Synthesis of the EF Fragment of Spongistatin 1

Shigeru Kawahara, Matthew J. Gaunt, Alessandra Scolaro, Shigeo Yamanoi, Steven V. Ley*

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

Received 16 June 2005

Abstract: The EF fragment of spongistatin 1 was prepared diastereoselectively from 3,4,5-tri-*O*-benzyl-D-glucal.

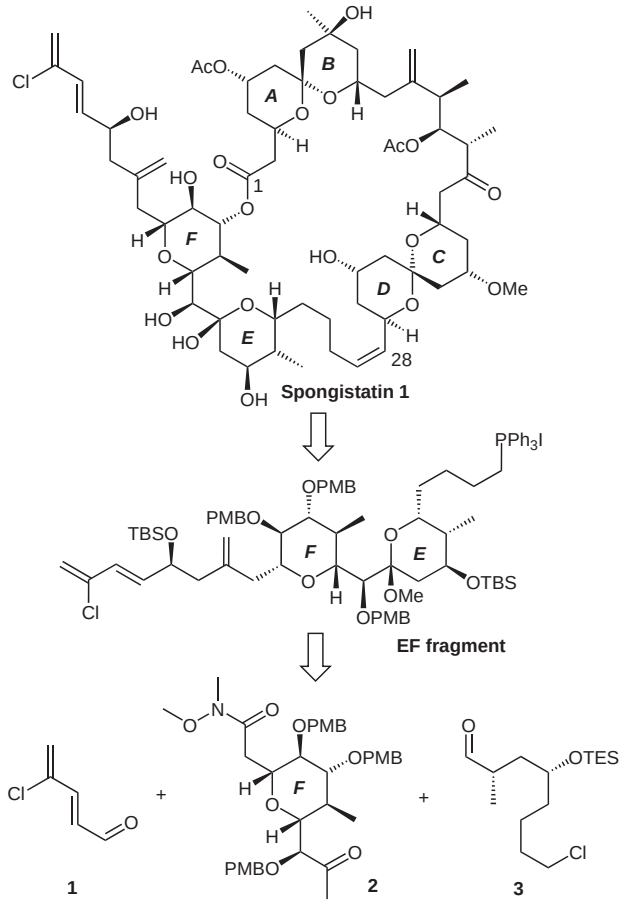
Key words: aldol, stereoselective synthesis, natural products, glycosides, spongistatin 1, spongistatins

The spongistatins are a family of highly cytotoxic macrolides that were isolated from marine sponges.[1–3] These compounds have been shown to exhibit potent antitumour activities against a number of human multi-drug resistant cell lines.[4] The limited supply from natural sources has stimulated significant efforts in the synthesis of these compounds.[5] Our route to spongistatin 1 calls for the assembly of a C1–C29 ABCD aldehyde,[6a,b] coupling via a Wittig process with a suitable EF fragment. This fragment ideally derives from the union of three building blocks **1**, **2**, and **3**, where the F-ring unit **2** acts as a core structure to which the side chains are appended via aldol coupling reactions. We now report the successful completion of the synthesis of the EF fragment based on this approach. Previous work in our group on a model system had established the viability of this general strategy (Scheme 1).[6c]

The synthetic effort began with the manipulation of glycol derivative **4**, which was prepared from 3,4,5-tri-*O*-benzyl-D-glucal.[6c] Anomeric acetate formation, Mukaiyama-type C glycosidation with 2-trimethylsilyloxy-propene and subsequent isomerisation introduced the 2-oxo-propane moiety of **5** in the required equatorial manner (Scheme 2). Protection of the carbonyl group as its dioxolane derivative and further manipulation delivered iodide **6**. Cyanide displacement of the iodide afforded the corresponding nitrile **7**, which was converted into ketone **2**; the crucial step of which is stereoselective introduction of the C38 hydroxyl group.

This was accomplished by Rubottom-type oxidation of the thermodynamic silyl enol ether readily generated from ketone **7**, affording **8** as the sole C38 epimer (Scheme 2).[7]

Nuclear Overhauser effect (NOE) was observed between C38–H and C40–H, and C36–Me and C38–H, respectively (Figure 1). This clearly indicated that one face of the silyl enol ether moiety was hindered by the C40 methyl substituent. Therefore, the Rhenium catalyst most reasonably approaches the silyl enol ether moiety from the less hindered front side, leading to the desired hydroxyketone



Scheme 1 Synthetic strategy for the EF fragment of spongistatin 1.

8. There is also a possibility that one of the two lone pairs of the pyran oxygen might direct the catalyst through coordination.

The C29–C35 aldehyde fragment **3** was conveniently obtained in 4 steps from commercially available oxazolidi-

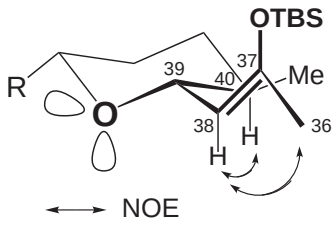
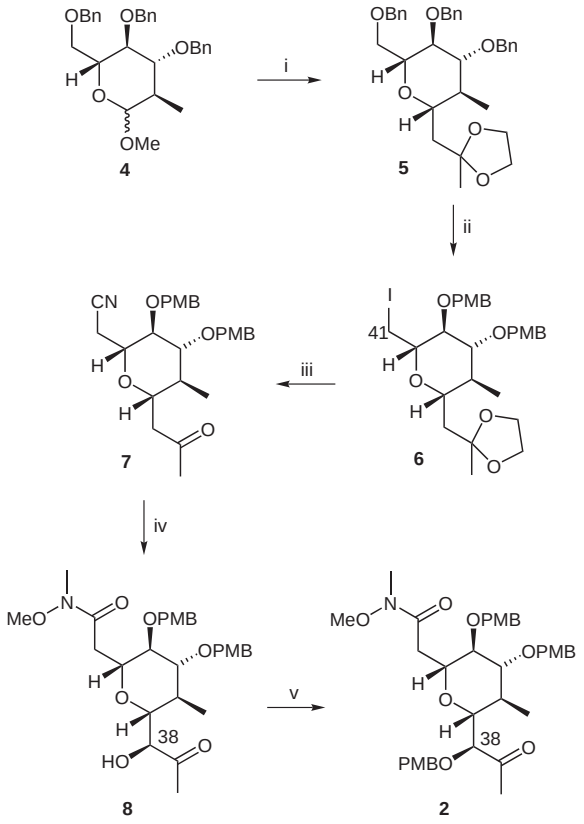


Figure 1 Proposed 3D structure of the silyl enol ether based on NOE analysis; two PMBO groups are omitted and the CH_2CON–MeOMe moiety is represented by R for clarity.

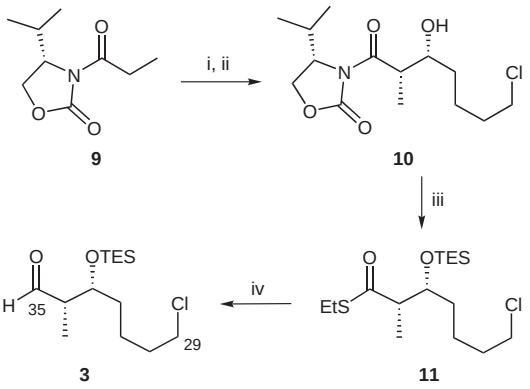
SYNLETT 2005, No. 13, pp 2031–2034
Advanced online publication: 12.07.2005
DOI: 10.1055/s-2005-871960; Art ID: D16305ST



Scheme 2 Synthesis of the F-ring fragment **2**. *Reagents and conditions*: i) (a) concd HCl, 1,4-dioxane, r.t., 4 h, 65%; (b) Ac_2O, pyridine, r.t., 5 h, 98%; (c) 2-trimethylsilyloxy-propene, TMSOTf, CH_2Cl_2, –78 °C to –40 °C, 25 h, 75%; (d) NaOMe, MeOH, r.t., 18 h, then 1,2-ethanediol, PPTS, benzene, (azeotropic), 85% over 2 steps; ii) (a) 10% Pd/C, H_2, AcOH, EtOH, r.t., 10 h, then TIPSCl, imidazole, DMF, r.t., 3 h, 97%, over 2 steps; (b) PMBCl, NaI, NaH, THF–DMF, r.t., 18 h, 98%; (c) TBAF, THF, r.t., 2 h, 88%; (d) I_2, PPh_3, imidazole, MeCN–Et_2O, quant; iii) (a) KCN, 18-crown-6, DMF, r.t., 3 h, 92%; (b) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 84%; (c) $NaClO_2$, 2-methyl-2-butene, pH 7 buffer–*t*-BuOH–THF, r.t., 1 h, then MeNHOMe·HCl, TEA, EDCI, HOBt, CH_2Cl_2, 93% over 2 steps; (d) PPTS, acetone–H_2O, reflux, 1 h, 90%; iv) (a) *t*-BuOK, *t*-BuOH, THF, –78 °C, 20 min, followed by addition of TBSCl, –78 °C, 1 h, quant.; (b) MTO, pyridine, H_2O_2, CH_2Cl_2, 0 °C to r.t., 4 h, then TBAF, CH_2Cl_2, 0 °C, 30 min, 78%, over 2 steps; v) (a) PMBTCA, BF_3·OEt_2, CH_2Cl_2, r.t., 50–80%. MTO = methyltrioxorhenium; PMBTCA = *para*-methoxybenzyl trichloroacetoimidate.

none **9** using Evans' aldol chemistry.[8] Stereoselective aldol coupling and protection of the resulting alcohol gave the protected *syn*-aldol product **10**. Substitution of the oxazolidinone with EtSLi afforded the thiol **11**, which was conveniently reduced to the corresponding C29–C35 aldehyde **3** with Et_3SiH in the presence of Pd/C[9] (Scheme 3).

The boron-mediated aldol coupling of ketone **2** with aldehyde **3** proceeded with high diastereocontrol, providing the desired aldol adduct **13** under Felkin–Ahn control (Scheme 4). This excellent diastereoselectivity suggests that 1,2 Felkin–Ahn control overrides the competing 1,3 effect of the chiral aldehyde.[10]



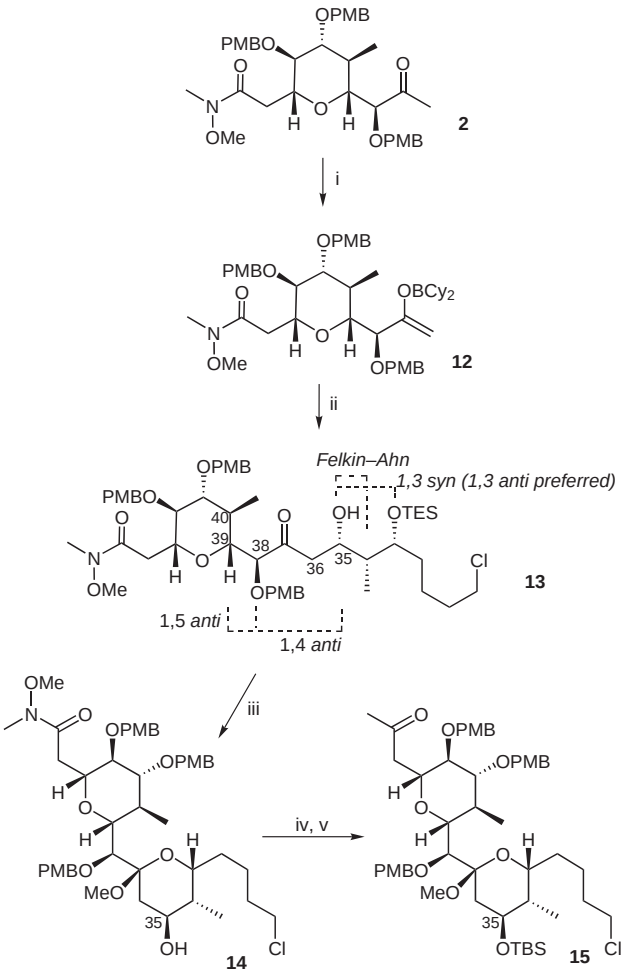
Scheme 3 *Reagents and conditions*: i) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, –78 °C to 0 °C, 30 min, followed by addition of 5-chloropentanal, –78 °C to 0 °C, 1.5 h, 78%; ii) TESCl, imidazole, DMF, r.t., 2 h, 78%; iii) EtSH, *n*-BuLi, THF, 0 °C, 0.5 h, 80%; iv) 10% Pd/C, Et_3SiH, CH_2Cl_2, r.t., 10 min, 98%.

The acid-catalysed removal of the triethylsilyl group from the C33 hydroxyl of **13** revealed the EF-ring system **14** via spontaneous cyclisation and in situ protection of the resulting hemiketal in the presence of MeOH as solvent. Silyl protection of the C35 hydroxyl group was best performed using *tert*-butyldimethylsilyl trifluoromethanesulfonate/2,6-lutidine and conversion of the Weinreb amide into methyl ketone **15** was effected by treatment with MeLi–$CeCl_3$. The organocerium reagent was chosen due to its reduced basicity compared with the analogous organolithium, successfully preventing competing unproductive enolisation.[11]

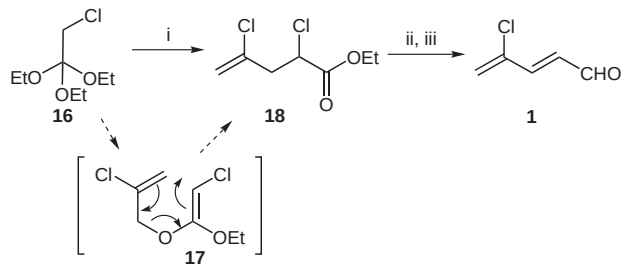
The chlorodiene fragment **1** was prepared in just four steps from commercially available orthoester **16** (Scheme 5). Johnson–Claisen rearrangement through the intermediacy of allylvinyl ether **17** afforded α-chloroester **18**.[12] Basic elimination with DBU in benzene provided an intermediate conjugated diene ester which was reduced with DIBAL-H and oxidised with MnO_2 to furnish chlorodiene **1**. This sequence represents the most efficient solution to the synthesis of the problematic chlorodienal aldehyde.

Coupling of chlorodiene **1** to methyl ketone **15** was achieved through a highly selective boron aldol reaction. Owing to its instability, immediate protection of the newly formed C47 alcohol was necessary to access **20** in excellent yield (Scheme 6). Interestingly, we found that the C35 *tert*-butyldimethylsilyl ether was essential for high selectivity in this reaction;[5m,6c] use of the corresponding C35 *para*-methoxybenzyl ether **19** resulted in poor diastereoselectivity in the side chain coupling reaction. The seemingly remote nature of the C35 protecting group indicates a key conformational requirement for the installation of the side chain motif via aldol coupling protocols.

Takai olefination installed the desired *exo*-methylene group at the C45 position affording **22** (Scheme 7).[13] Finkelstein conditions in the presence of *n*-PrI, which acted as a chloride scavenger, enabled us to obtain the corresponding iodide **23** as the sole product. Phosphonium salt

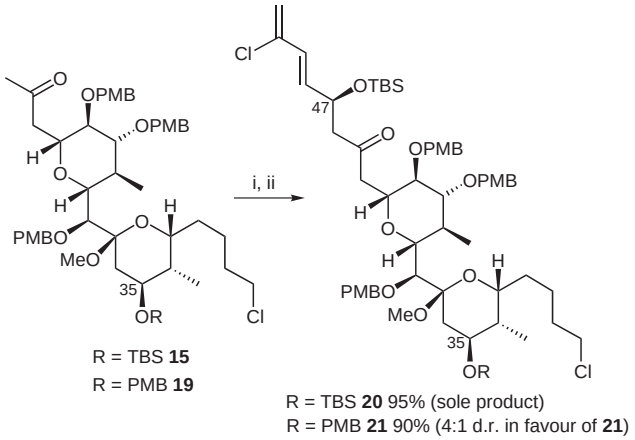


Scheme 4 *Reagents and conditions*: i) Cy_2BCl, TEA, Et_2O, 0 °C, 1.5 h; ii) **3**, –78 °C to 0 °C, 3 h, 96%; iii) PPTS, TMOF, MeOH–THF, r.t., 20 min, 89%; iv) *t*-$BuMe_2SiOTf$, 2,6-lutidine, THF, –78 °C, 20 min, 86%; v) $CeCl_3$, MeLi, THF, –78 °C, 20 min, 96%.



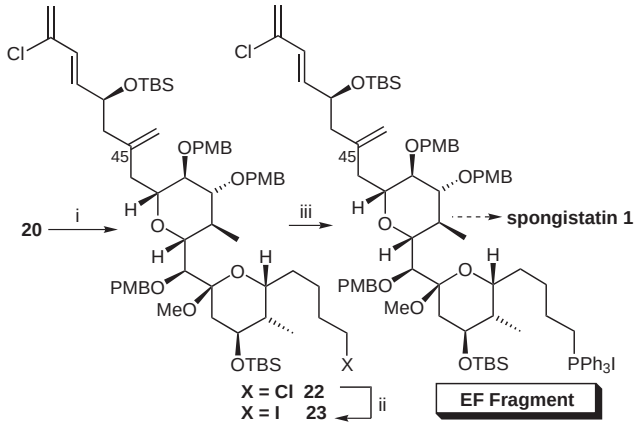
Scheme 5 *Reagents and conditions*: i) pivalic acid, 2-chloro-2-propene-1-ol, *o*-xylene, 140 °C, 17 h, 78%; ii) (a) DBU, benzene, 0 °C to r.t., 4 h; (b) DIBAL-H, CH_2Cl_2, –78 °C, 30 min, 74% over 2 steps; iii) MnO_2, CH_2Cl_2, r.t., 1 h, 81%.

formation was easily achieved with PPh_3 in the presence of *i*-Pr_2NEt, however, silica gel purification of the salt led to counteranion exchange between iodide and presumably HO^- or MeO^-. In order to avoid the problematic purification, we intend to use the crude salt in the following key Wittig coupling.



Scheme 6 *Reagents and conditions*: i) (a) Cy_2BCl, TEA, Et_2O, –78 °C, 3 h, followed by addition of aldehyde **1**, –78 °C, 16 h; (b) TBSCl, imidazole, DMF, r.t., 2 h, 97% over 2 steps.

In summary, we have completed an efficient synthesis of the EF fragment of spongistatin 1. Our route has produced gram quantities of the key fragment and we are currently optimising the completion of the synthesis of spongistatin 1. We are also developing a second-generation synthesis of the EF fragment which will be reported in due course.



Scheme 7 *Reagents and conditions*: i) Zn, PbI_2, Me_3SiCl, CH_2I_2, $TiCl_4$, CH_2Cl_2–THF, r.t., 4 h, 75%; ii) NaI, *n*-PrI, $NaHCO_3$, Na_2SO_3, acetone, 18 h, 93%; iii) PPh_3, *i*-Pr_2NEt, MeCN, 85 °C, quant.

Acknowledgment

We thank Pharmacia, Italy (A.S.), Ajinomoto Co. Inc. (S.K.), and Novartis for a fellowship (S.V.L.), as well as Dr. Matthew Ball, Adam Talbot and Huw Tanner for other important contributions to this work. We also gratefully acknowledge the work of Dr. Felix Rodriguez in performing crucial EF model studies.

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