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Synthetic studies on spongistatins: synthesis of the C29–C44 fragment†

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Abstract

A convergent synthesis of the C29–C44 fragment, the common subunit of the spongipyran macrolides is described. The key step of the synthesis is the *C*-glycosidation reaction which is based on coupling of the lithiated F-ring sulfone with the E-ring aldehyde, and subsequent reductive desulfonylation to afford the E–F bis (pyran) with high stereoselectivity at the anomeric carbon. © 2000 Elsevier Science Ltd. All rights reserved.

The spongipyran macrolides, a new family of marine natural products have been isolated from marine sponges: spongistatins 1–9 by Pettit,[1] altohyrtins A–C by Kitagawa,[2] and cinachyrolide A by Fusetani[3] groups. They display in vitro antitumor activities against a number of human cancer cell lines. Spongistatin 1 (**1**) (altohyrtin A) was found to be extremely potent (GI_{50}'s typically 2.5–3.5$\times 10^{-11}$ M) against NCI panel of 60 highly chemoresistant tumor cell lines.[1] Further investigations revealed that spongistatins efficiently inhibit mitosis by binding to tubulin and blocking microtubule assembly.[4] All of them feature two spiroketals AB and CD and highly substituted E- and F-rings in a 42-membered lactone with 24 stereocenters (Fig. 1). Due to their prominent biological activities and the paucity of available material from natural sources, these macrolides have stimulated considerable synthetic interests,[5] leading to total synthesis of altohyrtin C and A by Evans[6] and Kishi[7] groups. Both confirmed the absolute configuration of altohyrtins C and A originally proposed by the Kitagawa group,[2] and proved through spectroscopic analysis that altohyrtins C and A were identical to spongistatins 2 (**2**) and 1 (**1**).

In this paper we report our approach to the synthesis of the C29–C44 segment **3**, the common subunit of the spongipyran macrolides, as this fragment could be synthesized by coupling the E and F subunits in either clockwise or counterclockwise fashion. Previously, the strategy[6–9] used for the synthesis of this segment was based on coupling a lithiated species at C-37 of E-ring with the C-38 of F-ring subunit serving as electrophile. Our retrosynthetic plan for the synthesis of C29–C44 fragment **3** is shown in

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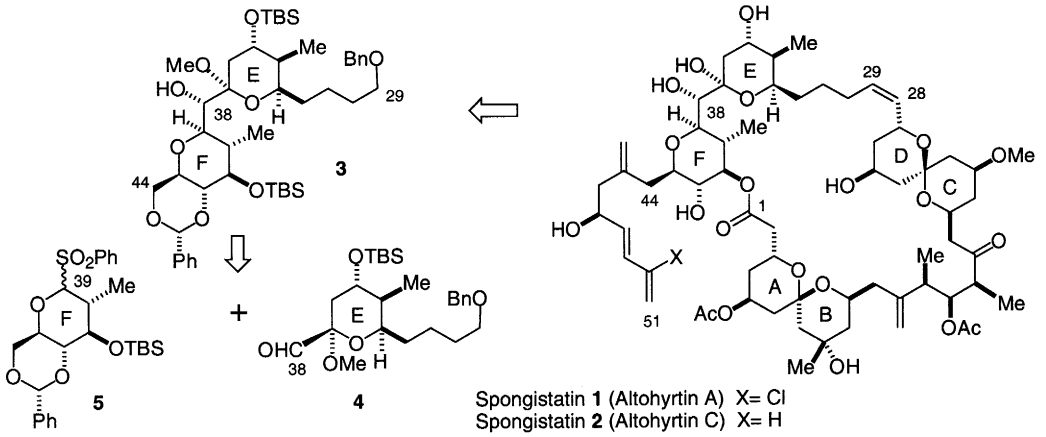


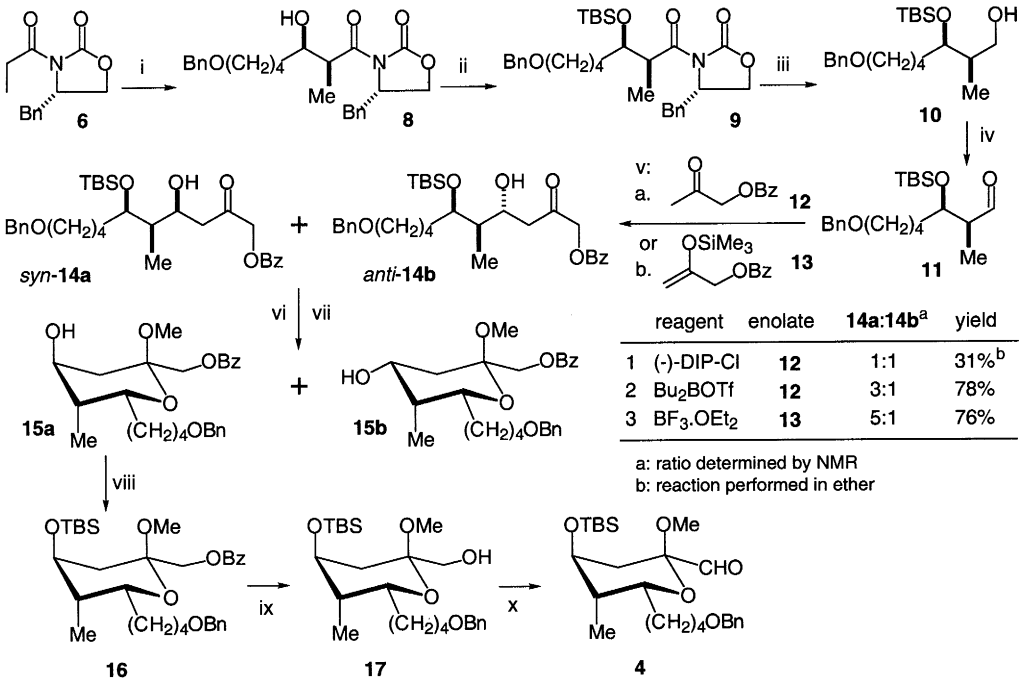
Fig. 1.

Fig. 1. We envisioned that the reverse coupling (counterclockwise) would be feasible, in that the lithium anion generated at anomeric carbon-C-39 of the F-ring sulfone **5** could be coupled with the C-38 E-ring aldehyde **4**, providing the E–F bis (pyran) **3**. As outlined below we describe first the synthesis of E and F subunits[10] and finally their coupling by exploiting the methodology previously developed[11] to achieve the *C*-glycosidation reaction.

The substituted E-ring aldehyde **4** was prepared through two aldol reactions. First stereoselective aldol coupling of the Evans oxazolidinone **6**[12] with the protected pentanal **7**[13] gave the *syn* adduct **8** (78%), followed by protection of the hydroxyl group (1.1 equiv. TBSOTf, 2.2 equiv. 2,6-lutidine, CH_2Cl_2) to furnish compound **9** in 98% yield. Reduction of the oxazolidinone moiety[14] (4 equiv. $NaBH_4$, THF–H_2O) gave alcohol **10** (74%), and subsequent oxidation (3 equiv. $SO_3 \cdot Py$, 7 equiv. Et_3N, DMSO) provided aldehyde **11** in 97% yield. Second aldol reaction of aldehyde **11** with the protected acetol **12**[15] mediated by Bu_2BOTf produced an inseparable mixture of the *syn* **14a** and *anti* **14b** adducts (3:1) in 78% yield (entry 2). The diastereoselectivity was improved (5:1) using Mukaiyama aldol reaction of aldehyde **11** with the silyl enol ether **13**[16] promoted by BF_3OEt_2 as Lewis acid[17] (entry 3). In contrast, no selectivity (1:1) was observed for the aldol coupling mediated by the chiralborane (−)-DIP-Cl (entry 1) (Scheme 1).

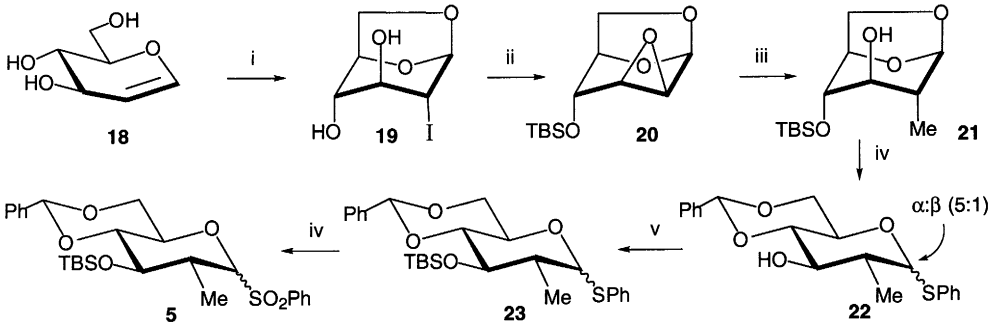
Subsequent deprotection of **14a**,**b** (TBAF, THF) and ketalization (cat. CSA, MeOH) gave the desired cyclic compound **15a** (58% over three steps from **11**) which was readily separated over column chromatography from its isomer **15b** (12%). Protection of the hydroxyl group (1.1 equiv. TBSOTf, 2.2 equiv. 2,6-lutidine, CH_2Cl_2) gave **16**, followed by deprotection of the benzoyl group (2 equiv. KOH, MeOH), afforded the primary alcohol **17** in 92% yield (over two steps). Further oxidation of the resulting alcohol (3 equiv. $SO_3 \cdot Py$, 7 equiv. Et_3N, DMSO) furnished the desired aldehyde **4** in 94% yield (Scheme 1).

The F-ring sulfone **5** was prepared starting from the readily available D-glucal **18** which was converted in one step to the known iodo compound **19** according to the procedure described.[18] Thus, selective protection of the less hindered hydroxyl group (1.1 equiv. TBSCl, 2.2 equiv. imidazole, DMF), followed by in situ treatment of the resulting protected iodo intermediate with NaH (3 equiv.) gave epoxide **20** in 86% yield. The methyl group was introduced through a *trans* diaxial addition of Me_2CuLi to the epoxide **20** to produce product **21** in 79% yield. Treatment of **21** with thiophenol (3 equiv. PhSH, MeCN) and PTSA (1 equiv.) which effects thioglycosylation and deprotection of the TBS ether, followed by in situ addition of $PhCH(OMe)_2$ (5 equiv.) furnished the protected thioglycoside **22** as a separable mixture of α and β isomers (5:1) in 93% yield.[19] The remaining hydroxyl group was protected as a TBS ether (1.1



Scheme 1. (i) Bu_2BOTf, Et_3N, **7**: $BnO(CH_2)_4CHO$, CH_2Cl_2, −78 to 0°C, 3 h (78%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 1 h (98%); (iii) $NaBH_4$, THF–H_2O, rt, 48 h, (74%); (iv) SO_3·Py, Et_3N, DMSO, rt, 1 h, (97%); (v) a. 2 equiv. of **12**, 2 equiv. of reagent, 2 equiv. of Et_3N, CH_2Cl_2, −78 to 0°C, 3 h; or b. 2.5 equiv. **13**, 2.5 equiv. BF_3·OEt_2, CH_2Cl_2, −78°C, 3 h; (vi) TBAF, THF, rt, 3 h; (vii) cat CSA, MeOH, rt, 1 h (58% for **15a**, and 12% for **15b**); (viii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 1 h; (ix) KOH, MeOH, rt, 1 h (92%); (x) SO_3·py, Et_3N, DMSO, rt, 1 h (94%)

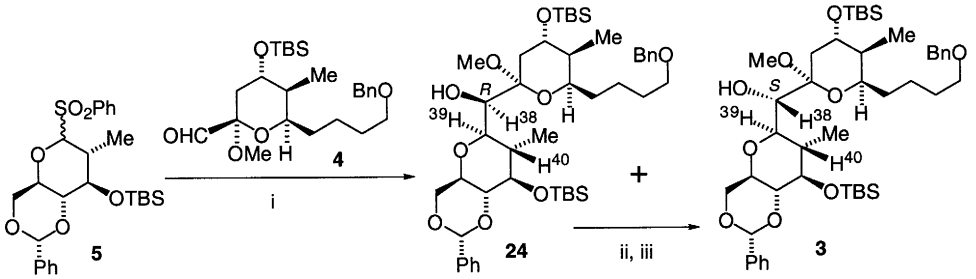
equiv. TBSOTf, 2.2 equiv. 2,6-lutidine, CH_2Cl_2) to give **23** and oxidation of the thiophenyl moiety (2.2 equiv. mCPBA, CH_2Cl_2) provided the desired F-ring sulfone **5** in 92% over two steps (Scheme 2).



Scheme 2. (i) see Ref. 18; (ii) TBSCl, imidazole, rt, 5 h, then NaH, DMF, 0°C to rt, 1 h (86%); (iii) Me_2CuLi, ether, 0°C to rt, 5 h (79%); (iv) PhSH, PTSA, 3 h, then MS 3 Å, $PhCH(OMe)_2$, MeCN, rt, 1 h (93%); (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0°C, 3 h; (vi) mCPBA, CH_2Cl_2, 0°C, 3 h (92%)

Finally, coupling of sulfone **5** through its lithium anion generated at anomeric carbon (LDA, THF, −78°C) in the presence of aldehyde **4**, followed by in situ reductive desulfonylation of the phenylsulfone moiety with lithium naphthalenide afforded the addition products **24**(*R*) and **3**(*S*) as a mixture of isomers (*R:S*, 4:1) in 52% yield. Both compounds **24** and **3** showed a coupling constant (J=10.8 Hz) corresponding to the axial–axial coupling of H-39 and H-40, which confirmed that the coupling reaction proceeds with high stereoselectivity at the anomeric carbon (C-39), leading to the equatorial C-β-

glycoside. The *R* alcohol **24** was converted to the desired *S* configuration by Ley oxidation[20] (TPAP, NMO, CH_2Cl_2) followed by Luche reduction[21] ($NaBH_4$, $CeCl_3$, MeOH) to give compound **3** as the sole observed isomer[22] in 88% yield. Further, the absolute configuration at C-38 was confirmed by Mosher esters analysis[23,24] (Scheme 3).



Scheme 3. (i) 1.2 equiv. LDA, 5 min, then **4**, 15 min, THF, −78°C, then 2.5 equiv. of Li-naphthalenide, 15 min, 5 equiv. of MeOH, 15 min, THF, −78°C (52%, 4:1); (ii) TPAP, NMO, MS 3 Å, CH_2Cl_2, rt, 2 h; (iii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C, 1 h (88%, over two steps)

In summary we have described a convergent synthesis of the C29–C44 subunit of spongistatins, starting from the readily available oxazolidinone **6** in 12 steps. Having this advanced intermediate in hand, studies toward the introduction of the triene side chain are currently underway.

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