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Spongipyran synthetic studies. Total synthesis of (+)-spongistatin 2

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ABSTRACT

Evolution of a convergent synthetic strategy to access (+)-spongistatin 2 (**2**), a potent cytotoxic marine macrolide, is described. Highlights of the synthesis include: development of a multicomponent dithiane-mediated linchpin union tactic, devised and implemented specifically for construction of the spongistatin **AB** and **CD** spiro ring systems; application of a Ca^{II} ion controlled acid promoted equilibration to set the thermodynamically less stable axial–equatorial stereogenicity in the **CD** spiroketal; use of sulfone addition/Julia methylenation sequences to unite the **AB** and **CD** fragments and introduce the C(44)–C(51) side chain; and fragment union and final elaboration to (+)-spongistatin 2 (**2**) exploiting Wittig olefination to unite the advanced **ABCD** and **EF** fragments, followed by regioselective Yamaguchi macrolactonization and global deprotection. Correction of the **CD** spiro ring stereogenicity was subsequently achieved via acid equilibration in the presence of Ca^{II} ion to furnish (+)-spongistatin 2 (**2**). The synthesis proceeded with a longest linear sequence of 41 steps.

1. Introduction

In 1993 the research groups of Pettit,[1] Kitagawa,[2] and Fusetani[3] independently reported the isolation of a new class of cytotoxic macrolides, termed, respectively, the spongistatins, altohyrtins, and cinachyrolides.[4] These macrolides, as well as a series of related congeners subsequently reported by the Pettit[5] and Kitagawa[6] laboratories, possess architecturally novel spongipyran skeletons endowed with 24 stereocenters, two [6.6] spiroketals, and a bis-tetrahydropyranylmethane moiety embedded in a 42-membered macrolactone, in conjunction with a delicate unsaturated side chain (Fig. 1). While the initial reports were in agreement with respect to the complete carbon skeleton, there were differences in the assigned relative configurations at various sites. In 1994, the Kitagawa group, exploiting 2-D NMR experiments, in conjunction with an elegant series of Mosher ester analyses and circular dichroism measurements assigned the complete relative and absolute stereochemistries of the spongipyrans,[7] that were subsequently verified by the total syntheses of (+)-spongistatin 2 (**2**) and (+)-spongistatin 1 (**1**), respectively, by the Evans and Kishi groups.[8,9]

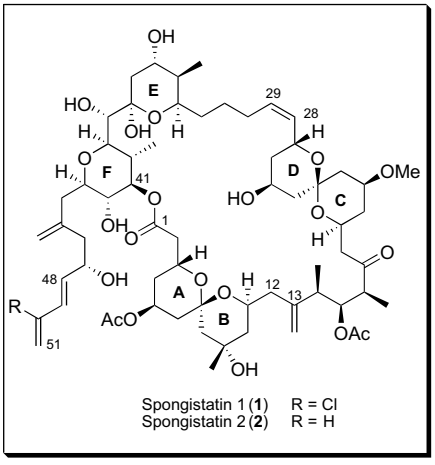

Figure 1. Structures of (+)-spongistatin 1 and (+)-spongistatin 2.

In addition to the daunting molecular architecture, the spongistatins possess remarkable biological profiles. In the NCI panel of 60 human cancer cell line assays, mean GI_{50} values in the 0.04 to 1.1 nM range were observed.[5,10] These results prompted Pettit to state that the spongistatin family of natural products 'appear to be

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the most potent cancer cell inhibitory antimiotic substances discovered to date.'[11] Even more promising than their in vitro activity were the early in vivo results. Spongistatin 1 [(+)-**1**] exhibited curative responses against human melanoma and ovarian xenografts without observed toxicity at 25 μg/kg.[12] Although the spongistatins clearly held considerable promise as chemotherapeutic leads, the extreme low natural abundance [e.g., 400 kg of wet sponge yielded only 13.8 mg of (+)-spongistatin 1 (**1**)],[1] represented a major obstacle for biomedical development.

Not surprisingly the remarkable biological activities, low natural abundances, and daunting molecular architectures, quickly engendered considerable interest in the synthetic community. To date seven total syntheses of the spongistatins have appeared,[8,9,13–17] along with numerous reports describing the synthesis of various advanced fragments.[18] While major contributions in both our understanding of the chemistry of the spongistatins in particular, and polyketide synthesis in general, have emanated from these efforts, collectively these reports did little to augment access to this important class of natural products. As a result, both the Heathcock group[16] and our laboratory[13c,d] initiated programs aimed at the development of synthetic routes capable of producing gram quantities of (+)-spongistatin 2 (**2**) and (+)-spongistatin 1 (**1**). In this full account, we provide a detailed description of our synthesis of (+)-spongistatin 2 (**2**).[13a,b] This synthetic venture provided the foundation that has recently led to a scalable, gram-scale synthesis of (+)-spongistatin 1 (**1**). For a detailed account of the latter see the following paper.[19]

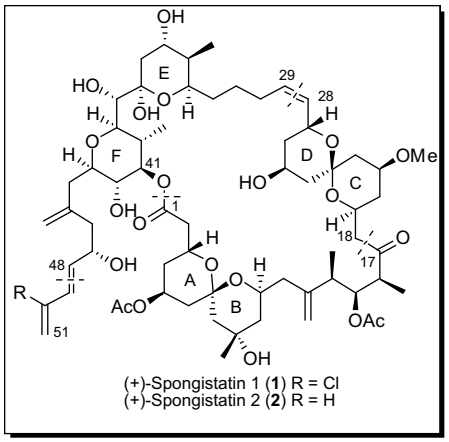
2. Results and discussion

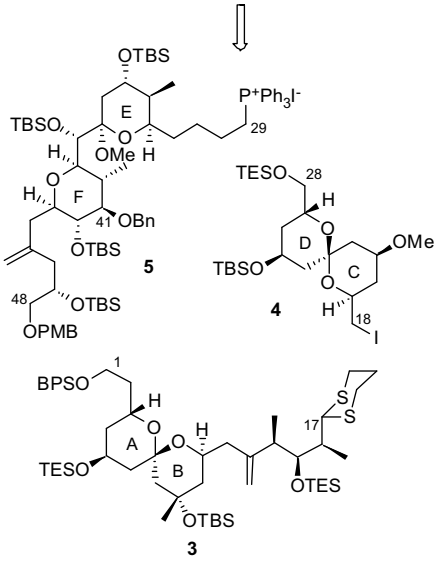
2.1. Synthetic analysis

Initial inspection of (+)-spongistatin 2 (**2**) revealed a number of synthetic challenges. First, a modular approach would be required by which the molecule would ultimately be assembled under mild conditions without compromising the anticipated sensitive triene side chain. We therefore envisioned that completion of the fully functionalized side chain would be required after construction of the macrocyclic core. With this scenario in mind, dissection of the molecule into three fragments of roughly equal complexity led to the **AB** dithiane **3**, the **CD** iodide **4**, and the **EF** Wittig salt **5** lacking the diene moiety (Scheme 1).[20] In the forward direction, union of dithiane **3** with iodide **4** would establish the **ABCD** 'eastern perimeter'. Conversion of the C(28) TES ether to an aldehyde and Wittig union with **EF** phosphonium salt **5** would then establish the C(1)–C(48) carboskeleton, which would be transformed to (+)-spongistatin 2 (**2**) via macrolactonization, final side chain elaboration and global deprotection.

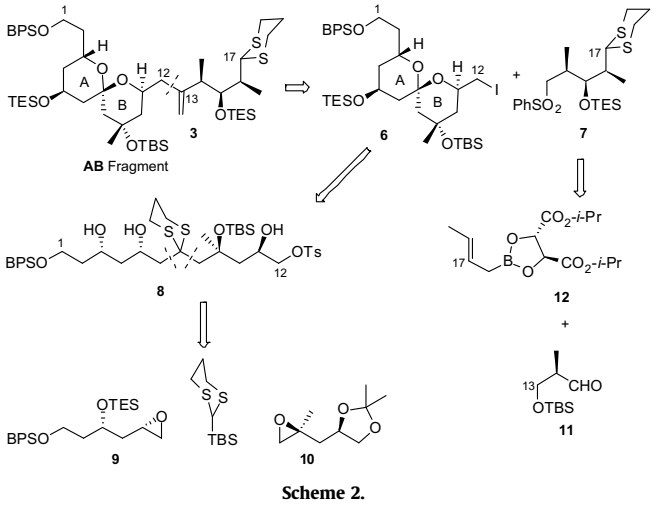
2.2. Synthesis of the C(1) to C(17) AB dithiane (3)

Further disconnection of the C(1)–C(17) subtarget at C(12)–C(13) revealed the **AB** spiroketal **6** and sulfone **7** (Scheme 2). From the synthetic perspective, the **AB** spiroketal possesses two anomeric interactions,[21] and as such was anticipated to be the thermodynamically more stable of the two possible spiro epimers at C(7), a conclusion supported by MM2 calculations.[22] Spiroketal **6** was thus expected to be readily available from a linear precursor such as dithiane **8**, that in turn was envisioned to arise from the two epoxides **9** and **10**, employing the multicomponent dithiane-mediated linchpin coupling tactic involving a 1,4-Brook rearrangement developed specifically for the spongistatin synthetic venture.[23] For the carbon backbone of sulfone **7**, a Roush crotylboration[24] of known aldehyde (−)-**11**[25] with (*E*)-crotylborane **12** appeared viable.[24]



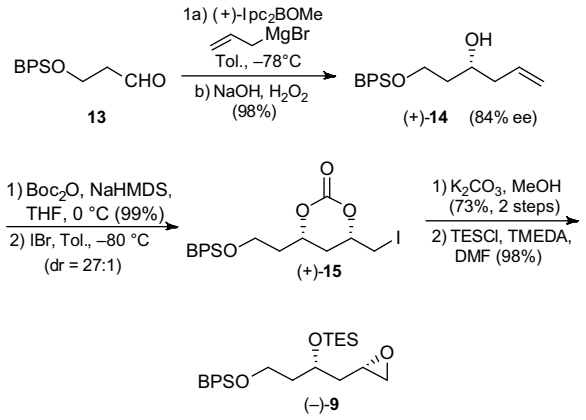


Scheme 1.



Scheme 2.

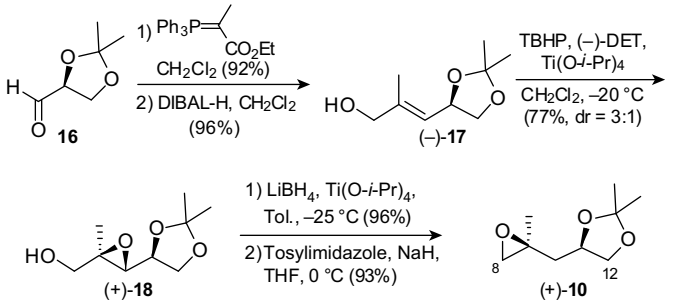
We began with construction of epoxide **9**. Addition of (+)-allyl(-diisopinocampheyl)borane[26] to known aldehyde **13**[27] furnished homoallylic alcohol (+)-**14** (Scheme 3), which was converted to the corresponding *tert*-butyl carbonate and subjected to Bartlett carbonate cyclization[28] employing IBr, an improvement introduced during our synthesis of the (+)-calyculins.[29] Iodocarbonate (+)-**15** was obtained as a mixture of diastereomers (27:1). Basic methanolysis of the carbonate functionality with concomitant epoxide



Scheme 3.

formation, followed by treatment with TESCl in the presence of TMEDA furnished epoxide (−)-**9**.

Construction of epoxide **10** began with Wittig olefination of the isopropylidene derivative of L-glyceraldehyde (**16**),[30] followed by DIBAL-H reduction to furnish allylic alcohol (−)-**17** (Scheme 4). Sharpless asymmetric epoxidation[31] next provided epoxide (+)-**18** in high yield as a mixture (3:1) of diastereomers. Although the selectivity was less than optimal due to a mismatched reagent–substrate pair,[32] the reaction proved reproducible on large scale (cf. 50 g), and thus remained the method of choice for installation of the epoxide. Lewis acid-mediated hydride opening of the epoxide in alcohol (+)-**18**,[33] followed by ring closure of the resultant diol via a modification of the Fraser-Reid cyclization protocol[34] furnished epoxide (+)-**10**.



Scheme 4.

With both epoxide coupling partners in hand, the stage was set for the linchpin union. The solvent controlled multicomponent dithiane-mediated linchpin union of diverse epoxides, developed for the spongistatin project, was based on earlier precedent from the Tietze laboratory.[35] Specifically, reaction of a 2-lithio-2-silyl-1,3-dithiane (Fig. 2) with an epoxide to generate the lithium alkoxide intermediate, followed upon complete reaction, by treatment of the intermediate with a highly polar aprotic solvent (such as HMPA, DMPU, THF, and/or DMF) results in a solvent promoted 1,4-Brook rearrangement[36] to generate the corresponding silyl ether and a new 2-lithio-1,3-dithiane, which can be reacted with a second different epoxide.[37] By proper choice of the epoxide linchpins, followed by careful removal of the dithiane and directed reduction of the carbonyl group, all possible diastereomers of the 1,3,5-polyol system encountered in a wide variety of polyketide natural products can be accessed. Extension of this multicomponent union tactic, now recognized as Type I *A*nion *R*elay *C*hemistry (ARC), comprises a technique that holds considerable potential for diversity oriented synthesis.[38]

The Type I ARC union between 2-(*tert*-butyldimethylsilyl)-1,3-dithiane, epoxide (+)-**10** and epoxide (−)-**9** proceeded smoothly to

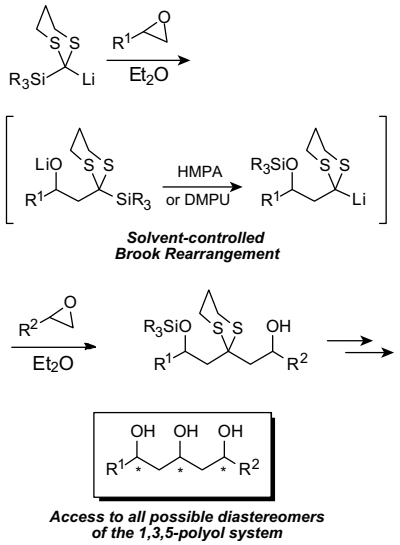


Figure 2. Mechanism of the solvent controlled multicomponent linchpin coupling.

provide polyol (−)-**19** in good yield (Scheme 5). Acid-mediated removal of both the acetonide and the TES protecting group, followed by treatment of the resultant polyol with *p*-toluenesulfonyl chloride in the presence of DMAP then provided triol (+)-**8**. Pleasingly, the Stork mercury perchlorate-mediated hydrolysis of the dithiane, our method of choice to remove dithianes, next proceeded with concomitant spiroketalization to afford the **AB** spiroketal as a mixture (26:1) of isomers, favoring the desired spiroketal (−)-**21** as determined by NOESY NMR studies (Fig. 3). On large scale, the minor axial–equatorial congener (−)-**20** could be isolated and converted to the desired spiroketal (−)-**21** via acid equilibration for purposes of material advancement. Protection of the C(5) hydroxyl as the TES ether and subsequent iodide formation completed the construction of (−)-**6**.

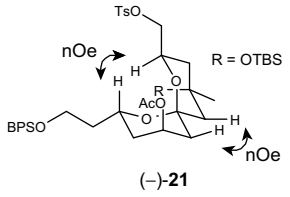
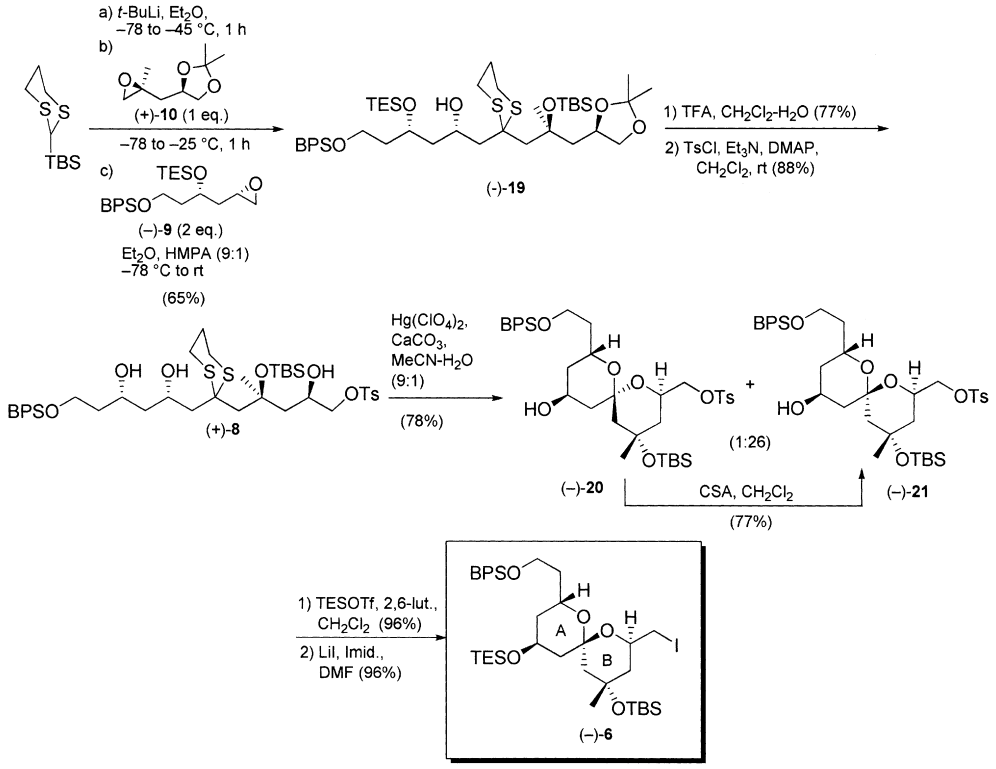


Figure 3. Relevant NOESY data for (−)-**21**.

Having developed an effective route to (−)-**6**, we turned to the synthesis of sulfone **7**. Known aldehyde (−)-**11**[25] was subjected to Roush crotylboration[24] to provide homoallylic alcohol (+)-**22** (Scheme 6). Removal of the TBS protecting group, followed by treatment with 3,4-dimethoxybenzaldehyde led to benzylidene acetal (+)-**23**, which upon DIBAL-H-mediated reduction, and conversion of the resultant primary alcohol to the sulfone furnished (−)-**24**. Oxidative cleavage of the alkene then produced aldehyde (+)-**25**, which was readily converted to dithiane (+)-**7**.

Completion of the C(1) to C(17) **AB** dithiane was envisioned to occur via application of the elegant Julia sulfone addition/methylenation[39] protocol. A model study of this tactic had already been established in our laboratory.[40] Thus, treatment of **AB** iodide (−)-**6** with the lithiated anion of sulfone (+)-**7**, followed in turn by in situ treatment with CH_2I_2/*i*-PrMgCl and a second equivalent of *n*-butyllithium furnished the complete C(1)–C(17) backbone of dithiane (+)-**3** (Scheme 7). The yield of the methylenation reaction however was low, due presumably to the crowded environment of the **AB** ring system. Despite numerous attempts to optimize this



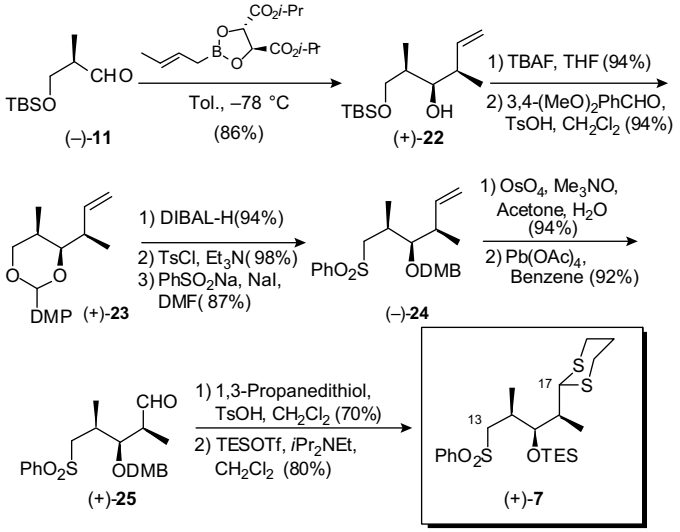
Scheme 5.

reaction, we were unable to improve the yield. Given our interest in verifying the viability of the subsequent union of dithiane (+)-**3** with **CD** iodide (−)-**4**, we decided to press forward and address the Julia methylenation issue later.

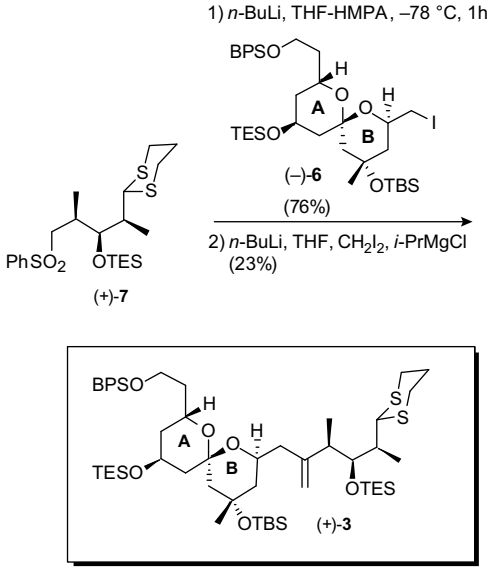
2.3. Construction of the C(18)–C(28) CD spiroketal 4: a serendipitous discovery

From the outset, we recognized that construction of any **CD** spiroketal fragment (cf. **4**) possessing the thermodynamically less stable axial–equatorial configuration at C(23) would represent a challenge given that a single anomeric effect is present. Molecular mechanics calculations indeed confirmed our concern (4.5 kJ/mol energy difference with MM2 forcefield). Nonetheless, we reasoned that when the spiroketal structural motif is embedded in the spongistatin macrocyclic ring, the axial–axial to axial–equatorial equilibrium might be perturbed in favor of the latter. This supposition proved correct (vida infra). Alternatively, it might be possible both to construct an advanced **CD** spiroketal fragment under kinetically controlled conditions and to maintain the integrity of the C(23) stereogenicity throughout the synthesis (vida infra).

We approached construction of the **CD** spiroketal **4** in a fashion similar to the **AB** spiroketal. Two routes were envisioned. First, a stepwise approach, involved alkylation of epoxide **27** with dithiane **28** (Scheme 8), the latter prepared by thioacetalization of the corresponding aldehyde. Alternatively, application of our multicomponent dithiane-mediated linchpin protocol involving 2-TBS-1,3-dithiane, epoxide **27**, and epoxide **29** held promise of providing a viable route to the desired target. Although we

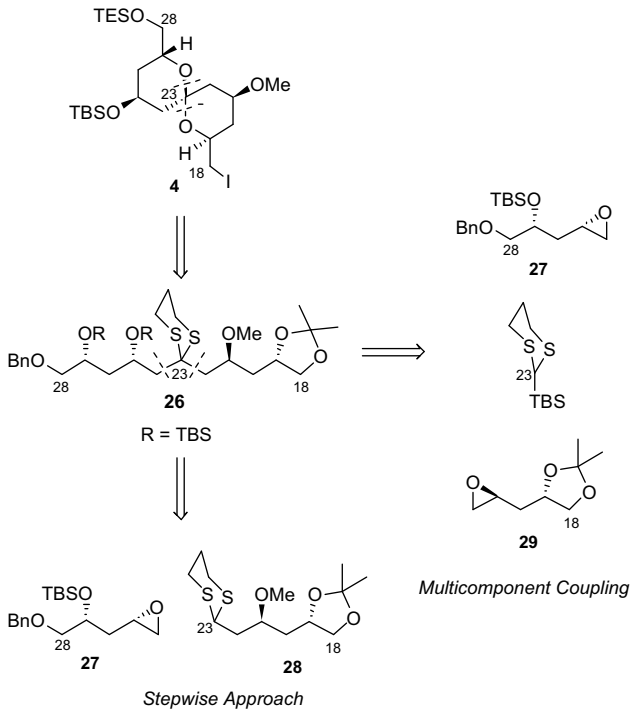


Scheme 6.



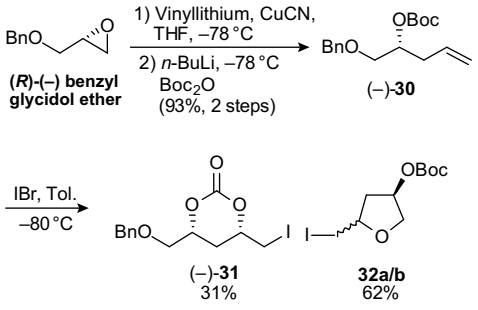
Scheme 7.

intended to examine both routes, the latter approach appeared more desirable, considering the higher convergency (Scheme 8).



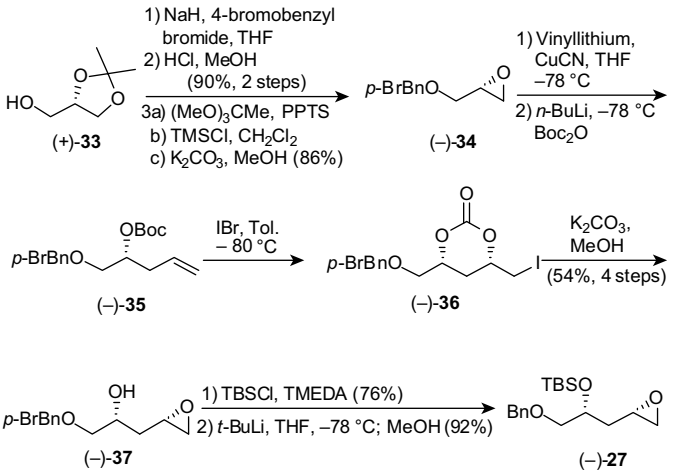
Scheme 8.

Nonetheless, with the stepwise approach initially in mind, construction of **CD** spiroketal **4** began with the synthesis of epoxide **27**, as this epoxide could be employed in both the stepwise and multicomponent tactics. Reaction of (*R*)-(−)-benzyl glycidol ether with the cuprate derived from vinyllithium, followed by protection of the derived alcohol with BOC anhydride furnished carbonate (−)-**30** (Scheme 9). Unfortunately, all attempts to effect the IBr-mediated iodocarbonate cyclization employing a variety of conditions, led to a mixture of (−)-**31** and tetrahydrofurans **32a**/**b**, favoring the tetrahydrofurans by 2–4:1.



Scheme 9.

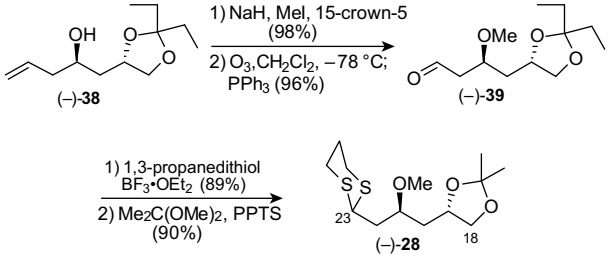
We reasoned that furan formation could be suppressed by decreasing the electron density on the benzyl ether oxygen. Examination of a number of electron deficient benzyl ethers eventually led to a 4-bromobenzyl group. Protection of (+)-**33** (Scheme 10) as the 4-bromobenzyl ether, followed by acid-mediated hydrolysis of the acetonide and epoxide formation via the Sharpless protocol[41] thus led to glycidol ether (−)-**34**, which upon treatment with vinyllithium in the presence of copper cyanide; protection of the resultant alcohol as a *tert*-butyl carbonate then furnished (−)-**35**. Pleasingly, the IBr-mediated cyclization now proceeded smoothly to give exclusively iodocarbonate (−)-**36**, which was subjected to basic methanolysis to



Scheme 10.

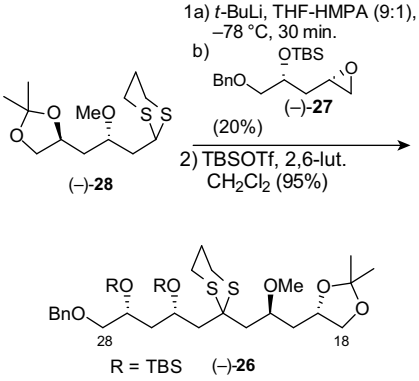
furnish epoxide (−)-**37**. Protection of the free alcohol as a TBS ether, followed by *tert*-butyllithium-mediated removal of the bromide completed construction of epoxide (−)-**27**.

For dithiane **28**, we began with known allylic alcohol (−)-**38**,[42] prepared in four steps from (*S*)-(−)-malic acid. Conversion to the methyl ether and ozonolysis led to aldehyde (−)-**39** (Scheme 11). Thioketalization under Lewis acidic conditions then proceeded with concomitant removal of the acetonide to produce a diol that was converted to isopropylidene acetal (−)-**28**.



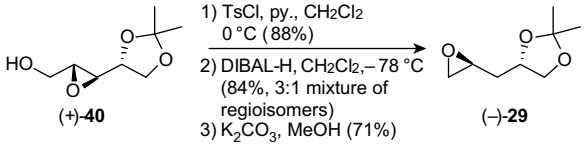
Scheme 11.

With both coupling partners in hand, lithiation of (−)-**28** with *t*-BuLi in THF/HMPA, followed by treatment with epoxide (−)-**27** produced the desired C(18)–C(28) adduct, albeit in disappointing yield, presumably due to incomplete lithiation (Scheme 12). Silylation of the resulting free alcohol completed construction of the spiroketalization precursor (−)-**26**. However, despite extensive effort to optimize the alkylation, we were unable to improve the yield above 20%. We therefore turned to the multicomponent route.



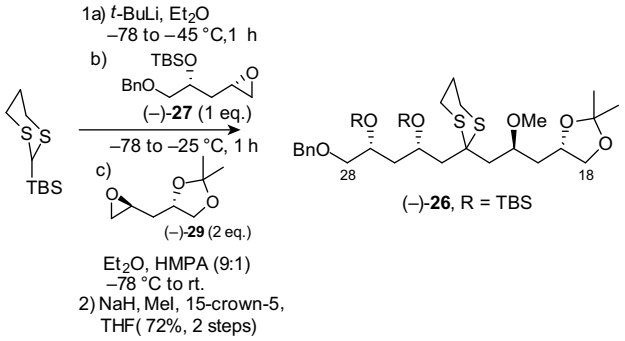
Scheme 12.

The required epoxide **29** was prepared by treatment of known alcohol (+)-**40** (available in three steps from D-glyceraldehyde acetonide)[43] with tosyl chloride, followed by hydride-mediated epoxide opening[44] to furnish a readily separable mixture (3:1) of 2- and 3-hydroxyl substituted tosylates (Scheme 13). Basic methanolysis of the major isomer led to epoxide (−)-**29** in good yield.



Scheme 13.

Alkylation of 2-lithio-2-(*tert*-butyldimethylsilyl)-1,3-dithiane with epoxide (−)-**27**, followed by HMPA-mediated 1,4-Brook rearrangement and union with epoxide (−)-**29** led to the desired coupling product, which upon O-methylation furnished (−)-**26** in 72% yield for the two steps (Scheme 14). Importantly, the multicomponent strategy not only eliminated two steps from the earlier sequence, but also proved far more efficient than the stepwise process.



Scheme 14.

Having established a viable route to the C(18)–C(28) carbon skeleton, we turned to completion of iodide **4** (Scheme 1). Treatment of (−)-**26** with methanolic HCl resulted in removal of both the acetonide and silyl ethers to furnish tetraol (+)-**41** in good yield (Scheme 15). The Stork mercury (II) perchlorate-promoted removal of the dithiane proceeded, as anticipated, with concomitant spiroketalization to produce a mixture (2:1) of the *undesired* axial–axial spiroketal (+)-**42** and the desired axial–equatorial product (−)-**43**. Surprisingly however, exposure of the unpurified reaction mixture to perchloric acid in CH_2Cl_2/MeCN (10:1) resulted in the formation of only the desired spiroketal (−)-**43**. The configuration at the C(23) stereocenter was established by silylation of the primary hydroxyl, followed by a NOESY NMR study, which proved consistent with the enhancements observed by both the Kitagawa[2] and Fusetani[3] groups in (+)-spongistatin 1 (Fig. 4).

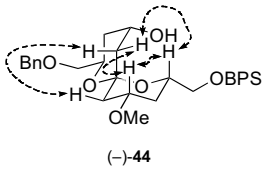


Figure 4. Relevant NOESY Data for (−)-**44**.

To understand the equilibration, we attempted to isomerize both pure (+)-**42** and the purified mixture of (+)-**42** and (−)-**43** to the desired spiroketal, employing conditions identical to those used with the unpurified mixture. Only a 1:1 mixture (at best) of the isomeric spiroketals resulted. After considerable analysis, we surmised that $Ca(ClO_4)_2$ generated during the dithiane hydrolysis might play a significant role in the equilibration process. Indeed, treatment of the purified mixture (2:1) of (+)-**42** and (−)-**43** with perchloric acid in the presence of 1 equiv of $Ca(ClO_4)_2$ led to a 9:1 mixture of isomers favoring the desired spiroketal (−)-**43** (Scheme 16). Although this ratio was moderately lower than that obtained when the crude mixture was employed, clearly Ca^{II} was playing a significant role in the equilibration process. Subsequent MM2 calculations[22] suggested that the Ca^{II} ion could coordinate to the C(18) and C(25) hydroxyls, as well as to the C-ring pyran, thus driving the equilibrium to favor (−)-**43** via chelation of the desired C(23) congener. Careful work-up to prevent isomerization furnished (−)-**43** (Fig. 5).

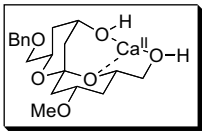
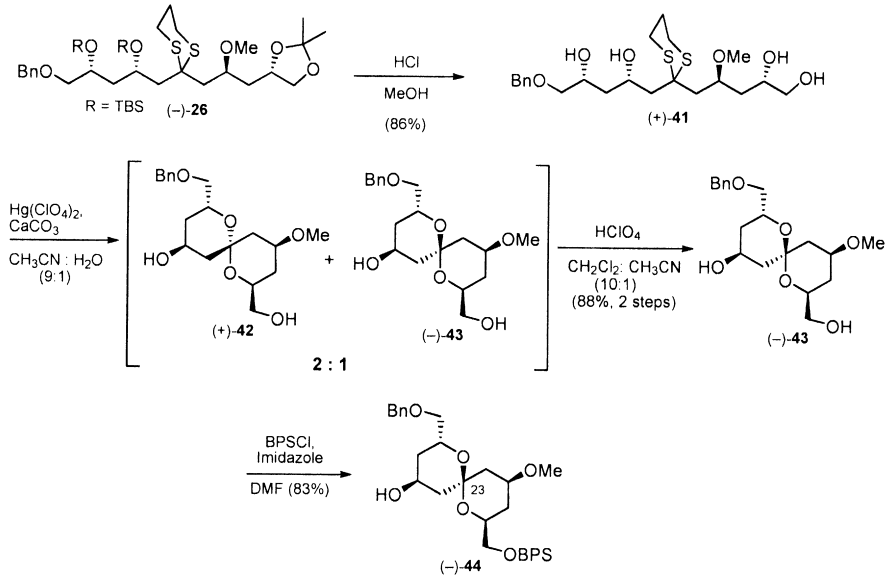
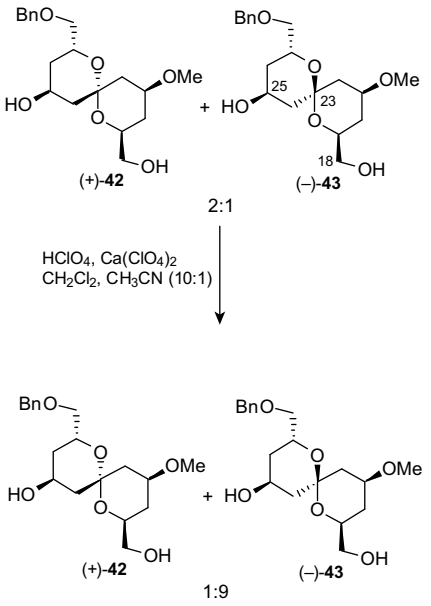


Figure 5. Model for how Ca^{II} templates the formation of the desired spiroketal.



Scheme 15.

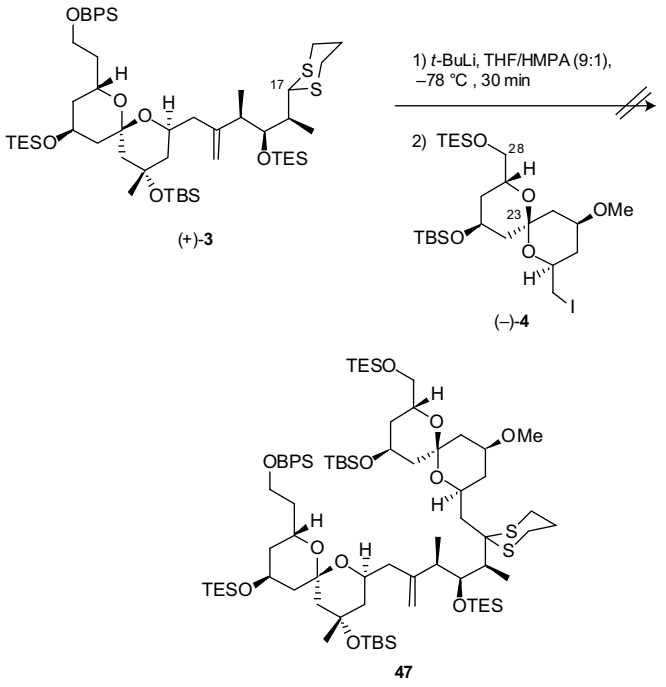


Scheme 16.

With the discovery of a preparatively viable route to the desired spiroketal in hand, we turned to completion of the synthesis of **CD** iodide **4**. Acylation of the primary hydroxyl in (−)-**43** with pivaloyl chloride, followed by protection of the C(25) hydroxyl as a TBS ether and conversion of the C(28) benzyl ether to a TES ether furnished (−)-**45** (Scheme 17). Removal of the pivaloate was then followed by treatment with tosyl chloride to provide (−)-**46**. Displacement of the tosylate with sodium iodide proceeded with concomitant removal of the TES group, which was reinstalled with TESOTf to complete coupling partner (−)-**4**.

2.4. Attempted fragment union: a significant frustration

Having developed routes to the **AB** and **CD** spiroketals, we turned to the dithiane-mediated **ABCD** fragment union. Unfortunately, multiple attempts to unite (+)-**3** with (−)-**4** met with failure (Scheme 18). At low temperature (−78 °C) no reaction was observed; on the other hand, carefully raising the temperature led only to decomposition. Presumably steric hinderance in iodide

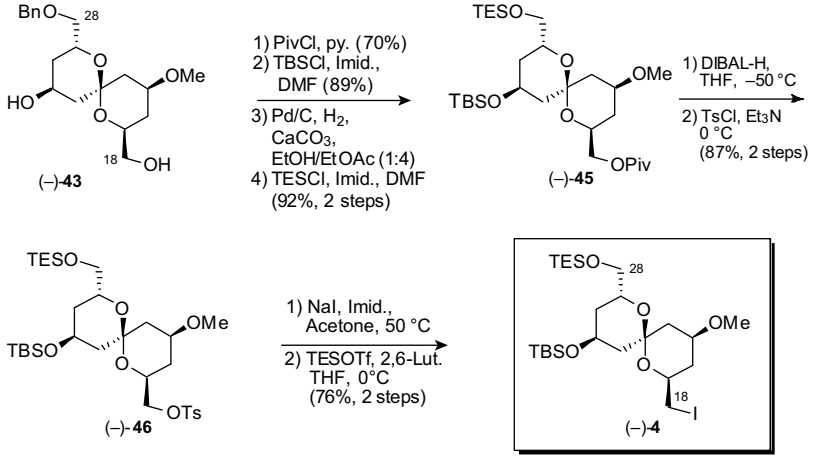


Scheme 18.

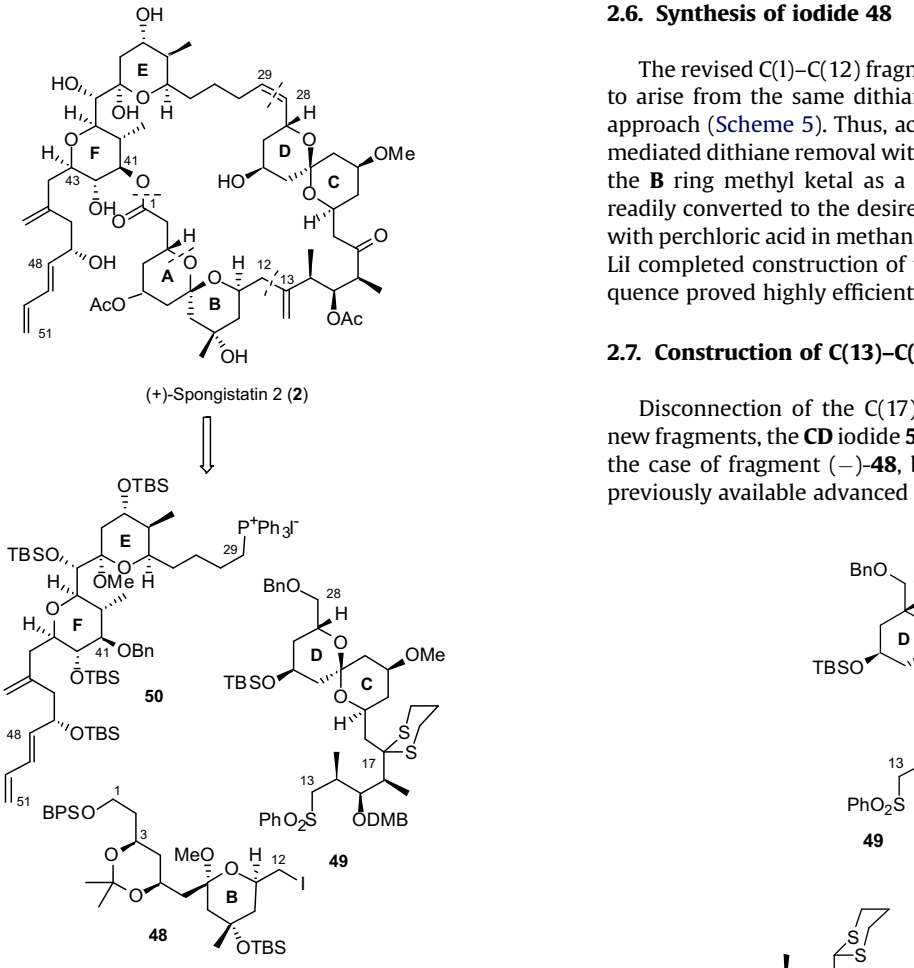
(−)-**4** precludes fragment union. Our inability to effect this transformation thus forced us to revisit our synthetic plan.

2.5. A second-generation synthetic strategy for (+)-spongistatin 2

In redesigning our initial approach to a more appropriate **ABCD** aldehyde, we reasoned that reducing the steric bulk of the C(1)–C(12) fragment, by postponing elaboration of the **A** ring until after the Julia union/exomethylene tactic might permit an effective union. Toward this end, a C(13)–C(17) fragment bearing a phenyl sulfone would be incorporated in the **CD** fragment prior to union, now with a simplified **AB** fragment (Scheme 19). A second significant change from our first-generation strategy would involve the **EF** side chain. Successful studies during the construction of a series of simplified spongistatin analogues[40] possessing the C(44)–C(51)

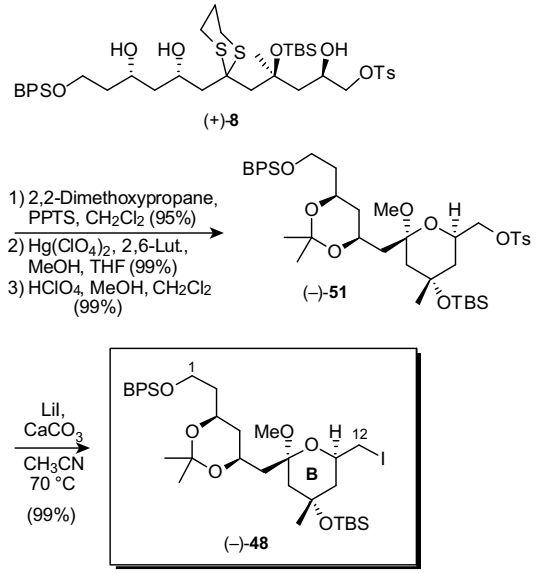


Scheme 17.



Scheme 19.

side chain convinced us that a fully elaborated side chain would not be a major liability in the proposed Wittig union required to unite the **ABCD** and **EF** fragments. Thus, we dissected (+)-spongistatin 2 (**2**) into three new fragments: the **AB** iodide **48**, the **CD** sulfone **49**, and the fully elaborated **EF** Wittig salt **50**.



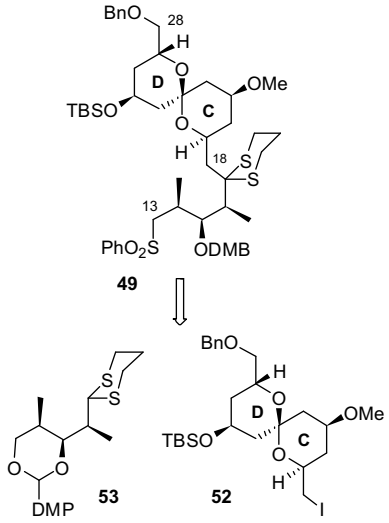
Scheme 20.

2.6. Synthesis of iodide 48

The revised C(1)–C(12) fragment **48** (Scheme 20) was envisioned to arise from the same dithiane (+)-**8** employed in our previous approach (Scheme 5). Thus, acetonide formation, followed by Hg^{II} mediated dithiane removal with concomitant cyclization, furnished the **B** ring methyl ketal as a mixture of anomers, that could be readily converted to the desired α-anomer (−)-**51** upon treatment with perchloric acid in methanol. Displacement of the tosylate with LiI completed construction of the iodide (−)-**48**. The four-step sequence proved highly efficient proceeding in 92% yield.

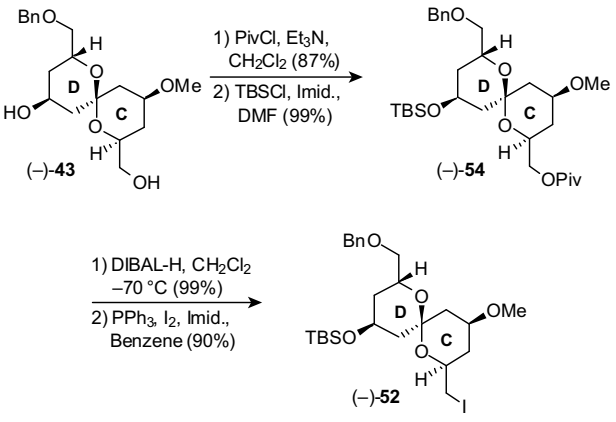
2.7. Construction of C(13)–C(28) spiroketal 49

Disconnection of the C(17)–C(18) σ-bond in **49** revealed two new fragments, the **CD** iodide **52** and dithiane **53** (Scheme 21). As in the case of fragment (−)-**48**, both were envisioned to arise from previously available advanced intermediates.

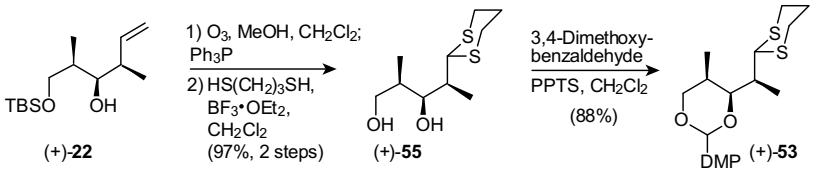


Scheme 21.

For the new **CD** spiroketal **52** we began with diol (−)-**43** (Scheme 22). Conversion of the primary hydroxyl to the corresponding pivalate, followed by TBS ether formation provided the fully protected **CD** spiroketal (−)-**54**. Removal of the pivalate was then followed by conversion of the alcohol to the corresponding iodide to furnish (−)-**52**. By retaining the C(28) hydroxyl protection (e.g., benzyl ether), we were able to limit the number of protecting



Scheme 22.

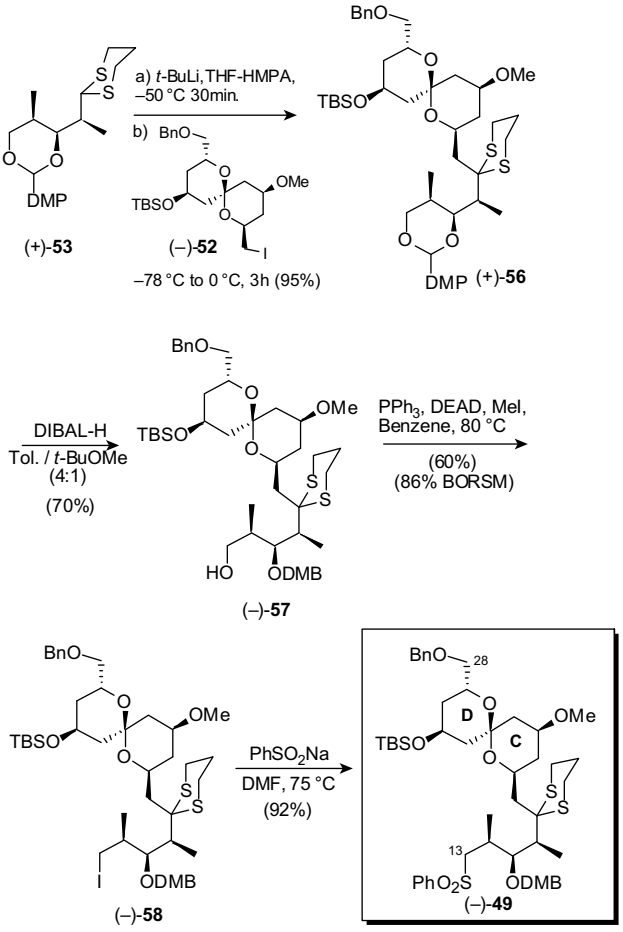


Scheme 23.

group manipulations, thereby reducing the length of the synthetic sequence by three steps.

Construction of the requisite C(13)–C(17) dithiane (**53**) began with homoallylic alcohol (+)-**22**, an intermediate available from our first-generation approach (Scheme 23). Ozonolysis, followed by thioketalization with concomitant removal of the TBS group afforded diol (+)-**55**; benzylidene acetal formation next led to (+)-**53**.

In contrast to our first-generation route, union of the **CD** spiroketal iodide (−)-**52** employing the lithium salt of dithiane (+)-**53** proceeded smoothly to produce (+)-**56** in excellent yield (Scheme 24). Presumably, the increase in efficiency is due to the predicted decreased steric bulk in dithiane (+)-**53**, relative to the fully elaborated C(1)–C(17) **AB** dithiane (+)-**3**. Reduction of the benzylidine acetal with DIBAL-H however, proved more problematic. In non-coordinating solvents such as methylene chloride, low yields were obtained due to competing reduction of the spiroketal. Polar coordinating solvents, such as THF on the other hand completely inhibited the reaction. Eventually we discovered that the use of a weakly coordinating solvent (cf. *t*-BuOMe) with toluene proved optimal, furnishing primary alcohol (−)-**57** in 70% yield. Conversion of the latter to iodide (−)-**58** was also not trivial. After considerable effort, iodide (−)-**58** was generated in moderate yield via a modified Mitsunobu protocol.[45] Displacement of the derived iodide with sodium benzenesulfonate completed construction of **CD** sulfone (−)-**49**.



Scheme 24.

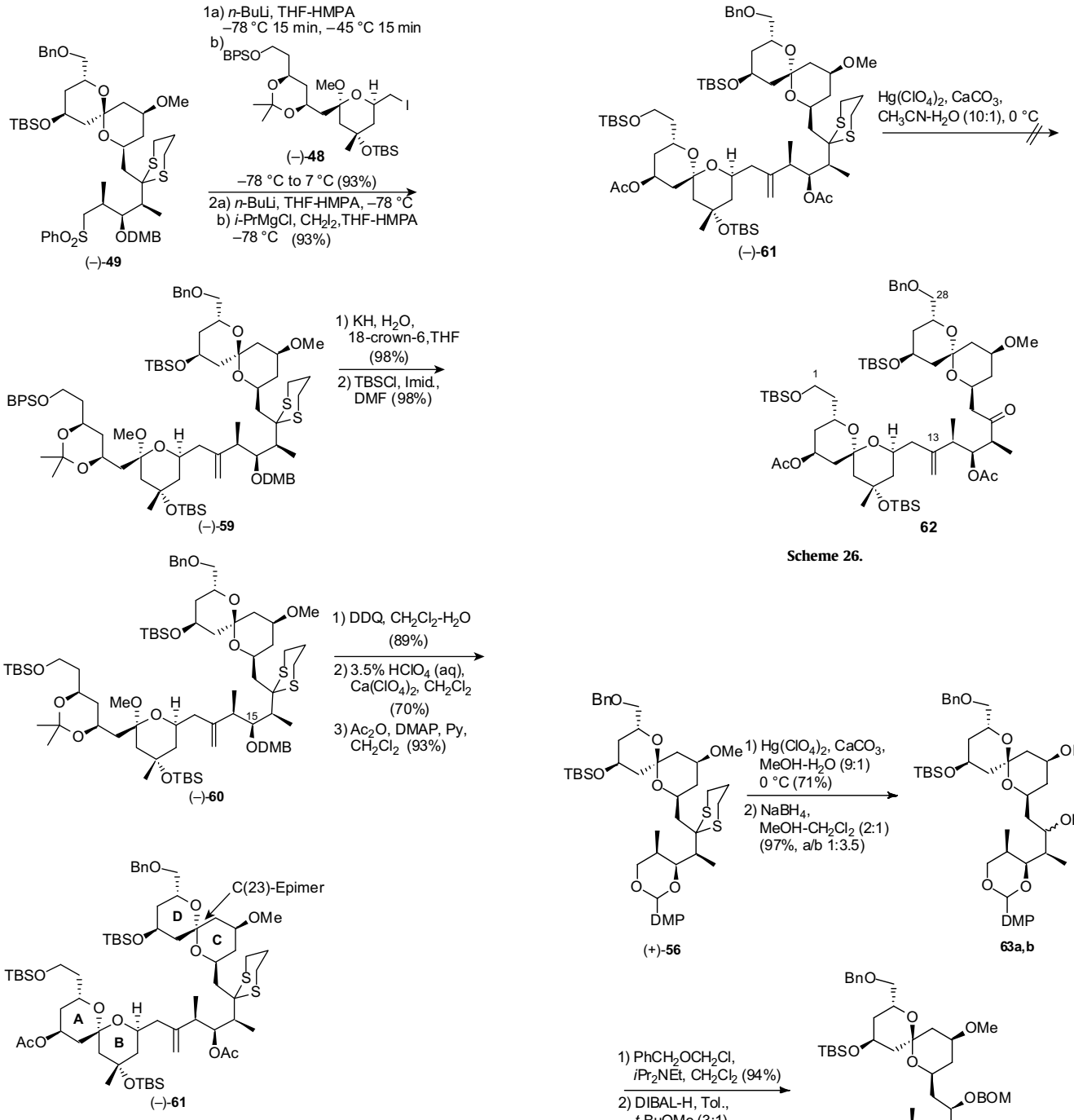
2.8. Fragment union and elaboration of ABCD aldehyde 65

With ample quantities of **AB** iodide (−)-**48** and **CD** sulfone (−)-**49** in hand, we turned our focus to the revised union strategy. Pleasingly, lithiation of (−)-**49** followed by reaction with iodide (−)-**48** proceeded in excellent yield to furnish the complete C(1)–C(28) carbon skeleton (Scheme 25). Our prediction that decreasing the steric bulk of the **AB** system would increase the yield of the Julia methylenation[39] proved correct; a 93% yield of *exo* olefin (−)-**59** was obtained. We next replaced the C(1) BPS protecting group with a TBS group [(a) KH and 18-crown-6 in THF/water; (b) TBSCl, imidazole],[46] anticipating that the basic conditions required for BPS removal would not be compatible with more advanced intermediates. Oxidative removal of the 3,4-dimethoxybenzyl (DMB) group in (−)-**60**, followed by acetonide hydrolysis with concomitant spiroketal formation under acidic conditions then furnished the **AB** spiroketal (−)-**61** after acetylation of the C(15) hydroxyl. The acidic conditions however led to epimerization of the **CD** spiroketal. While in hindsight this result is not surprising, the epimerization event went undetected until the spectroscopic properties of the synthetic material were found not to be identical to those (+)-spongistatin 2 (vida infra).

Continuing with the C(23)-epimeric spiroketal (−)-**61**, we next found, much to our dismay, that the C(17) dithiane was resistant to mercury-mediated hydrolysis (Scheme 26). A number of other conditions, including oxidative, alkylative, and/or heavy metal based protocols, also proved ineffective. We were thus forced to conclude that the C(17) dithiane would have to be removed at an earlier stage.

Reasoning that removal of the dithiane might prove more facile prior to union of the **AB** and **CD** fragments, we attempted the hydrolysis after coupling of the **CD** iodide (−)-**52** with the C(13)–C(17) dithiane (+)-**53**. Pleasingly, treatment of the previously prepared dithiane (+)-**56** (Scheme 24) with mercury perchlorate furnished the corresponding ketone, which was converted to an inseparable mixture (3.5:1) of alcohols **63a**/**b** upon reduction with $NaBH_4$ (Scheme 27). Generation of the corresponding BOM ethers next permitted facile separation. The major β-isomer, possessing the C(17) stereogenicity required for the spongistatins was in turn subjected to DIBAL-H-mediated acetal reduction to furnish primary alcohol (+)-**64**,[47,48] which was converted to the corresponding **CD** sulfone (+)-**65** as previously described.

As expected, both the union of **CD** sulfone (+)-**65** with **AB** iodide (−)-**48** and the subsequent Julia methylenation proceeded efficiently to furnish alkene (+)-**66** in 83% yield for the two steps (Scheme 28). The primary BPS ether was next exchanged for a TBS ether to provide (+)-**67**, which in turn was converted to the **AB** spiroketal (−)-**68** via DDQ-mediated removal of the 3,4-dimethoxybenzyl (DMB) moiety, acetonide hydrolysis, and acetate formation, as previously described for (−)-**61**. Epimerization of the C(23) stereocenter, which occurred during the acetonide hydrolysis under acidic conditions, again went undetected. Selective removal of the primary TBS ether was now followed by a two-step oxidation to provide acid (−)-**69**, which was



Scheme 25.

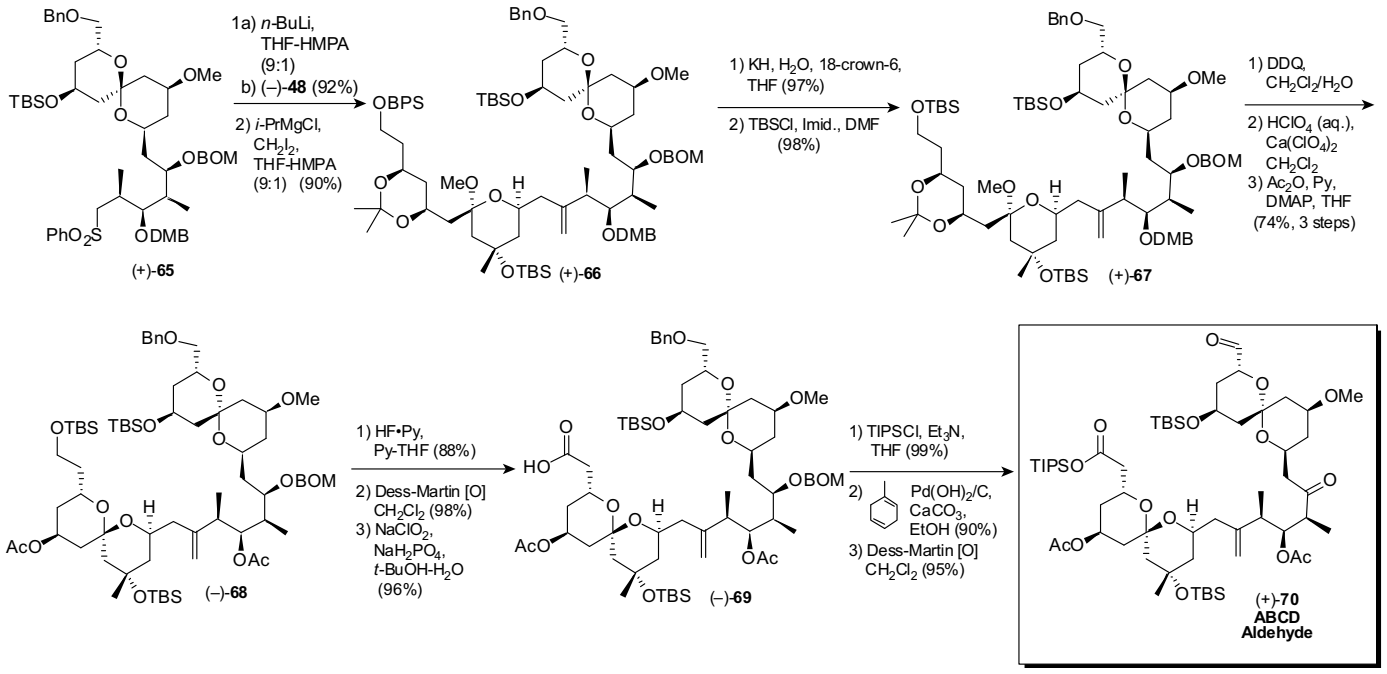
Scheme 26.

Scheme 27.

protected as the corresponding triisopropylsilyl (TIPS) ester. Removal of the benzyl protecting groups and Dess–Martin oxidation[49] of the resulting diol then furnished **ABCD** aldehyde (+)-**70**. From the perspective of material advancement, synthesis of the **ABCD** aldehyde required a longest linear sequence of 34 steps and proceeded with an overall yield of 1.5%.

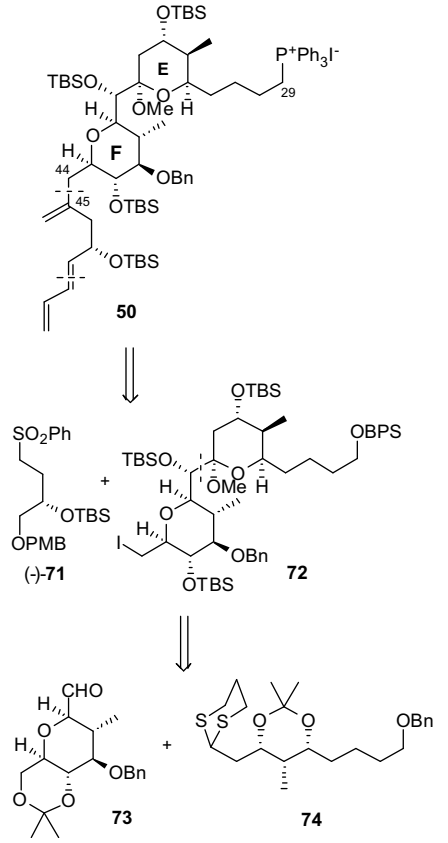
2.9. Construction of the C(29)–C(51) EF Wittig salt

Taking advantage of our success with the Julia union/methylenation protocol to construct the **ABCD** fragment, we envisioned elaboration of the **EF** Wittig salt **50** via addition of sulfone **71** to iodide **72**, followed by a similar Julia methylenation (Scheme 29).[39] Iodide **72** in turn would arise via chelation-controlled addition of dithiane **74** to aldehyde **73**, followed by **E**-ring formation and further elaboration.

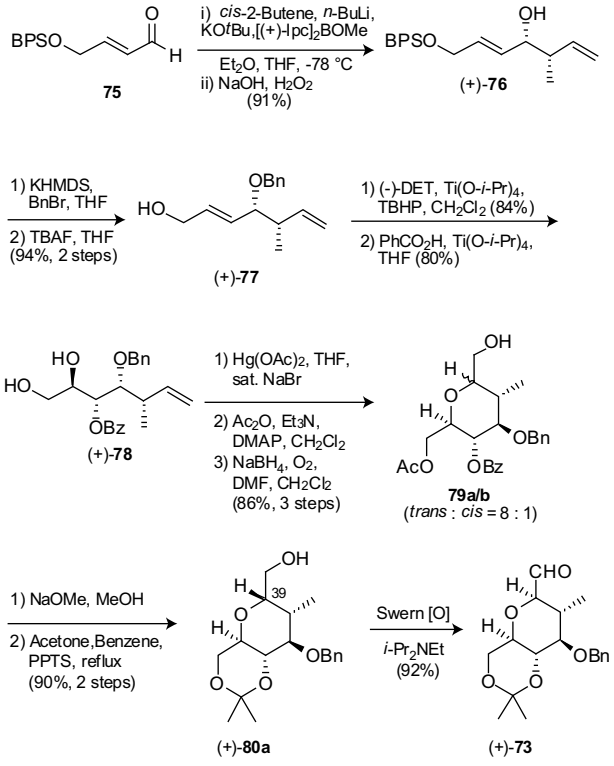


Scheme 28.

Construction of aldehyde **73** began with Brown crotylboration[50] of known silyloxy aldehyde **75**[51] (Scheme 30) to yield homoallylic alcohol (+)-**76** (91%, 89% ee).[48] Protection as the benzyl ether, followed by removal of the primary BPS group provided allylic alcohol (+)-**77**, which was subjected to Sharpless asymmetric epoxidation[31] to produce the corresponding epoxy alcohol (dr >15:1). Regioselective opening of the epoxide with benzoic acid in the presence of titanium isopropoxide next furnished diol (+)-**78** as the only isolable product. Mercuric acetate-mediated cyclization, in conjunction with an aqueous sodium bromide work-up, followed by acetylation and oxidation[52] of the intermediate organomercurial with O_2 led to the **E**-ring pyran, as a mixture of diastereomers **79a**/**b** (ca. 8:1) favoring the *trans*-pyran isomer. Methanolysis followed by acetonide formation then provided alcohol **80a**/**b**. Pleasingly the major isomer (+)-**80a** proved crystalline, thereby permitting structure verification via X-ray analysis. Clearly epimerization at C(39) would be required. Initially we



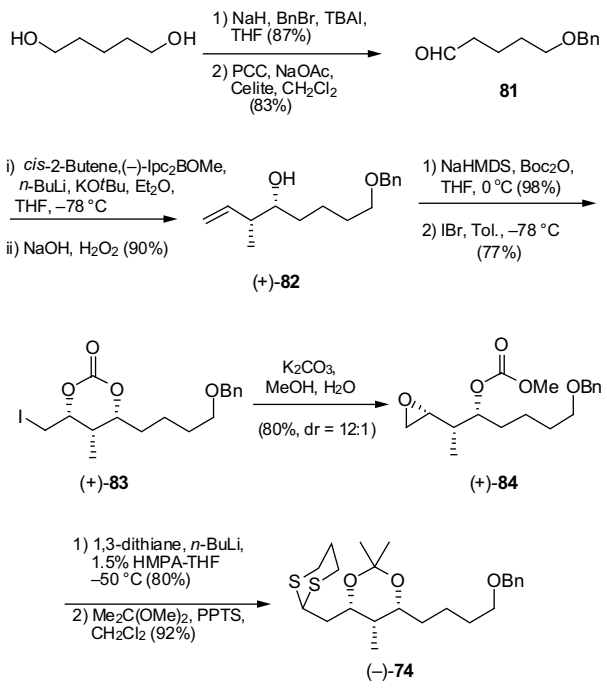
Scheme 29.



Scheme 30.

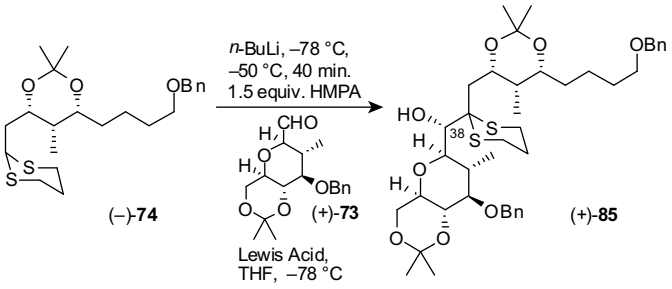
employed Swern oxidation[53] followed by epimerization of the resultant aldehyde with DBU to produce (+)-**73**, albeit in modest yield. Best results were obtained upon modification of the oxidation protocol to include use of Hünigs base (*i*-Pr_2NEt). Under these conditions, near quantitative epimerization occurred.

Construction of the requisite dithiane **74** began with the monobenzyl derivative of 1,5-propanediol (Scheme 31); PCC oxidation to provide aldehyde **81** followed by Brown crotylboration[50] furnished homoallylic alcohol (+)-**82** in excellent yield and enantioselectivity (90%, 96% ee), the latter determined by Mosher ester analysis.[48] Protection of (+)-**82** as the *tert*-butyl carbonate, followed by IBr-mediated cyclization,[29] and exposure to K_2CO_3 in methanol then yielded epoxy carbonate (+)-**84**, which upon treatment with 2-lithio-1,3-dithiane led to epoxide ring opening with concomitant removal of the methyl carbonate to furnish the corresponding diol. Acetonide formation was next accomplished without difficulty to give dithiane (−)-**74**.



Scheme 31.

With both coupling partners (+)-**73** and (−)-**74** in hand, we turned to their union. The major challenge here was to effect a chelation-controlled process in the presence of HMPA,[54] the latter required for efficient dithiane metalation. A number of Lewis acid additives were therefore examined. Use of both Mg^{II} and Zn^{II} provided excellent selectivity (10–20:1, Scheme 32), however yields were modest. Reasoning that the low efficiency might be due to enolization of (+)-**73**, we examined the use of $CeCl_3$.[55] While $CeCl_3$ improved the yield to 72%, a drop in selectivity to 3.7:1 occurred, still favoring the desired diastereomer. Since the increase in yield might be due to the formation of an organocerium species, we explored pregeneration of the cerium dithiane, followed by addition to aldehyde (+)-**73** precomplexed with $ZnCl_2$. These conditions proved rewarding; a reproducible 65% yield of a single diastereomer (+)-**85** was obtained (Scheme 33).[56] To the best of our knowledge, this observation represents the first example of employing a cerium dithiane species in the context of complex molecule synthesis.[57]



Additive	Selectivity (a/b)	Yield (%)
$MgBr_2$	>20:1	58
$ZnCl_2$	20:1	40
$ZnCl_2$, –50 °C	10:1	45
$CeCl_3$	3.7:1	72

Scheme 32.

Protection of the newly formed hydroxyl as a TBS ether, followed by hydrolysis of the acetonides led to tetraol (+)-**86** (Scheme 34). Mercuric perchlorate-promoted dithiane removal then proceeded with concomitant methyl ketal formation to furnish (+)-**87**, after protection of the primary hydroxyl as a pivalate. Exhaustive silylation employing TBSCl under forcing conditions generated the fully protected **EF** ring system (+)-**88**. A series of NOESY experiments verified the α-configuration of the methyl ketal (Fig. 6).

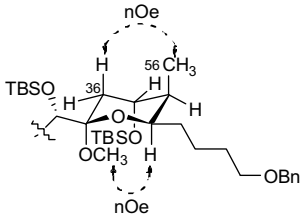
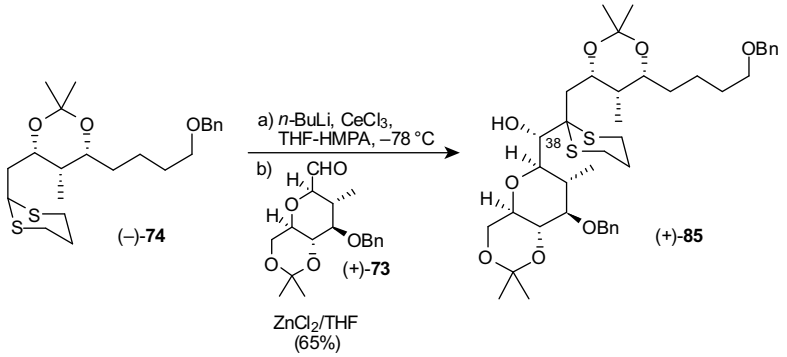
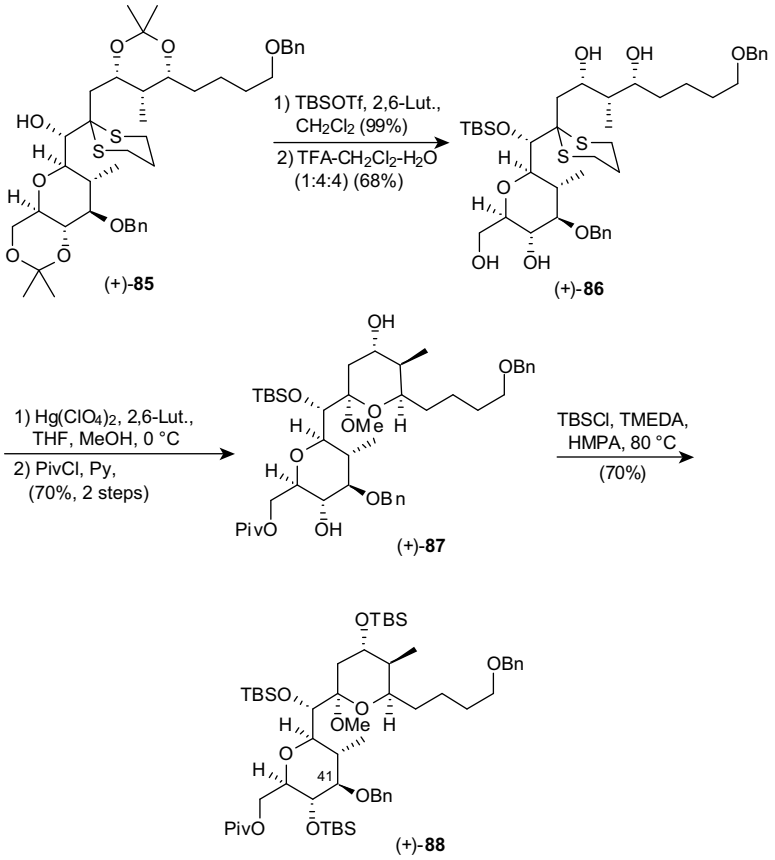


Figure 6. Critical NOESY data for (+)-**88**.



Scheme 33.



Scheme 34.

At this juncture, before attempting further elaboration of the fully functionalized **EF** side chain, we subjected (+)-**88** to a series of model studies to test the viability of our proposed endgame. This proved to be a wise decision, as attempts to remove the C(41) benzyl protecting group were plagued by both silyl group migration and low yields. Even more disappointing, all attempts to convert the resultant C(41) alcohol to the corresponding acetate met with failure, presumably due to steric crowding at C(41). During the course of these model studies, the Evans group reported a remarkable result: macrolactonization of the *seco*-acid of spongistatin 2 proceeded chemoselectively at the C(41) hydroxyl in the presence of an unprotected C(42) hydroxyl.[8] Based on these results, we decided to alter our protecting group strategy so that the C(41) and C(42) hydroxyls would possess the same protecting group, thereby eliminating both the possibility of unwanted silyl migration and steric hindrance in the macrolactonization event.

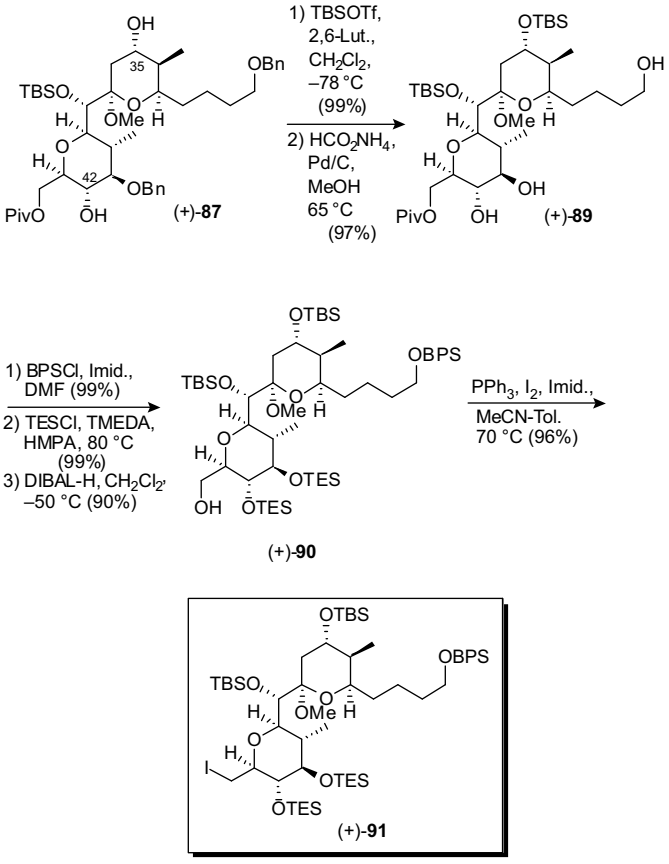
Construction of the newly envisioned **EF** fragment began with pivalate (+)-**87** (Scheme 35). Selective protection of the axial C(35) hydroxyl employing TBS triflate, followed by removal of the benzyl ethers under transfer hydrogenation conditions furnished triol (+)-**89** in 97% yield. Conversion of the liberated primary hydroxyl to a BPS ether, followed by exhaustive silylation and removal of the pivalate protecting group then provided alcohol (+)-**90** in good yield. Completion of the **EF** iodide (+)-**91**, the side chain precursor, was then achieved by treatment with triphenylphosphine and iodine.

Further development of the side chain now required sulfone (−)-**71**, available in three steps from commercially available (*R*)-(+)-glycidol (Scheme 36). Union of (−)-**71** with iodide (+)-**91** proceeded in moderate yield to furnish (+)-**92** as a mixture of diastereomers (ca. 1:1) at C(45), along with a significant amount of elimination product (+)-**93**. Attempts to minimize the formation of the enol ether by varying the metal ion, introduction of additives, and/or temperature and solvent regimes proved unrewarding. While this result was clearly disappointing, we were able to recycle (+)-**93** to alcohol (+)-**90** via a hydroboration–oxidation sequence, thereby minimizing loss of valuable material.

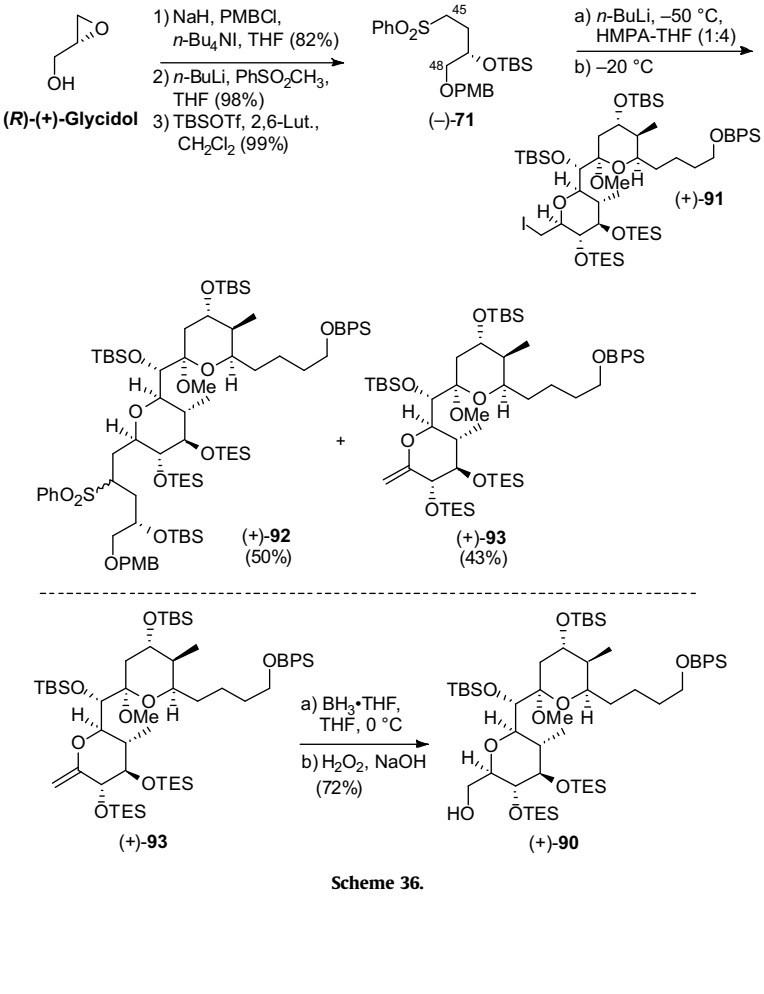
With sulfone (+)-**92** in hand, elaboration to the **EF** Wittig salt proved more difficult than we had initially anticipated. Julia methylenation[39] of (+)-**92** failed to proceed to completion, producing olefin (+)-**94** in only modest yield (Scheme 37). In addition, removal of the C(48) primary PMB protecting group to generate alcohol (+)-**95** required the use of a buffer (pH 6) to prevent hydrolysis of the **E**-ring methyl ketal. Dess–Martin[49] oxidation of (+)-**95**, followed by Horner–Wadsworth–Emmons olefination then led to triene (+)-**96**, possessing the fully functionalized side chain. Notwithstanding the modest yield of the olefination (cf. 37%), we decided to continue forward and explore the viability of the fully functionalized side chain in the key Wittig union. Toward this end, removal of the BPS and TES protecting groups, followed by a two-step conversion of the derived primary alcohol to the iodide furnished (+)-**97**. Protection of the C(41) and C(42) hydroxyls as the TMS ethers and displacement of the iodide with triphenylphosphine completed the synthesis of the **EF** Wittig salt (+)-**98**. The longest linear sequence required 32 steps from commercially available starting materials.

2.10. Union followed by macrolactonization

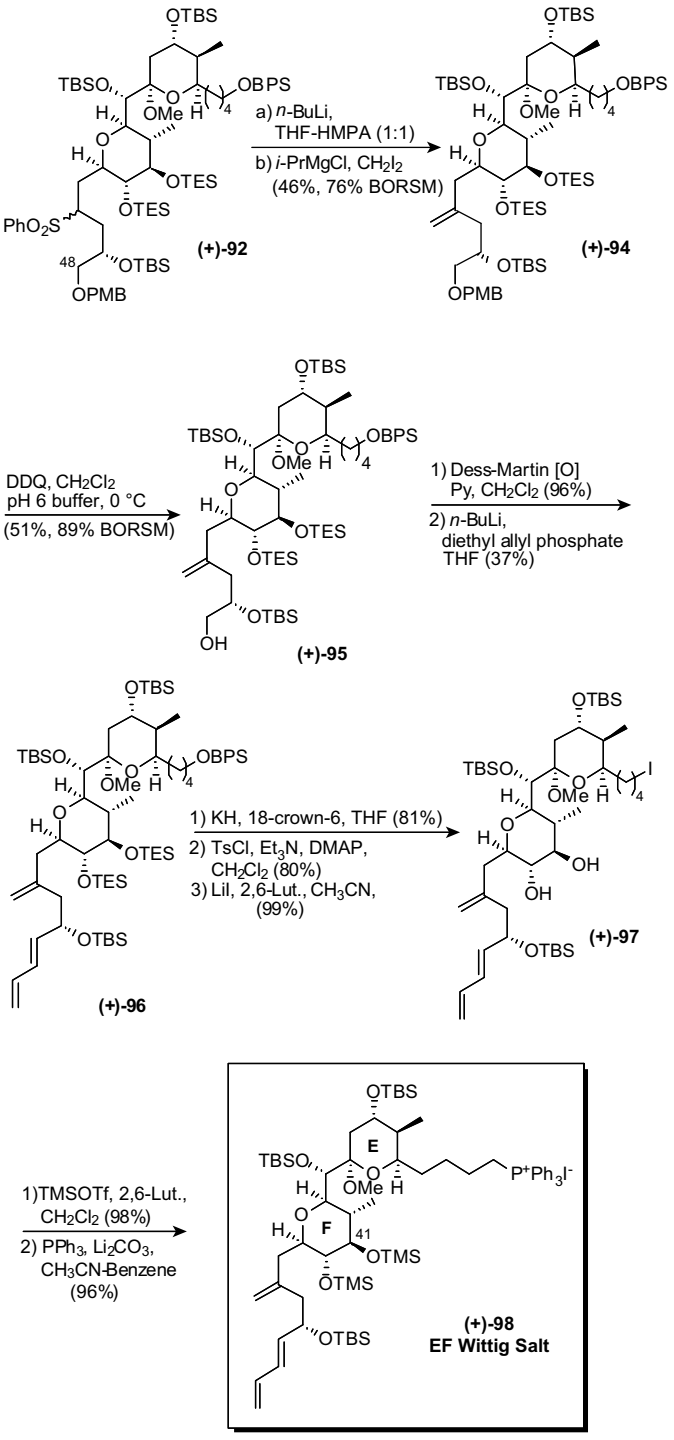
Having achieved syntheses of **ABCD** aldehyde (+)-**70** and **EF** Wittig salt (+)-**98**, we proceeded with the endgame. Wittig reaction between (+)-**98** and (+)-**70** under the titration conditions initially reported by Kishi[9] provided alkene (+)-**99** in 66% yield (Scheme 38). Clean removal of the TMS ethers and TIPS groups



Scheme 35.



Scheme 36.



Scheme 37.

mediated by KF then led to *seco*-acid (+)-**100**, which underwent smooth Yamaguchi macrolactonization[58] to furnish protected macrocycle (+)-**101**. Macrolactonization of C(41) was based on the Evans/Kishi[8,9] precedent, in conjunction with careful NMR comparisons with 23-*epi*-spongistatin 2 (vide infra). Unfortunately, all attempts at global deprotection proved challenging as decomposition of the substrate occurred at a rate faster than the removal of the TBS group to free the axial C(9) hydroxyl. Analysis of the successful routes to (+)-spongistatin 2 revealed that the Evans group employed TES groups at the C(9) and C(38) hydroxyls, while Kishi and co-workers chose to leave these positions unprotected. Based upon these observations, we were forced to redesign the late stage protecting group strategy for both the **ABCD** aldehyde and the **EF** Wittig salt, employing TES groups at C(9) and C(38).

2.11. A second-generation protecting group strategy for the ABCD and EF subunits

Construction of the revised **ABCD** aldehyde (+)-**105** began with the Julia union/methylenation product (+)-**66** (vide supra). Global removal of the silyl groups using TBAF was followed in turn by protection of both the resultant primary and secondary hydroxyls as TBS ethers and acid removal of the acetonide; the latter proceeded with concomitant spiroketalization to provide **ABCD** bisspiroketal (+)-**102** (Scheme 39). As in the earlier case, complete undetected epimerization of the **CD** spiroketal occurred during the acetonide removal. Exchange of the C(15) DMB protecting group for an acetate was then followed by protection of the C(9) hydroxyl as a TES ether to furnish the fully protected **ABCD** fragment (−)-**103**. Final elaboration of the Wittig union precursor, aldehyde (+)-**105** then proceeded in six straightforward transformations (Scheme 39). The yield for this 12-step sequence proved excellent (cf. 34%).

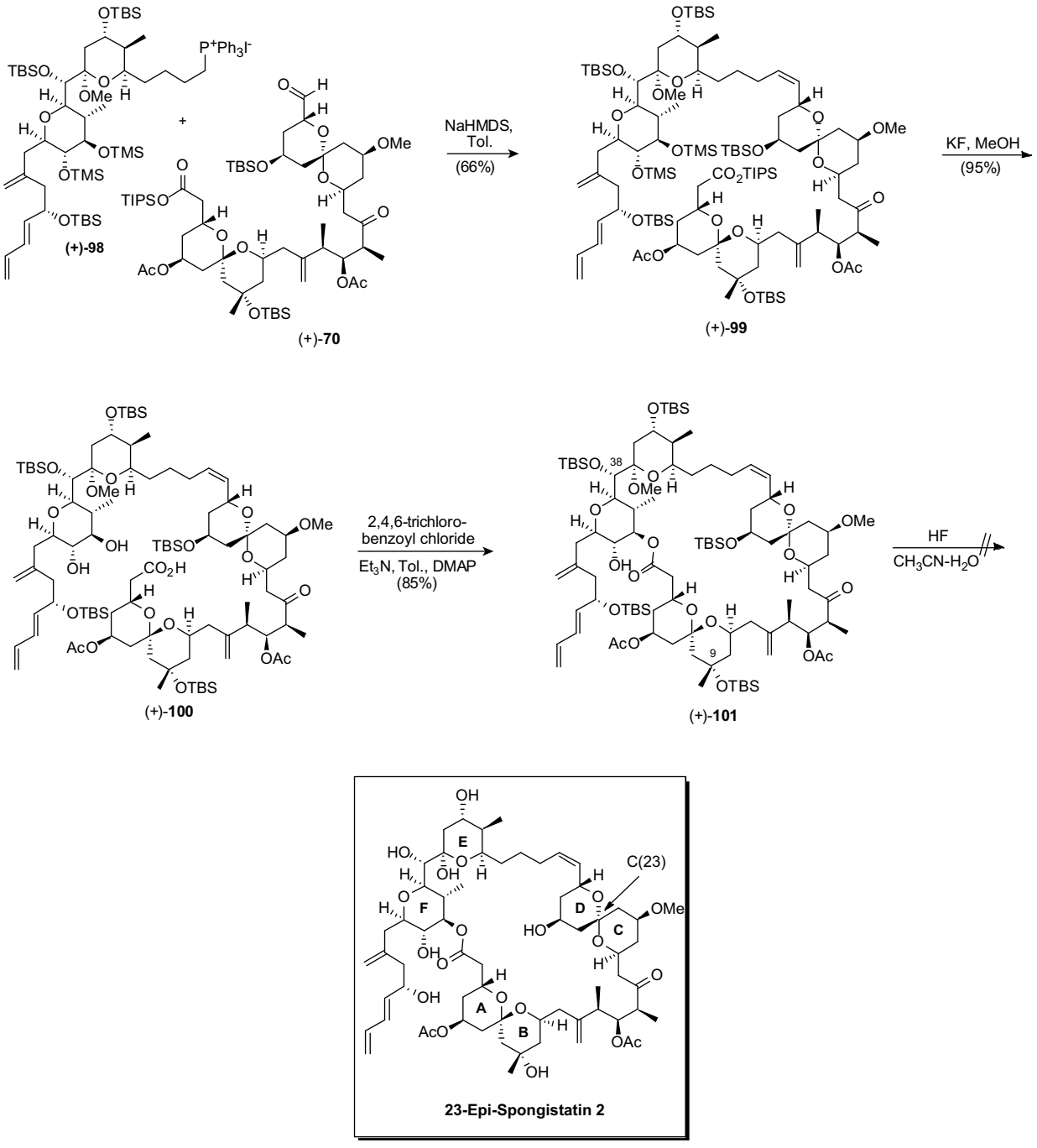
Construction of the revised **EF**-Wittig salt (+)-**112** (Schemes 40 and 41) began with dithiane coupling product (+)-**85** (vide supra). Removal of the acetonides, followed by dithiane hydrolysis with concomitant cyclization and subsequent protection of the C(44) primary hydroxyl with pivaloyl chloride furnished pivalate (+)-**106** (Scheme 40). The C(35) axial hydroxyl was then protected as a TBS ether and the benzyl groups removed via hydrogenolysis. Completion of **EF** iodide (+)-**108** was achieved in four straightforward steps. The overall yield for the nine-step sequence was again good (cf. 24%).

A number of additional problems were encountered in our original synthesis of the **EF** Wittig side chain (+)-**98** (Scheme 37), including inefficient Julia methylenation, difficult removal of the PMB protecting group, and a low yield upon installation of the diene moiety. We reasoned that coupling of a more elaborate sulfone unit to **EF** iodide (+)-**108** (Scheme 41) would circumvent these problems by reducing the number of transformations on advanced intermediates. The new side chain precursor, envisioned to be sulfone (−)-**109**, was constructed beginning with our first-generation sulfone (−)-**71**, via a five-step sequence. Pleasingly, union of sulfone (−)-**109** to iodide (+)-**108** proved to be much more efficient, producing a mixture (ca. 1:1) of sulfones in 80% yield. The efficiency of the Julia methylenation, however did not improve despite considerable effort, producing only a 25% yield of diene (+)-**110** (e.g., a 50% yield based on recovered starting material). Continuing with the synthesis, reductive removal of the primary benzyl group in (+)-**110** was followed by Dess–Martin oxidation, Wittig methylenation and removal of the BPS ether to furnish triene (+)-**111** in 46% yield for the four steps. Completion of the **EF** Wittig salt (+)-**112** was then achieved in four straightforward transformations.

2.12. Wittig union, macrolactonization, and anticipated final elaboration of (+)-spongistatin 2 (2)

With the **EF** Wittig salt (+)-**112** and the **ABCD** aldehyde (+)-**105** in hand, we turned our attention toward the Wittig olefination. However, in contrast to the earlier results, we were unable to obtain better than a 35% yield of alkene (+)-**113** in the key Wittig step (Scheme 42). The reason for this dramatic drop in yield, upon what was only a minor change in the protecting groups remains unclear. Nonetheless, selective removal of the TIPS and TMS protecting groups provided the corresponding *seco*-acid, which then underwent smooth Yamaguchi macrolactonization[58] to provide macrocycle (+)-**114**.

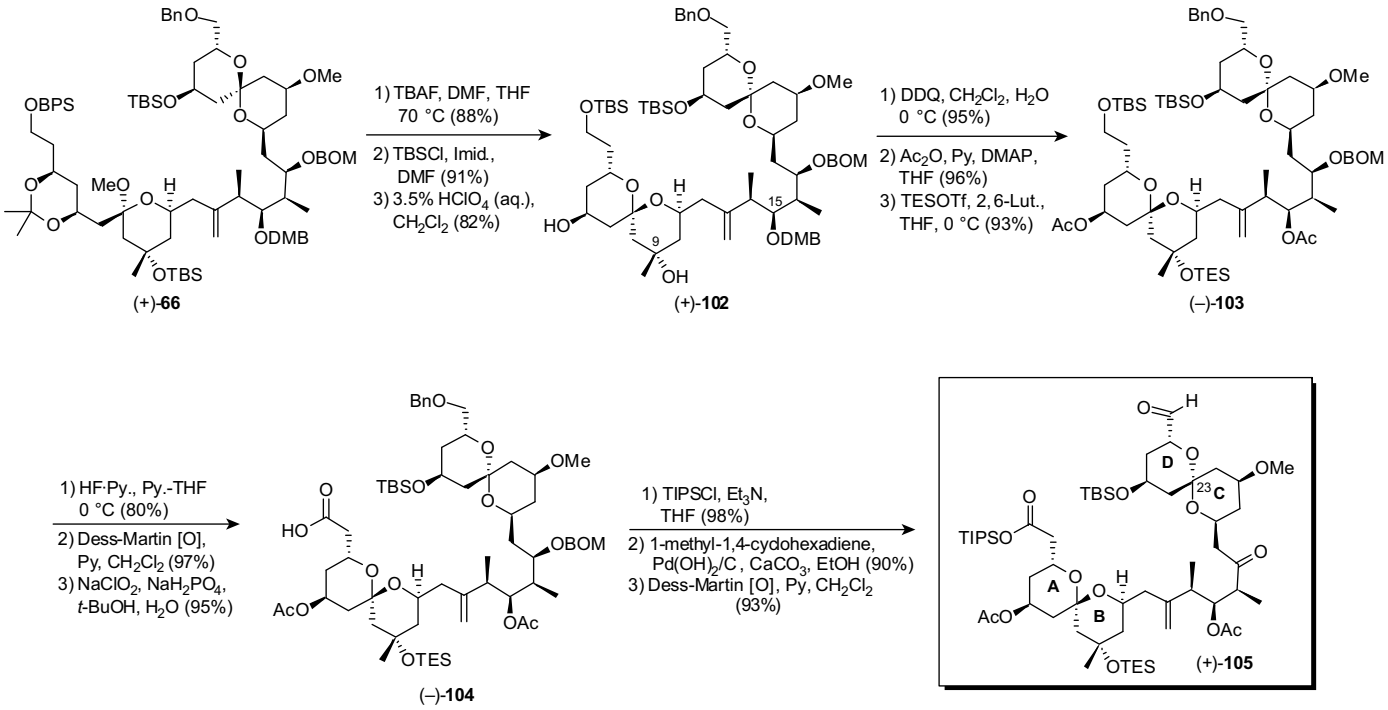
As foreshadowed, global deprotection of (+)-**114** did not afford pure (+)-spongistatin 2 (**2**), but instead a mixture (1:3) of (+)-**2**



Scheme 38.

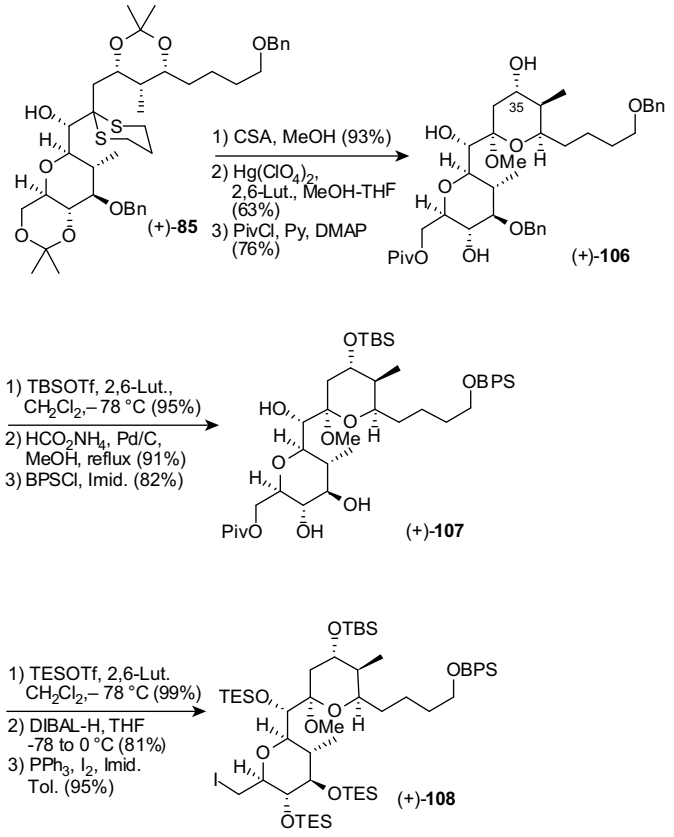
and (−)-C(23)-*epi*-spongistatin 2 (**115**). It was only at this point that we recognized that epimerization of the C(23) stereocenter had occurred. Indeed, epimerization had taken place on two fronts; first during the synthesis of the **ABCD** aldehyde and then again upon global deprotection, as we had entered deprotection with a single diastereomer. Fortunately, the loss of configuration at C(23) could be corrected by taking advantage of our previous experience with the interconversion of **CD** spiroketals (+)-**42** and (−)-**43**. Specifically, exposure of (−)-**115** to Ca^{II} ion in the presence of perchloric acid furnished a 3.9–2.3:1 mixture of C(23) spiroketal epimers favoring the natural product.[59] Synthetic (+)-spongistatin 2 (**2**) proved to be identical in all respects [500 MHz ^{1}H NMR, LRMS, HRMS, $[\alpha]_D^{26}$, TLC (three solvent systems), and HPLC] with an authentic sample kindly provided by Professor Evans.[60]

In summary, we achieved the total synthesis of (+)-spongistatin 2 (**2**) in 41 steps (longest linear sequence). Similar to other approaches, our synthesis takes advantage of a late stage Wittig coupling with EF salt followed by Yamaguchi macrolactonization to furnish (+)-spongistatin 2. Unique to our approach was the use of the multicomponent dithiane coupling protocol mediated by Brook rearrangement and the Julia union/methylenation protocols for complex fragment assembly. While the former tactic permitted reliable and rapid construction of both the **AB** and **CD** ring systems [(−)-**4** and (−)-**52**], the latter proved reliable only for the synthesis of the **ABCD** aldehyde.

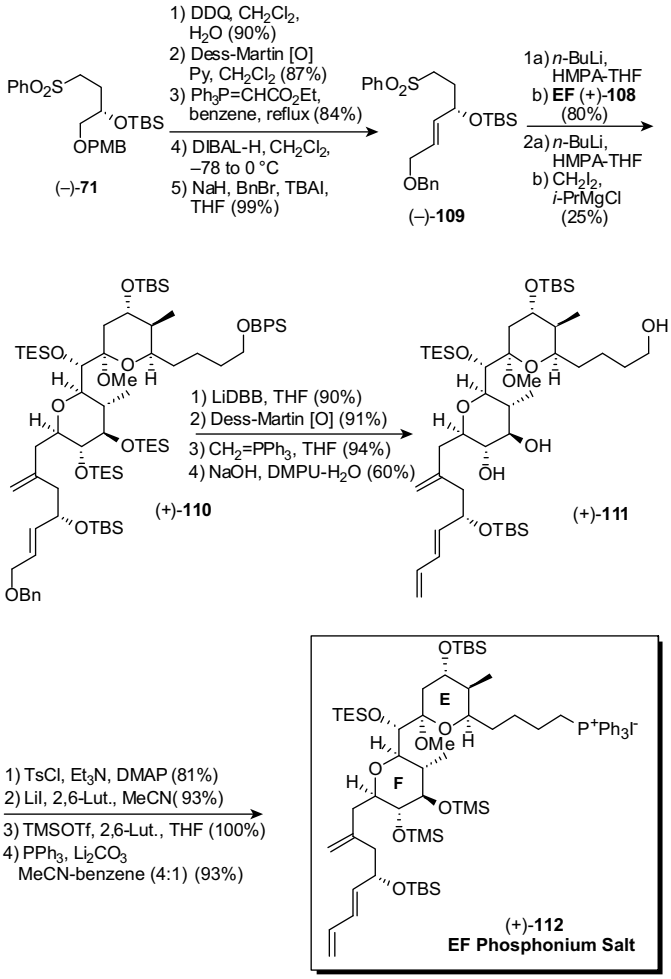


Scheme 39.

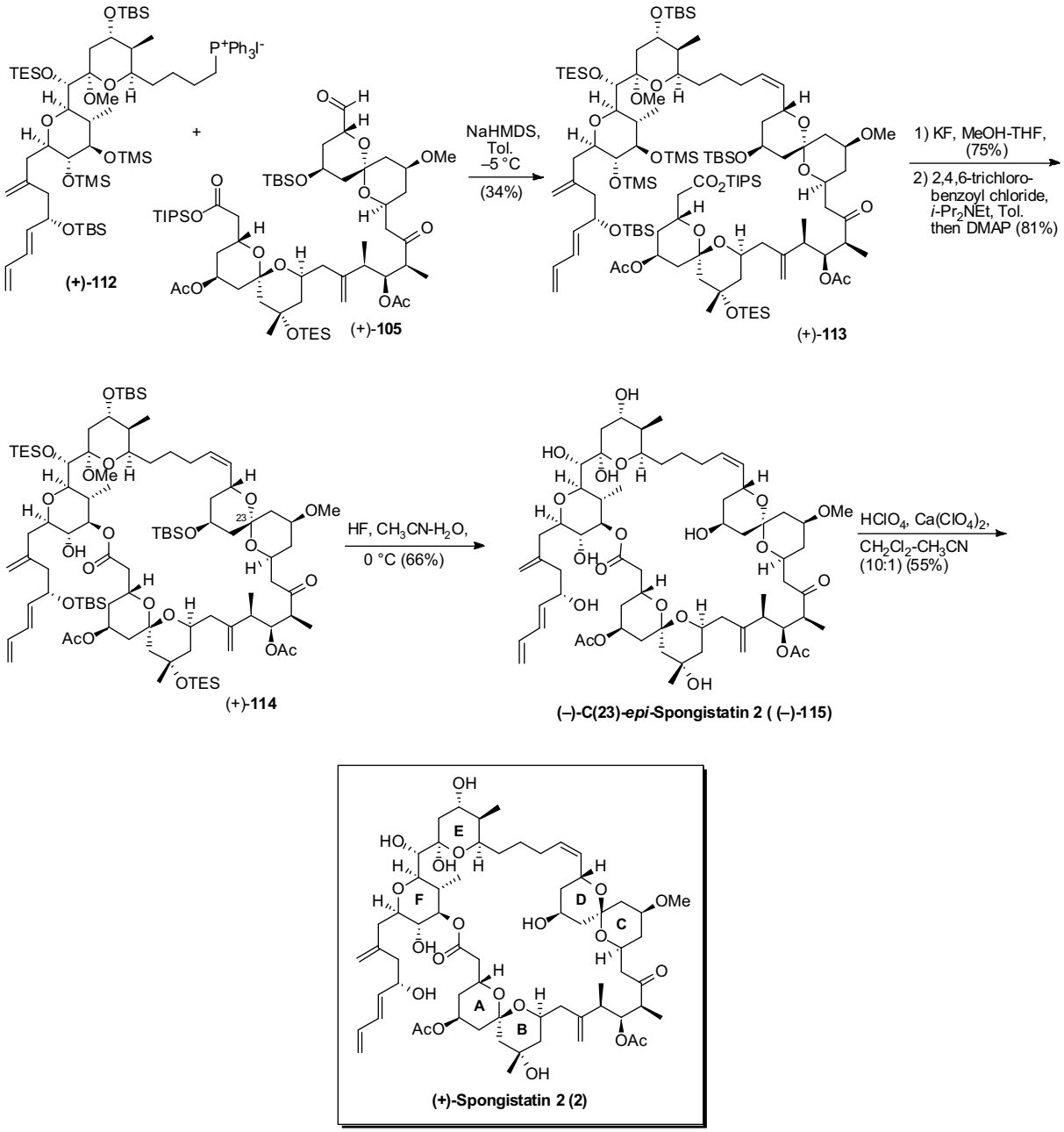
Significant drawbacks of the synthetic route entail a lengthy approach to the **ABCD** aldehyde (+)-**105**, coupled with a low yielding Julia methylenation required to complete of the **EF** side chain. While not sufficiently disabling to prevent completion of (+)-spongistatin 2 (**2**), these drawbacks would certainly prevent



Scheme 40.



Scheme 41.



Scheme 42.

large-scale production of the spongistatins. Clearly, significant redesign would be required to achieve our ultimate goal, a preparative scale synthesis of spongistatin. Evolution of a revised strategy leading to a gram-scale synthesis of (+)-spongistatin 1 is described in the accompanying paper.[19]

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Supplementary data

Spectroscopic and analytical data and selected experimental procedure associated with this article can be found, in the online version. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 725651. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.001.

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57. For an example of the use of a ceriated dithiane in methodology studies see: Li, P.; Wang, T.; Emge, T.; Zhao, K. *J. Am. Chem. Soc.* **1998**, *120*, 7391.
58. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613.
59. Kishi and co-workers reported that treatment of a protected C(23)-*epi*-macrocycle with HF·Py furnished only C(23)-*epi*-spongistatin 1, which could not be epimerized to (+)-spongistatin 1 (**1**) upon treatment with CSA/CH_2Cl_2 or HCl/$CHCl_3$. See Ref. 9.
60. We thank Professor Evans (Harvard University) for supplying an authentic sample of (+)-spongistatin 2 (**2**).