

Synthesis of spongistatin 2 employing a new route to the EF fragment†

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Helmut Kraus,^a Antoine François,^a Matthew O'Brien,^{ab} James Frost,^a Alejandro Diéguez-Vázquez,^a Alessandra Polara,^a Nikla Baricordi,^a Richard Horan,^a Day-Shin Hsu,^a Takashi Tsunoda^a and Steven V. Ley^{*a}

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An improved route to the EF fragment of the spongistatins has been developed and employed in a synthesis of spongistatin 2. The C48–C51 diene side chain, which lacks the chlorine substituent present in spongistatin 1, presented some compatibility issues during target assembly. These were overcome by implementing a late stage Stille cross coupling to construct the diene portion of the natural product.

Introduction

According to recent WHO figures, cancer is the 4th largest cause of death worldwide, accounting for 13% of total mortality in 2008.¹ With an increasingly aging population, the incidence of cancer is predicted to follow an upward trend.² In the urgent battle against this disease, natural products have (directly or indirectly) delivered many important therapeutic advances and remain an invaluable resource in this respect.³ Since they were isolated independently by Pettit,⁴ Kitagawa⁵ and Fusetani⁶ in 1993, the spongistatins have attracted considerable scientific interest, owing principally to their exceptional antitumour activity against a variety of cell types. Indeed, all nine members of the spongistatin family have displayed remarkable growth inhibition characteristics against the US National Cancer Institute's panel of 60 human cancer cell lines.⁷ Of the family, spongistatin 1 is the most active, having GI₅₀ values between 0.025–0.035 nM with particular efficacy against cell lines derived from human melanoma.⁷ Unfortunately, due to the very low abundance of these compounds, as well as the difficulties associated with isolation and purification, obtaining significant quantities of natural material for further research is neither practical nor economic. Consequently, significant research efforts have been made towards their total synthesis. The absolute stereochemistry of these complex 42 membered macrolides remained unknown until the first syntheses of spongistatin 2 by Evans⁸ in 1997 and spongistatin 1 by Kishi a year later.⁹ Since then, several additional total syntheses have been established by Crimmins,¹⁰ Heathcock,¹¹ Paterson,¹² Smith¹³ and ourselves.¹⁴

For our total synthesis of spongistatin 1 we developed an efficient and scalable route to the ABCD fragment which profited from the *pseudo*-C2 symmetry of this fragment.^{14d} It was clear, however, that despite successfully completing the total synthesis of spongistatin 1, access to biologically significant quantities of these natural products would require an improved synthetic route to the EF fragment; one which was more scalable, required fewer synthetic steps and provided a higher overall yield. We report herein our second generation synthesis of the EF fragment and its subsequent employment in a total synthesis of spongistatin 2.^{14e}

Retrosynthesis

In line with previous syntheses of the spongistatins,^{8–14} our initial retrosynthetic analysis begins with disconnection of the C41(O)–C1 ester and the C28–C29 olefin to afford the ABCD aldehyde fragment, along with the corresponding EF phosphonium salt (3) (Fig. 1). As we already had a satisfactory route to the ABCD fragment (with material in hand),^{14d} as well as a proven endgame strategy, we sought to use a similar protecting group regime for this new synthesis. However, whilst our earlier synthesis of spongistatin 1 used an EF fragment containing a fully assembled C48–C51 chlorodiene appendage, the nor-chlorodiene required for spongistatin 2 alerted us to potential compatibility concerns during the subsequent removal of the PMB protecting groups.^{11d} Conjugated dienes are prone to undergo side reactions when exposed to DDQ,¹⁵ the standard reagent used for the oxidative cleavage of PMB groups, and it seems the chlorine substituent in spongistatin 1 mitigates this.^{12a,14d} These concerns notwithstanding, we elected to continue with PMB protecting groups for the EF fragment. Experiments (including model studies) confirmed that the diene would likely not survive the conditions used to remove the PMB groups. For this reason we chose to append a vinyl iodide substituent which we hoped to transform at a late stage (after

^aDepartment of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK. E-mail: svl1000@cam.ac.uk; Fax: +44 (0)1223 336442; Tel: +44 (0)1223 336398

^bLennard-Jones Laboratories, Keele University, Keele, Staffordshire, ST5 5BG, UK. E-mail: m.obrien@keele.ac.uk; Tel: +44 (0)1782 734371

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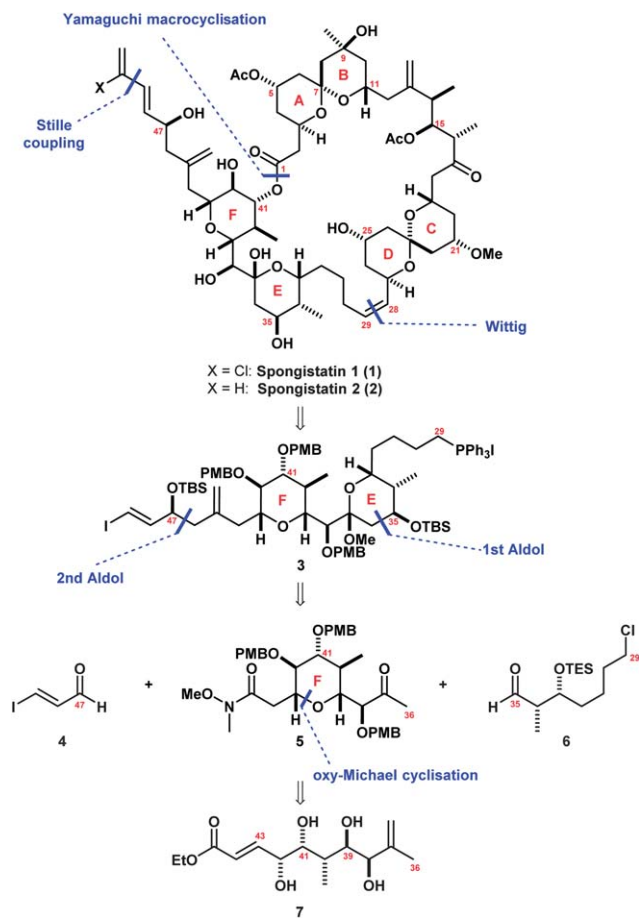


Fig. 1 Retrosynthetic analysis of spongistatin 2 and the EF fragment.

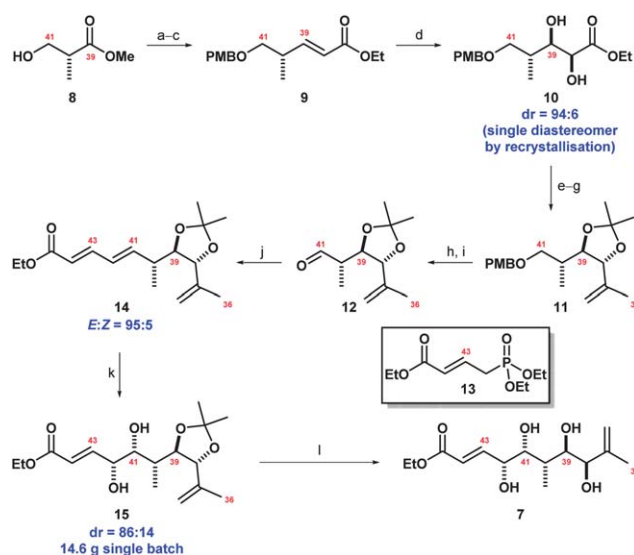
PMB deprotection) into the diene using a Stille coupling with tributyl(vinyl)tin.¹⁶ Further disconnection of EF fragment 3 via two aldol reactions leads to *trans* vinyl iodide 4, F ring-containing fragment 5 and aldehyde 6 as potential coupling partners. Fragment 5 would then derive from the intramolecular oxy-Michael cyclisation of substrate 7. Development of a sequence capable of furnishing multigram quantities of fragment 5 was therefore key to a scalable route to the EF fragment and thereafter the completion of spongistatin 2 (2) (Fig. 1).

Results and discussion

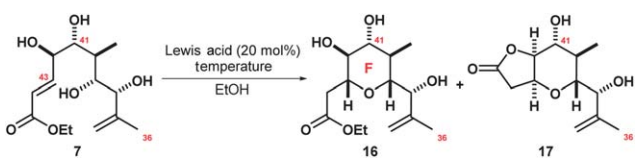
Our synthesis began from the commercially available (*S*)-Roche ester 8. This was protected as its *p*-methoxybenzyl ether, reduced to the corresponding aldehyde and reacted with $\text{Ph}_3\text{PCHCO}_2\text{Et}$ to furnish enoate 9 in excellent yield as a single (*E*)-isomer. Dihydroxylation using the Sharpless¹⁷ AD-mix- β provided 10 with excellent diastereoselectivity (*dr* = 94 : 6). Fortunately, this diol was highly crystalline and recrystallisation furnished a diastereomerically pure product in 92% yield. Protection as the acetonide followed by addition of $\text{MeLi} \cdot \text{LiBr}$ to the ester and Wittig reaction of the resulting ketone afforded 11. This 7 step sequence was carried out on large scale (100 mmol batches), allowing for the generation of 11 in substantial amounts. Removal of the PMB group, oxidation and Wittig-

Horner reaction with known phosphonate 13¹⁸ yielded 14, which underwent selective dihydroxylation (*dr* = 86 : 14, single isomer after chromatography) to afford diol 15 (Scheme 1). We next focused on the construction of the F ring by means of an oxy-Michael cyclisation reaction.

Encouraged by studies undertaken by Paterson and co-workers,^{12d} our initial efforts centred on removal of the acetonide protecting group in 15 under acidic conditions, which we hoped would be accompanied by spontaneous cyclisation to form the F ring in a one-pot procedure. However, although the acetonide could cleanly be removed (using MP-TsOH), the resulting tetraol 7 was resistant to subsequent cyclisation, despite assaying a range of conditions for this transformation (inc. Amberlyst A-15, TFA, TiF_2NH , TiOH , AcOH , $\text{TMSCl} : \text{EtOH}$ (0.3 M)). This being the case, we focussed our attention on the cyclisation process itself. The use of a variety of different bases (TBAF, NaH, KHMDS, *t*-BuOK, DBU, Et_3N , NaHCO_3) under different conditions (solvent and temperature) either failed to promote any reaction or afforded the desired product only in low yield ($\leq 50\%$).¹⁹ In many instances the desired thermodynamic pyran 16 was formed in varying ratio with products resulting from epimerisation at C42 or C43, the latter of which tended to form the 6,5-*cis* fused bicyclic lactone 17. Having achieved little success with bases, we turned instead to the use of Lewis acids in order to affect this crucial transformation. Although such methods to construct densely functionalised tetrahydropyran rings are not widely reported,²⁰ it seemed reasonable that a Lewis acid might activate the enoate towards nucleophilic attack. A selection of the additives which were screened are shown in Table 1.



Scheme 1 Synthesis of fragment 7. Reagents and conditions: (a) PMB-trichloroacetimidate, PPTS, CH_2Cl_2 , r.t., quant.; (b) DIBAL-H, CH_2Cl_2 , -78°C ; (c) $\text{Ph}_3\text{PCHCO}_2\text{Et}$, CH_2Cl_2 , r.t., 94% over 2 steps; (d) AD-mix- β , MeSO_2NH_2 , $t\text{-BuOH-H}_2\text{O}$ (1 : 1), 4°C , 92%; (e) 2,2-dimethoxypropane, CSA, r.t., 96%; (f) $\text{MeLi} \cdot \text{LiBr}$, Et_2O , -78°C , 95%; (g) $\text{CH}_3\text{PPh}_3\text{Br}$, *n*-BuLi, THF, 0°C to r.t., 96%; (h) DDQ, pH 7 buffer, CH_2Cl_2 , r.t.; (i) Dess-Martin periodinane, CH_2Cl_2 , 0°C to r.t.; (j) 13, LiHMDS, THF, -78°C then 12, -78°C to r.t.; 80% over 3 steps; (k) AD-mix- β , MeSO_2NH_2 , $t\text{-BuOH-H}_2\text{O}$ (1 : 1), 0°C , 89%; and (l) MP-TsOH, $\text{EtOH-H}_2\text{O}$ (1 : 1), 82°C , 98%.

Table 1 Selected Lewis acidic additives for the key oxy-Michael cyclisation


Entry	Lewis acid	Temp. [°C]	Method ^a	Result
1	TiCl ₄	80	A	Decomposition
2	PtCl ₄	80	A	No reaction
3	AuCl ₃	80	A	No reaction
4	CeCl ₃	80	A	No reaction
5	ZnCl ₂	80	A	No reaction
6	PtCl ₄	110	B	Decomposition
7	AuCl ₃	140	B	Decomposition
8	CeCl ₃	120	B	Decomposition
9	ZnCl ₂	180	B	16 (65%) + 17 (15%)
10 ^b	ZnX ₂	140	B	Decomposition
11	Zn(OTf) ₂	100	B	16 (75%) + 17 (15%)
12	Zn(OTf) ₂	100	C	16 (88%) + 17 (8%) ^c
13	TfOH	100	C	No reaction

^a Method A = conventional heating using a reflux condenser; Method B = microwave heating in a sealed vessel; Method C = sealed Schlenk tube. ^b X = F, Br, I. ^c The reaction was also conducted at r.t. at elevated pressure (50 bar) with no conversion observed.

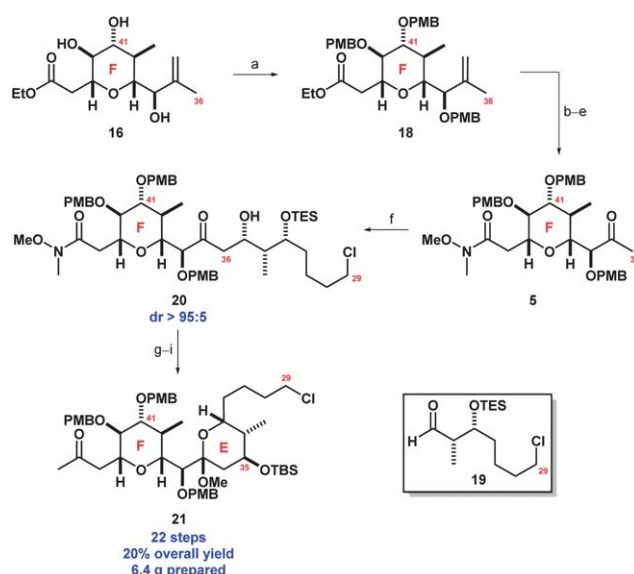
The presence of a variety of Lewis acids (20 mol%) at 80 °C in ethanol either led to no reaction or to decomposition (entries 1–5). The results for Pt(IV) and Au(III) were disappointing as we speculated that the propensity of these metals to activate ynones toward intramolecular reactions would extend to enones.²¹ In order to investigate the use of higher temperatures with the same solvent, a microwave reactor was used to conveniently allow the solvent to be superheated under pressure (ethanol b.p. = 78.4 °C at 1 atm) (entries 6–11).²² Extensive decomposition was observed in several cases (entries 6–8). However, ZnCl₂, which had no effect at 80 °C, afforded at 180 °C the desired product **16** in 65% yield, in addition to lactone **17** (15%). Whilst the use of other zinc(II) halogenide additives (ZnF₂, ZnBr₂, ZnI₂) were ineffective (entry 10), Zn(OTf)₂ proved to be the optimal choice, with the desired product produced in 75% yield (entry 11). Fortunately, this reaction proved to be both higher yielding (88%) and more scalable when performed in a sealed Schlenk tube, using conventional heating (oil bath) at 100 °C. Negating the need for a microwave reactor allowed multigram batches of material to be processed (entry 12). The origins of the superiority of Zn(OTf)₂ as a catalyst for this reaction are not clear, although it seems unlikely that any residual TfOH is acting as a catalyst (entry 13).

Having developed an effective procedure to ensure scalable and efficient access to the F-ring scaffold we required a method that would allow for the protection of all three hydroxyl groups present in **16**. PMB protection of hydroxyl groups is typically achieved using one of two sets of conditions: (a) base in conjunction with PMB-Cl/Br and a catalytic amount of TBAI/NaI²³ or (b) PMB-trichloroacetimidate (TCA) combined with a Brønsted or Lewis acid catalyst.²⁴ The latter method was

investigated initially since experience gained from the preceding oxy-Michael cyclisation had revealed the C43 stereo-centre to be highly prone to epimerisation. However, despite trying a variety of different acid catalysts (TfOH, La(OTf)₃, BF₃·OEt₂, Ph₃CBF₄) these efforts were met with decomposition or only low yields of the desired *tris*-PMB ether **18**. Little improvement was observed using tried-and-tested basic conditions. Wishing to avoid the daunting prospect of reworking our protecting group strategy, we persevered. After investigating a plethora of reagents and workarounds, we were pleased to find that a respectable 72% yield of **18** could be obtained using PMB-lepidine in the presence of MeOTf.²⁵ Use of this reagent offered several advantages compared to PMB-TCA: (a) it was stable at room temperature and could be easily prepared,²⁵ (b) the reactive intermediate could be formed under non-acidic conditions and (c) the lepidine byproduct could be easily removed by silica gel chromatography.

Hydrolysis of the ester functionality and formation of the corresponding Weinreb amide²⁶ proceeded smoothly. Thereafter dihydroxylation of the alkene and Pb(OAc)₄-mediated cleavage of the resulting diols furnished ketone **5**; allowing for interception of our first generation synthesis of spongistatin **1** (Scheme 2).^{14e}

With ketone **5** in hand, our efforts shifted to the construction of the E ring. The boron mediated aldol coupling of ketone **5** and aldehyde **19**²⁷ was achieved in high yield (82%) and in excellent diastereoselectivity (dr > 95 : 5), giving the Felkin-Anh product (**20**).²⁸ Presumably the 1,2-stereochemical induction predicted by the Felkin-Anh model overrides any 1,3-asymmetric induction favoured by the chiral aldehyde.²⁹ Treatment of **20** with PPTS in the presence of trimethyl orthoformate and MeOH effected C33(OH) silyl deprotection and triggered



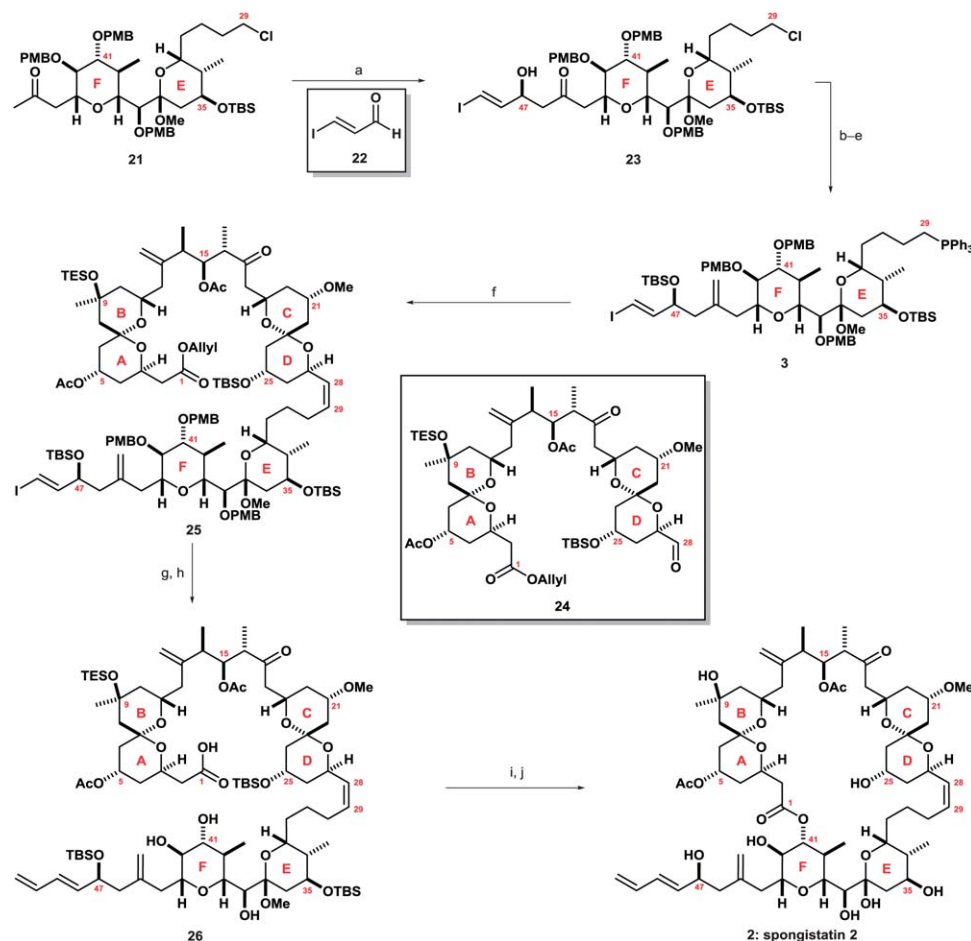
Scheme 2 Synthesis of EF fragment **21**. Reagents and conditions: (a) PMBO-lepidine, MeOTf, PhMe, 40 °C, 72%; (b) LiOH·H₂O, THF, H₂O, r.t.; (c) HCl·HN(OMe)Me, HOBT-EDCl, Et₃N, THF, r.t., 86% over 2 steps; (d) OsO₄, NMO, acetone-H₂O (1 : 1), r.t., 98%; (e) Pb(OAc)₄, PhMe, r.t., 98%; (f) cHex₂BCl, Et₃N, Et₂O, 0 °C, 2 h, then **19**, –78 °C, 2 h, 82%; (g) PPTS, CH(OMe)₃, MeOH, r.t., 89%; (h) TBSOTf, 2,6-lutidine, THF, –78 °C, 99%; and (i) MeLi, CeCl₃, –78 °C, quant.

spontaneous E ring cyclisation with concomitant formation of the C37 methyl acetal. The C35(OH) was then protected as its TBS ether, and the Weinreb amide functionality converted to the corresponding ketone (**21**) in quantitative yield by reaction with a methylcerium reagent prepared *in situ* from methyl-lithium and anhydrous ceric chloride.³⁰ Completion of EF fragment **21** via this new route resulted in a significantly shorter reaction sequence (22 linear steps) and a much higher overall yield of 20% compared to our first generation synthesis (27 linear steps and 5.6% overall yield).^{14e} This enabled the production of 6.4 g of highly functionalised compound **21**, and compares favourably with other routes reported towards similar EF fragments.^{12,13}

At this stage the route diverges from our original spongistatin 1 synthesis. Aldol coupling of **21** with an excess³¹ of 3-iodoacrolein **22**³² furnished compound **23** in high diastereoselectivity (*dr* > 95 : 5) and good yield (65%) (Scheme 3).³³ This was then TBS-protected, and subjected to the Takai-Lombardo methylenation³⁴ conditions followed by Finkelstein reaction³⁵ in a highly efficient 3 step sequence in 74% overall yield. Following

considerable experimentation, a Wittig olefination reaction between the corresponding phosphonium salt **3** (1.0 equiv.) and ABCD aldehyde **24** (1.3 equiv.)^{14d} in the presence of LiHMDS (3.0 equiv.) at -78°C resulted in a 56% yield of the (*Z*)-alkene. The three PMB protecting groups in this compound were then oxidatively cleaved in 71% yield using DDQ.

At this stage the C48–C51 diene side chain could be completed. Pleasingly, the necessary Stille cross coupling reaction was not perturbed by the C1 allyl ester protecting group. A one-pot Stille-coupling/deprotection sequence³⁶ was effected using Pd_2dba_3 (10 mol%), AsPh_3 (40 mol%), tributyl(vinyl)tin (5.0 equiv.) and morpholine (10.0 equiv.), affording **26** in an excellent yield of 84%. By installing the diene unit at this late stage, we effectively avoided the side reactions (oxidation, cycloadduct formation^{11d}), that we and others had previously observed using DDQ on a similar diene substrate.^{11d} Yamaguchi macrolactonisation³⁷ of *seco*-acid **26** using the conditions developed by Heathcock¹¹ led to a mixture of the desired product as well as some byproducts. From the ^1H NMR of the crude product mixture, it appeared that partial hydrolysis of the



Scheme 3 Completion of spongistatin 2. *Reagents and conditions:* (a) Cy_2BCl , Et_3N , Et_2O , -55°C , then **22**, -70°C , Et_2O , 65%; (b) TBSCl, imidazole, DMF, r.t.; (c) Zn, PbI_2 , TMSCl, CH_2I_2 , 0°C to r.t., then TiCl_4 , CH_2Cl_2 , r.t., followed by ketone, THF, r.t.; (d) NaI, NaHCO_3 , Na_2SO_3 , 1-iodopropane, acetone, 67°C , 74% over 3 steps; (e) PPh_3 , DIPEA, MeCN, 90°C ; (f) **3**, THF, r.t. then LiHMDS, -78°C , followed by aldehyde **24**, -78°C , 56% over 2 steps; (g) DDQ, pH 7 phosphate buffer, CH_2Cl_2 , 0°C , 71%; (h) Pd_2dba_3 (10 mol%), AsPh_3 (40 mol%), tributyl(vinyl)tin (5.0 equiv.), morpholine (10.0 equiv.), DMF–THF (1 : 1), r.t., 84%; (i) 2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, PhMe, 90°C ; and (j) 47–51% aq. HF, MeCN, -20°C , 42% over 2 steps.

methyl acetal at C37 had occurred, somewhat hampering full ^1H NMR analysis. However, treatment of the crude mixture with 47–51% aq. HF at -20°C resulted in global silyl deprotection and methyl acetal hydrolysis to deliver spongistatin 2 (**2**) in 42% over the two steps. The synthetic material was found to be identical to the natural product in all respects (^1H NMR, ^{13}C NMR, IR, mass spectrometry, optical rotation).^{4b,5c}

Conclusions

In summary we have developed a highly scalable and efficient preparation of the EF fragment of the spongistatins. This was made possible by the design of a route that gave access to multigram quantities of tetraol **7**. Satisfactory conditions for the F ring cyclisation initially proved elusive but this key transformation was eventually achieved in a yield of 88% using $\text{Zn}(\text{OTf})_2$. Further synthetic manipulation brought about interception with our first generation synthesis, leading to compound **21** in 22 steps (longest linear sequence) and 20% overall yield. With 5 fewer steps and a greater than threefold increase in yield, this clearly represents a significant gain in efficiency. A boron mediated aldol reaction using 3-iodo-acrolein (**22**) allowed us to install a truncated vinyl iodide side chain. By extending this to the diene at a late stage *via* a Stille cross coupling with tributyl(vinyl)tin, we managed to avoid serious incompatibility issues related to PMB deprotection and were able to complete a total synthesis of spongistatin 2 (**2**) with an overall yield of 1.3% (from Roche ester) over 32 steps (longest linear sequence). To date, 6.4 g of **21** have been prepared. With scalable routes to both the EF and ABCD fragments at our disposal, we are now in a position to synthesise spongistatin 2 (and other members of the family) in quantities useful for further biological investigation.

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