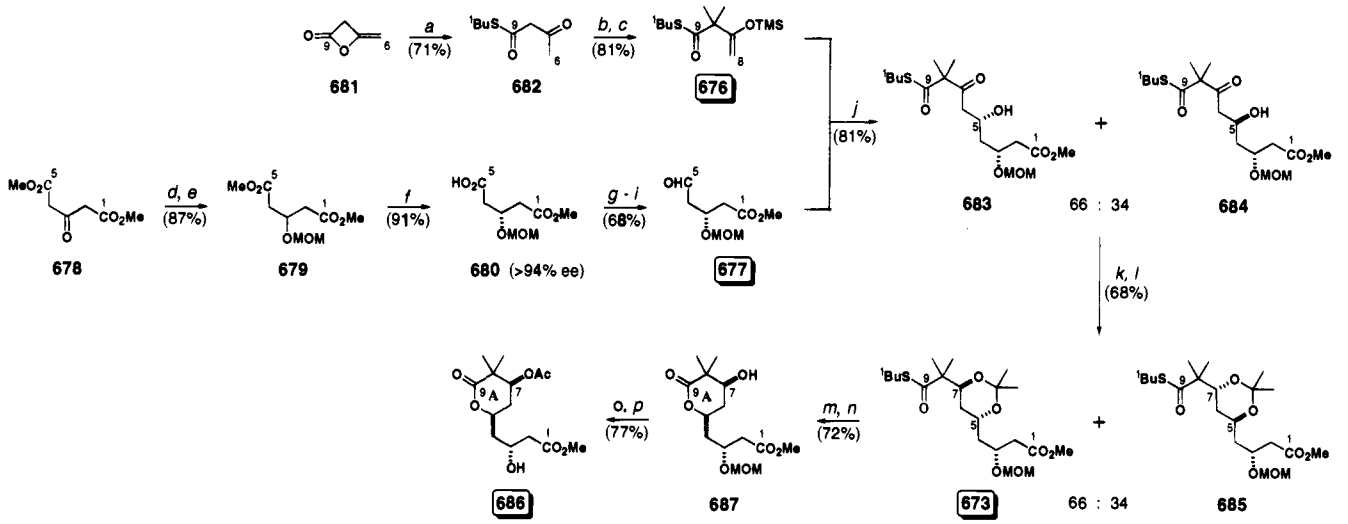
Scheme 60



was installed by a stereoselective Mukaiyama aldol reaction between silyl enol ether **676** and the five-carbon chiral building block **677**, which was obtained in high enantiomeric excess via enzymatic hydrolysis of a prochiral precursor (Scheme 61).[242] Stereoselective reduction of the resulting β-hydroxy ketone then introduced the remaining C_7 stereogenic center. Thus, borohydride reduction[243] of dimethyl 3-ketoglutarate (**678**) followed by protection of the resulting hydroxyl gave the prochiral enzyme substrate **679**. Selective hydrolysis of the *pro-S* ester group of **679** upon incubation with α-chymotrypsin then supplied the mono acid **680**,[242] and borohydride reduction of the mixed anhydride of **680** followed by PCC oxidation furnished aldehyde **677**. Meanwhile, reaction of diketene (**681**) with *tert*-butyl mercaptan gave β-keto thioester **682**.[244] Bis(methylation) at C_8 followed by silyl enol ether formation then afforded **676**.

β-Chelation-controlled Mukaiyama aldol reaction[245] between **676** and **677** was expected[246] to give selectively the β-hydroxy ketone **683** with the required configuration at C_5 (*si*-face attack). However, the use of both $TiCl_4$ and $SnCl_4$ as chelating Lewis acids led to formation of the unwanted isomer **684** as the major product (**683**/**684** = 40:60). This behavior may be a consequence of alternative modes of chelation—for instance, additional coordination by the C_1 carbomethoxy group, as proposed by Roy, or, alternatively, coordination by both oxygen atoms of the C_3 MOM ether—resulting in cagelike structures which favor *re*-face attack. In contrast, by employing the nonchelating Lewis acid BF_3·OEt_2 in the Mukaiyama aldol reaction, the desired isomer **683** could be obtained as the major product (**683**/**684** = 66:34). Note that stereochemical control in this reaction arises solely from electrostatic repulsion.[247] Reduction of the inseparable mixture of **683** and **684** using the Saksena-Evans reagent[35] occurred with >98% ds, to afford the corresponding C_5,C_7-*anti* diols, and acetonide protection then gave **673** and **685** which could be separated. Besides synthesizing the C_1–C_9 segment **673**, Roy *et al.* also prepared a C_1–C_9 segment (**686**) suitable for biological activity studies. Thus, selective cleavage of the acetonide of **673** and lactonization of the resulting diol furnished **687**; acetylation of the C_7 hydroxyl and cleavage of the C_3

Scheme 61. Roy Bryostatin 11 C_1–C_9 Synthesis[214b] [a]



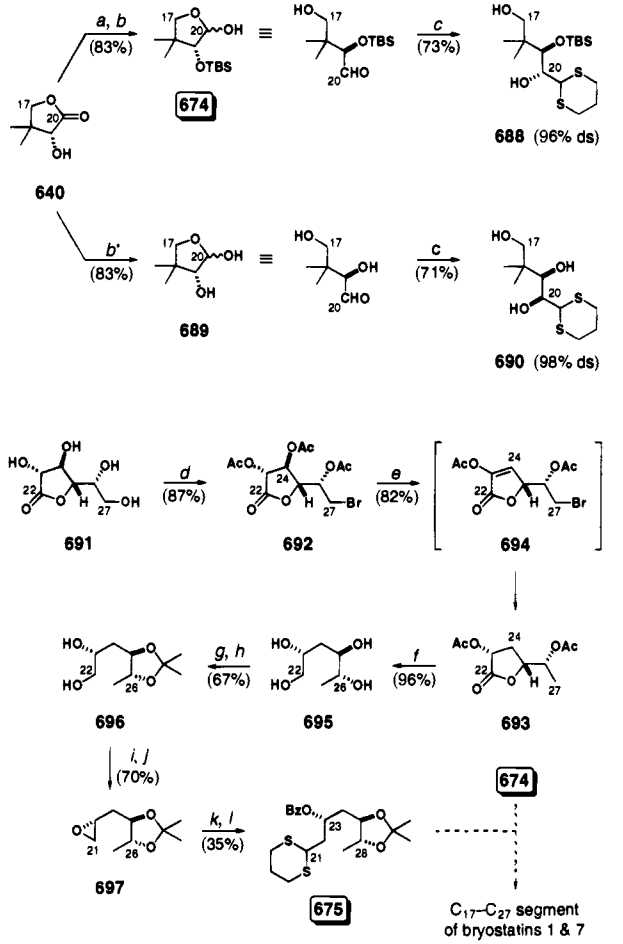
[a] (a) ^{t}BuSH, NaH; (b) ^{t}BuOK, MeI; (c) TMSOTf, Et_3N; (d) $NaBH_4$; (e) $(MeO)_2CH_2$, P_2O_5; (f) α-chymotrypsin; (g) EtOCOCl, Et_3N; (h) $NaBH_4$; (i) PCC; (j) **676** + **677**, BF_3·OEt; (k) $Me_4NBH(OAc)_3$; (l) $(MeO)_2CMe_2$, *p*-TsOH; (m) PPTS, MeOH; (n) $Hg(CF_3CO_2)_2$; (o) Ac_2O, py; (p) $TiCl_4$.

MOM ether then gave **686**. [C_1–C_9 segment **673**: 20% overall yield from **678**; 9 steps longest linear sequence; 12 steps total; 4 steps per stereogenic center.]

b. C_{17}–C_{20} and C_{21}–C_{27} Segment Syntheses.[214a] The C_{17}–C_{20} segment **674** was prepared from (*R*)-pantolactone (**640**) by a two-step sequence of hydroxyl protection followed by reduction (Scheme 62). The C_{19} stereogenic center in **674** was expected to permit diastereoselective addition of the C_{21}–C_{27} dithiane **675**, thus allowing controlled installation of the C_{20} stereogenic center in a synthesis of a bryostatin 7 C_{17}–C_{27} segment. Indeed, model studies[214c] revealed that 2-lithiodithiane added to **674** with high diastereoselectivity (96% ds) to afford the Cram adduct **688** having the required configuration at C_{20}. Note that use of the unprotected analogue of **674**, namely **689**, led to completely the opposite sense of stereochemical induction during the dithiane addition, yielding **690** as a consequence of chelation control.

The C_{21}–C_{27} segment **675** was obtained from D-galactono-1,4-lactone (**691**), which supplied the stereogenic centers at C_{23}, C_{25}, and C_{26}. Deoxygenation at C_{24} and C_{27} was therefore required. Thus, one-pot bromination and acetylation of **691** supplied **692**.[248] Heterogeneous hydrogenation in the presence of triethylamine then afforded **693** via reaction of the intermediate enol acetate **694** on its less-hindered β-face.[248] After borohydride reduction to give **695**, sequential bis(acetonide) formation and kinetic monoacetonide cleavage[249] furnished the diol **696**. Conversion to the epoxide **697** was then effected via the primary tosylate. Regioselective opening of epoxide **697** with 2-lithiodithiane followed by protection of the resulting C_{23} hydroxyl then provided the C_{21}–C_{26} segment **675**. On the basis of the model studies (*vide supra*),[214c] coupling of **675** and the C_{17}–C_{20} segment **674** is expected to proceed with high diastereoselectivity to afford a C_{17}–C_{27} segment of bryostatins 1 and 7. [C_{21}–C_{26} segment **675**: 11% overall yield from **691**; 9 steps; 3 steps per stereogenic center.]

Scheme 62. Roy Bryostatin 11 C_{17}–C_{20} and C_{21}–C_{27} Syntheses[214a] [a]

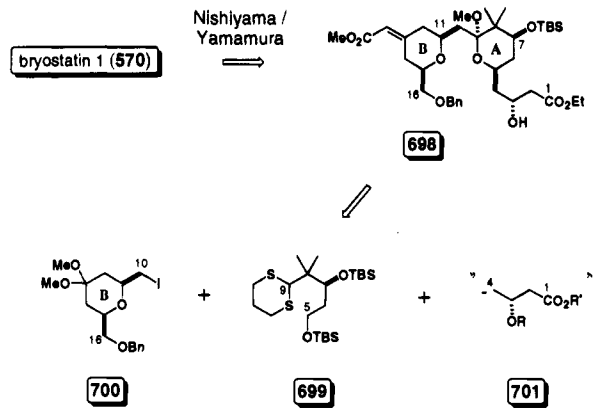


[a] (a) TBSCl, DMAP, Et_3N; (b) DIBAL; (b') BH_3·THF; (c) 1,3-dithiane, ^{n}BuLi; (d) HBr, AcOH; Ac_2O; (e) H_2, 5% Pd–C, Et_3N; (f) $LiBH_4$; (g) $(MeO)_2CMe_2$, *p*-TsOH; (h) *p*-TsOH, MeOH or I_2, MeOH; (i) TsCl, py; (j) K_2CO_3, MeOH; (k) 1,3-dithiane, ^{n}BuLi; (l) BzCl, py.

4. Nishiyama/Yamamura Segment Syntheses[217]

Nishiyama, Yamamura, and co-workers have synthesized a C_1–C_{16} segment **698** of the bryostatins via

Scheme 63



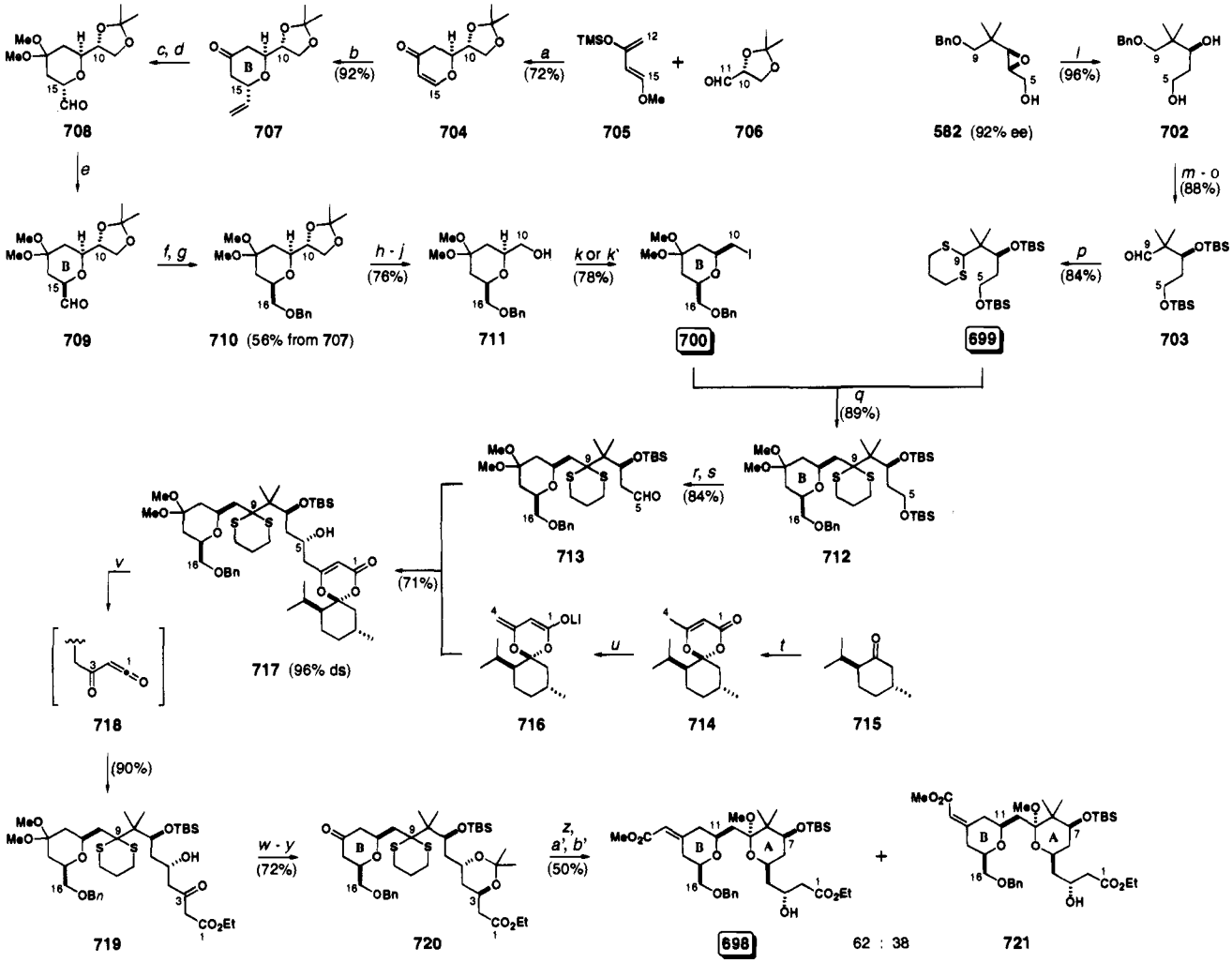
coupling of the C_5-C_9 and $C_{10}-C_{16}$ segments **699** and **700**, followed by addition of a chiral enolate representing C_1-C_4 synthon **701** (Scheme 63). Stereocontrolled introduction of the α,β-unsaturated ester at the C_{13} position was then attempted using a simple Horner–Emmons reaction.

a. C_5-C_9 and $C_{10}-C_{16}$ Segment Syntheses.[217] The route to the C_5-C_9 segment **699** began with epoxy alcohol **582**, which was an intermediate in the Masamune synthesis.[212c] Directed reduction with Red-Al then afforded the 1,3-diol **702** (Scheme 64).[29] After protection of the C_5 and C_7 hydroxyls, deprotection at C_9 followed by oxidation supplied aldehyde **703**, and thioacetal formation then gave **699**.

Meanwhile, synthesis of the $C_{10}-C_{16}$ segment **700** began with stereoselective conjugate addition of a vinyl group to enone **704**, the hetero-Diels–Alder adduct of the Danishefsky diene (**705**) and the glyceraldehyde derivative **706**.[250] After protection of the C_{13} carbonyl group of the resulting **707**, ozonolysis supplied the aldehyde **708**. Epimerization at the C_{15} α-carbon was then effected, to afford the thermodynamically more favorable C_{11},C_{15}-*cis* isomer **709**. Reduction at C_{16} and protection of the resulting hydroxyl furnished **710**; selective removal of the acetonide and subsequent glycol cleavage followed by reduction then gave alcohol **711**. Introduction of iodine at C_{10} was accomplished under standard conditions to afford **700** in readiness for coupling.

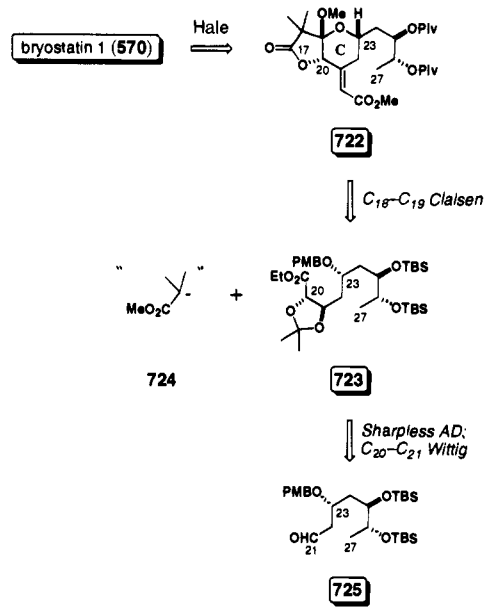
b. C_1-C_{16} Segment Synthesis.[217] Lithiation of the sterically encumbered dithiane **699** was best effected using *tert*-butyllithium and HMPA; addition to iodide

Scheme 64. Nishiyama/Yamamura Bryostatin 1 C_1-C_{16} Synthesis[217 a]



[a] (a) **705** + **706**, $ZnCl_2$; CF_3CO_2H; (b) $H_2C{=}CHMgBr$, CuI, TMSCl, DMPU; (c) $(MeO)_2CMe_2$, MeOH, PPTS; (d) O_3; Me_2S; (e) K_2CO_3, MeOH; (f) $NaBH_4$; (g) BnBr, NaH; (h) Amberlite IR-120 B (H^+), MeOH; (i) $NaIO_4$; (j) $NaBH_4$; (k) I_2, Ph_3P, imidazole; (k') TsCl, py; NaI; (l) Red-Al; (m) TBSCl, imidazole; (n) H_2, Pd–C; (o) Swern oxidation; (p) $HS(CH_2)_3SH$, $MgBr_2{\cdot}OEt_2$; (q) **699**, ^{t}BuLi, HMPA; **700**; (r) PPTS, MeOH; (s) DMSO, $SO_3{\cdot}$py; Et_3N; (t) $MeCOCH_2CO_2{}^t$Bu, Ac_2O, H_2SO_4; (u) **714**, LDA; **713**, LiI; (v) EtOH, Δ; (w) $Me_4NBH(OAc)_3$; (x) H_3O^+; (y) $(MeO)_2CMe_2$, PPTS, Me_2CO; (z) $(MeO)_2P(=O)CH_2CO_2Me$, NaH; (a') $HgCl_2$, HgO, H_2O; (b') PPTS, MeOH.

Scheme 65



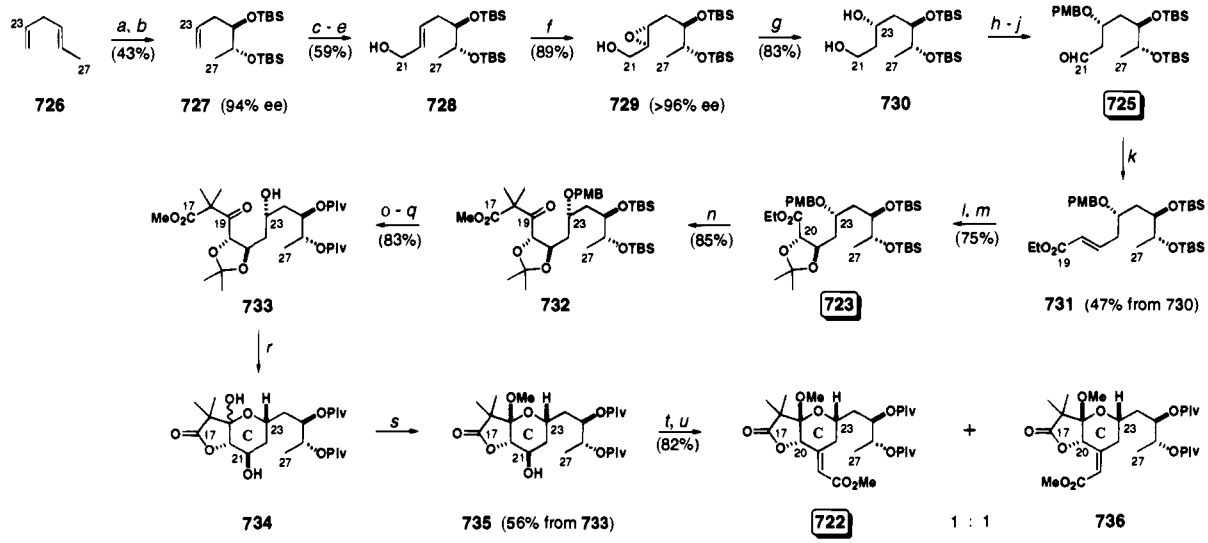
700 then afforded a high yield of the C_5-C_{16} segment **712**. After selective cleavage of the C_5 silyl ether of **712**, oxidation supplied aldehyde **713**. Meanwhile, enolization of the chiral enone **714**,[251] derived from (−)-menthone (**715**), afforded the lithium enolate **716**. In the presence of lithium iodide,[102] **716** underwent a highly diastereoselective aldol addition to aldehyde **713** to furnish the C_1-C_{16} segment **717** with the required configuration at C_5 (96% ds). Note that in the absence of the additive, the sense of diastereoselectivity of the coupling reaction was reversed, such that the C_5 epimer of **717** was now the major product. Upon treatment of **717** with ethanol in refluxing toluene, removal of the chiral auxiliary via ketene **718** furnished the β-keto ester **719**. After reduction to the corresponding C_3,C_5-*anti* diol using the Saksena–Evans reagent,[35] deprotection at C_{13} followed by acetonide protection at C_3 and C_5 supplied the ketone **720**. Horner–Emmons reaction of **720** then gave a mixture of the corresponding C_{13} exocyclic α,β-unsaturated esters. After removal of the C_9 thioacetal group, formation of the A ring via acid-catalyzed acetalization afforded a 62:38 ratio of **698** and **721**. In this synthesis, one stereogenic center (C_7) in the C_1-C_{16} segment **698** was introduced using reagent control (→ **582**). The remaining five stereogenic centers were installed using substrate-controlled reactions, including the use of a chiral auxiliary to construct the C_5 stereogenic center (**713** + **716** → **717**). [C_1-C_{16} segment **698**: 2.3% overall yield from **706**; 22 steps longest linear sequence; 28 steps total; ~4 steps per stereogenic center.]

5. Hale $C_{17}-C_{27}$ Segment Synthesis[215]

Hale *et al.* have recently synthesized a $C_{17}-C_{27}$ segment (**722** in Scheme 65) of bryostatin 1 via Claisen coupling of the $C_{19}-C_{27}$ segment **723** and an ester enolate representing synthon **724**. Compound **723** was obtained by a Wittig olefination of the $C_{21}-C_{27}$ segment **725**, followed by Sharpless asymmetric dihydroxylation[252] to introduce the C_{20} and C_{21} stereogenic centers. A combination of Sharpless asymmetric epoxidation (AE)[92] and a Sharpless asymmetric dihydroxylation (AD) was used to prepare segment **725**.

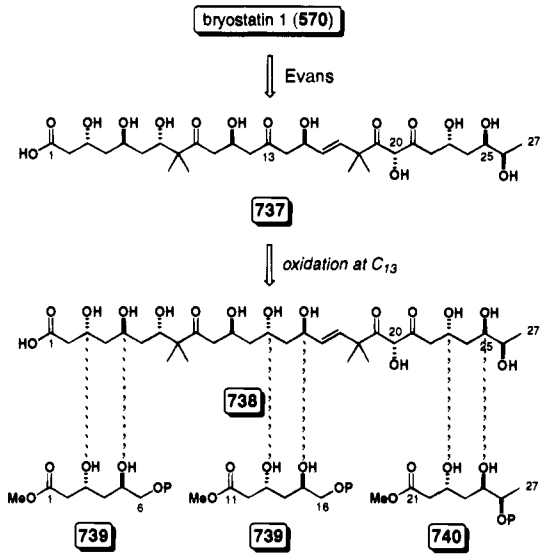
The synthesis of **725** began with regioselective Sharpless asymmetric dihydroxylation of the disubstituted double bond of (*E*)-1,4-hexadiene (**726**),[253] which introduced the C_{25} and C_{26} stereogenic centers with 94% ee (Scheme 66). Protection of the resulting diol then afforded **727**. After oxidative cleavage of the double bond of **727** to give the C_{23} aldehyde, Wittig olefination and subsequent reduction supplied the *trans* allylic alcohol **728**. Sharpless asymmetric epoxidation[92] then afforded epoxy alcohol **729** with >96% ee. Note that this second asymmetric reaction using a chiral substrate and a chiral catalyst led to product **729** of enhanced enantiomeric purity as a result of diastereomer formation. Directed reduc-

Scheme 66. Hale Bryostatin 1 $C_{17}-C_{27}$ Synthesis[215] a



[a] (a) AD-mix-β; (b) TBSCl, imidazole; (c) OsO_4, $NaIO_4$; (d) $Ph_3P{=}CHCO_2Et$; (e) DIBAL; (f) (−)-DET, $Ti(O^iPr)_4$, ^tBuOOH; (g) Red-Al; (h) *p*-$MeO(C_6H_4)CH(OMe)_2$, PPTS; (i) DIBAL; (j) Swern oxidation; (k) $Ph_3P{=}CHCO_2Et$; (l) AD-mix-β, $MeSO_2NH_2$; (m) $(MeO)_2CMe_2$, PPTS; (n) MeO_2CCHMe_2, LDA; **723**; (o) HF·py; (p) PivCl, py; (q) DDQ, H_2O; (r) Amberlyst-15 (H^+), MeOH; (s) AcCl, MeOH; (t) $RuCl_3$, $NaIO_4$; (u) $Ph_3P{=}CHCO_2Me$.

Scheme 67



tion[29] of **729** with Red-Al provided diol **730** with the required configuration at C_{23}, and protecting group manipulation and adjustment of oxidation state then furnished aldehyde **725**. Wittig homologation of **725**, to afford the α,β-unsaturated ester **731**, was followed by a second Sharpless AD reaction; protection of the resulting diol then supplied **723**. After a Claisen reaction between ester **723** and the lithium enolate of methyl isobutyrate, to provide the β-keto ester **732**, exchange of protecting groups gave the C-ring precursor **733**. Treatment of **733** with Amberlyst resin effected hemiacetal formation at C_{19} to form the C ring, along with acetonide cleavage and simultaneous cyclization onto C_{17} to give the γ-butyrolactone; Fischer glycosidation[254] of the resulting **734** then furnished the acetal **735** having the required configuration at C_{19}. Finally, oxidation[160] of **735** afforded the corresponding C_{21} ketone, and a nonstereoselective Wittig reaction then supplied the desired C_{17}–C_{27} segment **722** along with its double-bond isomer **736** in a 1:1 ratio. Thus, in this synthesis of **722**, four of the five stereogenic centers were installed using asymmetric induction from chiral catalytic reagents; the fifth stereogenic center, at C_{19}, was constructed using substrate control. [C_{17}–C_{27} segment **722**: 1.1% overall yield from **726**; 21 steps; ~4 steps per stereogenic center.]

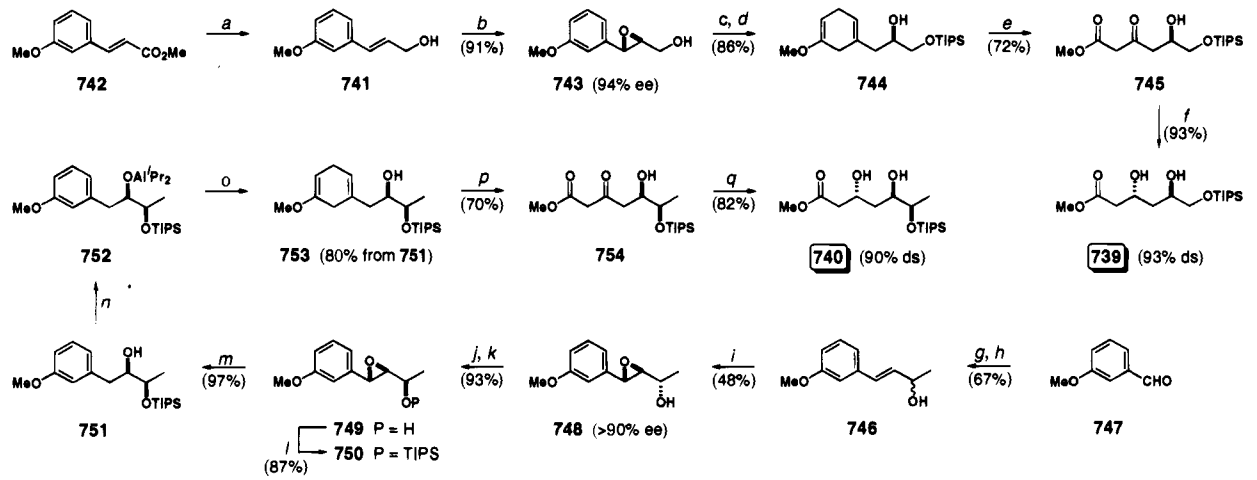
6. Evans Segment Syntheses[216b]

Evans *et al.* observed that the acetate-derived oxygenation pattern of the bryostatin backbone was especially apparent in seco-acid **737**, obtained by replacement of the unsaturated esters at C_{13} and C_{21} of the bryostatin skeleton (Scheme 67). The identification of recurring structural motifs was further enhanced by substitution of the C_{13} carbonyl with hydroxyl as in **738**. Thus inspection of **738** revealed that both C_1–C_6 and C_{11}–C_{16} segments could be obtained from the same triol ester **739**, while the C_{21}–C_{27} segment might be derived from the one-carbon homologue **740** containing an additional stereogenic center. A unified synthetic approach to all stereoisomers of **739** and **740** was developed.

a. C_1–C_6 and C_{11}–C_{16} Segment Syntheses.[216b] The syntheses of **739** and **740** were based upon the enantioselective asymmetric epoxidation/kinetic resolution of cinnamyl alcohols[255] and the use of *meta*-substituted anisyl rings as masked β-keto ester synthons[256] (Scheme 68). Thus, Sharpless epoxidation[92,255] of allylic alcohol **741**, derived from reduction of *trans*-cinnamate **742**, afforded epoxide **743** with 94% ee. After protection of the hydroxyl, Birch reduction gave dihydroanisole **744**. Ozonolysis then furnished the β-keto ester **745**. Finally, directed reduction of **745** using the Saksena–Evans reagent[35] afforded the *anti* 1,3-diol **739** with 93% ds, suitable for C_1–C_6 and C_{11}–C_{16} segments of the bryostatins.

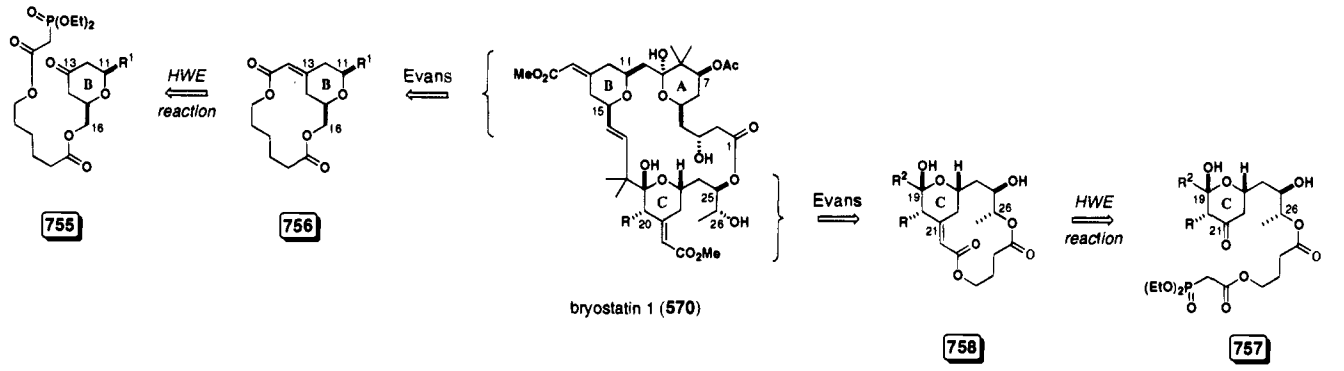
b. C_{21}–C_{27} Segment Synthesis.[216b] The racemic allylic alcohol **746** was prepared by aldol condensation of *m*-anisaldehyde (**747**) with acetone, followed by ketone reduction.[23] After Sharpless kinetic resolution[28] of **746**, which afforded the *anti* epoxy alcohol **748** with >90% ee, Mitsunobu inversion[85] and saponification of the resulting benzoate ester supplied the *syn* epoxy alcohol **749**. Protection of the hydroxyl then gave **750**. Birch reduction of **750** was accompanied by silyl group migration. However, mi-

Scheme 68. Evans Bryostatin 1 C_1–C_6, C_{11}–C_{16}, and C_{21}–C_{27} Syntheses[216b] [a]



[a] (a) DIBAL; (b) (+)-DIPT, $Ti(O^iPr)_4$, ^tBuOOH; (c) TIPSCl, imidazole, DMAP; (d) Li, liquid NH_3, ^tBuOH; (e) O_3; Me_2S; (f) $Me_4NHB(OAc)_3$; (g) Me_2CO, NaOH; (h) $NaBH_4$, $CeCl_3$; (i) (+)-DIPT, $Ti(O^iPr)_4$, ^tBuOOH; (j) DEAD, PPh_3, $PhCO_2H$; (k) K_2CO_3, MeOH; (l) TIPSOTf, Et_3N; (m) Pd–$BaSO_4$, H_2; (n) DIBAL; (o) Li, liquid NH_3, ^iPrOH; (p) O_3; Me_2S; (q) $Me_4NHB(OAc)_3$.

Scheme 69



gration was avoided by performing consecutive reductions under more controlled conditions. Thus, reductive cleavage of the epoxide via hydrogenolysis afforded **751**, and subsequent Birch reduction of the derived dialkylaluminum (**752**) cleanly supplied dihydroanisole **753**. Ozonolysis then furnished the β-keto ester **754**. Finally, directed reduction of **754** using the Saksena–Evans reagent[35] afforded the *anti* 1,3-diol **740** with 90% ds, suitable for a C_{21}–C_{27} segment of the bryostatins.

7. Evans C_1–C_{16} Segment Synthesis[216a]

The stereoselective construction of the exocyclic α,β-unsaturated esters present at C_{13} and C_{21} of the bryostatins represents one of the key synthetic challenges posed by this class of natural products. The Masamune total synthesis[212] and the Vandewalle C_{17}–C_{27} fragment synthesis[213b,c] both successfully applied existing methodology[224,228] for the stereoselective construction of trisubstituted double bonds (*vide supra*). In contrast, Nishiyama, Yamamura, and co-workers achieved modest stereocontrol for the introduction of the C_{13} α,β-unsaturated ester by using a simple Horner–Emmons reaction.[217] Evans and Carreira have investigated an entirely novel strategy for controlling the exocyclic olefin geometry at C_{13}, whereby a tethered phosphonate reagent anchored to a hydroxyl at C_{16} of the bryostatin fragment **755** underwent a highly selective Horner–Emmons macroolefination reaction[49] to afford macrolide **756** (Scheme 69). An analogous strategy could be used to control the olefin geometry at C_{21}, *i.e.* **757** → **758**.[257]

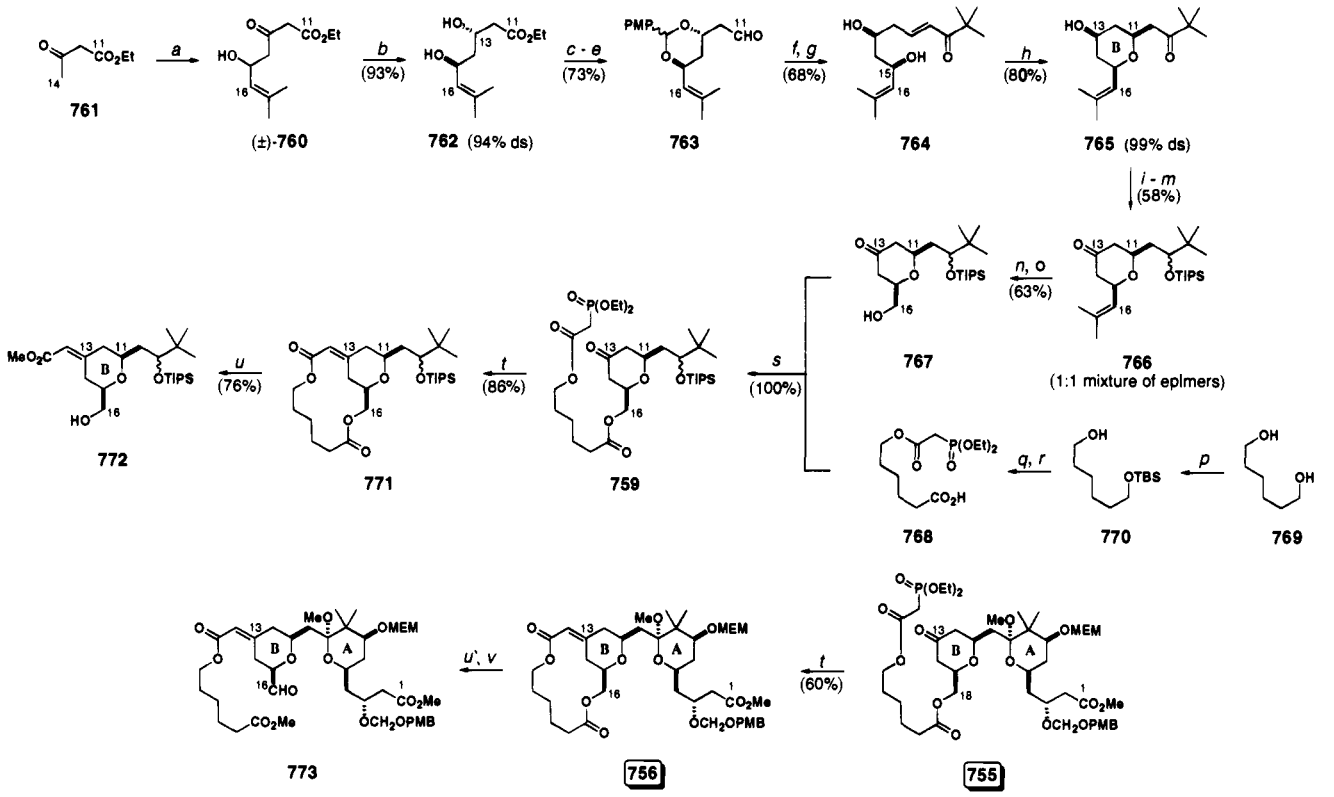
Parameters such as tether length and cyclization conditions were defined using the model substrate **759** (Scheme 70). Preparation of racemic **759** began with β-hydroxy ketone **760**, derived from aldol reaction of ethyl acetoacetate (**761**) with 3-methyl-2-butenal. Stereoselective reduction of **760** using the Saksena–Evans reagent[35] afforded the C_{13},C_{15}-*anti* diol **762**; protection of the C_{13} and C_{15} hydroxyls and reduction at C_{11} then supplied aldehyde **763**. After Horner–Emmons olefination using a model β-keto phosphonate, and subsequent deprotection to provide **764**, closure of the B ring via an intramolecular hetero-Michael reaction gave tetrahydropyran **765** with the required stereochemistry at C_{11}. Reduction and hydroxyl protection at C_9, and oxidation at C_{13}, then afforded **766** which was used in subsequent reactions as a 1:1 mixture of C_9 epimers. Ozonolysis of **766** supplied the corresponding ketoaldehyde; chemoselective reduction of the aldehyde group[258] then furnished alcohol **767**. Molecular modeling revealed that a six-carbon tether was optimal, since it would lead to formation of a 14-membered macrocycle in which the *Z* configuration of the double bond was calculated to be thermodynamically more stable than the *E* geometry. Thus, attachment of the corresponding β-keto phosphonate tether **768**, derived from hexane-1,6-diol (**769**) via **770**, supplied the olefination precursor **759**. Intramolecular Horner–Emmons reaction[49] of **759** was then effected using lithium chloride and triethylamine, affording the macrocycle **771** as a single olefin stereoisomer. Having served its function, the tether was then removed via methanolysis, to afford **772** with configuration of the C_{13} α,β-unsaturated ester as required for the bryostatins.

A similar cyclization was performed on an advanced intermediate (**755**) in the synthesis of a C_1–C_{16} segment of bryostatin 1. Thus, Horner–Emmons reaction of **755**[259] afforded the 14-membered macrodiolide **756** as a single olefin stereoisomer. Selective methanolysis of the saturated lactone supplied a primary alcohol at C_{16}; oxidation then furnished the C_1–C_{16} aldehyde segment **773**, in readiness for an envisaged coupling with a C_{17}–C_{27} sulfone segment via a *trans*-selective Julia–Lythgoe olefination. At the time of writing, no further work has been reported.

8. Thomas C_{10}–C_{16} Segment Synthesis[218]

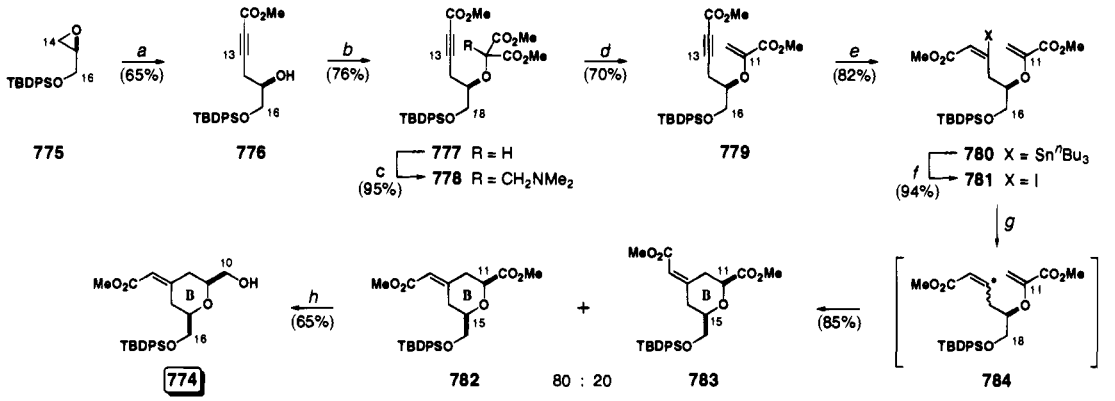
Munt and Thomas have developed a novel route to C_{10}–C_{16} segment **774** corresponding to the B ring of the bryostatins in which the geometry of the exocyclic double bond at C_{13} is established via cyclization of a vinyl radical (Scheme 71). Thus, Yamaguchi coupling[87] of epoxide **775** with methyl lithiopropynoate afforded alcohol **776**, which was converted into alkoxymalonate **777** upon treatment with dimethyl diazomalonate and $Rh_2(OAc)_4$. After alkylation with $Me_2N{=}CH_2{}^+I^-$ to give **778**, N-methylation and decarboxylative elimination supplied enol ether **779** as described by Ganem.[260] Conjugate addition of an organostannylcuprate, according to the procedure of Piers,[228] gave **780**; subsequent iodination then furnished the (*E*)-vinyl iodide **781**. Radical-mediated cyclization of **781** was effected upon treatment with tributyltin hydride and AIBN to afford an 80:20 mixture of exocyclic double bond isomers **782** and **783**. Note that the vinyl radical **784** equilibrates

Scheme 70. Evans Bryostatin 1 C_1–C_{16} Synthesis[216a] [a]



[a] (a) **761**, LDA; 3-methyl-2-butenal; (b) $Me_4NBH(OAc)_3$; (c) PMBOMe, DDQ; (d) LAH; (e) Swern oxidation; (f) $(MeO)_2P(=O)CH_2CO^tBu$, LiCl, $^iPr_2NEt$; (g) AcOH, H_2O; (h) ^{t}BuOK; (i) Ac_2O, py, DMAP; (j) $NaBH_4$; (k) TIPSOTf, Et_3N; (l) K_2CO_3, MeOH; (m) PDC, pyridinium trifluoroacetate; (n) O_3; Me_2S; (o) $LiAlH(OCEt_3)_3$; (p) NaH, TBSCl; (q) $(MeO)_2P(=O)CH_2CO_2H$, DCC, DMAP; (r) Jones oxidation; (s) **767** + **768**, DCC, DMAP; (t) LiCl, Et_3N; (u) K_2CO_3, MeOH; (u') Li_2CO_3, MeOH; (v) oxidation.

Scheme 71. Thomas Bryostatin 1 C_{10}–C_{16} Synthesis[218] [a]



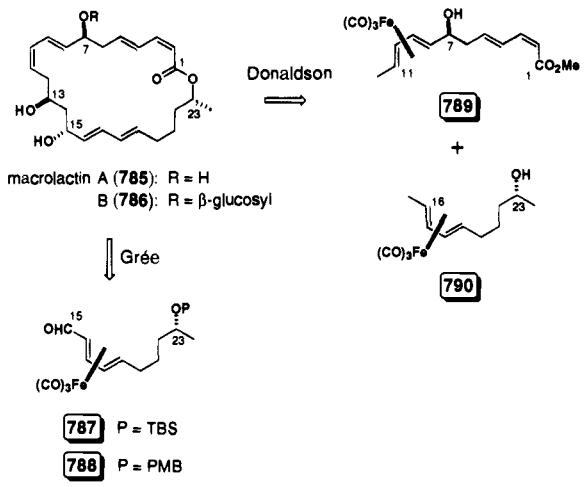
[a] (a) $LiC{\equiv}CCO_2Me$, $BF_3{\cdot}OEt_2$; (b) $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$; (c) $Me_2N{=}CH_2{}^+I^-$, Et_3N; (d) MeI; (e) $^nBu_3SnCu{\cdot}LiBr{\cdot}Me_2S$; (f) I_2; (g) $^nBu_3SnH$, AIBN, Δ; (h) $NaBH_4$.

prior to cyclization. The preferential formation of **782**, in which the terminal methoxycarbonyl group is *trans* to the newly formed carbon–carbon single bond, may be accounted for by cyclization of the (*Z*)-vinyl radical occurring faster than cyclization of the *E* isomer. Note also that selective formation of the C_{11},C_{15}-*cis*-disubstituted products **782** and **783** implies stereoselective H-atom abstraction from the axial direction. Finally, chemoselective reduction of the saturated ester provided the C_{10}–C_{16} bryostatin segment **774** [11% overall yield from **775**; 8 steps; 4 steps per stereogenic center].

H. The Macrolactins

The macrolactins are a group of polyene macrolides isolated from a taxonomically undefined deep sea bacterium.[261] Macrolactin A (**785** in Scheme 72), the parent aglycon, exhibits a number of interesting biological properties. These include selective antibacterial activity, inhibition of murine melanoma cancer cells, inhibition of mammalian *Herpes simplex* viruses, and protection of T-lymphoblast cells against human HIV replication.[261] Rychnovsky *et al.* have determined the absolute stereochemistry of macrolactin B (**786**) by a combination of spectral analysis, oxidative degradation, and chemical correlation studies.[262] Macrolactin A, the aglycon of macrolactin B, is assumed to have the same configuration. At the time of writing, no total synthesis of macrolactin A has been reported.[263] However, Grée and co-workers have prepared two differently protected C_{15}–C_{24}

Scheme 72



segments, **787** and **788**,[264] and Donaldson *et al.* have prepared the model C_1-C_{11} and $C_{16}-C_{24}$ segments, **789** and **790**.[265] Both groups independently adopted similar synthetic strategies exploiting the properties of diene–tricarbonyl complexes, whereby the $Fe(CO)_3$ group is used both as a temporary protecting group for 1,3-diene functionality, and as a means of directing stereocontrol in C–C bond formation at adjacent carbon atoms.[266]

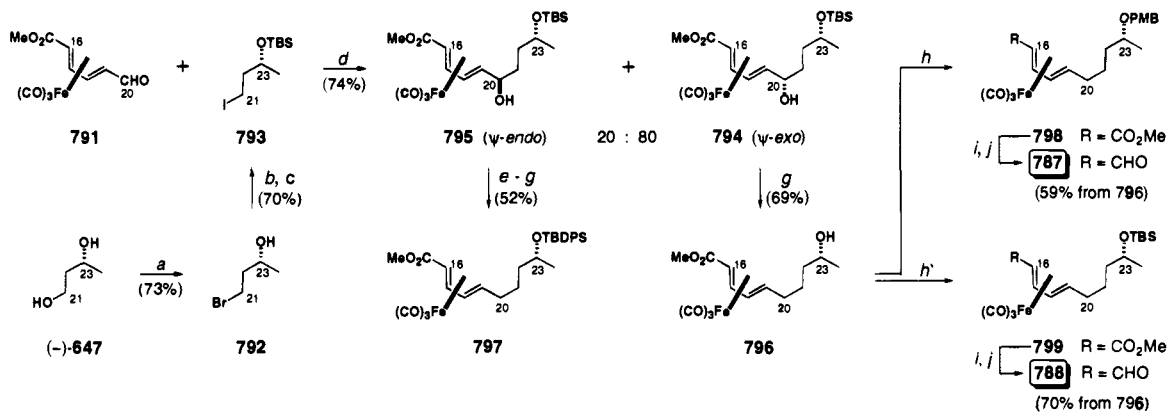
1. Grée Segment Synthesis[264]

Grée and co-workers synthesized the $C_{15}-C_{24}$ segments **787** and **788** starting from the optically pure diene–tricarbonyl complex **791**, obtained via resolution,[267] and (3*R*)-butanediol (**647**), which supplied the C_{23} stereogenic center (Scheme 73). Thus, selective monobromination of **647** gave **792**; hydroxyl protection and halogen exchange then supplied the iodide **793**. Reaction of **791** with the organolithium derived from **793** provided the diastereomeric alcohols **794** and **795** in a ratio of 80:20 in favor of the *ψ-exo* isomer **794**.[268] Deoxygenation at C_{20} was required in order to obtain the macrolactin A intermediates **787** and **788**. This was accomplished by means of ionic hydrogenation[269] via the $Fe(CO)_3$-stabilized pentadienyl cation;[266e] triethylsilane and trifluoroacetic acid proved to be the reagents of choice. Under these conditions, deoxygenation of the *ψ-exo* diastereomer **794** proceeded smoothly to afford **796**, in which the C_{23} silyl ether had been cleaved. The *ψ-endo* diastereomer **795** could also be used in the synthesis. However, in order for deoxygenation of **795** to proceed cleanly, exchange of the C_{23} TBS ether protecting group for the more robust TBDPS group was first required; subsequent deoxygenation then afforded **797**. Finally, reprotection of the C_{23} hydroxyl of **796**, either as the PMB ether (**798**) or the silyl ether (**799**), followed by adjustment of oxidation state[270] at C_{15} supplied the $C_{15}-C_{23}$ segments **787** and **788**. These were obtained in overall yields of 12% and 15%, respectively, over the eight steps from **647**. Note that in the synthesis, the C_{23} stereogenic center originated in the chiral pool.

2. Donaldson Segment Syntheses[265]

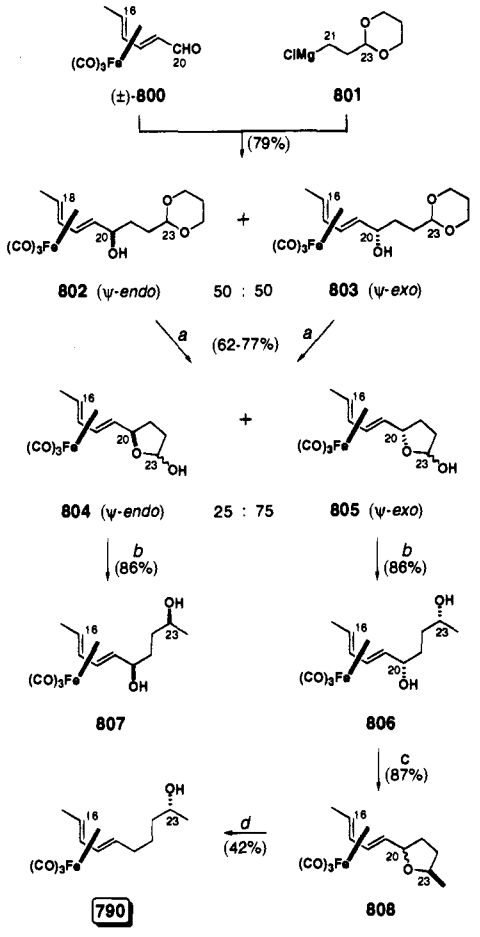
The synthesis of the model $C_{16}-C_{24}$ segment **790** by Donaldson *et al.* resembled the synthesis of the $C_{15}-C_{24}$ segments **787** and **788** by Grée and coworkers insofar as the key reactions involved construction of the $C_{20}-C_{21}$ bond by organometallic addition to an aldehyde, and subsequent deoxygenation at C_{20} by ionic reduction. However, the Donaldson synthesis differed in that the C_{23} stereogenic center was installed by employing asymmetric induction from the remote $Fe(CO)_3$ group, via the temporary installation of a stereogenic center at C_{20}, instead of relying upon the chiral pool. Thus, reaction of the racemic diene-tricarbonyl complex (±)-**800** with the achiral Grignard reagent **801** provided the diastereomeric racemic alcohols **802** and **803** in almost equal amounts (Scheme 74). The lack of diastereoselectivity for Grignard addition was of no consequence, since the C_{20} stereogenic center was epimerized in the following step. Thus, acid-catalyzed hydrolysis of either pure **802**, pure **803**, or a mixture of both, afforded a mixture of diastereomeric lactols **804** and **805** in a ratio of 75:25. Subjection of the undesired *ψ-endo* isomers (**804**) to the hydrolysis conditions afforded more of the mixture of **804** and **805**. The equilibration of **804** and **805** may be rationalized by ionization of the C_{20} lactol C–O bond under the acidic conditions to generate the $Fe(CO)_3$-stabilized pentadienyl cation.[266e] Rotation about the $C_{19}-C_{20}$ and attack of oxygen on the face opposite to the $Fe(CO)_3$ group then effects epimerization.[271]

Scheme 73. Grée Macrolactin A $C_{15}-C_{24}$ Synthesis[264] a



[a] (a) Ph_3P, Br_2; (b) TBSCl, imidazole; (c) NaI, CuI (cat.); (d) **793**, ^{t}BuLi; **791**; (e) PPTS, EtOH; (f) TBDPSCl, imidazole; (g) Et_3SiH, CF_3CO_2H; (h) $Cl_3CC(=NH)OPMB$, TfOH; (h') TBSCl, imidazole; (i) DIBAL; (j) ^{n}PrMgBr; azodicarbonyldipiperidine.

Scheme 74. Donaldson Macrolactin A $C_{16}-C_{24}$ Synthesis[265] a



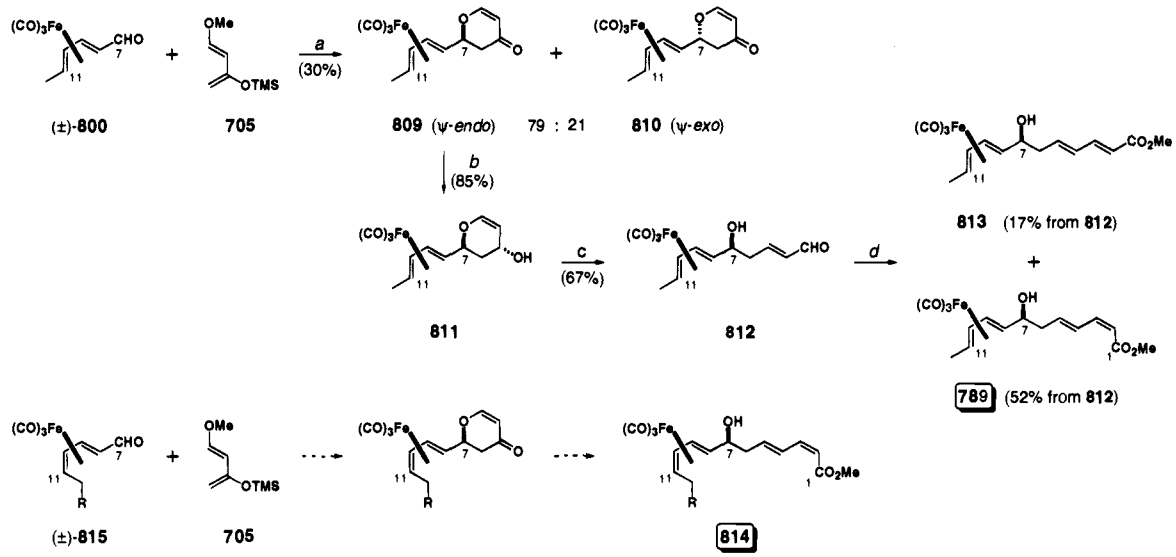
(a) H_2SO_4; (b) $MeTi(O^iPr)_3$; (c) *p*-TsOH; (d) $NaBH_3CN$, $BF_3{\cdot}OEt_2$.

Installation of the C_{23} stereogenic center was accomplished via treatment of the *ψ-exo* isomers **805** with $MeTi(O^iPr)_3$,[272] which furnished the C_{20},C_{23}-*syn* diol **806** as a single diastereomer. Note that the same reaction of the *ψ-endo* isomers **804** supplied the corresponding C_{20},C_{23}-*syn* diol **807** as a single diastereomer. The *ψ-exo* configuration at C_{20} of **806** positions the hydroxyl appropriately for ionization with anchimeric assistance from the metal center. Thus, treatment of **806** with acid led to loss of the C_{20} hydroxyl, and participation of the C_{23} hydroxyl then afforded the tetrahydrofuran **808**. Finally, ionic reduction[269] of **808** via the pentadienyl cation provided the $C_{16}-C_{24}$ segment **790** in an overall yield of 13% over five steps. Thus, in this synthesis, the $Fe(CO)_3$ group was used to control the installation of the temporary stereogenic center at C_{20}, which in turn was used to direct the formation of the C_{23} stereogenic center; the stereogenic center at C_{20} was then removed.

In the synthesis of the model C_1-C_{11} segment **789** by Donaldson *et al.*, the dienylic C_7 stereogenic center was installed by employing asymmetric induction from the neighboring $Fe(CO)_3$ group (Scheme 75). Thus, $TiCl_4$-induced hetero-Diels–Alder reaction of the racemic diene-tricarbonyl complex (±)-**800** with the Danishefsky diene **705** provided the diastereomeric dihydropyrones **809** and **810** in a a ratio of 79:21.[273] Note that use of $BF_3{\cdot}OEt_2$ as the Lewis acid in this reaction led to a turnover in stereoselectivity, affording **809** and **810** in a ratio of 25:75. After stereoselective DIBAL reduction of the *ψ-endo* isomer (**809**), acid-catalyzed ring opening of the resulting **811** then supplied the enal **812**. Finally, Horner–Emmons reaction of **812** using Still's conditions[91] gave the required (*Z,E*)-α,β,γ,δ-unsaturated ester **789**, together with the corresponding *E,E* isomer **813** in a ratio of 75:25. Thus, the model C_1-C_{11} segment **789** was obtained in an overall yield of 7.0% over four steps. Note that the diene–tricarbonyl complex **800** was chosen for the model studies due to its ready availability. Preparation of the C_1-C_{11} fragment **814**, having the *Z* configuration at C_{10} required for synthesis of macrolactin A, would require hetero-Diels–Alder cycloaddition of the (*E,Z*)-dienal complex **815**. Such a reaction has previously been demonstrated by Donaldson *et al.*[274]

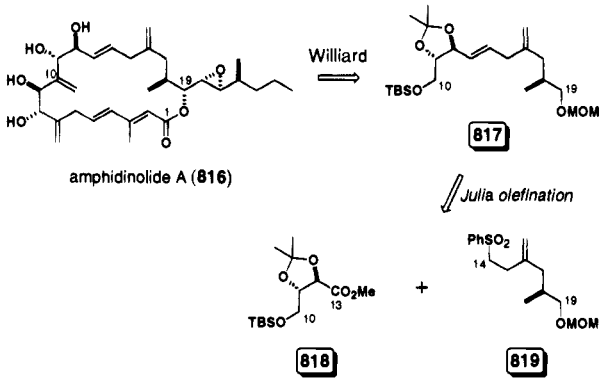
Note also that both **789** and **790** were obtained in racemic form, since their syntheses began with the racemate of the diene-tricarbonyl complex (±)-**800**.

Scheme 75. Donaldson Macrolactin A C_1-C_{11} Synthesis[265] a



[a] (a) **705** + (±)-**800**, $TiCl_4$; CF_3CO_2H; (b) DIBAL; (c) $HgSO_4$, H_2SO_4; (d) $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, K_2CO_3, 18-crown-6.

Scheme 76



Note: Absolute configuration of amphidinolide A is, at present, undetermined.

An enantiocontrolled synthesis would be possible by using the resolved[275] form of **800**.

I. The Amphidinolides

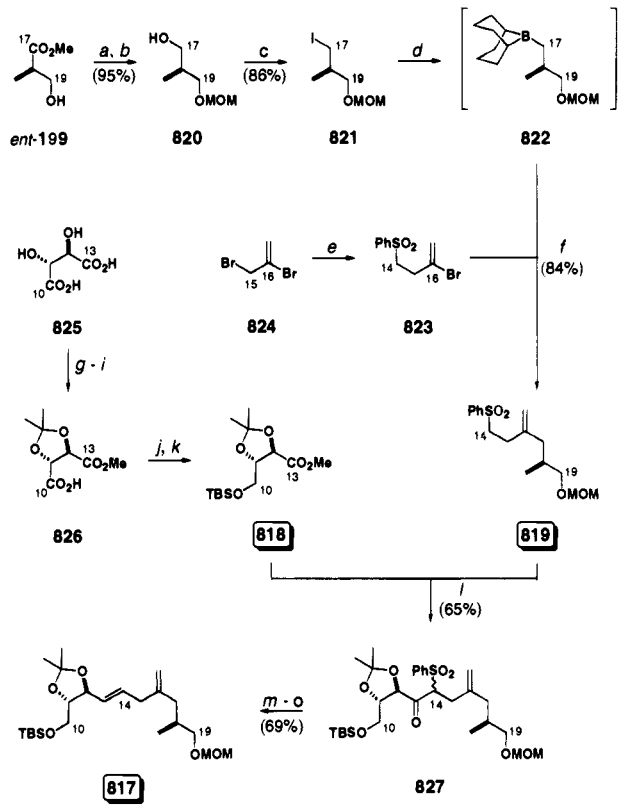
The amphidinolides are a class of cytotoxic polyene macrolides isolated from dinoflagellates of the genus *Amphidinium*, which are symbionts of Okinawan marine flatworm *Amphiscolops* sp.[276] All of these compounds exhibit significant *in vitro* activity against murine leukemia cells, and some congeners also display activity toward rabbit skeletal muscle actomyosin ATPase. The gross chemical structures of the various members of the amphidinolide family have been deduced by Kobayashi and co-workers.[276] The same group has proposed relative stereochemical assignments for a few congeners, *e.g.* amphidinolide A (**816** in Scheme 76), on the basis of spectroscopic studies.[277] However, absolute stereochemistry has been determined in only two cases, via synthesis of oxidative degradation fragments.[278] At the present time, no total syntheses of any of the amphidinolides have been reported. However, a $C_{10}-C_{19}$ segment of amphidinolide A has been prepared by O'Connor and Williard,[279] and Boden and Pattenden have reported the formation of the macrocyclic skeleton of amphidinolide A using a novel palladium-catalyzed macrocyclization reaction.[280]

1. Williard Segment Synthesis[279]

At the time that the synthesis of a $C_{10}-C_{19}$ segment of amphidinolide A was reported by O'Connor and Williard,[279] neither the relative nor the absolute stereochemistry of the natural product was known. Accordingly, the researchers sought to develop a synthetic strategy that could be used to prepare all of the possible diastereomers (*vide infra*). The $C_{10}-C_{19}$ segment **817** was obtained via Julia coupling of the $C_{10}-C_{13}$ and $C_{14}-C_{19}$ segments **818** and **819**, which were each available in either enantiomeric configuration from chiral pool starting materials (Scheme 76).

Construction of the $C_{14}-C_{19}$ segment **819** began with (*R*)-methyl 3-hydroxy-2-methylpropionate (*ent*-**199**), which supplied the C_{18} stereogenic center (Scheme 77).[281] Note that the (*S*) enantiomer (**199**) is also commercially available. Thus, protection of the hydroxyl of *ent*-**199** and subsequent reduction of the ester gave the alcohol **820**; iodination then

Scheme 77. Williard Amphidinolide A $C_{10}-C_{19}$ Synthesis[279] a

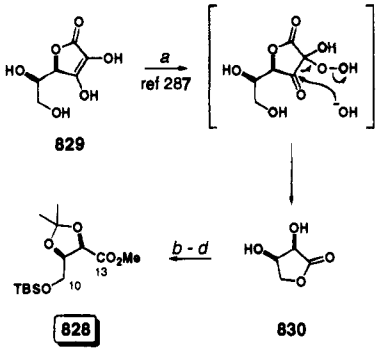


[a] (a) MOMCl, $^{i}Pr_2NEt$; (b) LAH; (c) Ph_3P, I_2, imidazole; (d) $^{t}BuLi$; 9-BBN-OMe; (e) $PhSO_2Me$, $^{n}BuLi$; **824**; (f) **822** + **823**, 3 mol % (DPPF)$PdCl_2$; (g) MeOH, H^+, molecular sieves; (h) $(MeO)_2CMe_2$, H^+, molecular sieves; (i) KOH, MeOH; (j) BH_3·THF; (k) TBSCl, imidazole; (l) **819** (1 equiv), $^{n}BuLi$; **818** (0.5 equiv); LDA; **818** (0.5 equiv); (m) $NaBH_4$; (n) MsCl, Et_3N; (o) Na–Hg, Na_2HPO_4.

provided **821**. After lithium–halogen exchange, reaction with 9-BBN-OMe afforded the borane **822**. Note that **822** is not available in sufficiently high enantiomeric purity via an alternative route involving asymmetric hydroboration of a methallyl alcohol derivative.[282] Suzuki coupling[283] of **822** with vinyl bromide **823**, derived from 2,3-dibromopropene (**824**),[284] then furnished **819**.

Meanwhile, the $C_{10}-C_{13}$ segment **818** was obtained from L-tartaric acid (**825**) according to the procedure of Musich and Rapoport.[285] Thus, bis(esterification) of **825** and subsequent acetonide protection was followed by selective saponification of one of the ester groups to afford **826**. Chemoselective reduction of the carboxylic acid group of **826** and protection of the resulting alcohol then gave **818**. Julia coupling of ester **818** and sulfone **819** under carefully controlled conditions[286] furnished the β-keto sulfone **827** as a mixture at C_{14} epimers. Reduction to the corresponding hydroxy sulfone followed by mesylation and reductive elimination then afforded the $C_{10}-C_{19}$ segment **817** with the required *E* double bond. Note that the stereochemistry of **817** is in agreement with the relative stereochemical assignment for amphidinolide A subsequently proposed by Kobayashi *et al.*[277a] Note also that, in the synthesis of **817**, all three stereogenic centers originated in the chiral pool. The use of D-tartaric acid and (*S*)-methyl 2-hydroxy-3-methylpropionate, therefore, would allow synthesis of the enantiomer of **817**. The absolute configuration

Scheme 78[a]



[a] (a) H_2O_2, Na_2CO_3; HCl; (b) $(MeO)_2CMe_2$, *p*-TsOH; (c) NaOMe, MeOH; (d) TBSCl, imidazole.

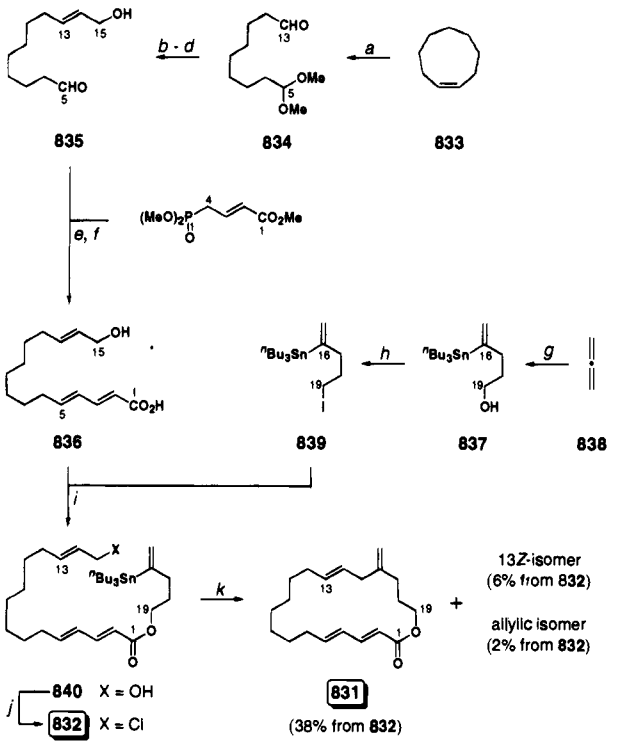
of amphidinolide A is, at present, undetermined. [C_{10}–C_{19} segment **817**: 31% overall yield from *ent*-**199**; 9 steps longest linear sequence; 15 steps total; 5 steps per stereogenic center.]

The "chiron strategy"[8] adopted by O'Connor and Williard was sufficiently flexible to be able to supply all the diastereomeric possibilities for the C_{10}–C_{19} segment. Thus, if it had proved necessary, upon determination of the relative stereochemistry of amphidinolide A, to use the C_{10}–C_{13} segment **828** (Scheme 78), then the depicted enantiomer of this intermediate was available by synthesis from D-isoascorbic acid (**829**) via lactone **830**.[287] Either enantiomer of **829** was also available by resolution of racemic DL-erythronic lactone **830**.[288]

2. Pattenden Macrocycle Synthesis[280]

Boden and Pattenden have prepared the macrocycle **831**, a model for the ring skeleton of amphidinolide A, from the vinyl stannane–allylic chloride **832** using a novel intramolecular Stille coupling procedure which results in the formation of 1,4-dienes (Scheme 79).[280] Thus, ozonolysis of cyclononene (**833**) in acidic methanol, followed by reductive workup, provided the aldehyde-acetal **834**. After Horner–Emmons olefination, subsequent reduction followed by acetal hydrolysis supplied the aldehyde **835**. A second Horner–Emmons olefination and subsequent saponification then afforded the acid **836**. Meanwhile, alcohol **837** was prepared by stannyl cupration of allene (**838**) followed by trapping with ethylene oxide according to the procedure of Fleming and Pulido.[289] After transformation to iodide **839**, coupling with the carboxylate anion derived from **836** furnished **840**. Introduction of chloride at C_{15}, via the mesylate derived from **840**, gave the cyclization precursor **832**. Finally, treatment of **832** with Pd(0) in the presence of triphenylarsine[290] led to smooth cyclization to afford the 20-membered macrocycle **831** with the required *E* configuration at C_{13} (38% cyclization yield), together with a small amount of the corresponding 13*Z* isomer, and a trace of the 18-membered macrocycle resulting from allylic isomerization of the starting material. Note that although the model **831** contains all the endocyclic double bonds found in amphidinolide, it lacks several other structural features present in the natural product: namely the C_{19} side chain, the exomethylene groups at C_7 and C_{10}, and the four hydroxyls at C_8, C_9, C_{11}, and C_{12}. All of these features might be expected to assist the cyclization to form the real macrocycle, by inducing a favorable conformation in the cyclization precursor. Accordingly, cyclization in the real system could proceed in a yield higher than that observed for the model **831**. The Pattenden cyclization methodology should also be applicable to the synthesis of other polyene macrolides possessing 1,4-diene functionality.

Scheme 79. Pattenden Amphidinolide A Macrocyclization Study[280] [a]



[a] (a) O_3, MeOH, *p*-TsOH; $NaHCO_3$, Ph_3P; (b) $(EtO)_2P(=O)CH_2CO_2Et$, LDA; (c) DIBAL: (d) *p*-TsOH, H_2O; (e) (*E*)-$(MeO)_2P(=O)CH_2CH=CHCO_2Me$, LDA; **835**; (f) NaOH; (g) $(^nBu_3Sn)_2CuLi$; ethylene oxide; (h) I_2, PPh_3, imidazole; (i) **836** + **839**, DBU; (j) MsCl, Et_3N, LiCl; (k) Pd_2dba_3, Ph_3As, Δ.

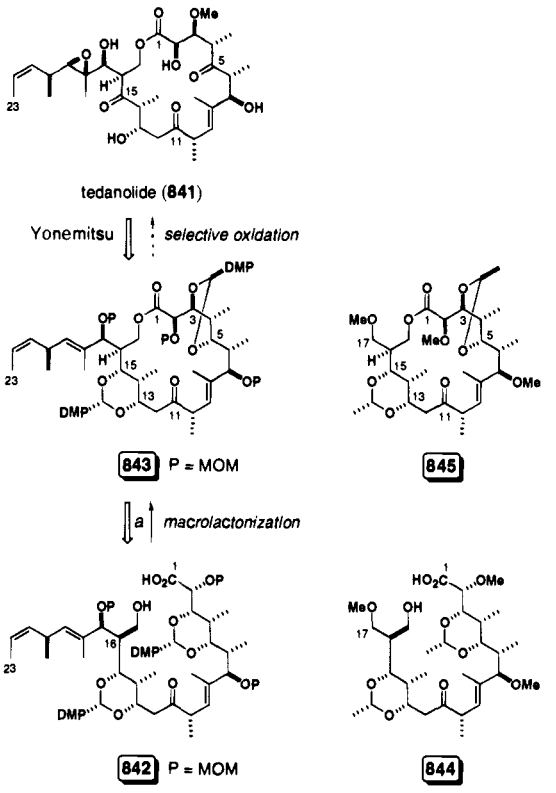
J. Tedanolide

Tedanolide (**841** in Scheme 80) is a potent cytotoxic macrolide, isolated from the Caribbean sponge *Tedania ignis*, which inhibits KB human carcinoma and PS lymphocytic leukemia *in vitro*.[291] At the time of writing, no total synthesis of tedanolide has been reported. However, Yonemitsu has described the macrolactonization of the seco-acid derivative **842**, to form the advanced intermediate **843**.[76e] The protecting group arrangement of **842** was selected as a result of molecular modeling studies (*vide infra*), and **842** was synthesized from (*R*)- and (*S*)-2-hydroxy-3-methylpropionic acids via four segments: C_1–C_7, C_8–C_{11}, C_{13}–C_{17}, and C_{18}–C_{21}. At the time of writing, no further details have been published.

1. Yonemitsu Macrolide Synthesis[76e]

To avoid the possibility of decomposition of the flexible acyclic precursors occurring as a result of retro-aldol cleavage reactions, Yonemitsu opted to replace some of the aldol relationships in tedanolide with protected 1,3-diols. Selective deprotection and

Scheme 80. Yonemitsu Tedanolide Macrolide Synthesis[76e] [a]



[a] (a) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N; DMAP.

oxidation would then be required, after macrolactonization, in order to obtain the natural product.

In determining the arrangement of protecting groups, Yonemitsu identified two criteria which must be met: firstly, that the conformation of the seco-acid should resemble as closely as possible the conformation of the corresponding macrolide, in order for macrolactonization to be efficient; and, secondly, that the conformation of the macrolactonization product must be similar to the conformation of tedanolide itself, in order for the necessary selective oxidation to be favorable. Computer-aided conformational analysis indicated that these requirements were likely to be satisfied by the seco-acid **842** and the corresponding macrolide **843**, in which the C_5 and C_{15} carbonyls were reduced to hydroxy groups and protected as *m,p*-dimethoxybenzylidene acetals. Thus, the calculated lowest energy conformation of **844** (a model for **842**) was very similar to that computed for **845** (a model for **843**). In turn, the calculated lowest energy conformation of **845** closely resembled the conformation of the lactone portion of tedanolide (**840**) as revealed by X-ray analysis.[291]

In practice, seco-acid **842** cyclized smoothly, without the need for high dilution, using the Yonemitsu modification[184] of the Yamaguchi procedure,[47] to afford an 89% yield of the corresponding macrolide **843**. The deprotection and selective oxidation of **843** to provide tedanolide has not yet been reported.

K. The Latrunculins

Latrunculins A and B (**846** and **847** in Figure 8), originally isolated from the Red Sea sponge *Latrunculia magnifica* (Keller) in 1980,[292a-c,293] were the first

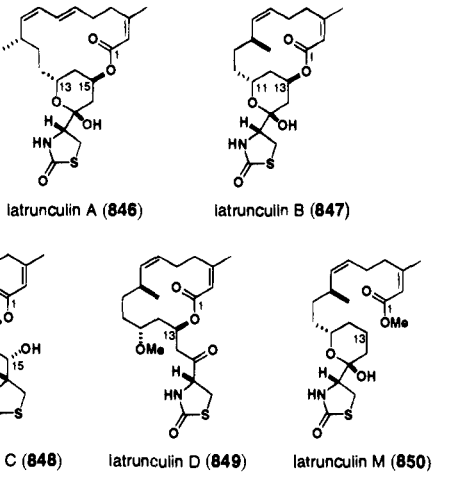


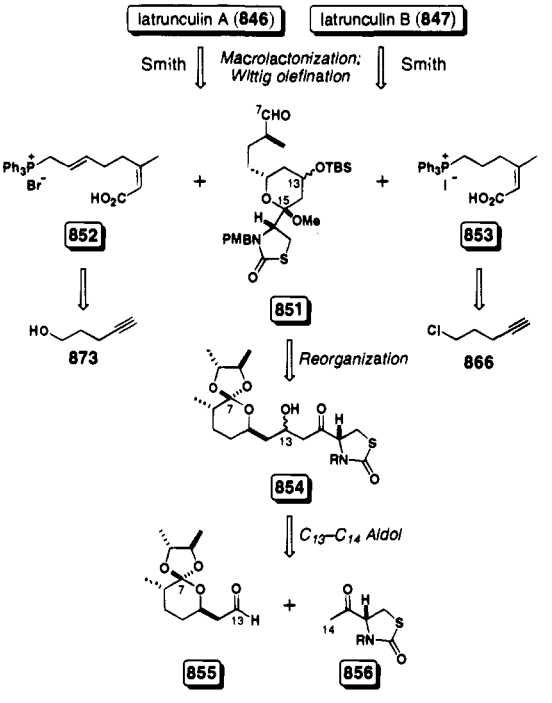
Figure 8. Structures of the latrunculins.

macrolides to be discovered from a truly marine source and the first natural products to embody the 2-thiazolidinone moiety.[294] Other congeners have since been found, such as latrunculins C (**848**),[292d,295] D (**849**),[292d] and M (**850**).[292g] Biological interest in the latrunculins stems from their powerful inhibition of the polymerization of the cytoskeletal protein actin,[292b,296a] and on their ability to reversibly disrupt microfilament organization.[292b,h,296b] The total synthesis of latrunculin B was reported by Smith and co-workers in 1986;[297a,c] and in 1990, Smith *et al.*[297b,c] and White and Kawasaki[298] independently completed total syntheses of latrunculin A. Kashman and co-workers have reported chemical modifications of the natural products[292c-g] and the *de novo* synthesis[292d,e] of model latrunculin tetrahydropyran ring systems.

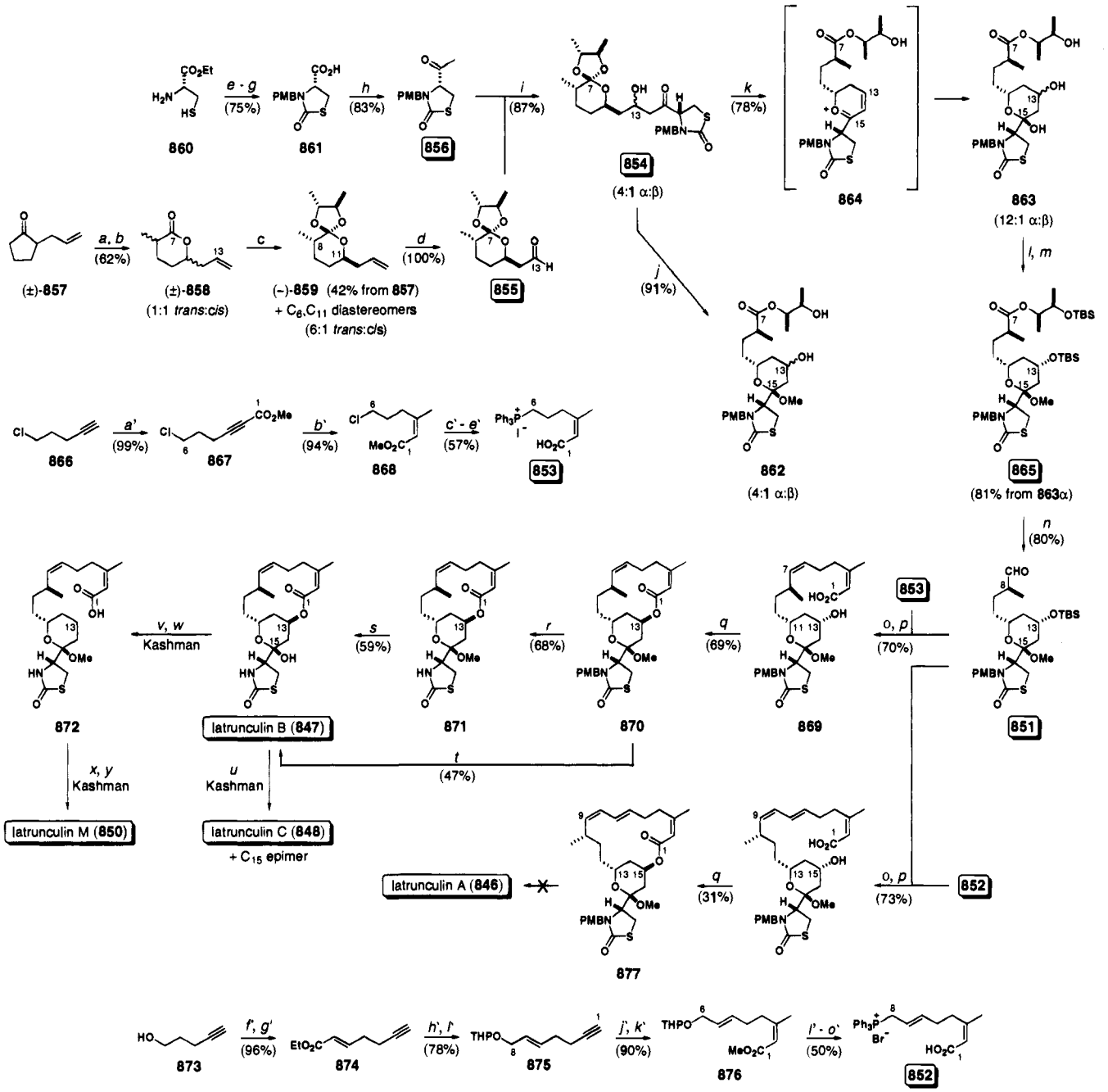
1. Smith Total Syntheses[297]

The syntheses of latrunculin A (**846**) and latrunculin B (**847**) by Smith and co-workers employed the same advanced intermediate **851** (Scheme 81). Wit-

Scheme 81



Scheme 82. Smith Latrunculin B Synthesis[297a,c] a



[a] (a) *m*-CPBA, $NaHCO_3$; (b) LDA; MeI; (c) (+)-(*R*,*R*)-2,3-butanediol, CSA; (d) O_3; PPh_3; (e) $COCl_2$; (f) PMBBr, NaH; (g) 1 N KOH; H_3O^+; (h) NaH, $(COCl)_2$; MeMgBr; (i) **856**, $^nBu_2BOTf$, $^iPr_2NEt$; **855**; (j) *p*-TsOH, MeOH; (k) 2 N HCl; (l) CSA, MeOH; (m) TBSCl, imidazole; (n) DIBAL; (o) **852** or **853**, KHMDS; **851**; (p) HF·py; (q) PPh_3, DEAD; (r) 0.25 M $(NH_4)_2Ce(NO_3)_6$, MeCN; (s) AcOH, H_2O; (t) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O; (u) $NaBH_4$; (v) MeOH, $BF_3{\cdot}OEt_2$; (w) Et_3SiH, $BF_3{\cdot}OEt_2$; (x) AcOH; (y) CH_2N_2; (a') ^{n}BuLi, $ClCO_2Me$; (b') Me_2CuLi; (c') 1 N LiOH; (d') NaI; (e') PPh_3; (f') Swern oxidation; (g') $(EtO)_2P(=O)CH_2CO_2Et$, NaH; (h') DIBAL; (i') DHP, PPTS; (j') ^{n}BuLi, $ClCO_2Me$; (k') Me_2CuLi; (l') Amberlyst-15; (m') LiOH; (n') NBS, Me_2S; (o') PPh_3.

tig reaction of **851** with either **852** or **853**, followed by macrolactonization, led to latrunculins A and B, respectively. Compound **851** was obtained by a novel acid-catalyzed reorganization of ortho ester **854**, which was in turn derived from aldol union of aldehyde **855** and methyl ketone **856**. Since aldol reactions of methyl ketones are often poorly stereoselective,[299] the synthesis was designed to accommodate both configurations at C_{13} in **854** (latrunculin B numbering). Thus, the α epimer of **854** required macrocyclization with inversion of configuration at C_{15} via the Mitsunobu reaction;[85] the β epimer would be lactonized with retention via carboxyl activation.[300]

a. Smith Latrunculin B Total Synthesis.[297a,c] Aldehyde **855** was prepared in four steps from racemic **857** (Scheme 82). Thus, Baeyer–Villiger oxidation followed by α-methylation gave **858** as a 1:1 mixture of diastereomers; ortho ester formation with (+)-(*R*,*R*)-2,3-butanediol then effected both resolution and equilibration, increasing the *trans/cis* ratio to 6:1.[301] HPLC separation of the diastereomers provided isomer (−)-**859**, which was ozonolyzed to provide the C_7–C_{13} aldehyde **855** in enantiopure form. Ketone

856 was derived from L-cysteine ethyl ester (**860**). Thus, formation of the thiazolidinone, PMB protection of the amide nitrogen, and ester hydrolysis gave acid **861**. Reaction of the derived acid chloride with MeMgBr then afforded methyl ketone **856**.

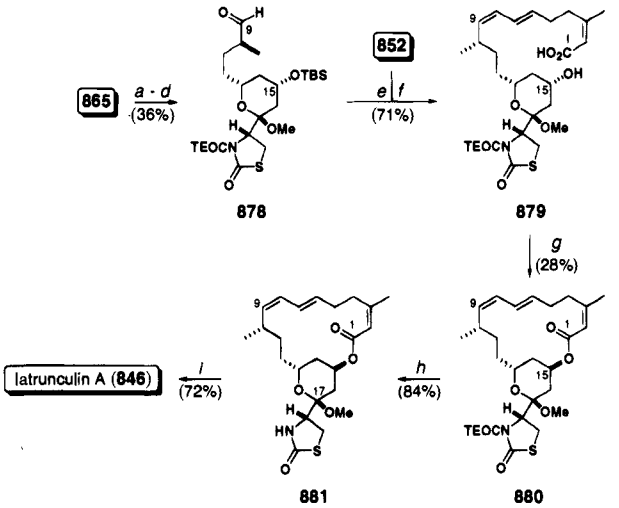
The $C_{13}-C_{14}$ bond was constructed by aldol coupling of the dibutylboron enolate[302] of ketone **856** with aldehyde **855**, giving β-hydroxy ketone **854** as an inseparable 4:1 (α/β) mixture of C_{13} epimers. Note that use of the lithium or zinc enolates of **856** gave similar diastereoselectivity but lower yields. Rearrangement of ortho ester **854** catalyzed by *p*-TsOH in methanol furnished the methyl acetals **862** as a 4:1 mixture of C_{13} epimers. However, use of aqueous HCl effected C_{13} equilibration as well, supplying hemiacetal **863** as a 12:1 mixture of α and β epimers.[303,304] Smith has postulated that equilibration occurs via equatorial addition of the C_{13} hydroxyl to oxonium ion **864**. The C_{15} hemiacetal stereochemistry is governed by the anomeric effect. Methanolysis of **863**α followed by TBS protection of the C_{13} hydroxyl gave **865** which was reduced with DIBAL to afford the key C_9 aldehyde **851**.

The phosphonium salt **853**, required for the C_1-C_6 segment of latrunculin B, was prepared in five steps from 5-chloro-1-pentyne (**866**). Thus, carbalkoxylation of **866** gave **867**, which underwent stereoselective[107a] carbocupration to afford **868**. Hydrolysis at C_1 and phosphorus introduction at C_6 then supplied **853**. A completely *Z*-selective Wittig coupling of aldehyde **851** with the dianion derived from **853**, followed by cleavage of the C_{13} silyl ether, furnished the seco-acid **869**. Macrocyclization of **869** using the Mitsunobu protocol,[85] with inversion of configuration at C_{13}, then afforded the lactone **870**. Deprotection of the thiazolidinone nitrogen using aqueous ceric ammonium nitrate (CAN)[305] gave **871** and subsequent acetal hydrolysis provided latrunculin B (**847**). The natural product could also be directly obtained from **870** by treatment with a more concentrated solution of CAN. Note that the choice of the *p*-methoxybenzyl group for the thiazolidinone nitrogen was critical: both the *N*-benzyl and *N*-(*m*,*p*-dimethoxybenzyl) derivatives of latrunculin B were synthesized, but the protecting groups could not be removed.

Kashman and co-workers have converted natural latrunculin B (**847**) into latrunculin C (**848**) and its C_{15} epimer by reduction with $NaBH_4$.[292d] They have also prepared latrunculin M (**850**) from **847** via acetalization at C_{15} with methanol and reductive opening of the macrolide with $Et_3SiH/BF_3{\cdot}OEt_2$ to give **872**, followed by deacetalization at C_{15} and, finally, methyl ester formation at C_1.[292g] The Smith total synthesis of latrunculin B thus achieves formal syntheses of two additional members of the latrunculin family. [Latrunculin B (**847**): 2.0% overall yield from (±)-**857**; 14 steps longest linear sequence; 23 steps total; ~4–5 steps per stereogenic center.]

b. Smith Latrunculin A Total Synthesis.[297b,c] The phosphonium salt **852** (Scheme 82), required for the C_1-C_8 segment of latrunculin A, was prepared in 10 steps from 5-hydroxy-1-pentyne (**873**). Thus, Swern oxidation and Horner–Emmons olefination to give **874** was followed by 1,2-reduction and hydroxyl

Scheme 83. Smith Latrunculin A Synthesis[297b,c] [a]



[a] (a) LAH; (b) ^{t}BuLi; O_2; (c) PCC, Al_2O_3; (d) $TMSCH_2CH_2OCOCl$, $^i Pr_2NEt$, DMAP; (e) **852**, KHMDS; **878**: (f) HF·py; (g) PPh_3, DEAD; (h) TBAF; (i) 3 N HCl.

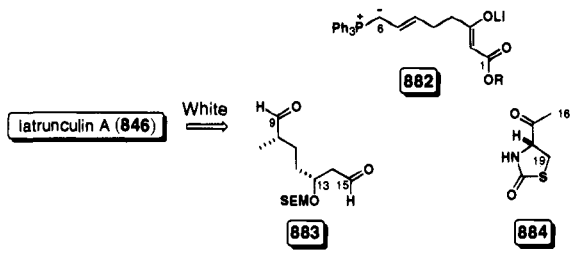
protection to afford **875**. Transformation of the terminal alkyne to the α,β-unsaturated ester **876** was accomplished as for the earlier conversion of **866** → **868**. Finally, hydrolysis at C_1 and phosphorus introduction at C_8 then supplied **852**. In an analogous manner to the synthesis of latrunculin B, Wittig coupling of aldehyde **851** with the dianion derived from **852**, followed by cleavage of the C_{15} silyl ether and macrocyclization, afforded the lactone **877**. Unfortunately, deprotection of the thiazolidinone nitrogen in **877** proved to be impossible due to interference from the sensitive diene moiety (not present in the latrunculin B analogue **870**). A change of protecting group earlier in the synthesis was required. Accordingly, **865** was converted in four steps, including removal of the PMB group using the Williams procedure (*tert*-butyllithium, O_2),[306] into the aldehyde **878** in which the thiazolidinone nitrogen atom was protected as its [β-(trimethylsilyl)ethoxy]carbamate (Scheme 83). Wittig olefination of **852** and **878** followed by cleavage of the C_{15} silyl ether gave seco-acid **879**, and macrocyclization under Mitsunobu conditions[85] then provided macrolide **880**. The TEOC nitrogen-protecting group was removed using fluoride ion, and then final hydrolysis of the C_{17} methyl acetal of **881** gave latrunculin A (**846**).

Thus, in this synthesis, the stereogenic center at C_{18} of latrunculin A was obtained from the chiral pool, the C_{10} and C_{13} stereogenic centers were constructed by using a combination of substrate control and resolution ((±)-**856** → (±)-**858** → (−)-**859**), and the stereogenic centers at C_{15} and C_{17} were set up using substrate-controlled reactions (**854** → **863**, and subsequent inversion at C_{15} during **879** → **880**). [Latrunculin A (**846**): 0.6% overall yield from (±)-**857**; 17 steps longest linear sequence; 31 steps total; ~6 steps per stereogenic center.]

2. White Latrunculin A Total Synthesis[298]

The synthesis of latrunculin A (**846**) by White and Kawasaki was designed to illustrate new methodology[307] for the synthesis of (*E*,*Z*)-1,3-dienes (*vide infra*). Accordingly, the target was divided into the

Scheme 84



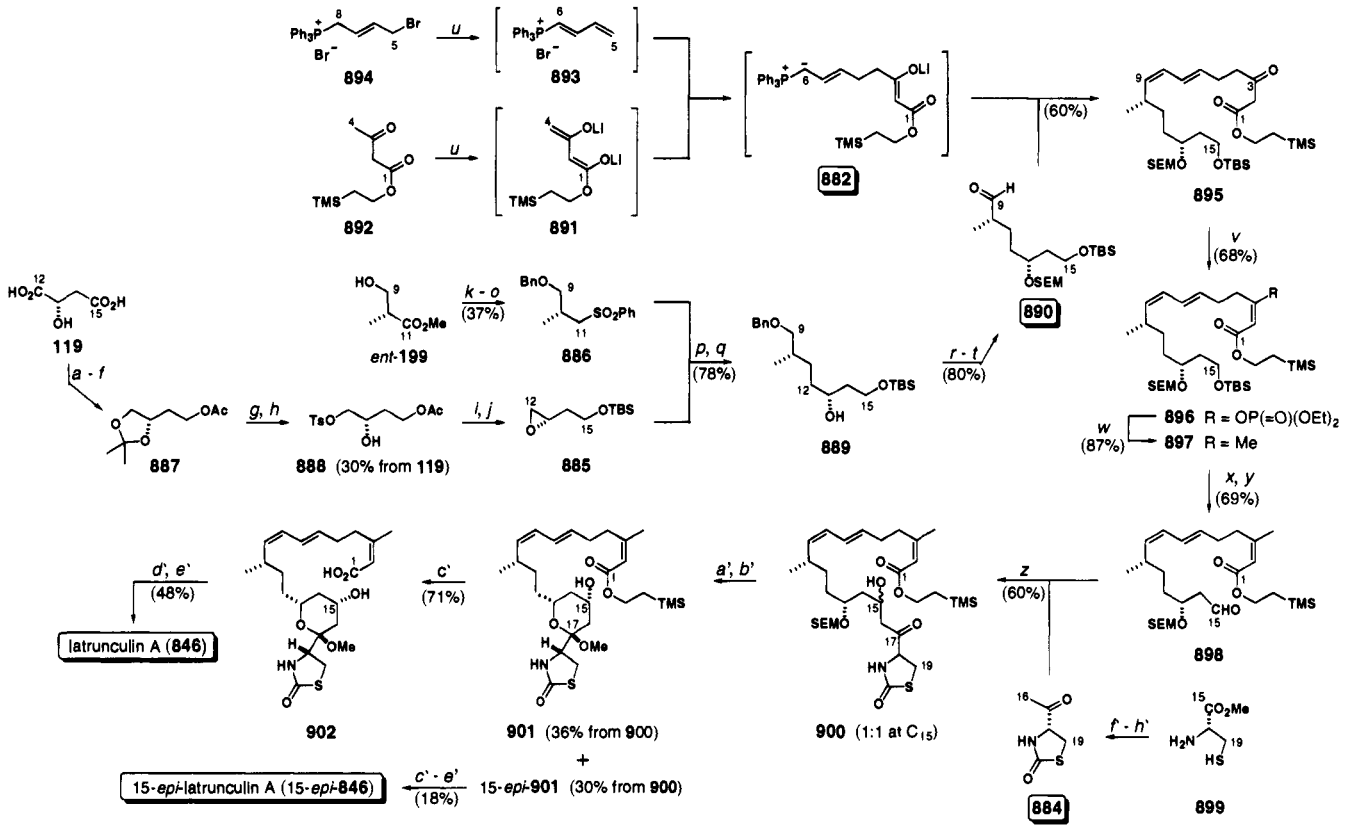
three principal segments **882**–**884** depicted in Scheme 84. A Wittig olefination was used for the C_8–C_9 bond construction, and an aldol reaction was employed for the C_{15}–C_{16} bond construction. After acetalization at C_{17}, macrocyclization was accomplished by means of the Mitsunobu reaction.[85] Note that the contemporaneous Smith synthesis of latrunculin A[297b,c] employed the same principal disconnections, but used a different order of segment assembly.

The C_9–C_{15} aldehyde segment representing synthon **883** was assembled from two four-carbon segments, **885** and **886** (Scheme 85). Epoxide **885** was prepared from (*S*)-(−)-malic acid (**119**).[308] An initial six-step sequence of protecting group exchanges and adjustment of oxidation level gave **887**, and acetonide deprotection and selective primary tosylation of the derived diol then furnished **888**. Treatment of **888** with base formed the epoxide and simultaneously cleaved the C_{15} acetate; finally, TBS protection at C_{15} provided the desired **885**. Meanwhile, sulfone **886** was obtained in five routine steps from methyl (*R*)-3-hydroxy-2-methylpropionate (*ent*-**199**). Coupling of the lithio anion of **886** with **885** followed by reductive removal of the sulfone group provided the C_9–C_{15} segment **889**. After protection of the C_{13} alcohol, deprotection at C_9 and Swern oxidation[38] then gave the key aldehyde **890**.

The White methodology for construction of (*E*,*Z*)-1,3-dienes involves addition of an enolate dianion to a dienylphosphonium salt followed by an *in situ* *Z*-selective Wittig reaction[309] of the derived *E*-ylide with an aldehyde.[307] Thus, the dilithio anion **891** of β-keto ester **892** was alkylated with diene **893**,[310] which was in turn obtained via deprotonation of the phosphonium bromide **894**,[311] to give the C_1–C_8 (*E*)-ylide **882**. Reaction of **882** with aldehyde **890** then afforded the C_1–C_{15} segment (*E*,*Z*)-**895**, along with a trace of the (*E*,*E*)-diene.[312] Stereoselective formation of the (*E*)-enolate of β-keto ester **895**[313] and trapping with diethylphosphorochloridate gave the (*E*)-enol phosphate **896**, which reacted with a methylmagnesiocuprate[314] with retention of configuration at C_3 to give the ester **897**. Selective silyl ether cleavage at C_{15}, followed by Swern oxidation,[38] then furnished aldehyde **898**.

Methyl ketone **884** was obtained in three steps from L-cysteine methyl ester (**899**), involving initial thiazolidinone formation by reaction with CO and O_2 in the presence of selenium.[315] Aldol reaction of the mixed lithio-cerio dianion of ketone **884** with alde-

Scheme 85. White Latrunculin A Synthesis[298] *a*

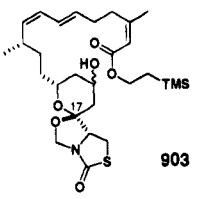


a (a) MeOH, AcCl; (b) DHP, H^+; (c) LAH; (d) MeOH, H^+; (e) Me_2CO, H^+; (f) Ac_2O, py; (g) AcOH, H_2O; (h) *p*-TsCl, py; (i) K_2CO_3, MeOH; (j) TBSCl, imidazole; (k) $Cl_3CC(=NH)OBn$, TfOH; (l) LAH; (m) *p*-TsCl, py; (n) NaI; (o) $PhSO_2Na$; (p) **886**, ^{n}BuLi; **885**; (q) Na(Hg); (r) SEMCl, $^i Pr_2NEt$; (s) H_2, 10% Pd–C; (t) Swern oxidation; (u) LDA; (v) $(EtO)_2POCl$, $^i Pr_2NEt$, DMAP; HMPA; (w) MeCu, MeMgCl; (x) MeOH, H^+; (y) Swern oxidation; (z) **884**, LDA; $CeCl_3$; **898**; (a') HF; (b') MeOH, H^+; (c') TBAF; (d') Ph_3P, DEAD; (e') AcOH, H_2O; (f') CO, O_2, Se; (g') AcOH, HCl; (h') MeLi, MeMgCl.

hyde **898**, without protection of the nitrogen atom in **884** (*vide infra*), gave C_1-C_{19} segment **900** as an inseparable 1:1 mixture of C_{15} epimers. Selective cleavage of the C_{13} SEM ether by acidic hydrolysis then led to a spontaneous ring closure to form the hemiacetal at C_{17}, and subsequent treatment with acidic methanol furnished the methyl acetals **901** and 15-*epi*-**901**. After separation, the 15α alcohol (**901**) was taken on to latrunculin A (**846**). Thus, cleavage of the (trimethylsilyl)ethyl ester from **901** gave seco-acid **902**. Cyclization under Mitsunobu conditions[85] occurred with inversion at C_{15}, and subsequent hydrolysis of the C_{17} methyl acetal then gave the natural product. In an analogous manner the 15β alcohol (15-*epi*-**901**) was transformed into 15-*epi*-latrunculin A. Note that, in theory, 15-*epi*-**901** could also supply the natural product, *i.e.* latrunculin A, by means of carboxyl-activated macrolactonization[300] which would be expected to occur with retention of configuration at C_{15}. This avenue was apparently not explored by White and Kawasaki.

Thus, in this synthesis, three of the five stereogenic centers in latrunculin A were obtained from the chiral pool (C_{10}, C_{13}, and C_{18}), the C_{17} stereogenic center was constructed using a substrate-controlled reaction (**900** → **901**), and the C_{15} stereogenic center was not controlled (**901** and its C_{15} epimer were separated). [Latrunculin A (**846**): 0.3% overall yield from (±)-**857**; 26 steps longest linear sequence; 35 steps total; 7 steps per stereogenic center.]

Finally, note that, as in the Smith synthesis of latrunculin A, the choice of group used to protect the thiazolidinone nitrogen atom proved to be critical. White and Kawasaki found it advantageous to use no protecting group at all. Use of the MOM protecting group, for instance, on thiazolidinone **884** led, after aldol coupling and hemiacetal formation at C_{17}, to participation of the formaldehyde unit thus forming the *N,O*-acetal **903**. This acetal proved to be extremely resistant to hydrolysis and **903** could not be converted to latrunculin A. Other protecting groups on the nitrogen atom of **884** proved to be difficult to remove after lactonization. The identification of suitable protecting groups thus continues to be a nontrivial issue when contemplating the synthesis of complex polyfunctional natural products.

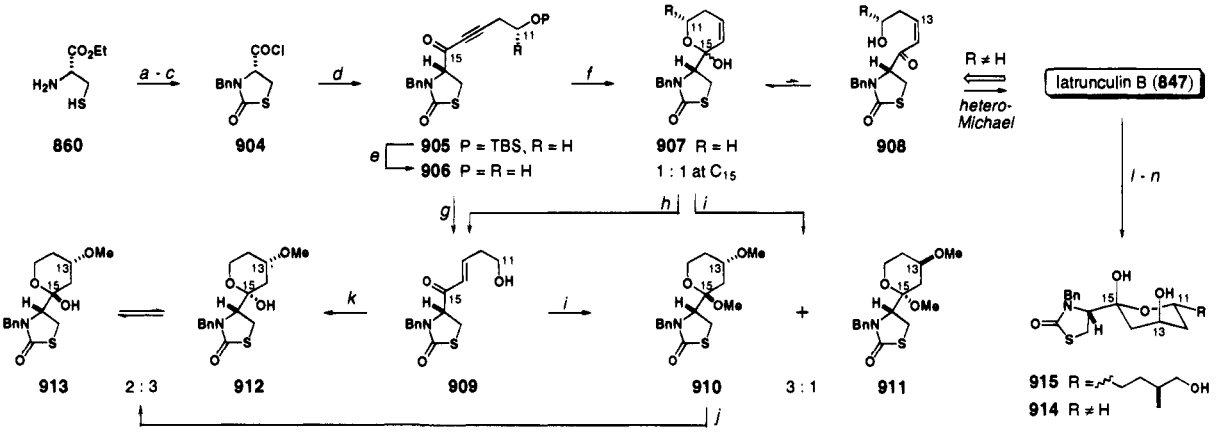


3. Kashman Model Studies on Latrunculin Tetrahydropyran Ring[292d,e]

Starting from L-cysteine, Kashman *et al.* have synthesized some model 2-thiazolidinone–tetrahydropyran ring systems of the latrunculins (Scheme 86). Reaction of L-cysteine ethyl ester (**860**) with phosgene afforded the thiazolidinone,[316] and then protection of the nitrogen atom and transformation of the C_{15} ester to the acyl chloride gave **904**. Palladium-catalyzed coupling[317] of **904** with an alkynyl stannane supplied the tetrahydropyran ring precursor **905**. After cleavage of the C_{11} TBS ether, to afford **906**, partial hydrogenation over Lindlar's catalyst and *in situ* hemiacetal formation gave **907** (as a 1:1 mixture of epimers at C_{15}, together with 5% of the open *cis* δ-hydroxy-α,β-unsaturated ketone **908**). Hetero-Michael addition to C_{13} of **908** (in the case R ≠ H) was suggested as a possible route to latrunculin B. Partial hydrogenation of **906** over Pd/$BaSO_4$ furnished the *trans* δ-hydroxy-α,β-unsaturated ketone **909**, which could also be obtained by basic equilibration of **907**.

Michael addition of methanol, in the presence of K_2CO_3, to either **907** or **909** followed by acetalization of the resulting hemiacetal by addition of $BF_3{\cdot}OEt_2$ to the methanolic solution led to two out of the four possible C_{13},C_{15} dimethoxy derivatives. Compounds **910** and **911** were obtained in a ratio of 3:1. Acid treatment of either **910** or **911** gave the corresponding hemiacetal: thus **910** provided **912** and **913** as a 3:2 equilibrium mixture. Methanol addition to **909** without acetalization also provided **912** and **913** as an equilibrium mixture. Note that none of the tetrahydropyrans **910**–**913**, which lack an alkyl substituent at C_{11}, possess the correct configurations for C_{13} *and* C_{15} of the latrunculins as depicted in **914**. Note also that NMR studies on an analogue **915** of **914** (R = $(CH_2)_2CH(CH_3)CH_2OH$), obtained by reduc-

Scheme 86. Kashman Latrunculin B THP Ring Model Studies[292d,e] a



[a] (a) $COCl_2$; (b) BnBr, NaH; (c) H^+; $SOCl_2$; (d) $TBSOCH_2CH_2C{\equiv}CSn^nBu_3$, $Pd(PPh_3)_4$; (e) H^+; (f) H_2, Lindlar catalyst; (g) H_2, Pd–$BaSO_4$, py; (h) MeOH, py; (i) MeOH, K_2CO_3; $BF_3{\cdot}OEt_2$; (j) H^+, SiO_2; (k) MeOH, K_2CO_3; (l) MeOH, $BF_3{\cdot}OEt_2$; (m) O_3; $NaBH_4$; (n) H^+.

tive ozonolysis of latrunculin B, showed that it exists in the single cyclic hemiacetal conformation illustrated. Thus the studies revealed that the presence of an alkyl substituent at C_{11} (*i.e.* R ≠ H for **908** → **914**) would be essential in order for the correct latrunculin configuration at C_{13} to be generated by hetero-Michael addition.

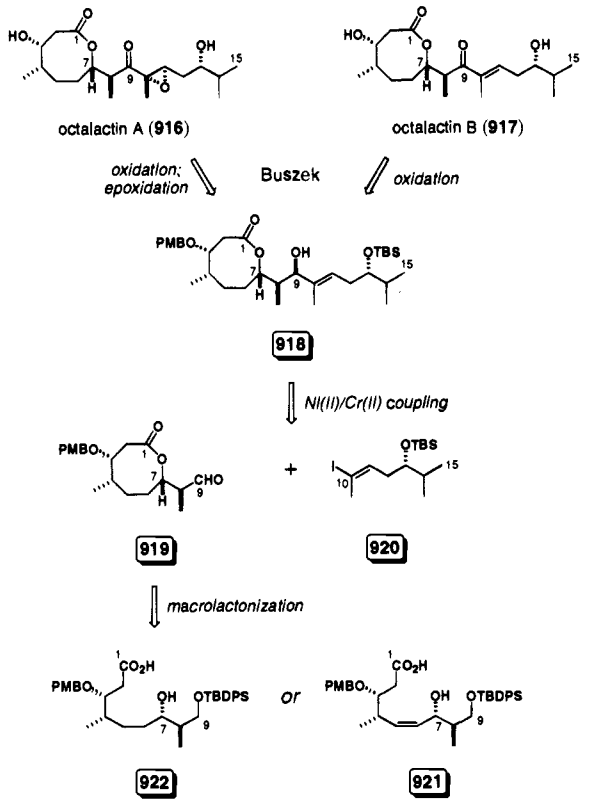
L. The Octalactins

Octalactins A and B (**916** and **917** in Scheme 87) are two eight-membered lactones which have been isolated from a marine-derived actinomycete found living on the surface of the Sea of Cortez gorgonian octocoral *Pacifigorgia* sp.[318] Whereas octalactin A exhibits strong cytotoxicity against certain melanoma and human colon tumor cell lines, octalactin B is completely inactive in the same assays. The octalactins are not, in the strictest sense, macrolides, but are included in this review owing to the fact that octalactin A represents one of the comparatively few examples of medium-ring marine lactones which displays significant biological activity.[319] The first total syntheses of both octalactin A and B were accomplished by Buszek *et al.* in 1994;[320] this work serving to establish the absolute configuration of the natural products. Total syntheses were also reported by Williams and Clardy later in the same year.[321]

1. Buszek Total Syntheses[320]

Buszek *et al.* synthesized octalactins A and B from a common intermediate (**918** in Scheme 87), which was obtained by Ni(II)/Cr(II)-mediated coupling[78] of the C_1-C_9 and $C_{10}-C_{15}$ segments **919** and **920**. The key step in the synthetic approach to **919** was intended to be lactonization of the unsaturated seco-acid **921**, which was expected to be facile owing to the conformational rigidity imparted by the double bond, followed by hydrogenation of the *cis* olefin.[322] However, in the actual synthesis of **919**, an unprecedented lactonization of the corresponding saturated seco-acid **922** was found to be preferable.

Scheme 87

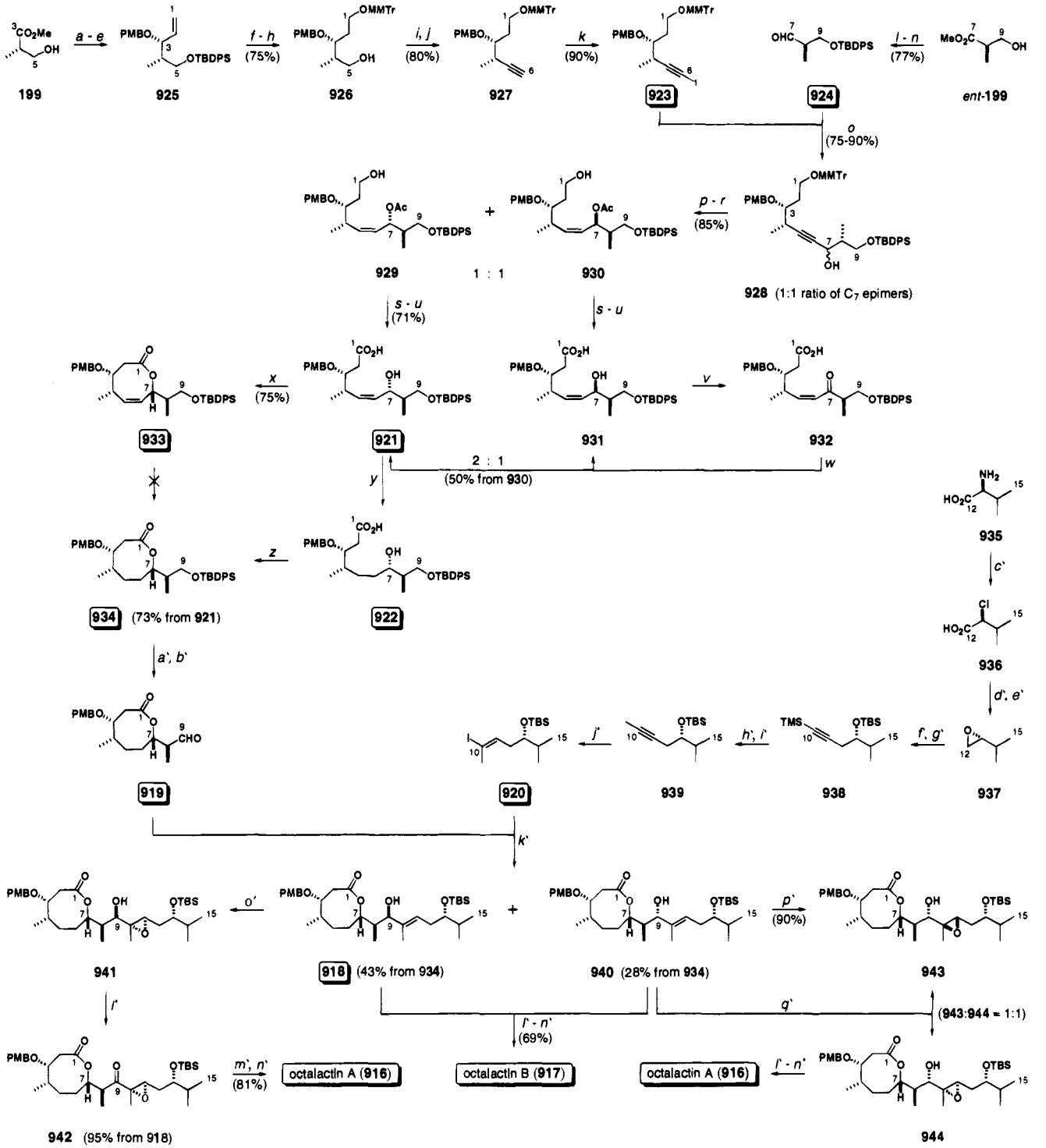


Construction of the C_1-C_9 segment **928** was based on coupling of the C_1-C_6 and C_7-C_9 segments **923** and **924** (Scheme 88). Compounds **923** and **924** were obtained from, respectively, the *S* and *R* enantiomers of methyl 3-hydroxy-2-methylpropionate, *i.e.* **199** and *ent*-**199**. Thus, **199** was converted to alkene **925** in five steps, with unspecified diastereoselectivity for the formation of the stereogenic center at C_3. Hydroboration of **925** followed by protection of the resulting primary alcohol and subsequent cleavage of the C_5 silyl ether furnished alcohol **926**. After oxidation of **926** to the C_5 aldehyde, condensation with Seyferths' reagent ($(MeO)_2P(=O)CHN_2$)[241a] gave alkyne **927**, and iodination then supplied **923**. Ni(II)/Cr(II)-mediated coupling[78] of iodide **923** with aldehyde **924**, obtained in three steps from *ent*-**199**, occurred with negligible stereoselectivity, affording the C_1-C_9 segment **928** as an inseparable mixture of C_7 epimers. Hydrogenation using Lindlar's catalyst, followed by acetylation of the C_7 hydroxyl and deprotection at C_1 then delivered alkene **929** with the correct configuration at C_7, together with its C_7 epimer **930**. After separation of **929** and **930**, two-stage oxidation at C_1 of **929** followed by deacetylation then supplied the unsaturated seco-acid **921**. Similarly, **931** was obtained from **930**. The undesired epimer **931** could be recycled via oxidation, to give **932**, followed by reduction, which gave a 2:1 ratio of **921** and **931**. Cyclization of **921** to provide the unsaturated lactone **933** was accomplished by means of the Corey–Nicolaou "double-activation" protocol (formation of the 2-pyridyl thioester of **921** followed by $AgBF_4$-mediated cyclization).[322,323] Unfortunately, all attempts to obtain the saturated lactone **934** by reduction of the double bond of **933** proved unsuccessful.

As an alternative, Buszek *et al.* investigated lactonization of the saturated seco-acid **922**, which was obtained by hydrogenation of **921** prior to cyclization. By using the Corey–Nicolaou procedure, cyclization of **922** was in fact straightforward: the corresponding lactone **934** was obtained in a yield (73%) comparable to that achieved for the unsaturated analogue **933**. Note that this represents the first example of a high-yielding synthesis of an eight-membered lactone from a *saturated* seco-acid precursor. The use of an olefin moiety to provide extra conformational rigidity in the seco-acid appears not to be necessary in this particular case: the combined influences of the stereochemical arrangement of **922** and the sterically demanding protecting groups apparently lead to a preferred conformation in the presumed transition state[324] that sufficiently facilitates ring closure. Note that other diastereomeric acyclic precursors exhibited varying propensity for cyclization: thus, whereas **934** and its C_7 epimer were both formed in 96 h, the C_3,C_7 bis-(epimer) was obtained after only 50 h and the C_3 epimer required 2 weeks.

Desilylation of **934** followed by oxidation gave the C_1-C_9 aldehyde segment **919**. Meanwhile, the $C_{10}-$

Scheme 88. Buszek Octalactin A and B Syntheses[320] [a]



[a] (a) DHP, *p*-TsOH; (b) DIBAL; $H_2C{=}CHMgBr$; separate C_3 epimers; (c) PMBCl, KH; (d) PPTS, EtOH; (e) TBDPSCl, imidazole; (f) 9-BBN; H_2O_2, NaOH; (g) MMTrCl, Et_3N; (h) TBAF; (i) Dess–Martin periodinane; (j) $(MeO)_2P(=O)CHN_2$, ^{t}BuOK; (k) I_2, morpholine; (l) TBDPSCl, imidazole; (m) DIBAL; (n) Dess–Martin periodinane; (o) **923** + **924**, $NiCl_2$ (1.0%)–$CrCl_2$; (p) H_2, Lindlar catalyst; (q) Ac_2O, DMAP, py; (r) PPTS, MeOH; (s) Dess–Martin periodinane; (t) $NaClO_2$, 2-methyl-2-butene, ^{t}BuOH; (u) K_2CO_3, MeOH; (v) Dess–Martin periodinane; (w) L-selectride, $CeCl_3$; (x) 2,2'-pyridine disulfide, PPh_3; $AgBF_4$; (y) H_2, 10% Pd–C; (z) 2,2'-dipyridyl disulfide, PPh_3; $AgBF_4$; (a') TBAF, AcOH; (b') Dess–Martin periodinane; (c') $NaNO_2$, HCl; (d') LAH; (e') KOH; (f') TMS–C≡C–Li, $BF_3{\cdot}OEt_2$; (g') TBSCl, imidazole; (h') 1 N NaOH; (i') ^{n}BuLi; MeI; (j') Cp_2ZrClH; I_2; (k') **919** + **920**, $NiCl_2$ (0.1%)–$CrCl_2$; (l') Dess–Martin periodinane; (m') HF; (n') DDQ, H_2O; (o') $VO(acac)_2$, ^{t}BuOOH; (p') *m*-CPBA; (q') $Mo(CO)_6$, ^{t}BuOOH.

C_{15} iodide segment **920** was prepared from L-valine (**935**). Thus, **935** was converted via **936** into epoxide **937**, according to the procedure of Koppenhoeffer and Schurig.[325] Yamaguchi coupling[87] of **937** with lithium (trimethylsilyl)acetylide followed by hydroxyl protection then gave **938**. Hydrolytic removal of the trimethylsilyl group followed by methylation supplied alkyne **939**, which was regioselectively hydrozirconated and iodinated[326] to generate **920**. Ni(II)/Cr(II)-mediated coupling[78] of **919** and **920** then afforded a 1.5:1 ratio of C_9 epimers **918** and **940**. Oxidation of both **918** and **940** followed by deprotection provided

octalactin B (**917**). Synthesis of the bioactive congener octalatin A required stereoselective epoxidation of the $C_{10}-C_{11}$ alkene. Thus, vanadium-mediated epoxidation[88] of the major coupling adduct **918** furnished **941** as a single isomer with the required epoxide configuration. Oxidation of **941** then gave **942** and deprotection afforded octalactin A (**916**). The minor coupling adduct **940** could also be transformed to octalactin A. Whereas epoxidation of **940** with *m*-CPBA led to the undesired epoxide stereochemistry (**943**), reaction with molybdenum-hydroperoxide[88a] delivered a 1:1 mixture of epoxides **943** and **944**. Oxidation of **944** followed by protecting group removal then supplied the bioactive natural product. In the synthesis of octalactin A by Buszek *et al.*, the stereogenic centers at C_4 and C_8 originate from the chiral pool (from **199** and *ent*-**199**, respectively), and the remaining five stereogenic centers are introduced by substrate-controlled reactions. Unfortunately, the stereochemical efficiency of the route is at present limited by the low stereoselectivity encountered in two of these reactions: namely the two instances of Ni(II)/Cr(II)-mediated coupling reactions: **923** + **924** → **928** and **919** + **920** → **918**. [Octalactin B (**917**): 4.8% overall yield from **925** with no recycling; 26 steps longest linear sequence; 37 steps total; ~7 steps per stereogenic center; octalactin A (**916**): 3.2% overall yield from **925** with no recycling; 27 steps longest linear sequence; 38 steps total; ~5 steps per stereogenic center.]

2. Clardy Total Syntheses[321]

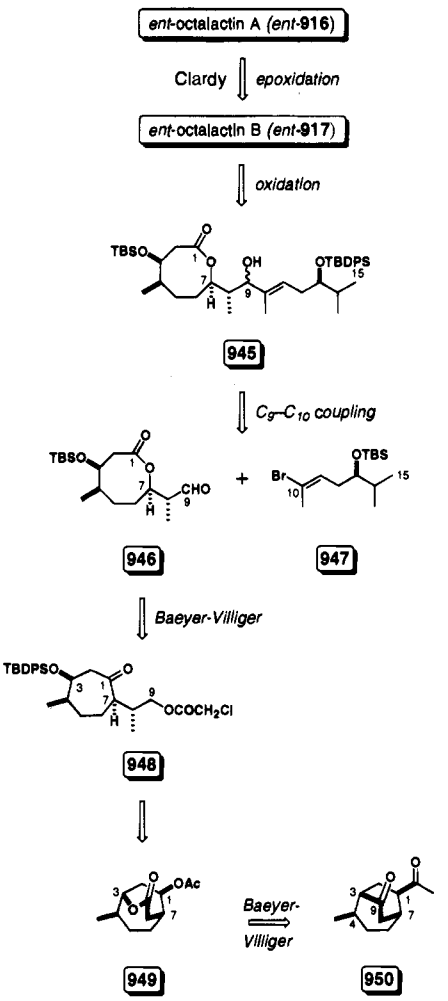
The absolute configurations of the octalactins were unknown when Williams and Clardy embarked upon their synthetic studies. Upon completion of the total syntheses, it was apparent that they had arbitrarily prepared the unnatural antipodes, *ent*-**916** and *ent*-**917**. The latter stages of the synthesis were similar to the route of Buszek in that the C_1-C_{15} segment **945** was prepared via coupling of C_1-C_9 segment **946** and $C_{10}-C_{15}$ segment **947** (Scheme 89, *cf.* **918** ⇒ **919** + **920** in Scheme 87). However, Williams and Clardy designed a route to **946** that was entirely different from the Buszek strategy, whereby formation of the eight-membered lactone was accomplished by a Baeyer–Villiger oxidation of ketone **948**. Compound **949**, the precursor to ketone **948**, was itself obtained via double Baeyer–Villiger oxidation of the key diketone intermediate **950**.

The synthesis of **950** began with (*R*)-citronellic acid (**951**), which supplied the C_3-C_7 portion, bearing a stereogenic center at C_4, along with C_9 (Scheme 90). Thus, esterification of **951** and subsequent ozonolysis gave the C_7 aldehyde; methylenation according to the procedure of Osima (Zn, CH_2I_2, $AlMe_3$)[327] then supplied the alkene **952**. After saponification of the ester and formation of the corresponding acid chloride, $SnCl_4$-induced cyclization afforded a mixture of β-chlorocycloheptanones (**953**); treatment with DBU then furnished cycloheptenone **954**. Kinetic deprotonation of **954** led to the cross-conjugated silyl dienol ether **955**, and a stereoselective Mukaiyama double-Michael reaction with methyl vinyl ketone[328] gave the diketone **950**, via intermediate **956**.

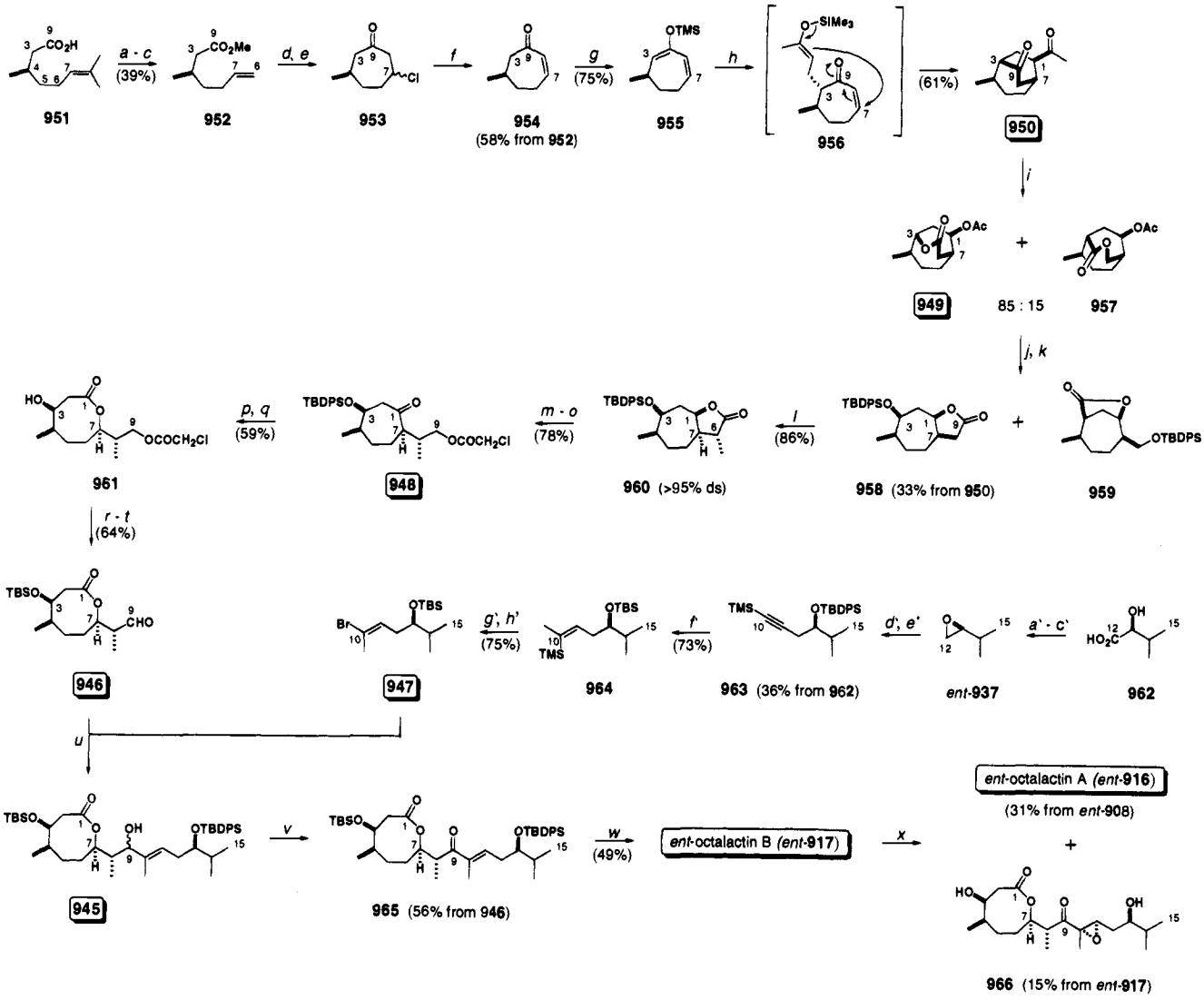
Double Baeyer–Villiger oxidation of **950** using peracetic acid afforded an 85:15 mixture of the regioisomeric lactones **949** and **957**. Note that the use of more reactive peracids led to lower selectivity for formation of the required **949**. Sequential saponification and acid-catalyzed lactonization of the inseparable mixture of **949** and **957** supplied the corresponding acyl-migrated hydroxylactones; protection of the hydroxyl then gave **958** and **959**. After separation, alkylation on the convex face of **958**[329] furnished **960** with >95% ds in favor of the required configuration at C_8. Reduction of the lactone to afford the C_1,C_9 diol was followed by selective protection of the C_9 hydroxyl; oxidation at C_1 then supplied the cycloheptanone **948**. Baeyer–Villiger oxidation of **948** proved troublesome. However, after cleavage of the silyl ether at C_3, the oxidation was straightforward, and under carefully controlled conditions provided the eight-membered lactone **961** with the correct configuration at all of its stereogenic centers. Reprotection of the C_3 hydroxyl under mildly acidic conditions,[330] ammonolytic deprotection at C_9, and subsequent oxidation then afforded the C_1-C_9 segment **946**.

Meanwhile, the $C_{10}-C_{15}$ segment **947** was prepared from (*S*)-2-hydroxy-3-methylbutanoic acid (**962**). Thus, reduction of **962** followed by regioselective mesylation of the resulting diol and subsequent base-induced cyclization gave the epoxide *ent*-**937**, which was elaborated to the alkynylsilane **963** via Yamaguchi coupling[87] with lithium (trimethylsilyl)acetylide followed by hydroxyl protection, as in the Buszek

Scheme 89



Scheme 90. Clardy *ent*-Octalactin A and B Syntheses[321] [a]



[a] (a) *p*-TsOH, MeOH; (b) O_3; Me_2S; (c) Zn, CH_2I_2, $AlMe_3$; (d) LiOH, H_2O; (e) $(COCl)_2$; $SnCl_4$; (f) DBU; (g) LDA; TMSCl; (h) $MeCOCH{=}CH_2$, $SnCl_4$; (i) CH_3CO_3H, AcOH, NaOAc; (j) KOH, MeOH; HCl; (k) TBDPSCl, imidazole; (l) LDA; MeI, HMPA; (m) $LiBH_4$; (n) $(ClH_2CCO)_2O$, Et_3N; (o) Swern oxidation; (p) HF; (q) CF_3CO_3H; (r) $MeCOCH{=}C(Me)OTBS$, *p*-TsOH; (s) liquid NH_3; (t) Dess–Martin periodinane; (u) **947**, ^{t}BuLi; **946**; (v) Dess–Martin periodinane; (w) HF; (x) $VO(acac)_2$, ^{t}BuOOH; (a') LAH; (b') MsCl, Et_3N; (c') K_2CO_3, MeOH; (d') TMS–C≡C–Li, $BF_3{\cdot}OEt_2$; (e') TBDPSCl, imidazole; (f') $(c\text{-}C_6H_{11})_2BH$; MeLi; MeI; (g') Br_2; (h') MeONa, MeOH.

synthesis[320] (*cf.* **937** → **938** in Scheme 88). Compound **963** was transformed into the vinylsilane **964** according to the method of Nozaki,[331] involving (i) regioselective *cis* hydroboration of **963**, (ii) transmetalation of the resulting vinylborane to generate the corresponding vinyllithium, and (iii) alkylation with methyl iodide with retention of the double-bond configuration. *Trans* bromination of **964** followed by base-induced *trans* desilicobromination, according to the procedure of Miller,[332] then afforded vinyl bromide **947** with inversion of the double-bond configuration. Note that the Buszek synthesis also involved transformation of an alkynylsilane into a vinyl halide, but utilized different methodology (*cf.* **938** → **939** → **920** in Scheme 88).

Coupling of aldehyde **946** with the vinyllithium derived from **947** furnished a mixture of C_9 epimers (**945**); oxidation of the mixture to provide **965**, followed by removal of the protecting groups, then supplied the unnatural antipode of octalactin B (*ent*-**917**). Finally, vanadium-mediated epoxidation[88] of *ent*-**917** proceeded with moderate stereoselectivity, affording a 2:1 mixture of unnatural enantiomer of octalactin A (*ent*-**916**) and its C_{10},C_{11} bis(epimer) **966**. In this synthesis, the C_4 and C_{13} stereogenic centers originated in the chiral pool (*cf.* in the Buszek synthesis, the C_4 and C_8 stereogenic centers were obtained from the chiral pool). All the other stereogenic centers were installed using substrate-controlled asymmetric induction. [*ent*-Octalactin B (**917**): 0.2% overall yield from **951**; 23 steps longest linear sequence; 31 steps total; ~6 steps per stereogenic center; *ent*-octalactin A (**916**): 0.1% overall yield from **951**; 24 steps longest linear sequence; 32 steps total; ~3 steps per stereogenic center.]

III. Concluding Remarks

The foregoing work demonstrates that rapid progress has been made in the field of organic chemistry concerned with the total synthesis of bioactive marine macrolides. Notably, most of these efforts have been concentrated over the last 5 years. The range of exquisite chemical structures fashioned by marine organisms, which seems to be limitless,

needs to be matched by the ingenuity and resourcefulness of synthetic chemists, and the challenge associated with macrolides like the halichondrins and swinholides is firmly at the cutting edge of contemporary synthetic organic chemistry. Such complex targets have provided an important impetus for the development of new methods and strategies.

Returning to the issues highlighted in the introduction, it can be seen that workable solutions have been developed, which have culminated in the completion of a significant number of total syntheses. The growing ascendancy of acyclic methods of stereocontrol has led to increasingly concise synthetic routes (1–2 steps per stereogenic center is now becoming a realistic goal). However, *de novo* chemical synthesis has not yet reached a level of efficiency to completely eclipse all other methods for obtaining supplies of marine macrolides. The only existing total syntheses of halichondrin B and bryostatin 7, for instance, require 120 and 80 steps, respectively. Although such syntheses represent impressive contributions to organic chemistry, even more practical synthetic routes must be developed if sufficient synthetic material is to be made available for clinical evaluation in cases where the natural supply is inadequate. This remains the key challenge for the future.

Acknowledgments

We thank the EPSRC for financial support, Mrs. Cheryl Cook for assistance in obtaining copies of articles not held by the Cambridge University libraries, and Dr. Cameron Cowden, Dr. Klaus Fessner, and Miss Christine Watson for their careful proofreading of this manuscript.

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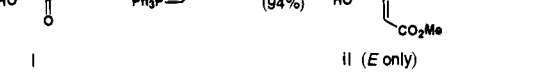

(1)

i ii (*E* only)

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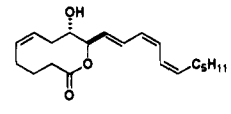
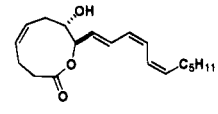


ascidiatrienolide A (iii)



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