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# Spongipyran Synthetic Studies. Evolution of a Scalable Total Synthesis of (+)-Spongistatin 1

**Amos B. Smith III**, **Chris Sfouggatakis**, **Christina A. Risatti**, **Jeffrey B. Sperry**, **Wenyu Zhu**, **Victoria A. Doughty**, **Takashi Tomioka**, **Dimitar B. Gotchev**, **Clay S. Bennett**, **Satoshi Sakamoto**, **Onur Atasoylu**, **Shohei Shirakami**, **David Bauer**, **Makoto Takeuchi**, **Jyunichi Koyanagi**, and **Yasuharu Sakamoto**
Department of Chemistry, Monell Chemical Senses Center and Laboratory of Research on the Structure of Matter, University of Pennsylvania, Philadelphia, PA, 19104

## Abstract

Three syntheses of the architecturally complex, cytotoxic marine macrolide (+)-spongistatin 1 (**1**) are reported. Highlights of the first-generation synthesis include: use of a dithiane multicomponent linchpin coupling tactic for construction of the **AB** and **CD** spiroketals, and their union via a highly selective Evans boron-mediated aldol reaction en route to an **ABCD** aldehyde; introduction of the C(44)–C(51) side chain via a Lewis acid-mediated ring opening of a glucal epoxide with an allylstannane to assemble the **EF** subunit; and final fragment union via Wittig coupling of the **ABCD** and **EF** subunits to form the C(28)–C(29) olefin, followed by regioselective Yamaguchi macrolactonization and global deprotection. The second- and third- generation syntheses, designed with the goal of accessing one gram of (+)-spongistatin 1 (**1**), maintain both the first-generation strategy for the **ABCD** aldehyde and final fragment union, while incorporating two more efficient approaches for construction of the **EF** Wittig salt. The latter combine the original chelation-controlled dithiane union of the **E-** and **F**-ring progenitors with application of a highly efficient cyanohydrin alkylation to append the **F**-ring side chain, in conjunction with two independent tactics to access the **F**-ring pyran. The first **F**-ring synthesis showcases a Petasis-Ferrier union/ rearrangement protocol to access tetrahydropyrans, permitting the preparation of 750 mgs of the **EF** Wittig salt, which in turn was converted to 80 mg of (+)-spongistatin 1, while the second **F**-ring strategy, incorporates an organocatalytic aldol reaction as the key construct, permitting completion of 1.009 g of totally synthetic (+)-spongistatin 1 (**1**). A brief analysis of the three syntheses alongside our earlier synthesis of (+)-spongistatin 2 is also presented.

## Introduction

The spongistatin family of marine natural products comprise some of the most potent antimiotic, growth inhibitory substances discovered to date (Scheme 1).[1] As such members of this remarkable class hold great potential as exciting new leads for cancer chemotherapy. The extremely low natural abundance of the spongistatins[2] however represents a major hurdle for clinical development. Not surprisingly, the potent biological activities and daunting molecular architectures of the spongistatins have attracted considerable interest in both the synthetic and biomedical communities. To date seven total syntheses of

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representatives of this class of natural products have been achieved.[3] While these elegant syntheses have taught much about the intricacies of the chemistry of the spongistatins, to date only the Heathcock report3m,n on spongistatin 2 begins to address the need for sufficient quantities of material for biomedical development.

Encouraged by our successful gram-scale synthesis of (+)-discodermolide, which led to Phase I clinical development,[4] we initiated a program aimed at the evolution of a synthetic strategy capable of delivering gram-quantities of (+)-spongistatin 1 (**1**). While we had already achieved a total synthesis of the closely related (+)-spongistatin 2 (**2**), as outlined in the preceding paper, 5,[3h] the length and overall efficiencies of several critical transformations would clearly not permit large-scale production. We therefore reengineered our (+)-spongistatin 2 (**2**) strategy, drawing on lessons learned in our laboratory, as well as the experiences of others, to permit access to (+)-spongistatin 1 (**1**) on a preparative scale.

## Results and Discussion

### Synthetic Analysis

Having in place a successful endgame for (+)-spongistatin 2 (Scheme 1), comprising Wittig olefination of an advanced Wittig salt (cf. **4a**) with **ABCD** aldehyde **3**, followed by macrolactonization and global deprotection,[3h] we turned to improve acquisition of both **3** and the requisite chloro sidechain fragment **4b** for (+)-spongistatin 1 (**1**). For the **ABCD** subunit **3**, we recognized that, although the elegant Julia union/methylenation[6] protocol proved to be a powerful method for uniting the **AB** and **CD** subunits in our spongistatin 2 effort,[3h] this tactic relied on a simplified **AB** precursor to permit high efficiency in the union event. Extensive structural remodeling was then required to obtain the fully functionalized **ABCD** subunit. Reasoning that a more convergent strategy would be required for significant material advancement, we turned to a revised disconnection of the **ABCD** fragment **3**, now at the C(15)–C(16) bond to reveal **AB** aldehyde **5** and **CD** ketone **6**. Their union would call on an aldol reaction similar to that employed in the pioneering Evans (+)-spongistatin 2 (**2**) synthesis.3a–d We were also cognizant of the ever present possible loss of configurational control of the C(23) **CD** spiroketal stereocenter via mild acid treatment both during assembly of the **ABCD** aldehyde, as well as final elaboration to (+)-spongistatin 1 (**1**).3a–f

Even greater challenges were evident in our synthesis of the **EF** Wittig salt **4a**. Here, the low efficiency of the Julia union/methylenation installation of the side chain, in conjunction with the difficulties associated with subsequent side chain elaboration were clearly evident.[3h] We therefore again chose to abandon the Julia tactic. In the end, three strategically independent approaches were developed (*vide infra*). The first called for appending a fully elaborated side chain [cf. **8**] exploiting chelation control to an advanced **EF** intermediate (**7**) to afford **4b**.

### Construction of ABCD Aldehyde 3 Beginning With AB Spiroketal 5

As now well recognized,[3] the **AB** spiroketal in the spongistatins adopts the thermodynamically favorable axial-axial (*AA*) spiro configuration at C(7); **5** was thus envisioned to be readily available via spiroketalization under thermodynamic control of linear precursor **9** (Scheme 2). The requisite precursor in turn would arise via our multicomponent linchpin tactic,[7] in this case employing 2-triethylsilyl-l,3-dithiane, epoxide **10** and epoxide **11**, the latter available by the addition of dithiane **13** to epoxide **12**. By exploiting more advanced epoxide coupling partners in the tri-component linchpin event, extensive remodeling to arrive at an advanced **AB** system would not be required.

Construction of **5** began with the elaboration of napthyl epoxide **10**. We selected the rarely utilized 2-napthylmethyl protecting group based on the reported potential for selective

removal in the presence of a benzyl ether,[8] the latter employed to protect the C(28) hydroxyl in **CD** spiroketal **6** (Scheme 1). Employing a sequence similar to that developed for (+)-spongistatin 2 (**2**), monoprotection of 1,3-propanediol as the 2-napthylmethyl ether, followed by oxidation furnished aldehyde **14** (Scheme 3). Brown allylboration[9] then furnished homoallylic alcohol (+)-**15** in both high yield and enantioselectivity (88% yield, 90% ee). Assignment of the C(3) configuration of the major diastereomer entailed Mosher ester analysis.[10] Protection of the alcohol as a *tert*-butylcarbonate was then followed by IBr-mediated cyclization exploiting our improved protocol[11] to furnish iodocarbonate (−)-**16**, which was then converted to epoxide (−)-**10**.

The synthesis of epoxide **11** began with Sharpless asymmetric epoxidation[12] of 2-methyl-2-propenol; *in situ* protection with *tert*-butyldiphenylchlorosilane (BPSCl) afforded epoxide (−)-**17** (Scheme 4). Treatment of the latter with vinylmagnesium bromide in the presence of copper ion, followed by protection of the resulting alcohol with Boc anhydride furnished carbonate (+)-**18**. Cyclic carbonate formation mediated by IBr proved less selective than anticipated, initially furnishing a mixture (3:1) of *syn*- and *anti*-iodocarbonates. However, by employing diethyl ether at −100 °C, the desired *syn*-iodocarbonate (+)-**19** was available as a mixture of diastereomers (ca. 8:1). Chromatographic separation, followed by exposure of the requisite iodocarbonate to $K_2CO_3$ in methanol led to epoxide (−)-**12**.

Completion of epoxide **11** began with a four-step synthesis of dithiane (−)-**13** employing the (+)-Roche ester (Scheme 5). Alkylation with epoxide (−)-**12** proceeded smoothly to provide diol (−)-**21**, which was subjected to removal of the BPS group, Fraser-Reid epoxidation,[13] and protection of the secondary alcohol as a TES ether to furnish (−)-**11**. The overall yield for the 8 step sequence was 31%.

With both epoxides in hand, we explored the multicomponent linchpin union developed in our laboratory specifically for the spongistatin program.[7] Initially we employed epoxide (−)-**11** as the first electrophile, as this would permit *in situ* protection of the tertiary C(9) hydroxyl as a TES ether.[14] Unfortunately, all attempts to achieve the union of 2-lithio-2-TES-l,3-dithiane with epoxide (−)-**11**, followed by HMPA induced 1,4-Brook rearrangement and alkylation with epoxide (−)-**10** failed to produce the desired product **22** (Scheme 6A). Instead, products corresponding to mono- and bis-addition of (−)-**10** to the dithiane were obtained (structures not shown). Reversal of the order of epoxide addition only led to a 13% yield of the desired adduct **23** (Scheme 6B).

Undaunted, we turned to the stepwise alkylation of the lithiated anion of TES dithiane with (−)-**10** and (−)-**11**; treatment with (−)-**10** followed by addition of HMPA resulted in clean formation of monoalkylation product (+)-**24** in 82% yield (Scheme 7). However, attempts to carry out the analogous alkylation with (−)-**11** failed. Clearly epoxide (−)-**11** was sterically too encumbered to permit dithiane alkylation.

Recognizing that the dithiane in epoxide (−)-**11** would ultimately be converted to a methylene, we attempted to alleviate the steric hinderence by installing the methylene prior to linchpin union. Synthesis of the requisite coupling partner (+)-**30** began with conversion of the *p*-methoxybenzyl (PMB) ether of Roche's ester15 to the corresponding Weinreb amide employing a Merck protocol,16 followed by addition of methylmagnesium bromide to furnish ketone (+)-**26** (Scheme 8). Condensation with 2,4,6-triisopropylbenzenesulfonyl hydrazide[17] proceeded efficiently to afford the trisyl hydrazone (−)-**27** as a crystalline solid. The latter underwent efficient Shapiro reaction[18] to generate the corresponding vinyllithium, which upon alkylation with epoxide (−)-**12** led to diol (+)-**28**. Removal of the BPS protecting group followed by epoxide ring formation, employing the Fraser-Reid protocol,[13] and hydroxyl protection completed construction of (+)-**30**.

Again, all attempts to employ (+)-**30** as the second electrophile in the linchpin event failed to produce the desired product (Scheme 9). Instead, significant quantities of the intermediate dithiane (+)-**24** (i.e., monoalkylation), as well as products arising from elimination of the homoallylic TES ether (product not shown), were observed. Steric hindrance of the epoxide was again presumed to be the culprit. As a last resort, we explored the lithium alkoxide derived from epoxide (+)-**29** as the second electrophile to lower further the steric encumberance near the epoxide (Scheme 10). This tactic proved rewarding; coupled product (+)-**33** was obtained reproducibly in 55–58% yield on large scale (ca. 10 grams). The above sequence of events provides a showcase for how multicomponent linchpin processes can be developed.

Removal of the dithiane and the silyl protecting groups with mercuric perchlorate as employed for spongistatin 2 (**2**), proceeded with concomitant spiroketalization to furnish **AB** spiroketal (−)-**34** as a single isomer (Scheme 11); the stereochemistry was assigned based on NOESY NMR experiments. While this one-pot deprotection/spiroketalization was attractive, the reaction sequence was not readily reproducible on large scale. We therefore adopted a two-step sequence involving TBAF-mediated desilylation to produce tetraol (+)-**35**, which in turn was readily transformed to spiroketal (−)-**34** by iodomethane-mediated hydrolysis of the dithiane. The two-step sequence proceeded reproducibly in 76% yield.

At this stage all that remained to complete the **AB** spiroketal **5** was adjustments of the protecting groups and oxidation state (Scheme 12). Selective acetylation of the C(5) hydroxyl followed by protection of the tertiary C(9) hydroxyl as a TES ether quickly afforded (−)-**36**. Unfortunately, attempts to remove the C(15) PMB protecting group under oxidative conditions resulted in competitive removal of the napthyl and/or TES protecting group.

Unable to unmask the C(15) hydroxyl in the presence of the 2-napthylmethyl ether, we explored the possibility of employing an ester at C(l) in the forthcoming aldol union of the **AB** with **CD** spiroketals. Selective removal of the napthyl group in (−)-**36** proceeded smoothly to furnish (−)-**38** (Scheme 13), which was then subjected to a two-step oxidation to provide acid (−)-**39**. Conversion of the acid to the corresponding TIPS ester, followed by DDQ-mediated removal of the C(15) PMB group led to alcohol (−)-**40**, which was transformed to aldehyde (−)-**41** via Dess-Martin oxidation.[19,20]

## Construction of the ABCD Aldehyde 3 Continued: Synthesis of the CD Ketone 6

In our (+)-spongistatin 2 (**2**) venture, we discovered that the requisite **CD** spiroketal fragment (cf. **6**; Scheme 1), which possesses the thermodynamically less stable axial-equatorial configuration at the C(23) spiro center, could be generated by the treatment of the more stable axial-axial congener with acid in the presence of $Ca^{II}$ ion.[21] Accordingly, we anticipated that the desired spiroketal would be available from the requisite linear precursor via a spiroketalization/equilibration protocol involving dithiane **42**, that in turn would again arise taking advantage of our multicomponent linchpin tactic employing TBS-dithiane, epoxide (−)-**43** [also utilized in construction of the **CD** spiroketal during our (+)-spongistatin 2 synthesis],[3g] and epoxide **44** (Scheme 14).

Construction of **44** began with the synthesis of aldehyde (−)-**45** (Scheme 15),[22] available in three steps from L-malic acid. Efforts to utilize the β-oxygen in (−)-**45** to direct formation of the C(19) stereocenter via Lewis acid catalyzed allylation failed to provide the desired adduct with an acceptable level of selectivity. Instead, reagent control was employed using allylstannane **46**, in conjunction with the $Ti(O\textit{i}\text{-}Pr)_4$/BINOL system reported by Keck;[23] homoallylic alcohol (−)-**47** was obtained in good yield and with excellent selectivity (ca. 20:1).[24] Removal of the ketal was then followed by sequential treatment of the resulting

primary hydroxyl with trimethylbenzenesulfonyl chloride and NaH to generate the epoxide, and TBSCl for *in situ* O-TBS protection to complete the synthesis of (−)-**44**.

Again, we initially investigated the stepwise construction of the C(16) to C(28) backbone to optimize each step of the pending multicomponent union. Lithiation of 2-triethylsilyl-l,3-dithiane followed by addition of (−)-**43** and subsequent treatment with HMPA furnished dithiane (+)-**49** in good yield (Scheme 16). However, attempts to effect deprotonation of (+)-**49** led only to decomposition of the substrate.

To circumvent this problem, we reasoned that we could postpone the 1,4-Brook rearrangement until the second epoxide alkylation, thereby permitting a directed deprotonation of the dithiane by the initially formed alkoxide. Towards this end, alkylation of the lithium anion of 2-TES-l,3-dithiane with (−)-**43**, now in the absence of HMPA, furnished alcohol (+)-**51** (Scheme 17A). With (+)-**51** in hand, deprotonation of the resultant alcohol followed by addition of HMPA led to 1,4-Brook rearrangement; subsequent C-alkylation with (−)-**44** furnished (+)-**52**. The yield for the two-step sequence was 57%. With a successful stepwise sequence in hand, we explored the one-pot scenario, in this case employing the lithium anion derived from 2-TBS-l,3-dithiane. Alkylation with epoxide (−)-**43**, followed by addition of epoxide (−)-**44** dissolved in THF/HMPA, furnished (+)-**42** (Scheme 17B). Importantly, this reaction proceeded in 63–69% yield and could be run reproducibly on large scale (10 g) permitting production of >50 g of (+)-**42**.

Having established both a reliable and scalable method for construction of the C(16)–C(28) backbone, we turned to elaboration of ketone **6** (Scheme 14). With the C(21) hydroxyl in (+)-**42** already differentiated by the linchpin event, installation of the requisite methyl ether was easily achieved employing iodomethane and sodium hydride in the presence of 15-crown-5 to furnish (−)-**53** (Scheme 18), which in turn was converted to triol (+)-**54** upon treatment with *p*-TsOH. Removal of the dithiane proved to be even more difficult than previously observed for (+)-**33**, en route to the **AB** spiroketal precursor. Standard mercuric perchlorate conditions[25] resulted in significant amounts of decomposition. We surmised that the culprit was the C(17) alkene. To circumvent this issue we examined a number of conditions to effect dithiane removal with concomitant spiroketalization. In the end, we settled on ceric ammonium nitrate (CAN), which furnished a mixture of spiroketals (+)-**55** and (−)-**56** (ca. 4:1). As expected, NOESY NMR experiments revealed that the major product was the undesired axial-axial spiroketal (+)-**55** (Figure 1).

As discussed previously, a key discovery during our spongistatin 2 synthesis3g,h comprised an effective protocol to achieve conversion of the **CD** axial-axial (*AA*) spiroketal to the axial-equatorial (*AE*) congener in the presence of $Ca^{II}$ ion, when appropriate chelation functionality was available. We surmised that the methylene moiety in (+)-**55** and (−)-**56** could be utilized to generate the required functionality. Toward this end, the mixture of spiroketals was dihydroxylated with $OsO_4$. Acid equilibration of the diol mixture mediated by $Ca^{II}$, followed by oxidative cleavage of the diols led to a mixture of spiroketals favoring the desired axial-equatorial (*AE*) spiroketal (−)-**58** (ca. 4:1); confirmation of both structures was achieved by NOESY NMR analysis upon separation (Figure 2).[26]

Intrigued by the possibility that the C(17) configuration might play a significant role in the equilibration process, we prepared the C(17) diastereomeric diols. Sharpless asymmetric dihydroxylation[27] with AD-mix-α provided access to a mixture (5:1) favoring the *S*-isomer **59** at C(17) (Scheme 20).[28] Alternatively, AD-mix-β proved highly selective, producing triol **60** (10:1); the latter clearly represents a matched case.

Exposure of the mixture enriched in the *S*-isomer (**59**) to the now standard $Ca^{II}$ equilibration conditions,3g,h followed by oxidative cleavage of the diol, produced a 1:3 mixture of

spiroketals favoring the required axial-equatorial ketone (−)-**58** (Scheme 21). Alternatively, exposure of the diol mixture rich in the *R*-isomer (**60**) to the identical conditions furnished a mixture (5:1) of diastereomers, once again favoring the desired (−)-**58**. Taken together, these results suggest that the configuration at C(17) plays only a minor role in the outcome of the equilibration event. For material advancement, as well as cost considerations, we employed dihydroxylation with $OsO_4$/NMO, followed by oxidative cleavage to furnish (+)-**57** and (−)-**58** (1:4) in 90% yield.

Completion of **CD** ketone (−)-**6** was achieved by protection of the free hydroxyl in (−)-**58** as the TBS-ether (Scheme 22). The overall sequence to (−)-**6** proceeded in 16 steps from L-malic acid with an overall yield of 20%. A total of 15 g of spiroketal (−)-**6** was prepared.

## Fragment Union and Completion of the C(l)-C(28) ABCD Aldehyde (3)

Having ample quantities of both (−)-**41** and (−)-**6**, we proceeded to the Evans aldol to unite the two fragments. As anticipated, the aldol reaction[3c] proceeded smoothly to afford the desired **ABCD** product (−)-**61** (Scheme 23), both in good yield and with high diastereoselectivity (9:l). Acetylation followed by removal of the benzyl group furnished alcohol (−)-**63**, which was readily oxidized to (−)-**3**.[29] From the preparative perspective, construction of the **ABCD** subunit (−)-**3** now entails a longest linear sequence of 22 steps and proceeds with an overall yield of 6.5%. This sequence is 15 steps shorter than our approach to the epimeric C(23) **ABCD** aldehyde employed in our spongistatin 2 synthesis, and as such represents a major synthetic advance.

## Synthesis of the EF Wittig Salt 4: A Most Challenging Synthetic Target

Development of effective synthetic routes to appropriately functionalized **EF** Wittig salts for the spongistatins has proved challenging to all who have engaged in the spongistatin synthetic enterprise. We report here three strategically different syntheses of this advanced intermediate, each taking advantage of the stereocontrolled **E** ring construction developed in our spongistatin 2 synthetic venture,[6] involving cerium (III) mediated addition of dithiane (−)-**64**[30] to an appropriate **F**-ring aldehyde employing zinc (II) chelation control. The first approach (Scheme 24) entailed introduction of a fully functionalized side chain via alkylation of ketone **7** with allyl iodide **8**. Further analysis of **7** reveals progenitors dithiane (−)-**64** and aldehyde **65**. The requisite allyl iodide side chain in turn would arise ultimately by allylation of chlorodiene aldehyde **66** with allyl(diisopinocampheyl)borane **67**, followed by functional group adjustments.

Construction of (+)-**65** began via Brown crotylboration[31] of known aldehyde (−)-**68**[32] to furnish homoallylic alcohol (−)-**69**, followed by protection as a benzyl ether and exposure to camphorsulfonic acid (CSA) in methanol to deliver diol (−)-**70** in 55% yield (three steps; Scheme 25). Selective sulfonation of the primary alcohol with 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl) and protection of the secondary alcohol as a PMB ether afforded alkene (+)-**71**, that was in turn converted to the **F**-ring pyran via Sharpless asymmetric dihydroxylation[27] and base promoted cyclization to furnish alcohol (+)-**72** in 85% yield. Parikh-Doering[33] oxidation then completed construction of (+)-**65**.

At this stage, we explored a model alkylation study prior to attempted union of aldehyde (+)-**65** with dithiane (−)-**64**. Conversion of the primary hydroxyl in (+)-**72** to the TBS ether, followed by transfer hydrogenolysis to remove the benzyl group and treatment with TESCl led to pyran (+)-**73**. Oxidative removal of the PMB moiety, followed by the Swern protocol[34] then furnished model **F**-ring ketone (+)-**74** (Scheme 26).

Initial attempts to effect alkylation of (+)-**74** employing kinetic deprotonation and treatment with either allylbromide or allyliodide failed to provide the desired adduct **75** (Scheme 27).

Silyl enol ether **76**, however, could be prepared by deprotonation of (+)-**74** with LiHMDS, followed by addition of TMSCl. Pleasingly, alkylation with allyl iodide promoted by silver trifluoroacetate then furnished **75** as a mixture of isomers (ca. 7.5:1), favoring the desired equatorial product.

Encouraged by these results, we turned to construction of the requisite fully functionalized side chain (+)-**8** (Scheme 28), beginning with oxidative cleavage of l,2,5,6-di-*O*-isopropylidene-D-mannitol to provide aldehyde (+)-**77**. Brown allylboration[9] furnished homoallylic alcohol (+)-**78**, which was subjected to a protection/deprotection sequence to yield diol (+)-**79**. Cleavage of the diol, followed by indium-mediated allylation[35] provided **80** as an inconsequential mixture of alcohols (ca. 1:1). Without separation, elimination of the hydroxyl groups furnished triene (−)-**81**, which upon Riley oxidation with $SeO_2$,[36] employing a reductive workup led to alcohol (+)-**82**, albeit in low yield (24%, 49% BORSM). Notwithstanding the modest yield, conversion of the allylic alcohol to the corresponding mesylate, followed by *in situ* displacement with LiI completed the synthesis of what proved to be an unstable iodide (+)-**8**. Unfortunately, attempts to alkylate enol ether **76** with (+)-**8**, employing the model conditions, proved unsuccessful (Scheme 29).[37]

Recognizing the instability of allyl iodide (+)-**8**, we turned instead to a Lewis acid promoted addition of an allylstannane to a glucal epoxide for side chain attachment, as employed in the Evans (+)-spongistatin 2 synthesis.3a–d However, given the anticipated sensitive nature of both the glucal and the side chain, we decided to first construct the **E** ring, again employing the tactic used in our spongistatin 2 synthesis. To this end, addition of the cerium salt of dithiane (−)-**64** to aldehyde (+)-**65** provided (+)-**84** in a highly stereocontrolled fashion (51%, *dr* >20:1) via the aforementioned chelation controlled process (Scheme 30).

Hydrolysis of the acetonide and in turn removal of the dithiane proceeded as expected with concomitant cyclization to furnish (+)-**85** (Scheme 31). Acid-catalyzed methyl ketal installation was then achieved in near quantitative yield to furnish (+)-**86** as a single isomer. Protection of the axial C(35) hydroxyl as the TBS ether, however, proved more difficult than initially anticipated due to extensive elimination of the methyl ketal to furnish the corresponding dihydropyran (structure not shown).

After extensive experimentation, we decided to install the mixed methyl ketal at a later stage. Pleasingly, protection of the C(35) hydroxyl in (+)-**85** proceeded selectively to furnish (+)-**87** (Scheme 32). Selective removal of the benzyl groups was then achieved using transfer hydrogenolysis in methanol employing 2,6-lutidine[38] to provide (+)-**88** as a mixture of methyl and hemiketals. Exposure of this mixture to PPTS in methanol led to complete mixed methyl ketal formation; exhaustive silylation then led to TES ether (+)-**89** in high yield. Removal of the PMB group was next achieved using medium-pressure hydrogenolysis (500 psi) to furnish alcohol (+)-**90**, which was converted without purification to the corresponding triflate and then to coupling partner (+)-**91** by treatment with LDA. The overall yield of (+)-**91**, requiring 17 steps from known aldehyde (−)-**68**, was 3%.

## Side Chain Construction, Union with the EF Fragment (+)-91 and Elaboration to Wittig Salt (+)-103

Having secured a viable route to the **EF** dihydropyran (+)-**91**, we turned to construction of the requisite stannane side chain required for the proposed Evans coupling. Although we had in hand a pathway to access the corresponding iodide (+)-**8** (Scheme 28), the route proved inefficient for large-scale synthesis. We therefore designed an alternative approach.

We began with $BiCl_3$-mediated allylation[39] of ethyl glyoxalate to furnish homoallylic alcohol **92** as an inconsequential mixture (ca. 1:1) of isomers (Scheme 33). Conversion of

the alcohol to a mesylate, followed by DBU-mediated elimination to provide **93**, and a two-step reduction/oxidation sequence furnished aldehyde **94**. Initial attempts to couple **94** with allylstannane **95** employing the Keck protocol[23] produced (−)-**96** with excellent selectivity (98% ee); however, the yield was at best modest (33%). Employing a bis-zirconium catalyst, [40] in place of the Keck catalyst, led to marked improvement (69%) without loss of selectivity. Silylation with TMSCl then furnished (+)-**97**, which was converted to the primary 2,4-dichlorobenzoate (+)-**98** in two steps. Displacement of the benzoate with $Bu_3SnAlEt_2$ mediated by $Pd^0$ employing the conditions of Trost[41] completed construction of allylstannane (+)-**99**.[42] The overall yield for the 10-step sequence from ethyl glyoxalate was 7.4%.

Having secured both coupling partners, we turned to the Evans union.3a–c Epoxidation of (+)-**91** with dimethyldioxirane followed without purification by treatment with stannane (+)-**99** in the presence of $Bu_3SnOTf$ furnished (+)-**100** as a single isomer in excellent yield (Scheme 34). Removal of the sterically more accessible TES and the TMS protecting groups generated tetraol (+)-**101**, which was selectively converted to (+)-**102** upon treatment with TrisCl, DMAP, and D*t*BMP (2,6-di-*t*-Butyl-4-methylpyridine). Interestingly, use of $Et_3N$ or Hünig's base resulted in lower yields of the primary sulfonate, in conjunction with loss of the methyl ketal. Conversion of the trisylate to the corresponding iodide, global TMS protection, and displacement of the primary iodide with $PPh_3$ completed the synthesis of the **EF** Wittig salt (+)-**103**.

## Fragment Union and Elaboration to (+)-Spongistatin 1: A First Generation Synthesis

In our spongistatin 2 synthesis, we employed the Kishi titration protocol[3m] to effect the critical union between (+)-**4a** (X=H) and (−)-**3**; however, in our hands the yield was less than satisfactory. In an effort to improve this transformation, we examined the modified conditions of Paterson (THF/HMPA) to unite (+)-**103** with (−)-**3**.[3j] S*eco*-acid (+)-**104** was obtained in 64% yield, after treatment with KF in methanol (Scheme 35). Selective protection of the side chain hydroxyl as the TES ether, followed by Yamaguchi macrolactonization[43] employing 2,4,6-trichlorobenzoyl chloride (2,4,6-TCBCl) and global deprotection with HF completed the synthesis of (+)-spongistatin 1, which was identical in all respects (500 MHz 'H NMR, 125 MHz $^{13}C$ NMR, HRMS, IR and chiroptic properties) with literature data.[3i,m] The synthesis proceeded with a longest linear sequence of 29 steps (based on the **EF** subunit) with an overall yield of 0.5%. Importantly, this route represents a significant improvement over our spongistatin 2 synthesis (ca. 18 fewer steps)!

## Second and Third Generation Scalable Syntheses of (+)-Spongistatin 1

While our first-generation synthesis entailed a significant improvement over our spongistatin 2 (**2**) synthetic venture, two significant obstacles remained prior to initiating a large-scale synthetic campaign. These include the modest yield observed during the dehydration required to furnish dihydropyran (+)-**91**, and the overall length and inefficiency required to access the highly unstable stannane (+)-**99**. Since both problems were encountered during construction of the **EF** side chain, redesign of this fragment was imperative. Two new strategies were developed (e.g., second and third generation syntheses). The modified target, **EF** Wittig salt **105**, employed in both was envisioned to differ from (+)-**103** in that the side chain hydroxyl would now be protected as a TBS ether, in order to permit selective endgame deprotection to reveal the *seco*-acid and thereby eliminate a reprotection step. With this scenario in mind, initial dissection of Wittig salt **105** at C(46)–C(47) revealed allyl bromide **107** and aldehyde **106** (Scheme 36). By not employing a fully elaborated side chain, a number of options for bond construction would be possible, including both nucleophilic allylation or use of an umpolung[44] tactic, (*vide infra*),

without having to significantly reengineer the coupling fragments. Such a scenario was of course appealing.

Continuing with this analysis, disconnection of **107** led to dithiane (−)-**64** and aldehyde **108**. We first envisioned **108** to arise from *cis*-4-heptanal and acid **109** via a Petasis-Ferrier[45] union/rearrangement (Path A), an effective tactic developed in our phorboxazole synthetic program to access 2,6-*cis*-disubstituted tetrahydropyrans.[46] Alternatively, an organocatalyzed aldol approach (Path B), patterned after the elegant work of MacMillan[47] for the preparation of carbohydrates, held promise of a viable approach to the **F** ring pyran **108**.

### Path A: The Petasis-Ferrier Union/Rearrangement Approach

Preparation of aldehyde **108** began with the TMSOTf-promoted condensation[48] of acid (−)-**109** (prepared in two steps employing the Evans oxazolidinone chemistry) with *cis*-4-heptanal to furnish dioxanone (−)-**113** (Scheme 37). Methylenation[49] and exposure of the enol ether to $Me_2AlCl$ led via Petasis-Ferrier rearrangement to pyranone (−)-**114** as a single isomer. After considerable experimentation, introduction of the C(42) hydroxyl was achieved by treatment of the potassium enolate of (−)-**114** with the Davis oxaziridine (+)-**115**[50] to provide alcohol (+)-**116** in good yield after epimerization of the C(40) methyl substituent. Silylation of the newly generated hydroxyl was then followed by selective axial-reduction and desilylation to furnish diol (+)-**117**, which was converted to **F**-ring aldehyde (+)-**108** in three additional steps: diol protection, removal of the *p*-methoxyphenyl (PMP) group, and oxidation.

### Path B: The Organocatalytic Aldol Approach

While the Petasis-Ferrier approach to the **F**-ring pyran successfully led to 700 mg of the desired **EF** ring system [ca. 80 mg of (+)-spongistatin 1 from 450 mg], we were intrigued that the two-step MacMillan[47] carbohydrate synthesis might further shorten our route to (+)-**108**. Initially, we sought to combine the MacMillan cross aldol reaction of aldehyde **118** with a Mukaiyama aldol reaction involving silyl enol ether **111** to access **110** (Scheme 38). Lactol **110** would then be elaborated to the desired **F**-ring pyran **108** in four chemical operations. Unfortunately, the Mukaiyama aldol reaction on large scale (ca. 100 g) was hampered both by the instability of the intermediate β-hydroxyaldehyde **112**[51] and the apparent sensitivity to impurities generated in the organocatalytic aldol process.

However, encouraged by the efficiency of the organocatalytic *anti*-aldol reaction (Scheme 39), **112** was directly subjected as a *syn/anti* (~1/5) mixture to a Horner-Wadsworth-Emmons reaction with methyl (triphenylphosphoranylidene)acetate to provide ester **119**. Sharpless asymmetric dihydroxylation, followed by lactonization then led to lactone (−)-**120**, which was isolated as a single isomer in good yield. Only the desired product arising from the *anti*-aldol reaction underwent cyclization, thereby permitting facile separation from the *syn*-aldol byproduct. Bis-benzylation was then followed by addition of the Grignard derived from bromide **122**, reduction of the resultant lactol with $Et_3SiH/BF_3{\bullet}Et_2O$,[52] the latter occurring with concomitant removal of the *O*-TBDPS protecting group, and Parikh-Doering oxidation to furnish aldehyde (+)-**108**. This 8-step reaction sequence proceeded with an overall yield of 50% from BPS-protected aldehyde **118**. In contrast, the Petasis-Ferrier approach, requiring a total of 12 steps from *p*-methoxyphenoxy acetaldehyde [two steps to (−)-**109]**, proceeded in 26% overall yield. Clearly, the organocatalytic route would be more applicable for the gram scale production of (+)-spongistatin 1 (**1**).[3j]

## Construction of Ring E

As with our earlier approaches to the spongistatins, fragment union to furnish (+)-**124** was achieved via addition of the cerium dithiane anion derived from (−)-**64** to aldehyde (+)-**108** premixed with zinc chloride. Although providing the desired adduct, a significant amount of what was presumed to be β-isomer **125** resulted (Scheme 40). Subsequent experiments revealed that by increasing the amount of metal additives, in conjunction with decreasing the amount of HMPA, the amount of **125** could be reduced. However, in the process we began to observe a third product (**126**) of undetermined stereochemistry at C(38). Eventually, we discovered that formation of both **125** and **126** could be suppressed by warming the initially generated aldehyde (+)-**108**-$Zn^{II}$ reaction mixture to −20 °C prior to addition of the cerium dithiane, using a minimal amount of HMPA (1.5 equiv.). Under these conditions, (+)-**124** was reproducibly generated in 65–68% yield on large scale (cf. 10 g).

With a reliable route to (+)-**124** securely in hand, we turned to elaborate ring **E**. Hydrolysis of the acetonide, followed by iodomethane-mediated dithiane removal proceeded with concomitant hemiketalization to furnish **EF** diol (+)-**127** in 77% for the two steps (Scheme 41). Selective silylation of the C(35) hydroxyl, followed by exposure to methanolic PPTS then led to methyl ketal (+)-**128**. Removal of the benzyl protecting groups via hydrogenolysis, however, proved to be more challenging than we had anticipated, being plagued with competitive olefin reduction. Use of LiDBB however proved highly effective to furnish (+)-**129** in 96% yield.

To set the stage for final elaboration of the **F**-ring side chain, (+)-**129** was globally protected as the tetra-TES ether (+)-**130** (Scheme 42). Ozonolysis employing reductive workup, followed without purification by treatment with Eschenmoser's salt[53] next furnished (+)-**131**. Selective 1,2-reduction with DIBAL-H then led to alcohol (+)-**132** which was converted to bromide (+)-**107** with $CBr_4$ in the presence of $PPh_3$. Alternatively, the corresponding iodide (+)-**133** could be prepared by treatment with $I_2$ in the presence of $PPh_3$.

## Elaboration of the EF Side Chain

Our initial approach focused on a tin-mediated Barbier allylation protocol[54] between known chlorodiene aldehyde **106**[55] and bromide (+)-**107** (Scheme 43). To this end, treatment of a premixed solution of bromide (+)-**107** and aldehyde **106** with $SnCl_2 \bullet 2H_2O$ in the presence of NaI proceeded to furnish **134** as a mixture (1:1) of C(47) alcohols. The yield, however, was only modest (ca 42%). We therefore turned to an umpolung approach.[56]

In this scenario, we envisioned addition of an O-protected cyanohydrin[57] to either bromide (+)-**107** or iodide (+)-**133** (Scheme 42). Accordingly, aldehyde **106** was treated with trimethylsilyl cyanide in the presence of $ZnI_2$ to furnish cyanohydrin **135** (Scheme 44).[58] Attempts to deprotonate **135** and trap the resulting ion with either (+)-**107** or (+)-**133**, however, resulted only in decomposition of the cyanohydrin or recovery of the allyl halide.

Reasoning that the extended conjugation of the cyanohydrin might be responsible for decomposition via an elimination pathway, we opted to mask the olefin as a protected β-hydroxyl. Construction of the revised cyanohydrin **141** began with an aldol reaction between the lithium enolate of *tert*-butyl acetate **137** and aldehyde **138** (generated *in situ* via Swern oxidation of the corresponding alcohol)[59] to furnish racemic **139** (Scheme 45). Protection of the alcohol without purification with TESCl provided **140,** which was converted to cyanohydrin **141** in two additional steps.

Pleasingly, cyanohydrin **141** underwent clean deprotonation and union with allylic iodide (+)-**133** to furnish diol **142**, after removal of the silyl groups at C(29) and C(49) (Scheme

46). Conversion of the C(29) hydroxyl to the corresponding iodide then fortuitously proceeded with concomitant elimination of the C(49) hydroxyl to provide (+)-**143**, which upon Corey reduction[60] with (*R*)-Me-CBS afforded allylic alcohol (+)-**144** with good diastereoselectivity (*d.r.* >10:1). Protection of the free hydroxyl, followed by treatment with $PPh_3$ completed construction of Wittig salt (+)-**105**.

Comparison of the three approaches to the **EF** Wittig salts [cf. (+)-**103** and (+)-**105**] from the prospective of step economy reveals near equivalency; the Evans glucal epoxide approach 24 steps, the Petasis-Ferrier tactic 26 steps, and organocatalytic aldol approach 24 steps. However, the efficiencies are markedly different, being 1.8, 8.3 and 9.4% respectively in overall yields from known starting materials.

## Fragment Union and Completion of the Second and Third-Generation Total Syntheses

Having improved our approach to **EF** Wittig salt (+)-**105**, all that remained was union with aldehyde (−)-**3** and final elaboration to the natural product (Scheme 47). Wittig reaction between (+)-**105** and (−)-**3** proceeded smoothly to provide alkene (+)-**145** as a single isomer in 62% yield when utilizing LHMDS[61] or in 64% when relying on MeLi•LiBr.[62] Removal of the TES and TIPS protecting groups was then achieved with TBAF in THF3m,n to furnish *seco*-acid (+)-**146,** which upon regioselective Yamaguchi macrolactonization[3c] furnished macrolactone (+)-**147** in 85% yield.

Completion of the total synthesis now only required global deprotection. While we had previously relied upon dilute HF-acetonitrile in our first-generation synthesis of (+)-spongistatin 1 (**1**), yields were highly variable. We therefore explored the Heathcock conditions,3m,n calling on a higher concentration of acid at lower temperature, as developed in their (+)-spongistatin 2 synthesis. These conditions furnished an 87% yield of (+)-spongistatin 1 (**1**). As such, the third-generation synthesis requires a longest linear sequence of 31 steps and proceeds with an overall yield of 3.1%. Using this protocol we have been able to prepare 80 mg of (+)-spongistatin 1 (**1**) via Petasis-Ferrier union tactic and 929 mg via the organocatalytic aldol strategy for a total of 1.009 g of synthetic (+)-spongistatin 1 (**1**). Importantly, this quantity of (+)-spongistatin 1 comprises more of the natural product than has arisen from all the isolation and synthetic studies combined.

## Conclusion

Three stereocontrolled total syntheses of (+)-spongistatin 1 have been achieved. Comparison of the three routes reveals that the third-generation route is roughly four times more efficient in terms of overall yield than the first-generation route. Given that the endgames of all three routes are similar, the differences in the overall efficiencies reside in the tactics employed to arrive at the subtargets. For the **ABCD** aldehyde (−)-**3**, our dithiane-mediated multicomponent linchpin coupling proved to be an extremely powerful method for construction of the **AB** and **CD** subunits. Clearly, the different fragment union protocols played a critical role in the outcome of the different syntheses. For example, the Julia union/methylenation process proceeded in high yield in our original (+)-spongistatin 2 (**2**) synthesis, a result of the simplified nature of the coupling partners. A large number of transformations, however, were required after fragment union to complete the **ABCD** aldehyde. By comparison, the boron aldol approach in the (+)-spongistatin 1 (**1**) synthesis permitted advancement with more highly functionalized fragments, thereby increasing both the convergency and overall efficiency for the **ABCD** aldehyde, as evidenced by an increase in the overall yield of this fragment from 1.4% to 6.5%.

An even more dramatic improvement in terms of efficiency can be seen in the diverse strategies to construct the **EF** Wittig salt. In both our (+)-spongistatin 2 (**2**) and (+)-

spongistatin 1 (**1**) syntheses, ring **F** was constructed from a linear precursor, coupled to an **E**-ring fragment precursor and then subjected to cyclization prior to side chain introduction. Unfortunately, side chain installation in the (+)-spongistatin 2 (**2**) synthesis was compromised by an unexpected low yield of the Julia union/methylenation tactic. This information in conjunction with the extensive number of transformations required to evolve the fully elaborated **EF** side chain in the (+)-spongistatin 2 synthesis proved inefficient. In contrast, elaboration of the partially functionalized side chain prior to union to the **EF** ring system proved more efficient as evidenced by the increase in the overall yield of this fragment from 0.3% in our (+)-spongistatin 2 synthesis to 1.8% in our first generation approach to (+)-spongistatin 1. Despite these improvements, the tedious nature of the **EF** dihydropyran construction, in conjunction with the sensitivity of the side chain, compromised large scale advancement of the material. We therefore developed an approach which incorporated an efficient cyanohydrin alkylation to complete the **F**-ring side chain. This approach proved to be much more effective than the earlier two tactics, removing the need to perform extensive manipulations on advanced intermediates and/or the synthesis of highly sensitive coupling partners. The improved efficiency is best exemplified by the fact that that we can now construct the **EF** Wittig salt with an overall yield of 9.5% from known materials. Finally, the integrity of the C(23) spiroketal stereocenter was maintained throughout the synthesis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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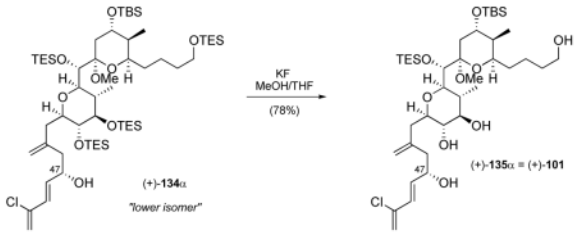


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61. Excess ABCD aldehyde (−)-3 can be recovered and purified following conversion to the corresponding ABCDCH$_2$OH with NaBH(OAc)$_3$.
62. Excess EF Wittig salt (+)-105 can be recovered with 94% purity via column chromatography, followed by precipitation of excess Ph$_3$P(O) with hexane.

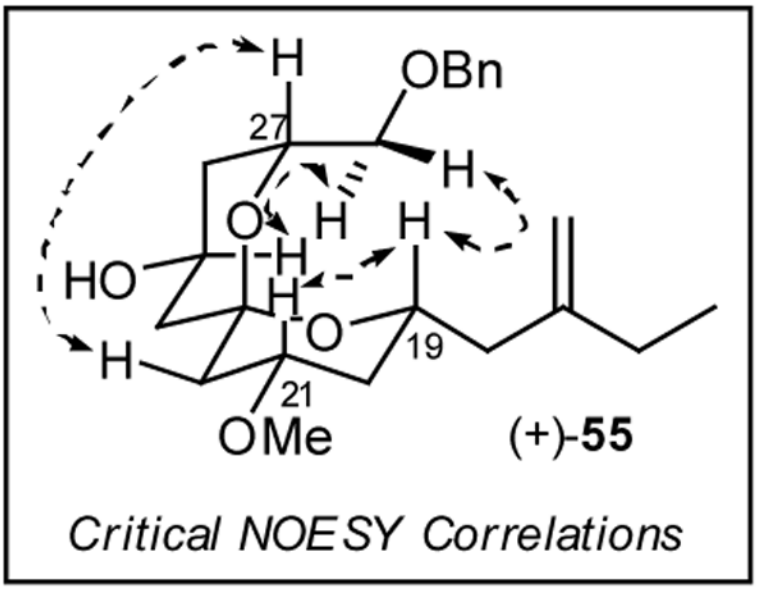



**Figure 1.**
Critical NOESY NMR correlations for spiroketal (+)-**55**.

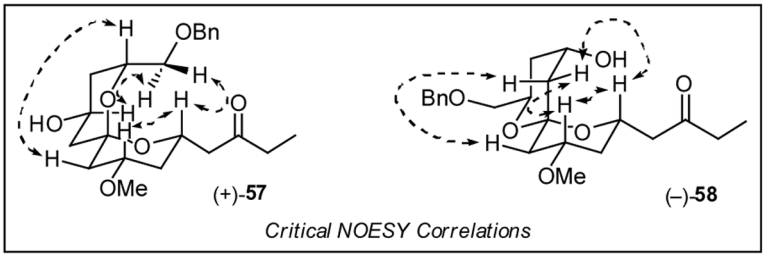
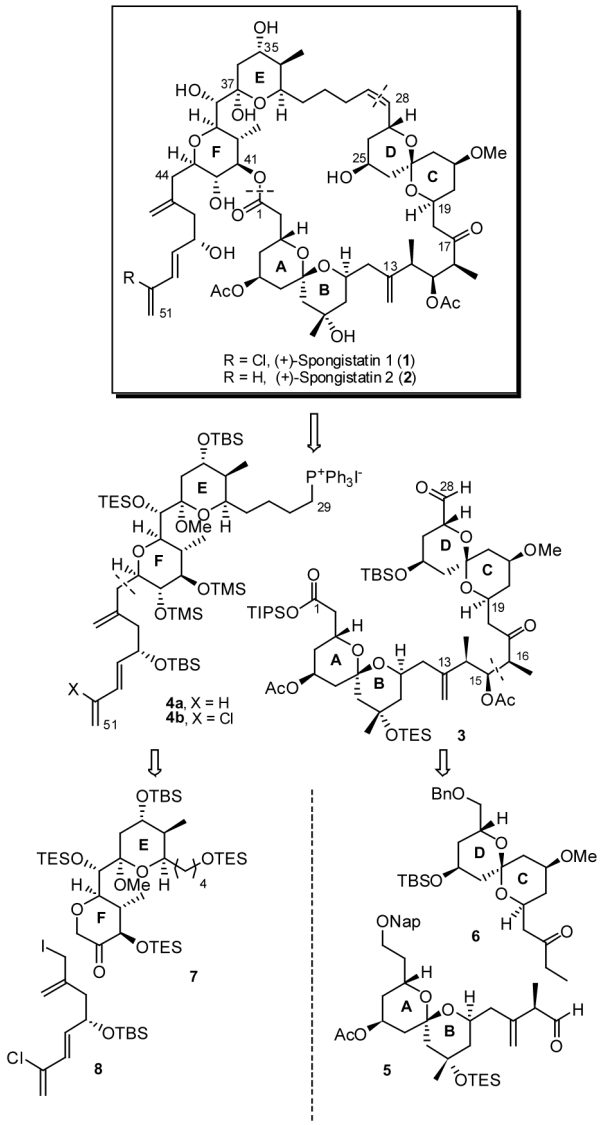
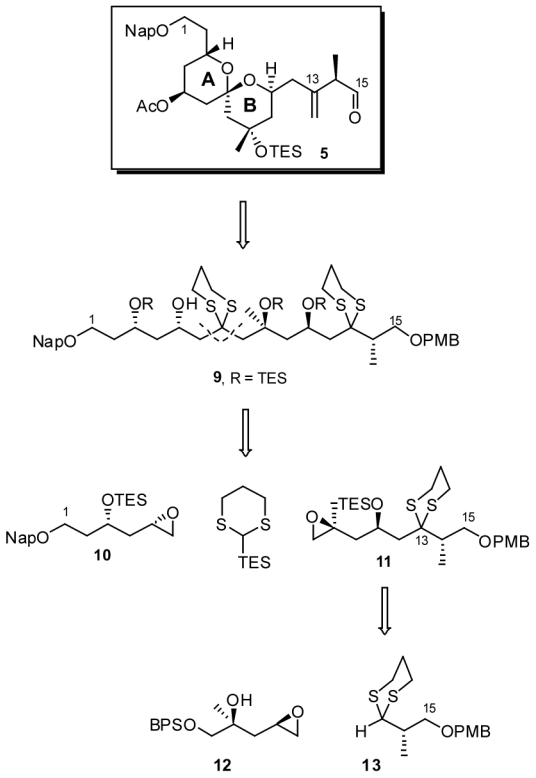


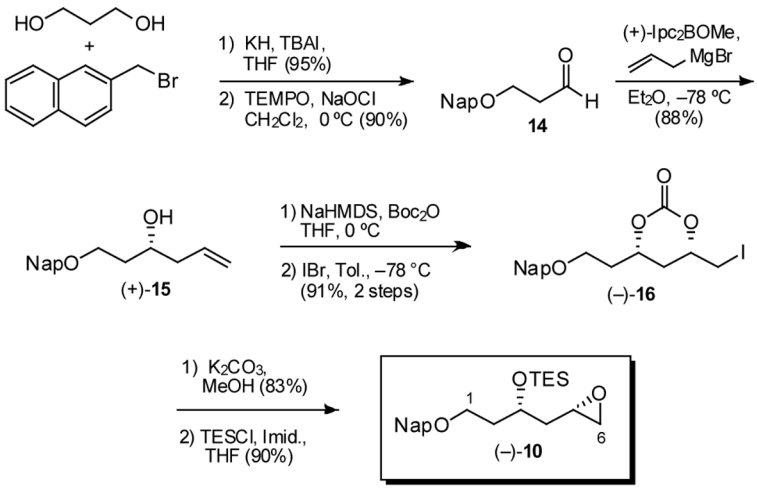

**Figure 2.**
Relevant NOESY data for (+)-**57** and (−)-**58**.



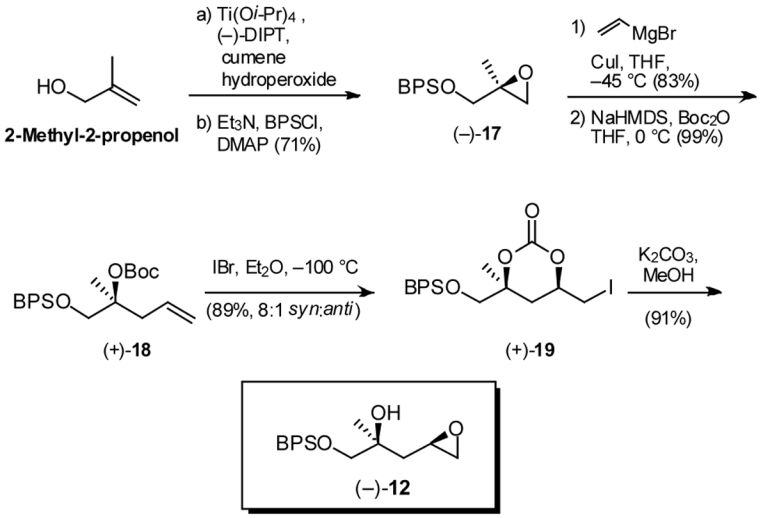

**Scheme 1.**



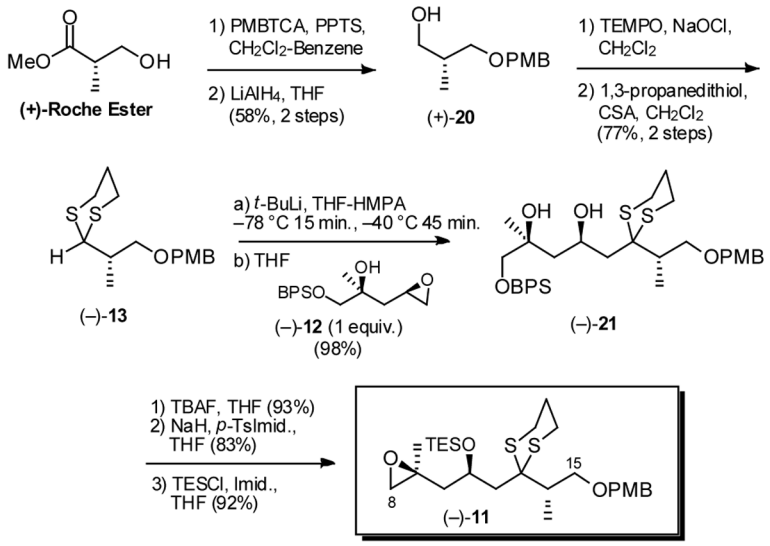

**Scheme 2.**



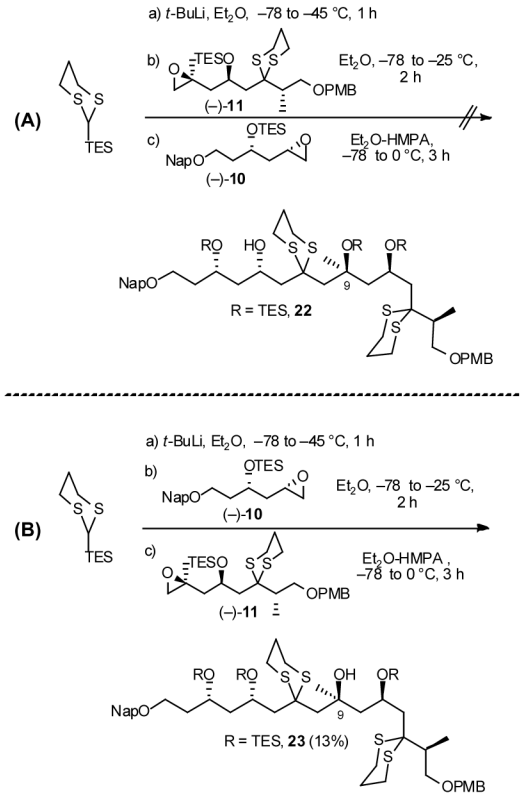

**Scheme 3.**



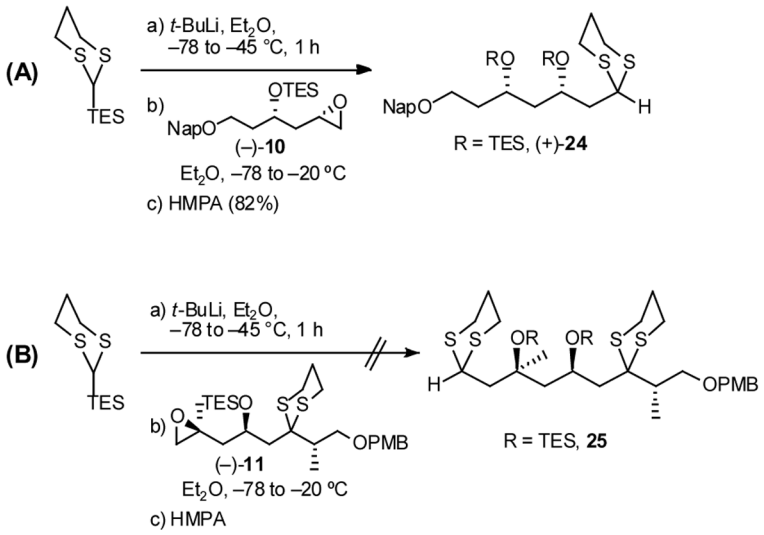

**Scheme 4.**



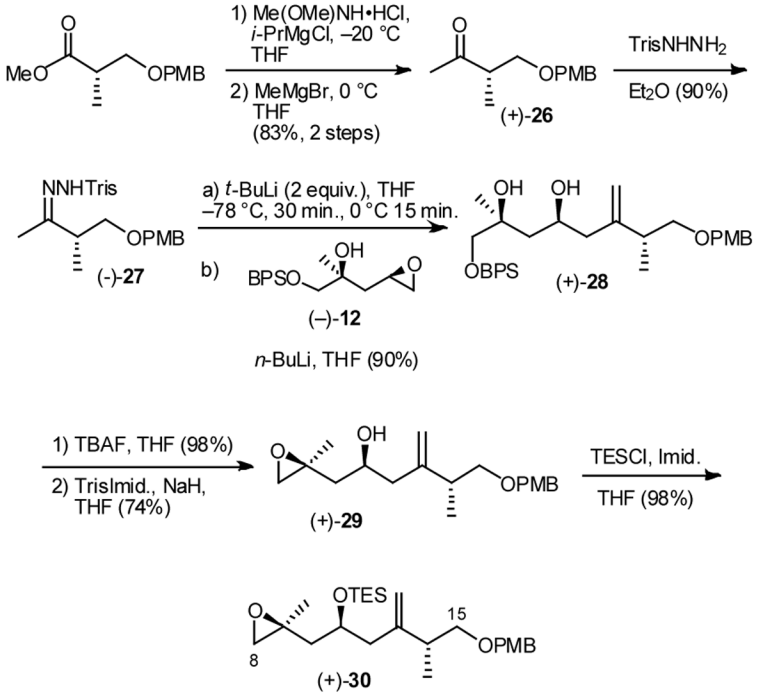

**Scheme 5.**



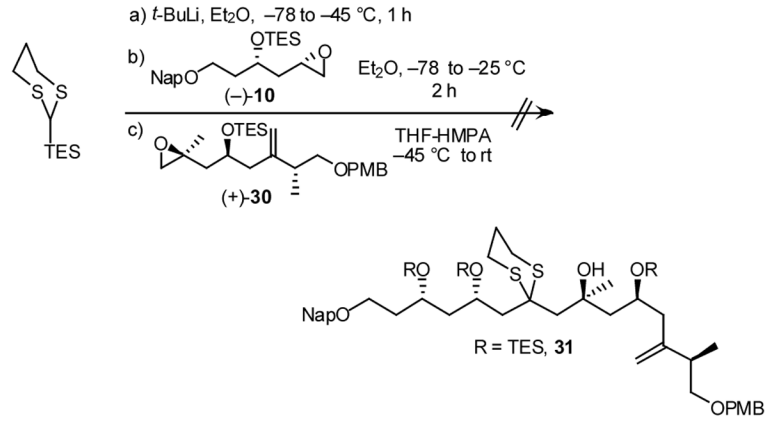

**Scheme 6.**



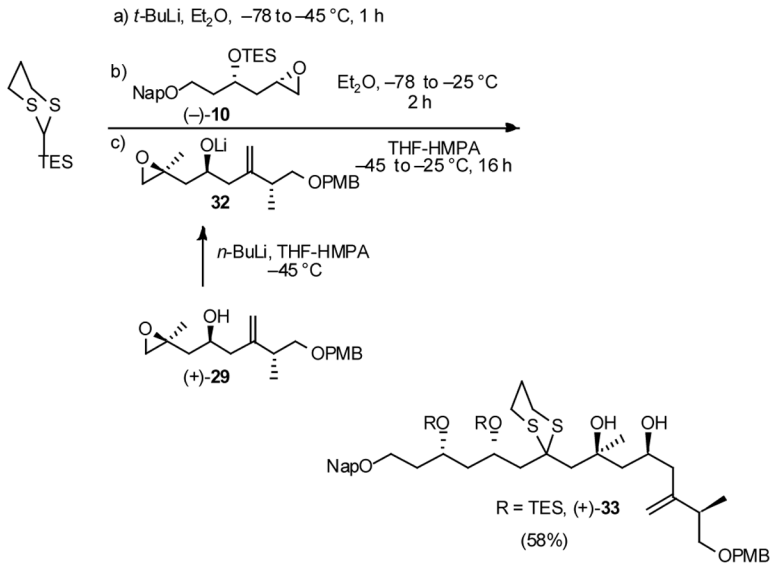

**Scheme 7.**



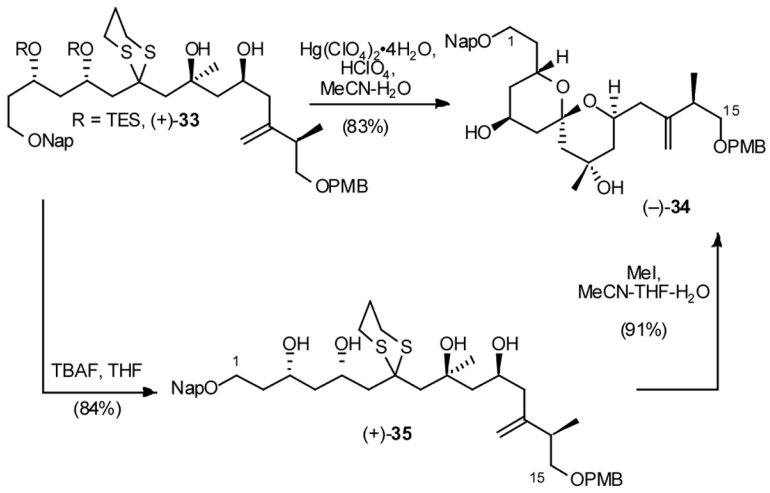

**Scheme 8.**



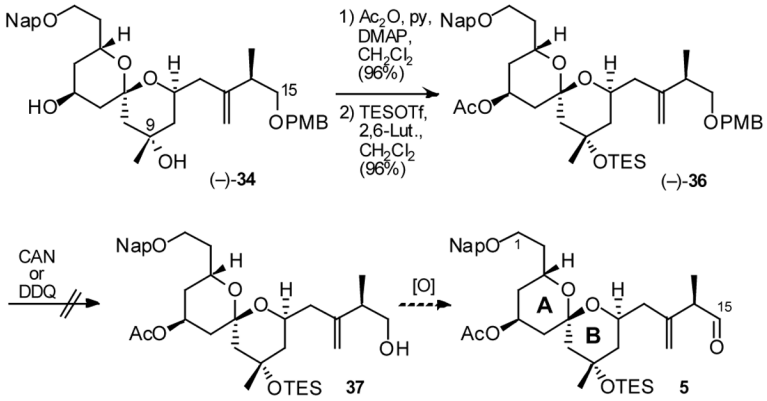

**Scheme 9.**



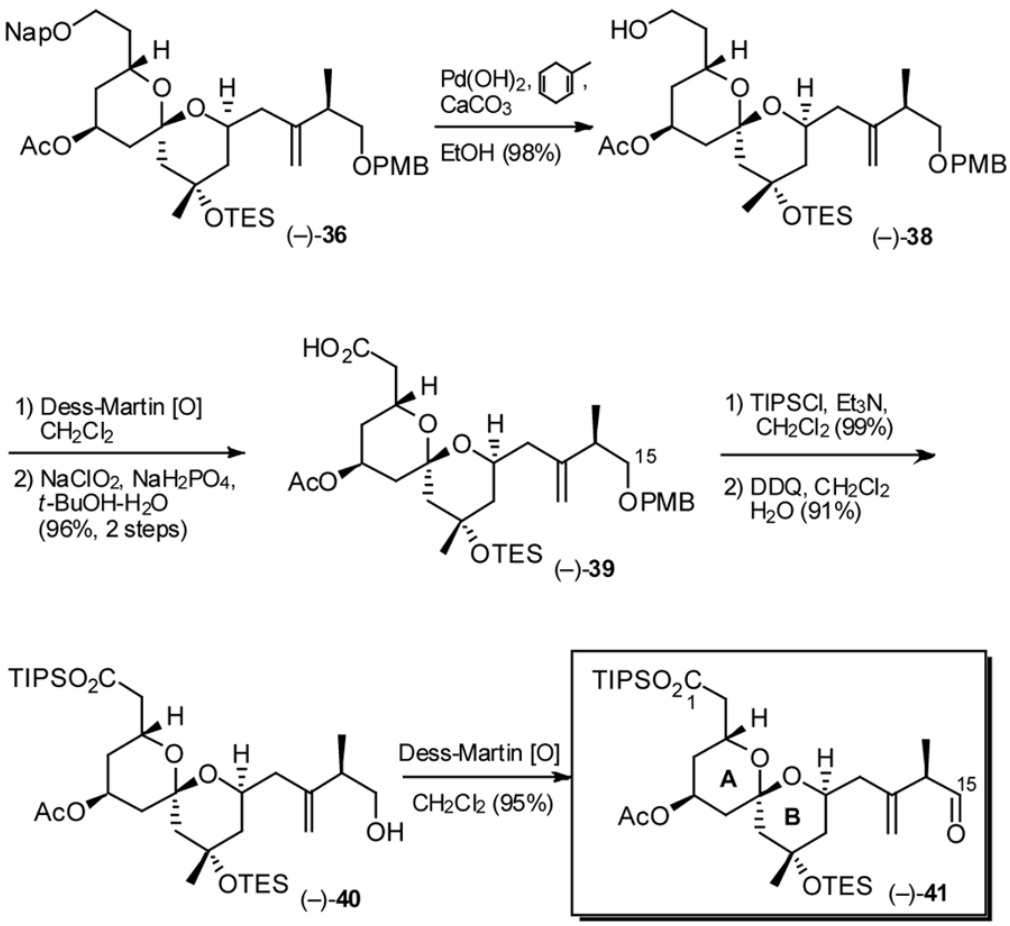

**Scheme 10.**



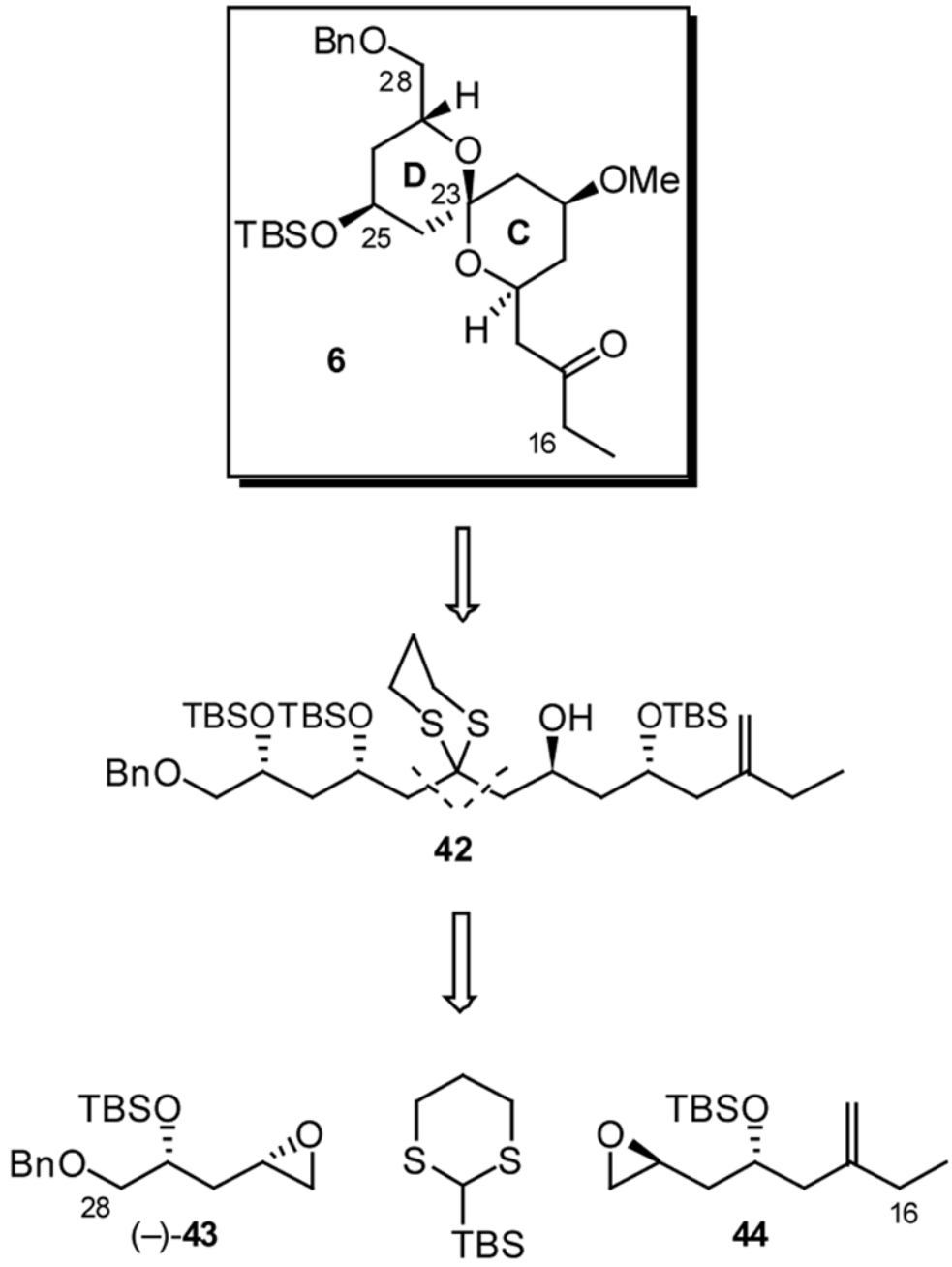

**Scheme 11.**



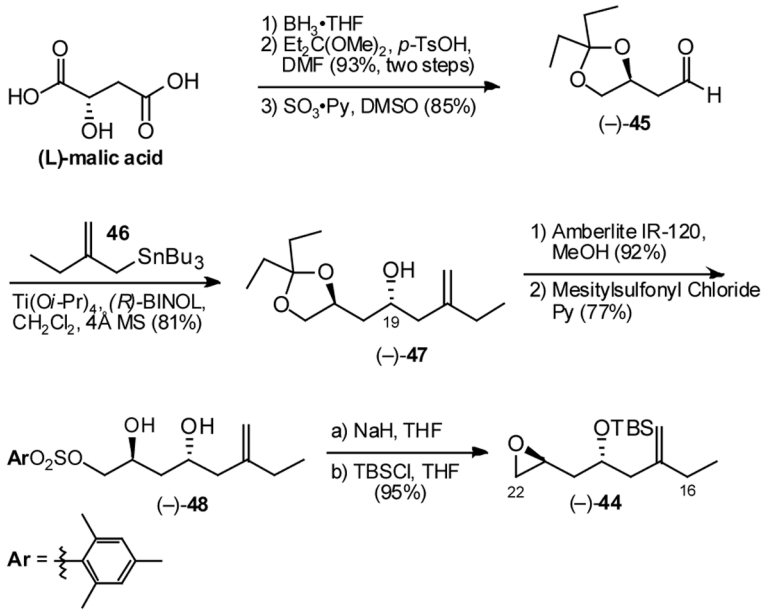

**Scheme 12.**



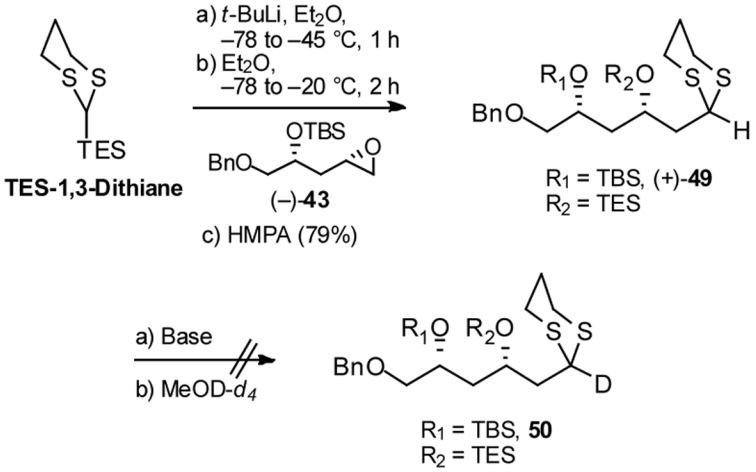

**Scheme 13.**



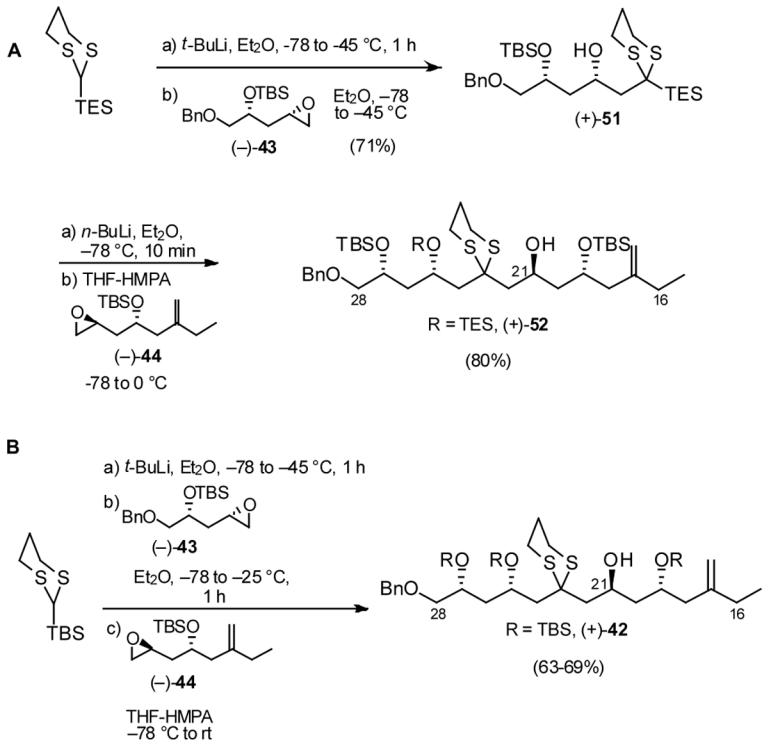

**Scheme 14.**



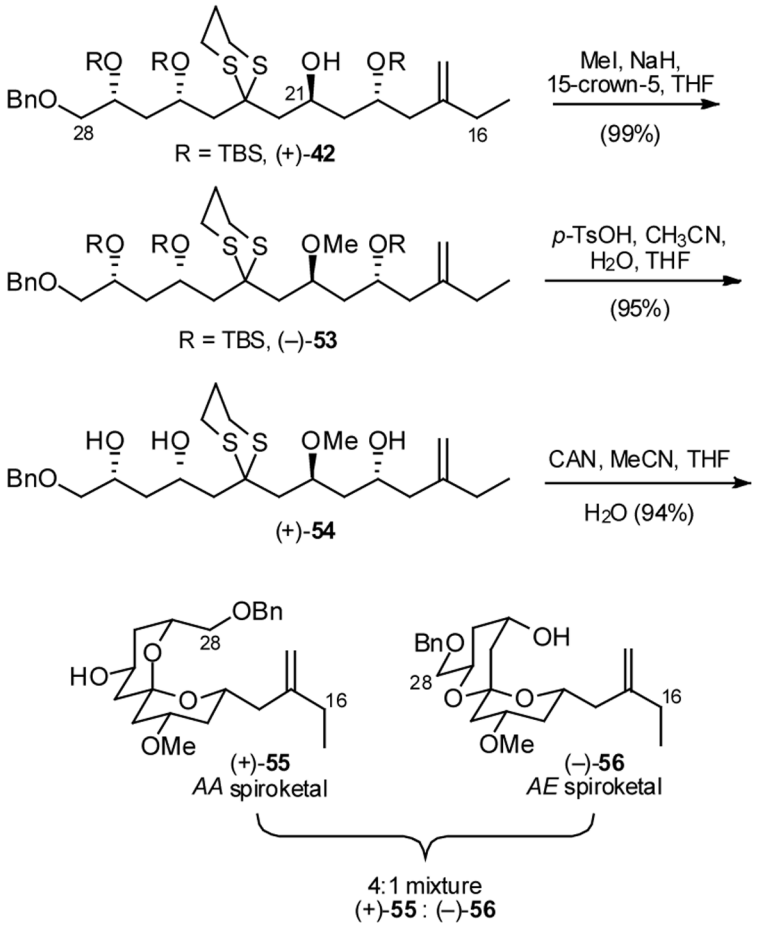

**Scheme 15.**



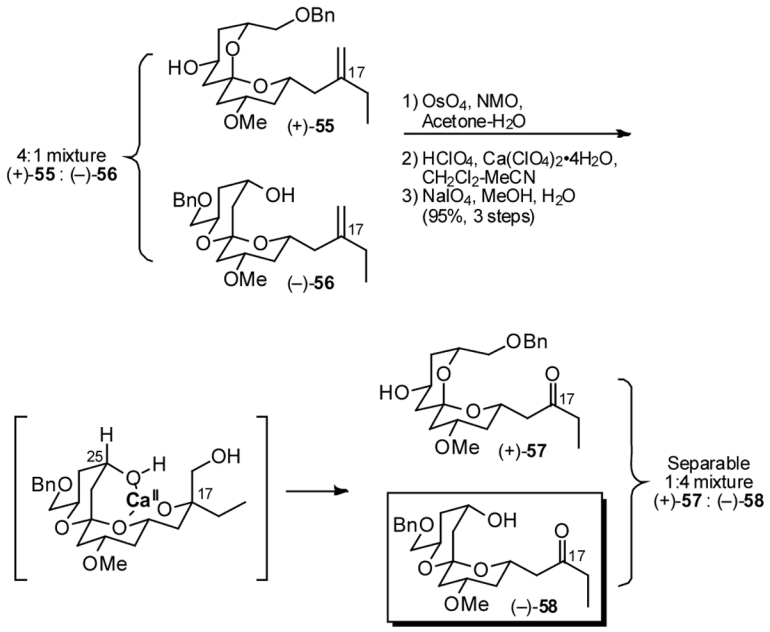

**Scheme 16.**



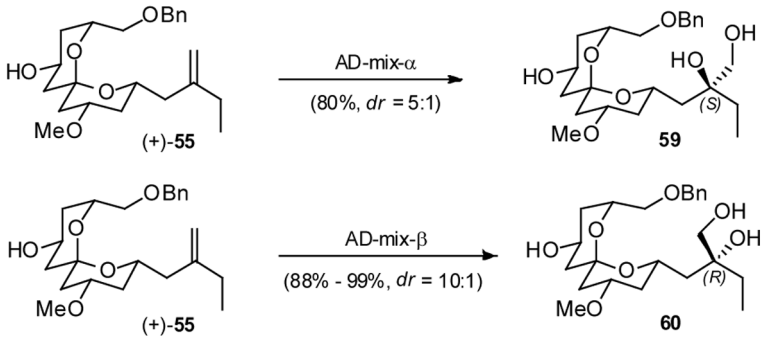

**Scheme 17.**



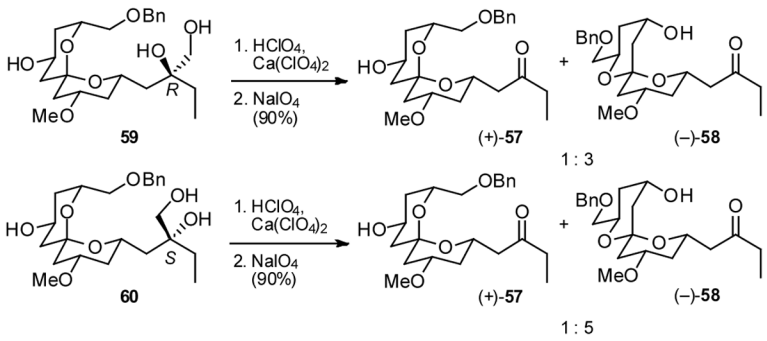

**Scheme 18.**



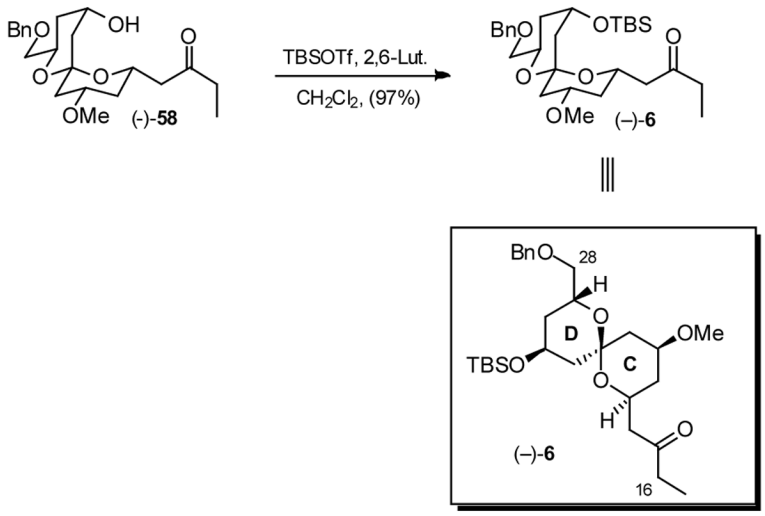

**Scheme 19.**



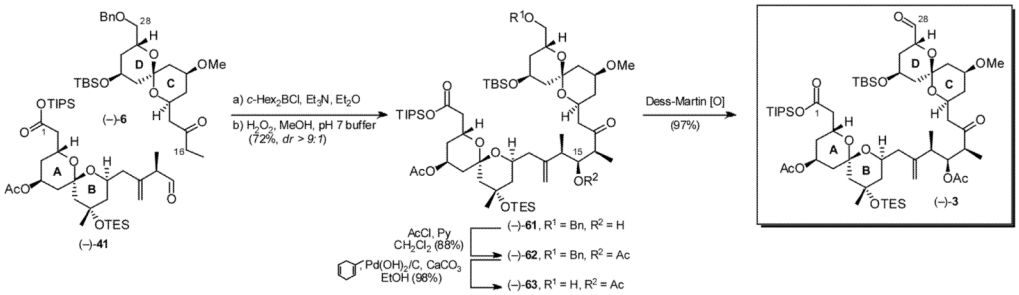

**Scheme 20.**



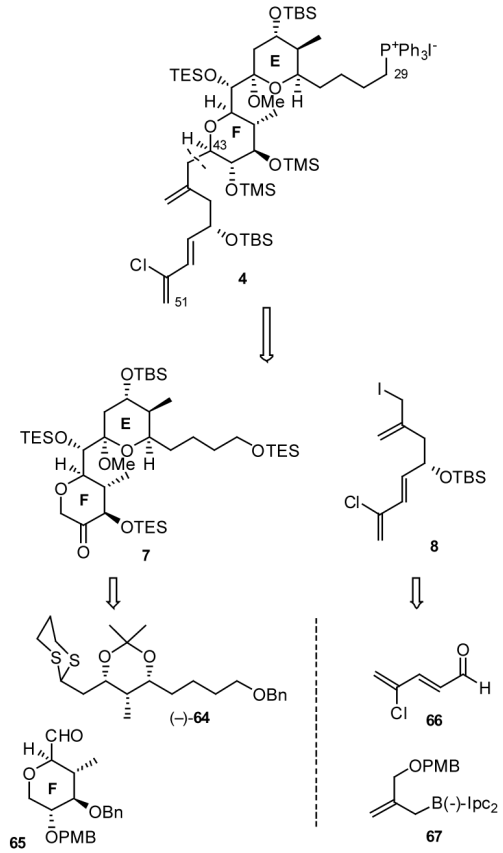

**Scheme 21.**



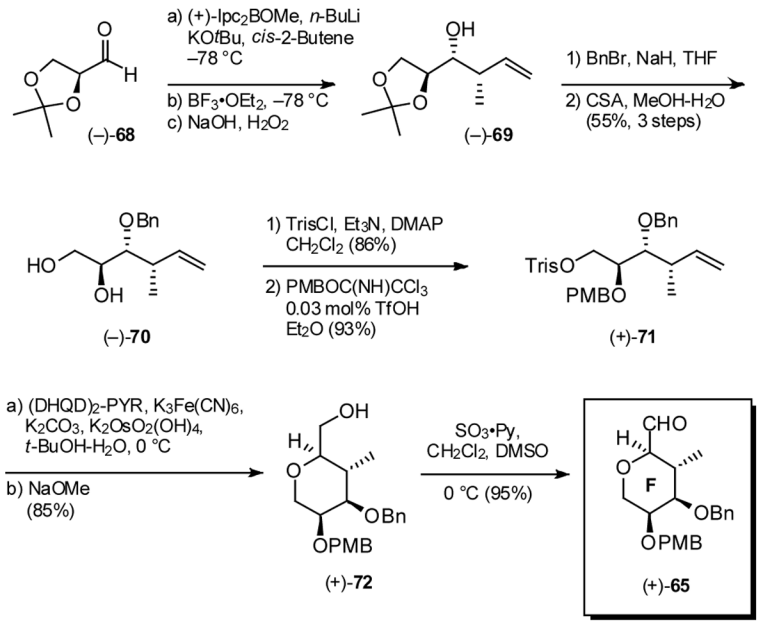

**Scheme 22.**



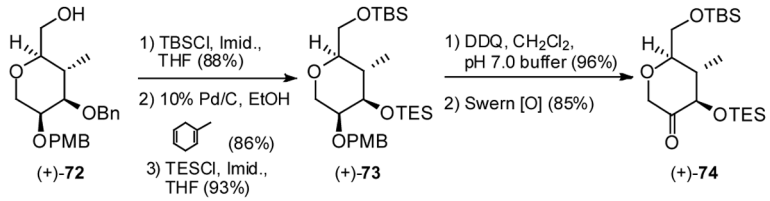

**Scheme 23.**



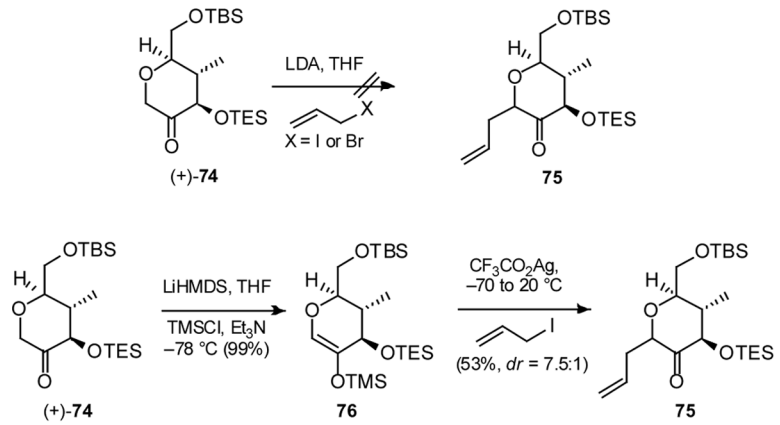

**Scheme 24.**



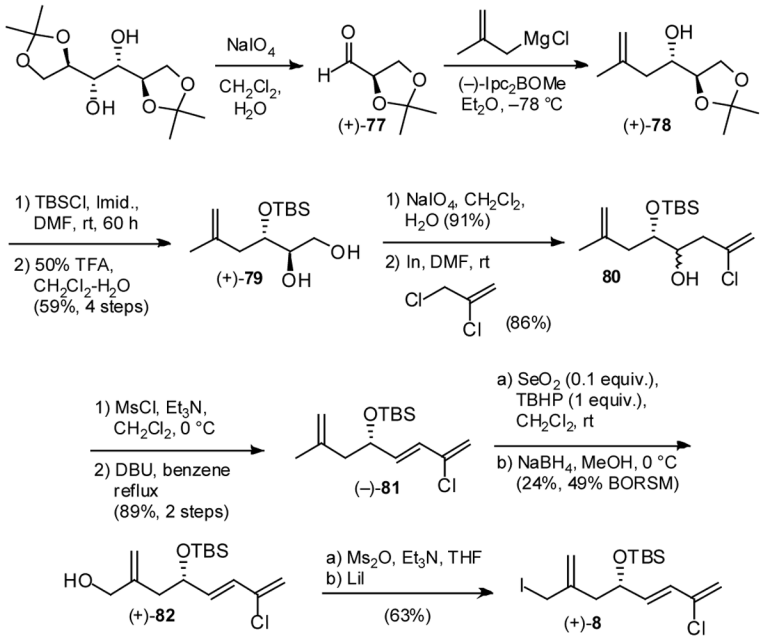

**Scheme 25.**



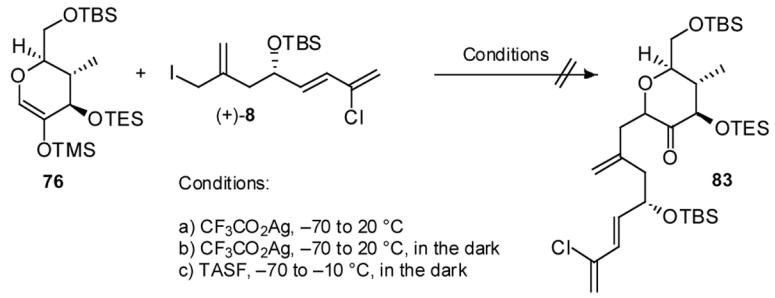

**Scheme 26.**



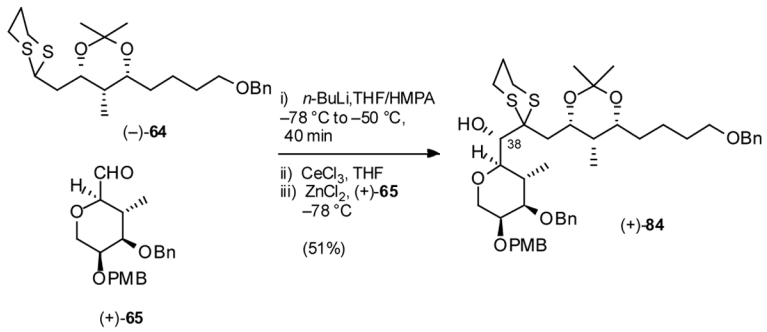

**Scheme 27.**



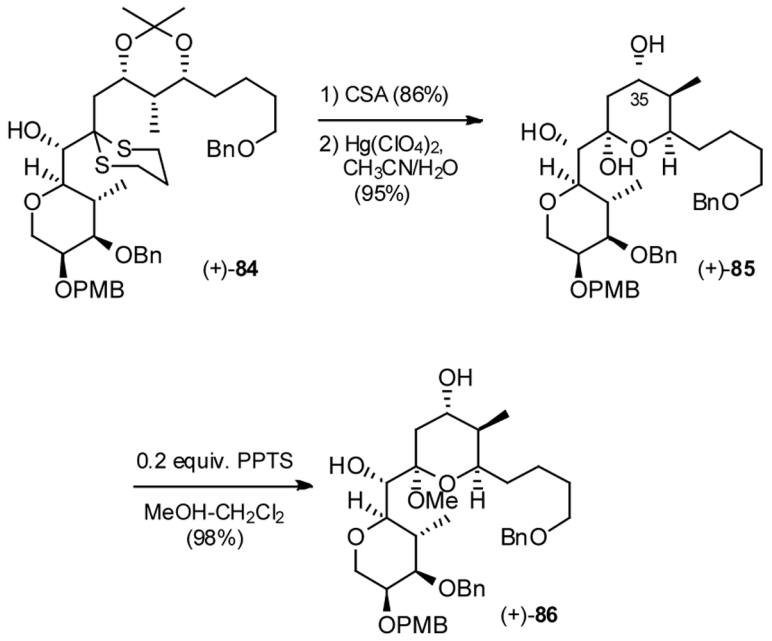

**Scheme 28.**



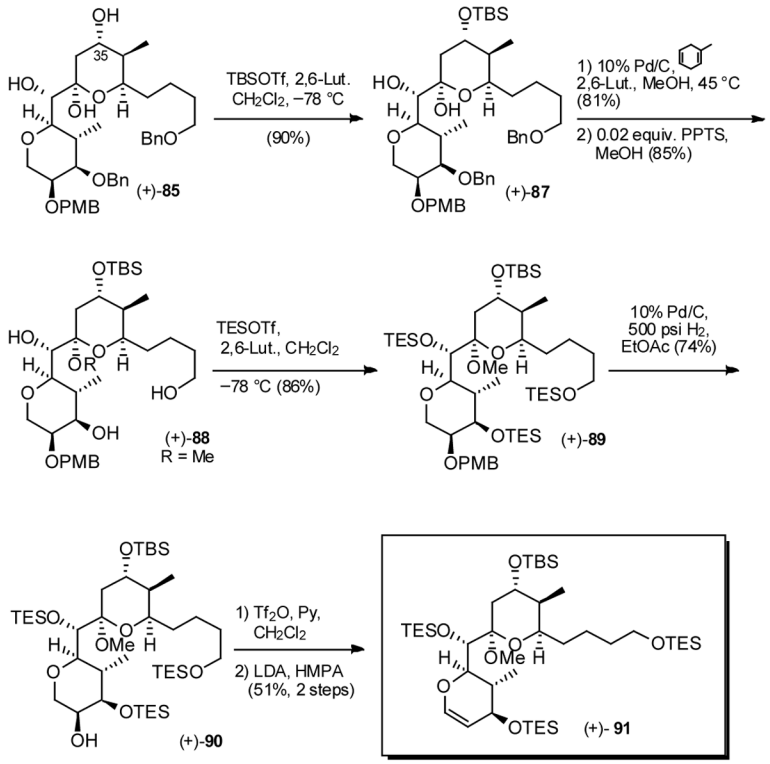

**Scheme 29.**



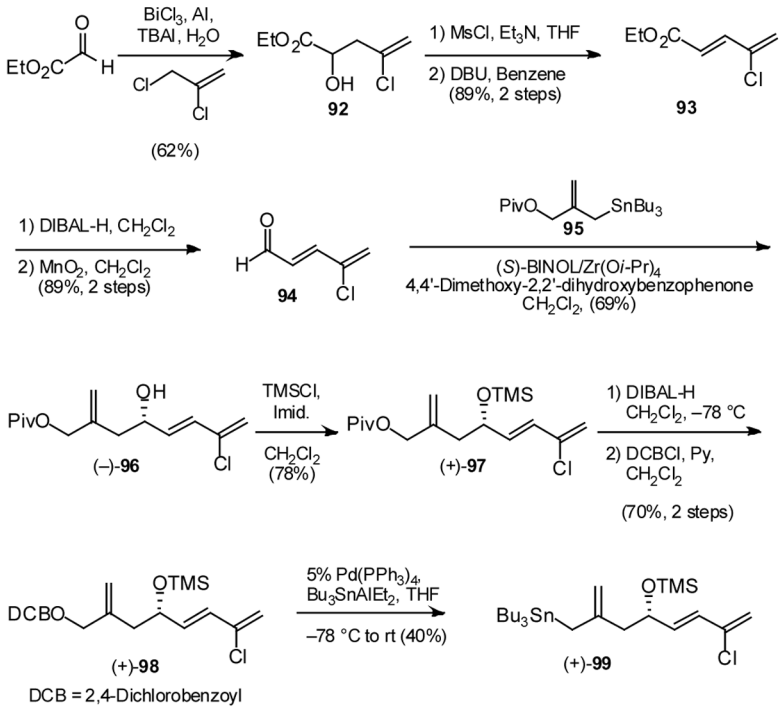

**Scheme 30.**



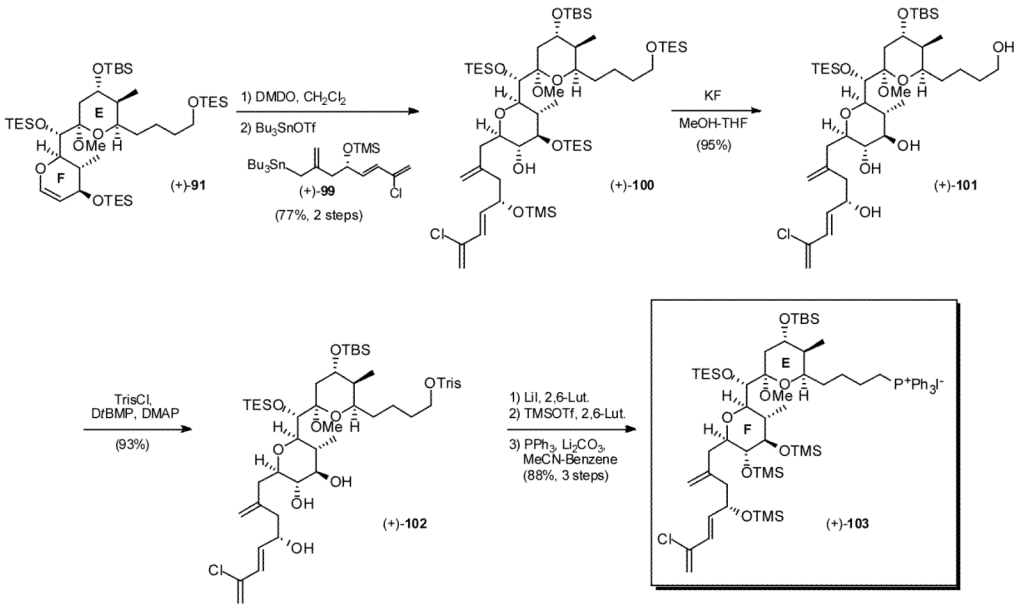

**Scheme 31.**



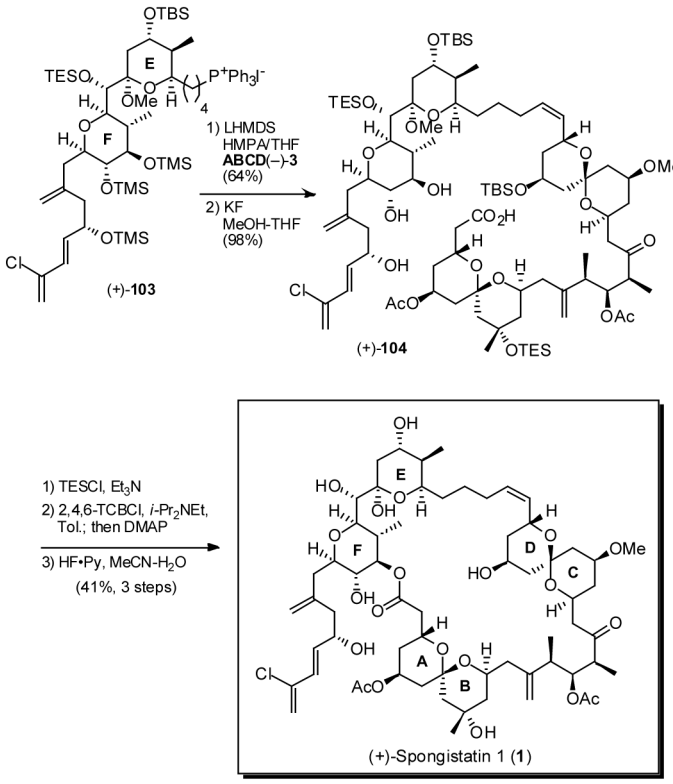

**Scheme 32.**



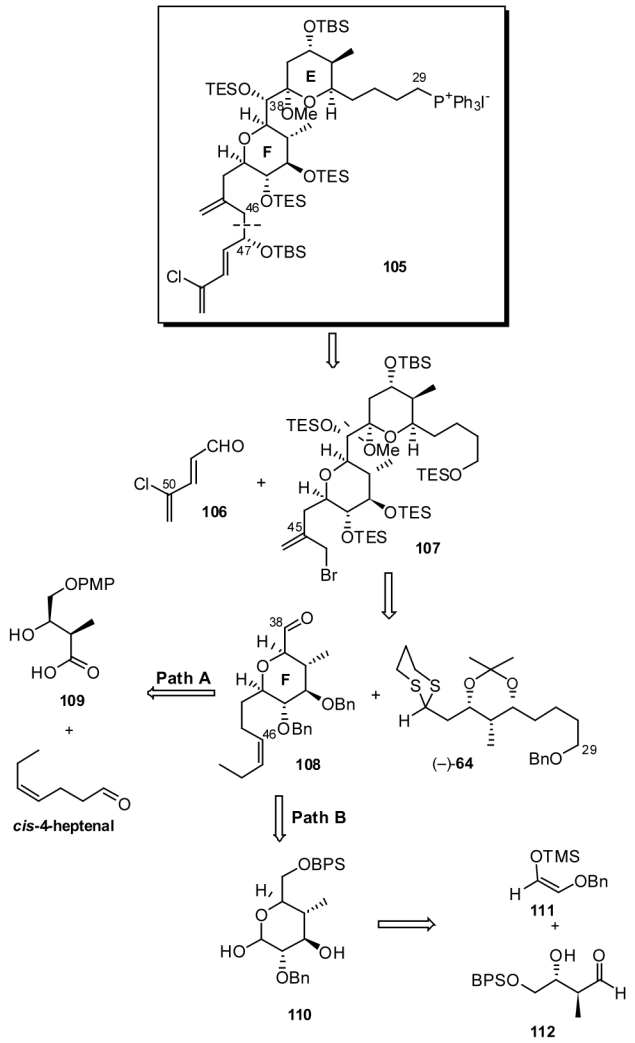

**Scheme 33.**



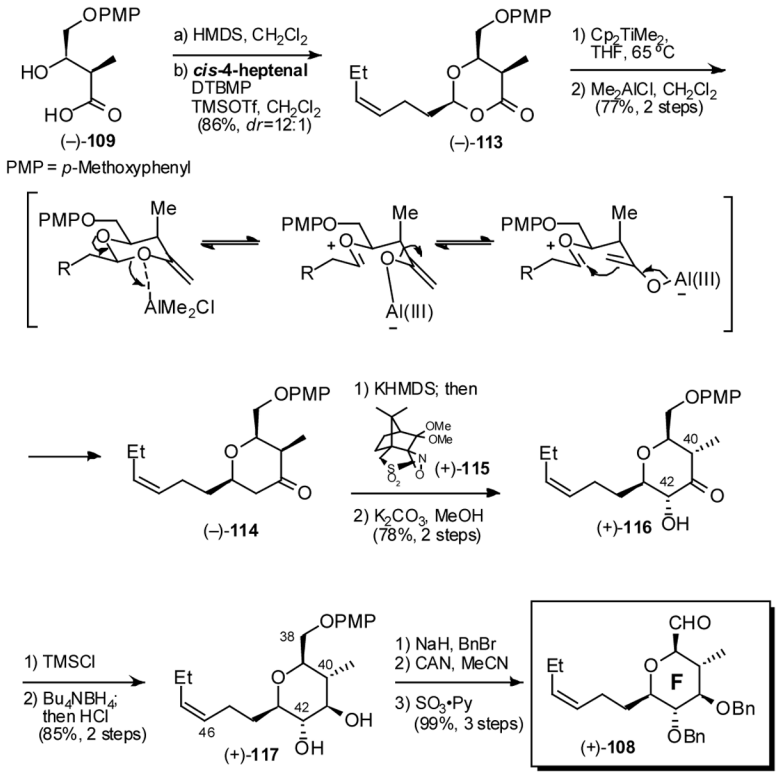

**Scheme 34.**



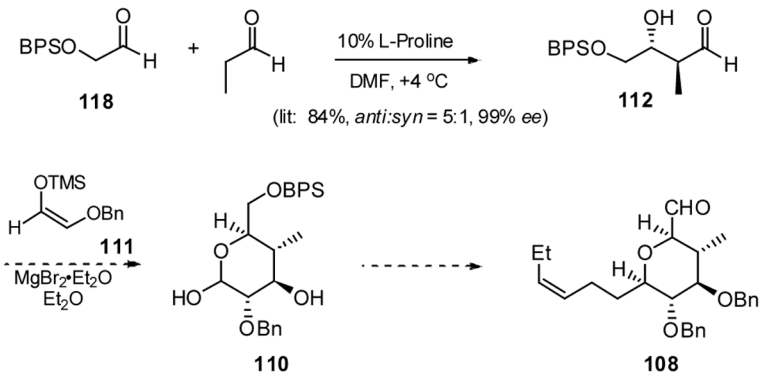

**Scheme 35.**



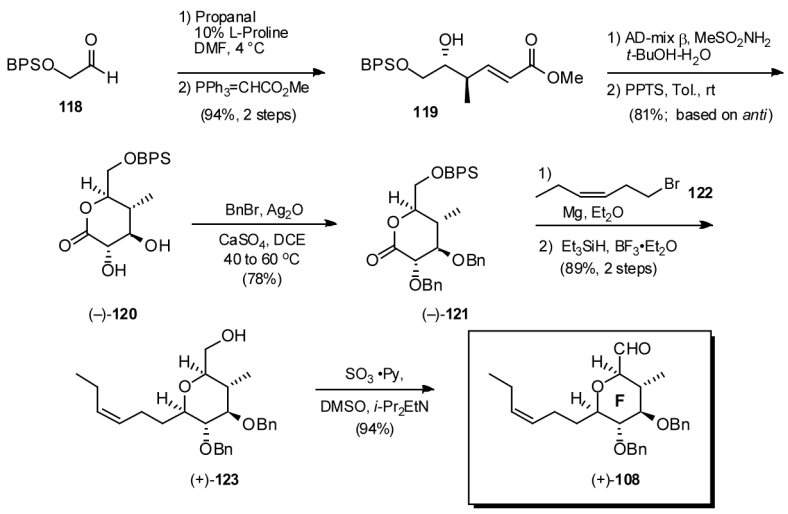

**Scheme 36.**



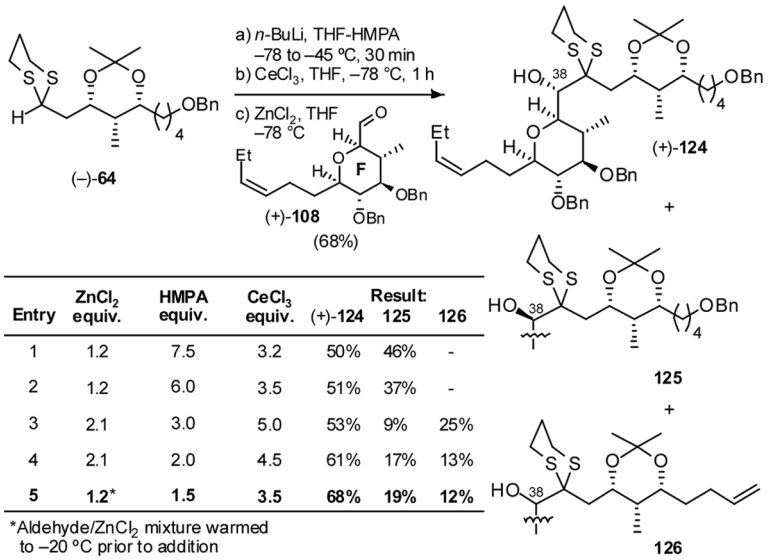

**Scheme 37.**




**Scheme 38.**



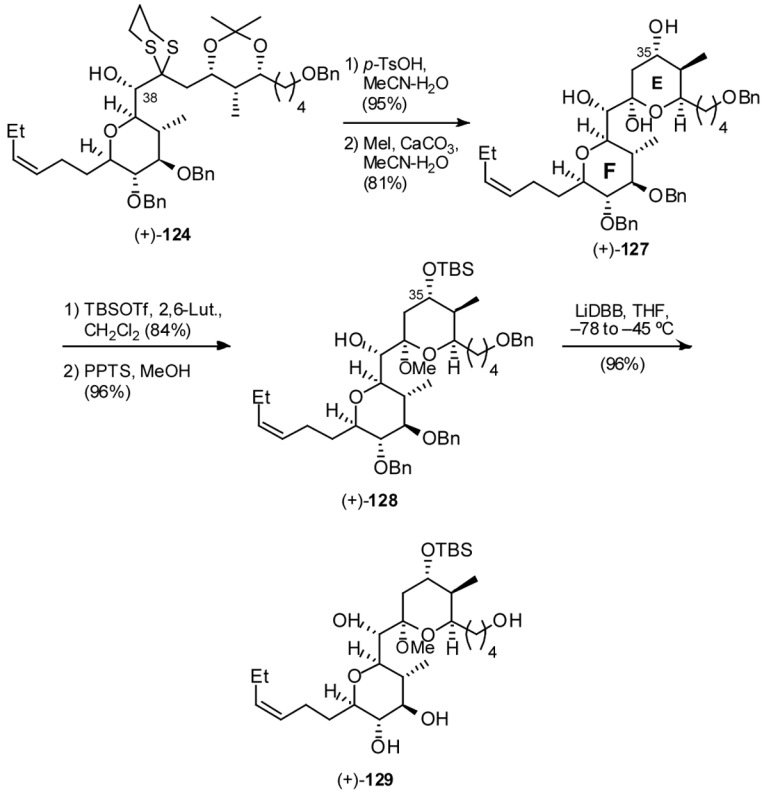

**Scheme 39.**



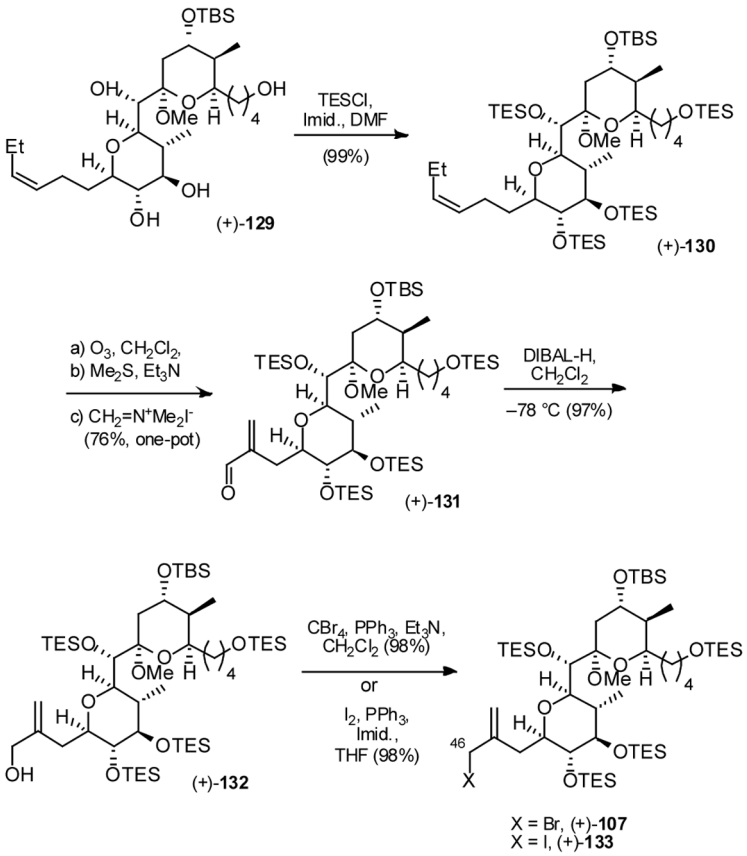

| Entry | $ZnCl_2$ equiv. | HMPA equiv. | $CeCl_3$ equiv. | Result: (+)-124 | 125 | 126 |
|---|---|---|---|---|---|---|
| 1 | 1.2 | 7.5 | 3.2 | 50% | 46% | - |
| 2 | 1.2 | 6.0 | 3.5 | 51% | 37% | - |
| 3 | 2.1 | 3.0 | 5.0 | 53% | 9% | 25% |
| 4 | 2.1 | 2.0 | 4.5 | 61% | 17% | 13% |
| **5** | **1.2*** | **1.5** | **3.5** | **68%** | **19%** | **12%** |

*Aldehyde/$ZnCl_2$ mixture warmed to –20 °C prior to addition

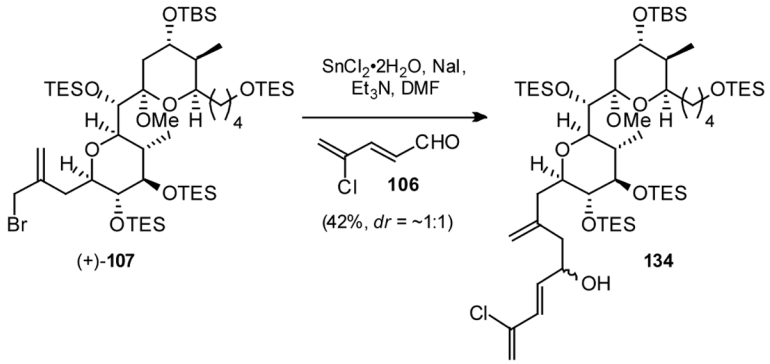
**Scheme 40.**



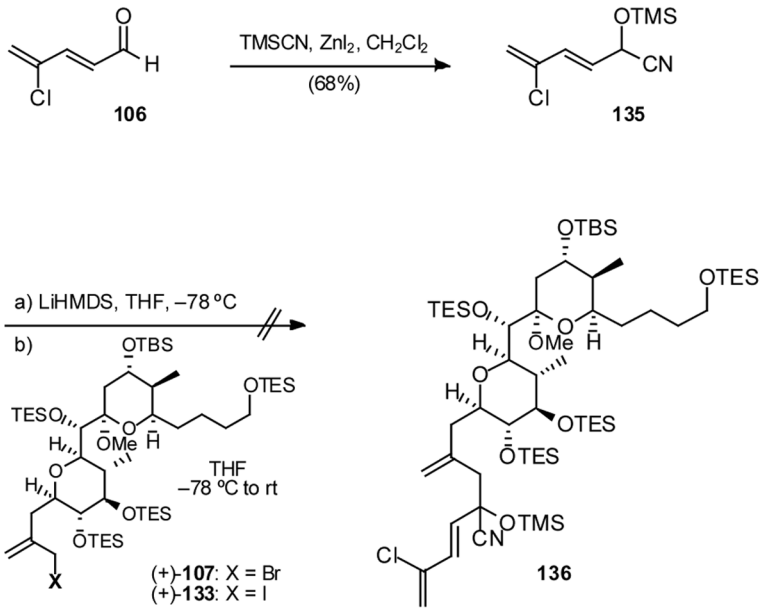

**Scheme 41.**



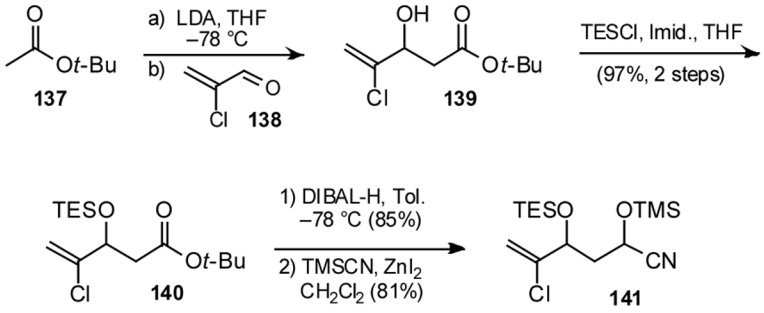

**Scheme 42.**



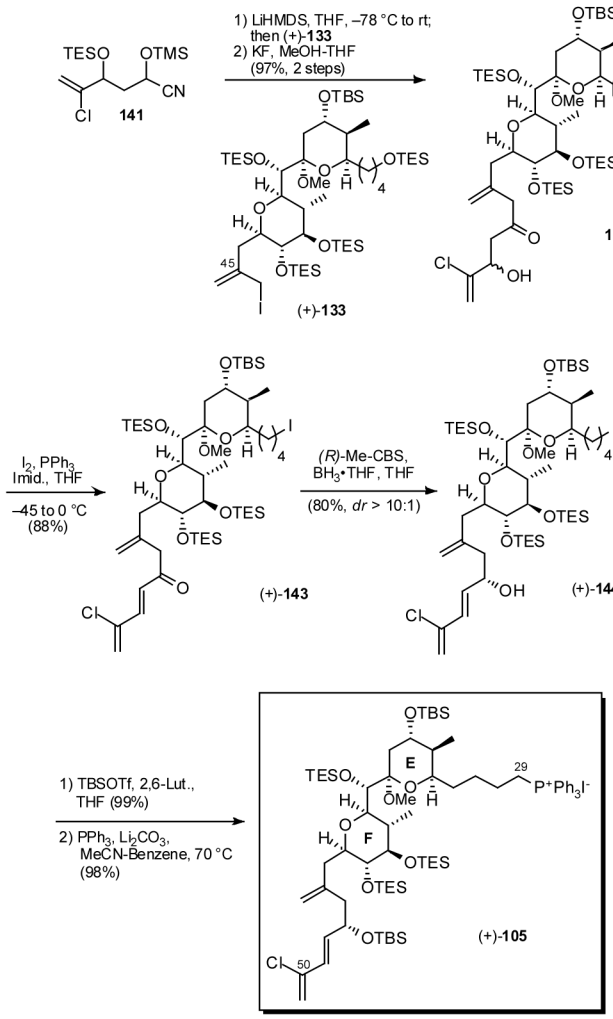

**Scheme 43.**



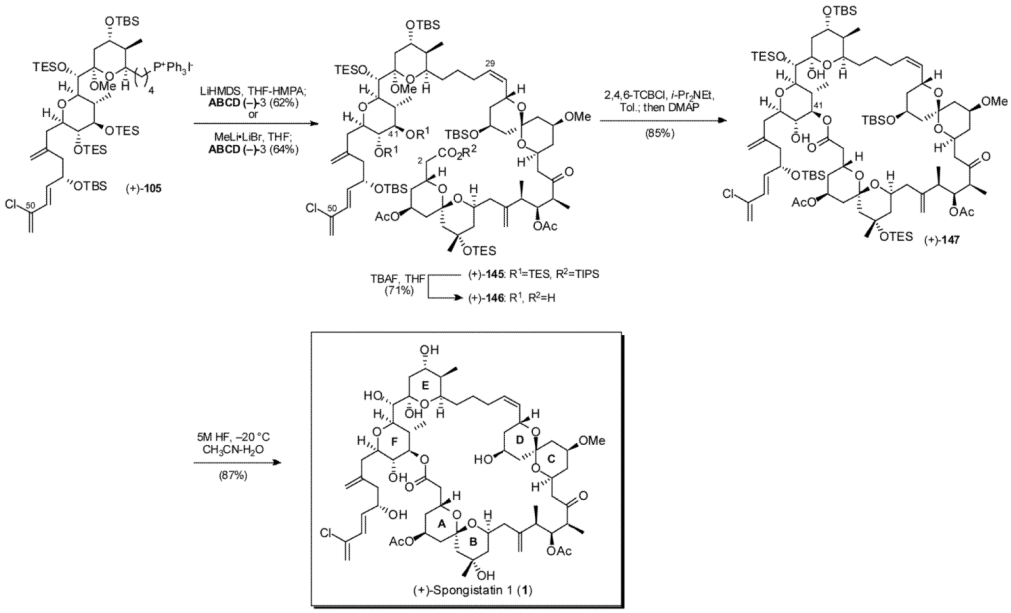

**Scheme 44.**




**Scheme 45.**




**Scheme 46.**




**Scheme 47.**