Advances in the Total Synthesis of Biologically Important Marine Macrolides†

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† Dedicated to the late Professor Herbert C. Brown.

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1. Introduction

Marine organisms, particularly sponge invertebrates and associated bacteria, are enormously rich sources of structurally diverse secondary metabolites with unique molecular architectures.[1] These marine natural products often possess unusual and sometimes unexpected biological activities, making them valuable molecular probes for the investigation of biochemical pathways. Among these fascinating and eye-catching structures, a prominent class is the marine macrolides—highly oxygenated and stereochemically elaborate polyketides having a macrocyclic lactone as a conformational constraint.[2] Many marine macrolides demonstrate potent cell growth antiproliferative properties and offer considerable promise as lead structures for the development of new anti-cancer chemotherapeutic agents, provided the supply issue can be resolved.

For the majority of these cytotoxic macrolides, interference with the polymerization dynamics of the major protein components, tubulin and actin, of the cytoskeleton appear to be the two predominant mechanisms of action. As discussed in sections 2.1, 2.2, and 2.3, important examples of marine macrolides that interact with microtubules, suppressing normal mitotic spindle formation, include the spongistatins/altohyrtins, dictyostatin, and peloruside A. In the case of antimicrofilament macrolides,[3] the crystal structures of the protein−ligand complexes formed between G-actin and kabiramide C (**1**), jaspisamide A (**2**), and ulapualide A (**3**) (Figure 1) have recently been obtained by Rayment and Marriott et al.[4] These structures (e.g., G-actin-ulapualide A,[5] Figure 2) reveal that the macrolactone ring binds to a surface patch between subdomain 1 and 3 of G-actin, while the side chain is directed into the hydrophobic cavity between these two subdomains. Such a binding mode is similar to that of the actin-capping protein, gelsolin. Moreover, biochemical assays showed that the G-actin-macrolide complex caps the (+)-end of F-actin in a manner similar to gelso-

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Kap-Sun Yeung was born in Fujian, China. His fascination with organic synthesis grew out of research conducted with Professor Henry N. C. Wong at the Chinese University of Hong Kong, from which he received his B.Sc. degree in Chemistry in 1990. He then worked as a research assistant with Professor Chi-Ming Che at the University of Hong Kong. In 1991, he was awarded a Croucher Scholarship to study at the University of Cambridge, where he worked on the total synthesis of swinholide A and scytophycin C under the guidance of Professor Ian Paterson. Following his Ph.D. work, he carried out postdoctoral research in Professor Chi-Huey Wong's group at The Scripps Research Institute, California. In 1996, he joined the drug discovery chemistry group of BMS in Connecticut. He has broad research interests in synthetic organic chemistry and drug design.

Ian Paterson was born in Dundee, Scotland. In 1976, after receiving his B.Sc. degree in Chemistry from the University of St. Andrews, he carried out his Ph.D. work with Professor Ian Fleming at the University of Cambridge. For part of this period (1978–79), he held a junior research fellowship at Christ's College. After spending 1 year as a SERC/NATO postdoctoral research fellow with Professor Gilbert Stork at Columbia University, New York, he returned to the United Kingdom in 1980 to take up a Lectureship in Chemistry at University College London. In 1983, he moved back to Cambridge, where he is presently Professor of Organic Chemistry and a Professorial Fellow of Jesus College. His research interests encompass the total synthesis and structure determination of biologically active natural products, particularly anticancer agents, and development of new synthetic methods.

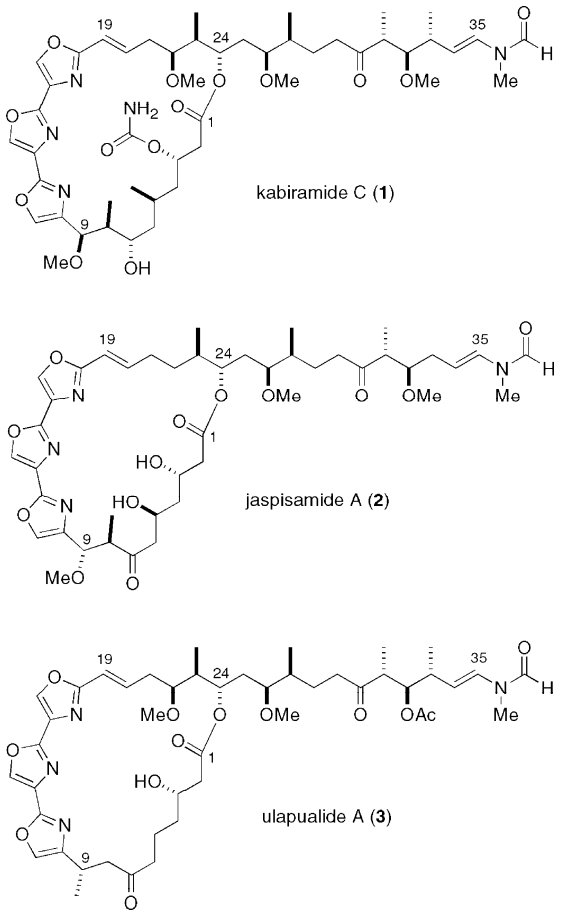


Figure 1. Structures of kabiramide C, jaspisamide A, and ulapualide A.

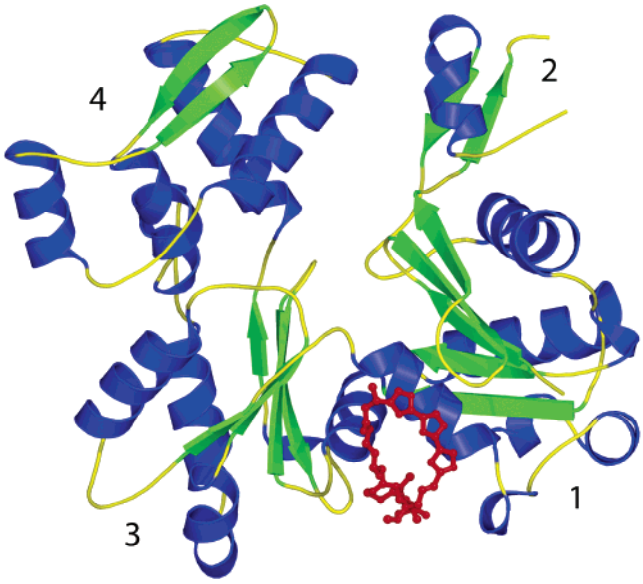
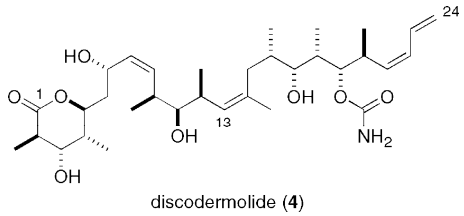


Figure 2. Structure of G-actin-ulapualide A (red) complex.[5] Actin subdomains 1−4 are labeled.

lin.[6] Importantly, these crystallographic studies also established the correct stereostructure of ulapualide A as shown in **3** (Figure 1).[5]

In general, the low natural abundance of these marine macrolides coupled with the unsustainable and unacceptable ecological impact of large-scale isolation of the producing organism preclude detailed biological evaluations, thus hampering their possible clinical development and exploitation in human medicine. These factors, combined with the impressive molecular architectures themselves, present compelling and formidable challenges to contemporary organic synthesis with regard to both strategy and methodology for their total synthesis in the laboratory. In this arena, synthesis is also important for structural elucidation, including determination of the full absolute configuration, where spectroscopic and crystallographic methods used to date may not



discodermolide (**4**)

Figure 3. Structure of discodermolide.

have permitted a full assignment. Moreover, the synthetic route selected has to meet the major challenge of being practical enough to deliver meaningful quantities of pure materials to enable extensive preclinical and possibly clinical testing as well as being sufficiently flexible to allow structural diversification to access analogues for SAR studies. A timely example, in this regard, is the recent large-scale synthesis of discodermolide (**4**, Figure 3) completed within Novartis,[7,8] enabling clinical trials of this otherwise rare anti-cancer agent, isolated originally from a deep-sea sponge.[9] Finally, such efforts directed toward marine macrolides also provide a cutting-edge platform for developing new and more efficient methodologies, particularly for realizing improved levels of stereocontrol, and novel strategies to streamline the entire synthetic route.

In this review we cover advances in the total synthesis of marine macrolides over the past 10 years (largely up to the close of 2004), following on from our extensive survey (published in 1995)[2c] and valuable contributions on this topic made by various other authors.[10] As impressive examples of biologically active marine macrolides we focus here on the recently completed total syntheses of the extraordinarily potent spongistatin/altohyrtin antimitotics as well as that of dictyostatin, peloruside A, leucascandrolide A, callipeltoside A, and miyakolide. Rather than detailing each individual step of these often lengthy and highly elaborate syntheses, we emphasize the different strategies adopted, highlight the key transformations, and compare the various methods employed based on substrate (blue disconnection labels in the retrosynthetic schemes) and reagent (red disconnection labels in the retrosynthetic schemes) control for establishing stereochemistry. Green labels are used in the retrosynthetic schemes to indicate other key bond disconnections, i.e., those that do not involve the selective installation of stereocenters.

2. Survey of Total Syntheses of Marine Macrolides

2.1. Spongistatins/Altohyrtins

In 1993, three research groups (Pettit, Kitagawa/Kobayashi, and Fusetani) independently reported a series of highly potent bis-spiroacetal-containing marine macrolides with captivating structures (Figure 4). The spongistatins, as represented by spongistatins 1 and 2, were isolated from an East Indian Ocean Perifera *Spongia* sp. by Pettit and co-workers.[11a–c] The altohyrtins, as represented by altohyrtins A (**5**), B (**6**), and C (**7**), were isolated from the Okinawan sponge *Hyrtios altum* by Kitagawa/Kobayashi,[12] and cinachyrolide A was isolated by the Fusetani group from the sponge *Cinachyra* sp., collected off Hachijo-jima Island.[13] These taxonomically different sponge sources indicate that this unique class of complex polyketides is highly likely to be produced by symbiotic bacteria. This unprecedented family of marine natural products was obtained in extremely meager quantities by bioassay-guided isolation, involving multiple extractions and chromatographic separations (e.g., 400 kg of sponge provided 13.8 mg of spongistatin 1, 112 kg of sponge provided 0.5 mg of altohyrtin A, and 6.6 kg of sponge gave 1.1 mg of cinachyrolide A). As an impressive accomplishment in structure determination in this area, the full relative and absolute configuration of the altohyrtins (as shown in Figure 4) was assigned correctly (as confirmed later by total synthesis) by Kitagawa and Kobayashi using extensive NMR studies of Mosher ester derivatives of 5-desacetylaltohyrtin A as well as employing the circular dichroism exciton chirality method.[14] In contrast, Pettit reported a partial stereostructure of spongistatin 1

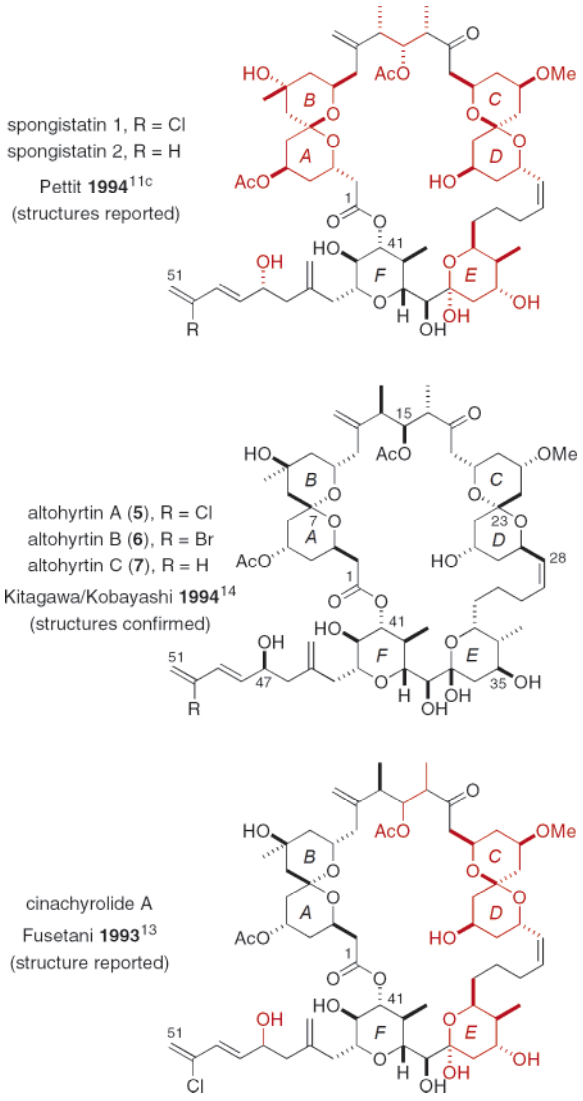


Figure 4. Structures of spongipyrans as originally reported. The structures of altohyrtin A and C, as shown, were confirmed by total synthesis[17,18] and are identical to spongistatin 1 and 2, respectively.

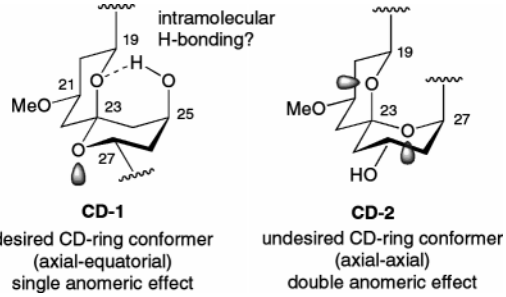


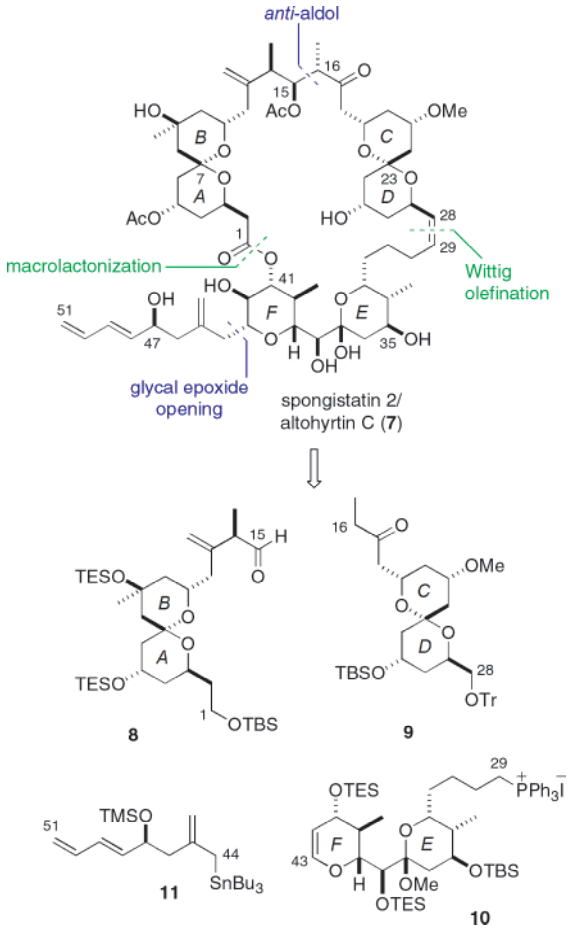
Figure 5. Conformations of spongistatin/altohyrtin CD-ring.

which differed in the regions highlighted in red,[11c] while the relative stereochemistry of cinachyrolide A was only proposed for the tetrahydropyran rings, with the configurations at C15−C16 and C47 undetermined.[13] Thus, major differences existed at the time in the relative configurations of the AB- and CD-spiroacetal rings, the E-ring tetrahydropyran, as well as the C14−C16 and C47 stereocenters, all of which needed to be considered in designing a suitably flexible synthetic approach along with accommodating variations in the side chain at C50 (R = H, Cl, or Br).

These marine macrolides stand out as among the most potent cancer cell growth inhibitory agents tested to date in the U.S. National Cancer Institute's primary panel of 60 human carcinoma cell lines having low nanomolar or picomolar GI_{50} values across the board. As the most potent member, spongistatin 1 (= altohyrtin A) exhibited an in-vitro mean panel GI_{50} of 0.15 nM and was also exceedingly potent against a subset of highly chemoresistant tumor types (typical GI_{50}, 0.03 nM),[11a,b] while in-vivo human melanoma and ovarian carcinoma xenograft studies showed curative responses at extremely low doses.[11d] Preliminary mechanistic studies demonstrated that these so-called spongipyrans inhibit mitosis by binding to tubulin in the vinca domain, preventing tubulin polymerization and thus interfering with microtubule assembly.[15]

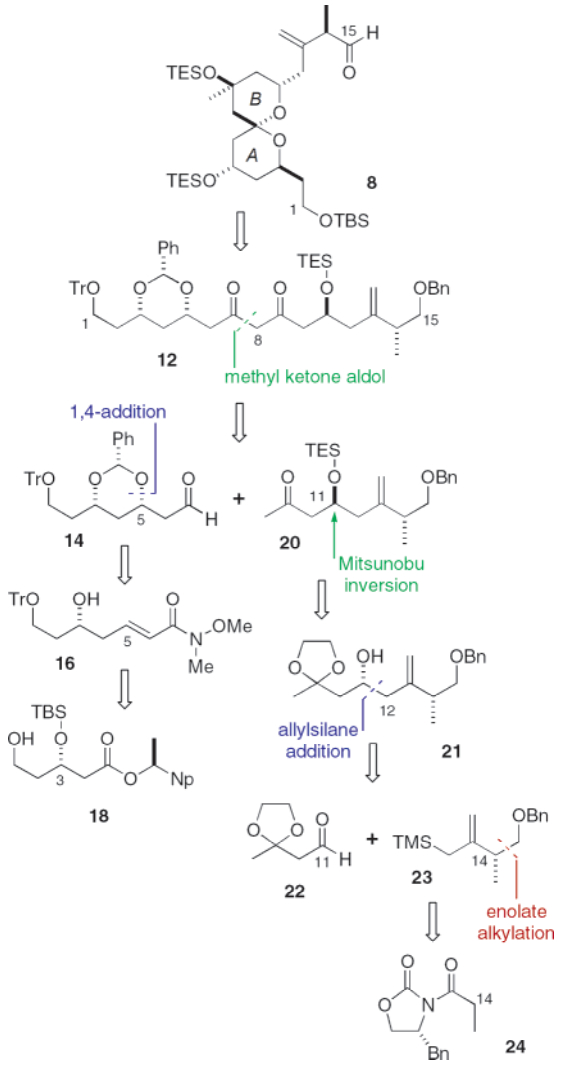
Despite these highly promising biological profiles, further testing of the spongistatins/altohyrtins was curtailed by the vanishingly small natural supply from the sponge sources. Over the past decade these appealing structures together with the need to reconcile uncertainties associated with the stereochemistry have stimulated enormous interest and efforts toward synthesizing these high-profile target molecules.[16] As described in the following sections, the Evans total synthesis of altohyrtin C reported in 1997[17] and the Kishi total synthesis of altohyrtin A,[18] reported shortly afterward, confirmed the relative and absolute stereochemical assignment made by Kitagawa and Kobayashi and established that they are in fact identical to spongistatin 2 and 1, respectively. Five other total syntheses, as reported in turn by the groups of Smith,[19] Paterson,[20] Crimmins,[21] and Heathcock,[22] have also been accomplished, each with the goal of achieving a practical solution to delivering meaningful quantities of this class of complex macrolide to resume its preclinical development.[23]

Scheme 1. Evans Strategy for the Total Synthesis of Spongistatin 2/Altohyrtin C



Structurally, the spongistatins/altohyrtins represent a formidable synthetic challenge. They contain an array of 24 stereocenters together with a 42-membered macrolactone ring embedded with two spiroacetal units (AB and CD) and two densely substituted tetrahydropyran rings (E and F) along with a delicate unsaturated side chain. Unlike the AB-spiroacetal unit, which exists in the thermodynamically stable "axial−axial" conformation and is stabilized by a double anomeric effect, the CD-spiroacetal exists in the "axial−equatorial" conformation stabilized by a single anomeric effect (**CD-1**, Figure 5). However, the required CD-ring conformation may gain some energetic benefit from hydrogen bonding between the axial C25−OH and the acetal oxygen at C23. For synthetic purposes, equilibration of the C23 acetal configuration under suitable acidic conditions can deliver the desired CD-spiroacetal subunit, but the danger is that it can reequilibrate at some later stage. In the natural product itself, the C23 configuration must presumably be governed largely by the influence of the entire macrolactone rather than merely the local environment of the CD-ring system. While the (*Z*)-alkene at C28 and the lactone linkage at C41 provide attractive points for Wittig-type fragment coupling and macrocyclization, major challenges come from how to efficiently construct both the ABCD bis-spiroacetal subunit and the highly substituted EF subunit (with or without its elaborate unsaturated side chain and the isolated

Scheme 2. Evans Strategy for the Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 2/ Altohyrtin C



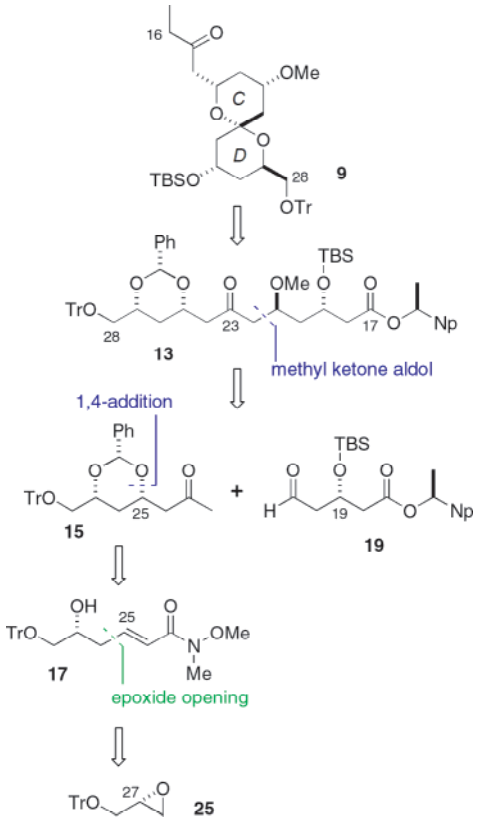
C47 hydroxyl group) and handle chemoselectivity and protecting group issues effectively for such a highly functionalized and oxygenated target.

2.1.1. Evans Synthesis of Spongistatin 2/Altohyrtin C[17]

Evans and co-workers adopted a modular synthetic approach (Scheme 1) to spongistatin 2/altohyrtin C (**7**) in which strategic disconnections at C1 (macrolactonization), C15−C16 (aldol), C28−C29 (Wittig), and C43−C44 (glycal epoxide opening) provided four principal segments, i.e., AB-subunit **8** (C1−C15), CD-subunit **9** (C16−C28), EF-subunit **10** (C29−C43), and side chain **11** (C44−C51). Major design considerations were achieving convergence and configurational flexibility as dictated by the then stereochemical discrepancies between the altohyrtins and spongistatins.

Similar strategies were adopted for the synthesis of the AB and CD spiroacetal segments **8** and **9** (compare Schemes 2 and 3). An aldol disconnection on their linear precursors, **12** and **13**, reveals 1,3-*syn* diols **14** and **15**, respectively—these being generated by an acetalization/1,4-addition sequence performed on **16** and **17**. Indeed, the (*S*)-2-naphthylethyl

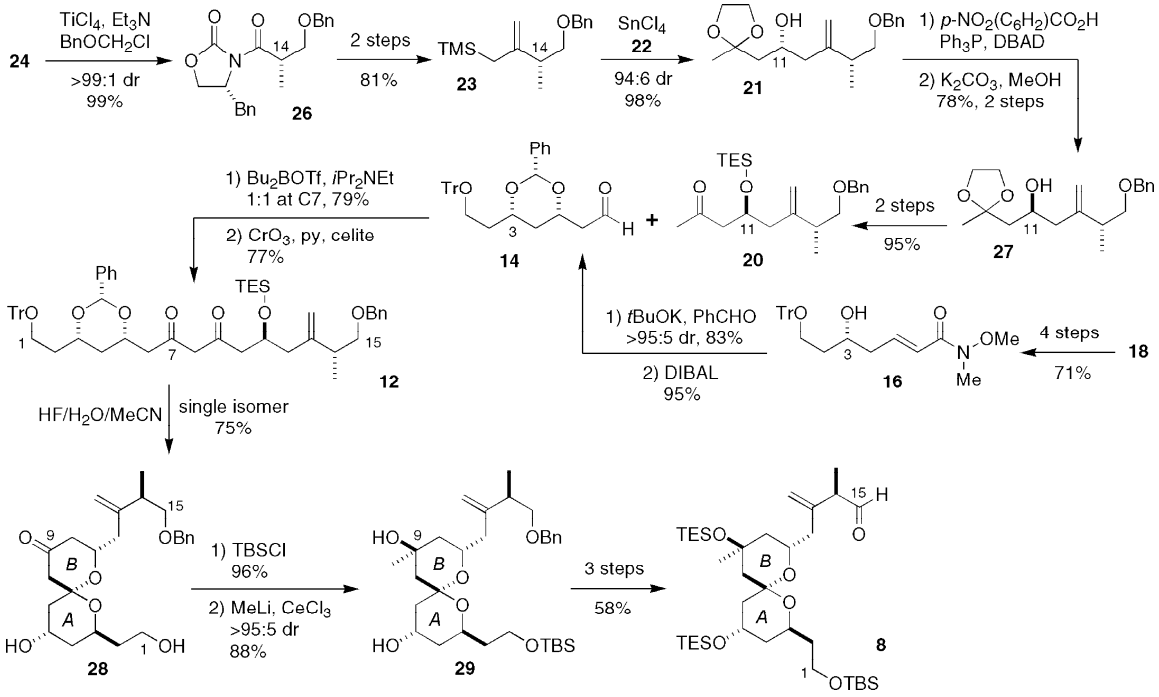
Scheme 3. Evans Strategy for the Synthesis of the C16−C28 CD-Ring Segment of Spongistatin 2/ Altohyrtin C



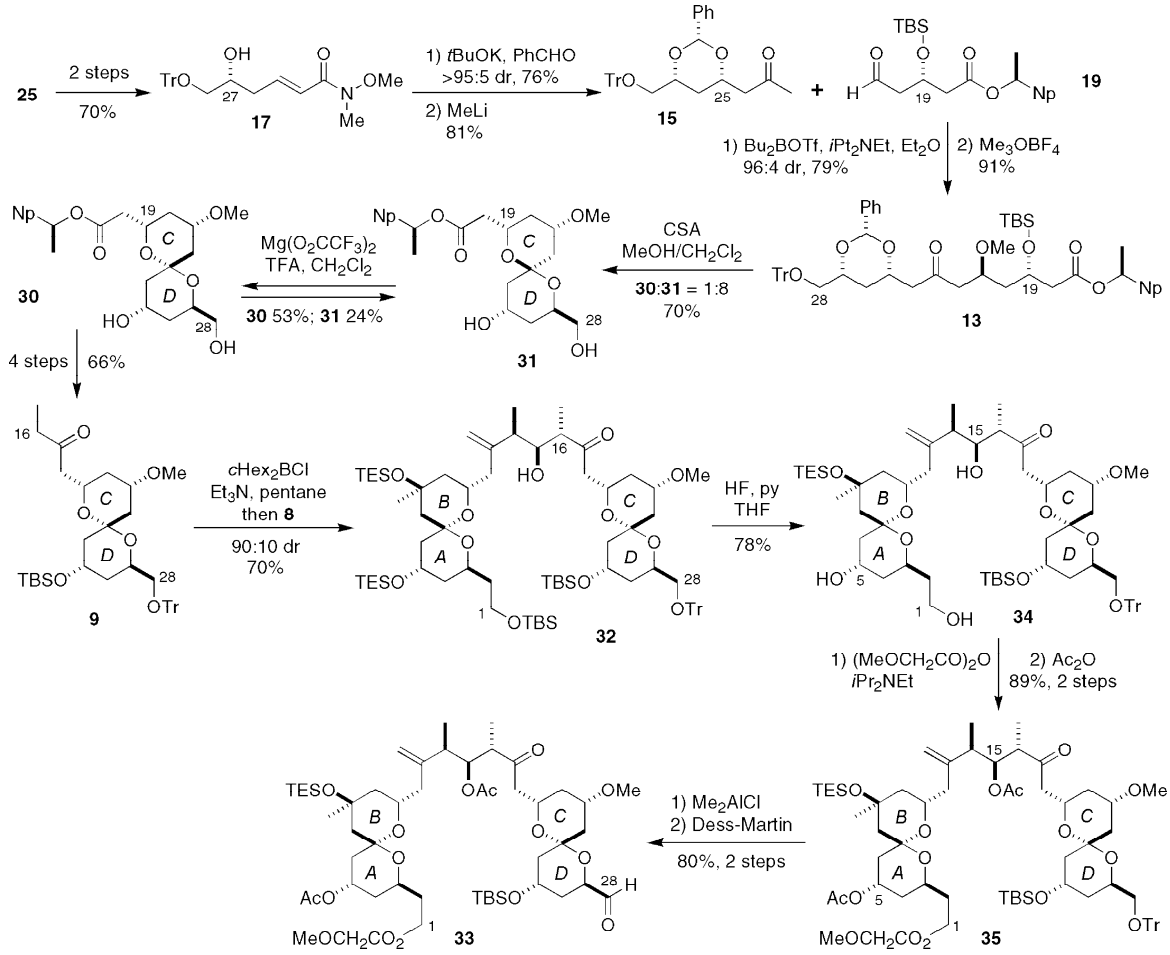
ester derivatives **18** and **19** were used in the synthesis of both the AB- and the CD-ring segments. For AB-ring segment **8**, primary alcohol **18** was converted into Weinreb amide **16** (Scheme 4), where its benzaldehyde hemiacetal derivative underwent 1,4-addition to provide 1,3-*syn* acetal (>95:5 dr) followed by its conversion into aldehyde **14** for coupling to methyl ketone **20**. This coupling partner was prepared by starting with a diastereoselective alkylation of oxazolidinone **24**. After conversion of imide **26** into allylsilane **23**, $SnCl_4$-promoted addition of **23** to aldehyde **22** installed the antipodal C11 configuration (94:6 dr). Correction of the C11 configuration in **21** by Mitsunobu inversion provided alcohol **27**, leading to methyl ketone **20**. Coupling of the boron enolate of **20** to aldehyde **14** provided an inconsequential mixture of epimeric C7 aldol products. Following oxidation to β-diketone **12**, acid treatment induced deprotection and spiroacetalization to give **28**, benefiting from a double anomeric effect. Addition of $MeLi/CeCl_3$ to ketone **28** established the C9−OH stereocenter (>95:5 dr), and diol **29** was transformed into the requisite AB-segment **8**.

The methyl ketone **15** used in the construction of the CD-ring segment was obtained (Scheme 5) in a manner similar to that of aldehyde **14**, wherein **17** derived from (*R*)-trityl glycidol (**25**) underwent a 1,4-addition via its benzaldehyde hemiacetal. Coupling of the boron enolate of **15** with aldehyde **19** was followed by conversion into methyl ether **13**. Here, 1,5-*anti* stereoinduction from the enolate component was instrumental in achieving 96:4 dr at C17.[24] Concomitant deprotection and spiroacetalization were

Scheme 4. Evans Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 2/Altohyrtin C

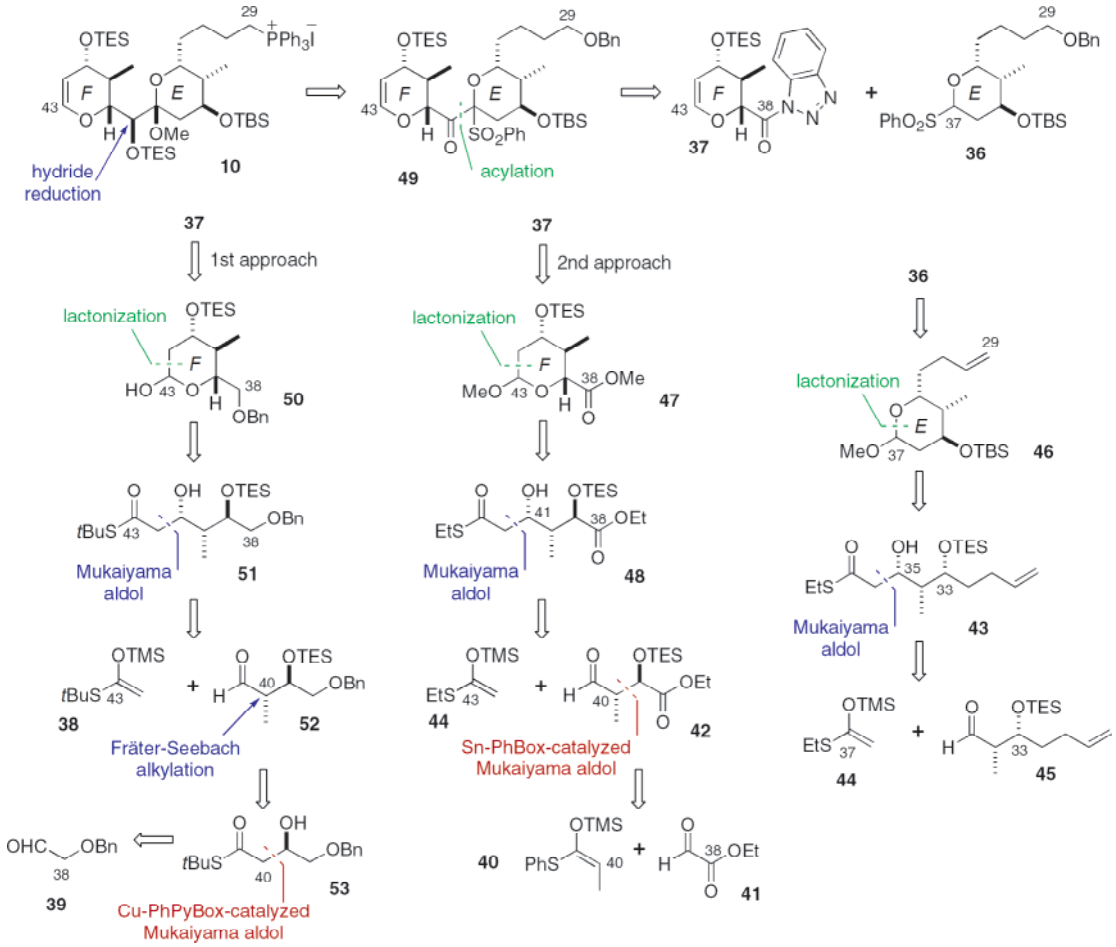


Scheme 5. Evans Synthesis of the C1−C28 ABCD-Ring Segment of Spongistatin 2/Altohyrtin C



induced by CSA to give an initial 1:8 mixture of **30** and **31**. Equilibration of unwanted acetal **31** was promoted by $Mg(OCOCF_3)_2$ to provide a 2.2:1 mixture of **30** and **31**, from which **30** was separated. The preferential formation of the desired axial−equatorial isomer **30** under these Lewis-acidic conditions was attributed to chelation from the C25−OH and C27 anomeric oxygen to the metal cation. Following

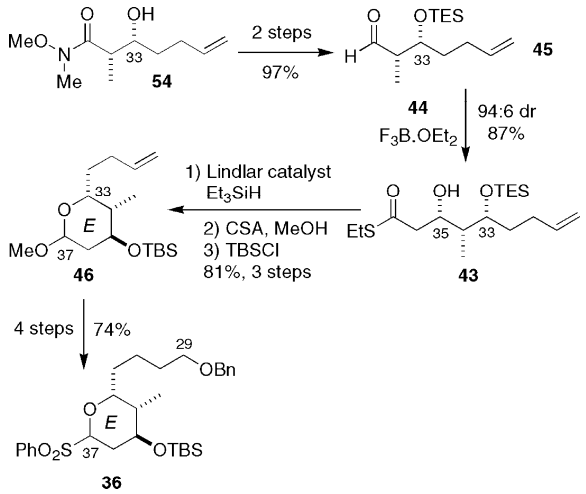
Scheme 6. Evans Strategy for the Synthesis of the C29−C43 EF-Ring Segment of Spongistatin 2/Altohyrtin C



elaboration to ethyl ketone **9**, union of its (*E*)-dicyclohexylboron enolate with AB-ring aldehyde **8** provided adduct **32** (90:10 dr). The Felkin−Anh stereoselectivity of this complex aldol coupling agreed with results reported concurrently by the Paterson group, who also proposed the strategic use of a pivotal C15−C16 *anti*-aldol coupling to assemble the full ABCD-segment.[20f−h] Adduct **32** was transformed into the C28 aldehyde **33** after installation of the two acetate groups (C5 and C15). Deprotection of the C28 trityl group proved to be challenging, where Lewis-acidic deprotection conditions generally promoted substantial isomerization of the CD spiroacetal (at C23) unless Me_2AlCl was used under special conditions.

The EF-ring segment **10** was constructed from an acylation of the E-ring sulfone **36** with a suitably activated F-ring anomeric carboxylic acid **37** (Scheme 6). The first reported approach to the synthesis of F-ring subunit used a Cu−PhPyBox-catalyzed Mukaiyama aldol reaction between silyl ketene acetal **38** and aldehyde **39** followed by a Fräter−Seebach alkylation and a later oxidation at C38. An improved route relied on a Sn(II)−PhBox-catalyzed *anti*-aldol between silylketene thioacetal **40** and ethyl glyoxylate (**41**). The C41 hydroxy-bearing stereocenter required for the macrolactonization was installed via a Mukaiyama aldol reaction on aldehyde **42**. A similar Mukaiyama aldol was used to construct the C33−C35 *all-syn* stereotriad in **43**, where the silyl

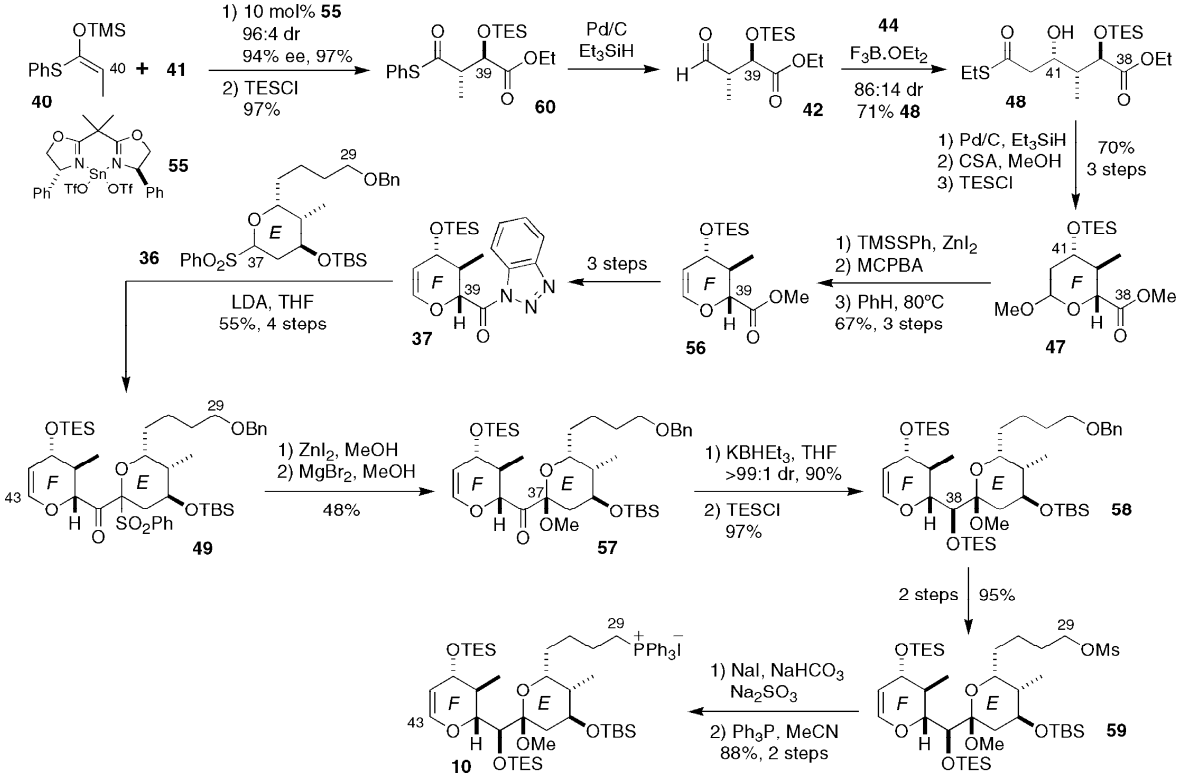
Scheme 7. Evans Synthesis of the C29−C37 E-Ring Segment of Spongistatin 2/Altohyrtin C



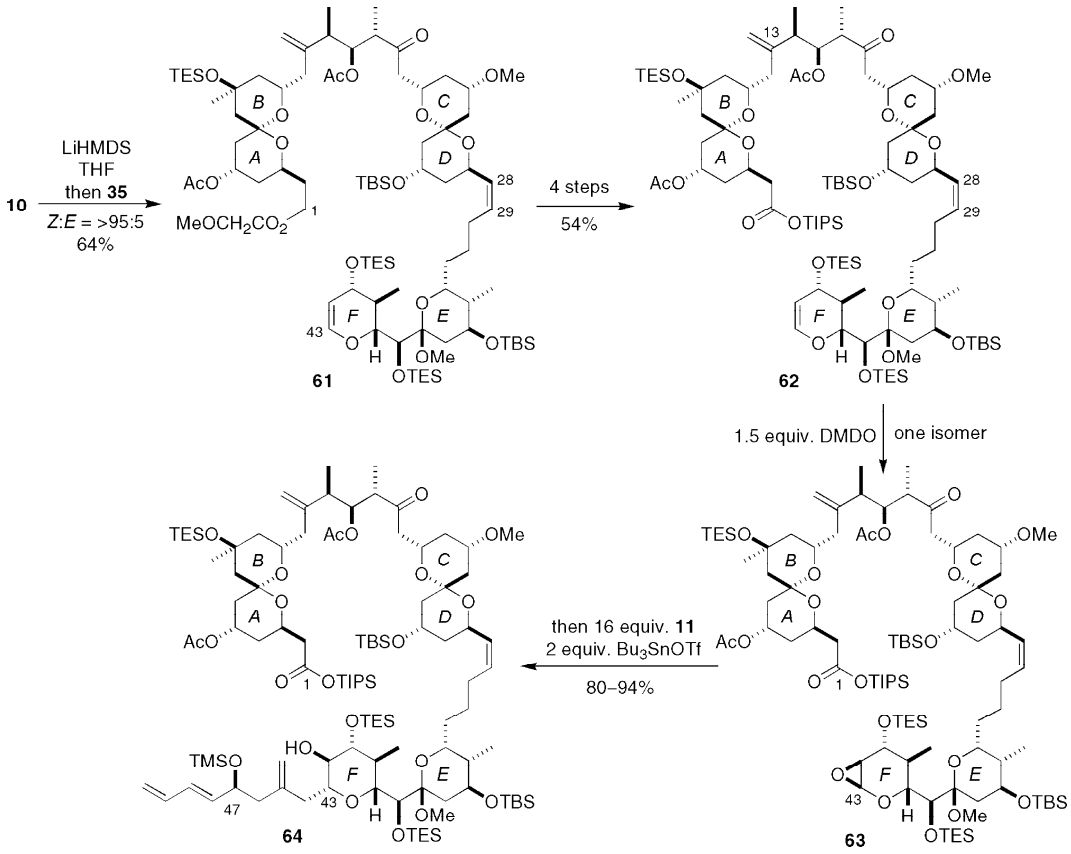
ketene acetal **44** added to aldehyde **45** to produce Felkin adduct **43** (94:6 dr) (Scheme 7). Reduction of the thioester under Fukuyama conditions and deprotection/cyclization produced the methyl acetal **46**, which was then converted into the E-ring sulfone **36**.

Synthesis of the F-ring subunit **37** (Scheme 8) comprised a similar series of transformations from aldehyde **42**, obtained (96:4 dr, 94% ee) from the *anti*-aldol reaction of silyl ketene acetal **40** catalyzed by the Sn(II) complex **55**. The methyl acetal **47** obtained

Scheme 8. Evans Synthesis of the C29–C43 EF-Ring Segment of Spongistatin 2/Altohyrtin C

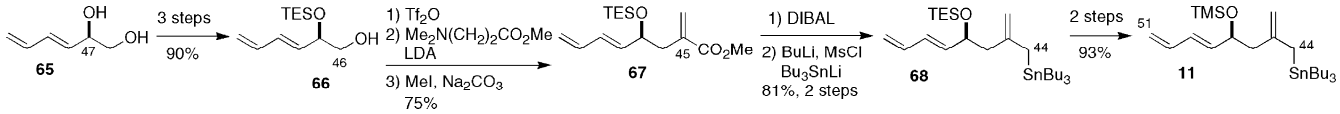


Scheme 9. Evans Synthesis of the Seco-Acid of Spongistatin 2/Altohyrtin C

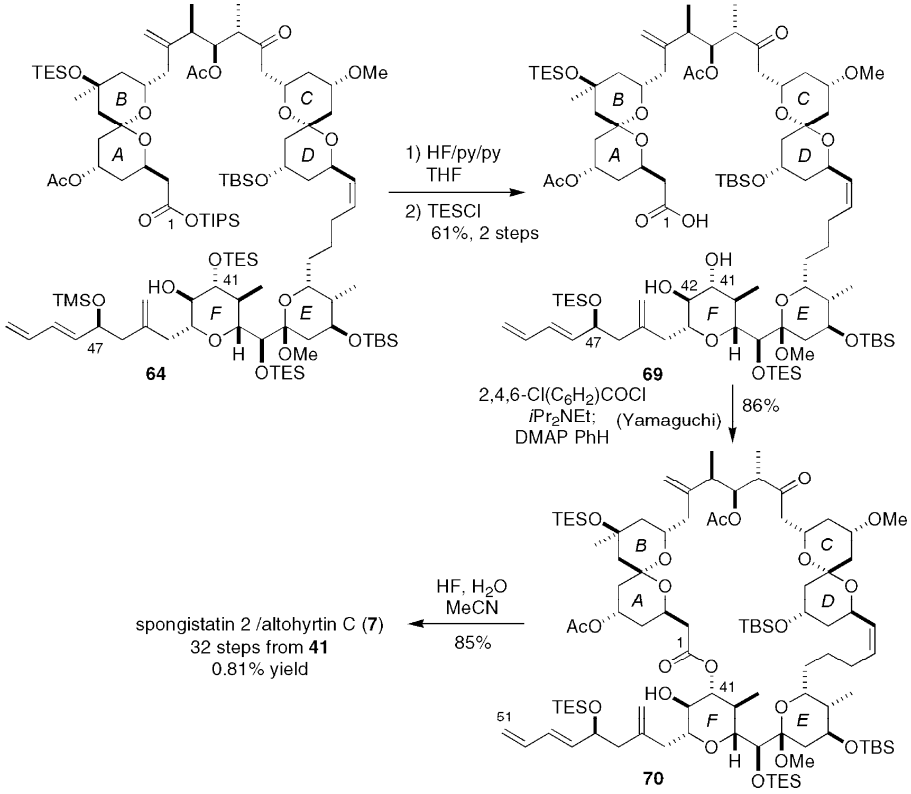


was then converted into dihydropyran **56** via sulfoxide elimination. The preferred coupling protocol involved adding the E-ring sulfone anion to benzotriazole amide **37**, derived from **56**, giving adduct **49**, which was converted under suitable methanolysis conditions into **57**. Reduction of the ketone by $KBHEt_3$ then installed the C38 stereocenter (>99:1 dr), presumably by Felkin–Anh control, to give **58**, which was converted into the C29 phosphonium salt **10** via the mesylate **59**.

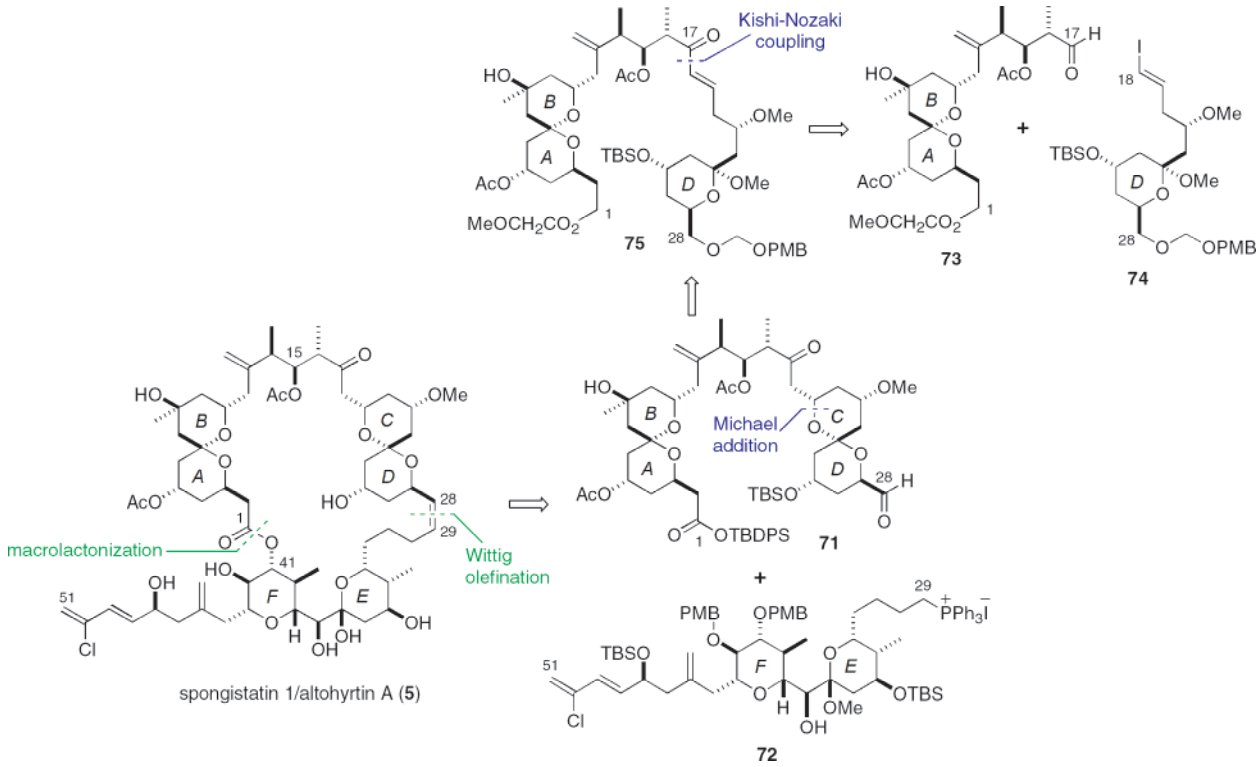
Scheme 10. Evans Synthesis of the C44−C51 Side Chain of Spongistatin 2/Altohyrtin C



Scheme 11. Evans Total Synthesis of Spongistatin 2/Altohyrtin C



Scheme 12. Kishi Strategy for the Total Synthesis of Spongistatin 1/Altohyrtin A



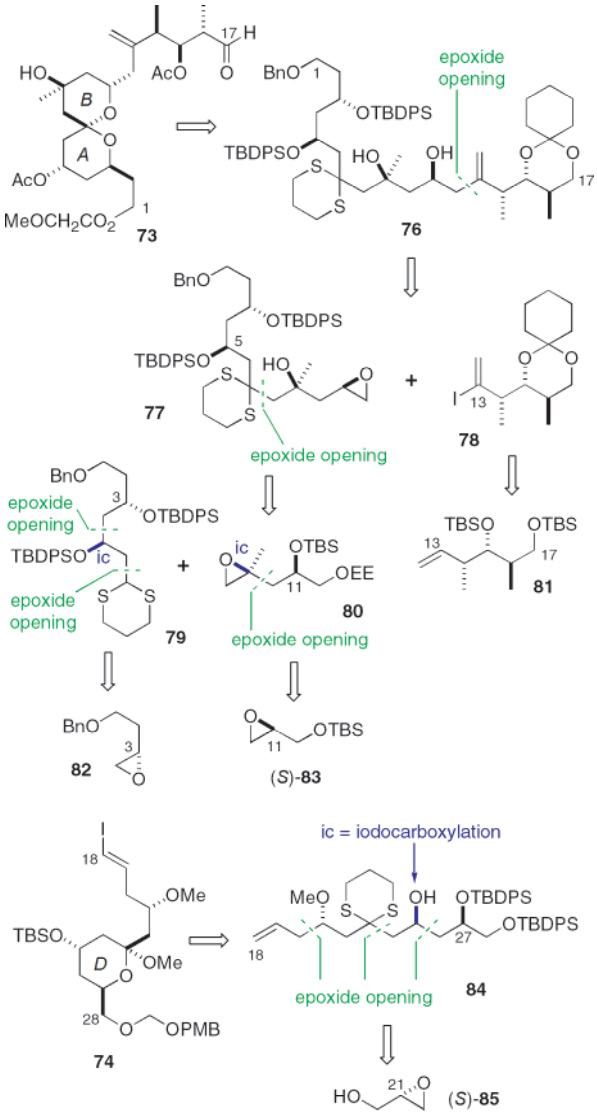
The challenging Wittig coupling between **10** and ABCD aldehyde **35** (Scheme 9) generated (*Z*)-alkene **61** in 64% yield, which was further elaborated into **62**. The allylic stannane **11** required for installation of the unsaturated side chain was obtained from the known alcohol **65**[25] (Scheme 10) via chain extension by enolate addition, formation of the C45 double bond, and introduction of the tributylstannyl group followed by swapping silyl protecting groups at the C47−OH in **68**. Glycal epoxide **63** obtained from **62** using DMDO (Scheme 9) was coupled with excess allylic stannane **11** to generate **64** exclusively. Selective silyl deprotection of **64** followed by reprotection of the C47−OH produced seco-acid **69** (Scheme 11). In the endgame, regioselective macrolactonization onto the C41−OH was achieved under Yamaguchi conditions to deliver the 42-membered macrolactone **70**, and global deprotection completed the first total synthesis of spongistation 2/altohyrtin C (**7**) in ca. 0.8% overall yield over the 32-step longest linear sequence from ethyl glyoxylate (93 total steps; about 4 steps per stereocenter).

2.1.2. Kishi Synthesis of Spongistatin 1/Altohyrtin A[18]

In the Kishi total synthesis of spongistatin 1/altohyrtin A (**5**) (Scheme 12), which features a chlorodiene side chain, the neighboring C41 and C42 hydroxyl groups were also left undifferentiated and relied on a regioselective macrolactonization to construct the 42-membered macrolactone. In contrast to the Evans strategy, the unsaturated side chain was incorporated into the EF-segment at an earlier stage, and the crucial Wittig coupling with the ABCD aldehyde **71** was performed using the fully elaborated C29−C52 segment **72**. Rather than utilizing an aldol-based coupling approach (at C15−C16) to connect the AB and CD spiroacetal segments, a Kishi−Nozaki-type Ni(II)/Cr(II)-mediated coupling (at C17−C18) using AB-segment **73** and D-ring vinyl iodide **74** was selected. The α,β-unsaturated enone **75** formed on oxidation at C17 then permits an intramolecular hetero-Michael addition to generate the C-ring, leading on to the ABCD-segment **71**.

The synthesis of segments **73** and **74** (Scheme 13) was almost entirely based on regioselective epoxide opening reactions. Epoxide opening of glycidol derivatives by organocuprates or dithiane anions was the principal strategy employed to build up the carbon skeletons of these two segments, and creation of 1,3-*syn* diols at C3−C5, C9−C11, and C25−C27 hinged on diastereoselective hydroxyl-directed iodocarboxylation reactions. Thus, chain extension by opening of epoxide **82** (Scheme 14) followed by iodocarboxylation and base-induced elimination of the intermediate iodocarbonate produced epoxide **86**, which was converted into dithiane **79**. A similar sequence was applied to protected glycidol (*S*)-**83** to provide carbonate **87,** which contained the tertiary C9−OH stereocenter and was converted into epoxide **80**. Addition of the lithiated dithiane **79** to **80** gave the C1−C12 segment **88**, which was converted into epoxide **77** for opening with the 2-thienyl cyanocuprate derived from vinyl iodide **78**. After silyl deprotection, the tetraol **76** underwent NIS-induced dithiane hydrolysis and then acid-catalyzed spiroacetalization to form the required AB-ring segment **89** as a single isomer. The C17 aldehyde **73** was obtained from **89** after protecting group adjustment and installation of the two acetate groups. Note that the C9 tertiary hydroxyl remained unprotected throughout the rest of the synthesis.

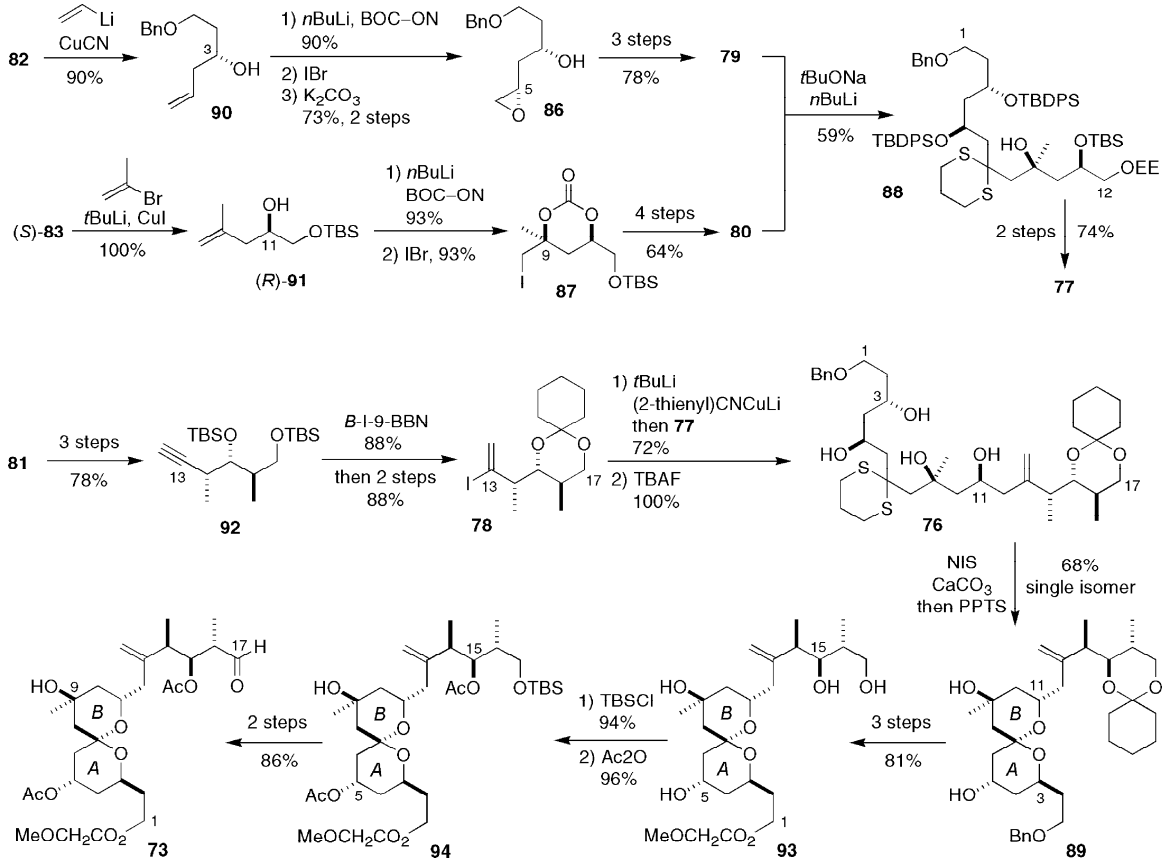
Scheme 13. Kishi Strategy for Synthesis of the C1−C17 AB-Ring Segment and C18−C28 D-Ring Segment of Spongistatin 1/Altohyrtin A



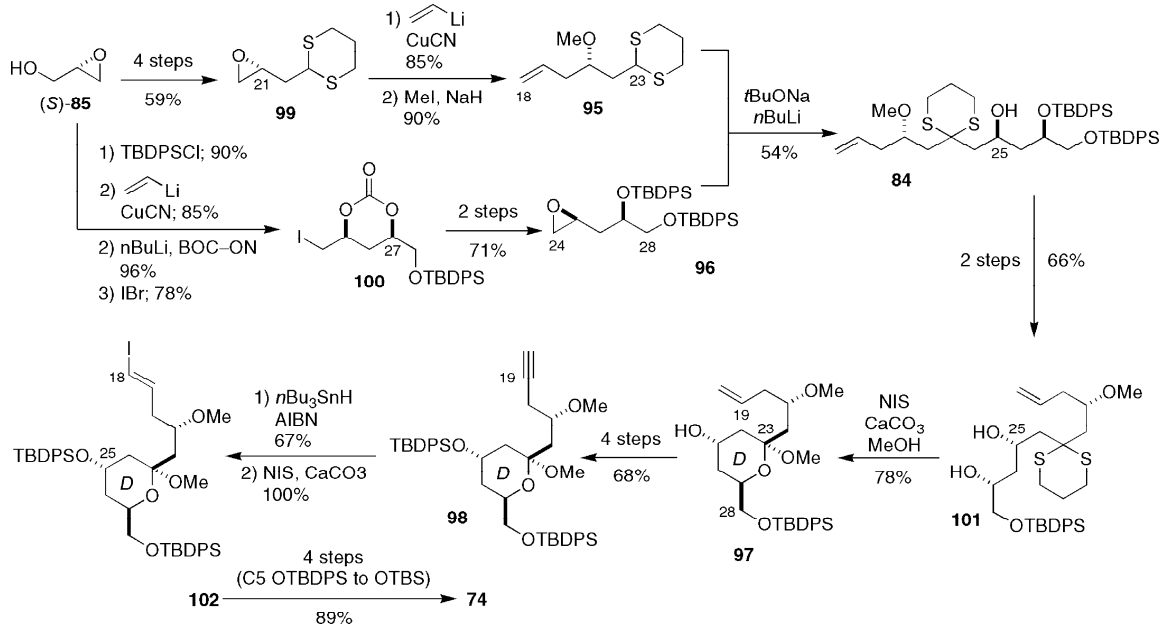
Analogous transformations were also applied to the synthesis of D-ring vinyl iodide **74** (Scheme 15). Glycidol (*S*)-**85** was first elaborated into dithiane **95**, which was combined with the C24−C28 epoxide **96** to provide alcohol **84**. Subsequent desulfurization in MeOH generated the methyl acetal **97** as a single isomer, and the terminal alkene was then converted into alkyne **98** to enable installation of the vinyl iodide by hydrostannylation. At this stage the C25 TBDPS ether was swapped over for a more labile TBS group to give D-ring segment **74** to facilitate the final deprotection to form altohyrtin A.

The fully functionalized EF-ring segment **72** was assembled by sequential coupling between side chain

Scheme 14. Kishi Synthesis of the C1−C17 AB-Ring Segment of Spongistatin 1/Altohyrtin A

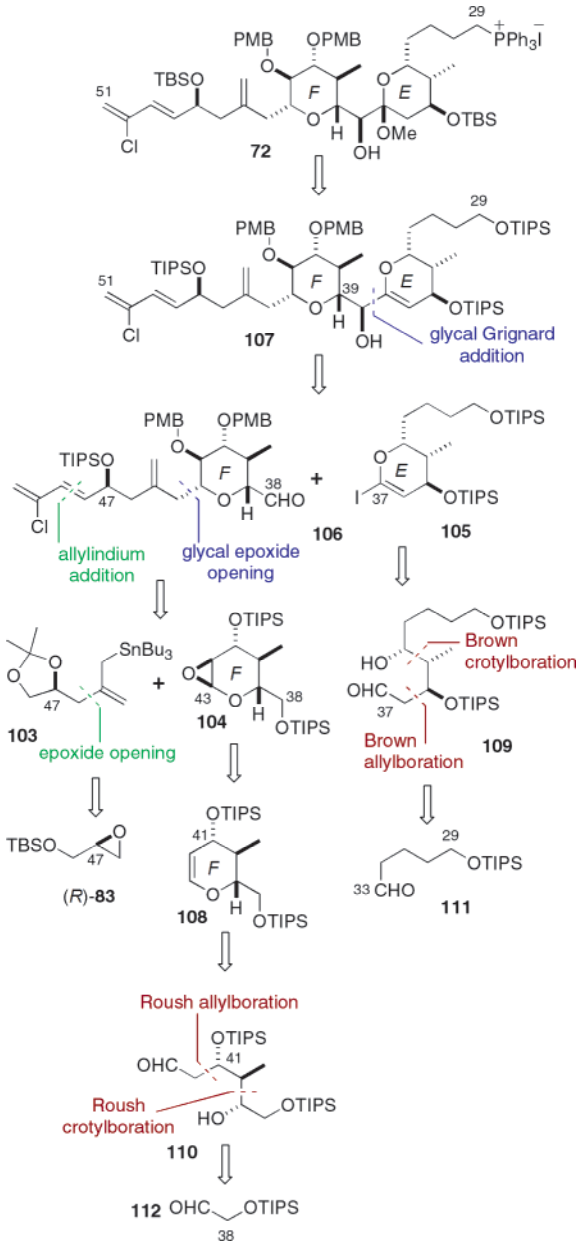


Scheme 15. Kishi Synthesis of the C18−C28 D-Ring Segment of Spongistatin 1/Altohyrtin A



segment **103**, F-ring glycal epoxide **104,** and E-ring iododihydropyran **105** (Scheme 16). Similar to the Evans strategy for side chain addition (**63** → **64**, Scheme 9), but in a much less complex situation, glycal epoxide opening by an allylstannane appended the side chain to the F-ring subunit **104**. The derived aldehyde **106** was connected to E-ring subunit **105** via its Grignard reagent, setting up the C38 stereocenter. In this case, the E-ring dihydropyran moiety of adduct **107** could be successfully hydrated to form the C37 methyl acetal in **72**. Judicious synthetic planning identified the structural resemblance between the E-ring dihydropyran **105** and F-ring dihydropyran **108**. Thus, similar approaches were employed for the synthesis of these individual subunits in which asymmetric crotylboration and allylboration reactions were employed to set up the stereotriads **109** and **110**. These open-chain alcohol precursors were subjected to dehydrative cyclization to provide the required dihydropyrans.

Scheme 16. Kishi Strategy for the Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A



The synthesis of F-ring segment **104** entailed the sequential application of Roush crotylboration and allylboration[26a] to transform aldehyde **112** into homoallylic alcohol **113** (Scheme 17). Cyclization of the derived aldehyde **110** to glycal **108** was performed by thermal elimination of the intermediate β-ketoester. Glycal **108** was then oxidized by dimethyldioxirane to provide solely epoxide **104**. Note that the bulky TIPS protecting groups at C38 and C41 were required to achieve this high diastereoselectivity. Coupling of epoxide **104** was performed with excess allylcuprate derived from stannane **103**, prepared via ring opening of (*R*)-glycidol ether **83** by the cuprate formed from bromoacrolein **114**, to produce the F-ring subunit **115**. At this stage the C41 and C42 hydroxyl groups were both protected as PMB ethers. The required F-ring aldehyde **106** was obtained after introduction of the chlorodiene moiety by addition of the allylindium reagent formed from 2,3-dichloropropene **116** to aldehyde **117** followed by dehydration using the Martin sulfurane ($(Ph_2S(OC(CF_3)_2Ph)_2$).

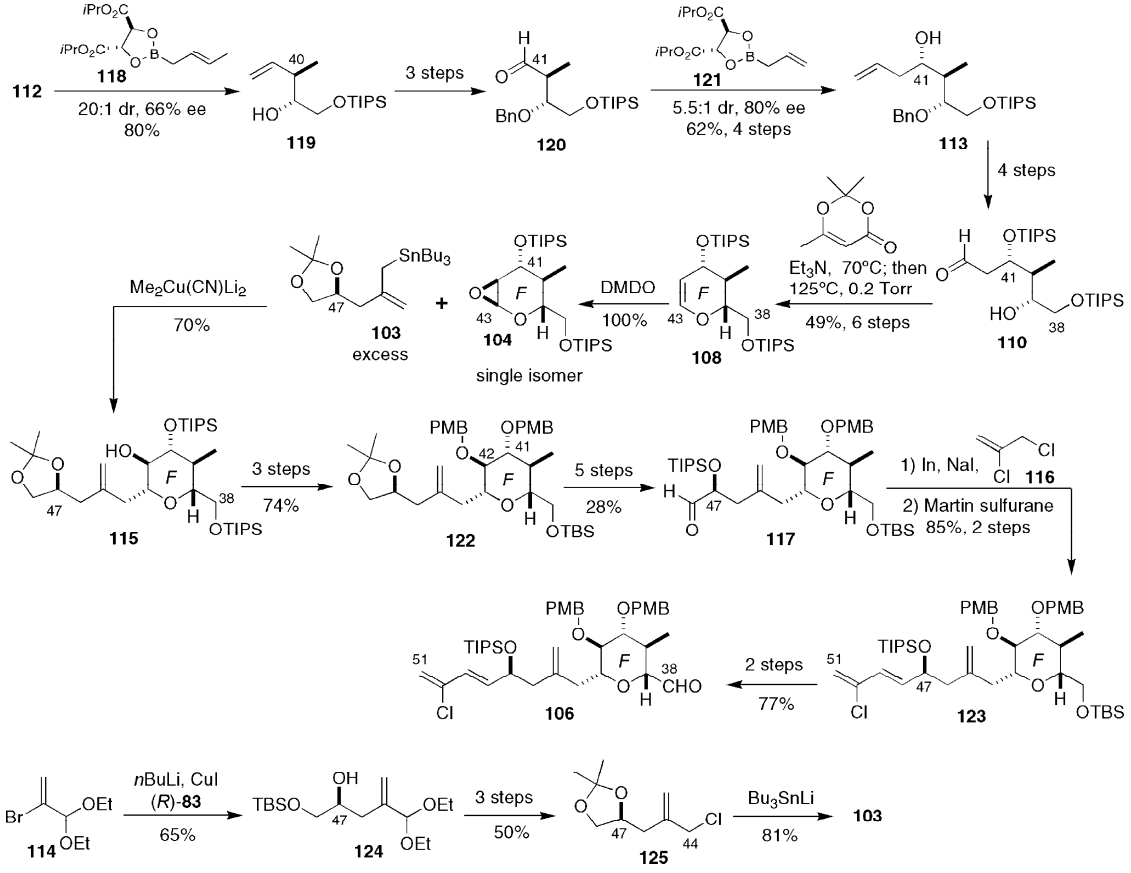
The E-ring dihydropyran **105** was prepared from aldehyde **111** (Scheme 18) by sequential use of Brown crotylboration,[27] allylboration,[26b,28] and cyclization to give **126** in an identical manner to that performed for the F-ring subunit, which was then converted into iodoglycal **105** via the vinylstannane. Generation of the Grignard reagent through lithiation of **105** (with C29 and C35 TIPS protecting groups) and transmetalation with $MgBr_2$ and addition to the highly elaborate F-ring aldehyde **106** gave adduct **107**, installing the C38 stereocenter in >7:1 dr by chelation control. Note that the C38−OH remained unprotected throughout the rest of the synthesis. Formation of the C37 methyl acetal **127** required iodomethanolysis of the E-ring glycal **107** and reductive deiodination (bromobenzene was added to ensure chemoselective reduction in the presence of the chlorodiene unit). At this point the C35 TIPS ether was switched to a TBS group to provide intermediate **128**. Its derived iodide at C29 was then converted into phosphonium salt **72** (in the presence of MeOH in order to suppress the elimination at C37 to regenerate the E-ring glycal).

The pivotal Ni(II)/Cr(II)-mediated coupling of **73** and **74** in the presence of bipyridyl ligand **134** provided the corresponding allylic alcohols, which were oxidized to enone **75** (Scheme 19). Intramolecular hetero-Michael addition generated the spiroacetal **135** as a single isomer with the desired C19 configuration; however, the undesired axial−axial configuration at the C23 spiroacetal stereocenter was obtained. This deficiency was remedied by equilibration under acidic deprotection conditions, as the CD-spirocenter was configurationally unstable with an unprotected C25 hydroxyl group, to give a 1:1 mixture of **136** and the desired isomer **137**. Recycling of the undesired isomer **136** provided further **137**. Protecting group manipulations and oxidation state adjustments at C1 and C28 then furnished the ABCD aldehyde **71**. This aldehyde was Wittig coupled to the fully functionalized EF-ring segment **72** to furnish the (*Z*)-alkene **139** (Scheme 20). Selective deprotection revealed the seco-acid **140**, where partial C37 methyl acetal hydrolysis occurred, while the C47 allylic TBS ether survived unscathed under DDQ conditions. At this point selective macrolactonization was accomplished by the Yamaguchi method to provide the 42-membered macrolactone **141**, which after TBS deprotection afforded the first synthetic spongistatin 1/altohyrtin A (**5**) in 39 linear steps and ca. 0.005% overall yield from aldehyde **112** (129 total steps; about 5 steps per stereocenter).

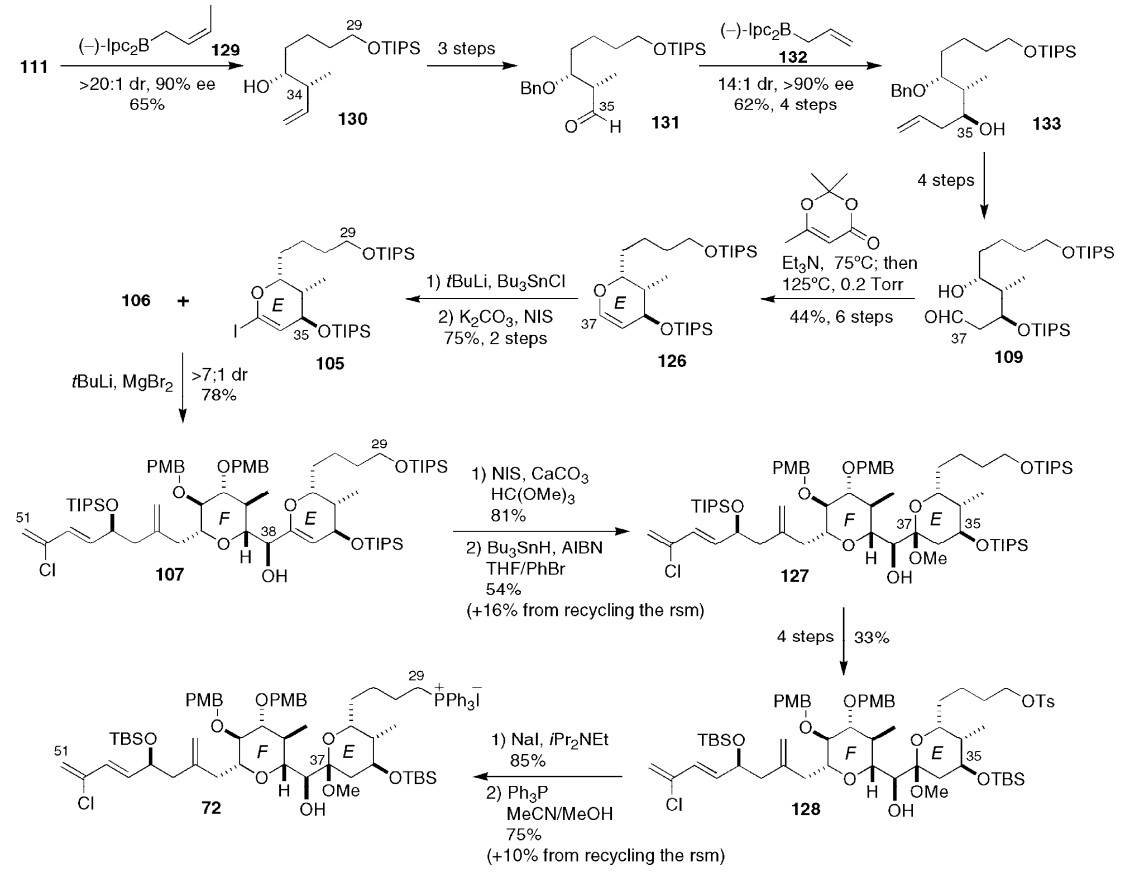
2.1.3. Smith Synthesis of Spongistatin 2/Altohyrtin C[19]

Smith's first-generation approach (Scheme 21) to spongistation 2/altohyrtin C (**7**) also relied on a late-stage Wittig coupling, employing the ABCD-segment **142** and EF-segment **143**, followed by regioselective macrolactonization on to the C41−OH. Segment **142** was available from alkylation of C13−C28 sulfone **144** with C1−C12 iodide **145** containing the B-ring. In a manner similar to Kishi's approach to the AB-

Scheme 17. Kishi Synthesis of the C38−C51 Segment of Spongistatin 1/Altohyrtin A

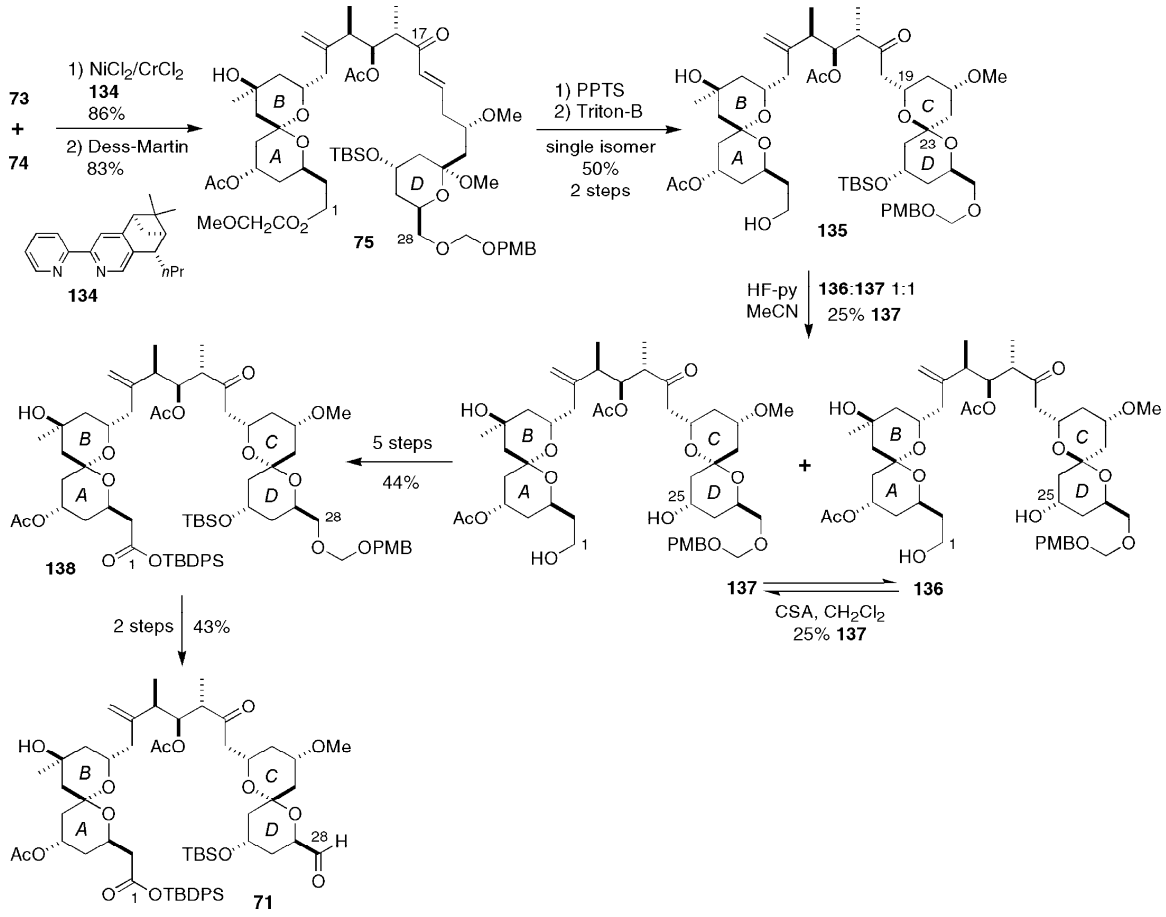


Scheme 18. Kishi Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A[a]

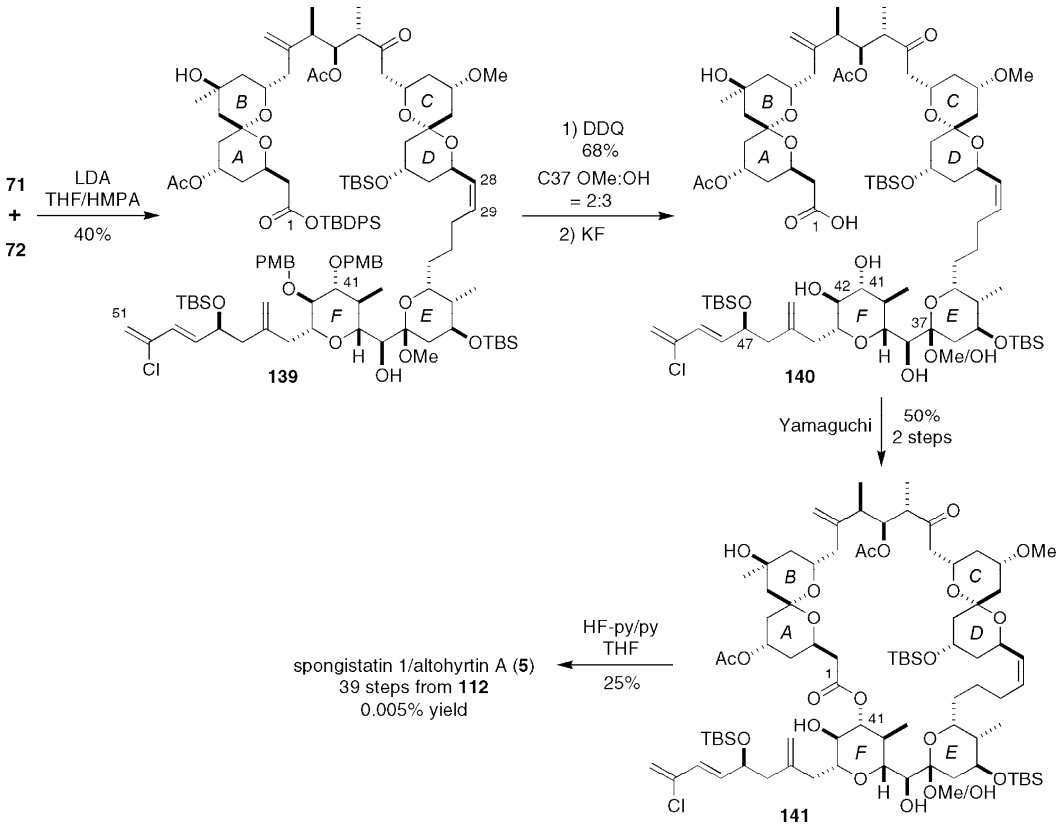


[a] The (+) descriptor on the crotyl (**129**) and allylborane (**132**) reagents (and the (−) descriptor on the corresponding *ent*-reagents) in this scheme and the schemes that follow refers to the sign of specific rotation of the Ipc_2BOMe used.

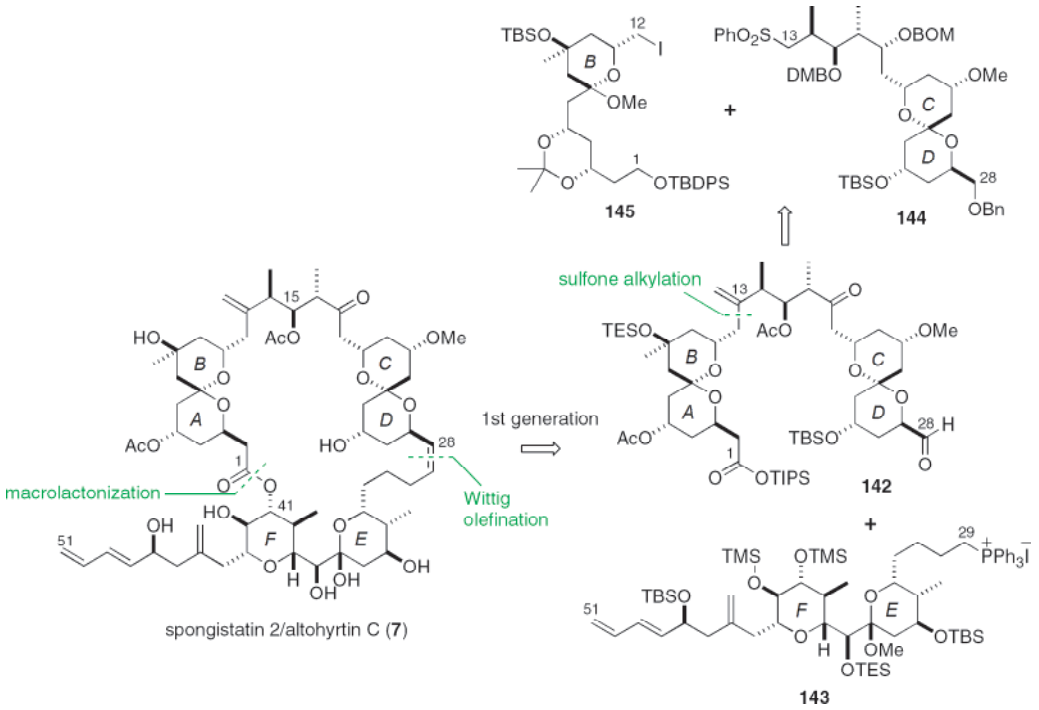
Scheme 19. Kishi Synthesis of the C1−C28 ABCD-Ring Segment of Spongistatin 1/Altohyrtin A



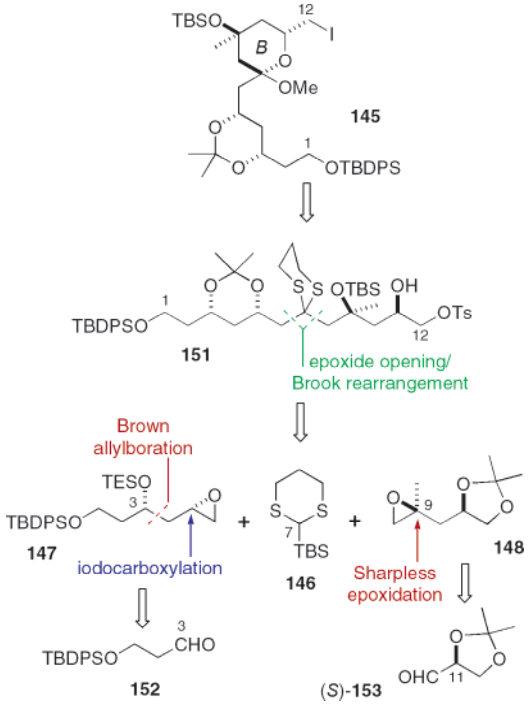
Scheme 20. Kishi Total Synthesis of Spongistatin 1/Altohyrtin A



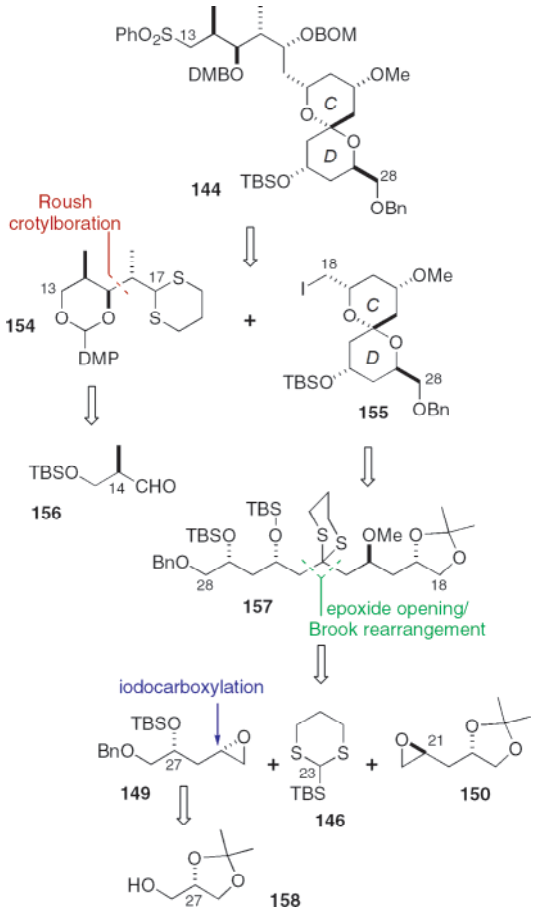
Scheme 21. Smith Strategy for the Total Synthesis of Spongistatin 2/Altohyrtin C



Scheme 22. Smith Strategy for the Synthesis of the C1−C12 B-Ring Segment of Spongistatin 2/Altohyrtin C



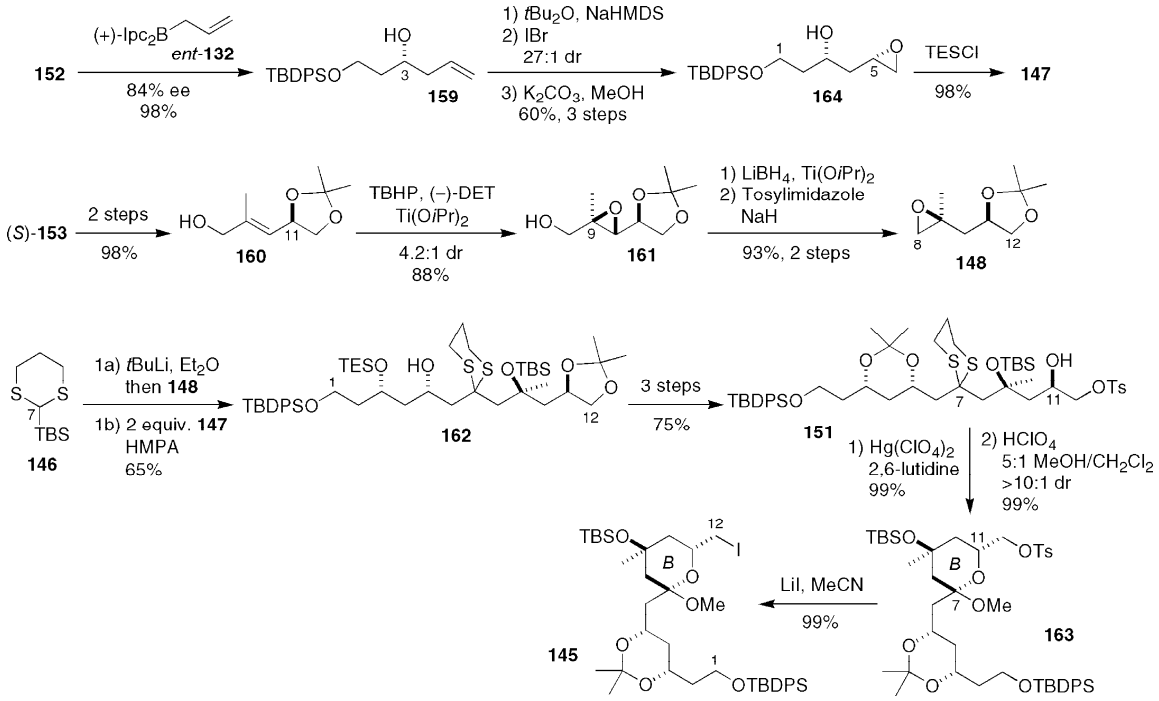
Scheme 23. Smith Strategy for the Synthesis of the C13−C28 CD-Ring Segment of Spongistatin 2/Altohyrtin C



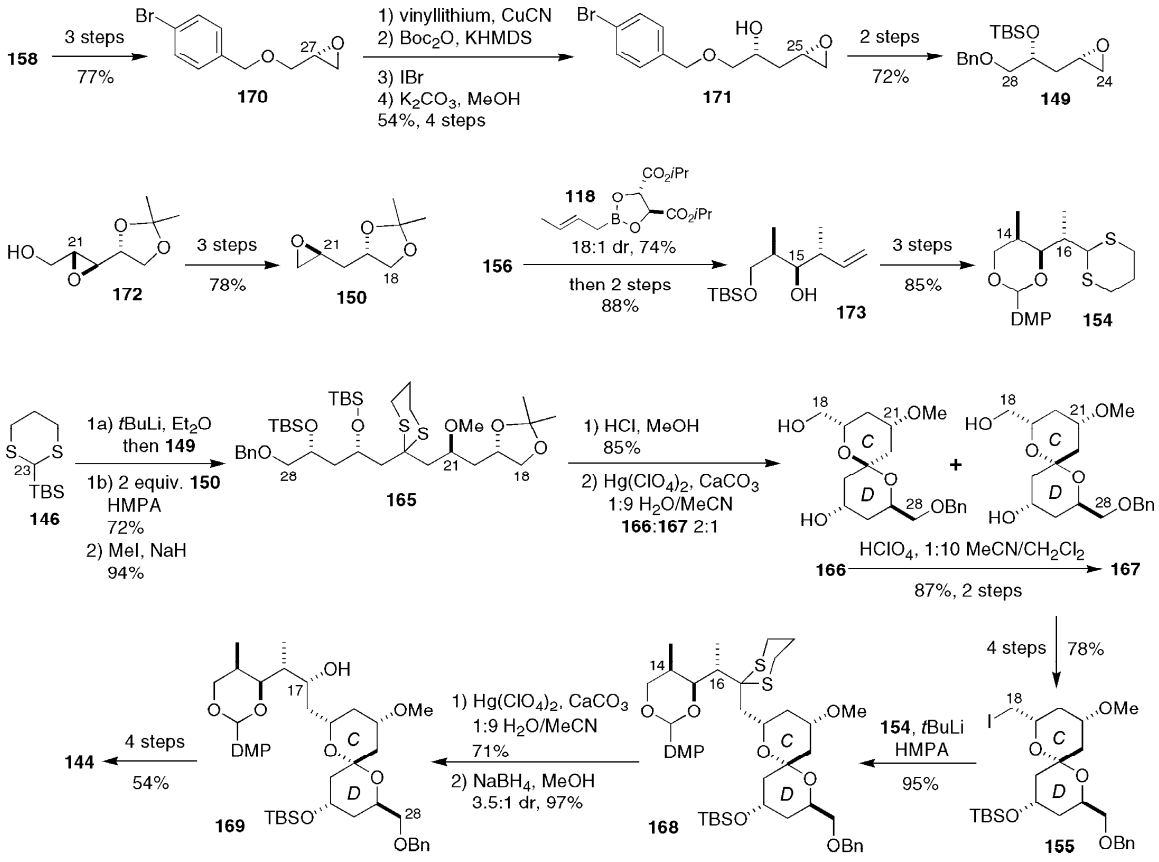
and CD-ring segments, dithiane opening of epoxides was the main strategy used to install the required 1,3-oxygenation pattern. By using the silylated dithiane **146** as an acyl anion equivalent, a Tietze-style epoxide opening/Brook rearrangement/epoxide opening reaction sequence served here to connect the appropriate acyclic precursors **147** and **148** leading to the AB-segment **145** (Scheme 22) and precursors **149** and **150** to give the CD-segment **144** (Scheme 23).

The synthesis of C1−C6 subunit **147** (Scheme 24) began with a Brown allylboration[28] reaction on aldehyde **152** followed by iodocarboxylation of alcohol **159** to introduce the C5 stereocenter (27:1 dr) and

Scheme 24. Smith Synthesis of the C1−C12 B-Ring Segment of Spongistatin 2/Altohyrtin C



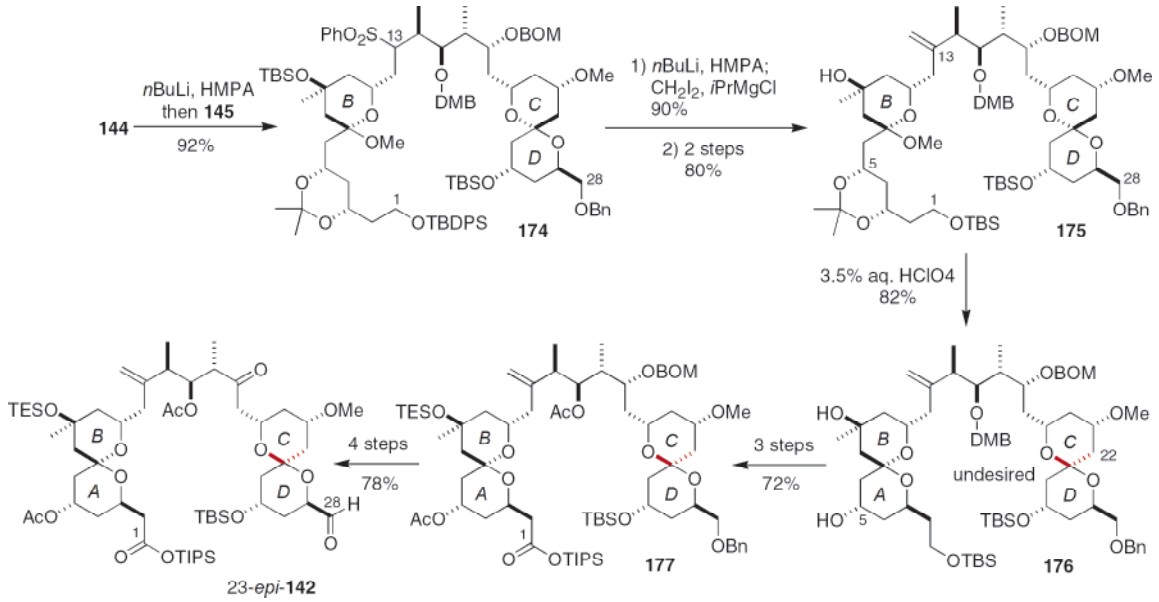
Scheme 25. Smith Synthesis of the C13−C28 CD-Ring Segment of Spongistatin 2/Altohyrtin C



install the terminal epoxide. The C8−C12 subunit **148** was produced from (*S*)-glyceraldehyde derivative **153**, with the C9 stereocenter (4.2:1 dr) installed by a mismatched Sharpless epoxidation on allylic alcohol **160**. Transposition of the epoxide ring was performed by hydride ring opening of **161** at C10 and then cyclization of the intermediate diol. A one-pot sequence of addition of the lithiated silyl dithiane **146** to epoxide **148**, HMPA-induced Brook rearrangement, and coupling to the epoxide **147** then generated C1−C12 subunit **162**. After elaboration into tosylate **151**, dithiane hydrolysis led to a mixture of methyl acetals, which was equilibrated under acidic conditions to give the B-ring containing **163** (>10:1 dr).

For the synthesis of the CD-segment **144**, epoxides **149** and **150** (Scheme 25) were united with the silyl

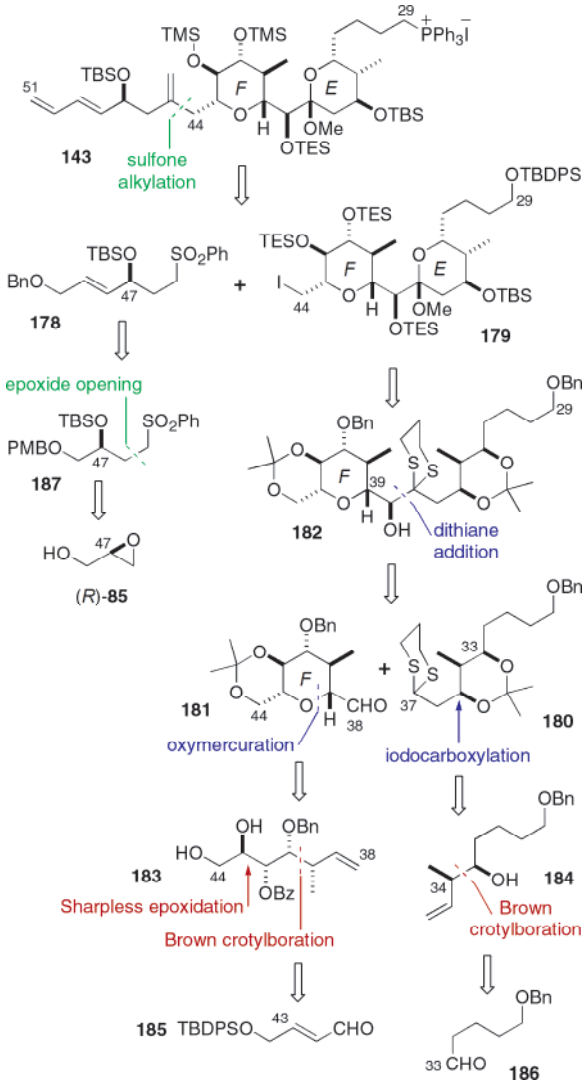
Scheme 26. Smith Synthesis of the C1−C28 ABCD-Ring Segment of Spongistatin 2/Altohyrtin C



dithiane **146** to produce **165** after methylation at C21. Consecutive acidic deprotection and dithiane hydrolysis of **165** under mercury perchlorate/calcium carbonate conditions led to a 2:1 mixture of spiroacetals **166** and **167**. Fortuitously, treatment of the mixture with perchloric acid provided the desired isomer **167** efficiently, presumably as a result of stabilization involving complexation with residual calcium ions. This protocol was used later to remedy the incorrect C23 configuration in the endgame. Incorporation of the C14−C16 stereotriad, obtained via a Roush crotylboration performed on Roche ester derived aldehyde **156**, involved alkylation of the dithiane **154** with iodide **155**, producing the CD-segment **168**. After dithiane hydrolysis, the C17 ketone group was temporarily masked by reduction (3.5:1 dr) in order to realize the key sulfone alkylation step. Coupling of the sulfone **144** (Scheme 26), derived from the major (17*R*)-isomer **169**, to iodide **145** followed by an unusual Julia methylenation reaction provided the C1−C28 intermediate **175** after a silyl protecting group swap at C1. The AB-spiroacetal ring was formed by exposure of **175** to acidic conditions, which (although it was presumably unexpected at the time) epimerized the CD-spiroacetal concurrently, giving the 23-*epi*-ABCD-segment **176** that was taken on to C1−C28 aldehyde 23-*epi*-**142**. This unwanted epimerization at C23 could have proved disastrous, but luckily it could be reequilibrated back right at the end of the synthesis. The Kishi group encountered a related problem, which forced them to be extra careful in retaining the correct CD spiroacetal stereochemistry throughout the synthesis.

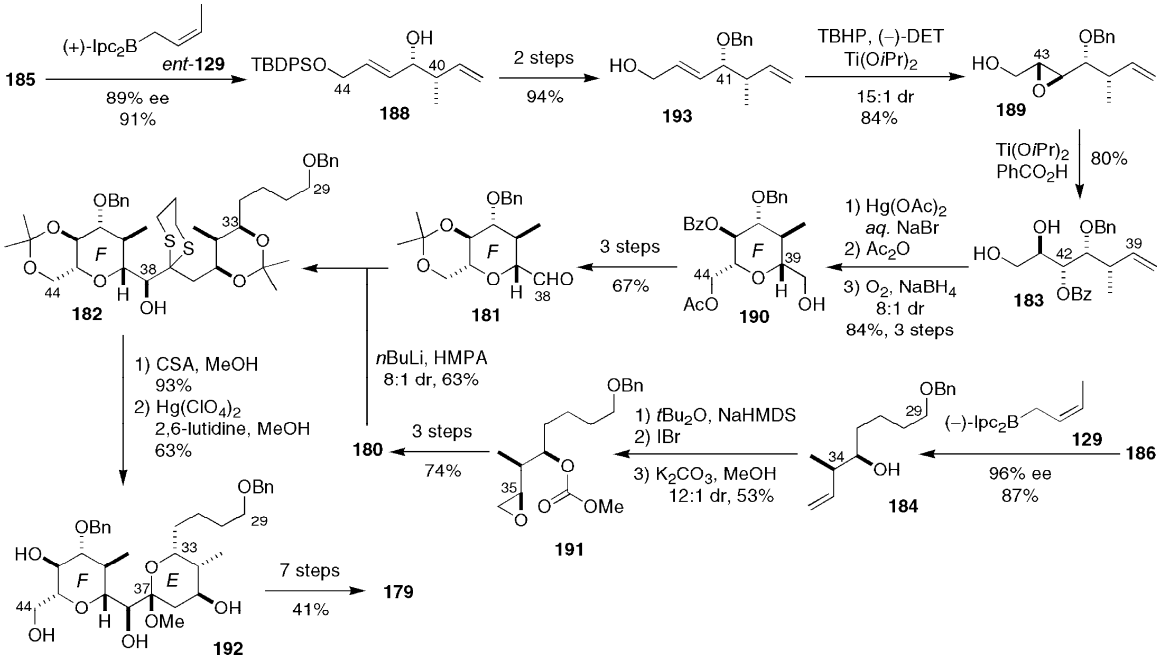
In contrast to the Evans and Kishi strategy for incorporation of the side chain, the Smith group employed an alkylation of sulfone **178** with EF iodide **179** and introduced the C45 methylene by a Julia methylenation (Scheme 27). Also in a different manner, the dithiane **180** was coupled to the F-ring aldehyde **181** followed by spiroacetalization to form the EF-segment **179**. A good level of stereoinduction

Scheme 27. Smith Strategy for the Synthesis of the C29−C51 Segment of Spongistatin 2/Altohyrtin C

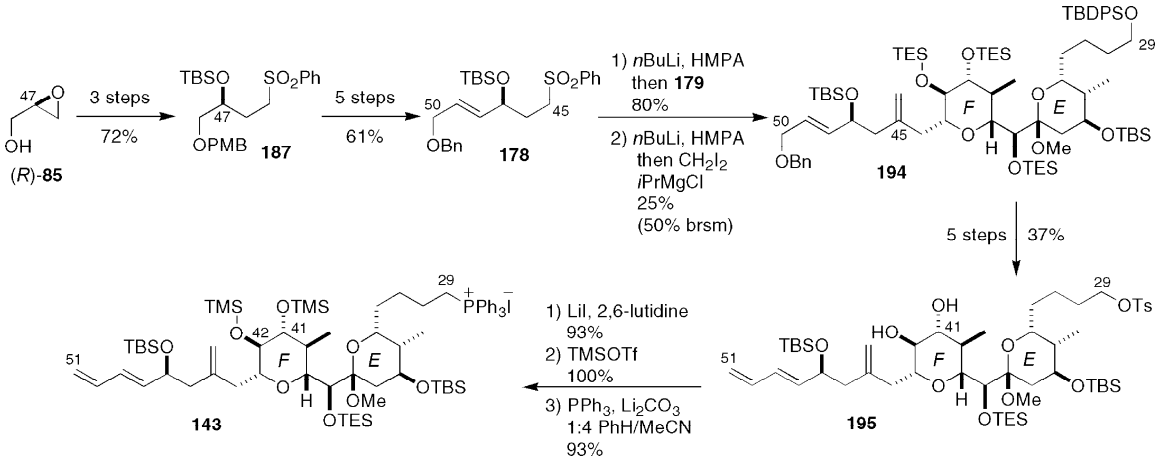


at C38 was realized, as observed in the analogous Kishi (**105** + **106** → **107**, Scheme 18) coupling steps.

Scheme 28. Smith Synthesis of the C29−C44 EF-Ring Segment of Spongistatin 2/Altohyrtin C



Scheme 29. Smith Synthesis of the C29−C51 Segment of Spongistatin 2/Altohyrtin C

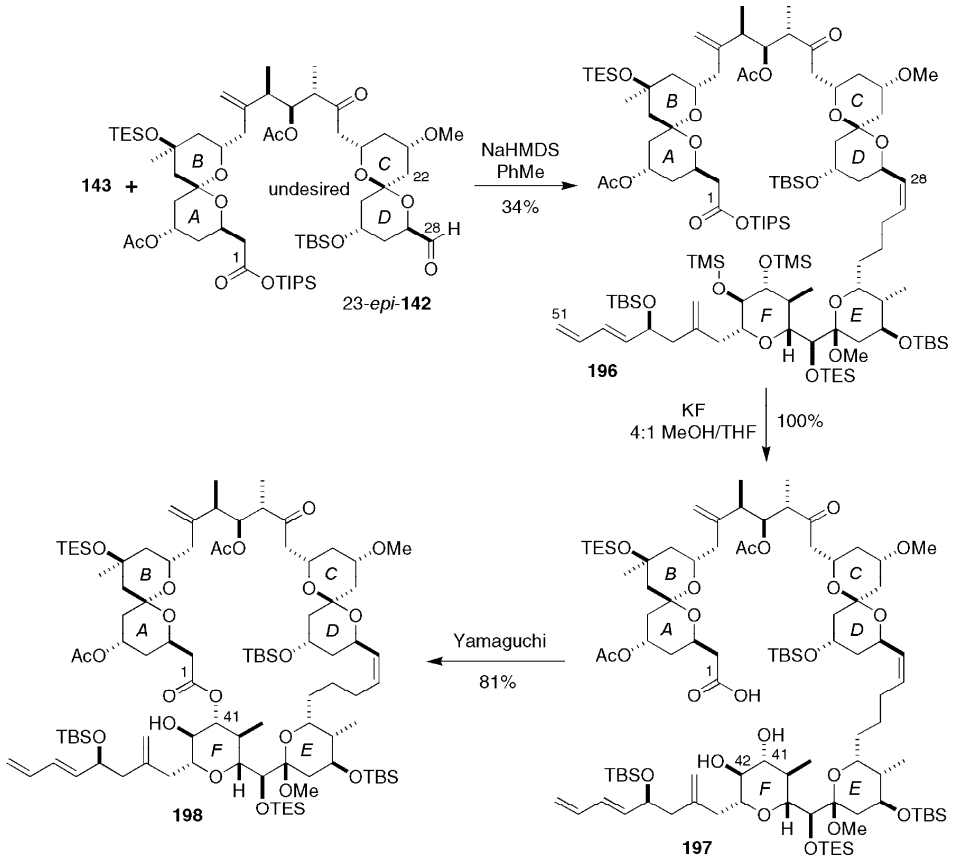


The stereochemistry of the E-ring precursor **180** was set up by Brown crotylboration[27] and iodocarboxylation.

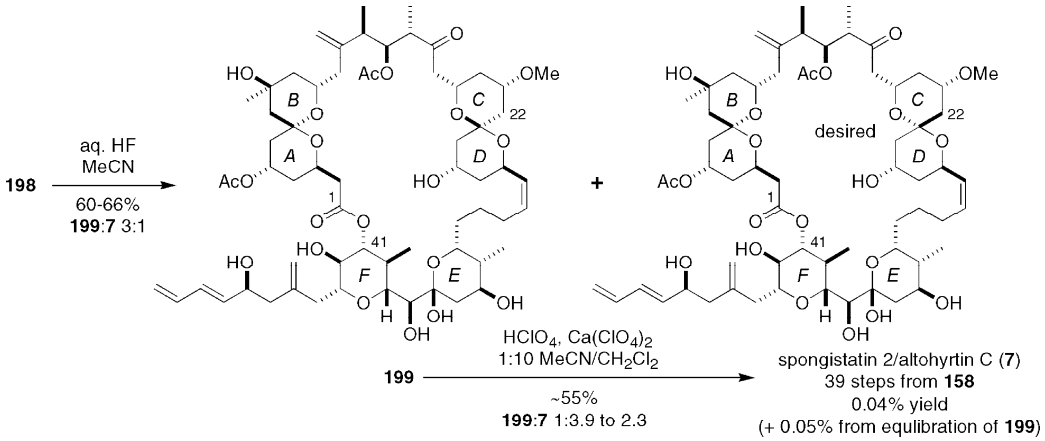
The synthesis of stereotetrad **183** started with a Brown crotylboration[27] to give the homoallylic alcohol **188** (Scheme 28) followed by Sharpless epoxidation to produce **189** (15:1 dr), which then underwent epoxide opening to produce benzoate **183**. Generation of the F-ring arose from an oxymercuration using Hg(OAc)$_2$ on **183**, which on oxidation produced alcohol **190** (8:1 dr). The E-ring dithiane **180** was synthesized via a Brown crotylboration[27] using **129** to obtain homoallylic alcohol **184** (96% ee). Iodocarboxylation of **184** then produced epoxide **191** and installed the C35 stereocenter (12:1 dr). Coupling of the derived dithiane **180** with aldehyde **181** obtained from **190** gave predominantly adduct **182,** setting up the C38 stereocenter (8:1 dr). Acetonide deprotection and dithiane hydrolysis then led to E-ring methyl acetal **192**, which was transformed into iodide **179** through protecting group manipulation. Addition of the side chain (Scheme 29) involved alkylation of sulfone **178**, derived from glycidol (*R*)-**85**, with iodide **179** to produce an intermediate adduct, which was subjected to a (low yielding) Julia methylenation to provide the advanced EF-ring-segment **194**. Following incorporation of the terminal alkene, the C29 tosylate **195** was converted into phosphonium salt **143**. At this stage the C41 and C42 TES groups were switched to TMS ethers to facilitate the subsequent deprotection to the seco-acid.

The Wittig coupling of **143** with the ABCD aldehyde 23-*epi*-**142**, having the undesired configuration at C23, provided access to the fully protected seco-acid **196** (Scheme 30). Liberating the C1 acid and the C41−C42 diol then enabled regioselective macrolactonization of **197** by the Yamaguchi method to produce macrolactone **198**. Interestingly, this C23-*epi*-seco-acid **197** also favored acylation onto the C41−OH. A global deprotection then generated spongistatin 2 (**7**) and its C23 isomer **199** in a 1:3 ratio (Scheme 31). To produce further spongistatin 2, **199** was subjected to a remarkable calcium-ion-mediated epimerization at C23, giving rise to an improved ~3:1 mixture of spongistatin 2 and **199**. The Smith total synthesis of spongistatin 2/altohyrtin C (**7**) proceeded

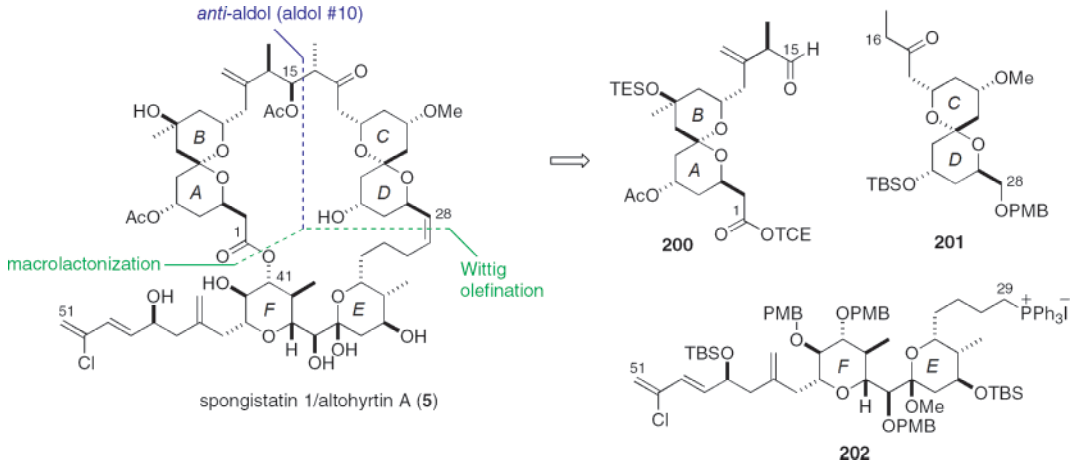
Scheme 30. Smith Synthesis of a Protected C23-*epi*-Spongistatin 2/Altohyrtin C (198)



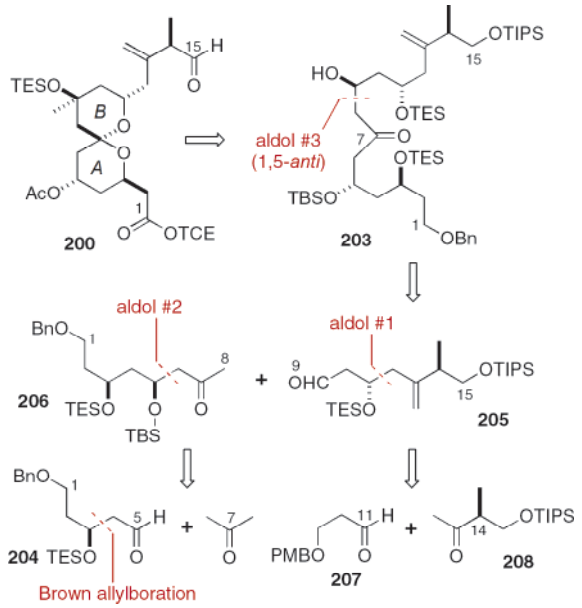
Scheme 31. Smith Total Synthesis of Spongistatin 2/Altohyrtin C



Scheme 32. Paterson Strategy for the Total Synthesis of Spongistatin 1/Altohyrtin A



Scheme 33. Paterson Strategy for the Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 1/Altohyrtin A

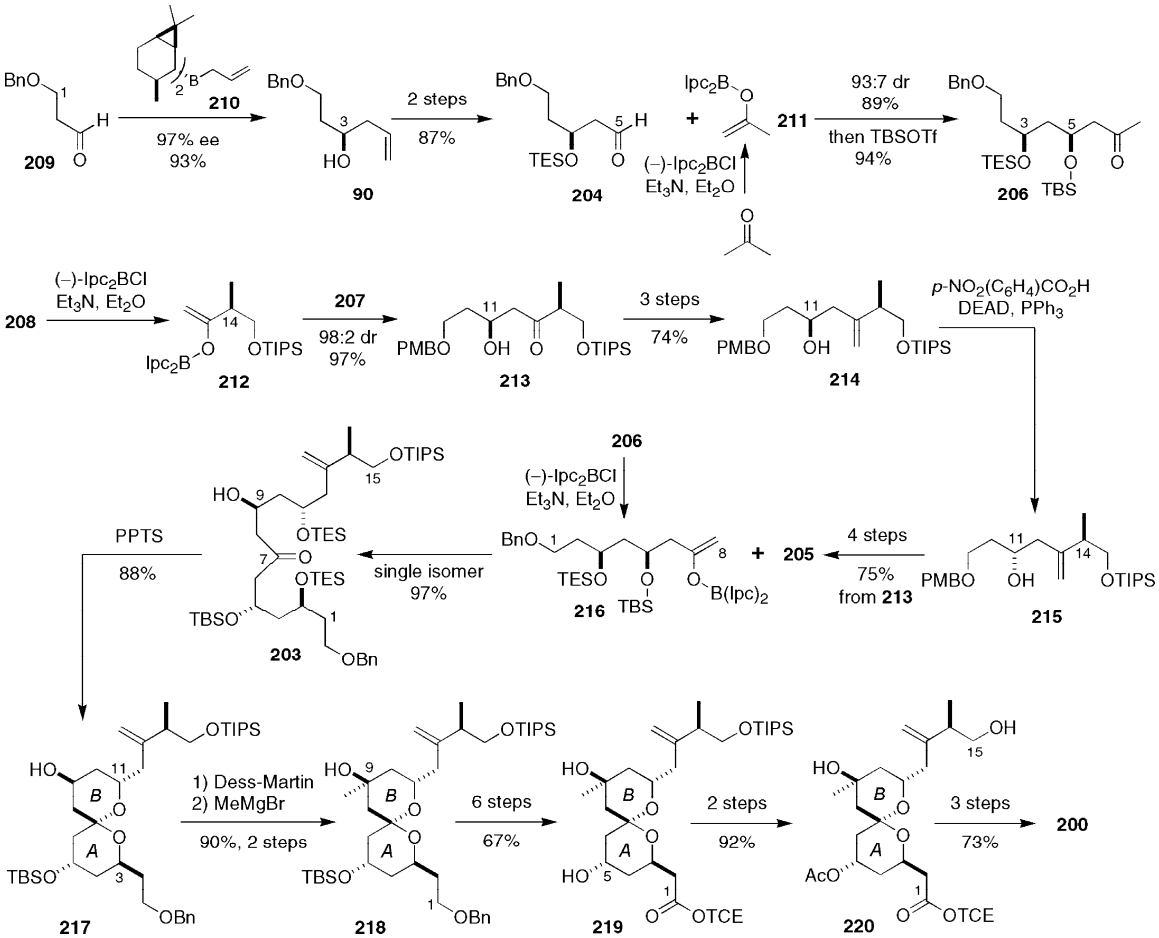


in 39 linear steps and 0.04% overall yield from alcohol **158** with a further 0.05% yield obtained by equilibration of C23 epimer **199** (114 total steps; about 5 steps per stereocenter). Following completion of this initial total synthesis, the Smith group reevaluated some aspects of their strategy for construction and coupling of the ABCD- and EF-segments (section 2.1.7).

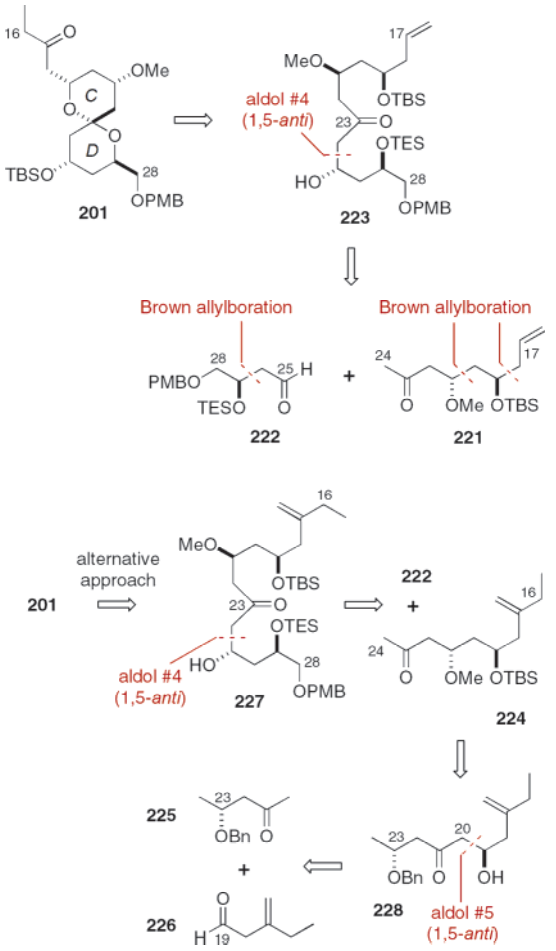
2.1.4. Paterson Synthesis of Spongistatin 1/Altohyrtin A[20]

The Paterson group's strategy (Scheme 32) for assembling spongistatin 1/altohyrtin A (**5**), as first outlined in 1997, is based on a 3-fold disconnection of the 42-membered macrolide to the fully functionalized AB-segment **200** (C1−C15), CD-segment **201** (C16−C28), and EF-segment **202** (C29−C51) incorporating the full side chain. This modular synthetic plan ensured a high degree of convergence with the sequential late-stage connection of these three principle segments. Coupling of the aldehyde **200** to the ethyl ketone **201** via a C15−C16 *anti*-aldol reaction was followed by a C28−C29 Wittig olefination employing the ylide derived from phosphonium salt **202**. Regioselective macrolactonization onto the C41 hydroxyl group was envisaged to generate the required 42-membered macrolactone ring, as precedented by a related transformation in the Paterson total synthesis of swinholide A.[29] The synthesis was characterized by the strategic use of both substrate- and reagent-controlled boron aldol reactions as key bond-forming and stereodefining processes[30] to generate the distinctive 1,3- and 1,5-dioxygenation patterns within the spongipyrans. Altogether, this particular example constitutes one of the most demanding applications of boron-mediated aldol methodology for complex polyketide synthesis.

Scheme 34. Paterson Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 1/Altohyrtin A

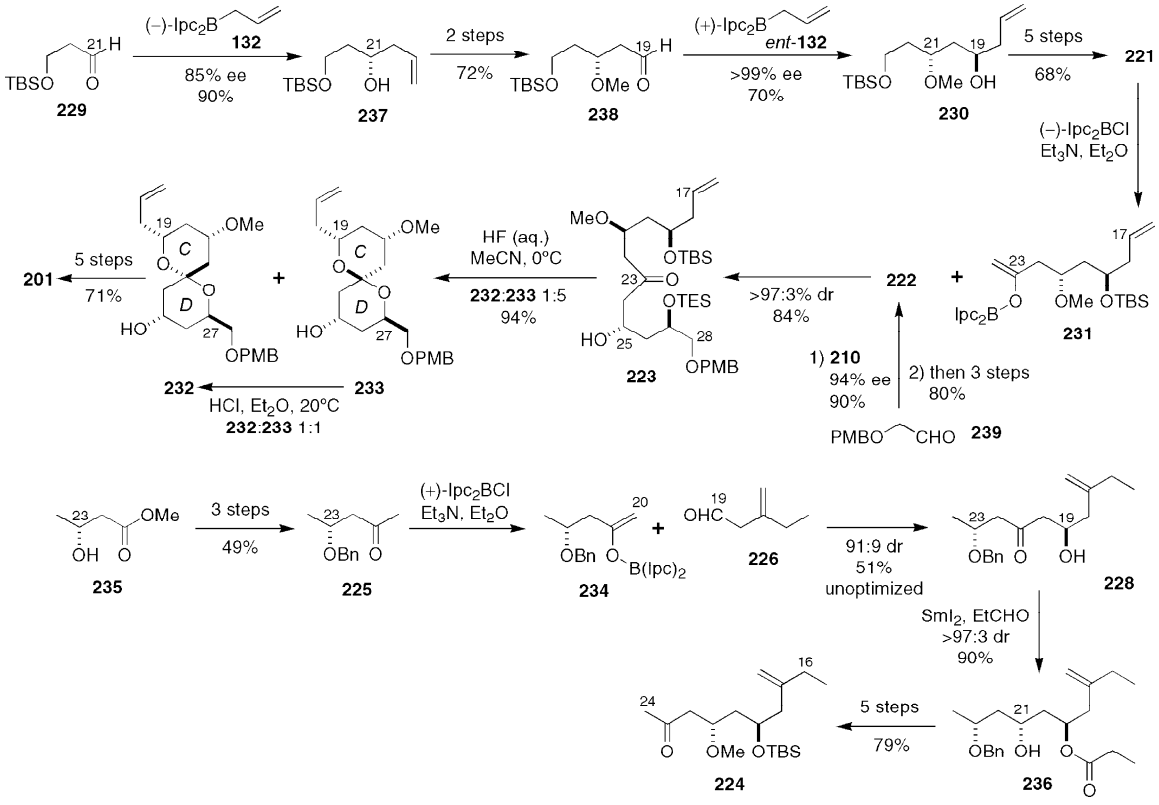


Scheme 35. Paterson Strategy for the Synthesis of the C16−C28 CD-Ring Segment of Spongistatin 1/Altohyrtin A



The assembly of the acyclic precursor **203** of the AB-segment **200** from appropriate building blocks involved three methyl ketone aldol bond constructions (Scheme 33) at C8−C9, C11−C12, and C5−C6, which relied on reinforcing substrate induction by use of a matched chiral boron reagent. In particular, acetone was employed as a three-carbon linking unit to connect the (C1−C5) aldehyde **204** and the (C9−C15) aldehyde **205**. Aldehyde **204** was prepared in 97% ee by allylboration of **209** using the (+)-2-carene-derived allylborane **210**[28a] (Scheme 34). Aldol addition of the Ipc_2−boron enolate **211** to **204** established the 1,3-*syn* (C3/C5) stereochemistry in a matched reaction (93:7 dr). The 1,4-*anti* (C11/C14) stereochemistry of the corresponding aldehyde partner **205** was set up by first coupling the Ipc_2−boron enolate **212** with aldehyde **207** to give the 1,4-*syn* product **213** (98:2 dr). This was then followed by a Mitsunobu inversion at C11 of the derived alcohol **214** to generate **215**. After conversion into the aldehyde **205**, an aldol reaction with the enolate **216** derived from methyl ketone **206** and (−)-Ipc_2BCl furnished adduct **203** as a single isomer. Here, the 1,3-*syn* preference of aldehyde **205**, the 1,5-*anti* preference of the ketone enolate **216,** and the stereodirecting influence of the boron reagent act in a synergistic fashion (triple asymmetric induction). Selective TES ether cleavage within **203** triggered spiroacetalization to provide the thermodynamically favored (axial−axial) product **217**. The tertiary hydroxyl stereocenter was installed by MeMgBr addition to the intermediate C9 ketone to provide axial alcohol **218**, which was transformed into the AB aldehyde **200**. On optimization, this key segment was prepared efficiently in 24 steps and 34% overall yield from aldehyde **208**.

Scheme 36. Paterson Synthesis of the C16−C28 CD-Ring Segment of Spongistatin 1/Altohyrtin A

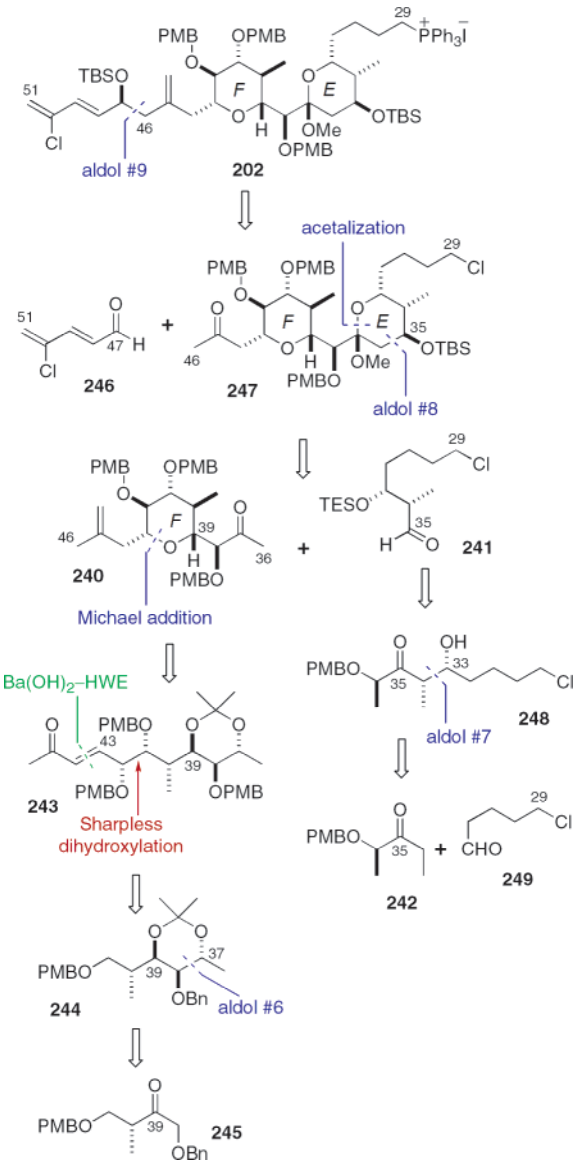


Similarly, the synthesis of the CD-segment **201** relied on a boron aldol reaction between methyl ketone **221** and aldehyde **222** (Scheme 35) to construct the skeleton of the CD-spiroacetal. The oxygen-bearing stereocenters in both coupling partners **221** and **222** were installed using Brown allylboration.[28] Subsequently, an alternative approach that generated the methyl ketone **224** via a 1,5-*anti*-aldol reaction between β-benzyloxy ketone **225** and aldehyde **226** was designed. The synthesis of methyl ketone **221** relied on consecutive allylations using antipodal borane reagents on aldehyde **229**, providing the 1,3-*anti* isomer **230** in >99% ee (Scheme 36). The key 1,5-*anti* aldol coupling, between the enolate **231** and aldehyde **222** (obtained via allylboration using the reagent **210**), resulted in the formation of the desired C25 isomer **223** (>97:3 dr). Acid-mediated desilylation of **223** and in-situ spiroacetalization gave initially a 1:5 mixture of the desired axial−equatorial isomer **232** and its C23-epimer **233**. The separated spiroacetal **233** was converted by equilibration under acidic conditions to provide access to multigram quantities of **232** after several cycles. Elaboration of the alkene at C17 to the ethyl ketone then provided the CD-segment **201**. On optimization this key segment was prepared in 18 steps and 16.5% overall yield from aldehyde **229**. In the alternative route, methyl ketone **224** was prepared by aldol coupling of the boron enolate **234** from ketone **225**, derived from (*R*)-hydroxybutrate **235**, with aldehyde **226**, providing β-hydroxy ketone **228** (91:9 dr).[20k] The requisite C21 stereocenter was then set up by an Evans−Tishchenko reduction. The resulting alcohol **236** was then converted into ketone **224**, which was subjected to a similar reaction sequence as before to assemble the same CD-segment **201**.

The synthesis plan used by the Paterson group to assemble the more demanding EF-segment **202** (C29−C51), containing the chlorodiene side chain attached to C43, is outlined in Scheme 37. Four strategic aldol bond constructions were utilized for the assembly of the full carbon framework of this segment. The F-ring tetrahydropyran **240** (C36−C46) was used as a nucleus, with chain extension in both directions via two challenging aldol reactions, to set up the E-ring and the C47−C51 portion of the side chain. The C33/C34 *syn*-stereochemistry within aldehyde **241**, used to generate the E-ring, was installed using the lactate-derived ketone **242**. The densely substituted F-ring **240** was obtained by an intramolecular hetero-Michael reaction on the linear precursor **243**. The (*E*)-enone moiety of **243** was constructed by a $Ba(OH)_2$-promoted HWE reaction,[31] while the C37−C40 *anti*−*syn*−*anti* stereorelationship in precursor **244** was obtained using benzyloxymethyl ketone **245**.

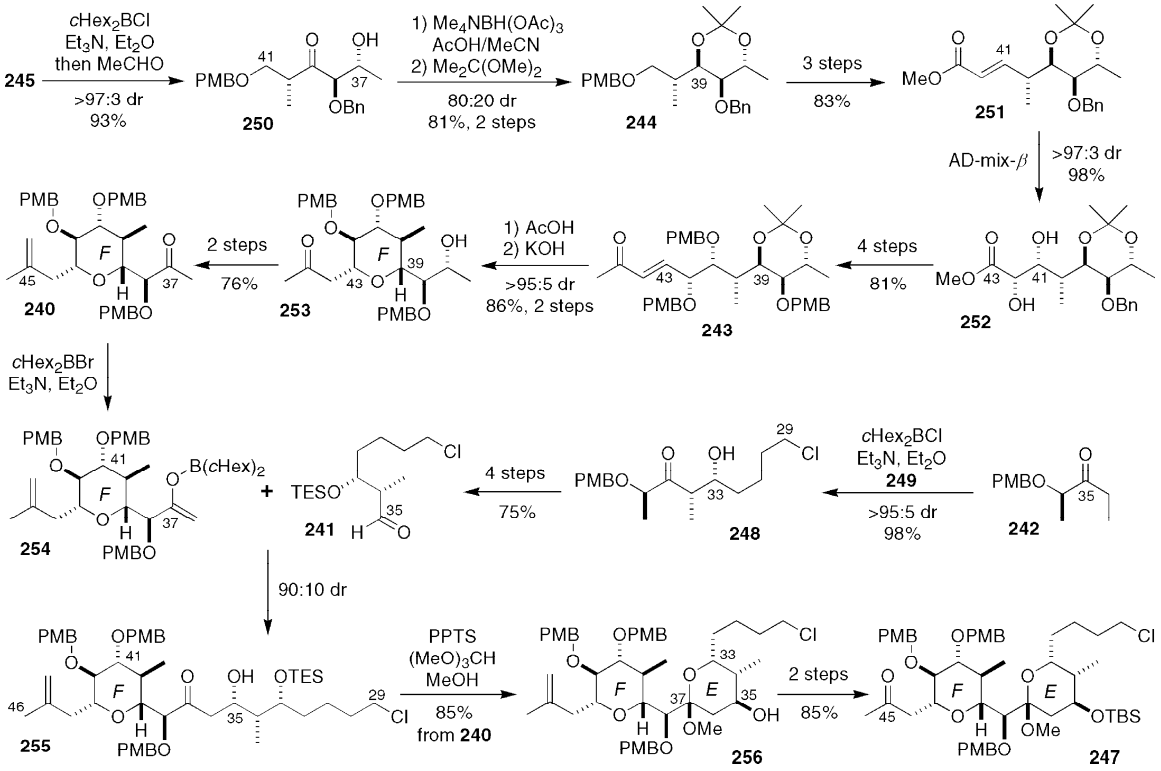
Addition of the (*E*)-dicyclohexylboron enolate of **245** to acetaldehyde (Scheme 38) produced the C37/C38 *anti*-aldol product **250** (>97:3 dr), which was followed by an Evans−Saksena reduction to install the C39 stereocenter. After conversion into the enoate **251**, Sharpless dihydroxylation using AD-mix-β furnished the *syn*-diol **252** (>97:3 dr). This was then transformed into enone **243**, which, on acetonide removal,

Scheme 37. Paterson Strategy for the Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A

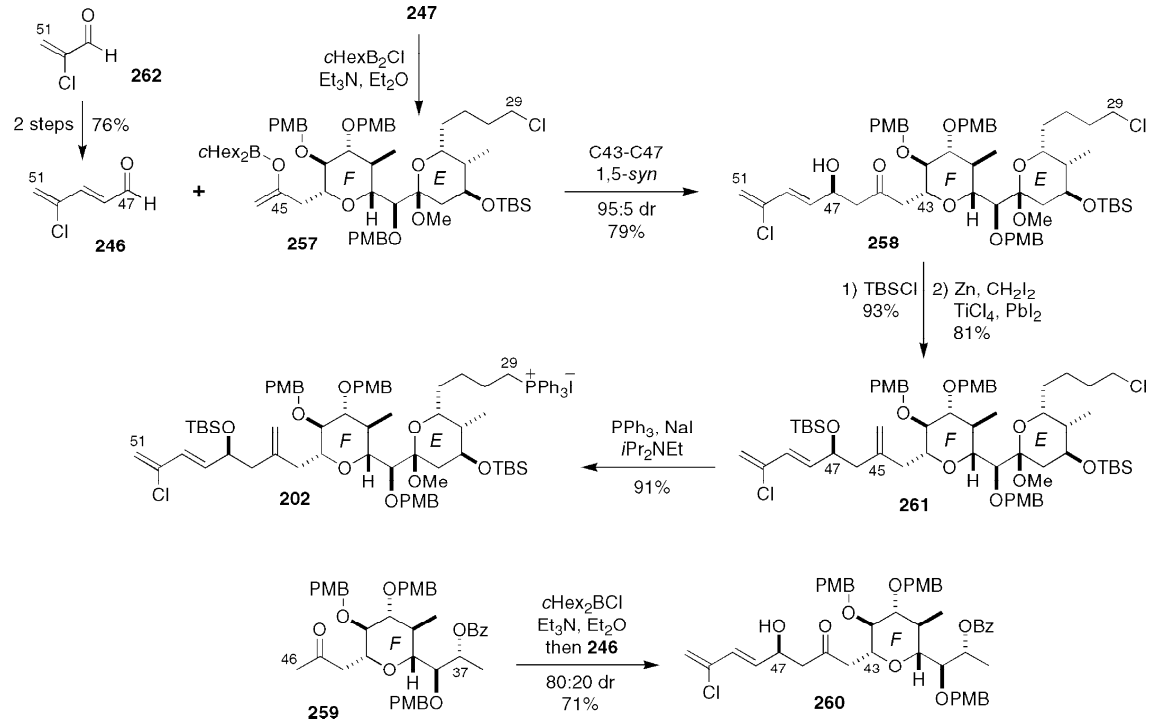


cyclization, and base equilibration, gave the F-ring **253** with the desired C43 configuration (>95:5 dr). Protection of the C45 ketone and oxidation of the C37−OH gave methyl ketone **240**, as required for coupling with aldehyde **241**. This aldehyde was prepared by a *syn*-aldol reaction of the (*Z*)-dicyclohexylboron enolate of ethyl ketone **242** with 5-chloropentanal **249** to give **248** (>95:5 dr) followed by cleavage of the auxiliary group. Successful aldol coupling of methyl ketone **240** necessitated the use of the more reactive *c*Hex_2BBr reagent. Addition of boron enolate **254** to aldehyde **241** gave β-hydroxy ketone **255** (90:10 dr), which was transformed into the E-ring methyl acetal **256**. This intermediate **256** was also used for the synthesis of a side chain truncated analogue of spongistatin.[32] A similar boron aldol/acetalization sequence, using a F-ring glycal, was adopted by Crimmins (section 2.1.5). Note that the use of a C29 chloride, which was carried unscathed through the rest of the EF-segment synthe-

Scheme 38. Paterson Synthesis of the C29–C46 EF-Ring Segment of Spongistatin 1/Altohyrtin A

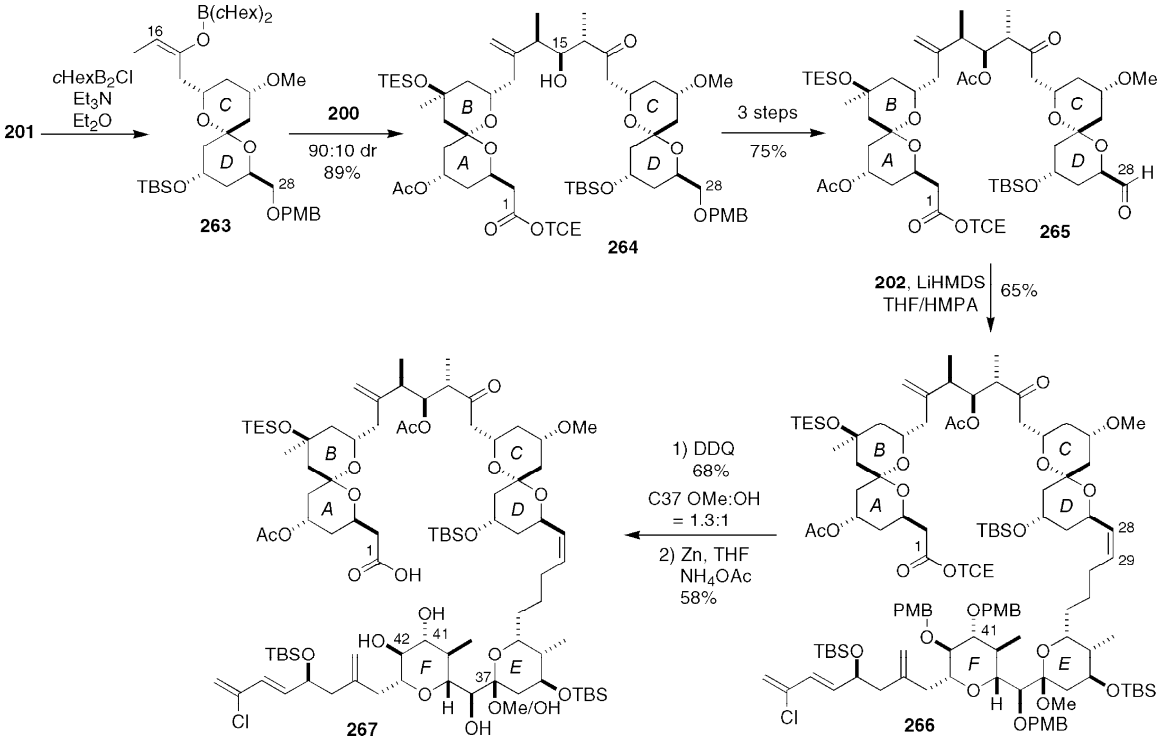


Scheme 39. Paterson Synthesis of the C29–C51 Segment of Spongistatin 1/Altohyrtin A

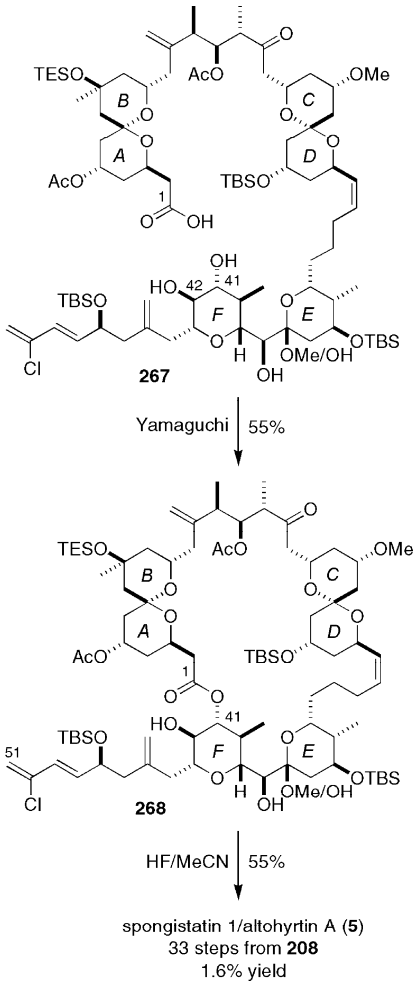


sis, eliminated the requirement for extra protection/deprotection steps and simplified the formation of the phosphonium salt. At this stage the C45 ketone was unmasked to give **247** for aldol coupling to the chlorodienal **246** (Scheme 39) with concomitant installation of the isolated C47 hydroxyl stereocenter. This remarkable substrate-controlled reaction using the dicyclohexylboron enolate **257** produced the β-hydroxy ketone **258** with a high level of control over the C47 configuration (95:5 dr). Notably, the stereoinduction arising from this complex enolate **257** is in the 1,5-*syn* sense, in contrast to the 1,5-*anti* induction observed with simple β-alkoxy methyl ketones, indicative of an overriding effect from the more remote stereocenters. A reinforcing effect from the E-ring is apparent, as the corresponding reaction with the analogous F-ring methyl ketone **259** provided **260** with reduced diastereoselectivity (80:20

Scheme 40. Paterson Synthesis of the Seco-Acid of Spongistatin 1/Altohyrtin A



Scheme 41. Paterson Total Synthesis of Spongistatin 1/Altohyrtin A



dr). After C47 silyl protection the required C45 alkene was generated via a modified Takai procedure and the C29 chloride was converted into the phosphonium salt **202**.

The key aldol coupling between the AB-segment **200** and the CD-segment **201** was conducted by enolization of **201** (cHex$_2$BCl/Et$_3$N, Et$_2$O) and addition of the resulting boron enolate **263** (Scheme 40) to aldehyde **200**, leading to formation of *anti*-adduct

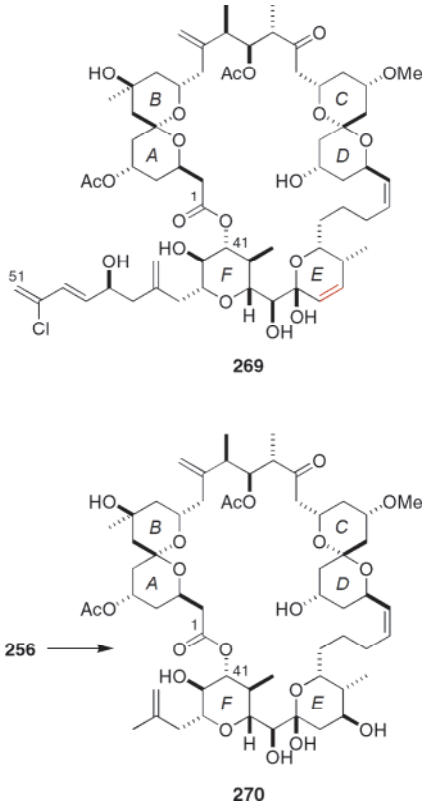
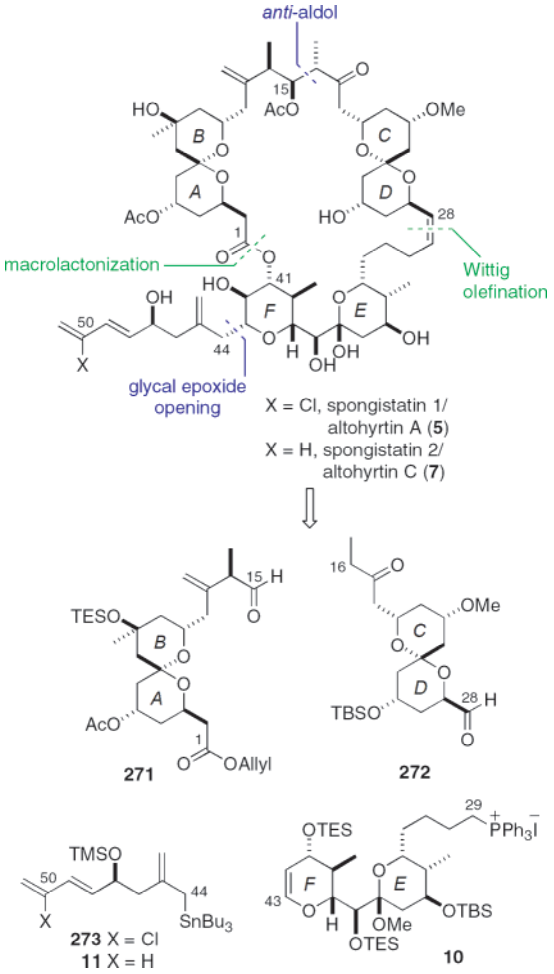


Figure 6. Structures of an E-ring dehydrated analogue **269** and a side chain truncated analogue **270** of spongistatin 1/altohyrtin A, as reported by Paterson.[32]

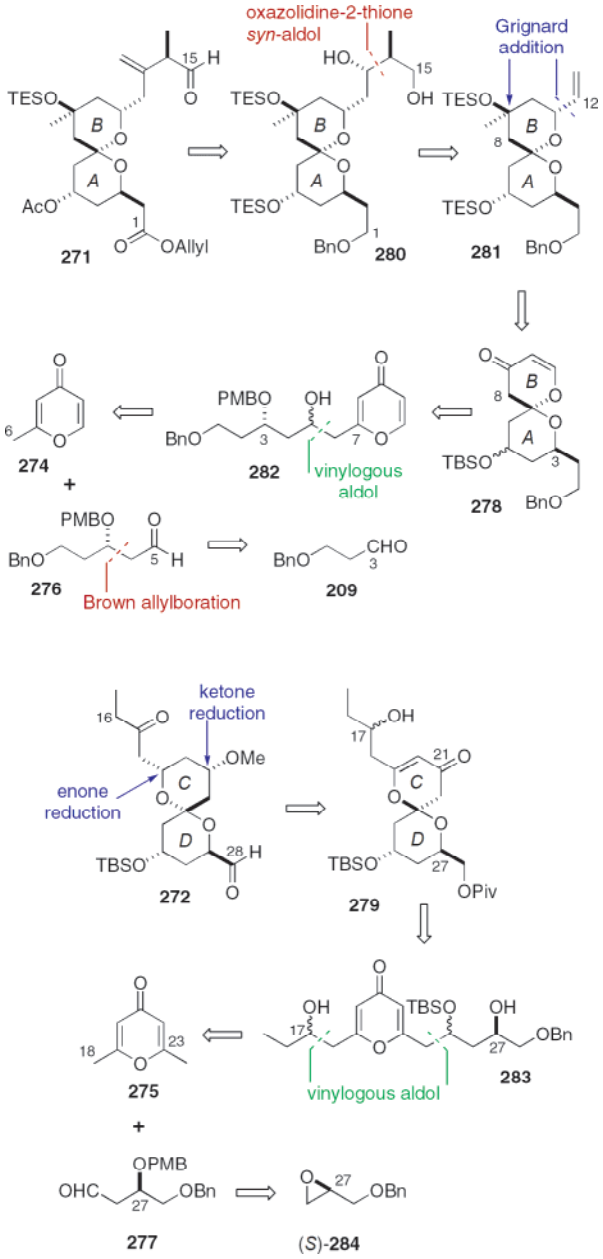
Scheme 42. Crimmins Strategy for the Total Synthesis of Spongistatin 1/Altohyrtin A and Spongistatin 2/Altohyrtin C



264 under Felkin−Anh control (90:10 dr). Following conversion into aldehyde **265**, the challenging Wittig coupling with the EF-segment **202** was best achieved using LiHMDS in THF/HMPA to furnish the fully protected seco-acid **266**. Under these conditions this pivotal Wittig olefination could be accomplished in 65% yield. Deprotection of the three PMB ethers (accompanied by partial methyl acetal hydrolysis) and cleavage of the 1,1,1-trichloroethyl (TCE) group gave seco-acid **267**, which on regioselective macrolactonization under Yamaguchi conditions generated the desired 42-membered macrolactone **268** (Scheme 41). Global deprotection of **268** then completed the total synthesis of spongistatin 1/altohyrtin A (**5**) in 33 linear steps and ca. 1.6% overall yield from methyl ketone **208** (89 total steps; about 4 steps per stereocenter).[33]

This synthesis proved efficient enough to provide sufficient spongistatin to resume its biological testing (in association with Professor Pettit) as well as enabling access to several novel analogues. The final deprotection led to formation of the E-ring dehydrated analogue **269** (Figure 6) as a minor byproduct. In cytotoxicity studies against a range of cancer cell lines, including paclitaxel-resistant strains, analogue **269** exhibited *enhanced* growth inhibitory potency in the low picomolar range over spongistatin 1 (altohyrtin A) itself, while the truncated analogue **270** led

Scheme 43. Crimmins Strategies for the Synthesis of the C1−C15 AB-Ring Segment and C16−C28 CD-Ring Segment of Spongistatin 1/Altohyrtin A

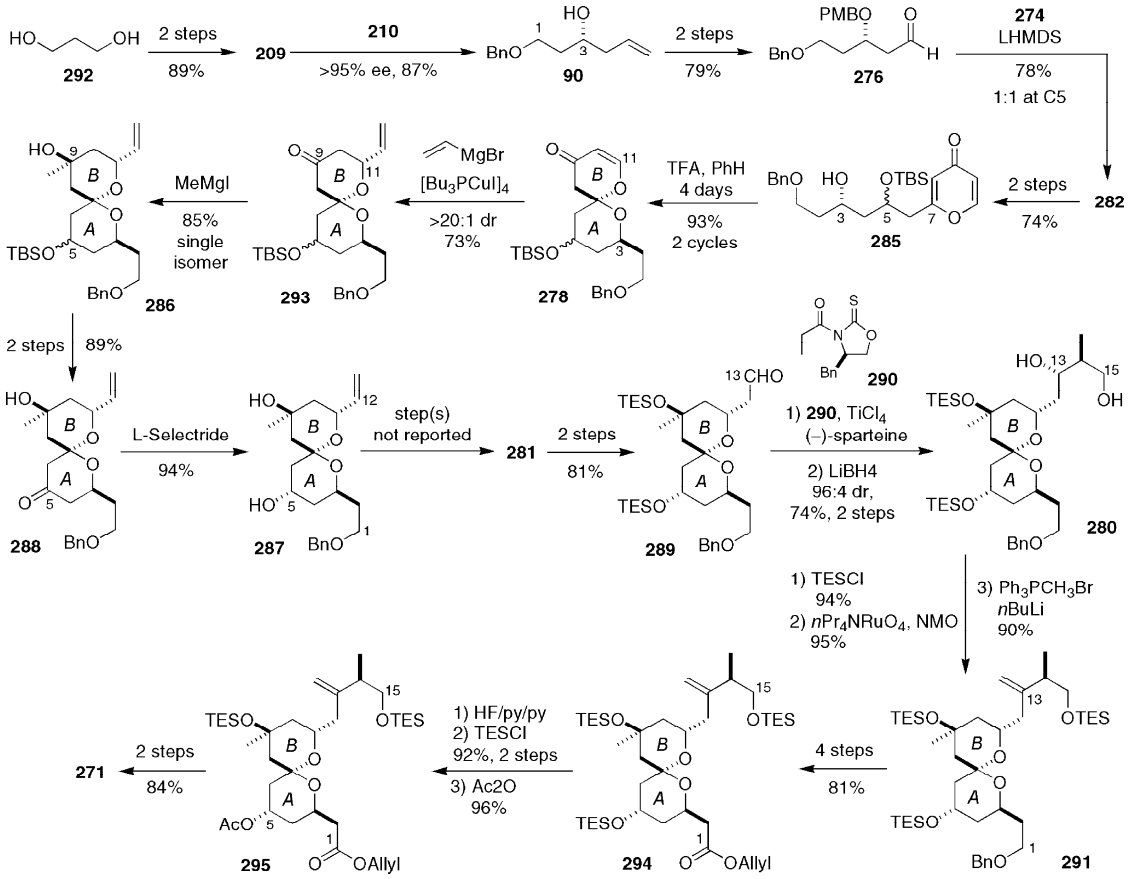


to a drastic drop off in activity, indicating the importance of the full side chain in determining the pharmacophore.[32]

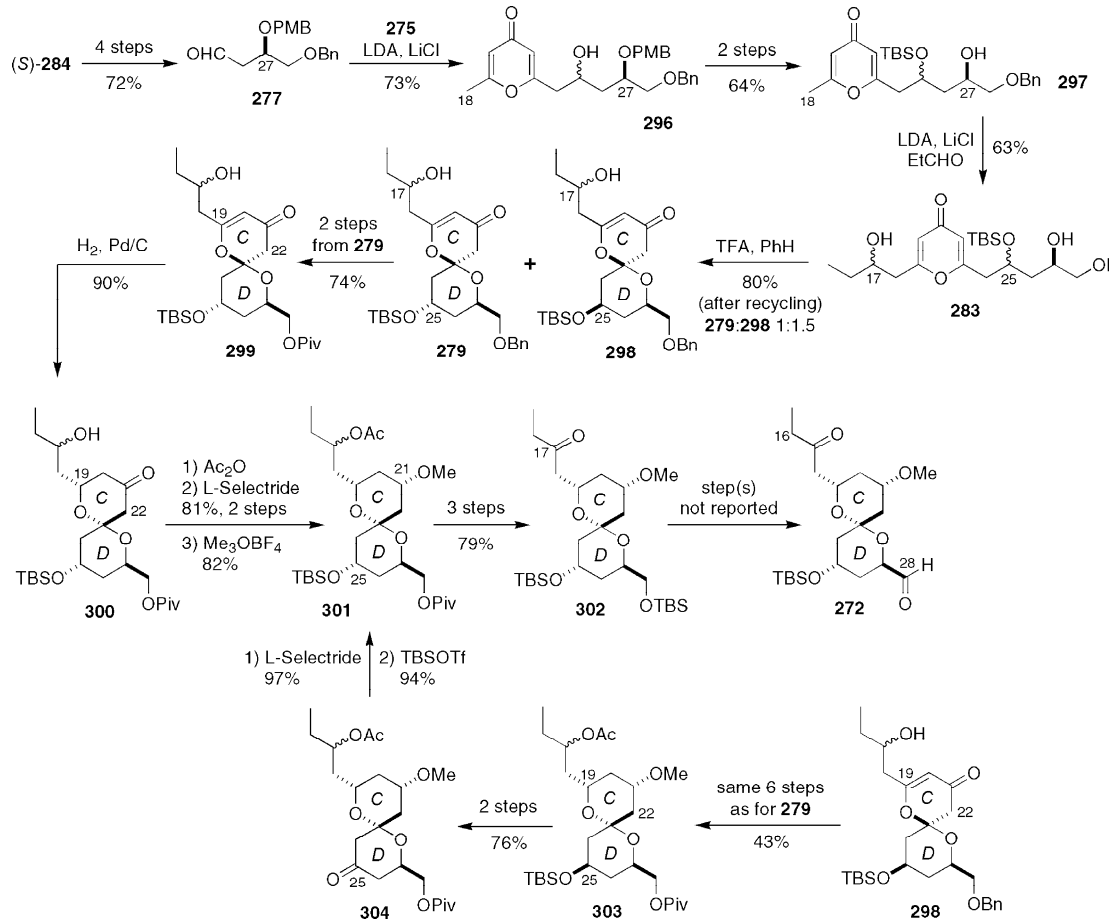
2.1.5. Crimmins Synthesis of Spongistatin 1 and 2/Altohyrtin A and C[21]

Crimmins adopted a similar plan for the synthesis of both spongistatin 1/altohyrtin A (**5**) and spongistatin 2/altohyrtin C (**7**) (Scheme 42). The 42-membered macrolide was disconnected into four principle segments: the AB-segment **271** (C1−C15), CD-segment **272** (C16−C28), EF-ring segment **10** (C29−C43), and appropriate side chain segment **273** or **11**. As in the earlier Evans synthesis, incorporation of the respective side chains employed the ring opening of an EF glycal epoxide by allylstannane reagents. The late-stage assembly of segments **271**, **272,** and **10** into a common glycal intermediate and

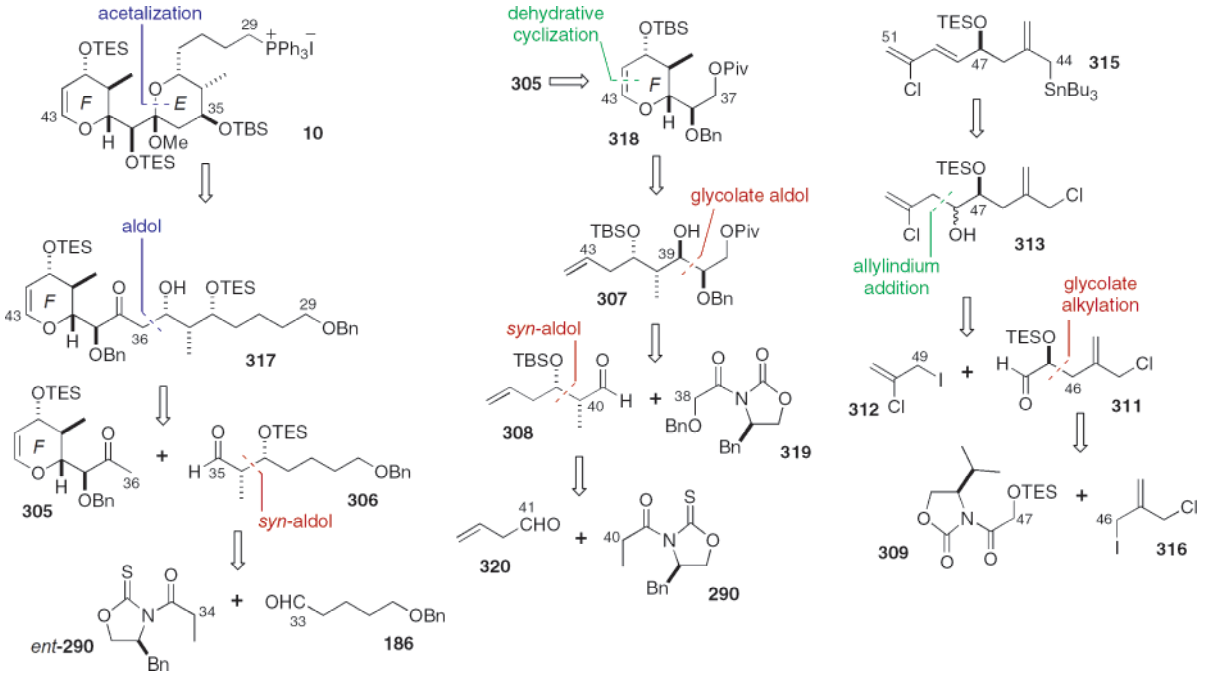
Scheme 44. Crimmins Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 1/Altohyrtin A



Scheme 45. Crimmins Synthesis of the C16−C28 CD-Ring Segment Synthesis of Spongistatin 1/Altohyrtin A



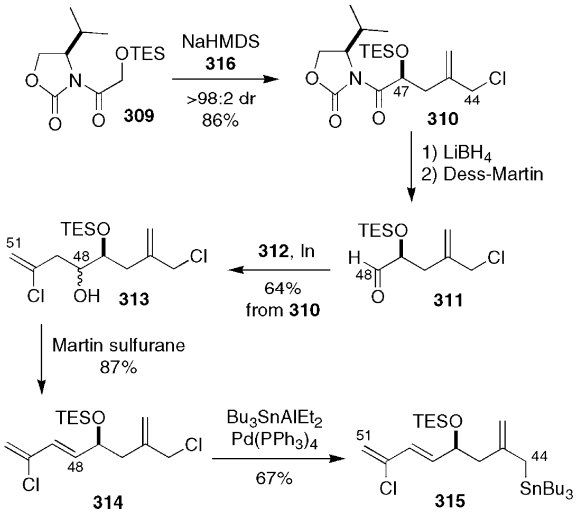
Scheme 46. Crimmins Strategy for the Synthesis of the C29−C43 EF-Ring Segment and C44−C51 Side Chain of Spongistatin 1/Altohyrtin A



introduction of the side chain using **273** or **11** allowed for the synthesis of spongistation 1 and 2, respectively. Rather than coupling together the three segments **271**, **272,** and **10**, as in the Evans and Paterson syntheses, the CD-segment **272** was first coupled with the EF-segment **10** via Wittig olefination before carrying out the *anti*-aldol coupling with the AB-segment **271**. The synthesis of both the AB-segment **271** and the CD-segment **272** (Scheme 43) centered on the aldol coupling of pyrones (**274** and **275**) with β-hydroxy aldehydes (**276** and **277,** respectively) followed by intramolecular hetero-Michael-type addition to form the corresponding spiro-dihydropyranones (**278** and **279** respectively), which were then elaborated into **271** and **272**. Unlike all the previous syntheses, which depended on acid-catalyzed spiroacetalization/equilibration and taking advantage of intramolecular hydrogen bonding or metal chelate formation, to access the correct CD-spiroacetal the Crimmins group exploited substrate-directed reduction of the enone **279** and avoidance of 1,3-diaxial interactions to access the desired axial−equatorial CD-ring configuration of **272**.

The β-hydroxy aldehyde **276**, bearing the C3−OH stereocenter, was prepared via a Brown allylboration[28] of aldehyde **209** (Scheme 44). Reaction of the lithiated methylpyrone **274** with **276** gave adduct **282** as a 1:1 mixture of C5 epimers. Two cycles of acid-catalyzed spirocyclization of the derived C5 TBS ether **285** gave spiro-dihydropyranone **278**, which served as a template for introduction of the remaining stereocenters. Two consecutive diastereoselective Grignard additions to **278** installed the C9 and C11 stereocenters on the B-ring, giving spiroacetal **286**. The mixture of C5 epimers was converted into diol **287** by L-Selectride reduction of the derived A-ring ketone **288**. After conversion to aldehyde **289**, aldol addition using the titanium enolate of oxazolidinethione **290**, as developed by Crimmins, provided the

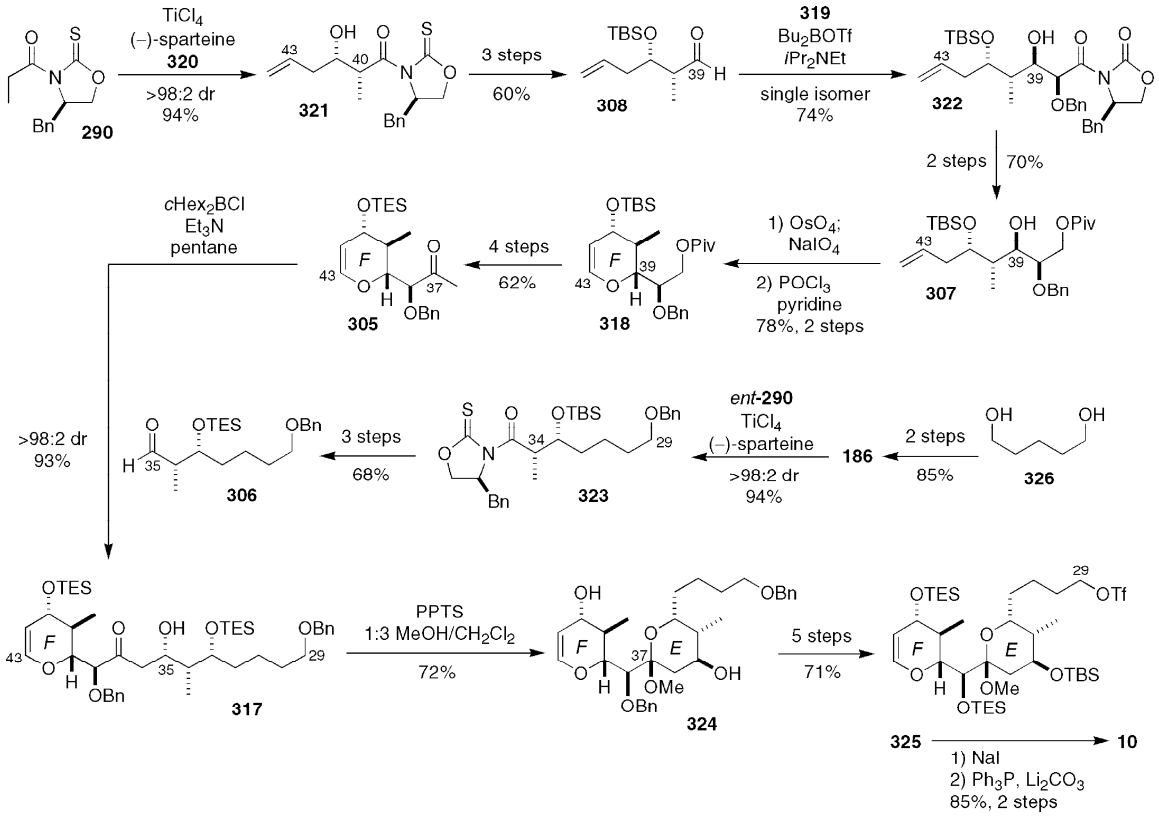
Scheme 47. Crimmins Synthesis of the C44−C51 Side Chain of Spongistatin 1/Altohyrtin A



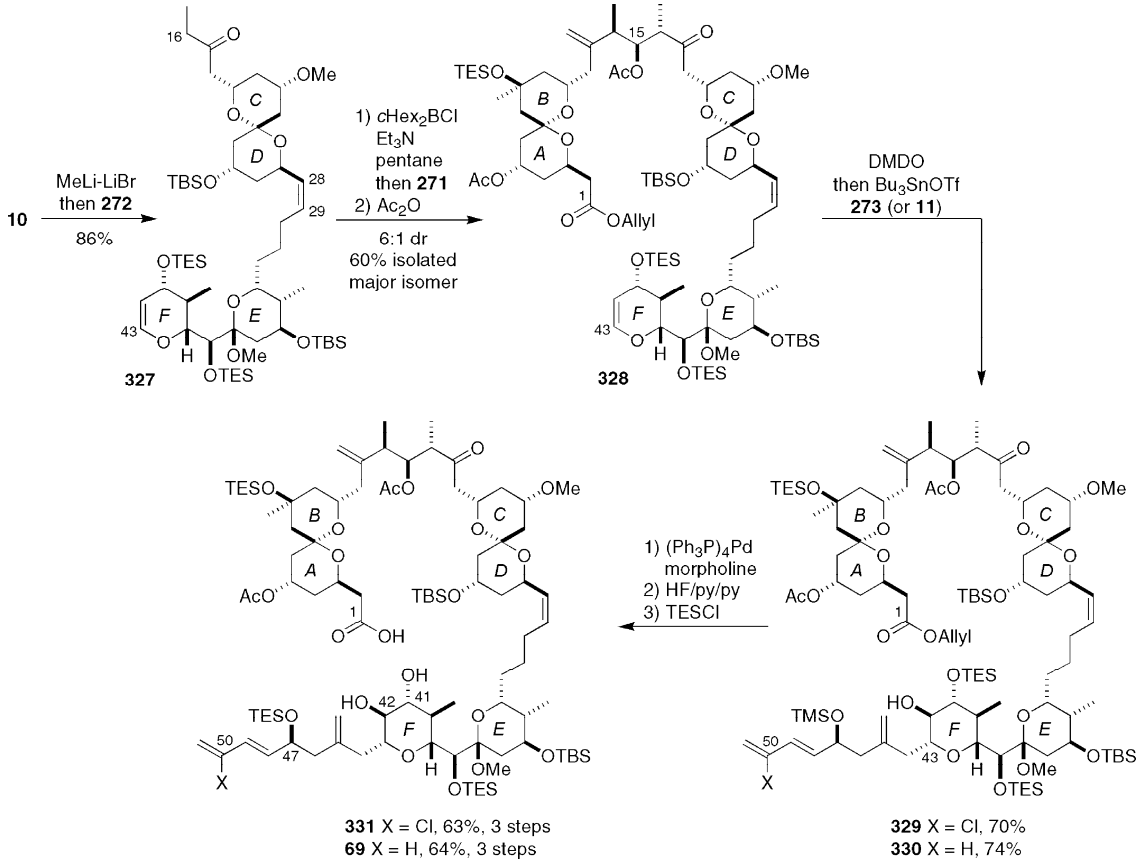
syn-adduct **280** (96:4 dr) after reductive removal of the chiral auxiliary. The temporary C13 stereocenter in **280** was removed by an oxidation/Wittig olefination to install the requisite methylene group. The intermediate **291** thus obtained was further manipulated and transformed into the fully elaborated AB-segment **271** through acetylation at C5.

The corresponding synthesis of the CD-segment **272** depended on a novel two-directional aldol chain extension of the dimethylpyrone **275** (Scheme 45). Addition of **275** to aldehyde **277**, obtained from the ring opening of (*S*)-benzyl glycidol **284**, provided **296**. A second aldol addition to propionaldehyde required the use of the dianion derived from **297**, giving **283** as a mixture of diastereoisomers. Acid-catalyzed spirocyclization of **283** (with recycling) gave a 1:1.5 mixture of desired C25 equatorial isomer **279** and its axial isomer **298**. Following conversion of **279** to its

Scheme 48. Crimmins Synthesis of the C29–C43 EF-Ring Segment of Spongistatin 1/Altohyrtin A

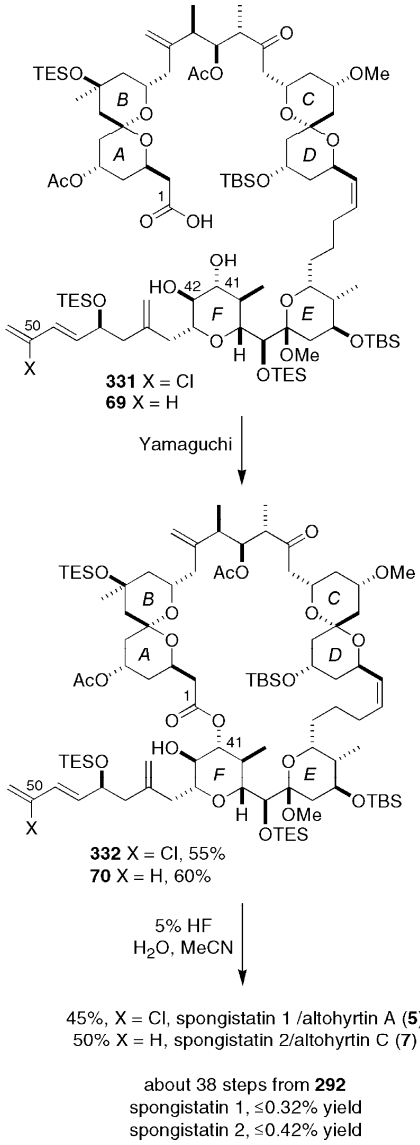


Scheme 49. Crimmins Synthesis of the Seco-Acids of Spongistatin 1/Altohyrtin A and Spongistatin 2/ Altohyrtin C



C1 pivalate ester **299**, hydrogenation of the enone provided an intermediate 1,6-diaxially substituted C-ring, which underwent ring inversion to give pyranone **300** having the requisite axial–equatorial disposition at the C23 center and an equatorial orientation of the C19 substituent. The remaining equa-

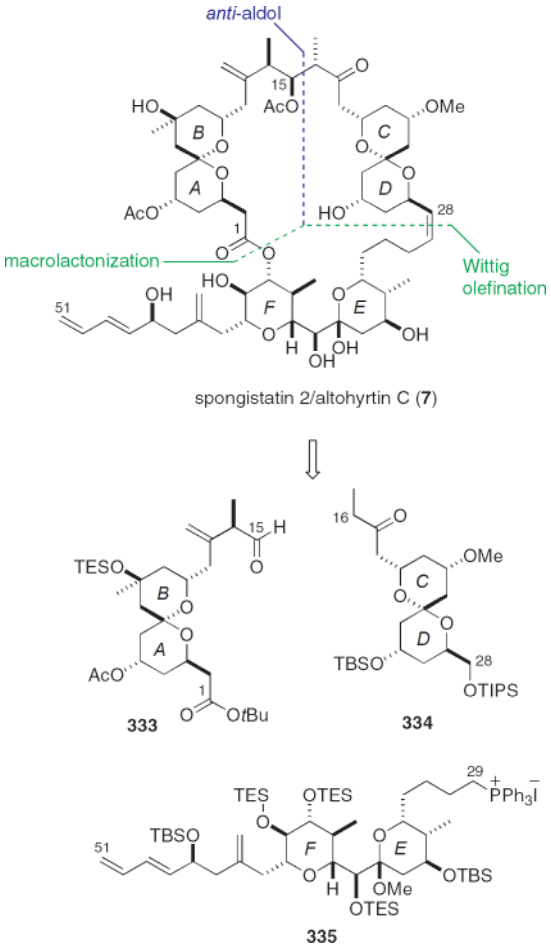
Scheme 50. Crimmins Total Synthesis of Spongistatin 1/Altohyrtin A and Spongistatin 2/Altohyrtin C



torial C21 methoxy group was then installed by hydride reduction followed by methylation. The product **301** was then transformed into ethyl ketone **272**. Fortunately, the undesired C25 axial isomer **298** could also be converted into ethyl ketone **272** via an oxidation−reduction sequence at C25.

As in the Paterson synthesis, the Crimmins construction of EF-ring glycal **10** also used a strategic C35−C36 aldol coupling between methyl ketone **305** and aldehyde **306** (C29−C35) to connect the E-ring to the F-ring (Scheme 46). The stereocenters contained in these two segments were generated using aldol methodology developed within the Crimmins group. The F-ring ketone **305** was derived from a dehydrative cyclization of the linear precursor **307** in which the 1,2-*syn* diol was installed by a glycolate aldol reaction on aldehyde **308**. The *syn* stereochemical relationships of aldehydes **306** and **308** were installed using antipodal oxazolidinethione reagents. The isolated C47−OH stereocenter of the chlorodiene side chain was introduced by an alkylation of glycolate derivative **309** to produce **310** (>98:2 dr) (Scheme

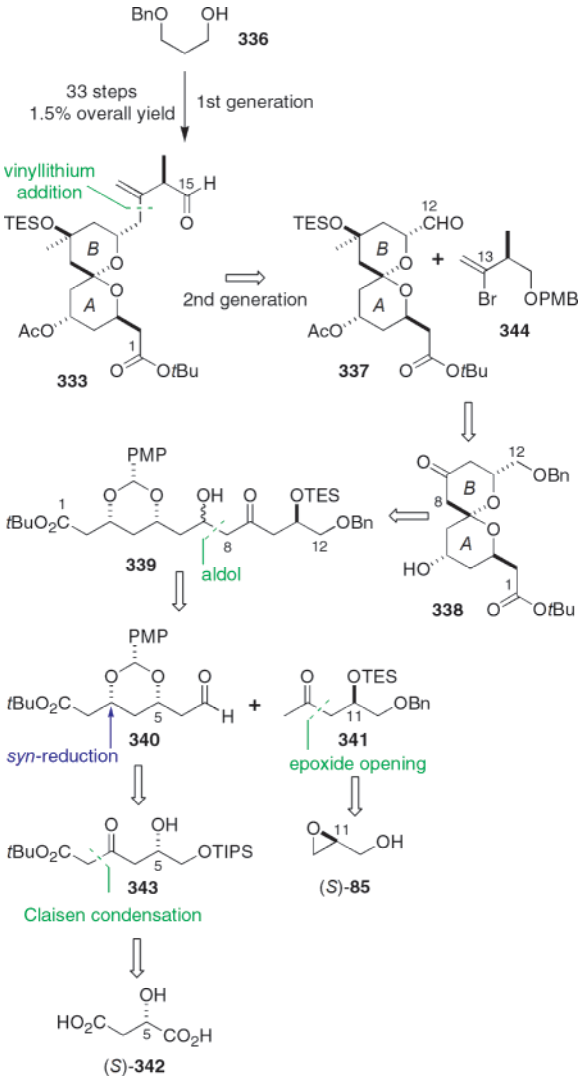
Scheme 51. Heathcock Strategy for the Total Synthesis of Spongistatin 2/Altohyrtin C



47). A reduction/oxidation sequence on the chiral auxiliary was performed to give aldehyde **311**. As in Kishi's synthesis of the chlorodiene (**117** → **123**, Scheme 17), addition of the allylindium reagent from **312** followed by dehydration of the resulting alcohol **313** using the Martin sulfurane provided the chlorodiene **314**. Introduction of the C44 tributylstannane group in **315** was then accomplished by displacement of the intermediate π-allyl palladium species generated from the allylic chloride **314**.

The synthesis of the F-ring glycal **305** began with the addition of the titanium enolate of *N*-propionyloxazolidinethione **290** to 3-butenal **320** producing *syn*-adduct **321** (>98:2 dr) (Scheme 48), which was converted into aldehyde **308** for a second aldol addition using the boron enolate of glycolate **319**. This gave adduct **322**, having the C38−C41 stereotetrad, as a single isomer. Cyclization was performed after reductive removal of the oxazolidinone and conversion into pivalate **307**, which upon oxidative cleavage of the alkene and dehydrative cyclization gave the F-ring glycal **318** and then the methyl ketone **305**. The corresponding C29−C35 component **306** was prepared via addition of the titanium enolate of *ent*-**290** to aldehyde **186**, which provided the *syn*-aldol product **323** (>98:2 dr). The key aldol coupling of the dicyclohexylboron enolate derived from **305** with **306** furnished the desired β-hydroxy ketone **317** (>98:2 dr). Note that enolization using dicyclohexylboron chloride was facile in this example. The E-ring

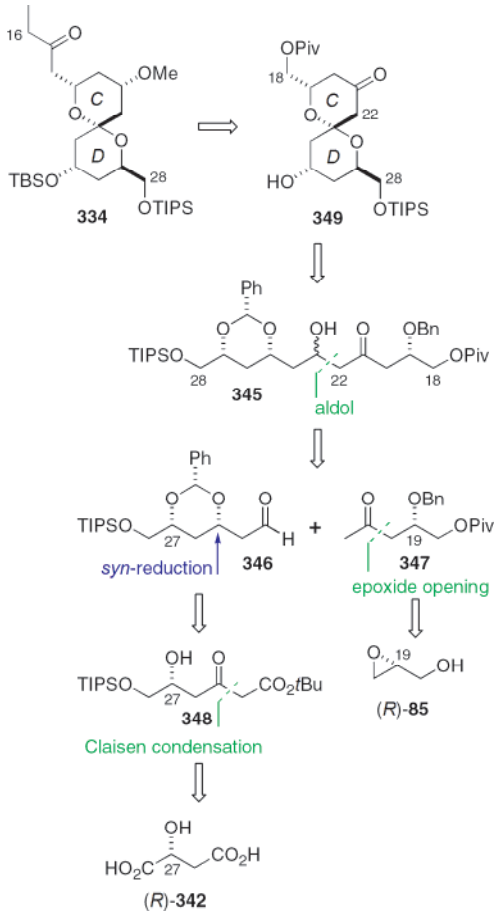
Scheme 52. Heathcock Strategy for the Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 2/Altohyrtin C



methyl acetal **324** was then obtained after desilylation. Protecting group manipulations on **324** and formation of the C29 phosphonium salt, through the tosylate **325**, then provided the EF-segment **10**.

The crucial connection of the four segments **271**, **272**, **10,** and **273** (or **11**) was executed first by chemoselective Wittig coupling of the CD aldehyde **272** with the ylide derived from phosphonium salt **10** to give (*Z*)-alkene **327** (Scheme 49). Addition of the dicyclohexylboron enolate derived from **327** to the AB aldehyde **271** gave the common advanced intermediate **328** (6:1 dr) after acylation of the C15−OH. Following the Evans protocol, introduction of the corresponding side chains of spongistatin 1 and 2 was accomplished by addition of allylstannane **273** or **11** to the intermediate glycal epoxide formed from **328**, providing seco-acid derivatives **329** and **330**. After deprotection of the more labile C41 and C47 silyl ethers it proved necessary to reprotect the C47 allylic hydroxyl group to allow for regioselective macrolactonization. Under Yamaguchi conditions, each of the seco-acids **331** and **69** were cyclized to provide the expected 42-membered macrolactone ring (**332** and **70,** respectively, Scheme 50). Note however that

Scheme 53. Heathcock Strategy for the Synthesis of the C16−C28 CD-Ring Segment of Spongistatin 2/Altohyrtin C



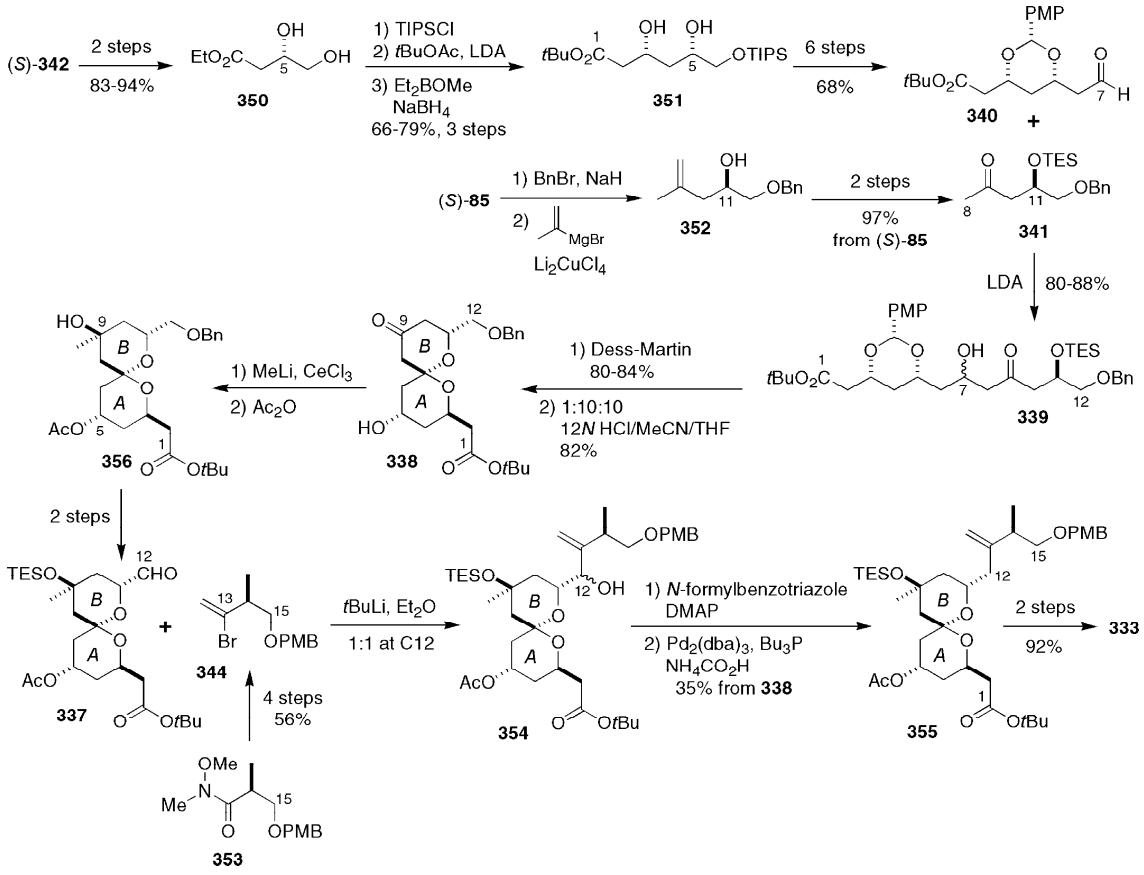
under Keck conditions (DCC, DMAP, DMAP−HCl) the unprotected C47−OH derivative of **331** cyclized to provide a 3:1 mixture of the C41 and C42 macrolactones. Final global deprotection then accomplished the synthesis of spongistatin 1/altohyrtin A (**5**) and spongistatin 2/altohyrtin C (**7**) in about 38 linear steps and ca. 0.32% and 0.42% overall yield, respectively, from 1,3-propanediol **292** (ca. 101 total steps; about 4 steps per stereocenter).

2.1.6. Heathcock Synthesis of Spongistatin 2/Altohyrtin C[22]

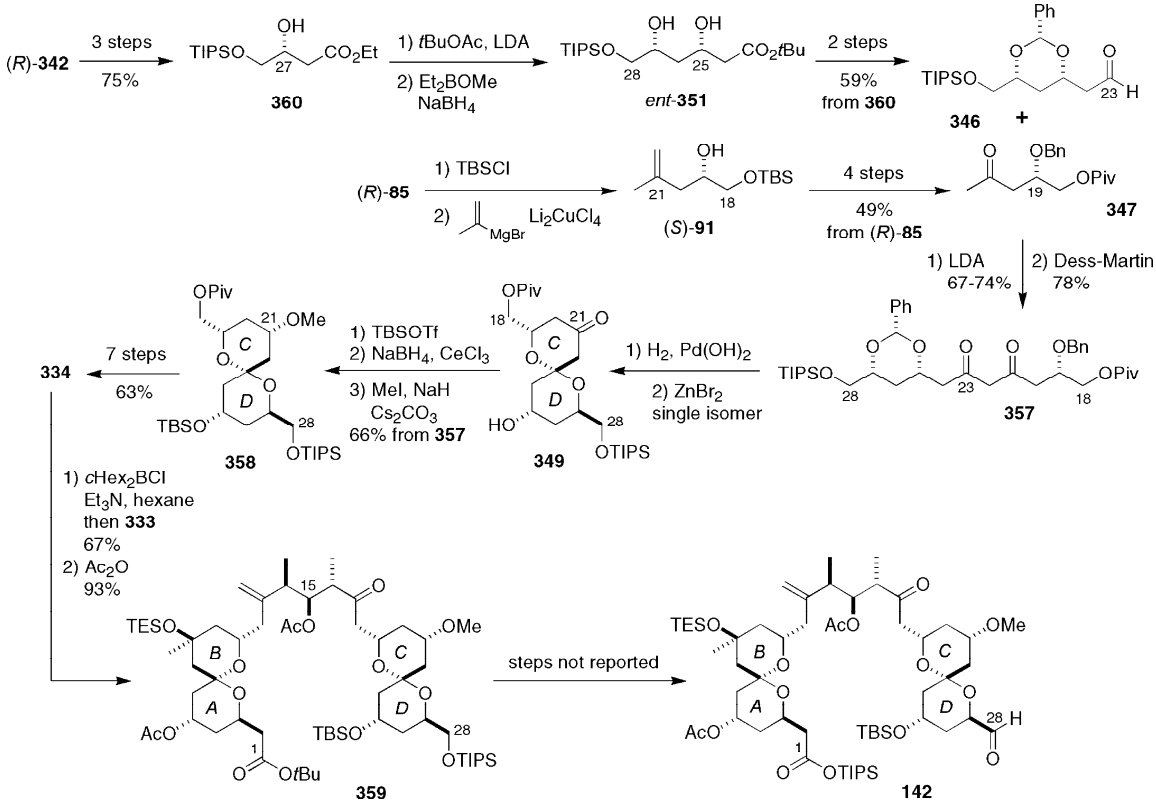
The Heathcock group developed a highly convergent synthetic route to spongistatin 2/altohyrtin C (**7**) and were able to scale this up to produce 250 mg of this complex macrolide. At the time this represented considerably more spongistatin than had ever been isolated from the sponge sources and synthesized by other groups, which ensured a good supply for further biological evaluation. As in the Paterson synthesis, the late-stage assembly of the 42-membered macrolactone involved regioselective macrolactonization onto the C41−OH of the seco-acid obtained from the *anti*-aldol coupling of the AB aldehyde **333** (C1−C15) to the CD ethyl ketone **334** (C16−C28) and then by a Wittig olefination with the fully functionalized EF-segment **335**, already incorporating the unsaturated side chain (Scheme 51).

The Heathcock first-generation synthesis of the AB-segment **333** from alcohol **336** required a total of

Scheme 54. Heathcock Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 2/Altohyrtin C



Scheme 55. Heathcock Synthesis of the C1−C28 ABCD-Ring Segment of Spongistatin 2/Altohyrtin C



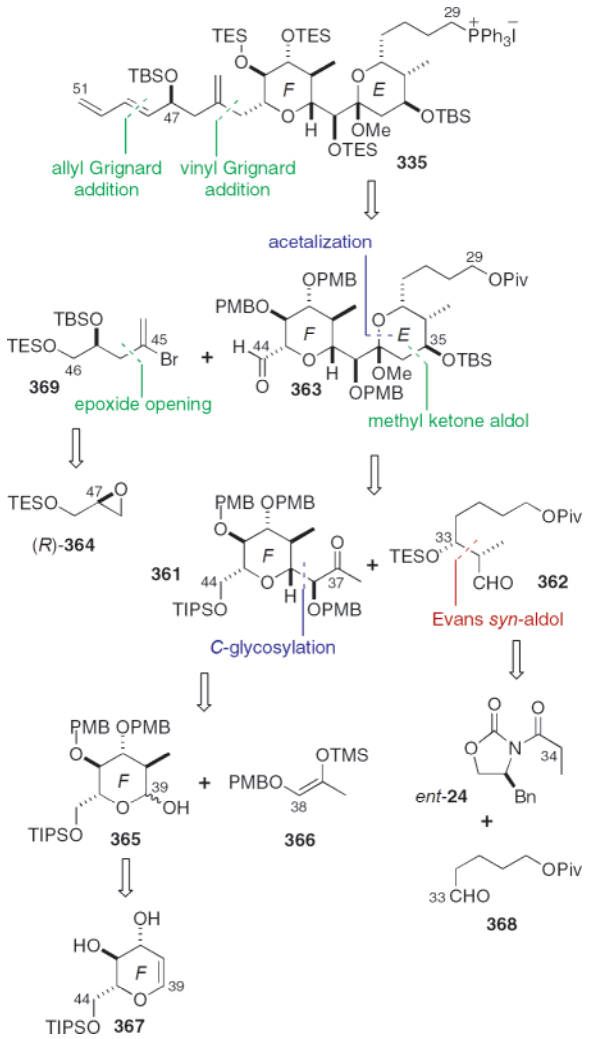
33 steps and proceeded in around 1.5% overall yield (Scheme 52).[22d] Subsequently, identical approaches were adopted for the syntheses of **333** and the corresponding CD-segment **334** by starting from antipodal chiral pool building blocks (Schemes 52 and 53). In the improved second-generation route to the AB-segment **333**, the C13−C15 portion was incorporated by a vinyllithium addition to the aldehyde **337**

(C1−C12), obtained by elaboration of the spirodihydropyranone **338**. This pivotal intermediate **338** arose in turn by spiroacetalization of the linear β-diketone derivative of β-hydroxy ketone **339**. An aldol disconnection across the C7−C8 bond of **339** led to the two coupling partners, aldehyde **340** and methyl ketone **341**. The stereocenters within these two components originated from (*S*)-malic acid **342** and (*S*)-glycidol **85**, respectively. As shown in Scheme 53, construction of the CD-segment **334** also relied on a spiroacetalization of the β-diketone derived from β-hydroxy ketone **345**. This open-chain precursor was assembled by an aldol coupling between aldehyde **346** and methyl ketone **347**, which were obtained from (*R*)-**342** and (*R*)-**85**, respectively.

Starting from (*S*)-**342**, the derived 1,2-diol **350** (Scheme 54) underwent a crossed Claisen condensation with the lithium enolate of *tert*-butyl acetate after protection of the C6 primary hydroxyl group. The resultant β-keto ester was then reduced under Prasad−Narasaka conditions to provide the 1,3-*syn* diol **351**, which was then converted into aldehyde **340** by a sequence involving a one-carbon homologation. The methyl ketone **341** was obtained from allylic alcohol **352,** which was prepared via ring opening by vinyl cuprate of the benzyl ether formed from (*S*)-**85**. Addition of the lithium enolate of **341** to aldehyde **340** provided a mixture of β-hydroxy ketones **339**, which was oxidized to an intermediate β-diketone. Acidic deprotection of the TES ether and the PMP acetal initiated spiroacetalization, giving (axial−axial) spiroacetal **338**. The C9 tertiary hydroxyl stereocenter was installed by methyllithium addition to ketone **338**. After C5−OH acetylation, the derived aldehyde **337** was coupled with the vinyllithium reagent formed from **344**, which was prepared from the known Weinreb amide **353**,[34] obtained in turn from the Roche ester. Deoxygenation of the 1:1 epimeric mixture of C12 alcohols **354** thus obtained was achieved by formylation followed by reduction of the resulting allylic formate to furnish alkene **355** as the only regioisomer.

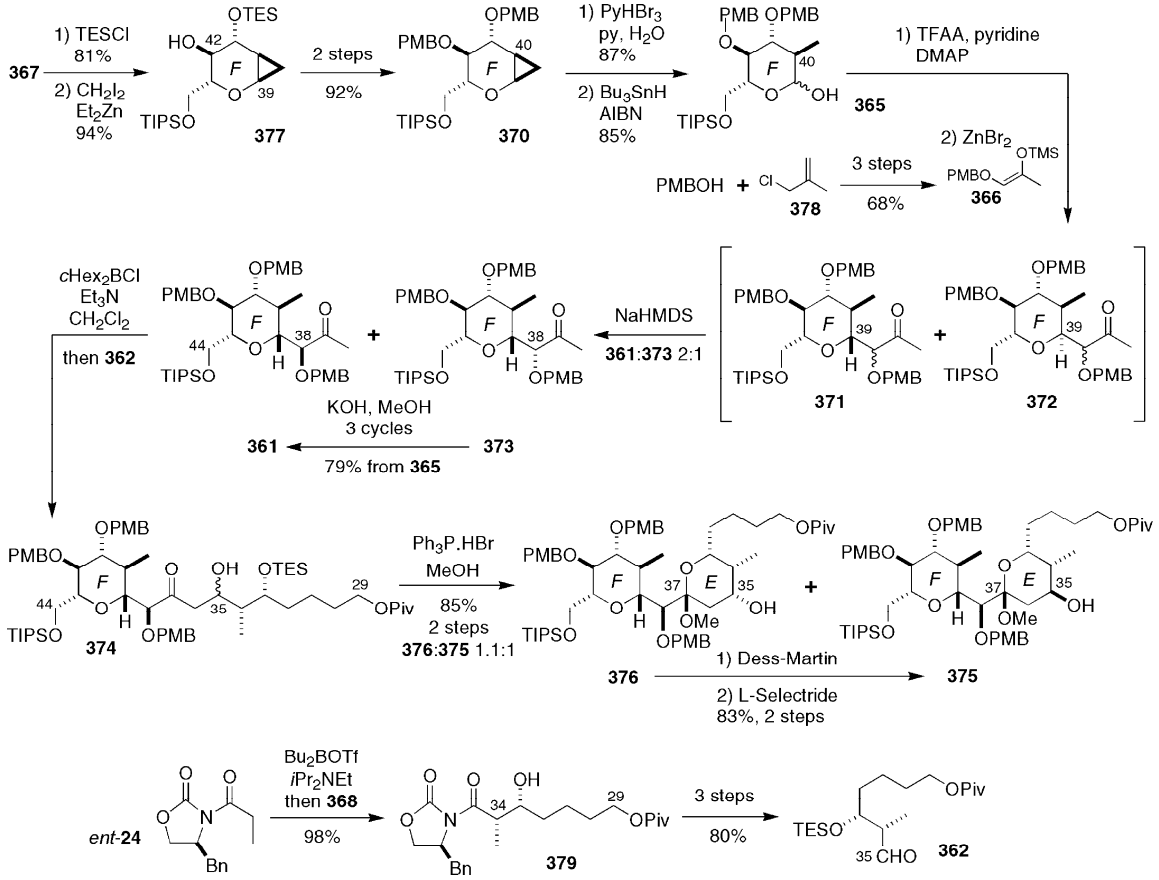
Synthesis of the CD-segment **334** involved similar sequences to those employed for the AB-segment to transform (*R*)-**342** and (*R*)-**85** into aldehyde **346** and methyl ketone **347**, respectively. Aldol coupling of the lithium enolate of methyl ketone **347** with **346** provided a mixture of β-hydroxy ketones, which was oxidized to give β-diketone **357** (Scheme 55). Hydrogenolysis of the benzyl ether and benzylidene acetal followed by treatment of the resultant triol with $ZnBr_2$ delivered the desired axial−equatorial spiroacetal **349** as a single isomer. The high diastereoselectivity of this spirocyclization was rationalized by kinetic control and a slower equilibration of the first formed product.[35] The remaining C21 methoxy stereocenter was installed by Luche reduction in a manner similar to the Crimmins synthesis (**300** → **301**, Scheme 45). The C16 ethyl ketone **334** was then obtained by elaboration of intermediate **358**. The critical C15−C16 aldol coupling of the dicyclohexylboron enolate of **334** with AB aldehyde **333** produced the *anti*-adduct **359**, which was then acetylated to give the fully elaborated ABCD-segment **142**.

Scheme 56. Heathcock Strategy for the Synthesis of the C29−C51 Segment of Spongistatin 2/ Altohyrtin C

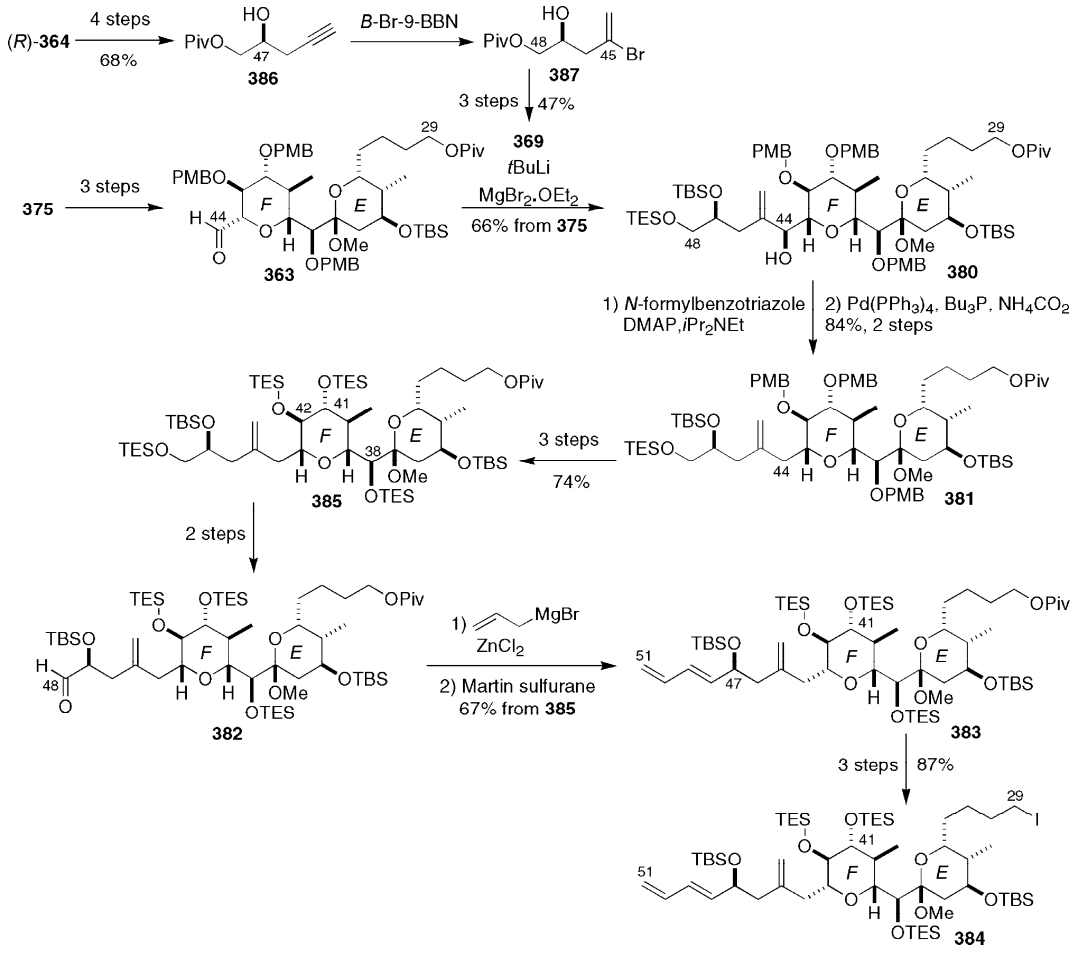


The Heathcock synthesis of the fully functionalized EF-segment **335** (C29−C51) was based on the key bond disconnections indicated in Scheme 56. As with the Paterson approach (Scheme 37), the F-ring ketone **361** (C36−C44) was used as a central linking unit. An aldol reaction between **361** and the aldehyde **362** (C29−C35) was used to connect the E-ring to the F-ring, as also employed in the Paterson and Crimmins syntheses (Schemes 37 and 46). Two consecutive Grignard additions were employed for attaching the side chain to the EF aldehyde **363** thus obtained. The isolated C47−OH stereocenter was derived from (*R*)-glycidol (**364**). Synthesis of the pivotal methyl ketone **361** was revised from an earlier approach using a Claisen rearrangement[22c] of a F-ring glycal derivative to generate the C38 and C39 stereocenters. The second approach (Scheme 56) adopted an anomeric alkylation of F-ring derivative **365** using silyl enol ether **366**. Synthesis of the tetrahydropyran **365** entailed a C42−OH-directed cyclopropanation of the bis-silylated derivative of glycal **367** (Scheme 57). After conversion into the bis-PMB ether **370**, the C40 methyl group was generated by opening of the cyclopropane via hydrobromination followed by Bu_3SnH reduction of the intermediate bromide. A $ZnBr_2$-promoted alkylation between the anomeric trifluo-

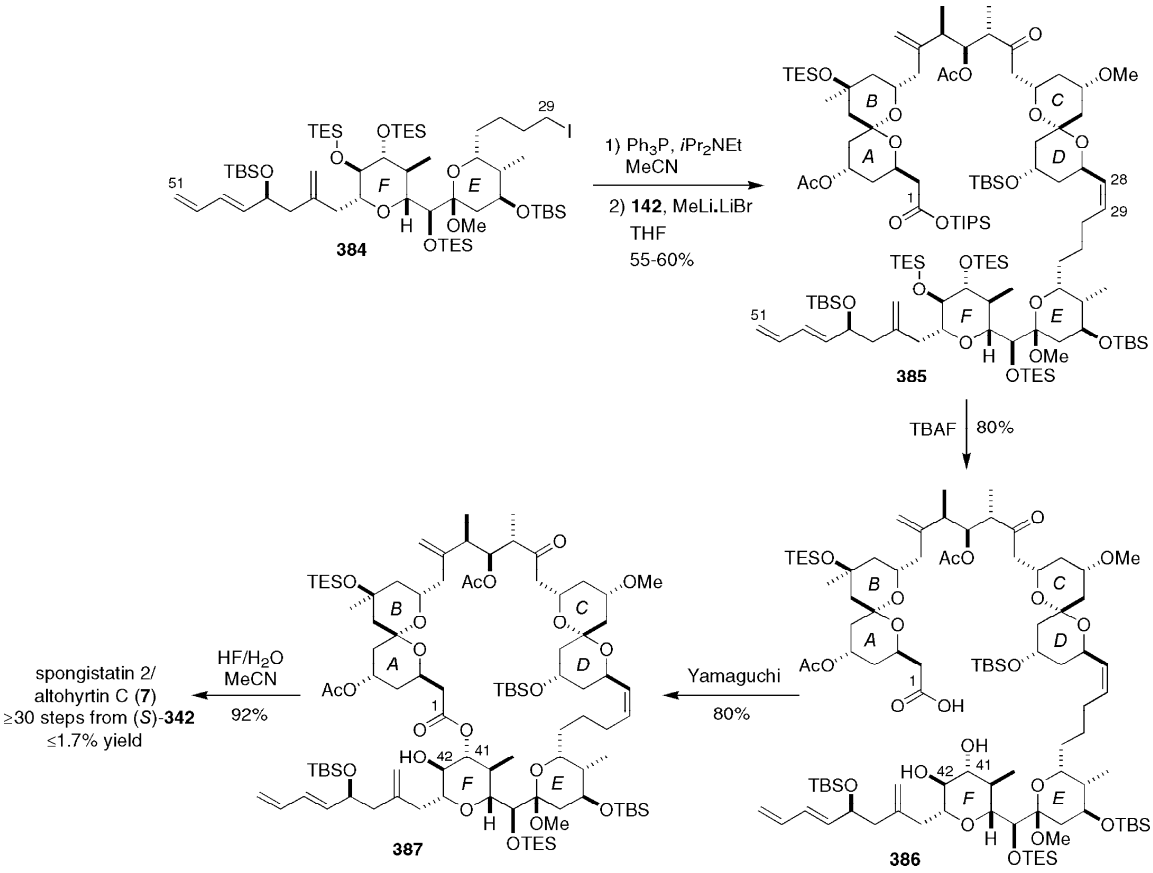
Scheme 57. Heathcock Synthesis of the C29−C44 EF-Ring Segment of Spongistatin 2/Altohyrtin C



Scheme 58. Heathcock Synthesis of the C29−C51 Segment of Spongistatin 2/Altohyrtin C



Scheme 59. Heathcock Total Synthesis of Spongistatin 2/Altohyrtin C



roacetate of **365** and silyl enol ether **366** produced a mixture of C39 epimers **371** and **372**. Anomeric equilibration using NaHMDS gave the desired isomer **361** and its C38-epimer **373** in a 2:1 ratio. Isomer **373** was separated and equilibrated upon KOH treatment (3 cycles) to provide more of the required isomer **361**.

Enolization of **361** to form the dicyclohexylboron enolate followed by aldol coupling in CH_2Cl_2 with aldehyde **362** prepared via an Evans *syn*-aldol on aldehyde **368** generated an epimeric mixture of adducts **374**. Removal of the C33 TES ether induced cyclization to deliver methyl acetal **375**, having the desired configuration at C35, and its epimer **376** in equimolar quantities. The undesired configuration at C35 of isomer **376** was corrected by an oxidation/reduction sequence to produce more of **375**. The derived C44 aldehyde **363** (Scheme 58) was then coupled with the Grignard reagent formed from vinyl bromide **369** to furnish the C44 alcohol **380** as a single isomer (chelation control), which was then deoxygenated using the protocol employed for a similar transformation in the AB-segment synthesis (**354** → **355**, Scheme 54). At this stage the three PMB ethers in **381** were switched to TES groups due to concerns over the stability of the C48−C51 diene moiety (lacking the electron-withdrawing chlorine substituent) toward late-stage oxidative PMB deprotection conditions. In contrast, deprotection of bis- and tris-PMB ether containing seco-acids using DDQ was achieved without problems in the Kishi (**139** → **140**, Scheme 20) and Paterson (**266** → **267**, Scheme 40) syntheses of spongistatin 1/altohyrtin A containing the chlorodiene side chain. In this case, the diene unit was installed via allyl Grignard addition to the derived C48 aldehyde **382** followed by dehydration of the intermediate allylic alcohol. This provided the fully elaborated C29−C51 EF-segment **383**, which was converted into C29 iodide **384** for coupling to the ABCD-segment **142**.

The final assembly of the 42-membered macrolactone entailed the conversion of the EF iodide **384** into the phosphonium salt (Scheme 59) followed by Wittig coupling with the ABCD aldehyde **142** using Crimmins procedure to produce the fully protected seco-acid **385** (55−60%). Selective deprotection of the TIPS ester and the C41 and C42 TES ethers was achieved by TBAF to give seco-acid **386**, which on regioselective macrolactonization, engaging the C41−OH, provided the 42-membered macrolactone **387**. Finally, global deprotection under optimized conditions with HF provided spongistatin 2/altohyrtin C (**7**) in around 30 linear steps and ca. 1.7% overall yield as calculated from (*S*)-malic acid **342** (ca. 110 total steps; about 5 steps per stereocenter). The E-ring dehydrated analogue **388** of spongistatin 2 (Figure 7) was also isolated during optimization of the final deprotection conditions. In agreement with the biological results obtained by Paterson on the E-ring dehydrated analogue **269** of spongistation 1 (Figure 6), **388** was found to be a more potent cell growth inhibitor than spongistatin 2.[22a]

2.1.7. Smith Synthesis of Spongistatin 1/Altohyrtin A[36]

The coupling strategy employed in Smith's second-generation approach, as applied to spongistatin 1/

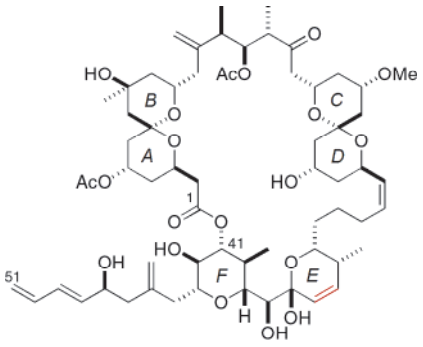


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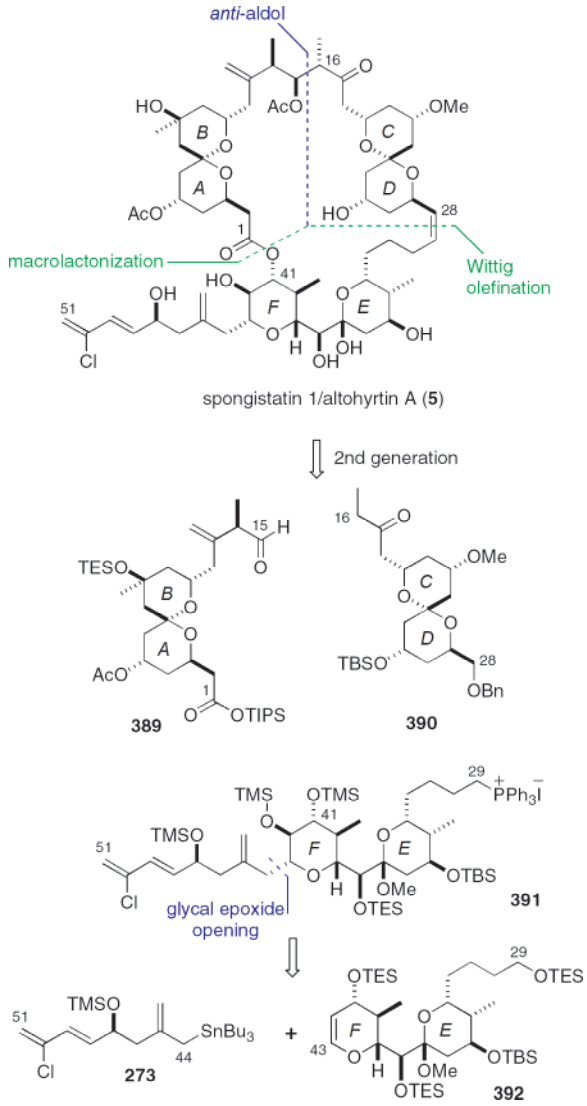
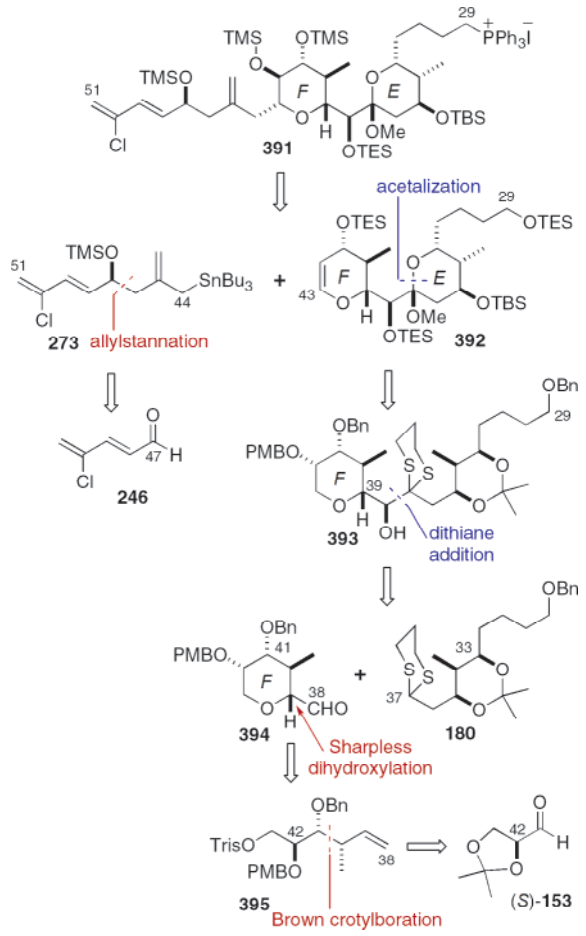
Figure 7. Structure of an E-ring dehydrated analogue of spongistatin 2/altohyrtin C, as reported by Heathcock.[22a]

Scheme 60. Smith Strategy for the Total Synthesis of Spongistatin 1/Altohyrtin A



altohyrtin A (**5**) (Scheme 60), is reminiscent of that implemented by Paterson in which an C15−C16 *anti*-aldol reaction is used to join the AB-segment **389** and CD-segment **390** followed by a Wittig coupling with the fully elaborated EF-segment **391**. Incorporation of the side chain was performed via addition of the allylic stannane **273** to the epoxide derived from F-ring glycal **392** in a manner similar to Evans and Crimmins. These revised tactics circumvented the

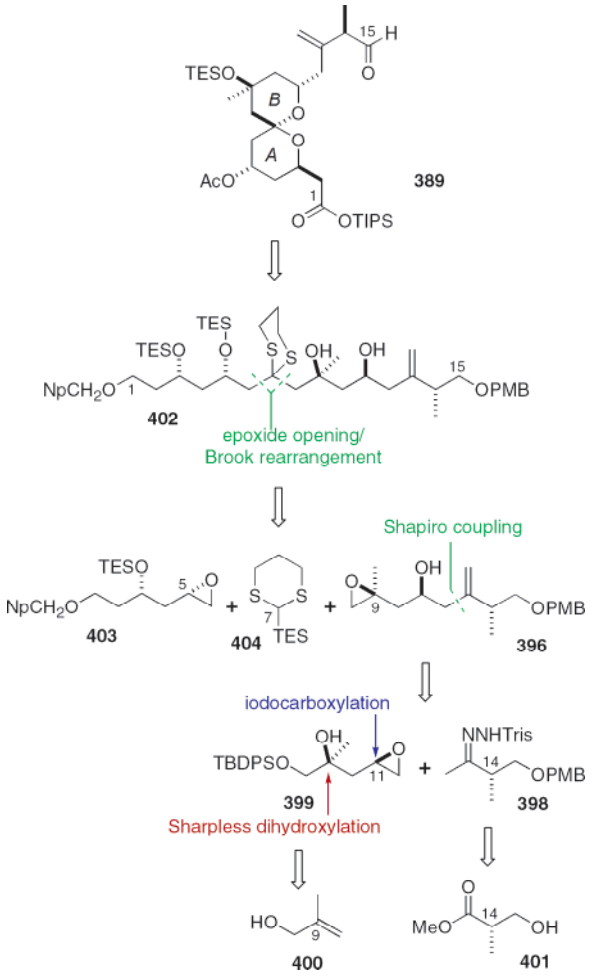
Scheme 61. Smith Strategy for the Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A



multiple protecting group exchanges during the Smith group's earlier route to the (C29−C51) EF-segment **143**, in particular, those following the diastereoselective addition of dithiane **180** to aldehyde **181** (Scheme 28). It also avoided the low-yielding Julia methylenation step that followed sulfone addition to the C44 iodide **179** (**178** → **194**, Scheme 29) and the troublesome epimerization at C23 in the CD spiroacetal. As in the Smith first-generation approach, a dithiane coupling strategy was used to connect the E-ring to the F-ring (**180** + **394**, Scheme 61). Rather than depend on glycidol as a chiral building block, a Keck-type asymmetric allylation was now used to create the isolated C47 stereocenter. The assembly of the key AB and CD intermediates **389** and **390** still relied on tandem epoxide opening by silyl dithiane reagents (Schemes 62 and 63). However, more elaborate epoxides **396** and **397** were now employed to allow for the more efficient incorporation of the corresponding C15 aldehyde and C16 ethyl ketone.

Synthesis of the C8−C15 epoxide **396** employed a Shapiro coupling between trisyl hydrazone **398** and epoxide **399**, which was prepared from alkene **400** (Scheme 62). Sharpless epoxidation on **400** served to introduce the C9 tertiary hydroxyl stereocenter (Scheme 64), and the derived homoallylic alcohol **407** was subjected to iodocarboxylation to set up the required C9−C11-*syn* configuration (7:1 dr). Addition

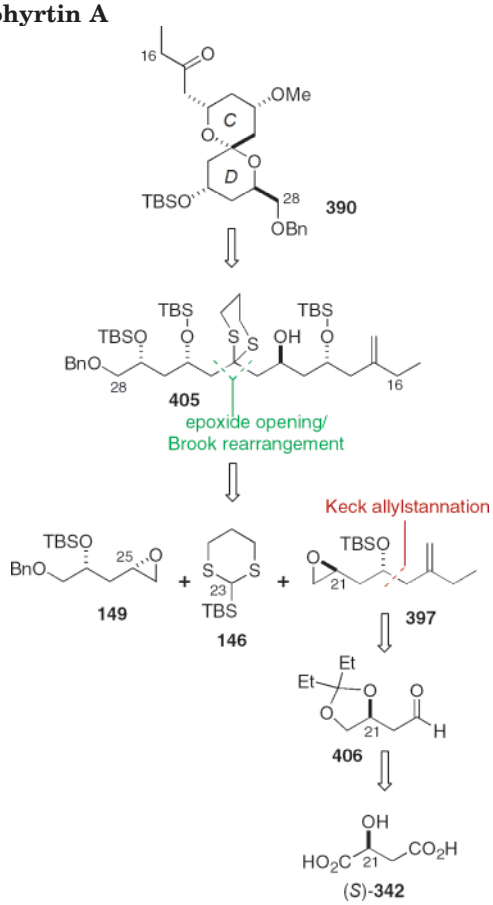
Scheme 62. Smith Strategy for the Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 1/Altohyrtin A



of the lithium alkoxide derived from epoxide **399** to the vinyllithium generated from hydrazone **398** produced the adduct **408**, with introduction of the C13 alkene. After generation of the terminal epoxide **396**, the corresponding alkoxide **409** was coupled with the C7 lithiated dithiane resulting from epoxide ring opening/Brook rearrangement of epoxide **403** (prepared in seven steps from 2-(bromomethyl)-naphthalene in a fashion similar to **147**, Scheme 24) using the TES-substituted dithiane **404**. This gave the acyclic precursor **402** required for the AB-segment. Hydrolysis of the dithiane and cleavage of the TES ethers with mercuric perchlorate delivered the AB-spiroacetal **410**. After selective C5−OH acetylation and C9−OH TES protection, the C1 naphthylmethyl group was removed (in the presence of the C13 methylene and the C15 PMB ether) by transfer hydrogenation to give alcohol **411**, which was then elaborated into the C15 aldehyde **389**.

Preparation of the C16−C22 epoxide **397**, as required for the synthesis of the CD ethyl ketone **390** (Scheme 65), employed a Keck-type allylstannation on aldehyde **406** derived from (*S*)-malic acid **342**, installing the C19 stereocenter (>10:1 dr). The resulting epoxide **397** obtained was then subjected to a three-component coupling with epoxide **149** and TBS-substituted dithiane **146**, as described before, to give CD-ring precursor **405**. Following C21−OH

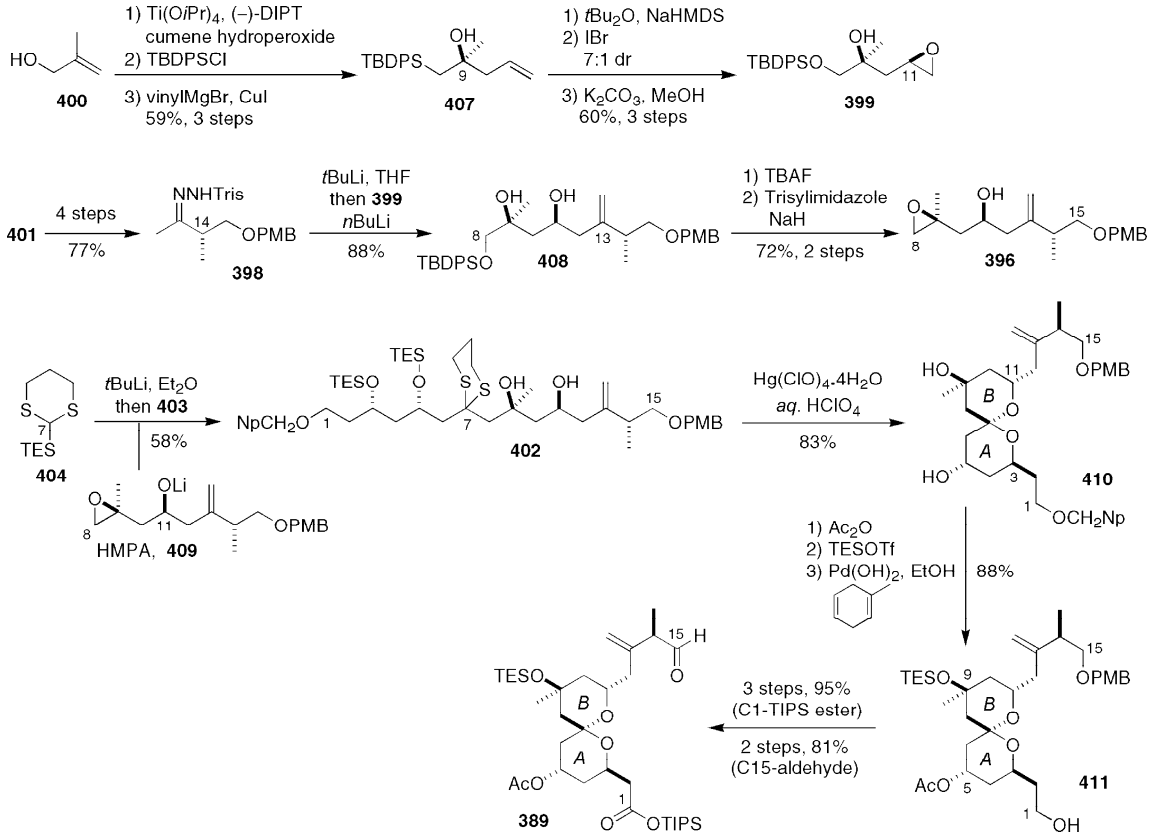
Scheme 63. Smith Strategy for the Synthesis of the C16−C28 CD-Ring Segment of Spongistatin 1/Altohyrtin A



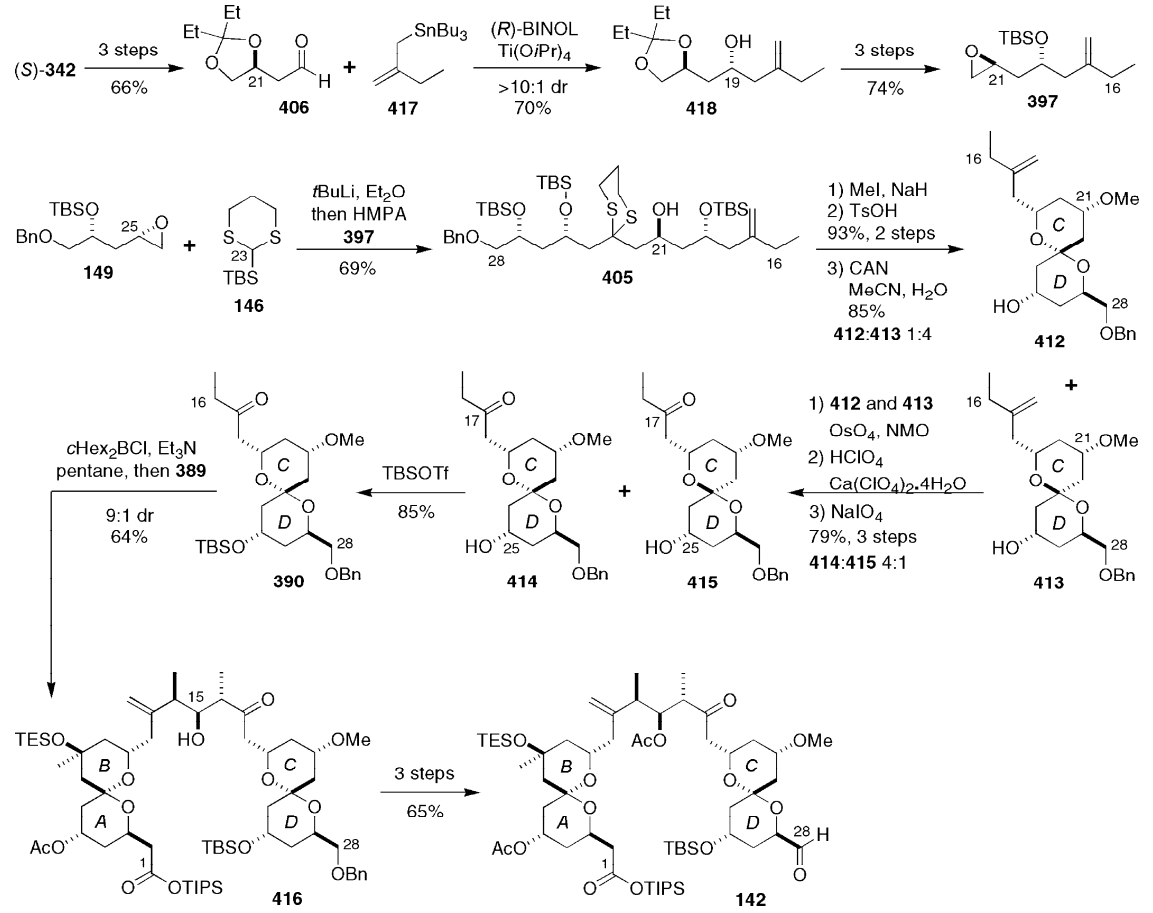
methylation and silyl deprotection, thioacetal hydrolysis using CAN led to spiroacetalization to generate a 1:4 mixture of the desired axial−equatorial isomer **412** and its C23-epimer **413**. As the calcium-ion-assisted equilibration necessitated an additional hydroxyl group at C17, this was performed after dihydroxylation to provide a 4:1 mixture of ethyl ketones **414** and **415** following periodate glycol cleavage. Selective enolization of **390** to generate the (*E*)-dicyclohexylboron enolate and addition to the AB aldehyde **389** gave adduct **416** (9:1 dr). After acetylation of the C15−OH, synthesis of the ABCD aldehyde **142** was completed.

Synthesis of the F-ring aldehyde **394** (Scheme 66) employed a Brown crotylboration[27] on aldehyde (*S*)-**153** to provide homoallylic alcohol **419** (>20:1 dr). Note that the unnatural (*S*)-configuration at C42 was required to facilitate the later elimination to form the glycal. After conversion into **395**, Sharpless dihydroxylation established the C39 stereocenter (6:1 dr) and the intermediate diol was cyclized to form the F-ring. Addition of the cerium anion of dithiane **180** to the derived aldehyde **394** in the presence of $ZnCl_2$ gave adduct **393** with improved diastereoselectivity (>20:1 dr) at C38 relative to the first-generation synthesis. Hydrolytic removal of the acetonide and dithiane groups within **393** led to concomitant formation of the E-ring hemiacetal **420**. After protection of the more accessible C35−OH, selective transfer hydrogenation removed the C29 and C41 benzyl ethers in the presence of the C42 PMB ether and

Scheme 64. Smith Synthesis of the C1−C15 AB-Ring Segment of Spongistatin 1/Altohyrtin A

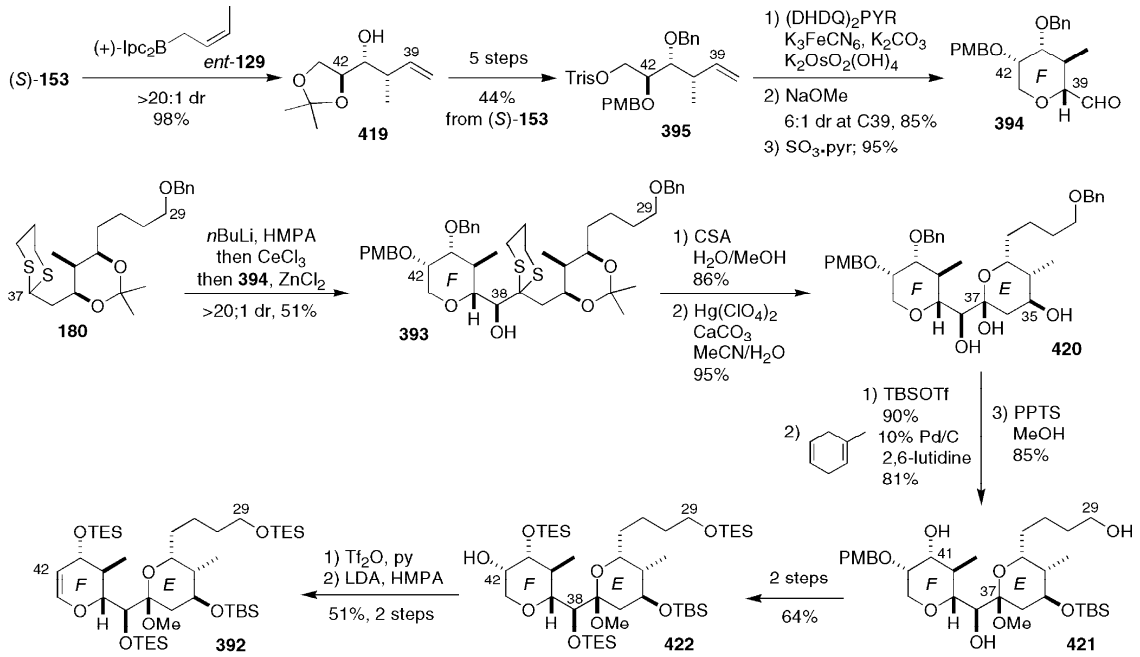


Scheme 65. Smith Synthesis of the C1−C28 ABCD-Ring Segment of Spongistatin 1/Altohyrtin A

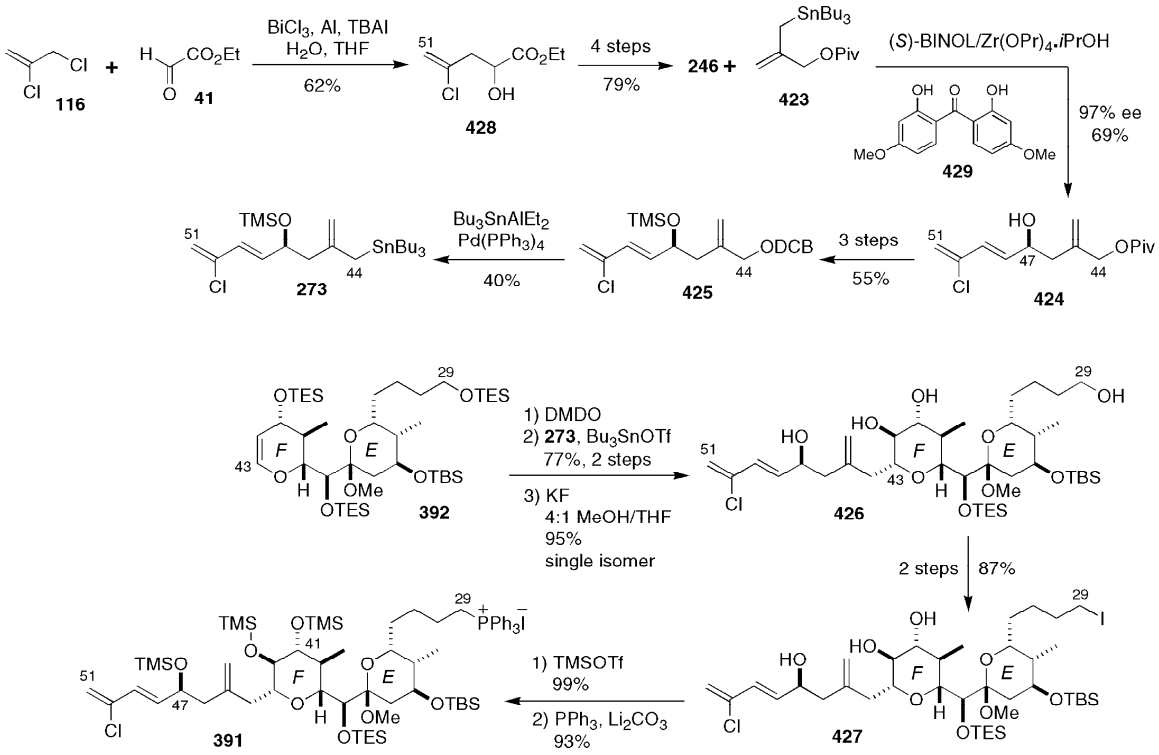


subsequent methanolysis provided the acetal **421**. Following silylation, the liberated C42−OH was eliminated via its triflate to form the F-ring glycal **392**.

Scheme 66. Smith Synthesis of the C29−C43 EF-Ring Segment of Spongistatin 1/Altohyrtin A

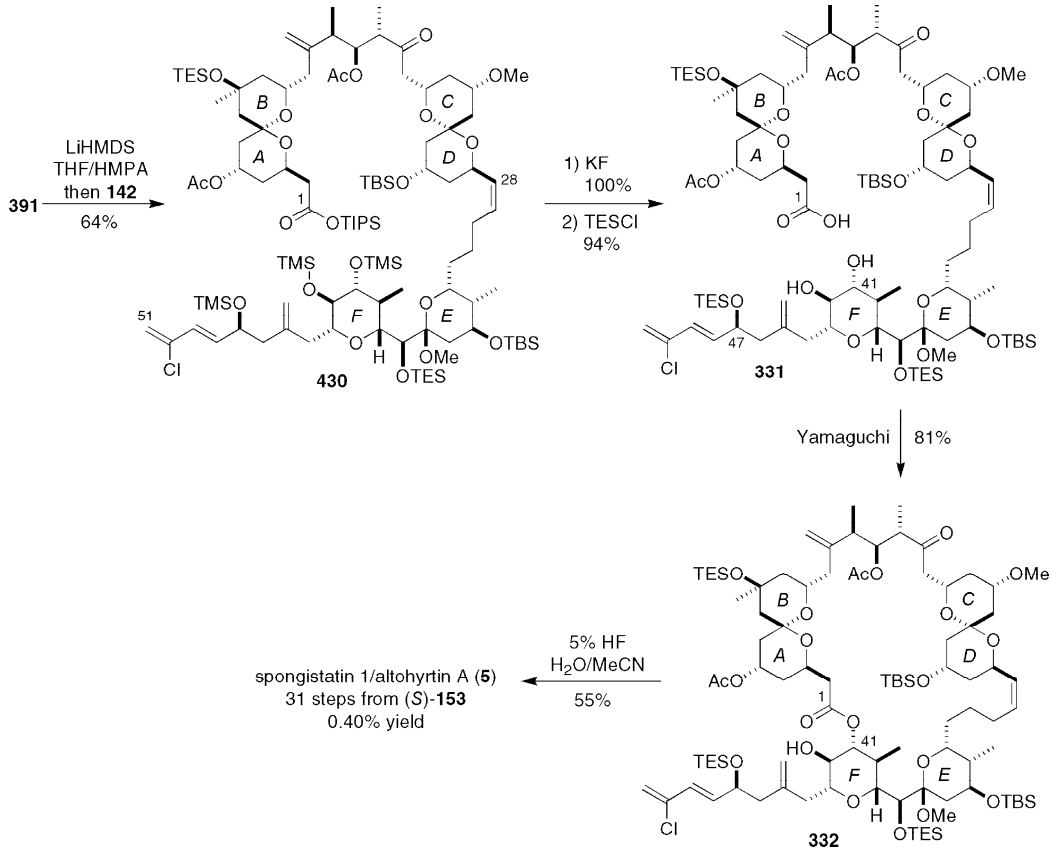


Scheme 67. Smith Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A

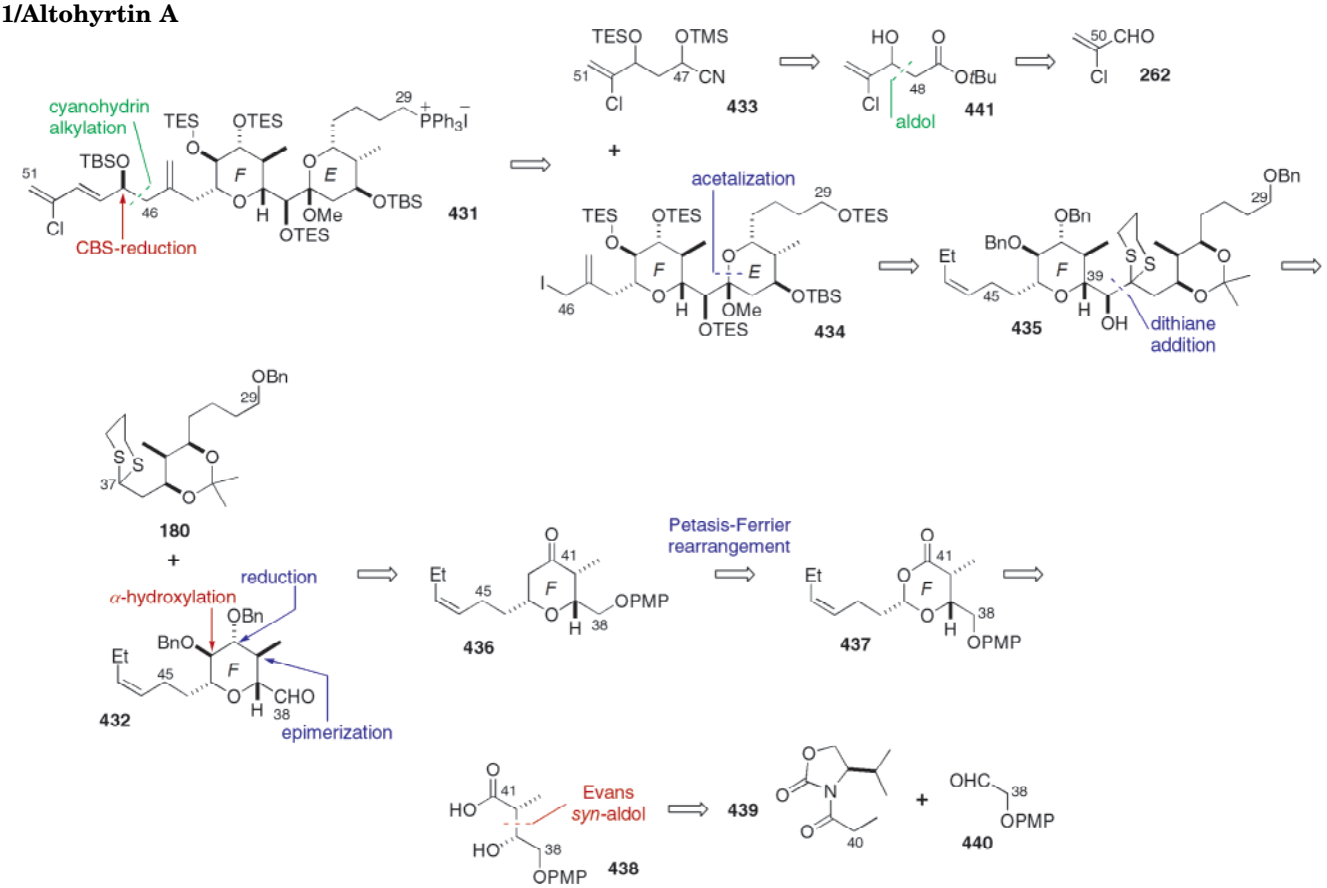


The synthesis of the chlorodiene side chain **273** (Scheme 67) featured a BINOL/zirconium-catalyzed addition of allylic stannane **423** to aldehyde **246**, which was generated via a $BiCl_3$-catalyzed addition of allylic chloride **116** to ethyl glyoxylate (**41**), to configure the isolated C47 stereocenter (97% ee). The resultant allylic alcohol **424** was then converted into the stannane **273** through a Pd-catalyzed displacement of the derived 2,4-dichlorobenzoate **425** using Crimmins protocol. Coupling of **273** with the epoxide generated from glycal **392** under Evans protocol furnished the tetraol **426** as a single isomer after deprotection. After conversion into the C29 iodide, the triol **427** was then reprotected as its tris-TMS ether to complete the synthesis of the EF-phosphonium salt **391**. The crucial Wittig coupling of **391** to the ABCD aldehyde **142** (Scheme 68) was achieved using Paterson's conditions to obtain the (*Z*)-alkene **430**. Selective silyl deprotection (at C1, C41, C42, and C47) followed by reprotection of the C47−OH gave seco-acid **331**. Selective macrolactonization under Yamaguchi conditions and global deprotection of the 42-membered macrolactone **332** then completed the Smith second-generation synthesis of spongistation

Scheme 68. Smith Total Synthesis of Spongistatin 1/Altohyrtin A



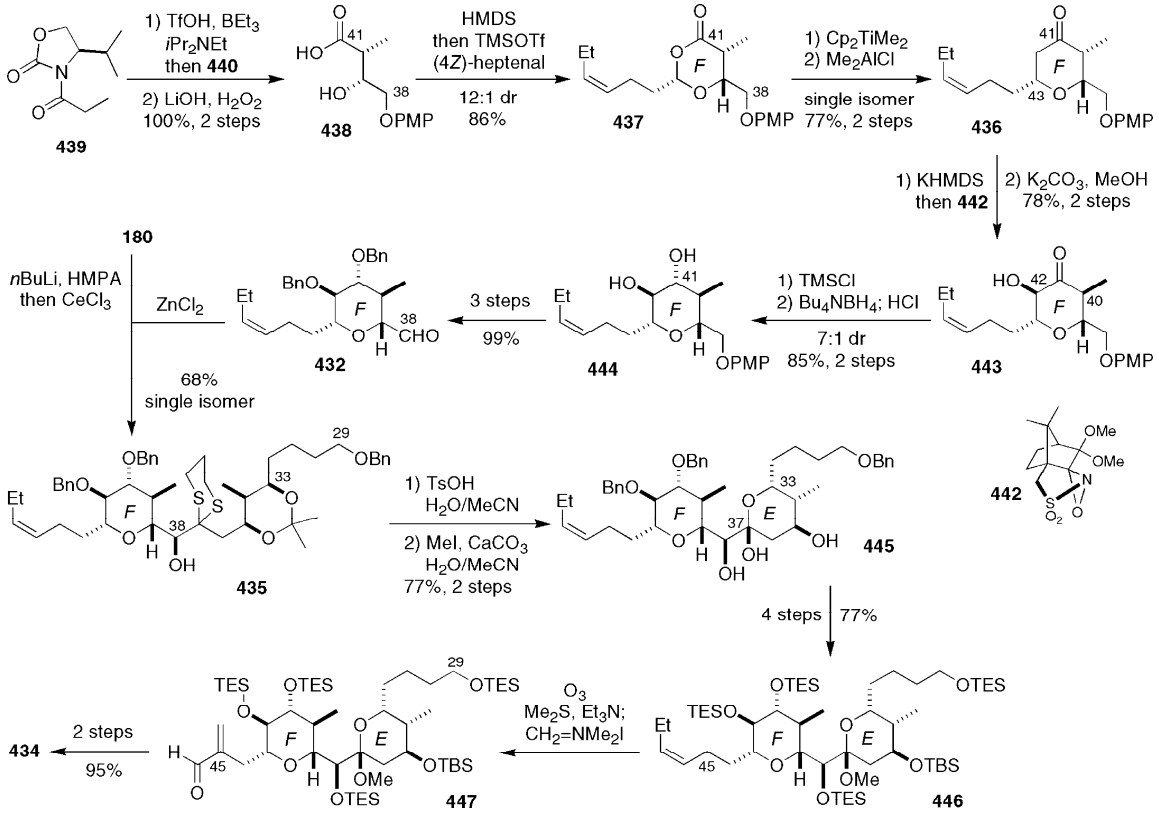
Scheme 69. Smith Second-Generation Strategy for the Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A



1/altohyrtin A (**5**) in 31 linear steps and 0.40% overall yield from aldehyde (*S*)-**153** (90 total steps; about 4 steps per stereocenter).

To further improve the efficiency of the route, synthesis of the EF-segment **431** (C29−C51) was revised (Scheme 69) and a Petasis−Ferrier rear-

Scheme 70. Smith Synthesis of the C29−C46 EF-Ring Segment of Spongistatin 1/Altohyrtin A



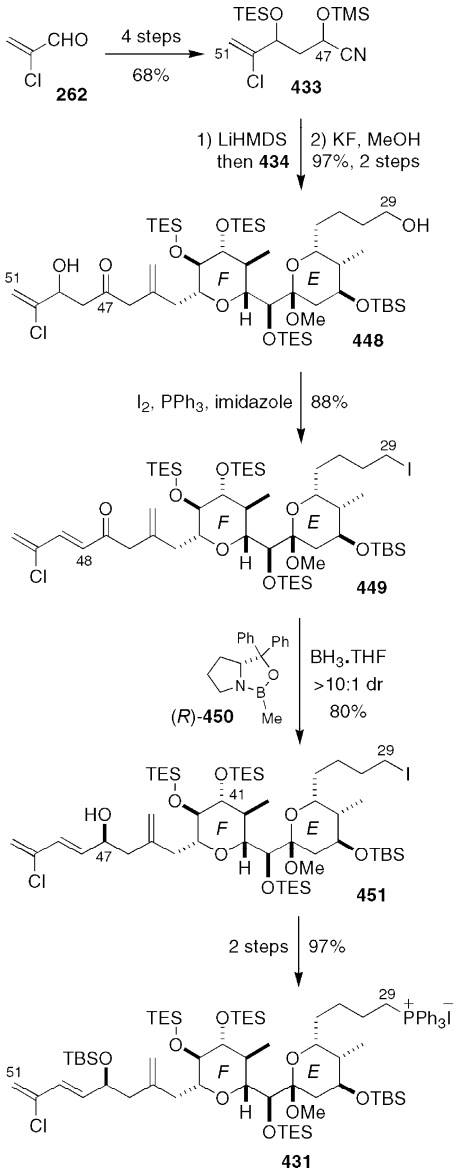
rangement was exploited to construct the F-ring aldehyde **432** for the established coupling with the dithiane **180**.[36c] It also relied on an alkylation of the cyanohydrin **433** with the EF iodide **434** for side chain elongation and a CBS reduction to establish the isolated C47 stereocenter. An Evans *syn*-aldol performed on aldehyde **440** followed by coupling with (4*Z*)-heptenal generated the dioxanone **437** (12:1 dr) (Scheme 70). A Petasis−Tebbe methylenation provided the intermediate enol ether, which underwent Me_2AlCl-promoted rearrangement to deliver the pyranone **436**. The C42−OH stereocenter was then installed via epoxidation of the potassium enolate of **436** with the Davis oxaziridine **442**, while the C40 configuration was corrected via base epimerization to provide α-hydroxy ketone **443**. The remaining C41 stereocenter was set up by ketone reduction to give diol **444** (7:1 dr). Coupling of the derived aldehyde **432** with the cerium anion of dithiane **180** provided the C38 alcohol **435** exclusively. The E-ring hemiacetal **445** was formed after deprotection and transformed into **446** for introduction of the C45 methylene group by oxonolysis to the aldehyde and alkylation with the Eschenmoser salt, $CH_2{=}NMe_2I$. The allylic iodide **434** derived from enal **447** was then coupled with the cyanohydrin **433** to give diol **448** after hydrolysis (Scheme 71). Introduction of the C29 iodide could be performed concurrently with elimination of the C49 hydroxyl group to provide enone **449**. Diastereoselective reduction of the C47 ketone group was accomplished using the CBS-reagent (*R*)-**450** to deliver alcohol **451** (>10:1 dr), which was then converted into the EF phosphonium salt **431**.

2.2. Dictyostatin

In 1994, Pettit et al. reported the isolation of dictyostatin from a marine sponge of the genus *Spongia* sp., collected in the Republic of Maldives, in 3.4×10^{-7}% yield (1.35 mg was obtained from 400 kg wet mass of sponges).[37a] The planar gross structure, comprising an unsaturated 22-membered macrolactone ring, 11 stereogenic centers, a (2*Z*,4*E*)-dienoate, and a pendant (*Z*)-diene moiety at C23, was determined based on analysis of 2D NMR spectroscopic data,[37a] and a partial stereostructure was proposed.[37b] More recently, dictyostatin was isolated from a *Lithistida* sponge of the family *Corallistidae* collected off the north Jamaican coast, by Wright and co-workers, in much higher yield (5.7 mg, 2.8×10^{-3}% of wet weight).[38] Paterson and Wright subsequently proposed a full stereochemical assignment for dictyostatin, as indicated in **452** (Figure 8), based on extensive high-field NMR experiments, including application of the Murata *J*-based configuration analysis, in combination with molecular modeling.[39] This assignment was also based on dictyostatin being biogenetically related to discodermolide (**4**). This stereochemical assignment was confirmed unequivocally by Paterson's total synthesis of dictyostatin[40] and validated independently by the total synthesis of Curran,[41] as described in sections 2.2.1 and 2.2.2.[42]

Dictyostatin displays low nanomolar growth inhibitory activity against a number of human cancer cell lines and retains activity against paclitaxel-resistant cancer cells that express active P-glycoprotein. Initial biological studies by Wright and co-workers demonstrated that dictyostatin arrested cells in the G2/M phase and shared the same microtubule-

Scheme 71. Smith Second-Generation Synthesis of the C29−C51 Segment of Spongistatin 1/Altohyrtin A



stabilizing mechanism of action as paclitaxel and discodermolide.[38] As shown in Figure 8, the lowest energy conformation of dictyostatin in solution overlays well with the solid-state conformation of discodermolide, suggesting that they bind to tubulin in a similar manner. Preliminary studies indicate that dictyostatin, like discodermolide, also binds to the taxoid binding site on β-tubulin but with higher affinity than paclitaxel.[40] The structural similarity between dictyostatin and discodermolide was also noted by Curran et al., who prepared macrocyclic hybrids of the two natural products for biological testing.[43] As nature's conformationally constrained analogue of discodermolide, dictyostatin represents a highly attractive template for rational drug design.

2.2.1. Paterson Synthesis of Dictyostatin[40]

With confidence in their stereochemical proposal, Paterson et al. designed a highly convergent synthetic strategy for dictyostatin, as shown in Scheme 72, which relied largely on substrate-directed stereo-

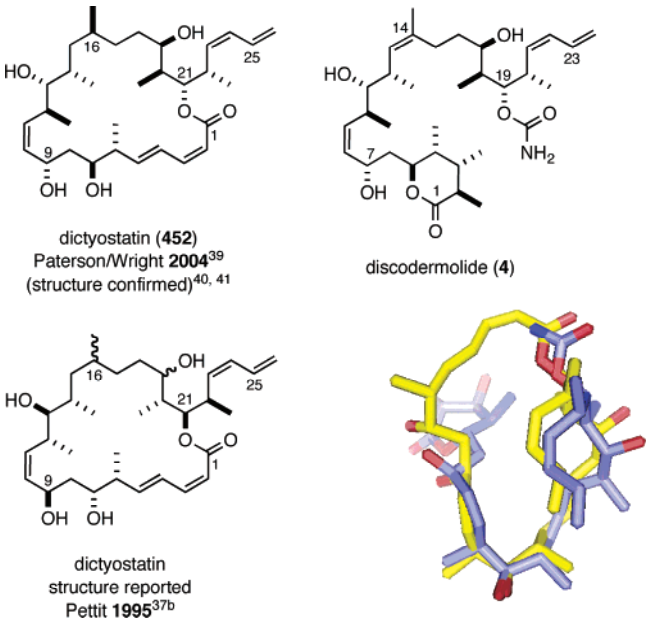
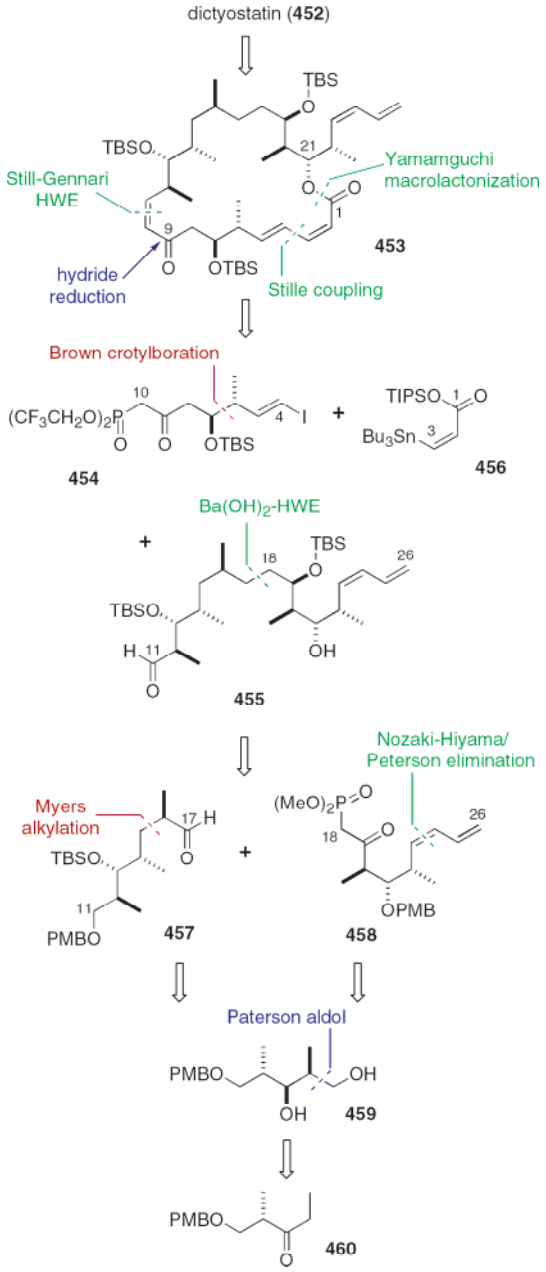


Figure 8. Structure of dictyostatin (**452**) as confirmed by total synthesis.[40,41] A partial stereostructure reported earlier is also shown. Overlay of preferred solution conformation of dictyostatin (**452**) in water (yellow) with conformation of discodermolide (**4**) obtained from X-ray crystal structure (blue).

oinduction. Two Horner−Wadsworth−Emmons (HWE) reactions were instrumental in joining the key subunits as well as providing enone substrates for stereoselective ketone reduction. The macrocyclic conformation of the 22-membered ring **453**, as predicted by molecular modeling studies, suggested a preference for hydride attack from the less hindered re-face of the carbonyl group to create the requisite C9 stereocenter. This macrocycle was assembled by a complex Still−Gennari-type HWE coupling between the elaborate β-keto phosphonate **454** and aldehyde **455** to generate the (*Z*)-enone in conjunction with the use of a Stille cross-coupling reaction with the three-carbon linking unit **456** to install the (*Z*)-enoate. The C11−C26 aldehyde **455** was accessible by a HWE reaction between aldehyde **457** and phosphonate **458**, which has the terminal diene moiety already incorporated. Recognizing that these two subunits share an identical stereotriad, they were prepared from the common intermediate **459**, which was readily available in multigram quantities through boron aldol methodology developed by the Paterson group.[44]

The C4−C10 phosphonate **454** was prepared from homoallylic alcohol **461** (Scheme 73) in which the C6/C7 *anti*-configuration was established by a Brown crotylboration[27] of aldehyde **229** (95% ee, 20:1 dr). The CF_3CH_2O-substituted phosphonate group was then installed by addition of the lithium reagent, $(CF_3CH_2O)_2P(O)CH_2Li$, to the acid chloride derived from acid **462**. The C11−C17 aldehyde **457** was obtained via elaboration of diol **459**, as shown in Scheme 74, with the C16 methyl-bearing stereocenter introduced by alkylation of the Myers pseudoephedrine-derived propionamide **465** with iodide **466** (19:1 dr). The 1,3-diol common intermediate **459** was synthesized by two substrate-controlled reactions

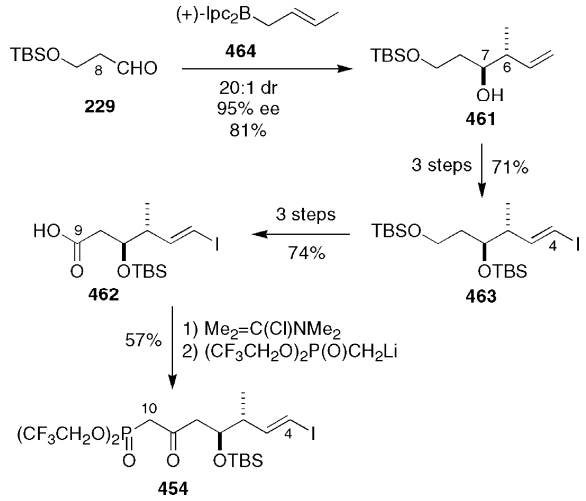
Scheme 72. Paterson Strategy for the Total Synthesis of Dictyostatin



involving addition of the (*E*)-dicyclohexylboron enolate of ethyl ketone **460** to formaldehyde and hydroxyl-directed reduction of the aldol adduct **467**. Diol **459** was also converted into aldehyde **468**, which was then subjected to sequential Nozaki−Hiyama allylation using the chromium reagent derived from **469** and Peterson olefination to generate the required (*Z*)-diene according to the procedure developed by the Paterson group for the synthesis of discodermolide.[34,44] Following conversion into the *β*-keto phosphonate **458**, HWE coupling with aldehyde **457** using $Ba(OH)_2$ provided the (*E*)-enone **470**.[31]

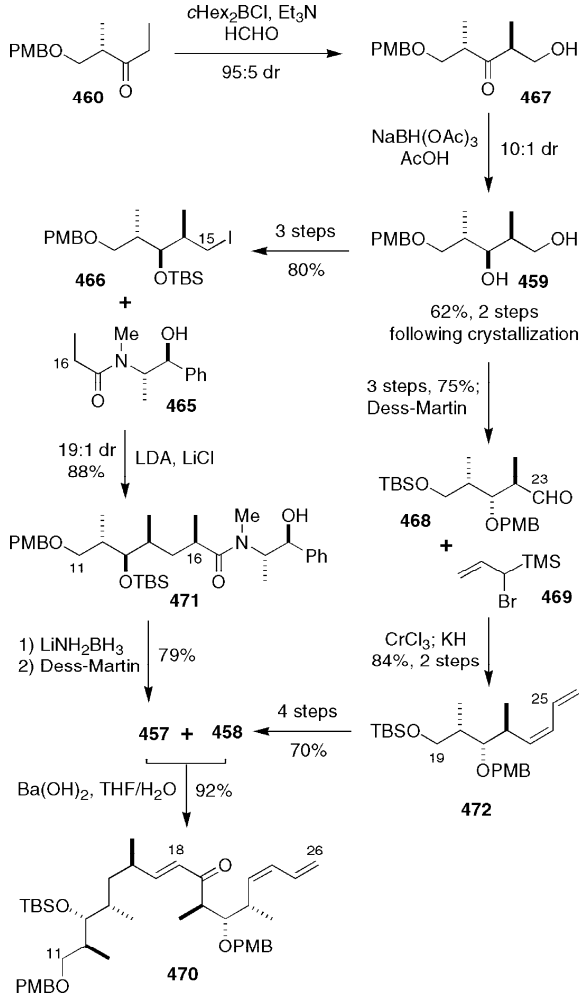
The (*E*)-enone in **470** was 1,4-reduced by Stryker's reagent (Scheme 75), and the derived *β*-hydroxy ketone was treated with $Zn(BH_4)_2$ in a 1,3-*syn*-selective manner to set the desired (19*R*)-configuration (>20:1 dr). The triol **473** thus obtained was selectively protected and oxidized to give aldehyde

Scheme 73. Paterson Synthesis of the C4−C10 Segment of Dictyostatin[a]



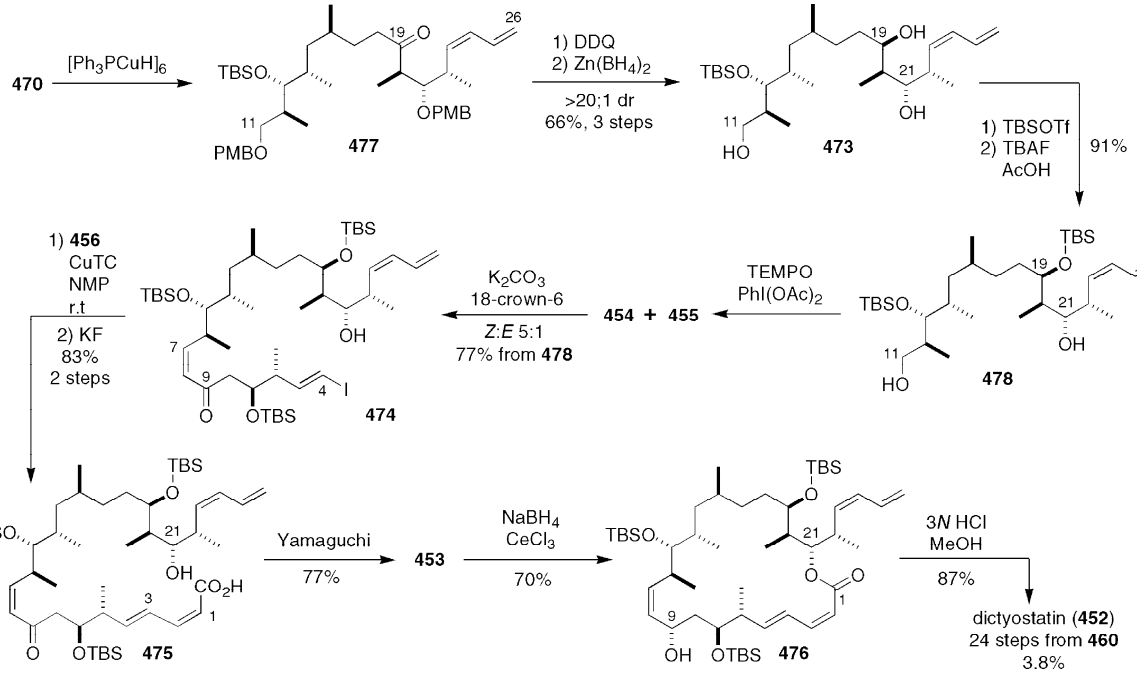
[a] The (+) descriptor on the crotylborane reagent **464** (and the (−) descriptor on the corresponding *ent*-reagent) in this scheme and the schemes that follow refers to the sign of the specific rotation of the Ipc_2BOMe used.

Scheme 74. Paterson Synthesis of the C11−C26 Segment of Dictyostatin



455, taking advantage of the reactivity differences between the hydroxyl groups. Note that the C21−OH remained unprotected through the rest of the transformations. The crucial Still−Gennari-type coupling using the elaborate *β*-keto phosphonate **454** was

Scheme 75. Paterson Total Synthesis of Dictyostatin



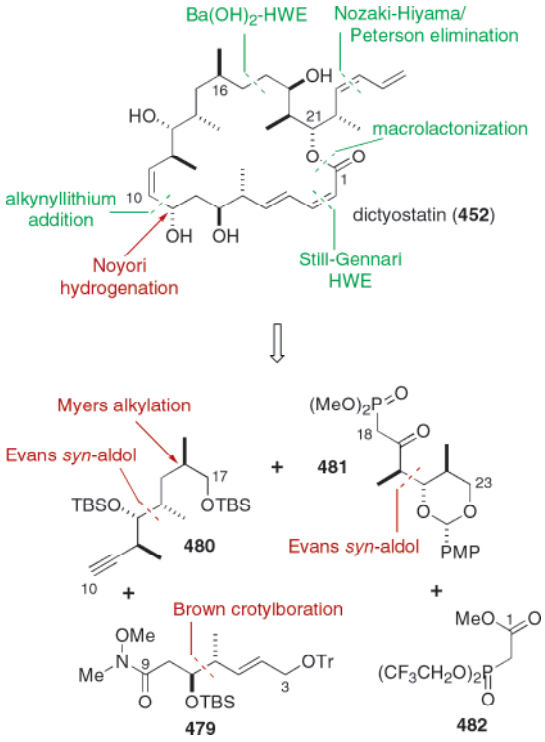
achieved under mild basic conditions, generating the (*Z*)-enone **474** selectively (5:1 *Z*:*E*). Installation of the final (*Z*)-alkene and completion of the dictyostatin carbon framework was accomplished by a Liebeskind-type Stille coupling of **474** with the stannane **456**. The seco-acid **475** was then cyclized under Yamaguchi conditions to form the 22-membered macrolactone **453**. By exploiting macrocyclic stereocontrol, the desired C9 hydroxyl configuration was generated by Luche reduction to give the allylic alcohol **476** selectively. Final global deprotection then delivered (−)-dictyostatin (**452**) in 3.8% overall yield over the 24-step linear sequence from ethyl ketone **460** (39 total steps; about 4 steps per stereocenter).

2.2.2. Curran Synthesis of Dictyostatin[41]

The Curran group's approach to the synthesis of dictyostatin is shown in Scheme 76. Strategic bond disconnections as indicated provided three key segments, the Weinreb amide **479** (C3−C9), the alkyne **480** (C10−C17), and *β*-keto phosphonate **481** (C18−C23). The synthetic plan was designed to allow for flexibility in configuring the stereocenters, which depended largely on reagent-based stereoinduction. While addition of an acetylenic anion to Weinreb amide **479** was used to couple **479** and **480**, a HWE reaction with phosphonate **481** was employed to form the C17−C18 bond during construction of the macrolactone. The C23−C26 diene unit was introduced toward the final stages of the synthesis, based on the Paterson protocol of Nozaki−Hiyama/Peterson olefination, as was the HWE coupling using the Still−Gennari-type phosphonate **482** to introduce the (*Z*)-enoate.

The Weinreb amide **479** was derived from the enoate **483**, obtained from 1,3-propanediol **292** (Scheme 77). The alkyne **480** was prepared by manipulation of the amide **471**, which was also used in Paterson's synthesis and obtained by Myers alky-

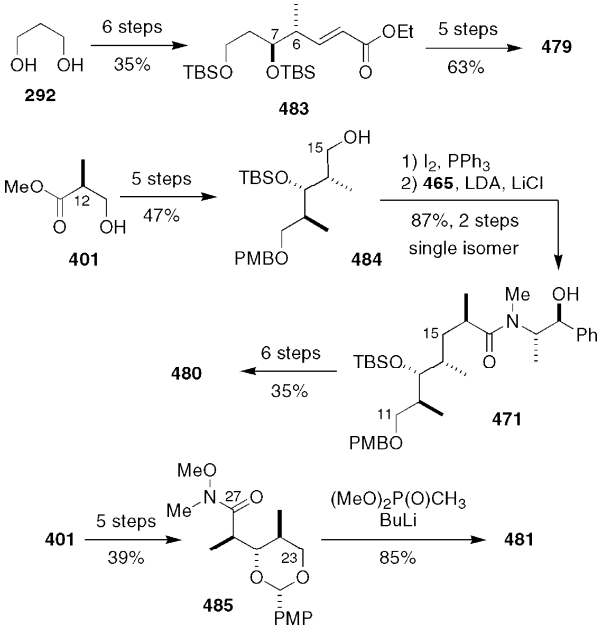
Scheme 76. Curran Strategy for the Total Synthesis of Dictyostatin



lation of the C15 iodide derived from alcohol **484** using the chiral imide **465** (**466** → **471**, Scheme 74). The synthesis of the C18−C23 phosphonate **481**, which contains the same stereotriad as **480**, also originated from the Roche ester **401**.

The assembly of the three key coupling partners started with the addition of the lithium acetylide derived from **480** to Weinreb amide **479** (Scheme 78). The C9 propargylic ketone obtained was reduced by a Noyori asymmetric transfer hydrogenation in the presence of ruthenium catalyst (*S*,*S*)-**486**. Lindlar hydrogenation then produced the allylic alcohol **487**

Scheme 77. Curran Synthesis of the C3−C9, C10−C17, and C18−C23 Segments of Dictyostatin

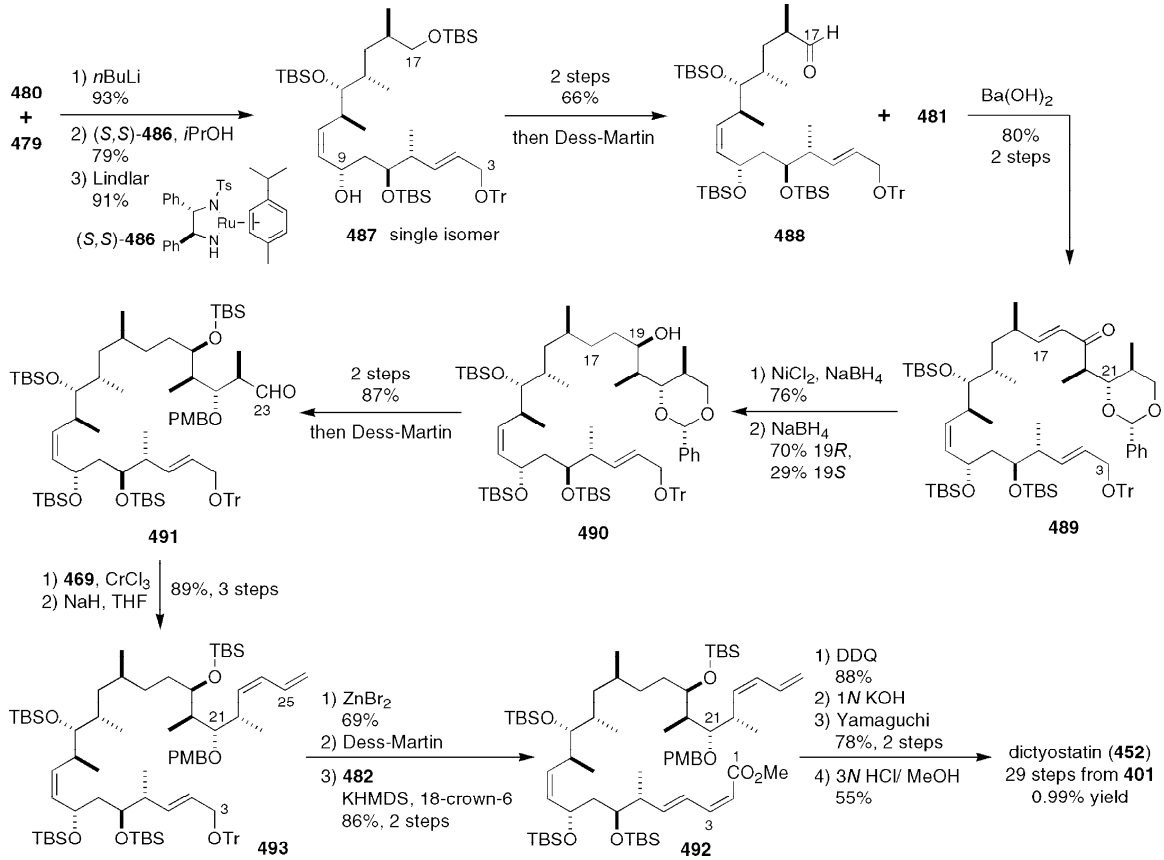


as the (Z)-isomer. After transformation of **487** into the C17 aldehyde **488**, a $Ba(OH)_2$-promoted HWE coupling with the β-keto phosphonate **481** gave the (*E*)-enone **489**. Following 1,4-reduction of the enone **489** by nickel boride, the C19 ketone was reduced by $NaBH_4$ to provide the desired (19*R*)-isomer **490** and its epimer (2.4:1 dr). At this stage the (*Z*)-diene at C23 was introduced by allylation of aldehyde **491** using the allyl chromium reagent derived from **469** followed by Peterson elimination. The final (*Z*)-alkene of dictyostatin was installed by a standard Still−Gennari HWE reaction using phosphonate reagent **482**, providing the fully protected seco-acid **492**. Completion of the total synthesis followed with a Yamaguchi macrolactonization formed the 22-membered macrocyclic ring and TBS deprotection, providing (−)-dictyostatin (**452**) in 0.99% overall yield over the 29 step longest linear sequence from Roche ester **401** (51 total steps; about 5 steps per stereocenter).

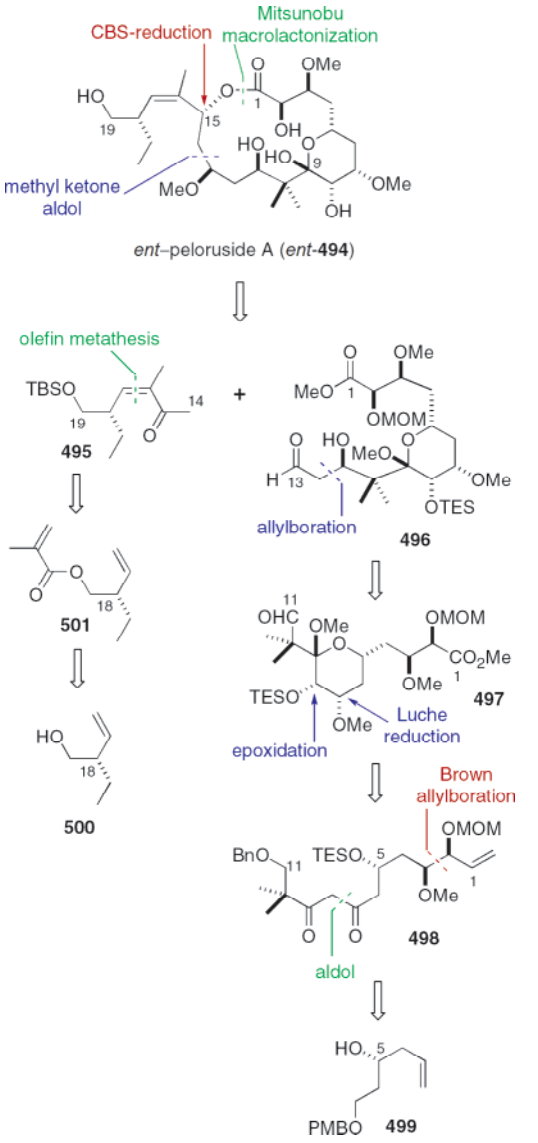
2.3. Peloruside A

Peloruside A was isolated in 2000 by Northcote et al. from the marine sponge *Mycale hentscheli* (170 g wet weight yielded 3.0 mg), collected from Pelorus Sound on the north coast of the South Island of New Zealand.[45a] Extensive NMR studies revealed a polyoxygenated 16-membered macrolide, which contains a pyranose ring with an adjacent *gem*-dimethyl group and a branched unsaturated side chain appended at C15, as well as enabling determination of the relative configuration of the 10 stereocenters. It was not until the total synthesis of the antipodal structure, i.e., *ent*-peloruside A (*ent*-**494**, Scheme 79), by De Brabander,[46] as described in the following section, that the absolute configuration was established. Peloruside exhibits pronounced cytotoxicity, at low nanomolar concentrations, against a range of cancer cell lines and retains potency against multidrug-resistant cells. Significantly, recent studies have demonstrated that this novel polyketide arrests the cell cycle in the G2/M phase, leading to apoptosis, by promoting tubulin polymerization in a manner similar to pacli-

Scheme 78. Curran Total Synthesis of Dictyostatin



Scheme 79. De Brabander Strategy for the Total Synthesis of *ent*-Peloruside A

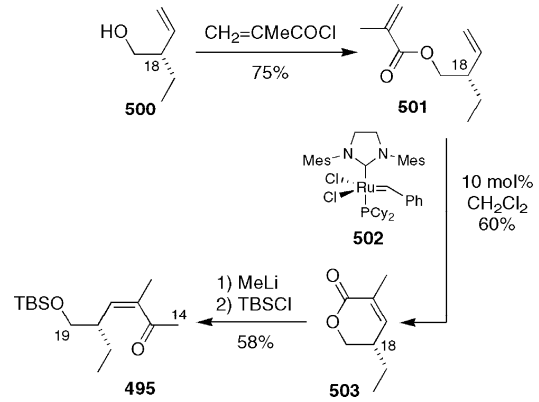


taxel but with a different (and as yet undefined) binding site.[45b,c]

2.3.1. De Brabander Synthesis of ent-Peloruside A[46]

The synthetic plan adopted by De Brabander for peloruside A (Scheme 79) relied on a late-stage aldol coupling between the methyl ketone **495** and the fully elaborated aldehyde **496**. This approach allowed flexibility in the macrolactonization step via reagent-controlled reduction of the C15 ketone group and use of either conventional acylation (e.g., the Yamaguchi procedure) or a Mitsunobu-type cyclization with inversion of configuration. Due to difficulties encountered in the deprotection of the C11−OH in the initial sequence, it was decided to proceed with the C1−C13 segment **496** without protecting this hydroxyl group. The C11 stereocenter was created adventitiously in a challenging substrate-controlled allylboration of the sterically demanding *gem*-dimethyl-substituted aldehyde **497**. The tetrahydropyran ring was derived from a dihydropyranone obtained by cyclization of β-diketone **498**, obtained from the known homoallylic alcohol **499**.[47] An olefin metathesis was employed to

Scheme 80. De Brabander Synthesis of the C14−C19 Segment of *ent*-Peloruside A



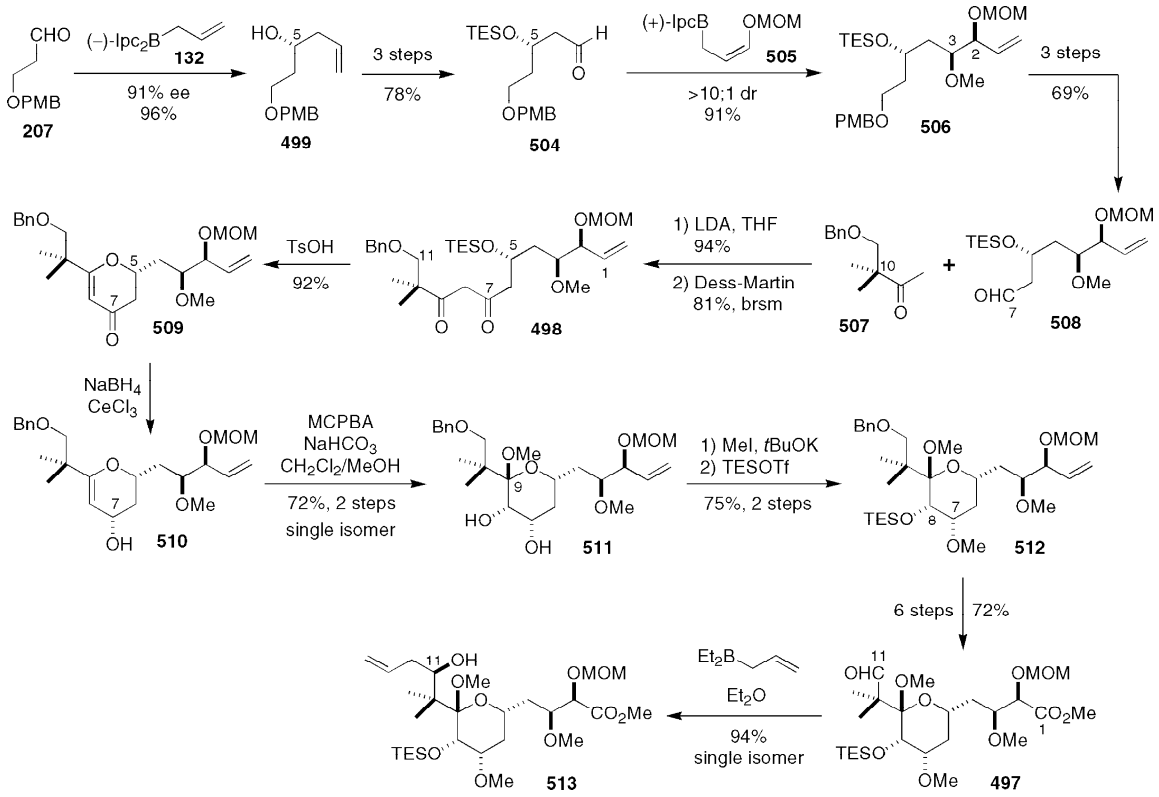
configure the (*Z*)-trisubstituted alkene in methyl ketone **495**, which was prepared from alcohol **500**,[48] as shown in Scheme 80. After acylation with methacryloyl chloride, an olefin metathesis performed on the resulting diene **501** using Grubbs second-generation catalyst **502** provided δ-lactone **503**. The (*Z*)-enone **495** was then generated by ring opening using methyllithium.

The synthesis of the C1−C13 subunit employed a Brown oxyallylation[28b] of aldehyde **504** using the (*Z*)-alkoxyallylborane **505** to configure the MOM-protected 1,2-*syn* glycol **506** (>10:1 dr) (Scheme 81). Addition of the lithium enolate derived from **507** to aldehyde **508**, obtained from **506**, followed by oxidation of the resulting aldol adduct provided the β-diketone **498**. Acid-induced TES deprotection and cyclization/dehydration then gave dihydropyranone **509**, providing a platform for introducing the C7 to C9 stereocenters. This was accomplished by Luche reduction to provide the equatorial C7 alcohol in **510**, which then directed the epoxidation step. In-situ methanolysis of the incipient epoxide then gave methyl acetal **511**. The sterically encumbered aldehyde **497** was obtained by derivatizing the C7 equatorial and C8 axial hydroxyl groups of **511** followed by functional group manipulation. The chain extension of **497** proved demanding and was achieved by allylation using diethylallylborane to deliver the homoallylic alcohol **513**, obtained fortuitously as a single isomer.

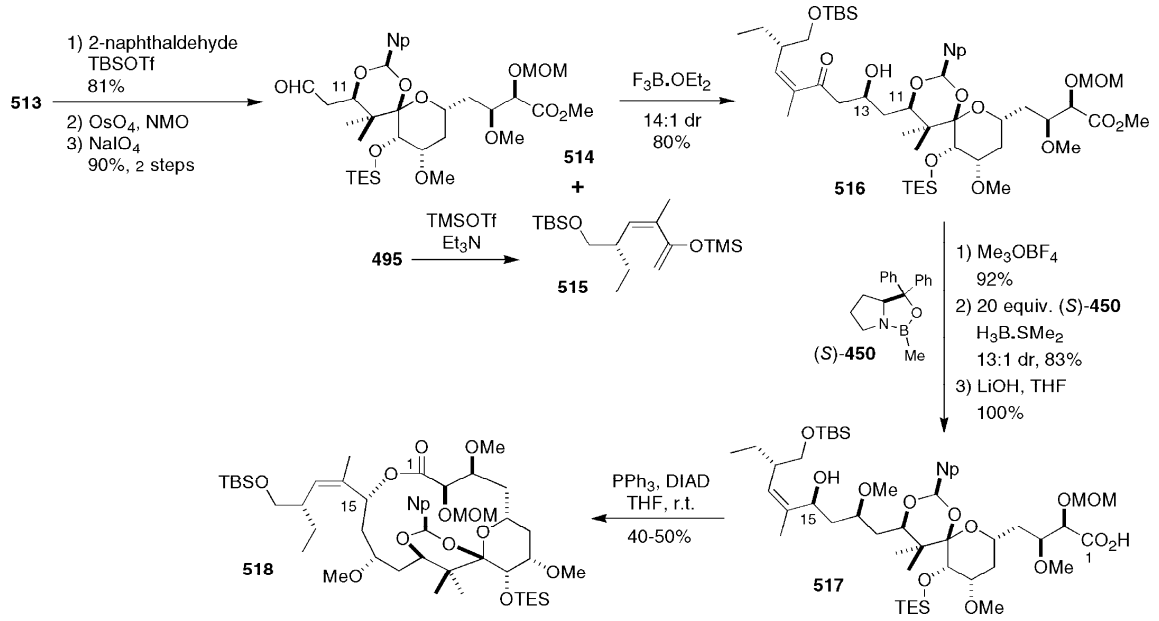
Initially the C11−OH in **513** was protected via the formation of a 2-naphthyl acetal, as shown in Scheme 82. The aldehyde **514** thus obtained was subjected to a Mukaiyama aldol coupling with silyl enol ether **515** derived from ketone **495** to give β-hydroxy ketone **516** (14:1 dr). In contrast to literature precedent for related β-alkoxy aldehydes,[49] this proceeded by apparent 1,3-*syn* stereoinduction leading to the incorrect C13 configuration. The seco-acid **517**, obtained in three steps through a sequence involving CBS-reduction of the C15 ketone (13:1 dr), was cyclized under Mitsunobu-type conditions to give the macrolactone **518**. At this stage the difficulties encountered in removing the C11 protecting group and correcting the C13 stereocenter forced a revision of the synthetic plan.

Thus, the allylic alcohol **513** was transformed into aldehyde **496** without hydroxyl protection at C11

Scheme 81. De Brabander Synthesis of the C1−C13 Segment of *ent*-Peloruside A

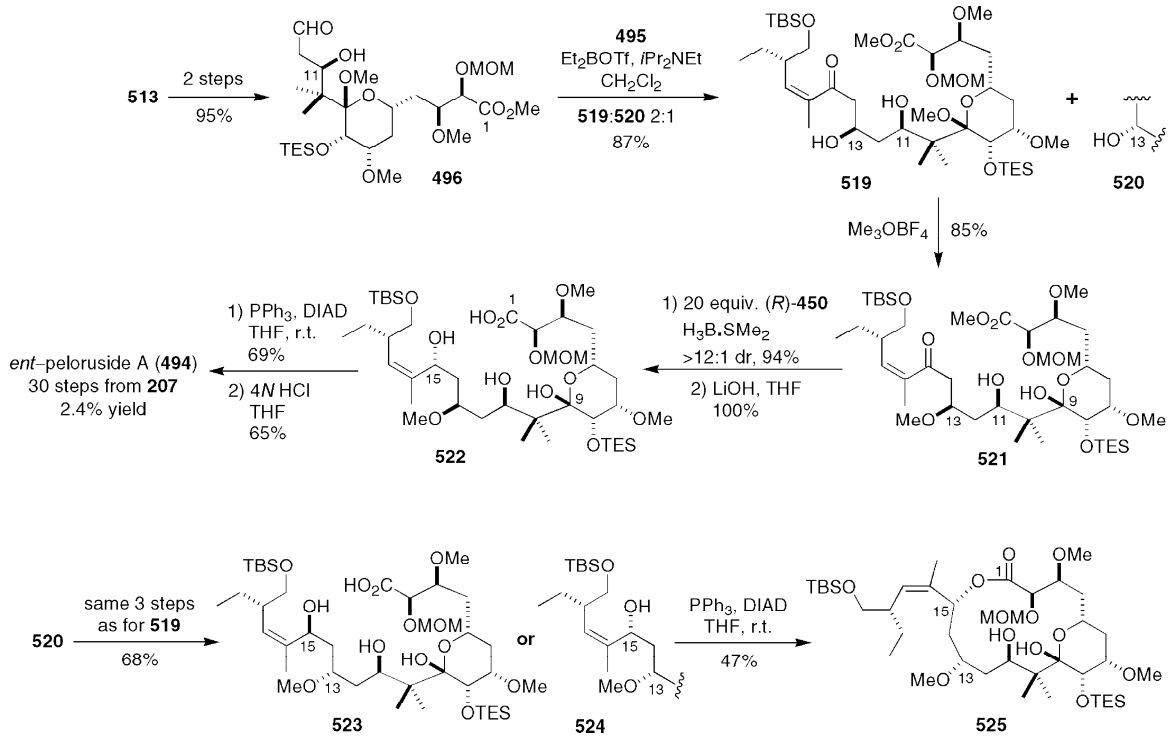


Scheme 82. De Brabander Synthesis of a Fully Protected C13-Epimer of *ent*-Peloruside A



(Scheme 83). An aldol coupling with the diethylboron enolate of **495** provided the desired isomer **519** and its C13 epimer **520** (2:1 dr). After selective methylation of the less hindered C13−OH and concomitant acetal hydrolysis to give hemiacetal **521**, the C15 stereocenter was configured by CBS reduction (>12:1 dr). Interestingly, the C9 hemiacetal survived even in the presence of excess reducing agent. The seco-acid **522** was then liberated by basic hydrolysis of the methyl ester. Likewise, the two C15 epimeric seco-acids **523** and **524** were obtained from the minor isomer **520** via the use of the appropriate CBS reagent, (*R*)- or (*S*)-**450**. Surprisingly, these two seco-acids provided the same macrolactone **525** under identical Mitsunobu conditions without any allylic transposition. This stereochemical outcome may arise from a diastereoselective S_N1-type process determined by geometrical/conformational constraints in ring closure. Macrolactonization of the seco-acid **522** (with the correct C13 and C15 stereochemistry) under the same Mitsunobu conditions followed by deprotection of the MOM and silyl groups then gave (−)-peluroside A (*ent*-**494**) (2.4% overall yield over the 30-step linear sequence from aldehyde **207**; 34 total steps; 3.4 steps per stereocenter), which proved to be the enantiomer of the natural product and was found

Scheme 83. De Brabander Total Synthesis of *ent*-Peloruside A



to be inactive against selected human cancer cell lines.[46] With this synthetic route validated, it should be straightforward to adapt it to give (+)-peloruside A itself.

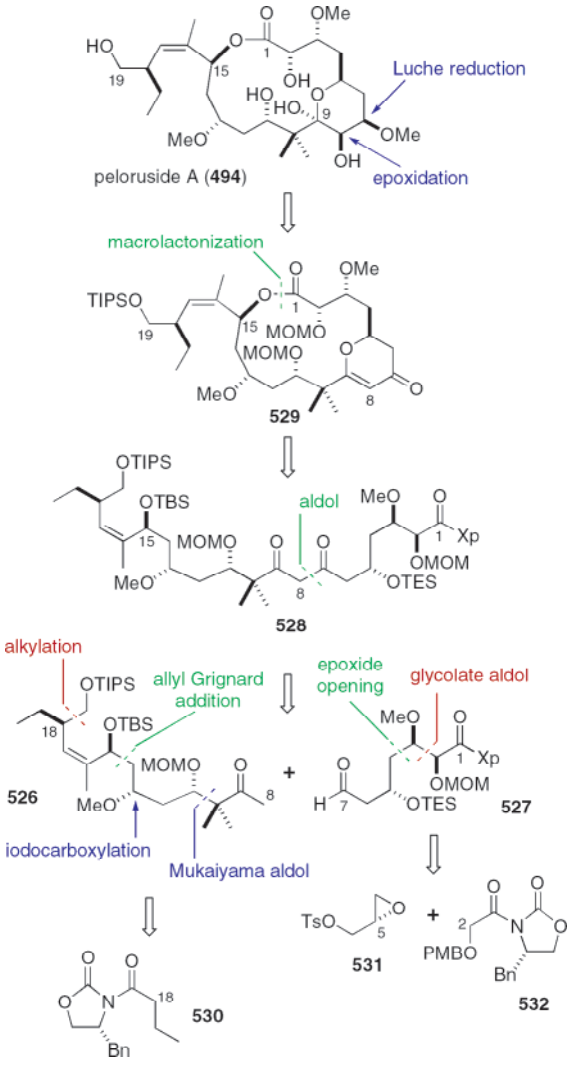
2.3.2. Taylor Synthesis of Peloruside A[50]

With the absolute configuration now established through De Brabander's synthesis of (−)-peloruside A, several groups focused their efforts on achieving the total synthesis of the natural antipode, (+)-peloruside A (**494**). The strategy employed in the total synthesis completed recently by Taylor is outlined in Scheme 84. This synthesis relied on a key aldol coupling reaction between the C8−C19 methyl ketone **526** and the C1−C7 aldehyde **527** to give access to the elaborate β-diketone **528** that possesses the full carbon framework of peloruside A (although lacking the C8 oxygenation) and a dehydrative cyclization to install a dihydropyranone ring (as in **529**) on which the three contiguous stereocenters at C7−C9 of the requisite tetrahydropyran were established. Similar transformations were successfully implemented in the preparation of the C1−C11 segment (e.g., **497**, Scheme 79) employed in the De Brabander synthesis.

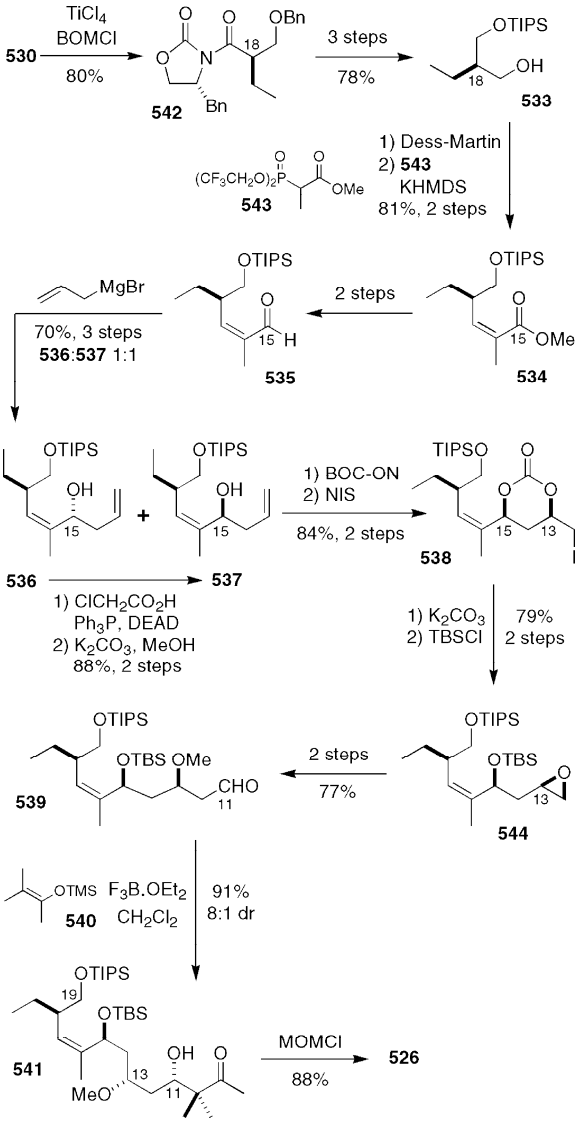
The methyl ketone **526** was constructed in a linear manner starting with an Evans alkylation using the titanium enolate derived from the imide **530** to set up the C18 stereocenter of the side chain (Scheme 85). After conversion into the alcohol **533**, the (*Z*)-trisubstituted alkene was installed by a Still−Gennari HWE reaction on the derived aldehyde to give the enoate **534**. Although the desired C15−OH stereocenter could be configured by a Brown allylboration[28] on the aldehyde **535**, a nonselective Grignard allylation protocol followed by a two-step recycling of the undesired isomer **536** by Mitsunobu inversion was pursued. The 11,13-*anti*-13,15-*syn* sequence in **526** was then set up by two consecutive substrate-controlled reactions. The C13−OH stereocenter was first configured by a site-selective iodocarboxylation on homoallylic alcohol **537**, and the resultant cyclic carbonate **538** was transformed into the aldehyde **539**. Next, a Mukaiyama aldol reaction between **539** and silyl enol ether **540** provided the desired C11 alcohol **541** preferentially (8:1 dr) as a result of 1,3-*anti* induction from the aldehyde partner. The choice of the C11−OH protecting group was crucial for the subsequent formation of the tetrahydropyran ring, and was best protected as a MOM ether to give the methyl ketone **526**.

The C1−C7 aldehyde component **527** was prepared from (*S*)-glycidol tosylate **531** (Scheme 86). After epoxide ring opening, a glycolate aldol reaction using the PMB-protected Evans-type imide **532** with the aldehyde obtained by hydrolysis of the dithiane derivative **545** was employed to set up the 2,3-*syn* stereochemistry. This aldol coupling was unsuccessful when using a MOM-protected derivative of **532**, necessitating a protecting group switch at C2 during the conversion of the aldol product **546** into the aldehyde **527**. Note that the chiral imide was carried forward as a masked C1 acid group and was not hydrolyzed until macrolactonization. Addition of the lithium enolate of **526** to aldehyde **527** provided the β-diketone **528** after oxidation. Formation of the dihydropyranone **547** from **528** was best achieved under De Brabander's TES ether deprotection/dehydrative cyclization protocol (cf. **507** + **508** → **498** → **509**, Scheme 81). Deprotection at C15 and hydrolysis at C1 revealed the seco-acid derivative, which was subjected to Yamaguchi conditions to give the advanced 16-membered macrolactone intermediate **529**. The remaining C7−C9 stereocenters were installed by Luche reduction followed by epoxidation of the

Scheme 84. Taylor Strategy for the Total Synthesis of Peloruside A



Scheme 85. Taylor Synthesis of the C8–C19 Segment of Peloruside A



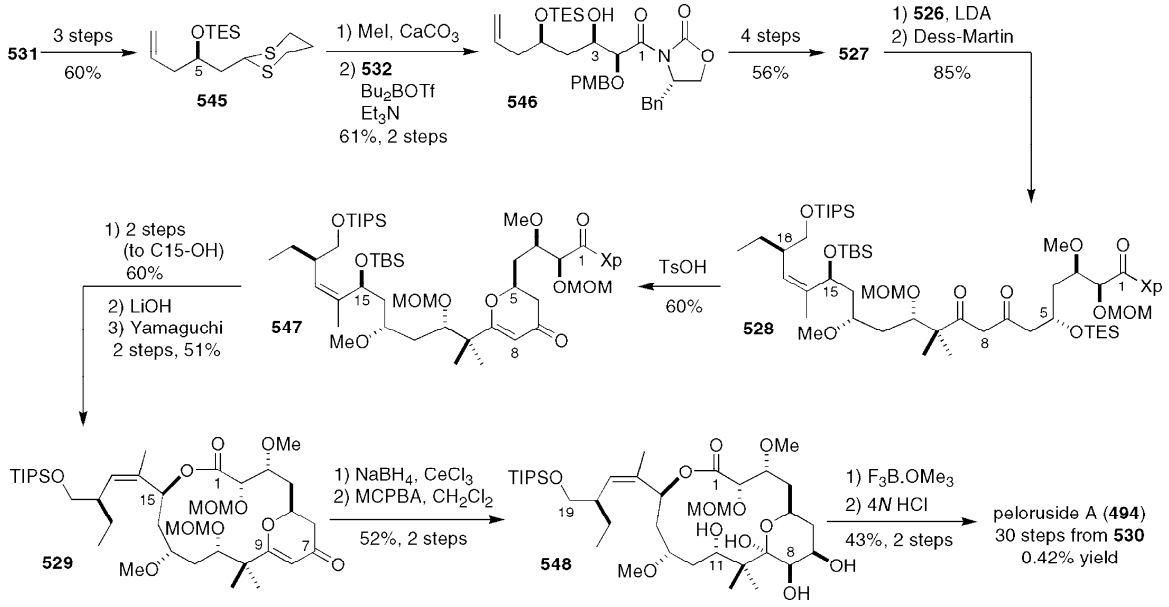
dihydropyranone unit in **529** (cf. **509** → **510** → **511**, Scheme 81). Interestingly, MCPBA epoxidation of the intermediate allylic alcohol in CH_2Cl_2 installed the C8 hydroxyl stereocenter and resulted in the formation of the C9 acetal with concomitant removal of the C11 MOM group, presumably as a result of an intramolecular glycal epoxide ring opening by the MOM group followed by hydrolysis of the intermediate oxo-carbenium ion. Selective methylation of the C7 equatorial hydroxyl group and acidic deprotection of **548** then delivered (+)-peloruside A (**494**)[51] in 0.42% overall yield over the 30-step linear sequence from imide **530** (39 total steps; 3.9 steps per stereocenter).

2.4. Leucascandrolide A

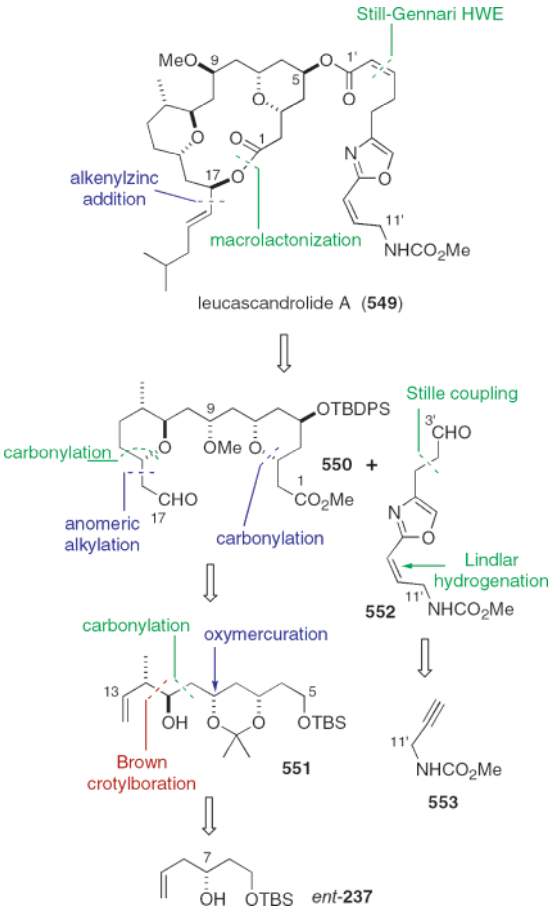
Leucascandrolide A (**549**, Scheme 87) was isolated in 1996 from the New Caledonian calcareous sponge *Leucascandra caveolata* by Pietra and co-workers.[52a] In preliminary biological testing, leucascandrolide A exhibited in-vitro cytotoxicity against KB throat epithelial carcinoma and P388 murine leukemia cell lines with an IC_{50} of 0.05 and 0.25 μg/mL respectively, as well as strongly inhibiting the growth of the pathogenic yeast *Candida albicans*.[52a] Although leucascandrolide A was isolated in ample quantities (in contrast to the spongistatins/altohyrtins) from the first collection of *L. caveolata*, later harvesting of this sponge failed to give any trace of the macrolide. These findings suggest that the actual source of this structurally novel macrolide is bacteria colonizing the sponge.[52b] It also suggests that total synthesis can potentially provide a reliable supply of leucascandrolide A and its analogues to enable further biological evaluation as well as probe its molecular target and mechanism of action.

Leucascandrolide A contains an 18-membered macrolactone ring embedded with two trisubstituted tetrahydropyrans with an unusual unsaturated oxazole-containing side chain attached by an ester linkage to the axial C5 hydroxyl group. The characteristic 1,3-oxygenation pattern embodied in leucascandrolide A has proved to be a popular testing ground for a variety of methodologies, thus far culminating in four total syntheses and four formal total syntheses (based on synthesis of the macrolactone used in Leighton's total synthesis), where each of these differ in the way that the stereocenters

Scheme 86. Taylor Total Synthesis of Peloruside A



Scheme 87. Leighton Strategy for the Total Synthesis of Leucascandrolide A



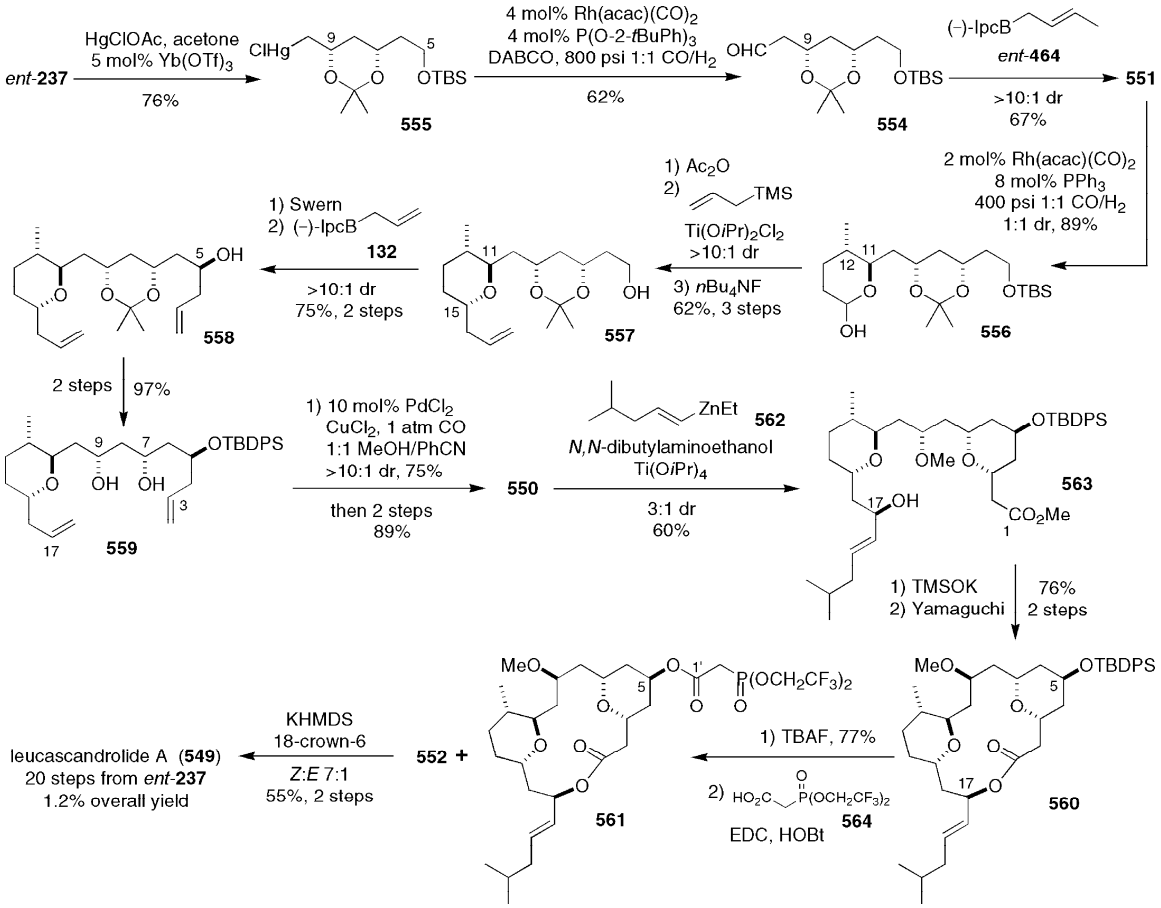
within the macrocyclic lactone as well as the *cis*- and *trans*-tetrahydropyrans are generated.[53]

2.4.1. Leighton Synthesis of Leucascandrolide A[54]

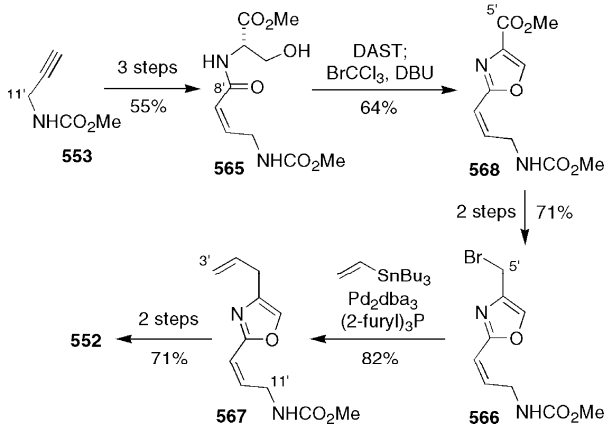
Leighton's first total synthesis of leucascandrolide A (**549**) confirmed the relative and absolute stereochemical assignment made by Pietra based on extensive NMR studies and Mosher ester analyses. This synthesis also demonstrated the application of carbonylation reactions, as developed within the Leighton group, to assembling complex polyketide natural products. The strategic bond disconnections selected are indicated in Scheme 87. The side chain at C5 was attached to the macrolactone by a Still−Gennari-type HWE reaction to install the *cis*-alkene, while the C17 side chain was introduced via an organometallic addition to the C17 aldehyde **550**. The two tetrahydropyran rings were each constructed using a key carbonylation reaction during two-directional chain extension of homoallylic alcohol *ent*-**237**[20g] via **551**.

The synthesis of aldehyde **554** employed a Yb(OTf)$_3$-catalyzed oxymercuration of *ent*-**237** coupled with a Rh(I)-catalyzed formylation of the resulting organomercury intermediate **555** to install the C9 stereogenic center (Scheme 88). A Brown crotylboration[27] reaction on **554** then provided the C11/C12 *anti*-relationship in alcohol **551** (>10:1 dr). This was followed by construction of the first tetrahydropyran ring, where a Rh(I)-catalyzed hydroformylation gave hemiacetal **556**. The 2,6-trans-substituted tetrahydropyran was then established by a Ti(O*i*Pr)$_2$Cl$_2$-promoted allylation on the derived anomeric acetate using allyltrimethylsilane (>10:1 dr). Chain extension of alcohol **557** via a Brown allyboration[28] on the derived aldehyde gave **558** (>10:1 dr), leading to diol **559**, which was subjected to a Pd-catalyzed alkoxycarbonylation using the Semmelhack protocol. In this key transformation the two hydroxyls and two alkenes in **559** were differentiated and the *cis*-tetrahydropyran ring (as in **550**) was formed selectively (>10:1 dr) together with installation of the C1 carboxylate. The first side chain was then introduced by an alkenyl zinc addition to **550**, generating the C17 stereocenter with 3:1 dr. Following a Yamaguchi macrolactonization, the macrolactone **560** was converted by acylation of the C5−OH into phosphonate **561**, in preparation for a Still−Gennari-type HWE coupling to introduce the oxazole-containing side chain. The aldehyde component **552** was prepared from carbamate **553** (Scheme 89), which was con-

Scheme 88. Leighton Total Synthesis of Leucascandrolide A



Scheme 89. Leighton Synthesis of the Side Chain C3′ Aldehyde of Leucascandrolide



verted into amide **565** in three steps via a Lindlar hydrogenation of the alkyne. Oxazole formation using the Wipf–Williams method and conversion into bromide **566** was followed by an sp^3–sp^2 Stille coupling. Finally, a HWE coupling of the aldehyde **552** with phosphonate **561** generated leucascandrolide A (Scheme 88) together with its C2′–C3′ (*E*)-isomer in 1.2% overall yield over the 20-step linear sequence from *ent*-**237** (18 total steps to leucascandrolide macrolactone **569**; 2.3 steps per stereocenter).

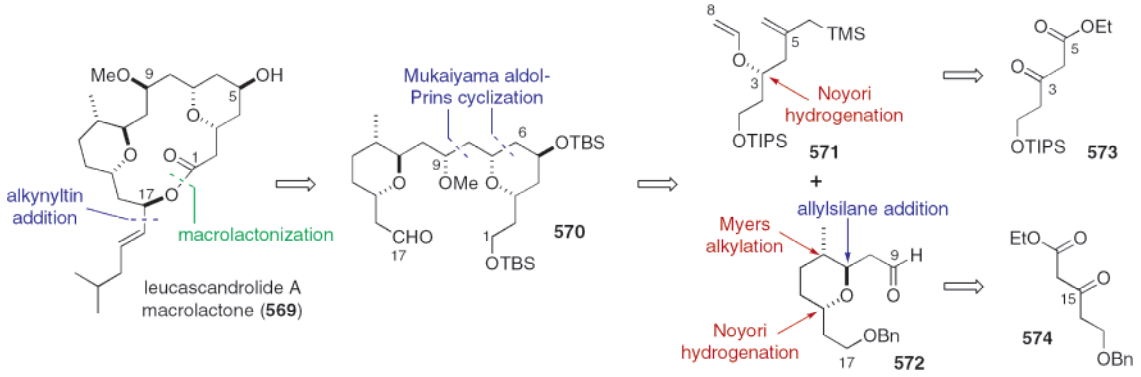
2.4.2. Rychnovsky Synthesis of Leucascandrolide Macrolactone[55]

Rychnovsky's convergent synthesis of the leucascandrolide macrolactone **569** demonstrated the use of a Mukaiyama aldol–Prins cyclization cascade reaction, as developed by Rychnovsky's group, to complex polyketide synthesis. As shown in Scheme 90, the macrolactone was elaborated from intermediate **570** via a late-stage alkynyl tin addition to C17 followed by macrocyclization. Disconnections at the C6–C7 and C8–C9 bonds of **570** revealed enol ether **571** and C9–C17 aldehyde **572** as the coupling partners. These two segments were each prepared by a Noyori asymmetric hydrogenation performed on the β-keto esters **573** and **574**, which differ in the choice of hydroxyl protecting group.

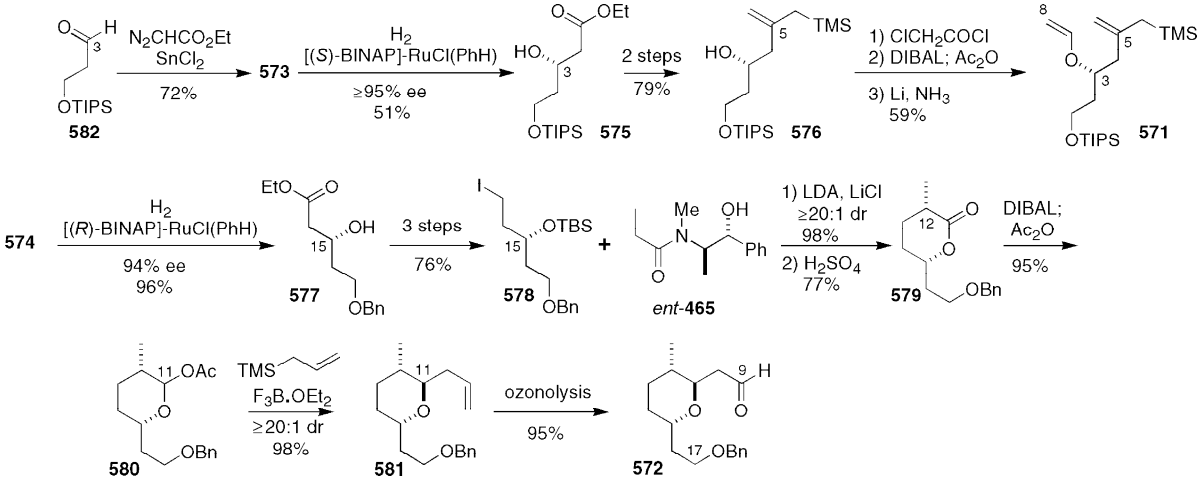
The β-hydroxy ester **575** was obtained in ≥95% ee by hydrogenation of **573** using the (*S*)-BINAP-ruthenium complex (Scheme 91). After conversion into the allylsilane **576**, the labile enol ether was installed in a three-step sequence wherein the double bond arose by a β-elimination of chloride and acetate groups. The "enantiomeric" β-hydroxy ester **577** was obtained (94% ee) using the corresponding (*R*)-BINAP reagent. Following derivatization to give the iodide **578**, a Myers alkylation using the pseudoephedrine propionamide *ent*-**465** installed the C12 stereocenter (≥20:1 dr) followed by cyclization to give the δ-lactone **579**. Formation of the 2,6-*trans*-tetrahydropyran was then achieved (≥20:1 dr) by an allylsilane addition to the anomeric acetate **580**.

As a key step (Scheme 92), an intermolecular aldol–Prins cyclization between **571** and **572** introduced the C9 stereocenter (5.5:1 dr) and the *cis*-tetrahydropyran ring, generating the C1–C17 segment **583**.

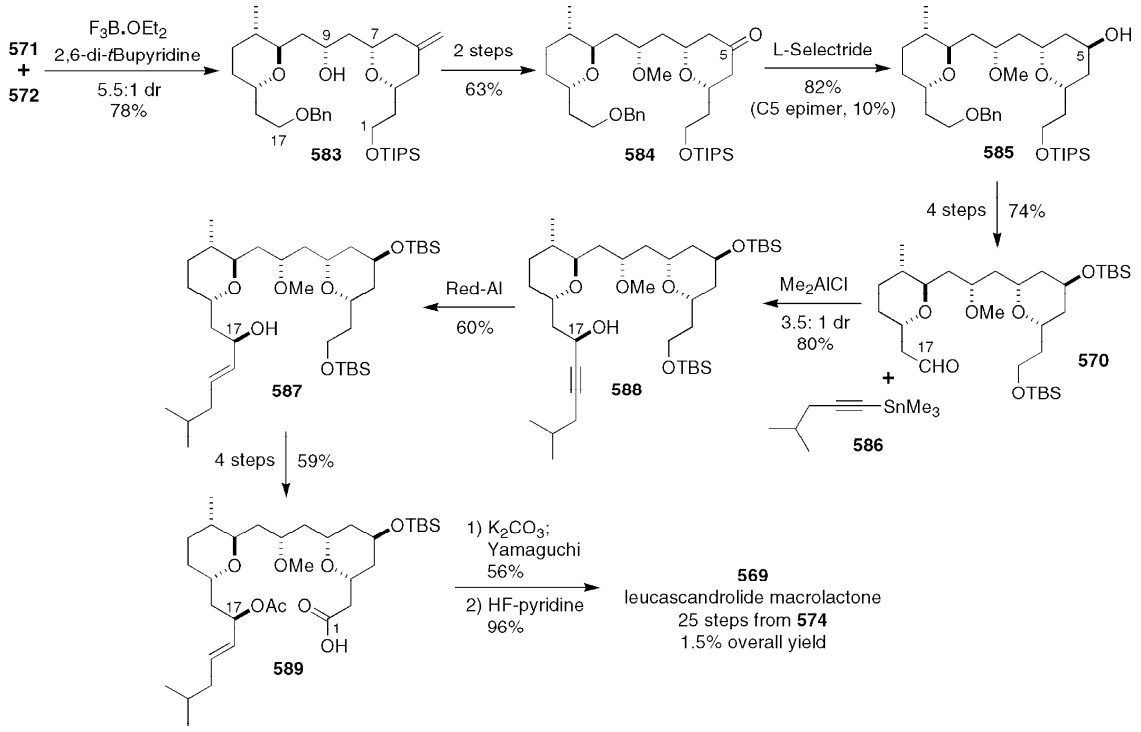
Scheme 90. Rychnovsky Strategy for the Synthesis of Leucascandrolide Macrolactone



Scheme 91. Rychnovsky Synthesis of the C1−C8 and C9−C17 Segments of Leucascandrolide

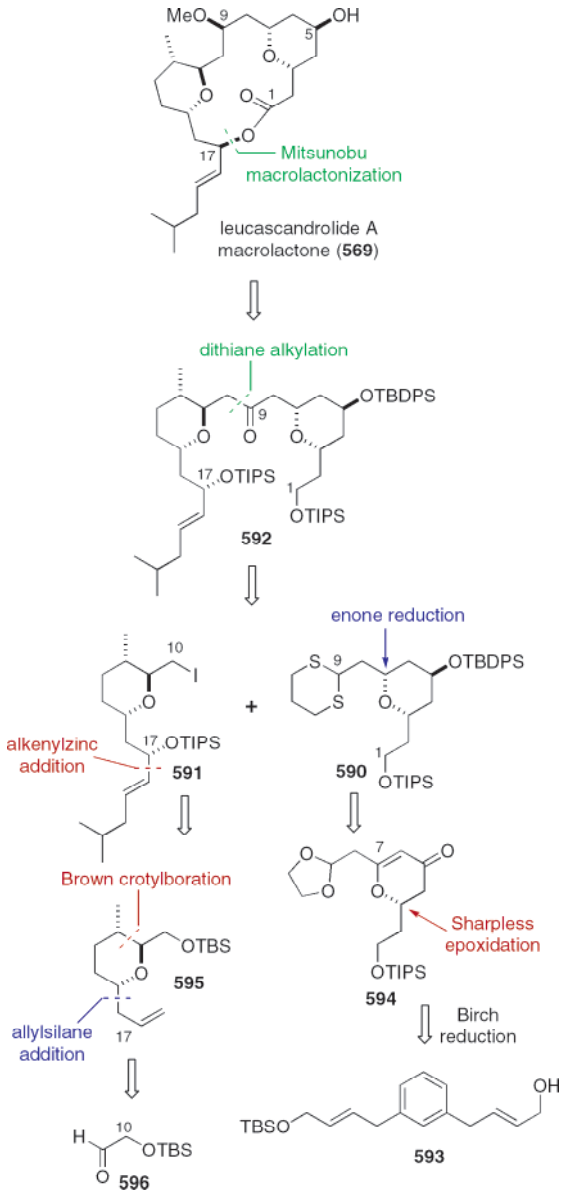


Scheme 92. Rychnovsky Synthesis of Leucascandrolide Macrolactone



The diastereoselectivity at C9 was consistent with the expected 1,3-*anti* induction imparted by a β-alkoxy aldehyde in a Mukaiyama aldol reaction.[49] Reduction of ketone **584** using L-Selectride then delivered the desired C5−OH in **585**. The remaining C17 stereocenter was established by a chelation-controlled addition of the alkynyl stannane **586** to aldehyde **570**. The diastereoselectivity (3.5:1 dr) was similar to that obtained in Leighton's synthesis (**550** → **563**, Scheme 88). The (*Z*)-alkene in **587** was obtained by Red-Al

Scheme 93. Wipf Strategy for the Synthesis of Leucascandrolide Macrolactone



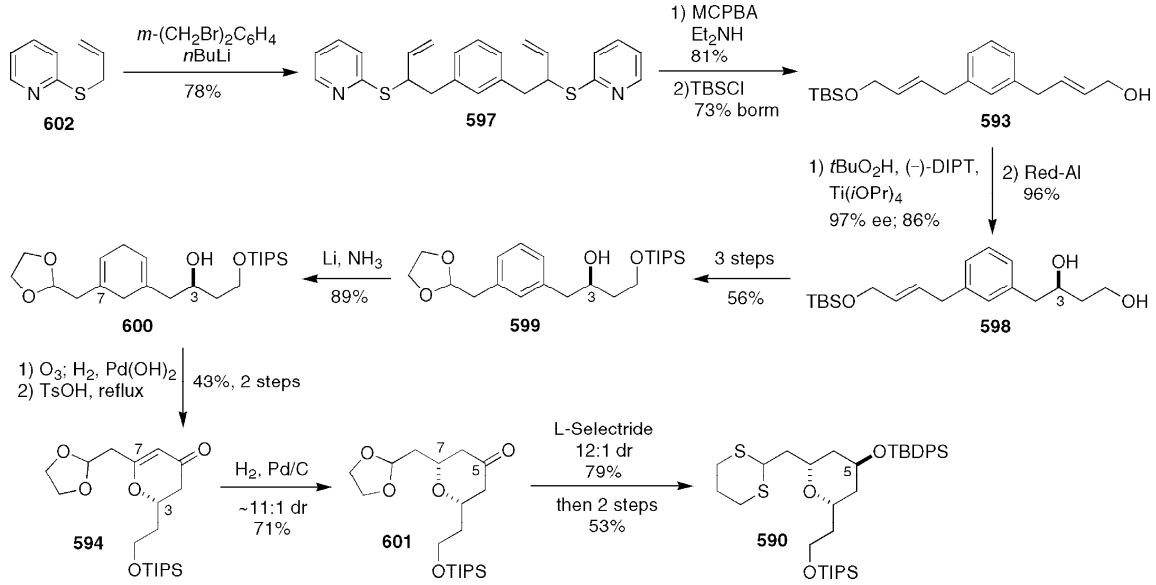
reduction of the propargylic alcohol **588** followed by elaboration into the seco-acid precursor **589**. Following acetate hydrolysis, a Yamaguchi macrolactonization and C5−OH deprotection then completed the synthesis of the leucascandrolide macrolactone **569** in 1.5% overall yield over the 25-step linear sequence from β-keto ester **574** (32 total steps; 4 steps per stereocenter).

2.4.3. Wipf Synthesis of Leucascandrolide Macrolactone[56]

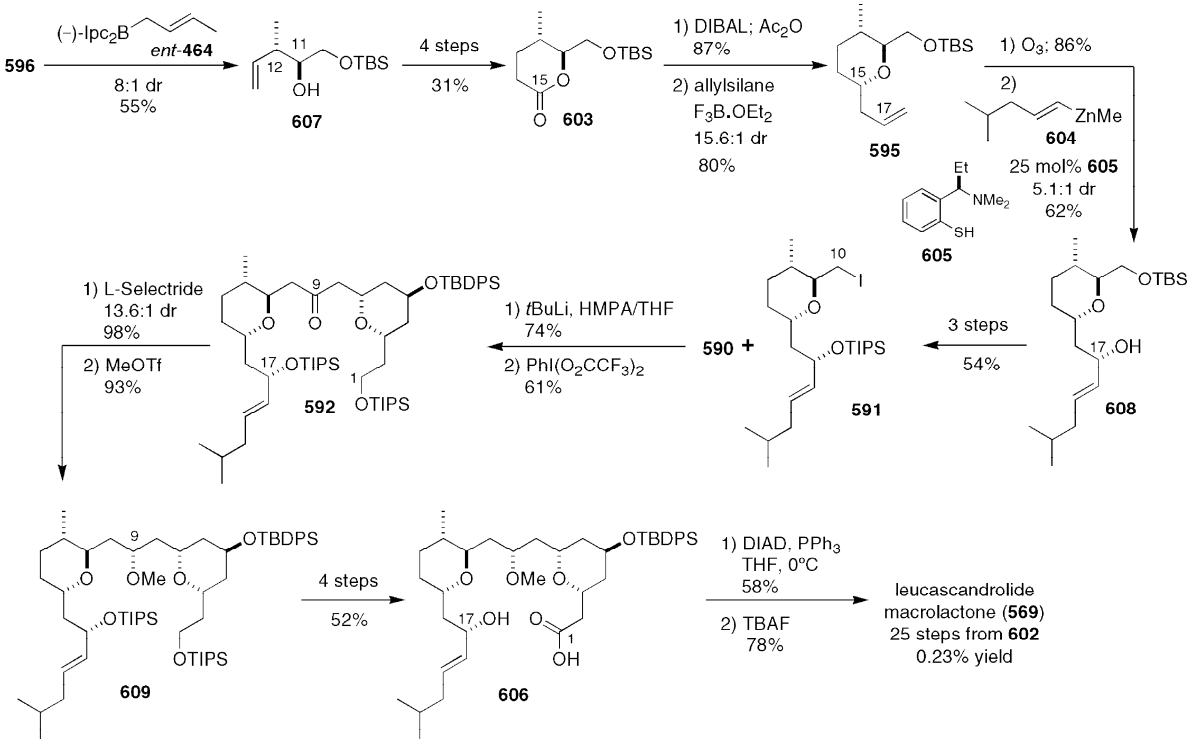
Wipf's synthesis of the leucascandrolide macrolactone **569** employed a C9−C10 coupling between dithiane **590** and iodide **591** to assemble the full C1−C17 seco-acid precursor **592** (Scheme 93) and used a Mitsunobu-type macrolactonization. The tetrahydropyran ring in **590** was constructed via a Birch reduction involving a derivative **593** of *m*-xylene. In this route (Scheme 94) a double Mislow−Evans rearrangement of the bis-sulfoxide derived from **597** provided **593** after monosilylation. Sharpless epoxidation and reductive ring opening then installed the C3 stereocenter (97% ee) in **598**. Formation of the 2,6-*cis*-tetrahydropyran involved a Birch reduction on **599** to provide the 1,4-cyclohexadiene **600**, which, after ozonolysis to generate a β-diketone, underwent dehydrative cyclization to give dihydropyranone **594**. The 2,6-cis relationship was introduced by hydrogenation (11:1 dr), while the C5 axial hydroxyl group in **590** was installed by L-Selectride reduction (12:1 dr).

Synthesis of the iodide **591** began with a Brown crotylboration[27] on aldehyde **596** to introduce the C11/C12 *anti*-configuration (Scheme 95). As in Leighton's synthesis (**556** → **557**; **550** → **563**, Scheme 88), an allylsilane addition to the anomeric acetate, obtained from the δ-lactone **603** by Rychnovsky's procedure, provided the 2,6-*trans*-tetrahydropyran **595** (15.6:1 dr). Setting the C17 configuration and incorporation of the side chain relied on the addition of alkenyl zinc **604** in the presence of the chiral aminothiol ligand **605**. While the natural (*R*)-configuration was predicted based on the ligand configuration and chelation control, the (*S*)-configuration

Scheme 94. Wipf Synthesis of the C1−C9 Segment of Leucascandrolide



Scheme 95. Wipf Synthesis of Leucascandrolide Macrolactone

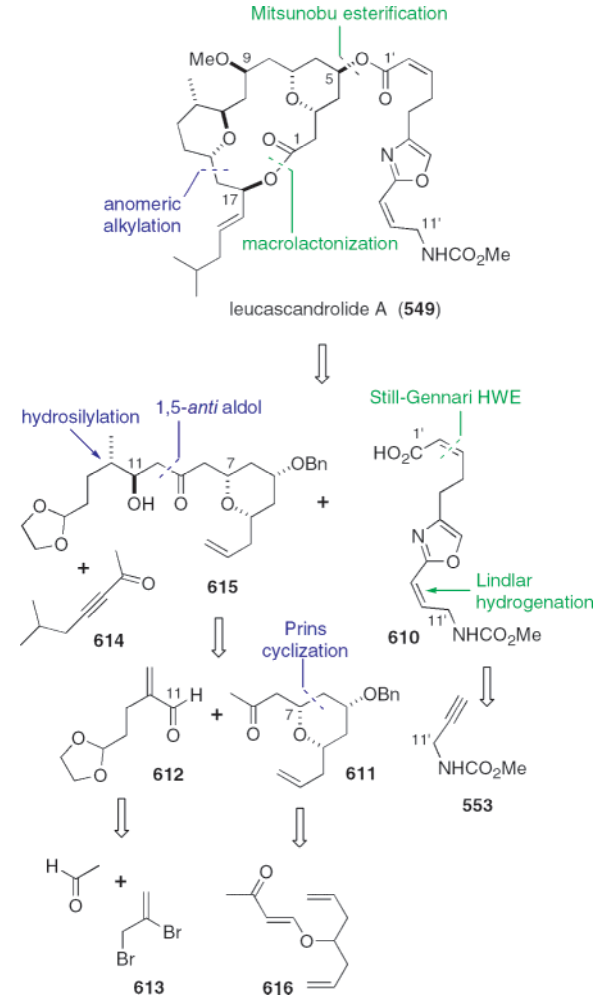


was obtained unexpectedly (5.1:1 dr), necessitating a change of plan to using a Mitsunobu macrolactonization. Coupling of the lithiated dithiane from **590** with the iodide **591** and oxidative desulfurization gave ketone **592**. The remaining C9 stereocenter was created by L-Selectride reduction of **592** (13.6:1 dr). Following elaboration to the seco-acid **606** and employing an intramolecular Mitsunobu esterification with clean C17 inversion, the macrolactone **569** was obtained after C5 deprotection in 0.23% overall yield over the 25-step linear sequence from sulfide **602** (37 total steps; about 5 steps per stereocenter).

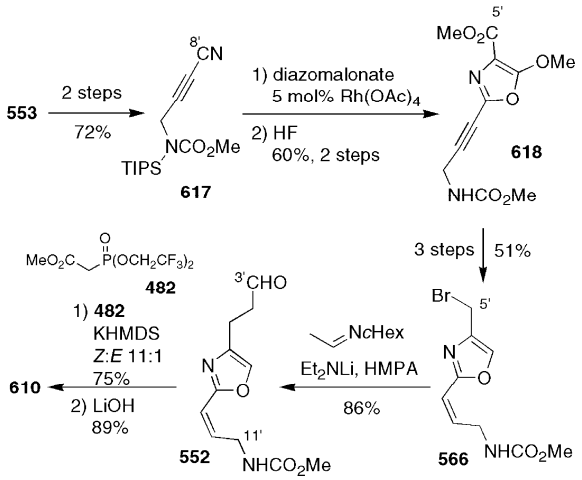
2.4.4. Kozmin Synthesis of Leucascandrolide A[57]

Kozmin's racemic synthesis of leucascandrolide A is characterized by the use of a series of substrate-controlled reactions to set up all eight stereocenters of the macrolide and an unprecedented closure of the macrocycle by formation of a stable internal hemiacetal. As outlined in Scheme 96, the side chain acid **610** was joined to the macrolactone at C5 via use of a Mitsunobu esterification in the final step. It proved necessary to invert the C5 configuration due to the stereochemical outcome of the Prins cyclization during construction of the *cis*-tetrahydropyran **611** (cf. Rychnovsky synthesis, Scheme 90). En route to the macrolactone, remote 1,5-stereoinduction was exploited to generate the C11 stereocenter during the C10−C11 aldol coupling of **611** to aldehyde **612**, which was assembled from dibromide **613** and acetaldehyde. The C11−OH was then used to direct the diastereo- and regioselective hydrosilylation in setting up the C12 configuration. In a similar way to Leighton's synthesis (Scheme 87), formation of the *trans*-tetrahydropyran and attachment of the C17 side chain were performed via alkylation of an anomeric acetate, however now using the silyl enol ether derived from acetylenic ketone **614**.

Scheme 96. Kozmin Strategy for the Total Synthesis of Leucascandrolide A



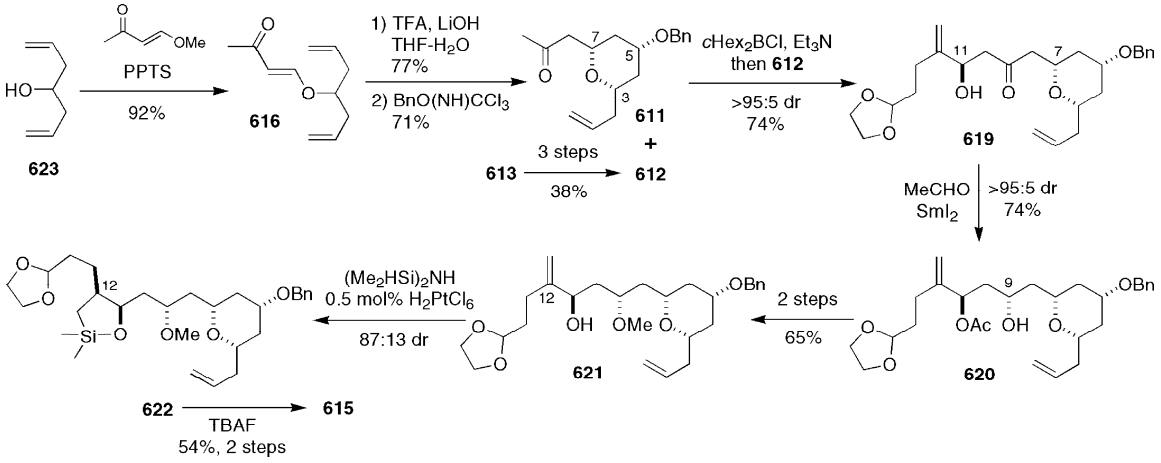
Scheme 97. Kozmin Synthesis of the Side Chain of Leucascandrolide



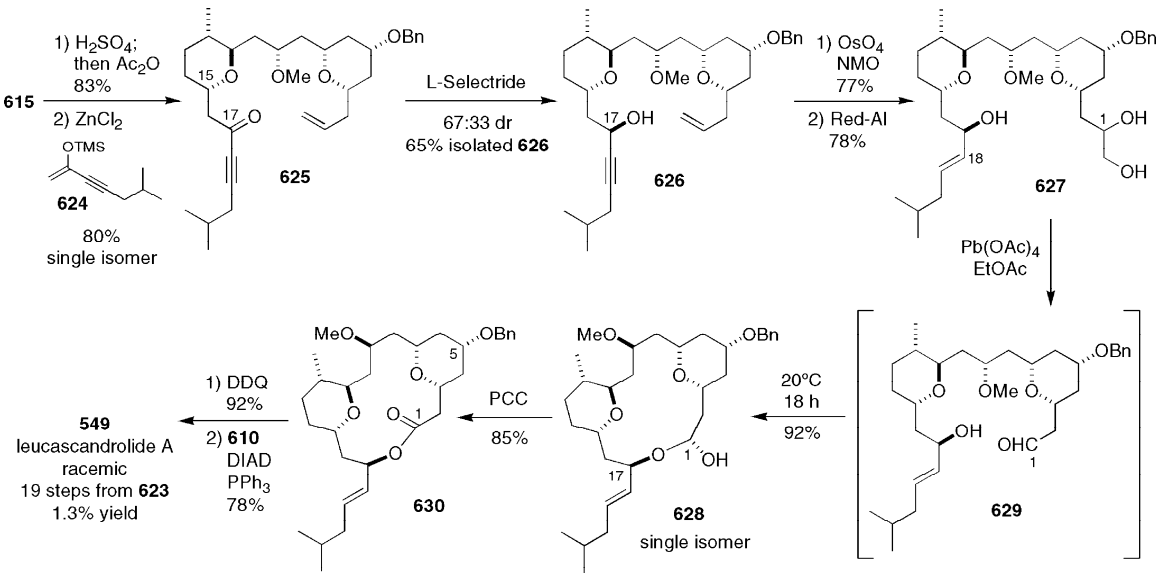
The side chain acid **610** was synthesized from carbamate **553** (Scheme 97), which was elaborated into bromide **566** and then into the aldehyde **552**, all of which were also used in the Leighton synthesis (Scheme 89). A Rh(II)-catalyzed condensation of the nitrile **617** with diazomalonate formed the oxazole **618**, which was converted via a Lindlar hydrogenation into the bromide **566**. A two-carbon homologation by azaenolate alkylation of **566** gave aldehyde **552**, which was combined with the Still−Gennari reagent **482** to install the (*Z*)-alkene with slightly improved selectivity over the final step of Leighton's synthesis (**561** + **552**, Scheme 88).

The synthesis of the C1−C15 segment **615** began with acid treatment of the Prins cyclization precursor **616** to provide the tetrahydropyran **611** with cis relative configurations at C3, C5, and C7 (Scheme 98). Regioselective enolization of the methyl ketone **611** with dicyclohexylboron chloride using Paterson's protocol[24a] followed by addition to the aldehyde **612** in a 1,5-*anti* manner furnished the aldol adduct **619** (>95:5 dr). The C11−OH thus created then directed an Evan−Tischenko reduction to generate the C9 stereocenter in **620**, as well as a platinum-catalyzed hydrosilylation of the C12 alkene in **621** to give the silacycle **622** (87:13 dr). Protodesilylation then provided the C1−C15 segment **615**, which was converted into the anomeric acetate (Scheme 99) for displacement by TMS enol ether **624** (prepared in five steps from isobutyraldehyde) to provide the *trans*-tetrahydropyran **625**. The remaining C17 stereocenter was

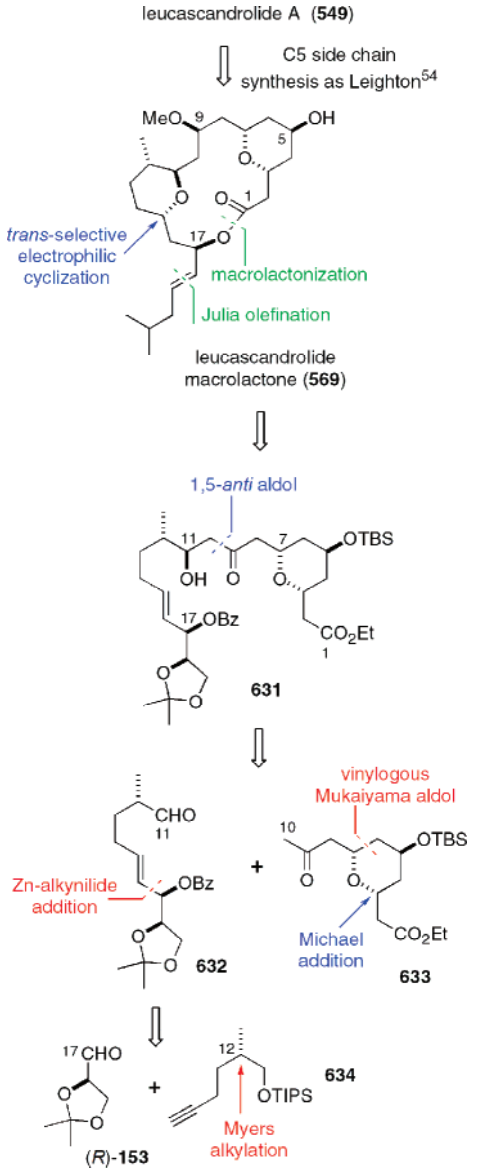
Scheme 98. Kozmin Synthesis of the C1−C15 Segment of Leucascandrolide



Scheme 99. Kozmin Total Synthesis of Racemic Leucascandrolide A



Scheme 100. Carreira Strategy for the Total Synthesis of Leucascandrolide A

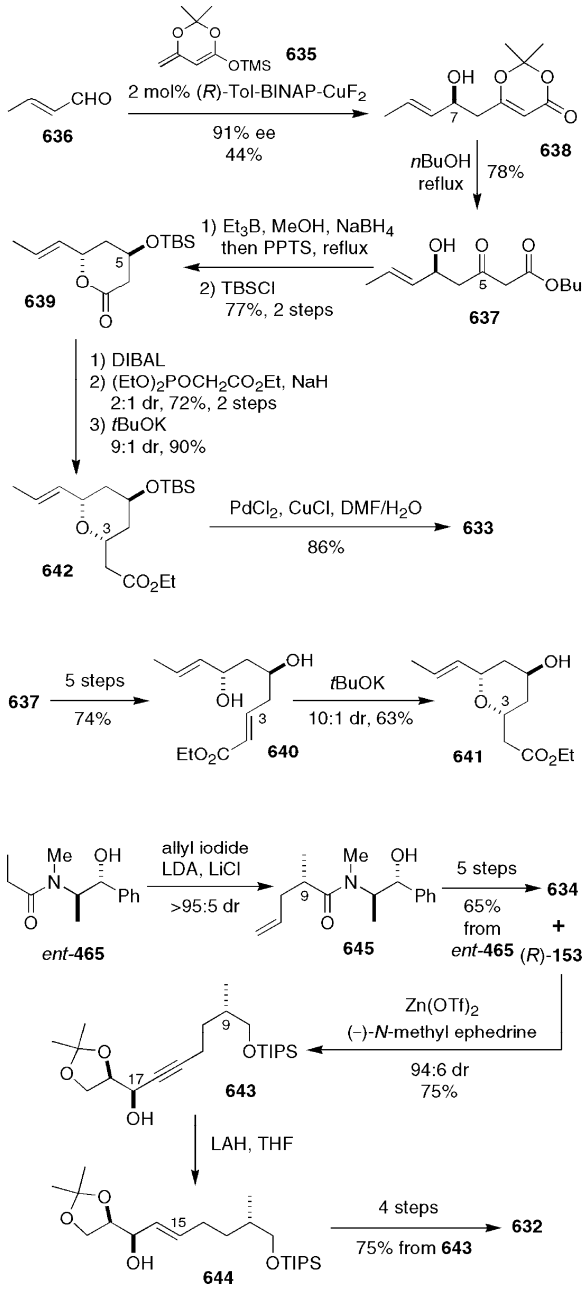


introduced by reduction of the ynone using L-Selectride, which, however, only delivered a 2:1 mixture. The undesired epimer was converted into more **626** via a Mitsunobu inversion. Following Red-Al reduction to install the (18*E*)-alkene, cleavage of the diol in **627** using $Pb(OAc)_4$ led to formation of the unanticipated macrocyclic lactol **628** as a single isomer, indicating that the hydroxy aldehyde **629** is conformationally preorganized to cyclize. It is worth noting that the corresponding C17 epimer of **627** only provided the uncyclized aldehyde under the same conditions. After PCC oxidation to deliver the macrolactone and C5 deprotection, Mitsunobu esterification with the side chain acid **610** then furnished racemic laucascandrolide A in 1.3% overall yield over the 19-step linear sequence from alcohol **623** (25 total steps to leucascandrolide macrolactone **569**; 3 steps per stereocenter).

2.4.5. Carreira Synthesis of Leucascandrolide A[58]

The planning behind Carreira's synthesis of leucascandrolide A is summarized in Scheme 100, where

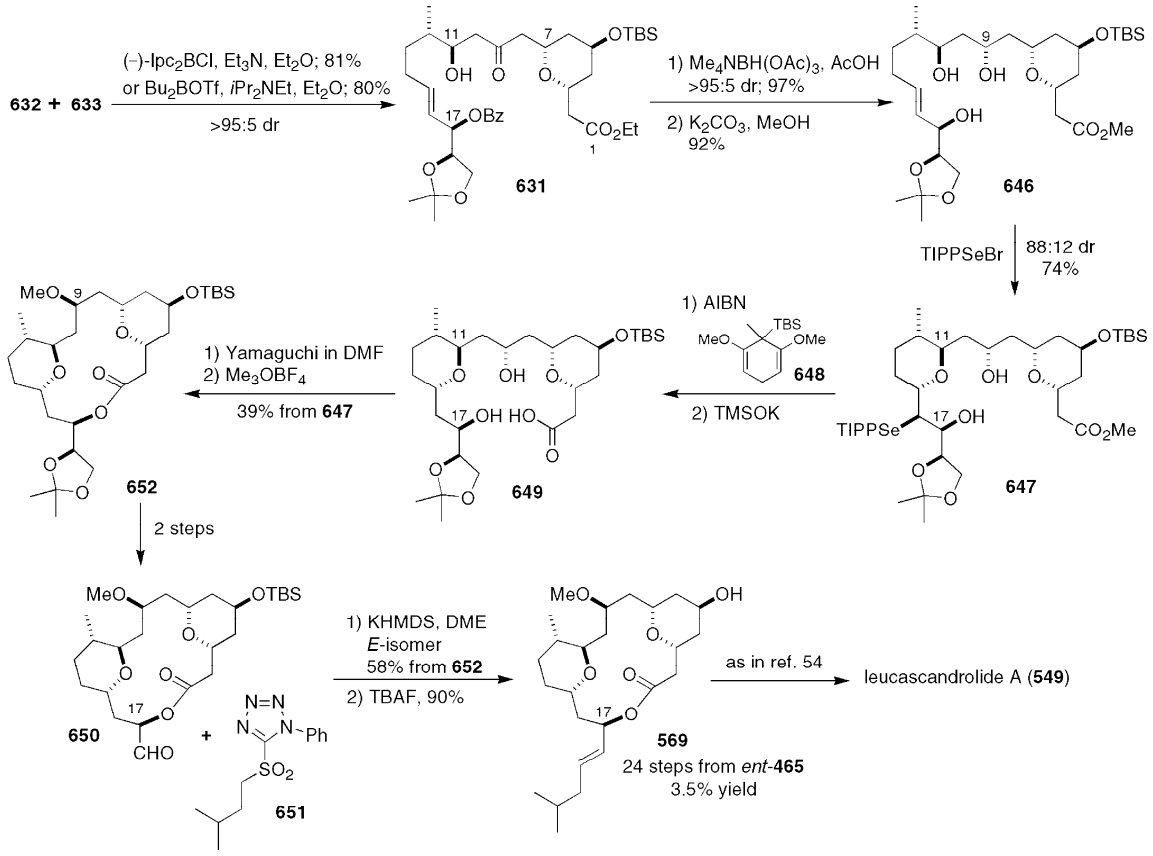
Scheme 101. Carreira Synthesis of the C1−C10 and C11−C18 Segments of Leucascandrolide



the strategic bond disconnections are indicated. The synthesis of the C5 side chain as well as its coupling to the macrolactone **569** were performed according to Leighton's synthesis. The C17 side chain was introduced by a Julia-type olefination after macrolactonization of a seco-acid intermediate, which in turn was derived from the advanced intermediate **631**. This β-hydroxy ketone was assembled by a key boron aldol coupling between the C11 aldehyde **632** and C10 methyl ketone **633**, exploiting 1,5-stereoinduction from the C7 stereocenter. The synthesis of these two coupling partners featured an asymmetric Zn−alkynilide addition and a Mukaiyama aldol reaction developed within the Carreira group.

As shown in Scheme 101, synthesis of the C10 methyl ketone **633** entailed addition of TMS dienolate **635** to crotonaldehyde **636**, catalyzed by (*R*)-Tol-BINAP copper(I) fluoride complex, to install the

Scheme 102. Carreira Total Synthesis of Leucascandrolide A



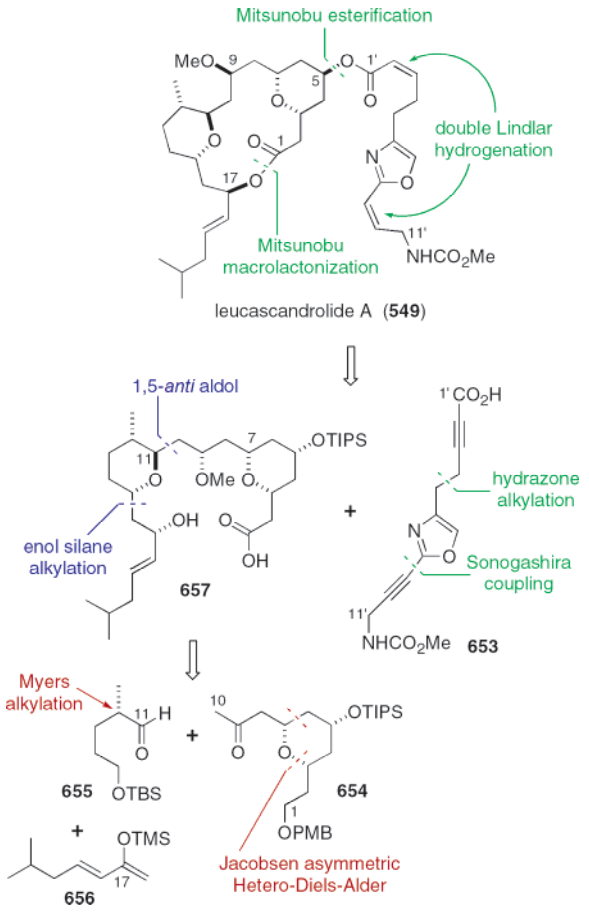
requisite C7 configuration (91% ee). The β-keto ester **637**, which was obtained via a thermal retro-Diels–Alder reaction on **638**, was converted into the lactone **639** after *syn*-reduction to install the C5–OH stereocenter. A HWE reaction on the derived lactol intermediate then introduced the *cis*-tetrahydropyran ring selectively following base equilibration (9:1 dr). An alternative sequence involved a five-step elaboration of **637** to produce the Michael precursor **640,** which gave the *cis*-tetrahydropyran product **641** with similar diastereoselectivity. The synthesis of the alkyne component **634** employed the lithium enolate derived from pseudoephedrine propionamide *ent*-**465**, under the Myers protocol, to create the C9 stereogenic center (>95:5 dr). Addition of the derived Zn alkynilide to the protected glyceraldehyde (*R*)-**153**, in the presence of (−)-*N*-methyl ephedrine, provided the propargylic alcohol **643** (96:4 dr). A stereoselective reduction of the alkyne to the *trans*-alkene **644** was then followed by functional group manipulation to provide C11 aldehyde **632**.

The aldol coupling of the boron enolate derived from methyl ketone **633** with aldehyde **632** (Scheme 102) proceeded with similar selectivity under conditions of either double- or triple-asymmetric induction[24] to furnish the 1,5-*anti* adduct **631** (>95:5). As an Evans–Tischenko reduction was unsuccessful on **631**, an Evans–Saksena 1,3-*anti*-reduction was performed instead to set up the required C9 configuration and led to the cyclization precursor, unprotected triol **646**. The bulky electrophilic selenium reagent 2,4,6-triisopropylphenylselenyl bromide (TIPPSeBr) induced a C17–OH directed cyclization to provide the *trans*-tetrahydropyran **647** (88:12 dr). The selenium was then removed under tin-free conditions using the cyclohexadiene **648**. Interestingly, in contrast to similar successful macrolactonizations of a seco-acid that possessed a C9 methoxy group (**563** → **560**, Scheme 88; **589** → **569**, Scheme 92), seco-acid **649** was reported to be reluctant to cyclize under standard Yamaguchi conditions. This phenomenon was attributed to a hydrogen-bond network that engaged the C17 and C9 hydroxyl groups with the two tetrahydropyranyl oxygen atoms of the intermediate activated ester. Accordingly, performing the Yamaguchi macrolactonization in DMF as a polar solvent enabled the activated ester to adopt a productive conformation and provided the macrolactone. After selectively engaging the C11 and C17 hydroxyl groups, the required methyl ether was introduced at C9. The C17 side chain was then appended to the derived aldehyde **650** with the sulfone **651** using the Kocienski modification of the Julia olefination to provide the (*E*)-alkene exclusively. After deprotection, the synthesis of the macrolactone **569** was completed in 3.5% overall yield over the 24-step linear sequence from propionamide *ent*-**465** (40 total steps; 5 steps per stereocenter).

2.4.6. Paterson Synthesis of Leucascandrolide A[59]

Paterson's synthesis of leucascandrolide A achieved essentially complete stereocontrol. The synthetic planning offered flexibility in the method adopted for macrolactonization at C17 and appendage of the side chain acid **653** at C5, depending on the configuration of these two stereocenters resulting from ketone reduction. As shown in Scheme 103, the optimum sequence involved two Mitsunobu reactions to obtain

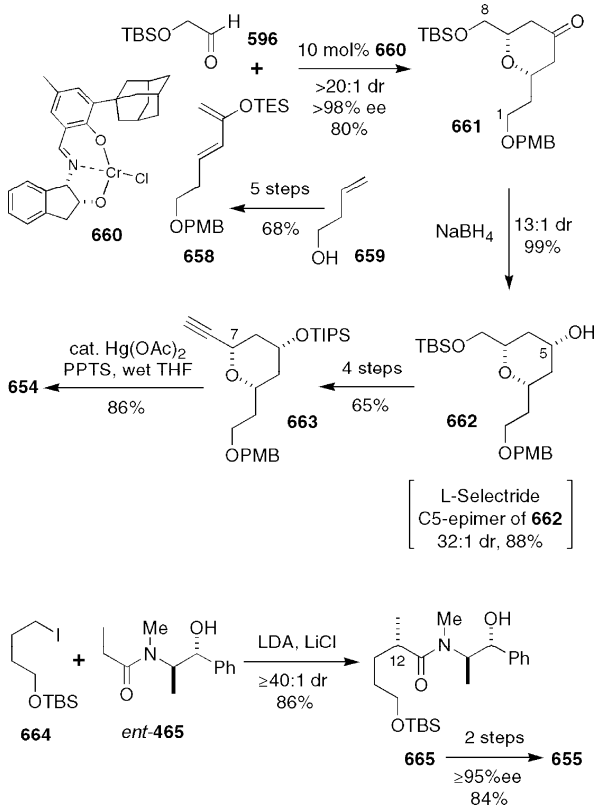
Scheme 103. Paterson Strategy for the Total Synthesis of Leucascandrolide A



the penultimate intermediate, which was followed by a double Lindlar hydrogenation to install the two (*Z*)-alkenes on the side chain to provide leucascandrolide A directly. The macrolactone was constructed by sequential coupling of the methyl ketone **654**, aldehyde **655,** and 2-silyloxy diene **656**. Recognizing the 1,5-*anti* configurational relationship between C7 and C11, this coupling sequence relied first on a 1,5-*anti*-aldol reaction, as developed in the Paterson group,[24a] between **654** and **655**. The resulting C11 stereocenter then directed the anomeric alkylation to generate the *trans*-tetrahydropyran with concomitant installation of the full C17 side chain.

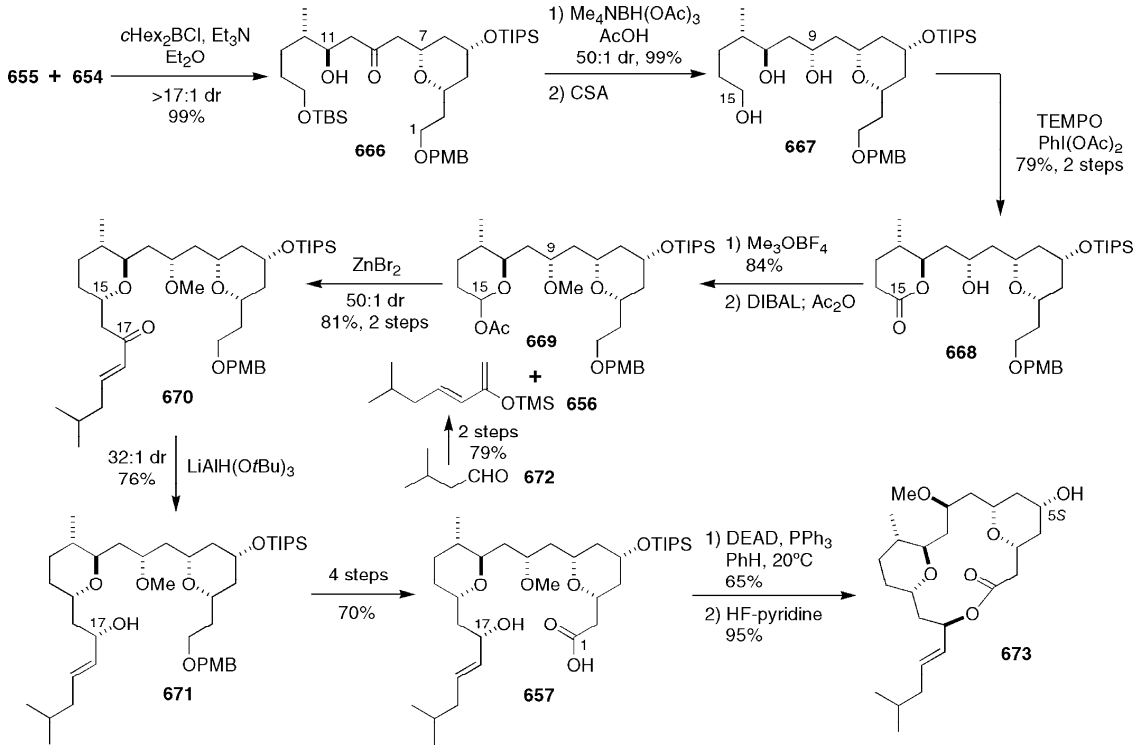
The synthesis of the *cis*-tetrahydropyranyl methyl ketone **654** started with a Jacobsen asymmetric hetero-Diels–Alder reaction between aldehyde **596** and 2-silyloxy diene **658**, which was prepared from homoallylic alcohol **659**. The chromium Schiff base complex **660** catalyzed a [4 + 2] cycloaddition to provide the 2,6-*cis*-pyranone **661** (>20:1 dr, >98% ee) (Scheme 104). Reduction of the ketone using $NaBH_4$ provided the C5 equatorial alcohol **662** (13:1 dr). The corresponding reduction employing L-Selectride produced the epimeric axial alcohol (32:1 dr) (cf. Rychnovsky example (**584** → **585**, Scheme 92) and Wipf example (**601** → **590**, Scheme 94)). After conversion into an alkyne at C8, the requisite methyl ketone was generated by hydroxymercuration. The aldehyde component **655** was synthesized (≥95% ee) via a Myers alkylation using chiral amide *ent*-**465**.

Scheme 104. Paterson Synthesis of the C1–C10 and C11–C15 Segments of Leucascandrolide



Regioselective enolization of **654** under standard Paterson conditions and addition of the resulting dicyclohexylboron enolate to aldehyde **655** provided the desired 1,5-*anti* aldol product (>17:1 dr) (Scheme 105). As also evidenced from the Komins and Carreria examples, the *β*-oxygenated C1–C7 methyl ketone subunit (**611**, **633,** and **654**) exhibited a strong 1,5-*anti*-directing influence not only with achiral aldehyde **612**, but also with chiral aldehydes **632** and **655**. After an Evans–Saksena reduction of the C9 ketone and C15 deprotection, the three hydroxyl groups in **667** were effectively differentiated by means of a TEMPO-promoted oxidative *δ*-lactonization to give **668**, leaving the C9–OH free for subsequent methylation. This obviated the need for extra protecting group steps. Addition of silyloxy diene **656** to the anomeric acetate **669**, prepared by the Rychnovsky one-pot protocol, cleanly delivered the *trans*-tetrahydropyran **670** (50:1 dr). The C17 configuration required for the Mitsunobu macrocyclization was then installed by reduction using $LiAl(OtBu)_3$ (32:1 dr), resulting from 1,3-*syn* stereoinduction via a lithium chelate or operation of the Evans polar model.[49] The high level of selectivity achieved is in contrast to a similar C17 ketone reduction using L-Selectride to obtain the natural configuration (**625** → **626**, Scheme 99). In this manner, incorporation of the full C17 side chain and creation of the C15 and C17 stereocenters were achieved with higher selectivity than the corresponding anomeric alkylation/alkenylzinc addition approach utilized in the first Leighton synthesis (Scheme 88). After elaboration into the seco-acid **657** closure of the 18-membered macrolactone ring by a Mitsunobu reaction proceeded

Scheme 105. Paterson Synthesis of Leucascandrolide (5*S*)-Macrolactone



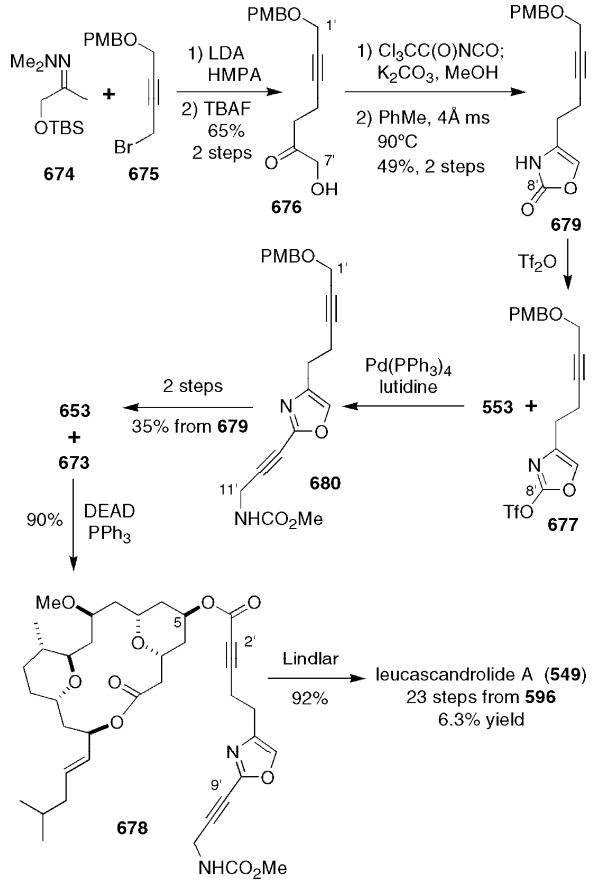
with complete inversion and without any allylic rearrangement, as in the Wipf example (**606** → **569**, Scheme 95).

The synthesis of C5 side chain acid involved coupling between the hydrazone **674** and bromide **675**, followed by formation of the oxazole ring via condensation between the α-hydroxy ketone **676** and trichloroacetyl isocyanate, and then a Sonogashira coupling of the oxazolyl triflate **677** with carbamate **553** (Scheme 106). A Mitsunobu coupling between the side chain acid **653** and the macrolactone **673** then gave the ester **678**. It is worth noting that the natural (5*R*)-epimer **569** could not be directly acylated with acid **653** under a variety of conditions, presumably due to the hindered nature of the axial hydroxyl group. This is in contrast to the successful acylation of (5*R*)-macrolactone with the simpler phosphonoacetic acid **564** in Leighton's synthesis (**560** → **561**, Scheme 88). The alkynes in ester **678** were then subjected to a Lindlar hydrogenation to introduce the two (*Z*)-alkenes, completing the total synthesis of leucascandrolide A in 6.3% overall yield over the 23-step linear sequence from aldehyde **596** (31 total steps to leucascandrolide macrolactone **673**; 4 steps per stereocenter).

2.4.7. Crimmins Synthesis of Leucascandrolide Macrolactone[60]

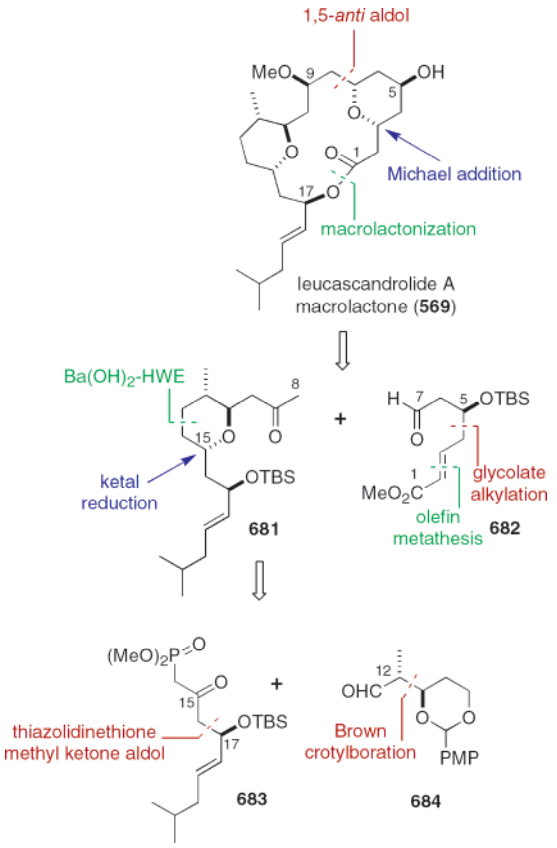
As outlined in Scheme 107, Crimmins also elected to explore a boron-mediated 1,5-*anti* methyl ketone aldol reaction as a key stereodefining step in his synthesis of leucascandrolide macrolactone. However, the planned 1,5-stereoinduction was in the C7−C8 aldol bond construction between the elaborated C8 methyl ketone **681** and C7 aldehyde **682** instead of the C10−C11 bond-forming process utilized in each of the Kozmin, Carreira, and Paterson syntheses

Scheme 106. Paterson Total Synthesis of Leucascandrolide A



(Schemes 96, 100, and 103). The C8 methyl ketone **681** contained the full C17 side chain and was derived from a HWE reaction between ketophosphonate **683** and aldehyde **684** followed by a sub-

Scheme 107. Crimmins Strategy for the Synthesis of Leucascandrolide Macrolactone

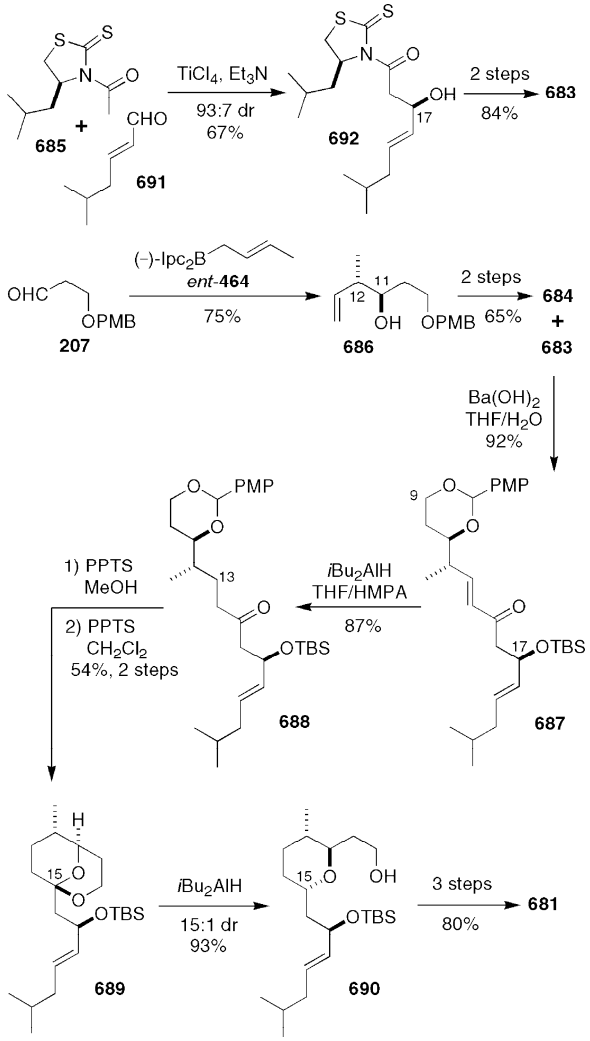


strate-directed acetal reduction to construct the *trans*-tetrahydrofuran ring, while, as in Carreira's synthesis (Scheme 100), an intramolecular hetero-Michael addition was used to construct the *cis*-tetrahydropyran ring. Chiral imide-based transformations, as developed by the Crimmins group, were employed to install the isolated stereocenters at C5 and C17.

As shown in Scheme 108, the ketophosphonate **683** was obtained in three steps via a methyl ketone aldol of the titanium enolate derived from thiazolidinethione **685** to set up the C17 stereocenter (93:7 dr). A Brown crotylboration[27] of aldehyde **207** supplied homoallylic alcohol **686**, which after PMP acetal formation and oxidative cleavage of the double bond provided the required aldehyde **684**. The HWE reaction between **683** and **684** under $Ba(OH)_2$-promoted conditions provided enone **687**, which was then subjected to a 1,4-reduction to give the ketone **688**. Following a two-step protocol to form the bicyclic acetal **689**, intramolecular delivery of hydride, presumably directed by the acetal oxygen, provided the desired *trans*-tetrahydrofuran **690** (15:1 dr).

The synthesis of the C7 aldehyde **682** commenced with an alkylation of the sodium enolate of glycolate **693** to set up the C5 stereocenter (>98:2 dr) (Scheme 109). After reductive cleavage of the chiral auxiliary, a cross-metathesis on the alkene **694** using Grubbs second-generation catalyst **502** then introduced the unsaturated ester. Unlike the similar methyl ketone aldol transformations documented in the Kozmin, Carreira, and Paterson syntheses (Schemes 98, 102, and 105), aldol addition of the dicyclohexylboron

Scheme 108. Crimmins Synthesis of the C8−C22 Segment of Leucascandrolide

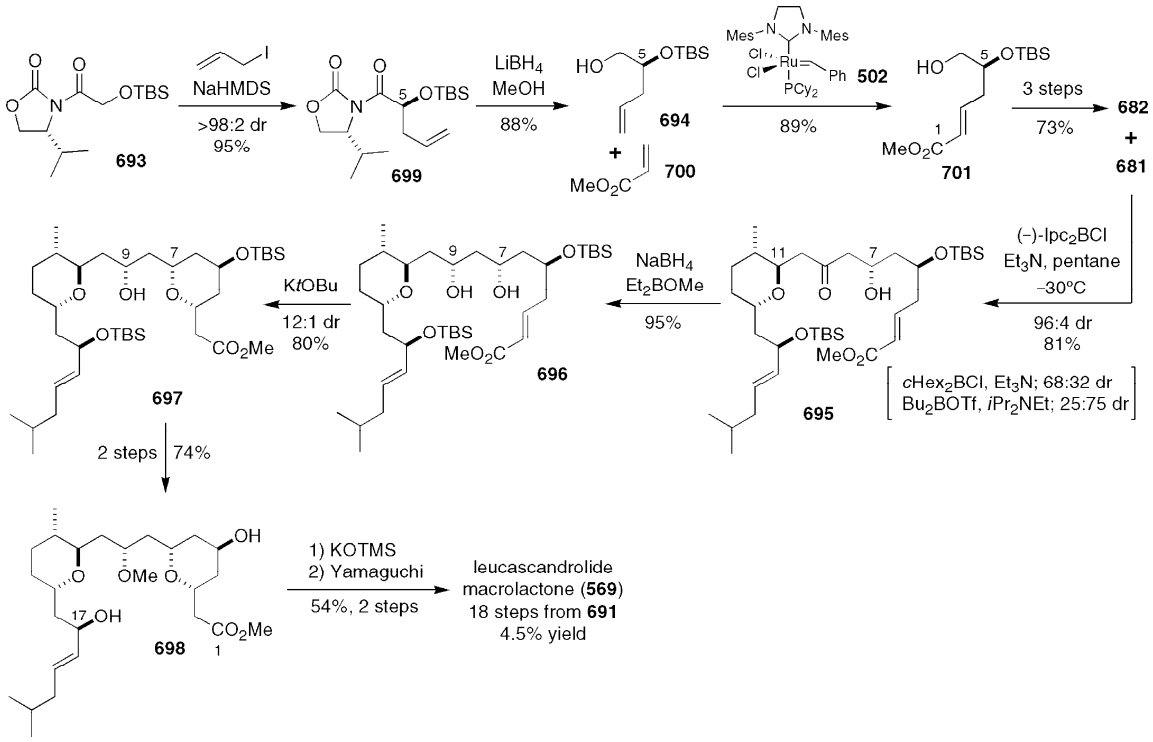


enolate of the C8 methyl ketone **681** to aldehyde **682** only provided a 2:1 mixture of the desired *anti*-Felkin−Anh C7 isomer **695** and its epimer. Interestingly, the selectivity was reversed using the corresponding dibutylboron enolate.[24b] Fortunately, this key aldol reaction could be rendered highly diastereoselective by employing the matched reagent, (−)-Ipc_2BCl,[24a] in a triple asymmetric induction manner to provide **695** (96:4 dr). The C9 stereocenter was then set up by a Narasaka−Prasad reduction to produce the 1,3-*syn*-diol **696**. A hetero-Michael addition of the C7 hydroxyl group to the α,β-unsaturated ester delivered the *cis*-tetrahydropyran (12:1 dr), leaving the C9−OH available for methylation. Sequential deprotection revealed the requisite seco-acid, which was subjected to Yamaguchi macrolactonization to give leucascandrolide macrolactone **569** in 4.5% overall yield over the 18-step linear sequence from aldehyde **691** (27 total steps; 3.4 steps per stereocenter).

2.4.8. Williams Synthesis of Leucascandrolide Macrolactone[61]

Williams synthesis of the leucascandrolide macrolactone depended heavily on the use of reagent-controlled reactions to install the stereocenters of the

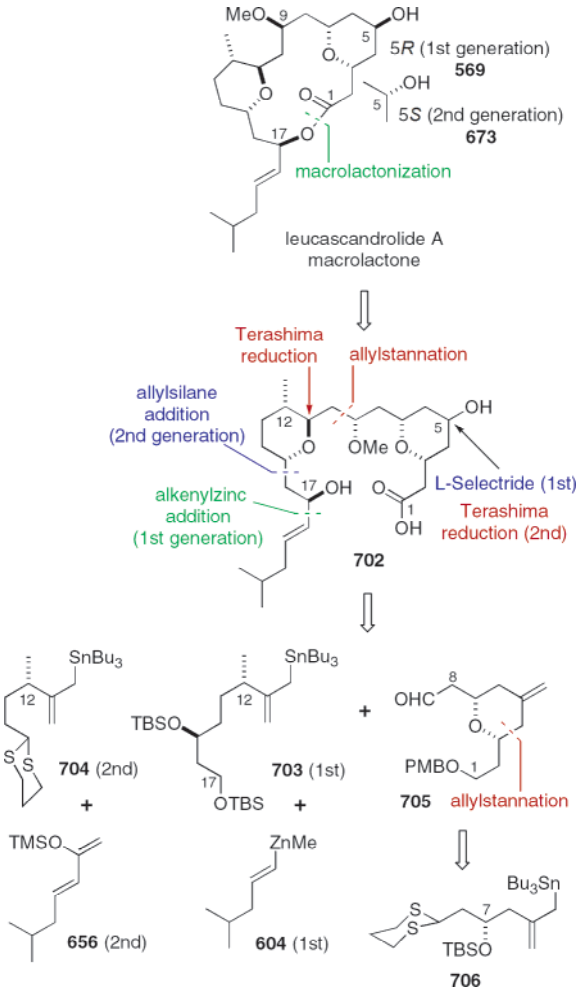
Scheme 109. Crimmins Synthesis of Leucascandrolide Macrolactone



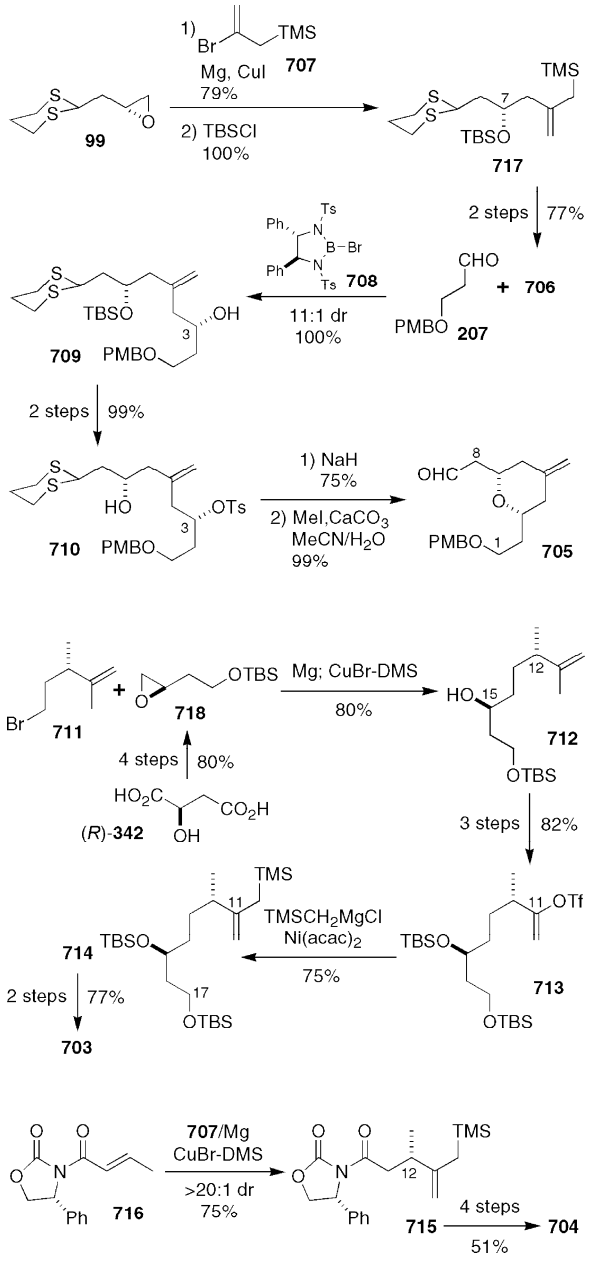
macrolide in both his first-generation synthesis of the natural (5*R*)-macrolactone **569**[61a] and the second-generation synthesis of its (5*S*)-epimer **673**.[61b] As shown in Scheme 110, the two syntheses differ mainly in the manner that the C15−C17 segment of the molecule was incorporated. The first synthesis involved addition of alkenyl zinc reagent **604** to a C17 aldehyde, an approach similar to that adopted by Leighton, while, as in the Paterson synthesis, the second synthesis employed an addition of 2-silyloxydiene **656** to an anomeric acetate. Thus, different allylstannane subunits (**703** and **704**) were used for the key asymmetric allylstannation reaction, as developed by the Williams group based on Corey methodology, of the C1−C9 aldehyde **705** during construction of the corresponding seco-acids. An allylstannation was also instrumental in the synthesis of aldehyde **705**. Another key feature of the Williams leucascandrolide synthesis is the use of Terashima's asymmetric reduction in setting up the C5 and C11 stereocenters. In particular, this method was used to simultaneously reduce the C5 and C11 ketones in the second synthesis.

The synthesis of the C1−C9 aldehyde **705** started with the copper-catalyzed opening of the epoxide **99** (prepared by the alkylation of 2-lithio-1,3-dithiane with (*R*)-epichlorohydrin) by the Grignard reagent derived from (2-bromoallyl)trimethylsilane (**707**) (Scheme 111). Transmetalation of the corresponding allylstannane **706**, using the C_2-symmetric boron reagent **708**, and coupling to aldehyde **207** provided the allylic alcohol **709** (11:1 dr). The *cis*-tetrahydropyran ring was then generated by intramolecular S_N2 displacement on the tosylate **710**. Similarly, copper-catalyzed epoxide opening by the Grignard reagent derived from bromide **711** was applied to the synthesis of C10−C17 stannane **703**. The alcohol **712** obtained was converted into the enol triflate **713** for

Scheme 110. Williams First- and Second-Generation Strategies for the Synthesis of Leucascandrolide Macrolactone



Scheme 111. Williams Synthesis of the C1−C9, C10−C17, and C10−C15 Segments of Leucascandrolide



a nickel-promoted cross coupling with (trimethylsilyl)methylmagnesium chloride to provide allylsilane **714** and then metal exchange. The C10−C15 stannane **704** was synthesized from allylsilane **715**, which was obtained from conjugate addition of the organocopper derived from the Grignard reagent of silane **707** to the chiral imide **716** (>20:1 dr).

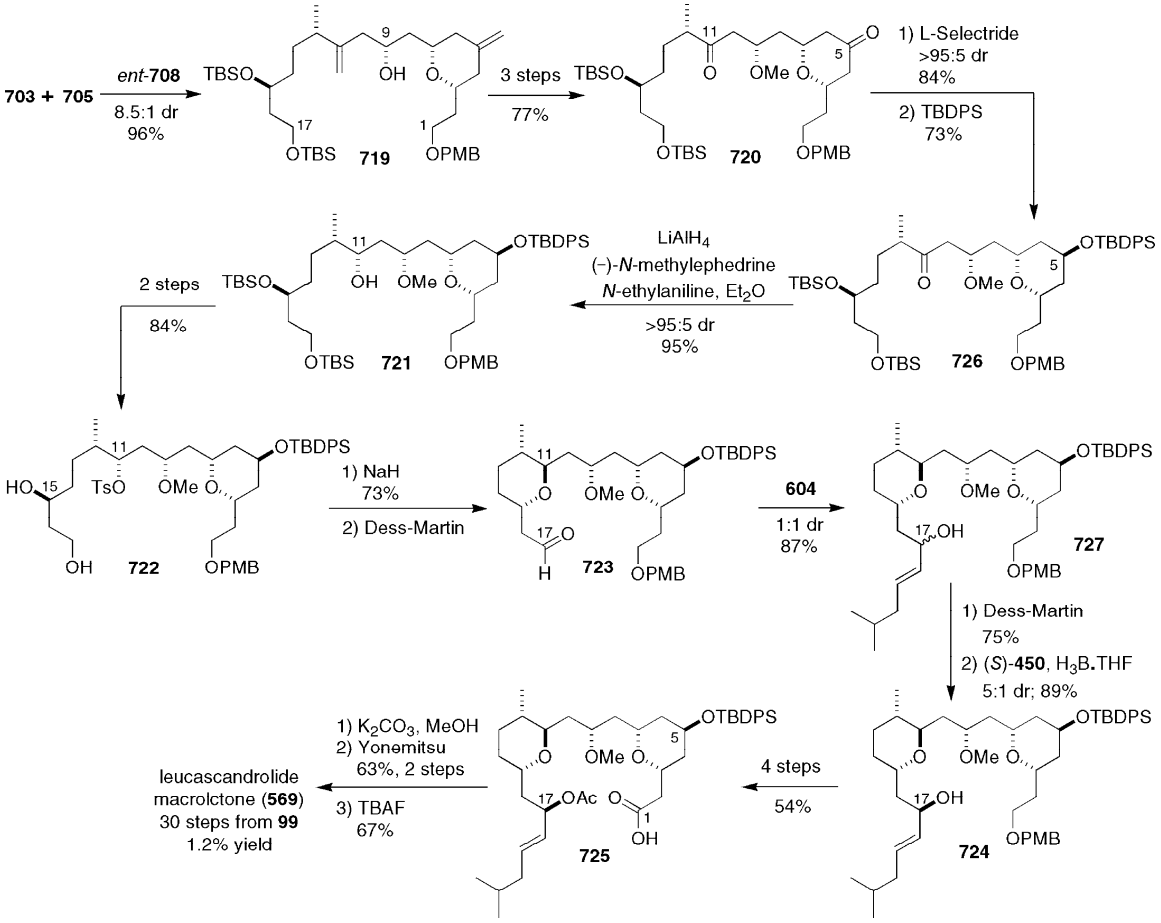
In the first-generation synthesis (Scheme 112) the key coupling reaction between the C10−C17 stannane **703** and the aldehyde **705** was performed using reagent *ent*-**708** in a matched sense to obtain the homoallylic C9 alcohol **719** (8.5:1 dr). After conversion of the C5 and C11 alkenes to ketone groups, selective reduction of the more accessible C5 ketone of **720** by L-Selectride provided the axial alcohol selectively (cf. a similar reduction in the Rychnovsky synthesis, **584** → **585**, Scheme 92). The C11 ketone group was then reduced by the Terashima protocol using the (−)-*N*-methylephedrine ligand to provide the alcohol **721** (>95:5 dr). This introduced the required C11 configuration for formation of the 2,6-*trans*-tetrahydropyran ring via S_N2 displacement of the tosylate by the C15−OH of **722**. The C17 side chain was then incorporated by addition of alkenylzinc **604** to aldehyde **723**. Interestingly, in contrast to the Leighton and Wipf syntheses that employed an amino alcohol or a chiral aminothiol as ligands (**550** → **563**, Scheme 88; **595** → **608**, Scheme 95), this substrate-based addition was nonselective. This necessitated oxidation of the allylic alcohol to the enone, and the C17 stereocenter in **724** was then installed (5:1 dr) by a CBS reduction. Following elaboration into the seco-acid precursor **725**, C17 deacetylation, Yonemitsu−Yamaguchi macrolactonization, and C5 deprotection then gave leucascandrolide macrolactone **569** in 1.2% overall yield over the 30-step linear sequence from epoxide **99** (41 total steps; 5 steps per stereocenter).

The second-generation synthesis of the epimeric (5*S*)-alcohol **673** followed a similar sequence to that involved in the allylation of aldehyde **705** using stannane **704** (Scheme 113). The reagent-controlled coupling proceeded with the same level of diastereoselectivity as before to obtain the diketone **728**, which was then reduced by Terashima's protocol using (+)-*N*-methylephedrine as the ligand. The C5 stereocenter was thus introduced with 8:1 dr, while the C11 stereocenter was configured with a >25:1 dr. After transformation into the anomeric acetate, addition of 2-silyloxydiene **656** incorporated the C17 side chain and generated the 2,6-*trans*-tetrahydropyran ring in **729**. As in the Paterson example (**669** → **670**, Scheme 105), a high level of diastereoselectivity (>25:1 dr) was achieved. In contrast to Paterson's use of substrate control in the C17 ketone reduction (**670** → **671**, Scheme 105), reagent (*S*)-**450** was again employed as in the first route to provide alcohol **730** (5:1 dr), which was further elaborated into the unprotected seco-acid **731** for Yamaguchi macrolactonization. In this improved synthesis, the (5*S*)-leucascandrolide macrolactone **673** was obtained in 7.1% overall yield over the 24-step linear sequence from epoxide **99** (29 total steps; about 4 steps per stereocenter).

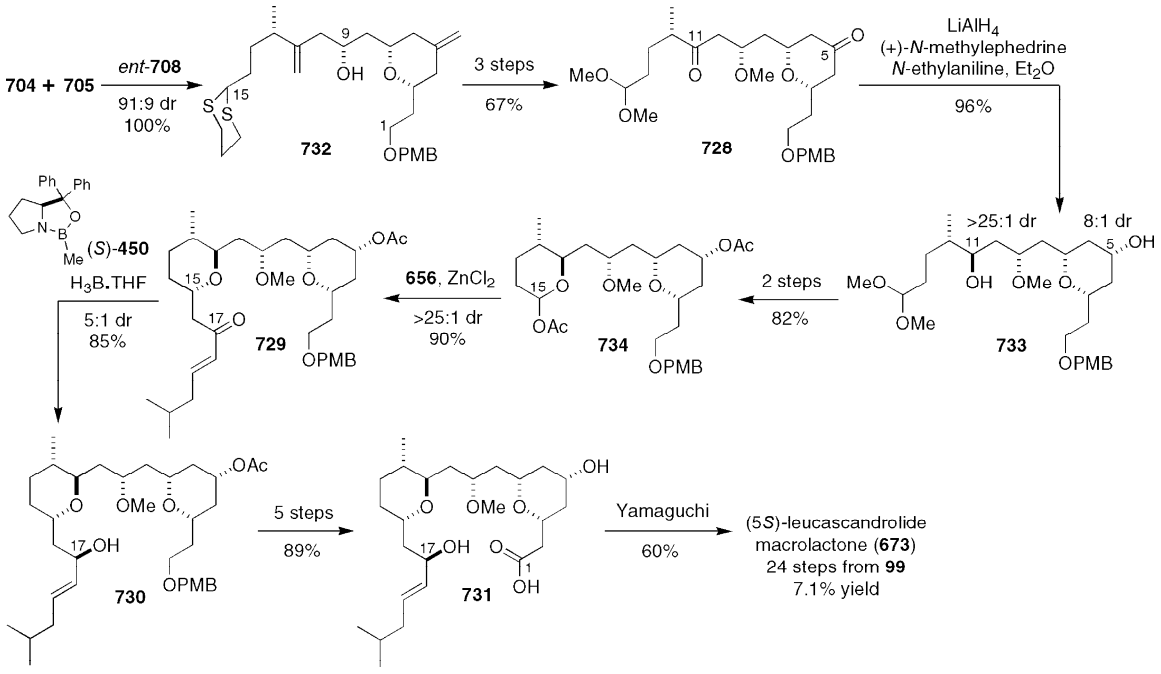
2.5. Callipeltoside A

In 1996, the Minale group reported the isolation of callipeltoside A (**735**, Figure 9) from the shallow-water lithistid sponge *Callipelta* sp., collected off the east coast of New Caledonia. This marine macrolide was obtained in low natural abundance (3.5 mg from 2.5 kg of freeze-dried sponge, 1.4×10^{-4} % yield), which limited its full structural determination and biological evaluation.[62a] Callipeltoside A is a highly unusual glycosylated 14-membered macrolide featuring an aminodeoxy sugar unit (callipeltose) at C5 and a novel dienyne *trans*-chlorocyclopropane side chain appended to C13. The structural assignment and the relative configuration were based on extensive NMR studies; however, the full stereostructure could not be established. While the configuration of the sugar unit relative to the aglycon was assigned by NOE analysis, structural ambiguities remaining included

Scheme 112. Williams Synthesis of Leucascandrolide Macrolactone



Scheme 113. Williams Synthesis of Leucascandrolide (5*S*)-Macrolactone



the relative configuration at the C13 stereocenter, as well as the stereochemical relationship between the cyclopropane ring and the macrolactone core. Total synthesis proved imperative to resolve the remaining stereochemical issues, including establishment of the absolute configuration.

Although callipeltoside A only showed moderate in-vitro cytotoxicity against NSCLC−N6 human bronchopulmonary non-small-cell lung carcinoma and P388 (IC_{50} values of 11.26 and 25.26 μg/mL respectively), preliminary studies indicated its activity to be cell-cycle dependent, blocking proliferation in the

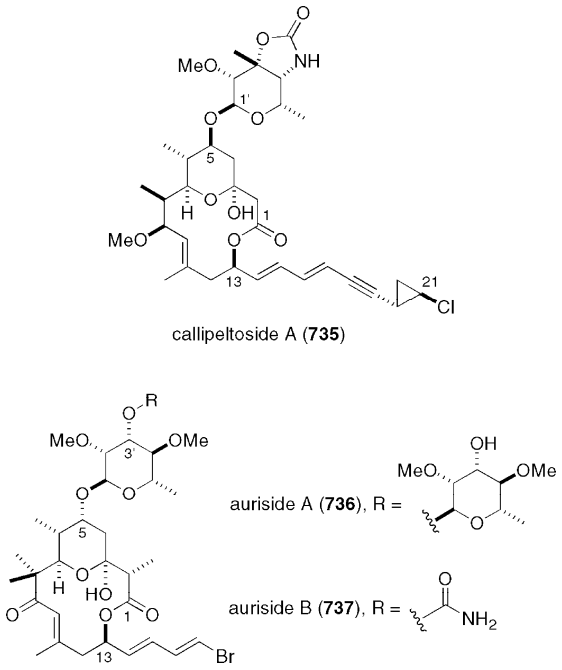


Figure 9. Structures of callipeltoside A and auriside A and B.

G1 phase.[62a] Further study of its interesting cellular functions also awaits the availability of a sizable quantity of synthetic callipeltoside A and its analogues, as all the natural material obtained from the initial isolation has been consumed. Two marine macrolides that are structurally similar to the callipeltosides are auriside A (**736**) and B (**737**) (Figure 9), which were isolated from the Japanese sea hare *Dolabella auricularia* by Yamada in 1996.[63a] Their absolute configurations were proposed to be as shown based on NOESY analysis and degradation studies and have been confirmed by the total synthesis recently completed by Paterson.[63b]

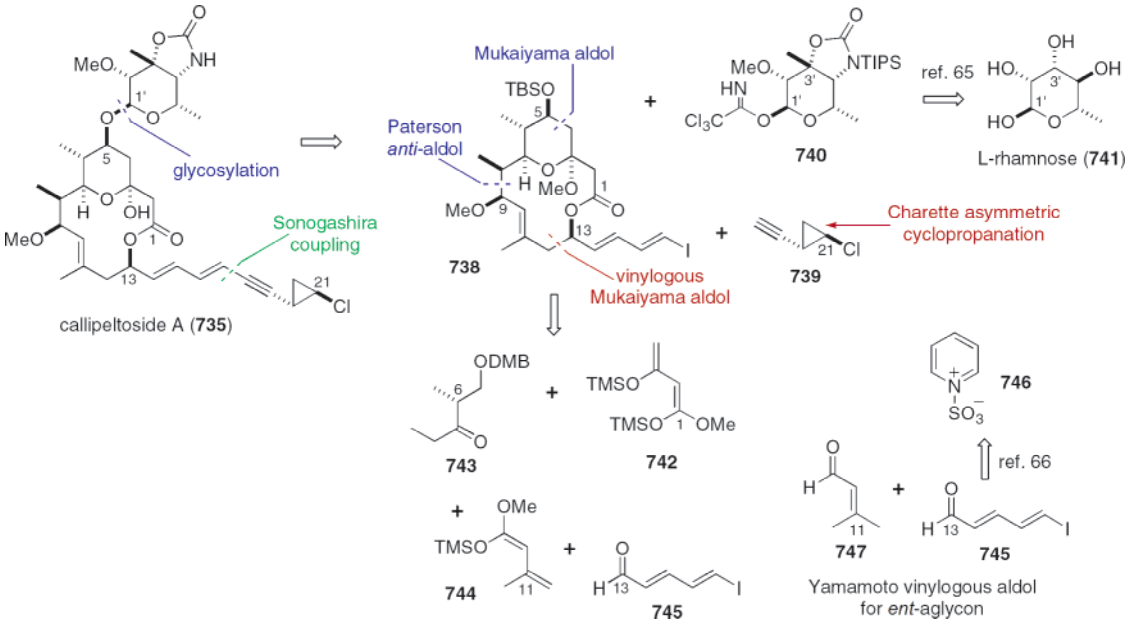
2.5.1. Paterson Synthesis of Callipeltoside A[64]

Paterson developed an expedient synthesis of callipeltoside aglycon[64a] and, subsequently, accomplished the total synthesis of the natural callipeltoside A (**735**)[64b] by adapting this same synthetic sequence. As shown in Scheme 114, callipeltoside A was assembled from the aglycon **738** by a Sonogashira coupling using the alkyne **739** followed by glycosylation at C5 using the trichloroacetimidate **740**, prepared from L-rhamnose (**741**) according to the Giuliano procedure.[65] Three strategic aldol bond disconnections at C4−C5, C8−C9, and C12−C13 of the aglycon **738** revealed the four coupling segments **742**, **743**, **744**, and **745**.

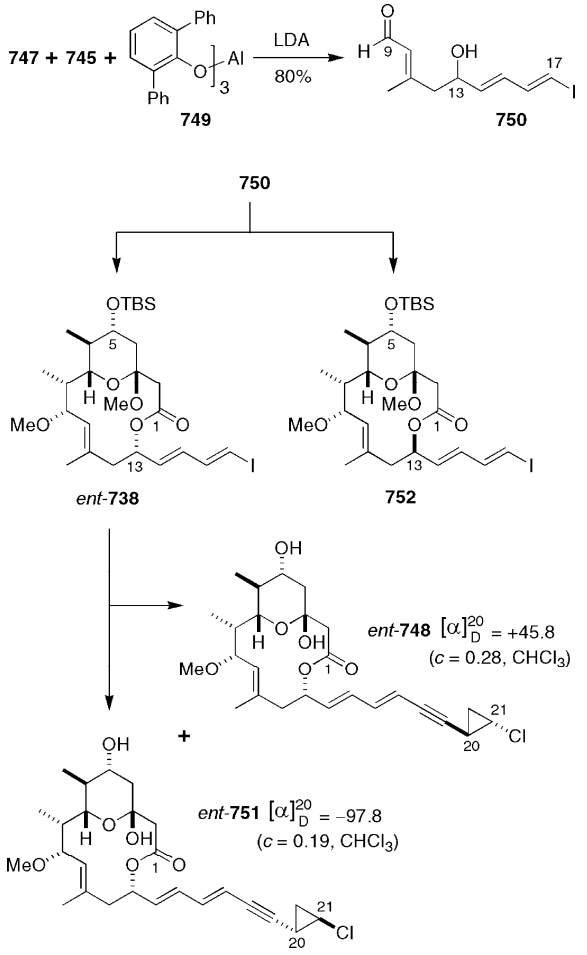
In contrast to the Trost and Evans total syntheses (as described in sections 2.5.2 and 2.5.3), the potentially delicate diene portion of the macrolide was incorporated at the onset of the synthesis by starting from aldehyde **745**, which was prepared in two steps from pyridinium-1-sulfonate **746**.[66] This adventurous approach necessitated that the (*E,E*)-geometry of the iododiene was retained through the synthesis. During the initial synthesis of the *ent*-callipeltoside aglycon (*ent*-**748**, Scheme 115) Yamamoto's bulky aluminum Lewis-acid **749** was employed to promote a directed aldol coupling between aldehyde **745** and aldehyde **747** to provide the C9−C17 subunit **750**, with complete control of the trisubstituted alkene geometry. By comparison with the reported NMR spectroscopic data, this initial work established the relative configuration at C13 and led to a re-assignment of the C20 and C21 resonances in the ^{13}C NMR spectrum. It also demonstrated that antipodal chlorocyclopropane segments induced marked differences in the magnitude of the optical rotation (compare *ent*-**748** and *ent*-**751**), although no effect on the ^{1}H and ^{13}C NMR spectra was found.

For callipeltoside A itself, the synthesis of aglycon **738** began with an aldol reaction between the acid-sensitive silyl dienolate **744** and iododienal **745** (Scheme 116). This (*R*)-BINOL-Ti(O*i*Pr)$_4$-catalyzed asymmetric Mukaiyama aldol reaction provided the adduct **753**, installing the (*E*)-trisubstituted alkene and the isolated C13 stereocenter (94% ee). Adduct **753** was converted into aldehyde **754** for a second

Scheme 114. Paterson Strategy for the Total Synthesis of Callipeltoside A



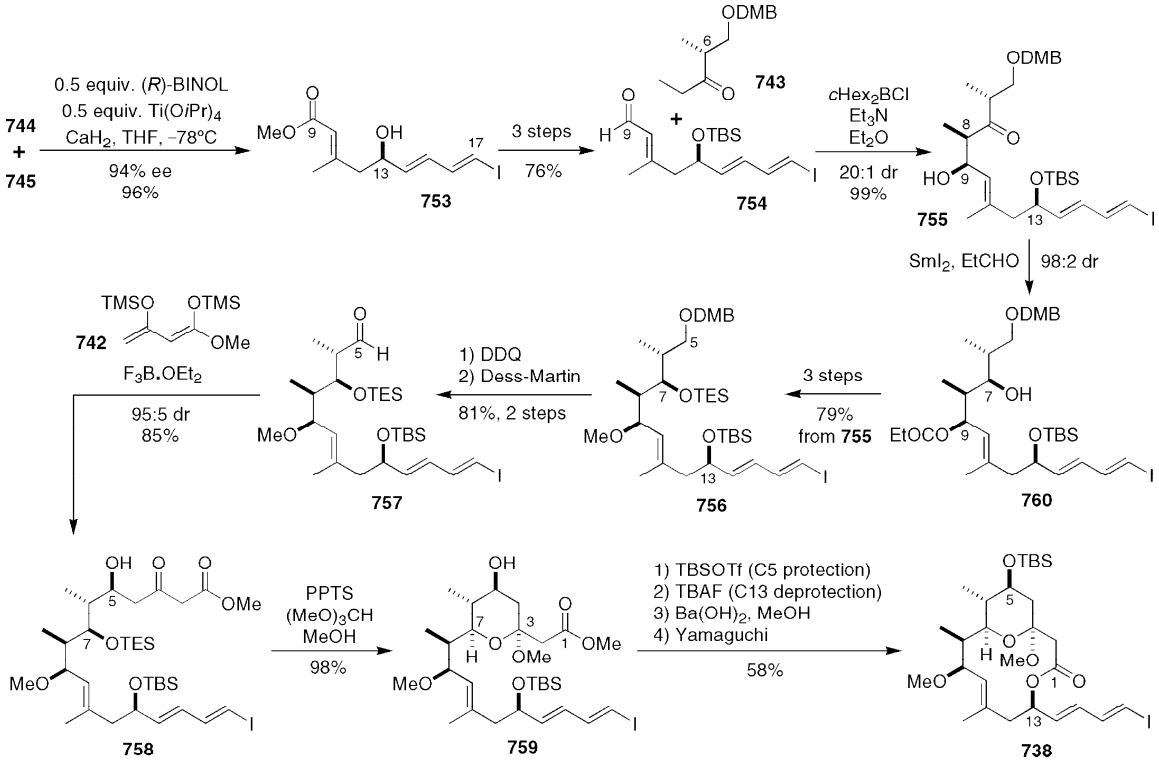
Scheme 115. Paterson Synthesis of the Aglycon (*ent*-748) of *ent*-Callipeltoside A



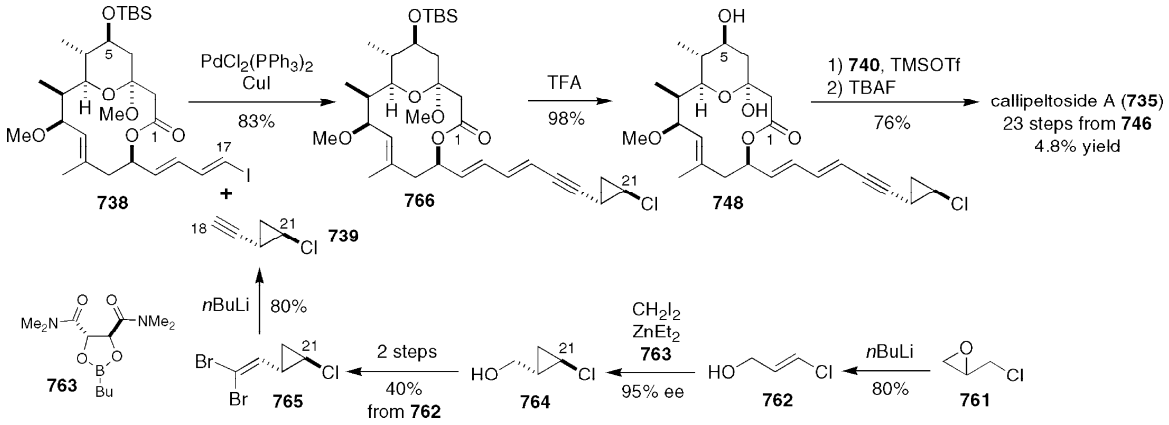
aldol addition using the (*E*)-dicyclohexylboron enolate of ethyl ketone **743** to produce the *anti*-isomer **755** cleanly (20:1 dr). Significantly, the remote C13 stereocenter has minimal influence on the stereoinduction. An Evans−Tischenko *anti*-reduction on **755** then established the C7 hydroxyl stereocenter (98:2 dr). Following derivatization to give the C7 TES ether **756**, the 3,4-dimethoxybenzyl (DMB) ether at C5 was removed oxidatively in the presence of the C13 allylic TBS ether. The resulting alcohol was oxidized to the aldehyde **757** for the third aldol addition, which involved a Mukaiyama-type homologation using 1,3-bis(silyloxy)diene **742**, to provide the Felkin−Anh product **758** (95:5 dr). Concomitant TES ether cleavage and methyl acetal formation then generated the seco-acid precursor **759**, which was efficiently elaborated into the macrolactone **738** via selective cleavage of the C13 allylic TBS ether, sponification using $Ba(OH)_2$, and Yamaguchi macrolactonization.

The requisite chlorocyclopropane **739** was synthesized from *epi*-chlorohydrin **761** via an asymmetric Simmons−Smith cyclopropanation performed on the vinyl chloride **762** using Charette's dioxaborolane ligand **763** (Scheme 117). The cyclopropane **764** (95% ee) was then converted into vinyl dibromide **765** by the Corey−Fuchs protocol. This sequence delivered key intermediate **765**, which provided alkyne **739** after *n*BuLi treatment. Sonogashira coupling between the macrolactone **738** and **739** then gave the protected aglycon **766** with retention of the diene geometry. Completion of the total synthesis followed glycosylation using the trichloroacetimidate **740** and then *N*-TIPS cleavage. Callipeltoside A was thus obtained in 4.8% overall yield over the 23-step longest linear sequence from pyridinium-1-sulfonate **746** (about 37 total steps; about 3 steps per stereocenter).

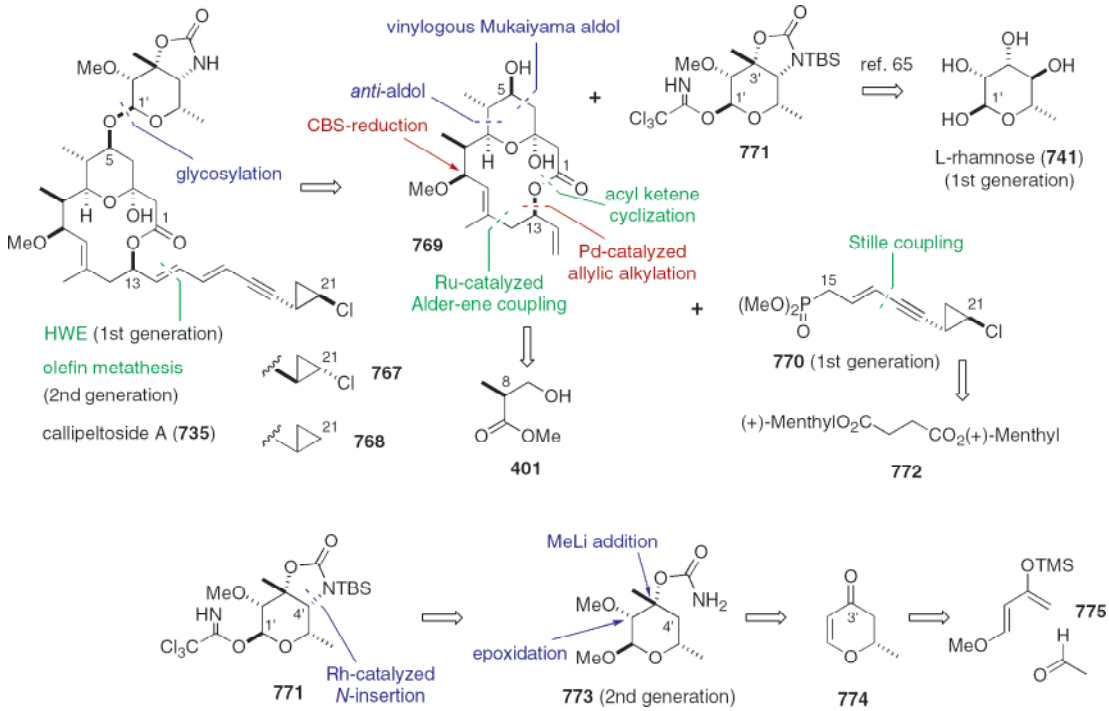
Scheme 116. Paterson Synthesis of a Fully Protected Callipeltoside Macrolactone



Scheme 117. Paterson Total Synthesis of Callipeltoside A



Scheme 118. Trost Strategy for the Total Synthesis of Callipeltoside A



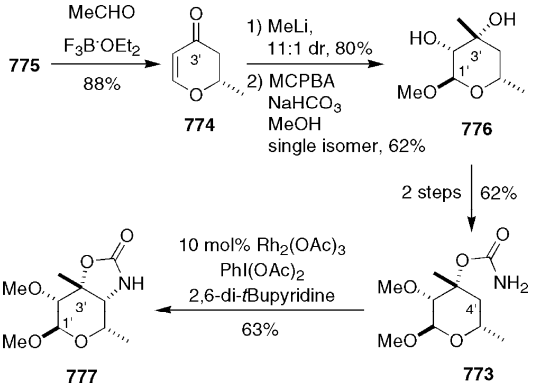
2.5.2. Trost Synthesis of Callipeltoside A[67]

Trost completed the total synthesis of natural callipeltoside A (**735**),[67a] its C20−C21 diastereomer **767**, and the C21 *des*-chloro congener **768**,[67b] which served to establish unequivocally the relative and absolute stereochemistry. The proposed absolute configuration was based initially by analogy with auriside B (**737**), which has its sugar unit also derived from L-rhamnose (**741**). These syntheses are based on the plan illustrated in Scheme 118 in which the full side chain was appended to the aglycon **769** via a HWE olefination using the phosphonate **770**. Due to the moderate *E*:*Z* geometric selectivity experienced in this reaction, a second approach using olefin metathesis to set up the C14−C17 diene portion was subsequently developed. The synthesis of the aglycon showcases a Trost Pd-catalyzed asymmetric allylic alkylation to set up the isolated C13 stereocenter and an alkyne-alkene coupling reaction, as also developed by the Trost group, to install the *E*-trisubstituted double bond.

The callipeltose derivative **771** was initially also prepared from L-rhamnose according to the Giuliano method.[65] A concise and highly diastereoselective racemic synthesis of this sugar moiety utilizing a rhodium-catalyzed nitrogen insertion, as developed by Du Bois, into the C4′ C−H bond was later devised.[67c] As shown in Scheme 119, a boron-trifluoride-promoted hetero-Diels−Alder reaction between Danishefsky diene **775** and acetaldehyde provided the dihydropyranone **774**, which served as the platform for directing the subsequent methyllithium addition (11:1 dr) and epoxidation/methanolysis to obtain diol **776**. The key nitrogen insertion of the derived carbamate **773** was then performed using 10 mol % of rhodium acetate to give callipeltose methyl ether **777**.

The chlorocyclopropyl subunit **770** was derived from dimenthyl succinate **772**, as outlined in Scheme 120. Thus, bisalkylation using the lithium dianion of **772** provided the cyclopropane **778** (99:1 dr after recrystallization). The chloride was then introduced by a Barton−Crich−Motherwell decarboxylation of

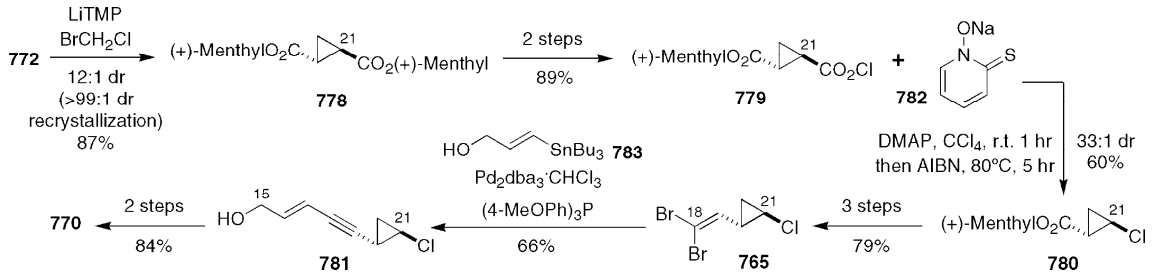
Scheme 119. Trost Synthesis of Methyl Callipeltose



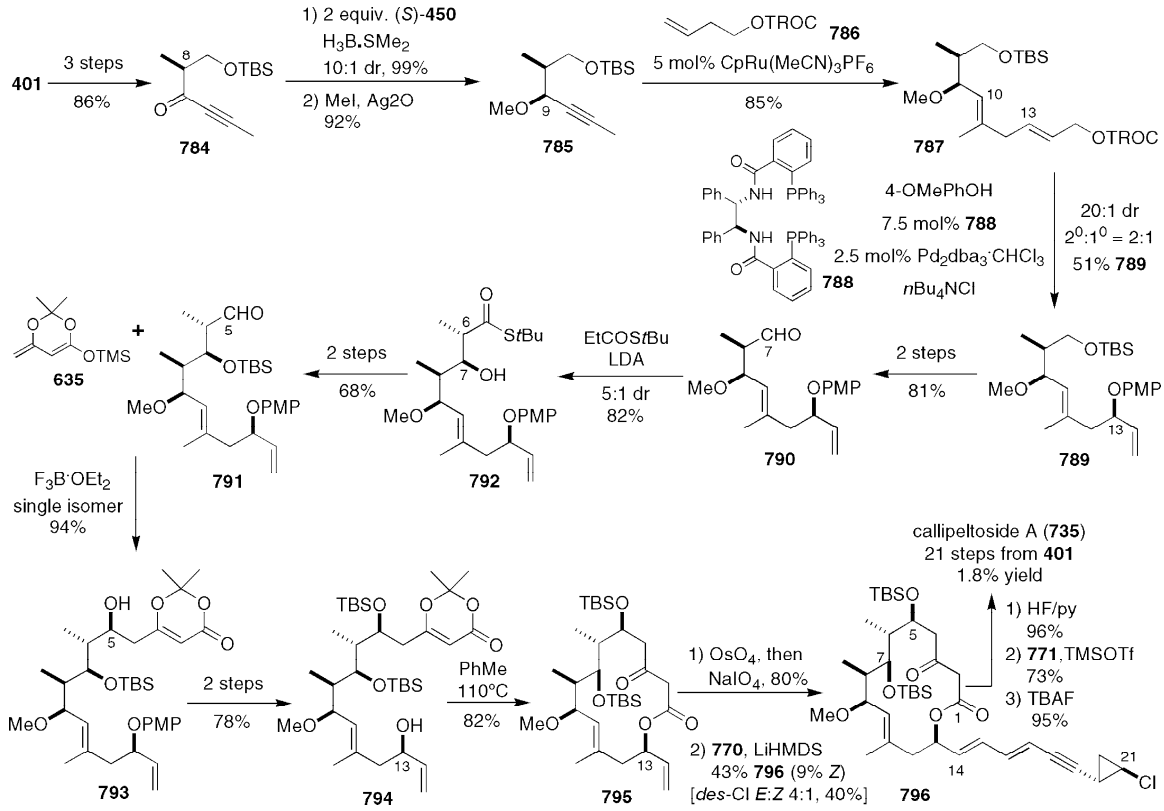
the derived acid chloride **779**. The optimum conditions were to generate the Barton ester and perform the radical reaction in one pot to give chlorocyclopropane **780** (33:1 dr). After derivatization to give the alkenyl dibromide **765** via a Corey−Fuchs reaction, a Suzuki coupling under the Shen conditions was then used to generate the alkyne **781**, from which phosphonate **770** was obtained. Phosphonate *ent*-**770** was obtained in an identical manner from *ent*-**772**.

The aglycon was constructed by diastereoselective reactions performed on Roche ester **401** (Scheme 121). The propargyl ketone **784** was subjected to a CBS reduction to provide **785** after methylation. However, it required 2 equiv of the oxazaborolidine reagent (*S*)-**450** to obtain a high diastereomeric ratio (10:1 dr). The alkyne was then coupled with alkene **786** in a ruthenium-catalyzed Alder−ene-type reaction to install the trisubstituted alkene in **787** with complete regioselectivity. This set the stage for the key palladium-catalyzed allylic alkylation using 4-methoxyphenol as the nucleophile to create the C13 stereocenter. Using the C_2-symmetric ligand **788**, although a 20:1 diastereoselectivity was obtained, this transformation proceeded with only moderate regioselectivity (2:1 secondary vs primary alcohol). The allylic PMP ether **789** was obtained and then converted into aldehyde **790** for an aldol reaction with the lithium enolate of *tert*-butylthiopropionate, which established the C6/C7 *anti*-relationship (5:1 dr). Next, a Mukaiyama aldol reaction between the aldehyde **791** derived from **792** and silyl dienolate **635** provided the Felkin−Anh product **793** exclusively.

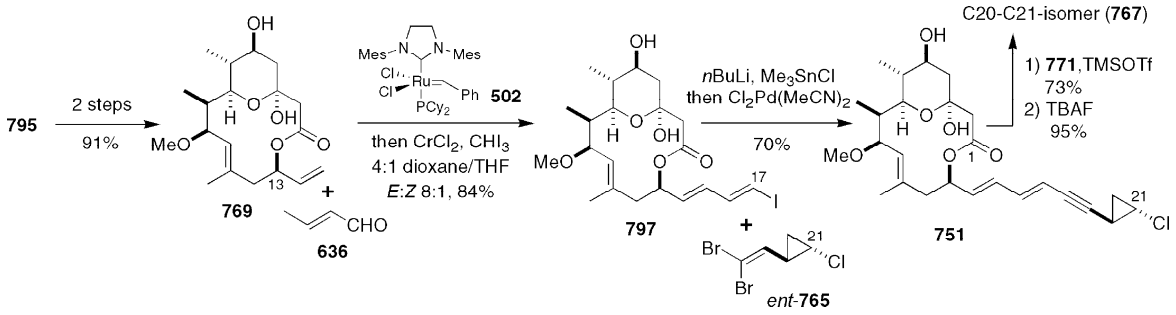
Scheme 120. Trost Synthesis of Callipeltoside Side Chain



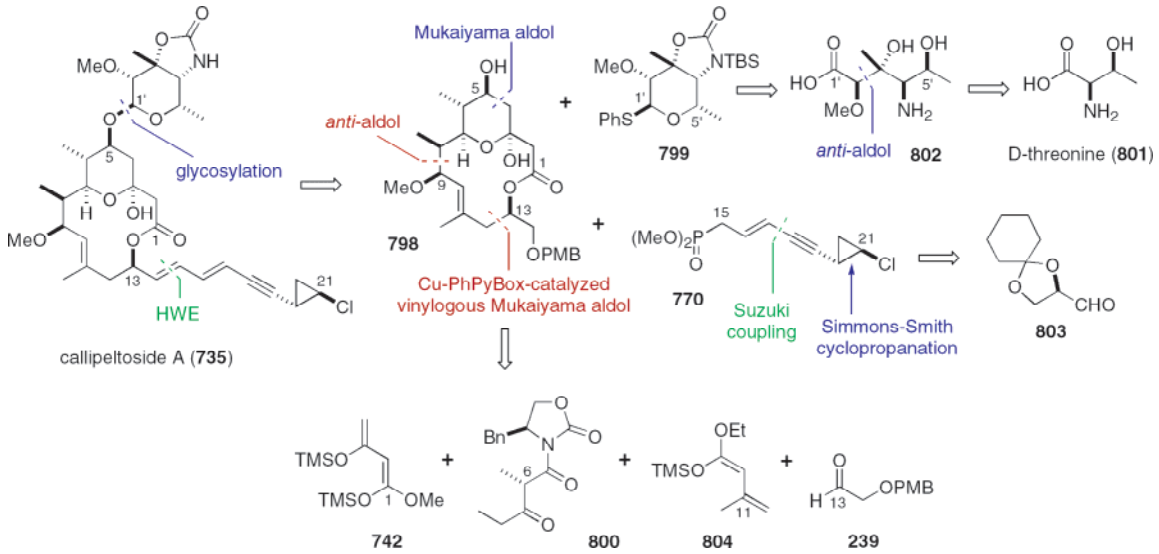
Scheme 121. Trost Total Synthesis of Callipeltoside A



Scheme 122. Trost Synthesis of a C20−C21-Isomer of Callipeltoside



Scheme 123. Evans Strategy for the Total Synthesis of Callipeltoside A



The crucial cyclization of seco-acid derivative **794** involved thermal cleavage of the acetonide and trapping of the intermediate ketene by C13−OH, which generated the requisite 14-membered macrolactone **795**. After oxidative cleavage of the C14 alkene to the aldehyde a HWE reaction with phosphonate **770** proceeded with 4:1 *E*/*Z*-selectivity, as also found with *ent*-**770** and the corresponding *des*-chloro series. Following deprotection at C5 and C7 and concomitant hemiacetalization and then glycosylation using trichloroacetimidate **771** to provide a single anomer, a final *N*-TBS cleavage provided callipeltoside A in 1.8% overall yield over the 21-step longest linear sequence from Roche ester **401** (about 37 total steps; about 3 steps per stereocenter).

An alternative approach to attach the side chain employed olefin metathesis using Grubbs second-generation catalyst **502** and Takai olefination to give the vinyl iodide **797** (cf. macrolactone **738** in Paterson synthesis, Scheme 117) with an improved 8:1 *E*/*Z*-selectivity (Scheme 122). This was then followed by a Stille coupling with the alkynylstannane, formed from alkenyl dibromide *ent*-**765** under ligand-free conditions, to provide the algycon **751**.

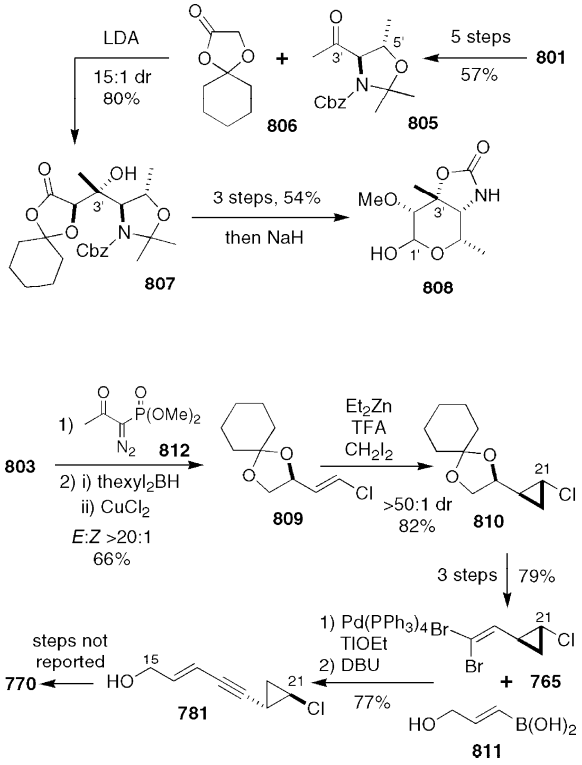
2.5.3. Evans Synthesis of Callipeltoside A[68]

An overview of the Evans strategy for the synthesis of callipeltoside A (**735**) is presented in Scheme 123. The aglycon **798** was prepared first, followed by introduction of the callipeltose sugar using the thioglycoside **799** and a HWE reaction with phosphonate **770** to attach the chlorocyclopropane-containing side chain. The aglycon was constructed in a fashion similar to Paterson's synthesis (Scheme 114), wherein the same three aldol bond disconnections at C4−C5, C8−C9, and C12−C13 were adopted; however, the oxazolidinone-based ethyl ketone **800** was used instead for the crucial C8−C9 *anti*-aldol reaction.

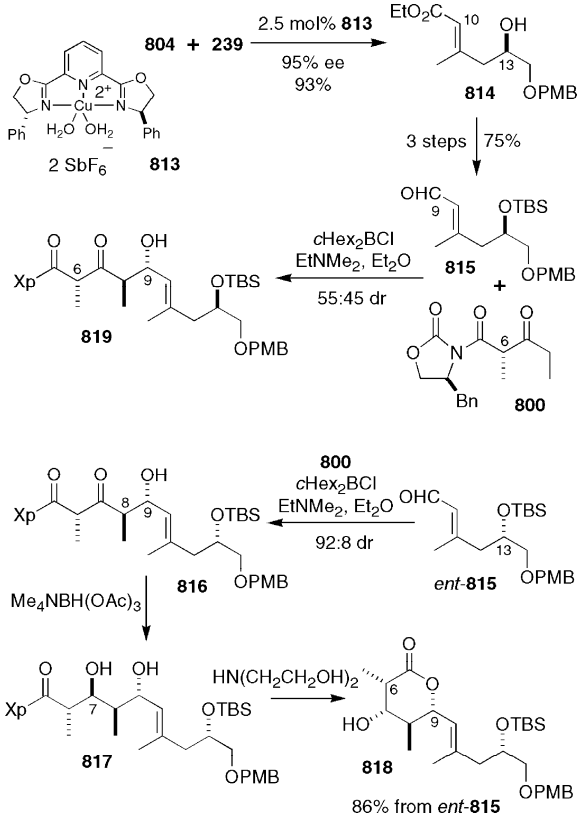
Disconnection of the C2′−C3′ bond in the open-chain form of callipeltose revealed D-threonine (**801**) as a suitable chiral building block, which was converted into the methyl ketone **805** (Scheme 124). Addition of the lithium enolate derived from glycolate **806** to this ketone provided the *anti*-aldol isomer **807** (15:1 dr), creating the quaternary C3′ stereocenter, which was then converted into lactol **808**. The synthesis of the side chain phosphonate **770** made use of a substrate-directed Simmons−Smith cyclopropanation, performed under Shi conditions, on the vinyl chloride **809**, obtained from aldehyde **803**, giving cyclopropane **810** (>50:1 dr). After conversion into the dibromide **765** via the Corey−Fuchs protocol, a Suzuki coupling with boronic acid **811** using Roush-type conditions followed by elimination provided the enyne **781**.

The synthesis of the callipeltoside aglycon began with a Mukaiyama aldol reaction between aldehyde **239** and silyl dienolate **804**, promoted by the Evans Cu−PhPyBox catalyst **813**, installing the C13 stereocenter (95% ee) and *E*-trisubstituted alkene in adduct **814** (Scheme 125). After transformation into aldehyde **815**, an *anti*-aldol addition using the (*E*)-

Scheme 124. Evans Synthesis of Callipeltose and Callipeltoside Side Chain



Scheme 125. Evans Synthesis of the C5−C14 Segment of Callipeltoside



boron enolate derived from the oxazolidinone-based ketone **800** proved surprisingly unselective due to it being a mismatched situation (55:45 dr). However, by switching to the enantiomeric aldehyde *ent*-**815** the corresponding *anti*-adduct **816** was obtained satisfactorily (92:8 dr). In contrast, in a similar *anti*-aldol reaction using ethyl ketone **743** in the Paterson synthesis of callipeltoside A (**743** + **754** → **755**, Scheme 116), the remote C13 stereocenter appeared to exert little diastereofacial bias. In the Evans route, the stereochemical outcome of this aldol reaction necessitated adoption of a macrolactonization protocol that involved inversion of the C13 configuration. Following an Evans−Saksena reduction to install the C7 secondary alcohol, the 1,3-*anti* diol **817** was converted into the *δ*-lactone **818** and then into aldehyde **820** (Scheme 126), ready for a Mukaiyama aldol reaction employing bis-siloxydiene **742**. As in the related aldol reaction used in the Paterson synthesis (**742** + **757** → **758**, Scheme 116), this chain extension established the C5 stereocenter with excellent Felkin−Anh selectivity (>95:5 dr). The pyran ring was subsequently formed after C5−OH TBS protection and removal of the acetonide to give the fully protected seco-acid **821**.

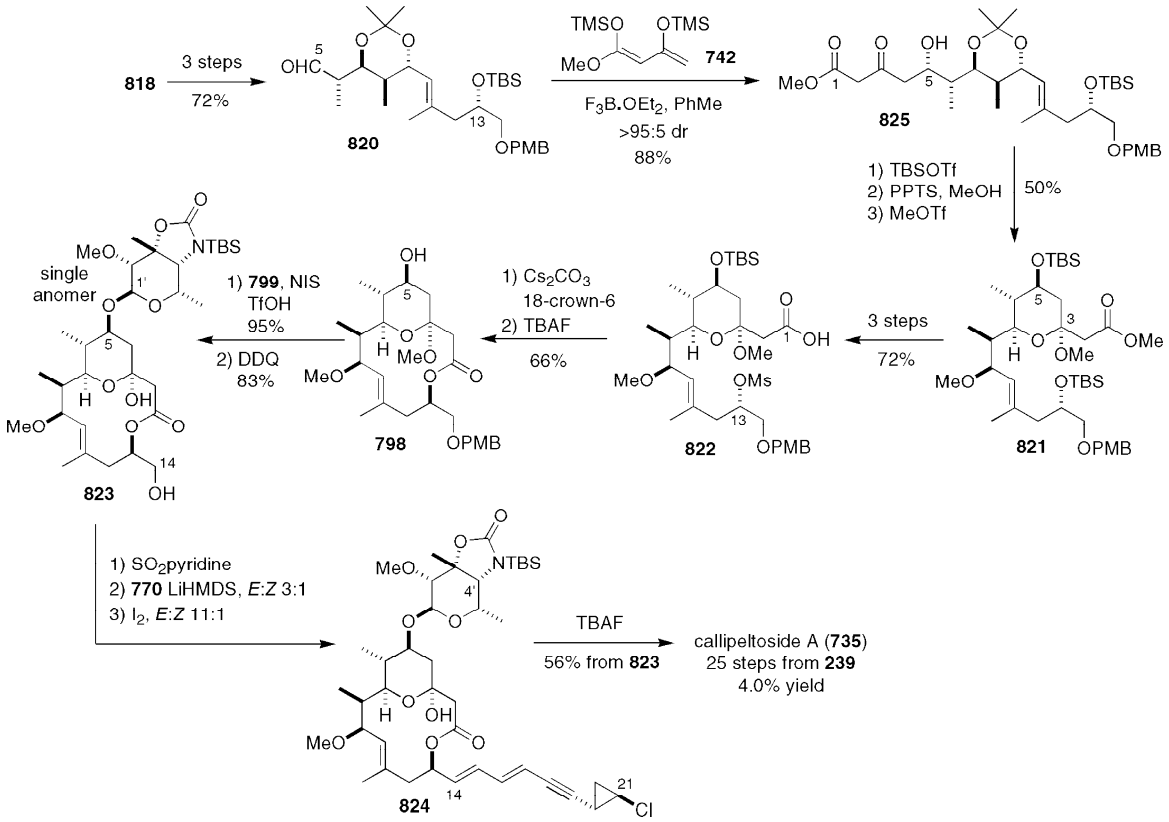
Attempts to perform a Mitsunobu-type macrolactonization were unsuccessful. This impasse was circumvented by converting **821** into the C13 mesylate **822** followed by nucleophilic displacement by a C1 cerium carboxylate, leading to macrolactone **798**. In a reversed sequence to that used by Trost (Scheme 121), completion of the synthesis entailed the NIS-promoted glycosylation at the C5−OH using thioglycoside **799** to give a single anomer **823**. The chlorocyclopropyl side chain was then attached via a HWE olefination, which in accordance with Trost's results, provided moderate *E*:*Z* selectivity. The stereoselectivity could be improved to 11:1 by an I_2-catalyzed isomerization to produce the penultimate intermediate **824**, which delivered callipeltoside A after *N*-TBS deprotection in 4.0% overall yield over the 25 linear steps from aldehyde **239** (around 42 total steps; about 3 steps per stereocenter).

2.5.4. Panek Synthesis of Callipeltoside A[69]

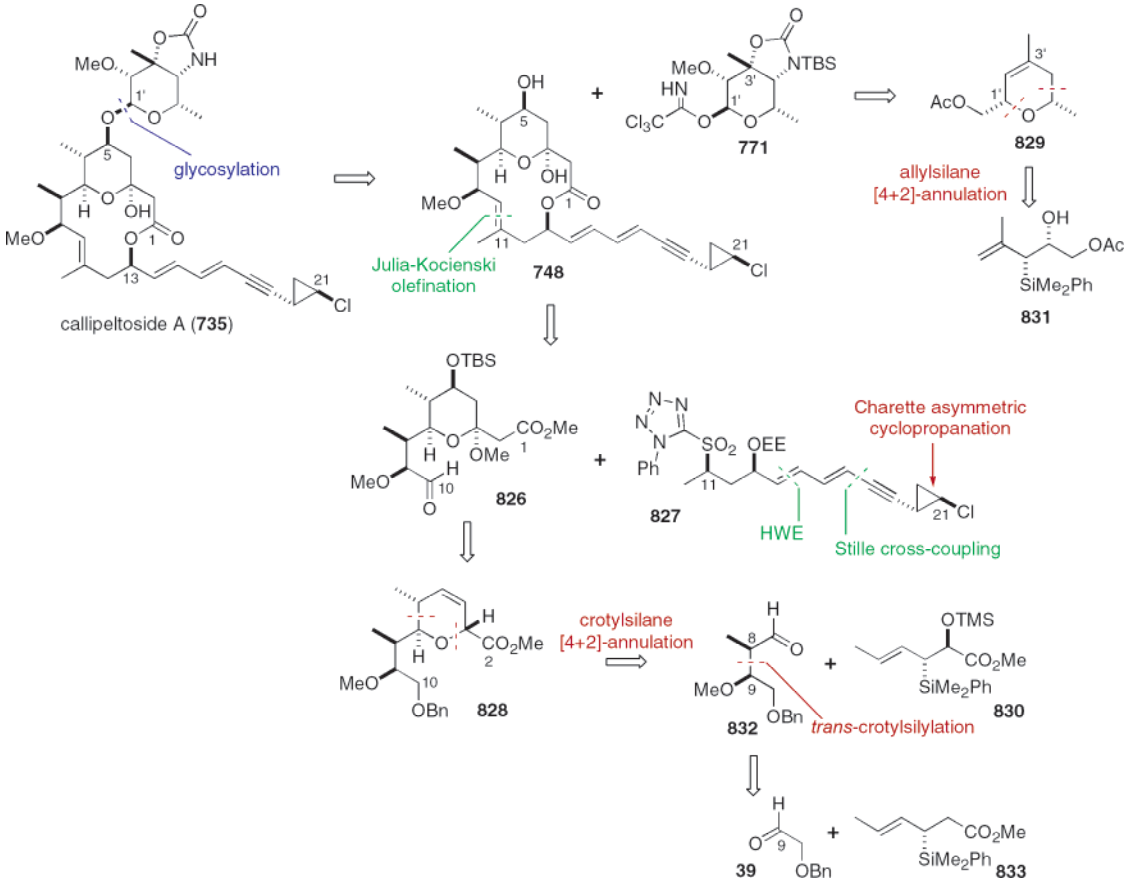
Panek's strategy for the synthesis of callipeltoside A (**735**) relied on a challenging Julia−Kocienski olefination performed between the C1−C10 aldehyde **826** and the C11−C21 sulfone **827**, which contained the full chlorocyclopropane side chain, to install the (*E*)-trisubstituted double bond during the assembly of the algycon **748** (Scheme 127). This synthesis also showcased allylsilane [4 + 2]-annulations, as developed by Panek, for the construction of the two highly substituted tetrahydropyran units. Aldehyde **826** and callipeltose derivative **771** were obtained from elaboration of dihydropyrans **828** and **829**, which were in turn synthesized using allylsilane reagents **830** and **831**, respectively. The C8/C9 *anti* relationship, as in aldehyde component **832**, was established by a chelation-controlled crotylsilylation using silane **833**.

The synthesis of the sulfone **827** (Scheme 128) began with a Charette asymmetric cyclopropanation on the vinyl chloride **762** using the chiral borolane **763**, as used previously in the Paterson synthesis of callipeltoside (Scheme 117), to obtain the chlorocyclopropane **764** (97% ee). After conversion into the vinyl dibromide **765**, Shen conditions for Stille cou-

Scheme 126. Evans Total Synthesis of Callipeltoside A

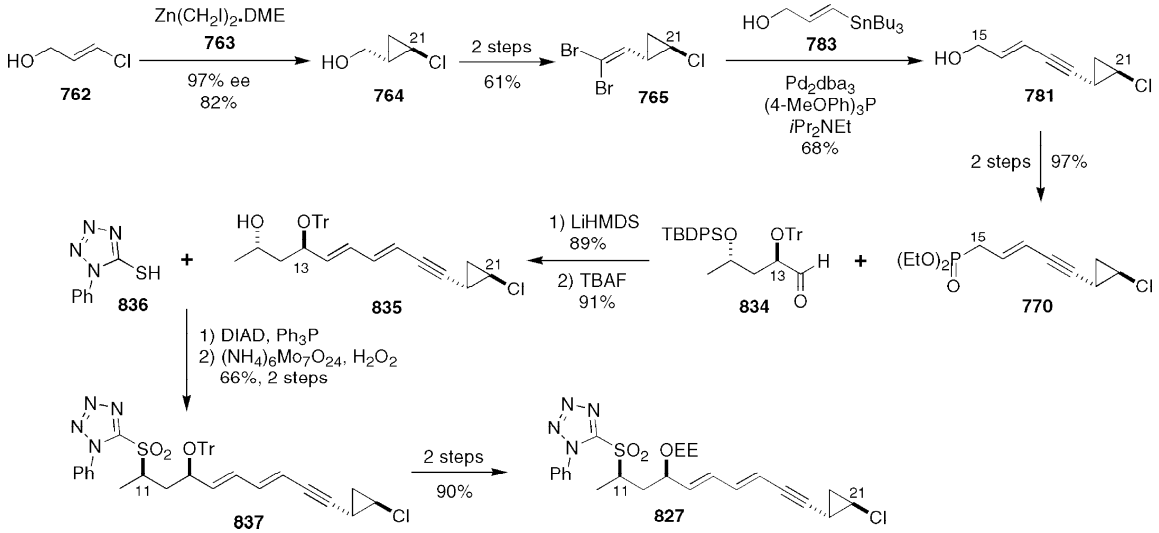


Scheme 127. Panek Strategy for the Total Synthesis of Callipeltoside A

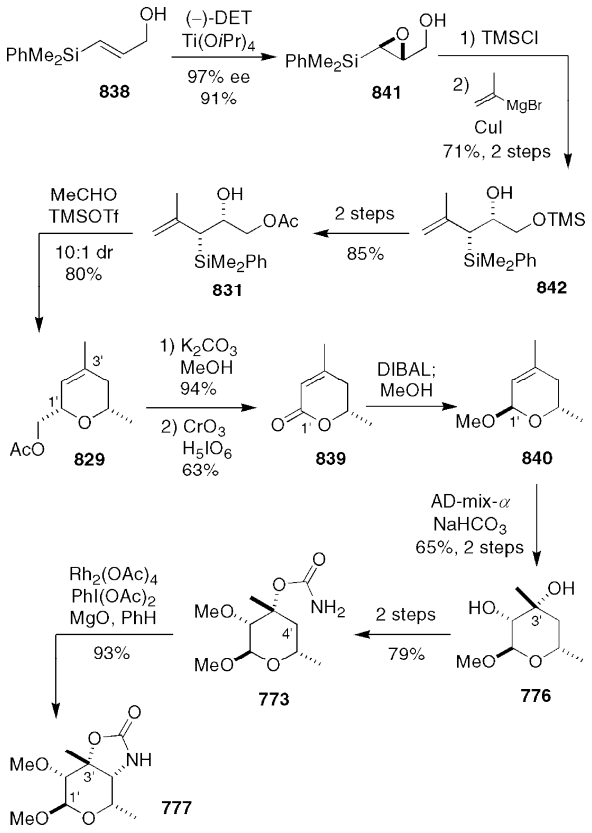


pling/elimination, as in the Trost synthesis (Scheme 120), were used to introduce the enyne functionality to give alcohol **781**. The resulting phosphonate **770** was then HWE coupled with aldehyde **834** to provide alcohol **835** after deprotection. The phenyltetrazoyl sulfone substituent at C11 was incorporated via a

Scheme 128. Panek Synthesis of the C11−C21 Side Chain of Callipeltoside



Scheme 129. Panek Synthesis of Methyl Callipeltose



Mitsunobu/oxidation sequence to complete the synthesis of **827**.

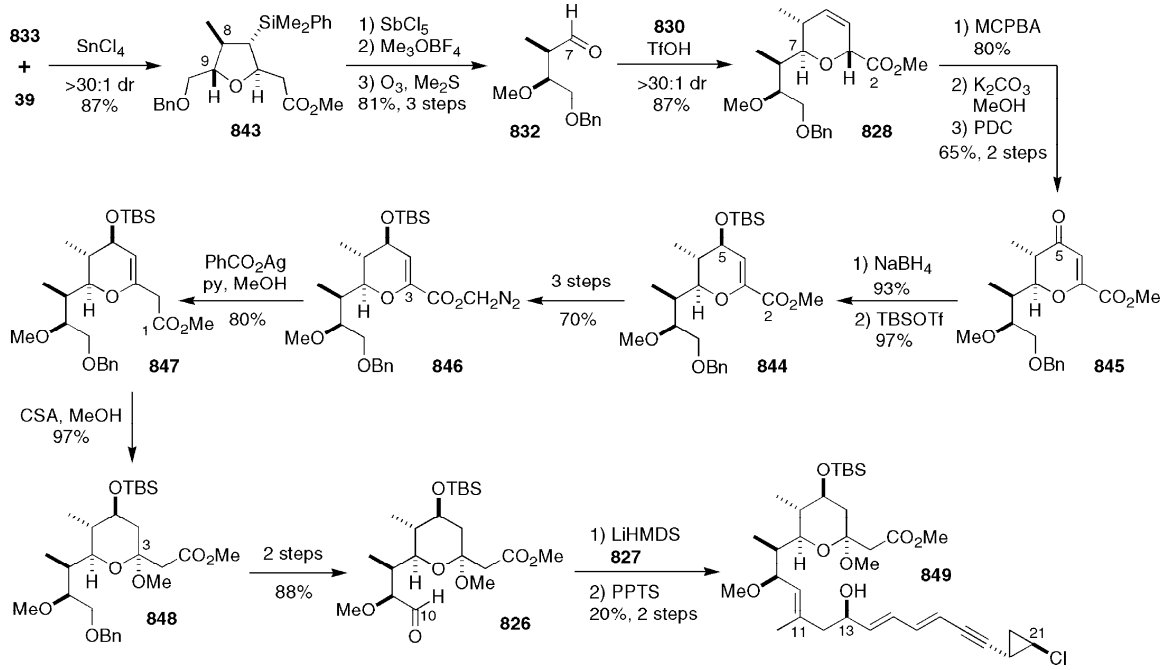
The synthesis of methyl-L-callipeltose **777** is shown in Scheme 129. The silane reagent **831** was obtained from allylic alcohol **838** through a sequence involving Sharpless epoxidation and regioselective epoxide ring opening. The Lewis-acid-promoted [4 + 2] annulation of **831** with acetaldehyde led to the formation of dihydropyran **829** (10:1 dr). After hydrolysis, the resulting primary alcohol underwent oxidative bond cleavage to give the dihydropyrone **839**. The use of a Sharpless dihydroxylation to generate the C2′ and C3′ oxygenation necessitated the use of the more electron-rich methyl acetal **840**, giving tetrahydropyran **776**. Similar to the Trost synthesis, the remaining C4′ stereocenter was then set up by a Du Bois Rh-catalyzed nitrogen insertion reaction of the carbamate **773** to give methyl callipeltose **777**.

The synthesis of the central C1−C10 aldehyde **826** started with the condensation between silane **833** and aldehyde **39** to give *trans*-2,5-disubstituted tetrahydrofuran **843** (>30:1 dr) (Scheme 130). A Lewis-acid-promoted β-elimination to give the intermediate homoallylic alcohol was followed by ozonolysis to produce aldehyde **832**, having the requisite C8/C9 *anti* stereochemistry. The acid-promoted annulation of **832** with silane **830** resulted in formation of the *trans*-2,6-disubstituted dihydropyran **828** (>30:1 dr). Due to the low stereoselectivity observed in epoxidation of **828**, an indirect epoxidation/elimination/oxidation/hydride reduction sequence was used to configure the C5 hydroxyl stereocenter. This provided pyran **844** via the sodium borohydride reduction of enone **845**. One-carbon homologation was achieved by an Arndt−Eistert reaction of the diazo derivative **846** to provide ester **847**, which then underwent acid-catalyzed methanolysis to give the C3 methyl acetal **848**. The crucial coupling between the derived aldehyde **826** and the sulfone **827** proceeded to provide the seco-acid derivative **849**, albeit in 20% yield after C13 deprotection. The subsequent macrolactonization of the seco-acid under Yamaguchi conditions (Scheme 131) provided a 1:1 mixture of the desired macrolactone **766** and its dihydropyran derivative **850**. Each of these was converted into the C3 acetal **748**, which after Schmidt-type glycosylation with trichloroacetimidate **771** and *N*-deprotection delivered callipeltoside A[70] in 0.84% overall yield over the 25-step linear sequence from aldehyde **39** (about 52 total steps; about 4 steps per stereocenter).

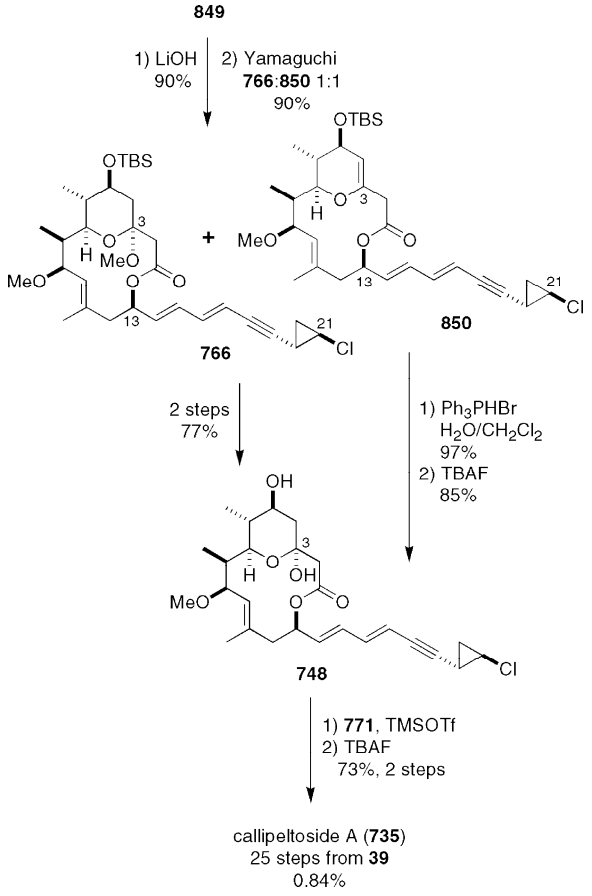
2.6. Miyakolide

In 1992, miyakolide was isolated in 0.0012% yield from a marine sponge of the genus *Polyfibrospongia*, collected off the island of Miyako, by Higa and coworkers.[71] Its structure and relative stereochemistry

Scheme 130. Panek Synthesis of a C1−C21 Seco-Acid Derivative of Callipeltoside



Scheme 131. Panek Total Synthesis of Callipeltoside A



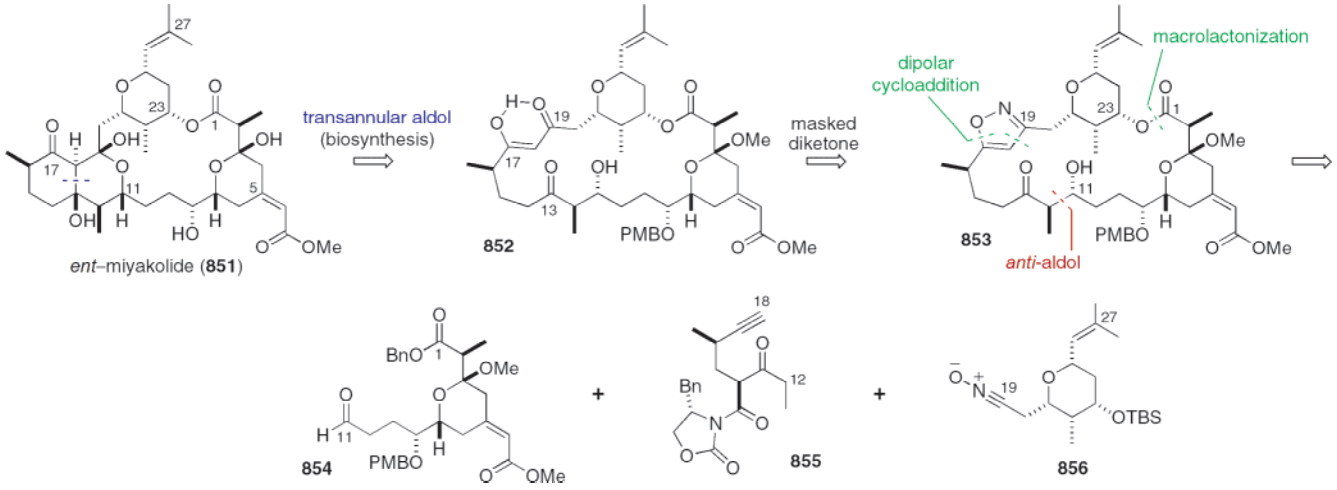
were determined by X-ray crystallography and NMR studies. The successful total synthesis of the unnatural (+)-enantiomer **851** (Scheme 132) by the Evans group,[72] as described below, enabled assignment of the absolute configuration of this unusual macrolide.[73] In contrast to the structurally similar bryostatins,[10c] which are potent cytotoxins, preliminary biological studies demonstrated that miyakolide has only weak in-vitro and in-vivo anticancer activities. To date, other possible biological functions of miyakolide have not been explored.

2.6.1. Evans Synthesis of ent-Miyakolide[72]

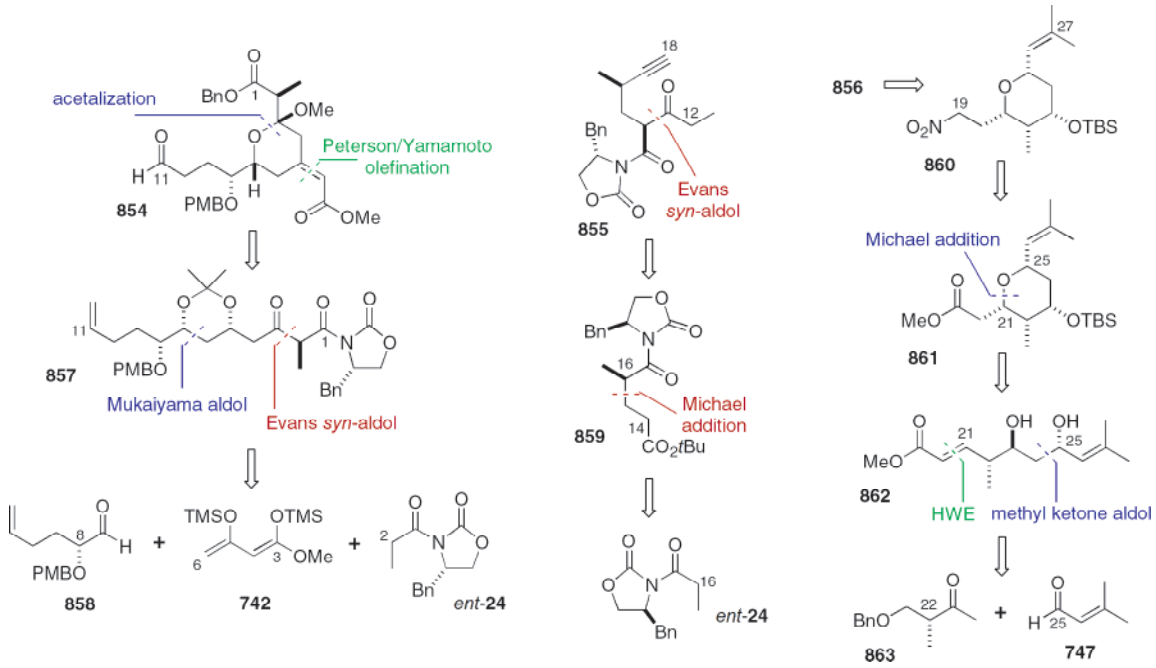
The Evans total synthesis of (+)-miyakolide (**851**) is based on the biosynthetic proposal that it is derived from a macrocyclic β-diketone, e.g., **852** (Scheme 132), in which the C11−C19 oxydecalin subunit is assembled by a transannular aldol reaction and hemiacetalization, where stereoinduction at C13 and C18 was anticipated to result from the conformational preference of the macrocyclic precursor. The C11 hydroxyl group was left unprotected, such that the aldol adduct would undergo spontaneous hemiacetalization, while the β-diketone was masked as an isoxazole in the precursor **853**. This advanced intermediate was assembled from three key segments, C1−C11 aldehyde **854**, C12−C18 ethyl ketone **855,** and C19−C27 nitrile oxide **856**. Notably, the ordering of these fragment coupling steps, i.e., [3 + 2] dipolar cycloaddition, C11−C12 *anti*-aldol reaction, and esterification/macrolactonization, could be varied, thus offering considerable flexibility. An (oxazolidinyl)-carbonyl moiety was incorporated into ketone **855** as a control element for regioselective enolization as well as ensuring the correct diastereoselectivity in the *anti*-aldol coupling step.

The tetrahydropyran-containing aldehyde **854** was constructed from the linear precursor **857** (Scheme 133), which was assembled from the three segments, **858**, **742,** and *ent*-**24** via two aldol couplings. Thus, a $TiCl_2(OiPr_2)$-promoted Mukaiyama addition of bissilyloxydiene **742** to the glycidol-derived aldehyde **858** (Scheme 134) provided the 1,2-*syn*-adduct **864** (95:5 dr). The C5 ketone group was carried forward as a protected hydroxyl group in the form of a 1,3-acetonide for the subsequent Evans *syn*-aldol coupling of aldehyde **865** with ethyl ketone *ent*-**24**. The

Scheme 132. Evans Strategy for the Total Synthesis of Miyakolide



Scheme 133. Evans Strategy for the Synthesis of the C1−C11, C12−C18, and C19−C27 Segments of Miyakolide

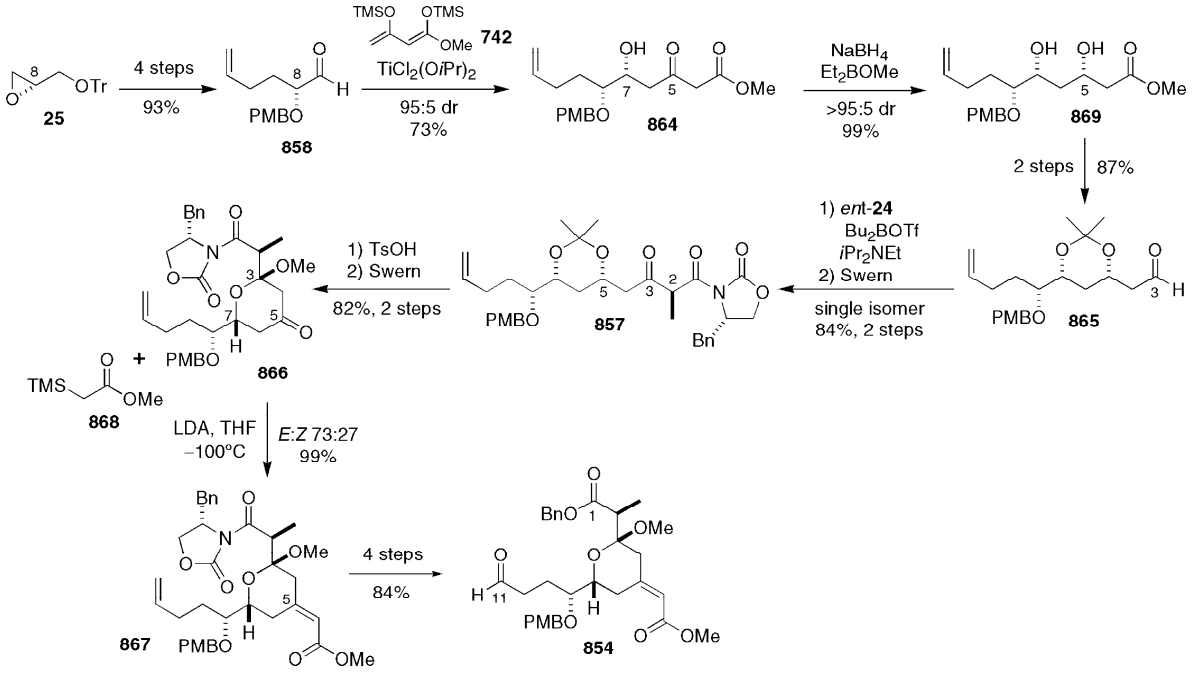


resulting C3 hydroxyl group was then oxidized to give the β-keto imide **857**. The chiral auxiliary was retained to prevent epimerization of the C2 methyl-bearing stereocenter in the subsequent steps. Acid-induced deprotection/cyclization and Swern oxidation of the C5−OH produced the methyl acetal **866**. The exocyclic (*E*)-enoate was then introduced in **867** with a 73:27 isomer ratio via a Peterson−Yamamoto olefination of ketone **866** using TMS−acetate **868**. The desired isomer was then elaborated in four further steps to give the C1−C11 aldehyde **854**.

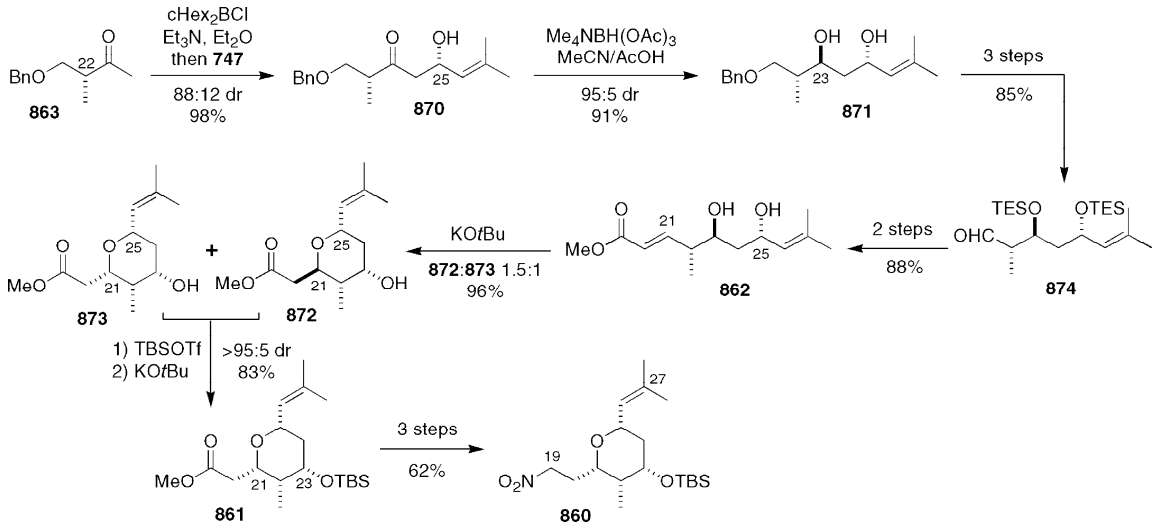
As shown in Scheme 133, the 2,6-*cis*-tetrahydropyran within the intended nitrile oxide **856** was constructed by an intramolecular hetero-Michael addition of the linear precursor **862**, derived from a substrate-controlled aldol reaction of methyl ketone **863** exploiting 1,4-stereoinduction. Following the Paterson protocol, enolization of **863** to generate its dicyclohexylboron enolate and addition to enal **747** delivered the β-hydroxy ketone **870** (88:12 dr) (Scheme 135). The C25 hydroxyl stereocenter then directed the reduction step to provide the 1,3-*anti* diol **871**. Following conversion into the enoate **862**, a KO*t*Bu-promoted hetero-Michael addition then provided a 1.5:1 mixture of tetrahydropyrans **872** and **873**. Resubmission of the derived C23 TBS ethers to the basic cyclization conditions allowed equilibration to favor the *cis*-isomer **861** (>95:5 dr). The methyl ester was then converted into the nitroalkane **860**, which served as a precursor to nitrile oxide **856**.

The synthesis of the C12−C18 ethyl ketone **855** began with a Michael addition of the titanium enolate of chiral imide *ent*-**24** to *tert*-butyl acrylate (Scheme 136), which installed the C16 methyl-bearing stereocenter (>95:5 dr). The product **859** was then transformed into the alkyne via the vinyl dibromide **875** by the Corey−Fuchs protocol, and then the oxazolidinone auxiliary was reintroduced to give **876**. The ethyl ketone **855** was obtained by an Evan *syn*-aldol reaction with propionaldehyde and oxidation. Three fragment coupling strategies were evaluated by the Evans group: (i) aldol → cycloaddition → macrolac-

Scheme 134. Evans Synthesis of the C1−C11 Segment of Miyakolide

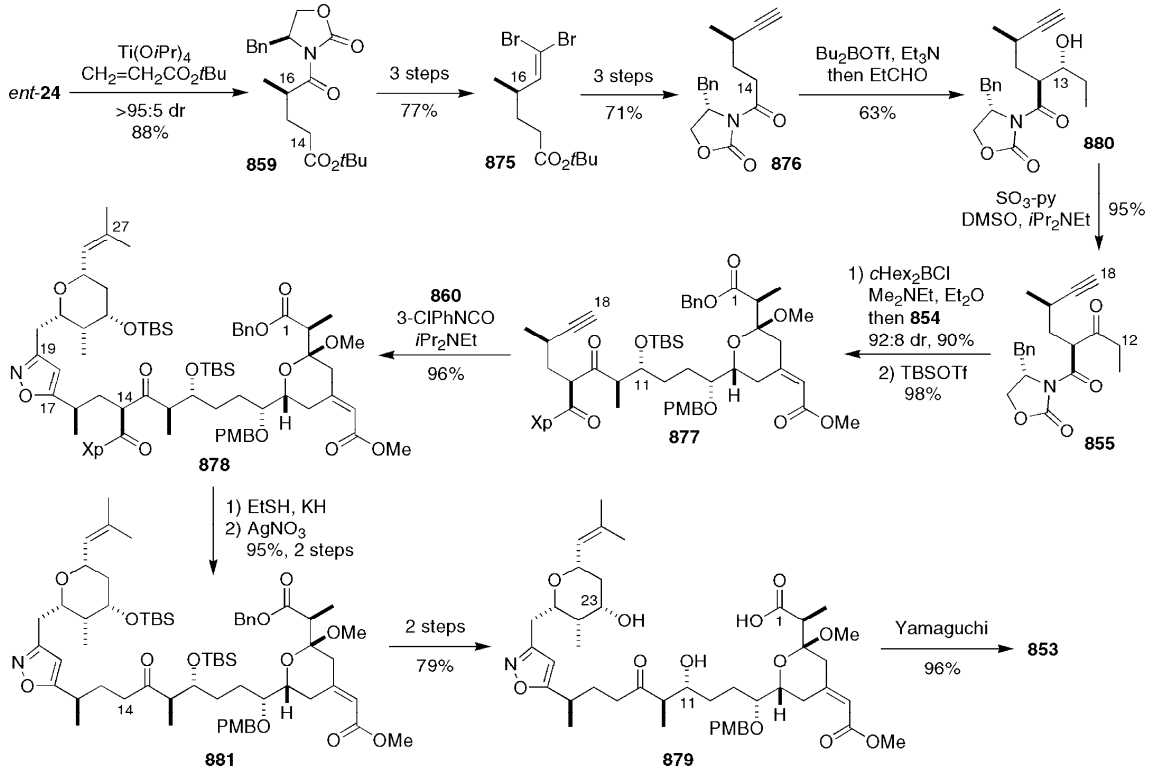


Scheme 135. Evans Synthesis of the C19−C27 Segment of Miyakolide

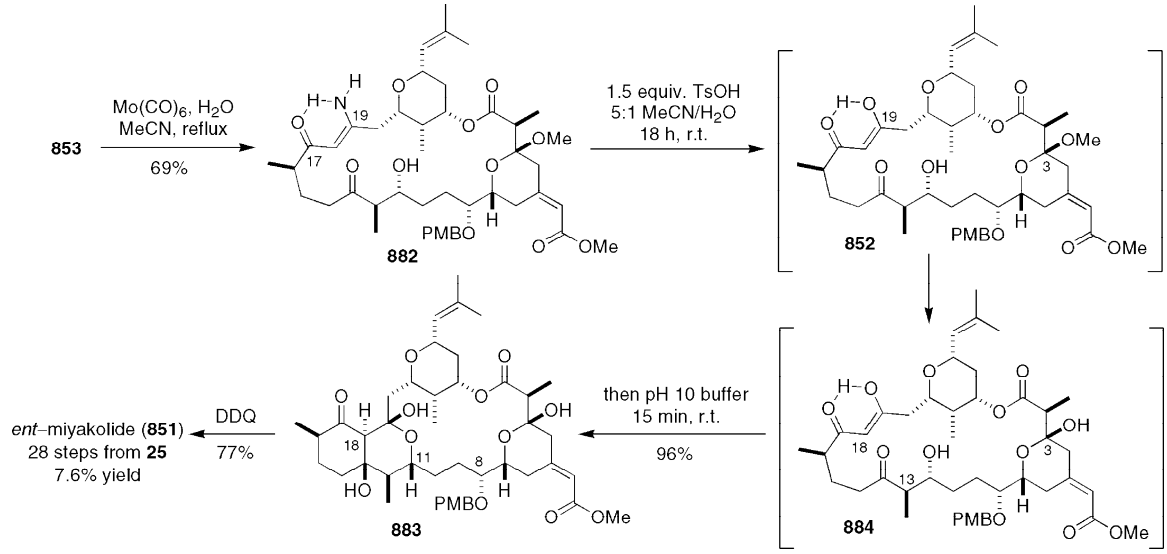


tonization (**854** + **855** + **856**), (ii) cycloaddition → aldol → macrolactonization (**855** + **856** + **854**), and (iii) aldol → esterification → cycloaddition (**854** + **855** + **856**). The most efficient sequence found was to first perform the aldol coupling between ethyl ketone **855** and aldehyde **854** (Scheme 136). Enolization of **855** to generate its (*E*)-dicyclohexylboron enolate, followed by addition to aldehyde **854**, produced the *anti*-aldol adduct (92:8 dr), which was TBS protected to give **877**. Coupling of the nitrile oxide, obtained by in-situ dehydration of the nitroalkene **860**, to the alkyne **877** generated the isoxazole **878**. At this stage the auxiliary at C14 was removed via the Ag(I)-promoted hydrolysis/decarbonylation of the derived thiol ester. After transformation into the seco-acid **879**, regioselective macrolactonization under Yamaguchi conditions then gave the 24-membered macrolactone **853**, without forming any 12-membered ring product. Reduction of the isoxazole N−O bond in **853** to the enaminone **882** (Scheme 137) was best achieved by the Nitta procedure using $Mo(CO)_6$. This enaminone, however, did not directly undergo the perceived intramolecular cyclization. However, submission of **882** to acidic hydrolytic conditions, followed by exposure to pH 10 buffer, delivered the C8-protected miyakolide **883**, resulting from three consecutive transformations, whereby the enamine was first hydrolyzed selectively to give the ketone **852**, followed by hydrolysis of the C3 methyl acetal to **884**, and then transannular aldol cyclization. Cleavage of the PMB ether provided (+)-miyakolide (**851**) in 7.6% overall yield over the 28-step linear sequence from epoxide **25** (50 total steps; about 4 steps per stereocenter). This was found to be spectroscopically identical to the natural material but had the opposite sign of specific rotation, thus allowing assignment of the absolute configuration. With this synthetic route validated, it should be straightforward to adapt it to give (−)-miyakolide A itself.

Scheme 136. Evans Synthesis of a Macrolactone Derivative of Miyakolide



Scheme 137. Evans Total Synthesis of *ent*-Miyakolide



3. Conclusions and Outlook

As demonstrated in the foregoing illustrative examples, various strategies and methodologies have been applied to achieve the total synthesis of these biologically important marine macrolides. Considerable advances have been made since we last reviewed the topic in 1995.[2c] The successful total syntheses of spongistatin 1/altohyrtin A (**5**), spongistatin 2/altohyrtin C (**7**), dictyostatin (**452**), peluroside A (**494**), leucascandrolide A (**549**), callipeltoside A (**735**), and *ent*-miyakolide (**851**) highlight the state of the art of contemporary organic synthesis and the level of progress made in constructing these challenging molecular architectures, particularly in correctly installing the stereocenters by exploiting substrate and reagent control as well as handling a multitude of delicately balanced chemoselectivity issues in such complex systems. These completed syntheses also served to confirm or establish the absolute stereostructures of these different classes of marine macrolides. Progress toward realizing efficient and scalable synthetic pathways to provide workable routes to several of these rare compounds, and their analogues, for biological studies and preclinical evaluation has been made. In this regard, a remarkable achievement is Heathcock's synthesis of 250 mg of spongistation 2/altohyrtin C (**7**).[22a] At the time of writing, the Smith group is also making considerable headway toward synthesizing significant quantities of spongistatin 1/altohyrtin A (**5**).[74]

These complex natural product targets continue to provide a challenging platform for showcasing innovative synthetic strategies and methodologies. Strategies that enable minimum protection and oxidation-state adjustment are especially desirable. Although significant progress has been made, many challenges still remain and improvements are still required in several areas: (i) developing even more efficient (catalytic) asymmetric reactions for setting up multiple stereocenters in acyclic situations and for construction of ring systems (e.g., tetrahydropyrans); (ii) devising new general strategies and methodologies for efficient coupling of highly functionalized, advanced segments; (iii) developing highly stereoselective routes to (*E*) and (*Z*), di- and trisubstituted alkenes; (iv) further minimizing the use of functional group protection and deprotection steps as well as oxidation-state adjustments; (v) achieving efficient macrocyclization reactions to provide the large ring sizes (e.g., the 42-membered macrolactone ring of spongistatins/altohyrtins) commonly associated with this class of polyketides.

The important biological activities, e.g., of the microtubule-interacting spongistatins/altohyrtins, dictyostatin and peluroside A, coupled with the supply issue and the enticing structural complexity of these marine macrolides demand that organic chemists keep pushing back the limits of what they can synthesize in the laboratory and how well they can do it. Even more practical and scalable routes to these and other highly bioactive marine natural products are certainly highly desirable, particularly if sufficient synthetic material is to be made available for clinical evaluation in cases where the natural supply is inadequate, as in the case of discodermolide.[7−9]

4. Acknowledgments

I.P. thanks the EPSRC and Merck for support. We thank Professor Ivan Rayment (University of Wisconsin at Madison) for providing the original picture file of the G-actin-ulapualide A structure (Figure 2) and Dr. Mark J. Coster (University of Sydney) for providing the cover artwork.

5. Abbreviations

acac	acetylacetonate
AIBN	azobisisobutylronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1′-bi(2-naphthol)
Boc	*tert*-butoxycarbonyl
BOC-ON	2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile
BOM	benzyloxymethyl
(b)rsm	(based on) recovered starting material
CAN	cerium ammonium nitrate
CBS	Corey−Bakshi−Shibata
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
dba	*trans,trans*-dibenzylideneacetone
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
DCB	2,4-dichlorobenzoyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
$(DHDQ)_2PYR$	hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-*N,N*-(dimethylamino)pyridine
DMB	3,4-dimethoxybenzyl
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMP	3,4-dimethoxyphenyl
DMS	dimethyl sulfide
dr	diastereomeric ratio
EE	1-ethoxyethyl
*c*Hex	cyclohexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HWE	Horner−Wadsworth−Emmons
Ipc	isopinocampheyl
KHMDS	potassium hexamethyldisilylamide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine
MCPBA	*meta*-chloroperbenzoic acid
Mes	2,4,6-trimethylphenyl
MOM	methoxymethyl
Ms	methanesulfonyl
NaHMDS	sodium hexamethyldisilylamide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidinone
Np	2-naphthyl
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PhBox	2,2′-isopropylidene-bis(4-phenyl-2-oxazoline)
PhPyBox	2,2′-(2,6-pyridinediyl)-bis(4-phenyl-2-oxazoline)
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
TCE	2,2,2-trichloroethyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyl-oxy free radical
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluroacetic anhydride
TIPPSeBr	2,4,6-triisopropylphenylselenyl bromide
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol-BINAP	2,2′-bis(di-*p*-tolyl-phosphino)-1,1′-binaphthalene
Tr	triphenylmethyl
Tris	2,4,6-triisopropylbenzenesulfonyl
TROC	trichloroethoxycarbonyl
TsO	*para*-toluenesulfonate
Xp	(4*S*)-benzyl-2-oxazolidinone

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