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Gram-Scale Synthesis of (+)-Spongistatin 1: Development of An Improved, Scalable Synthesis of the F-Ring Subunit, Fragment Union, and Final Elaboration

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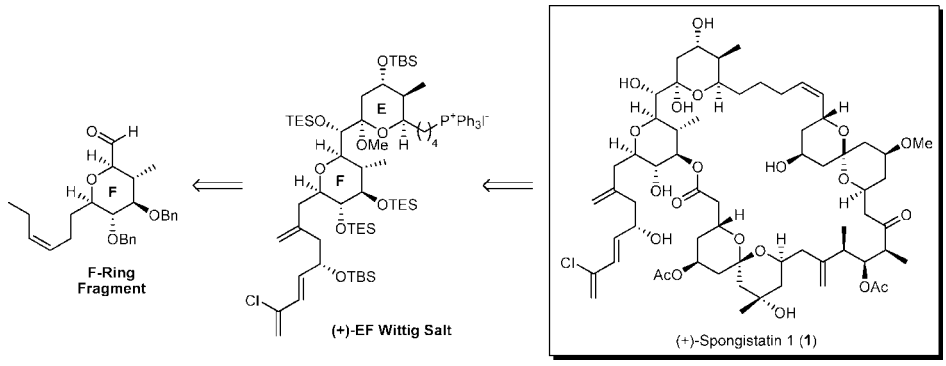
ABSTRACT



In a quest to develop an effective, scalable synthesis of (+)-spongistatin 1 (1), we devised a concise, third-generation scalable synthesis of (+)-7, the requisite F-ring tetrahydropyran aldehyde, employing a proline-catalyzed cross-aldol reaction. Subsequent elaboration to (+)-EF Wittig salt (+)-3, followed by union with advanced ABCD aldehyde (−)-4, macrolactonization and global deprotection permitted access to >1.0 g of totally synthetic (+)-spongistatin 1 (1).

The spongipyrans comprise an architecturally unique family of macrolides that display extraordinary cytotoxicity against several highly chemo-resistant tumor cell lines.[1] Among the natural congeners, (+)-spongistatin 1 (**1**) is one of the most potent tumor cell growth inhibitors reported to date (average GI_{50} values of 25−35 pM against the NCI panel of 60 human cancer cell lines) (Scheme 1). Since their independent isolation by the research groups of Pettit,[2] Kitagawa,[3] and Fusetani,[4] the spongistatins have been the focus of considerable attention in both the chemical and biological communities.[5]

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(2) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1805.

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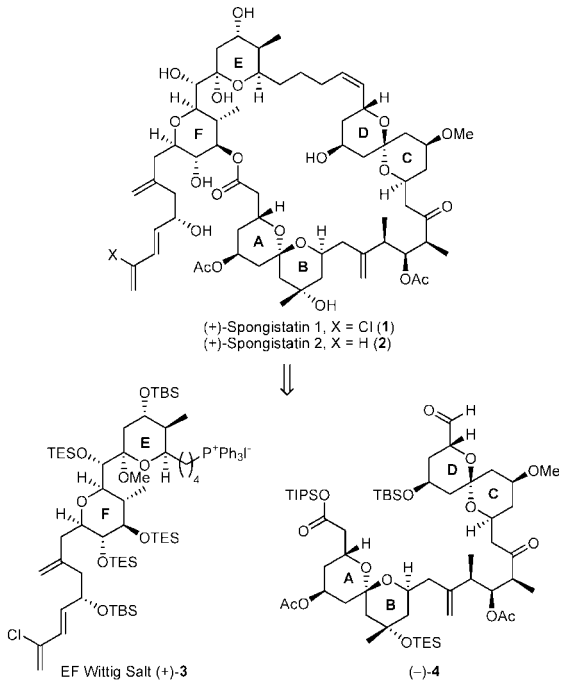
Scheme 1

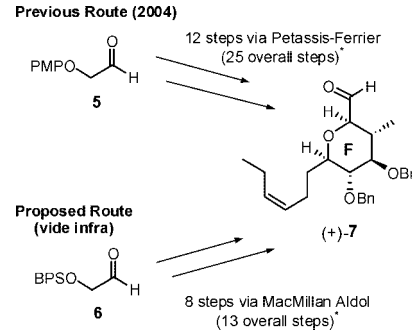


The spongistatins possess a striking array of structural features, including a 42-membered macrolactone incorporating two spiroketals, in conjunction with a hemiketal, a fully substituted tetrahydropyran unit, and a highly unsaturated side chain. The relative and absolute stereochemistries, first deduced by Kitagawa,[3] were confirmed by the Evans total synthesis of spongistatin 2 (**2**)[6] and the Kishi total synthesis of spongistatin 1 (**1**).[7] More recently, successful total syntheses have been also achieved by the Smith,[8] Paterson,[9] Crimmins,[10] Heathcock,[11] and the Ley[12] laboratories. In addition, several synthetic approaches to the spongistatins have been disclosed.[13]

However, even with these seminal synthetic achievements, the scarcity of the spongistatins has prohibited further biological testing. Indeed, a reisolation by the Pettit group afforded only 35 mg of the natural product from 13 tons! of wet sponge.[14] Given the limited supply from nature, our group initiated an ambitious program to develop a scalable approach to (+)-spongistatin 1 (**1**), capable of delivering ca. 1 g, not only for further biological development but also as an integral part of a program to design simpler congeners possessing potent tumor cell growth inhibitory activity.

To this end, we recently reported an effective synthesis of the EF fragment of (+)-spongistatin 1 (**1**) via (+)-**7** (Scheme 2) exploiting the Petasis-Ferrier union/rearrangement,[15] a synthetic tactic employed extensively in our laboratories to access *cis*-2,6-disubstituted tetrahydropyrans.[16] This approach successfully provided more than 700 mg of the EF Wittig salt, which eventually led to 80 mg of spongistatin 1 (from 450 mg of the EF Wittig salt).[17] Shortly thereafter, the MacMillan group reported an elegant two-step synthesis of carbohydrates,[18] combining a highly enantioselective proline-catalyzed cross-aldol reaction of oxy-

Scheme 2[a]



[a]Including reagent preparations.

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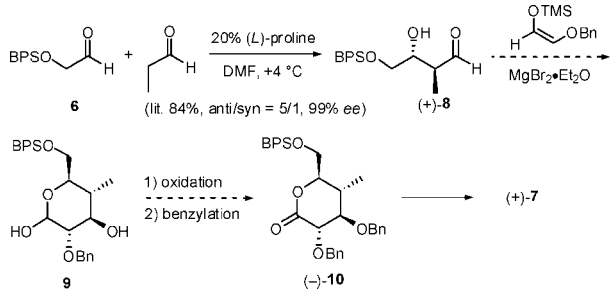
aldehydes[19] with a Mukaiyama aldol reaction. This approach to carbohydrates via the intermediacy of a lactone held the promise of an even more concise approach to (+)-**7** possessing the requisite *cis*-tetrahydropyran F-ring of (+)-spongistatin 1.[20] The potential benefits of this strategy would include: (1) a shorter reaction sequence, (2) excellent cost of goods, (3) stable intermediates, (4) simple operations, including purifications, (5) high reproducibility and efficiency, and most important, (6) scalability.

At the outset of what now constitutes a third-generation synthesis in the spongistatin area, we envisioned a five-step approach to (+)-**7** from known[21] aldehyde **6** taking advantage of the MacMillan protocol (Scheme 3). However, initial

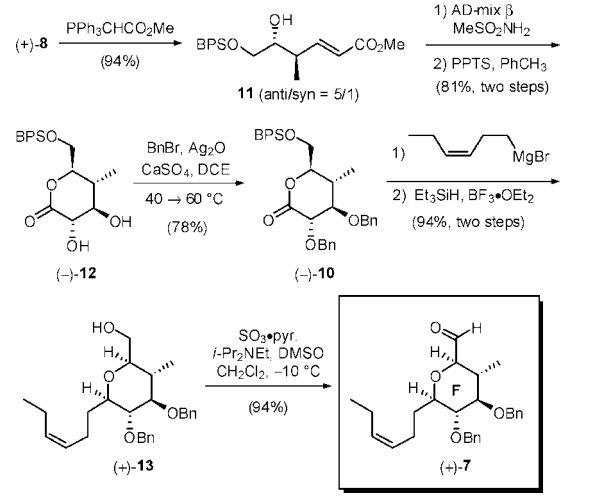
Scheme 3



efforts indicated that the Mukaiyama aldol was not applicable for large-scale production of **9** (>100 g scale). The issue was attributed to the instability of the β-hydroxyaldehyde (+)-**8**.[22] As a result, an approach that permitted production of (+)-**7** on large scale had to be developed.

In keeping with the MacMillan aldol route, conversion of **6** to (+)-**8** was easily performed on large scale (>100 g). Exhaustive extraction with water eliminates >90% of both the homoaldol byproduct and the reaction solvents (cf. DMF/dioxane) without compromise in yield[23] or the need for chromatography. The resultant diastereomeric mixture of aldehydes (5:1) could then be treated without separation with (methoxycarbonyl-methylene)-triphenylphosphorane to furnish unsaturated esters **11** (still a 5:1 mixture) in 94% yield. Sharpless asymmetric dihydroxylation using AD-mix β,[24] followed by cyclization with pyridinium *p*-toluenesulfonate, successfully provided the corresponding lactone (−)-**12** in 81% yield (based on the *anti* diastereomer). Pleasingly, the only triol diastereomer to undergo lactone formation was the *anti* isomer that places all substituents in pseudoequitorial orientations; facile separation of the diastereomeric triols was thus possible. Treatment of the lactone diol (−)-**12** with silver oxide, benzyl bromide, and calcium sulfate in 1,2-dichloroethane then provided (−)-**10** in 78% yield. In this transformation, monobenzylation occurs first at the α-position at 40 °C over a 24 h time period; increasing the temperature to 60 °C, with additional silver oxide and benzyl bromide, leads to the second benzylation after 8 h in 78% yield. Recovered monobenzylated lactone (ca. 17−20%) can be converted to the desired bis-benzylated product (−)-**10** upon exposure to the original benzylation conditions. In this fashion, a two-step yield of 91% can be achieved. Continuing with the synthesis, addition of the Grignard reagent derived from *cis*-1-bromo-3-hexene to lactone (−)-**10**, followed by reduction of the derived lactol with Et_3SiH and $BF_3{\cdot}Et_2O$, employing the Kishi protocol,[25] cleanly produced the desired *cis*-tetrahydropyran (+)-**13** in high yield (89%; two steps) (Scheme 4). Removal of the BPS protecting group also

Scheme 4



occurred during the reductive Et_3SiH process.[26] Final Parikh-Doering oxidation[27] of the primary hydroxyl provided the F-ring aldehyde (+)-**7** in 94% yield (50% overall yield from **6**). To date, the third-generation route to the F-ring aldehyde (+)-**7** has provided more than 68 g.

Construction of Wittig salt (+)-**3** from (+)-**7** followed our previous reported[15] sequence (Scheme 5). This sequence proved highly efficient and enabled the production of multigram quantities of (+)-**3**. Specifically, conversion of (+)-**7** to EF Wittig salt (+)-**3** begins by addition of dithiane (−)-**14**[15] under chelation controlled conditions to construct the linear precursor of the E-ring of (+)-spongistatin 1, (+)-**15**. After a 9-step sequence that includes an acid-catalyzed spiroketalization, ozonolysis, and α-methylenation with Eschenmoser's salt, allyl iodide (+)-**16** is obtained in 43%

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(23) Twenty water extractions successfully removed most major impurities, unreacted propanal, homoaldol byproduct, and reaction solvents (cf. DMF/dioxane).

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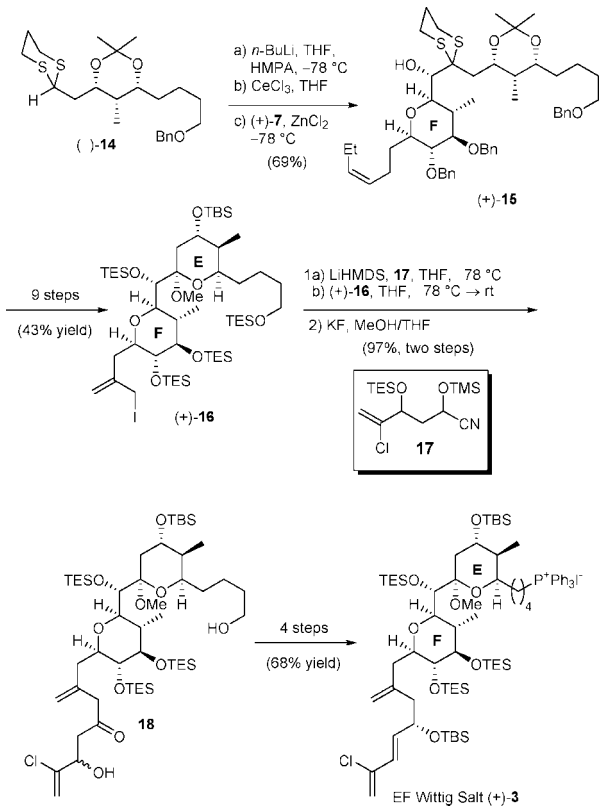
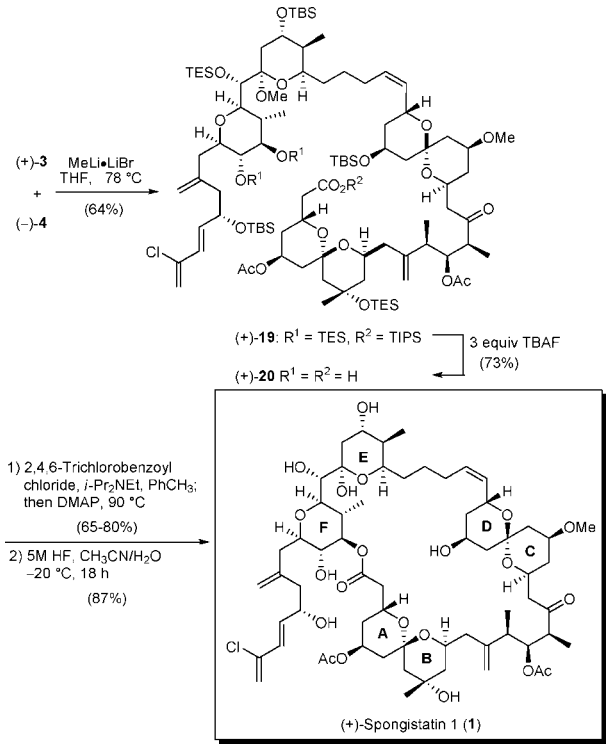
Scheme 5



Scheme 6



overall yield.[15] Alkylation of the latter with cyanohydrin **17** next successfully installs the chlorinated side-chain of (+)-spongisatin 1. Final conversion to the EF Wittig salt is then achieved in 4 steps and 68% yield. Employing the now scalable approach to (+)-**7**, we had in hand >5.8 g of EF Wittig salt (+)-**3**.

Completion of the third-generation synthesis of (+)-spongistatin 1 began with fragment union of EF Wittig salt (+)-**3** with advanced aldehyde (−)-**4**.[8d] Wittig union employing the MeLi•LiBr conditions originally introduced by Crimmins[10] in their synthesis of (+)-spongistatin 1 and 2, and subsequently utilized by Heathcock[11] and Ley,[12] provided alkene (+)-**19** in 64% yield.

For final elaboration to (+)-spongistatin 1 (**1**), the two-step deprotection/reprotection sequence utilized in our second-generation synthesis to reveal seco-acid (+)-**20** was not applicable, due to the failure of KF to remove cleanly the TES protecting groups (formally TMS groups).[7b] Use of TBAF, as employed by Heathcock to remove selectively the TES ethers at C(41) and C(42), and the TIPS ester[11] was therefore employed. Selective Yamaguchi macrolactonization then provided the desired 42-membered macrolide in 65−80% yield.[15] Global deprotection employing 5 M HF in acetonitrile (1:1) completed the synthesis of (+)-spongistatin 1 (**1**) in 87% yield. Synthetic (+)-spongistatin 1 was identical in all respects with the natural product.

In summary, an effective, scalable synthesis of the F-ring subunit of (+)-spongistatin 1 (+)-**7** exploiting an L-proline organocatalyzed cross-aldol reaction has been achieved; the sequence requires 8 steps compared to the 12 steps in our second-generation synthesis, and proceeds in 50% overall yield from **6**. On 10 to 100 g scales, the average yield for each step was over 85%. With this achievement, the third-generation synthesis of Wittig-salt (+)-**3** now proceeds with a longest linear sequence of 27 steps from commercially available *cis*-1,4-butenediol (9.5% overall), and as such represents a significant improvement, not only in yield, but also scalability. For (+)-spongistatin, the longest linear sequence is 31 steps (based on EF Wittig salt) and proceeds with an overall yield of 3.1%. To date, employing the second- and third-generation strategies, we have prepared 1.009 g of totally synthetic (+)-spongistatin 1 (**1**).

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Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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