

## Stereocontrolled Total Synthesis of (+)-Altohyrtin A (Spongistatin 1)\*\*

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First reported in 1993 by three groups (Kitagawa/Kobayashi, Pettit and Fusetani),<sup>[1]</sup> the altohyrtins/spongistatins/cinachyrolides are a unique family of antimetabolic macrolides,<sup>[2-5]</sup> obtained from marine sponges in trace amounts by bioassay-guided isolation, which display exceptional potency against a wide variety of human cancer cells. Structurally (Figure 1, 1–3), they feature a highly substituted 42-membered macrolide ring, comprising two spiroacetals (AB and CD rings) and a *bis*(tetrahydropyran) unit (E and F rings), with a triene side chain (varying in substitution at C50, X = Cl, Br, H), along with having 24 stereogenic centres. Initial discrepancies in the configurational assignments were resolved in 1997 by the first total synthesis of altohyrtin C (3) by the Evans group,<sup>[6]</sup> and soon after altohyrtin A (1) by the Kishi group,<sup>[7]</sup> which confirmed the full assignment proposed for the altohyrtins by Kobayashi and Kitagawa and co-workers,<sup>[2d]</sup> and that they were identical to spongistatins 2 and 1 respectively, as reported by Pettit *et al.*<sup>[3a,b]</sup> More recently, the Smith group have completed a second total synthesis of 3.<sup>[8]</sup>

Spongistatin 1/altohyrtin A (1) constitutes one of the most potent cytotoxic compounds tested by the US National Cancer Institute (NCI),<sup>[2,3]</sup> having sub-nanomolar growth inhibitory activity (mean GI<sub>50</sub> = 0.03 nM) against highly chemoresistant tumour types (including lung, colon and brain cancers), while *in vivo* human melanoma and ovarian carcinoma xenograft experiments showed curative responses at extremely low doses.<sup>[3h]</sup> It inhibits mitosis by binding to tubulin and blocking microtubule assembly.<sup>[3g]</sup> Despite this highly promising profile, the unreliable and extremely meagre supply (e.g. 3.4 × 10<sup>-7</sup>% isolation yield for spongistatin 1)<sup>[3a]</sup> has effectively halted further preclinical development in cancer chemotherapy.

The exceptional biological activity, combined with the supply problem, has provided an impetus to develop a practical route to these synthetically challenging *bis*-spiroacetal macrolides.<sup>[9,10]</sup> Herein, we describe a highly stereocontrolled total synthesis of the most active congener, altohyrtin A/spongistatin 1 (1), which produces useful quantities for further biological evaluation, as well as enabling access to novel analogues for SAR studies. Throughout our synthesis, asymmetric boron aldol reactions of ketones are exploited as a powerful bond-forming and stereodefining process.<sup>[11]</sup>

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[ ] Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

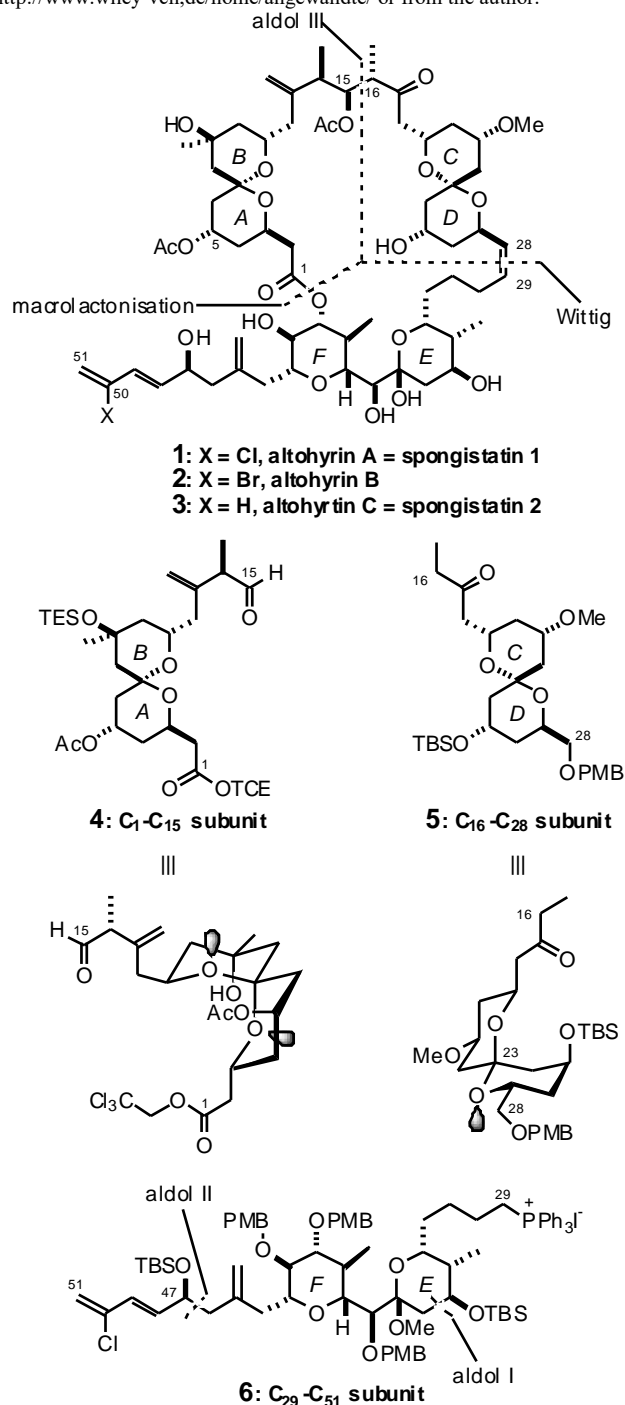
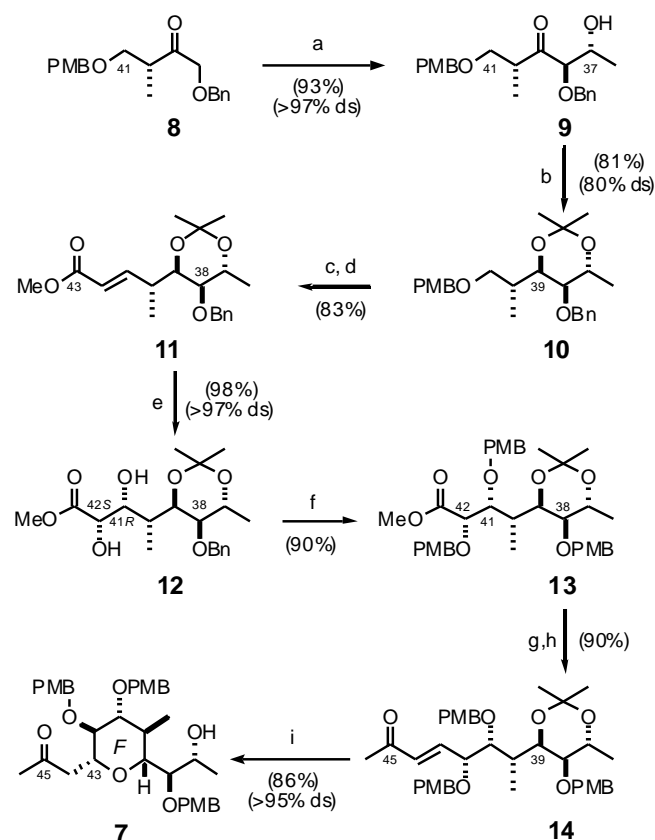


Figure 1. Representative structures of altohyrtins/spongistatins and key subunits for synthesis. TES = triethylsilyl, TCE = trichloroethyl, TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.

As shown in Figure 1, our proposed synthetic route to 1, which is based on a threefold disconnection of the 42-membered macrolide ring, employs macrolactonisation, Wittig and aldol couplings. We planned<sup>[9]</sup> a modular route based on the late-stage, sequential connection of the fully functionalised spiroacetal subunits 4 and 5, followed by the *bis*(tetrahydropyran) subunit 6. Notably, the AB spiroacetal ring is stabilised by a double anomeric effect, while the CD spiroacetal subunit benefits from only a single anomeric effect, and thus epimerises readily at C23 under acidic

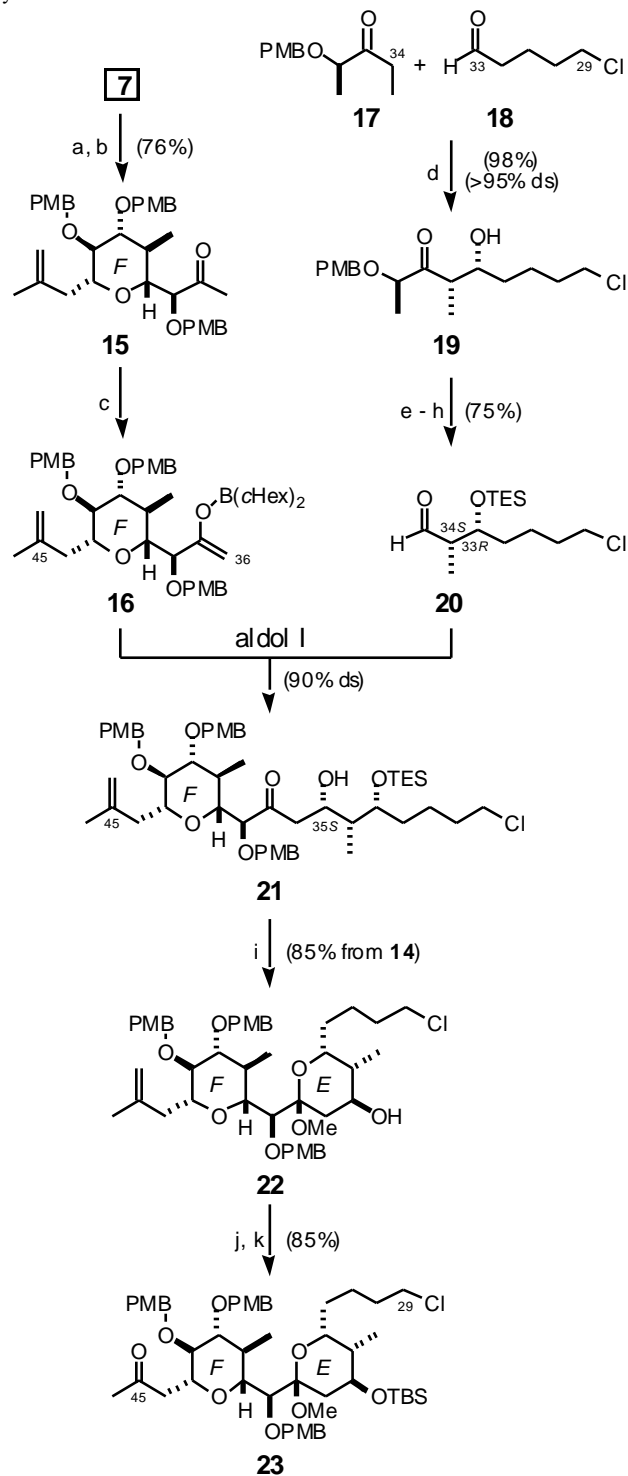
conditions. Introduction of the bridging chain between the AB and CD ring systems in **4** and **5**, and the connection of the E to the F ring in **6** were identified as strategic aldol bond constructions (aldols I and III), along with the installation of the terminal chlorodiene and isolated C47 stereocentre in **6** (aldol II).

As outlined in Scheme 1, the synthesis of the F ring subunit **7** began with a boron-mediated *anti* aldol reaction between the readily available<sup>[12]</sup> ketone (*R*)-**8** and acetaldehyde to give **9**, followed by Me<sub>4</sub>N.BH(OAc)<sub>3</sub> reduction<sup>[13]</sup> to the 1,3-*anti* diol and formation of the acetonide **10**. Following *para*-methoxybenzyl (PMB) deprotection (and separation of the minor C39 epimer), Dess-Martin oxidation and chain extension by Horner-Wadsworth-Emmons (HWE) olefination furnished the (*E*)-enoate **11**. This alkene having a benzyl ether at C38 proved to be an excellent substrate for Sharpless dihydroxylation<sup>[14]</sup> with enriched AD-mix-β, giving solely the (41*R*,42*S*)-diol **12** in 98% yield.<sup>[15]</sup> For the remainder of the synthesis, we now chose to install PMB protecting groups at the C38, C41 and C42 hydroxyls. Hydrogenolysis of **12** (Pd(OH)<sub>2</sub>, NaHCO<sub>3</sub>), followed by PMB protection using *para*-(methoxybenzyl)trichloroacetimidate under mild acidic catalysis<sup>[16]</sup> with Ph<sub>3</sub>CBF<sub>4</sub> gave *tris*-PMB ether **13**. Reduction of **13** with DIBAL-H and HWE chain extension<sup>[17]</sup> using dimethyl 2-oxopropylphosphonate and



Scheme 1. Synthesis of the C<sub>36</sub>-C<sub>46</sub> subunit **7**: a) *i*) cHex<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, -78 °C, 2 h; MeCHO, -78 → -20 °C, 16 h; *ii*) H<sub>2</sub>O<sub>2</sub>, MeOH/pH 7 buffer, 0 → 20 °C, 3 h; b) *i*) Me<sub>4</sub>NBH(OAc)<sub>3</sub>, MeCN/AcOH, 4 °C, 60 h; *ii*) PPTS, Me<sub>2</sub>C(OMe)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 16 h; c) *i*) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer, 0 °C, 90 min; *ii*) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 3 h; d) (MeO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Me, LiCl, *i*Pr<sub>2</sub>NEt, MeCN, 20 °C, 16 h; e) enriched AD-mix-β, *i*BuOH/H<sub>2</sub>O, 20 °C, 8 h; f) *i*) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, NaHCO<sub>3</sub>, MeOH, 20 °C, 20 h; *ii*) PMBTCA, Ph<sub>3</sub>CBF<sub>4</sub>, THF, 0 °C, 2 h; g) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 30 min; h) (MeO)<sub>2</sub>P(O)CH<sub>2</sub>COMe, Ba(OH)<sub>2</sub>, THF/H<sub>2</sub>O,

20 °C, 16 h; *i*) AcOH, THF/H<sub>2</sub>O, 20 °C, 48 h; *ii*) KOH, MeOH, 20 °C, 24 h. Bn = benzyl, PPTS = pyridinium *para*-toluenesulfonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, PMBTCA = *para*-(methoxybenzyl)trichloroacetimidate, Dibal-H = diisobutylaluminium hydride.



Scheme 2. Synthesis of the C<sub>29</sub>-C<sub>46</sub> subunit **23**: a) Cp<sub>2</sub>TiMe<sub>2</sub>, PhMe, 120 °C, 2 h; b) TPAP, NMO, 4Å mol. sieves, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 30 min; c) *i*) cHex<sub>2</sub>BBr, Et<sub>3</sub>N, Et<sub>2</sub>O, -78 °C, 2.5 h; **20**, -78 → -20 °C, 16 h; *ii*) H<sub>2</sub>O<sub>2</sub>, MeOH/pH 7 buffer, 0 → 20 °C, 2 h; d) *i*) cHex<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, -78 °C, 60 min; **18**, -78 → -20 °C, 16 h; *ii*) H<sub>2</sub>O<sub>2</sub>, MeOH/pH 7 buffer, 0 → 20 °C, 2 h; e) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1 h; f) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer, 20 °C, 16 h; g) LiAlH<sub>4</sub>, THF, -78 °C, 30 min; h) Pb(OAc)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 40 min; i) PPTS, (MeO)<sub>3</sub>CH, MeOH, 20 °C, 1 h; j) TBSCl, Im, Et<sub>3</sub>N, DMF, 20 °C, 16 h; k) *i*) OsO<sub>4</sub>, Me<sub>3</sub>NO, acetone/H<sub>2</sub>O, 20 °C, 16 h; *ii*) Pb(OAc)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 40 min. Cp = cyclopentadienyl, TPAP = tetrapropylammonium perruthenate, TESOTf =

triethylsilyl trifluoromethanesulfonate, Im = imidazole; DMF = *N,N*-dimethylformamide. NMO = *N*-methylmorpholine *N*-oxide.

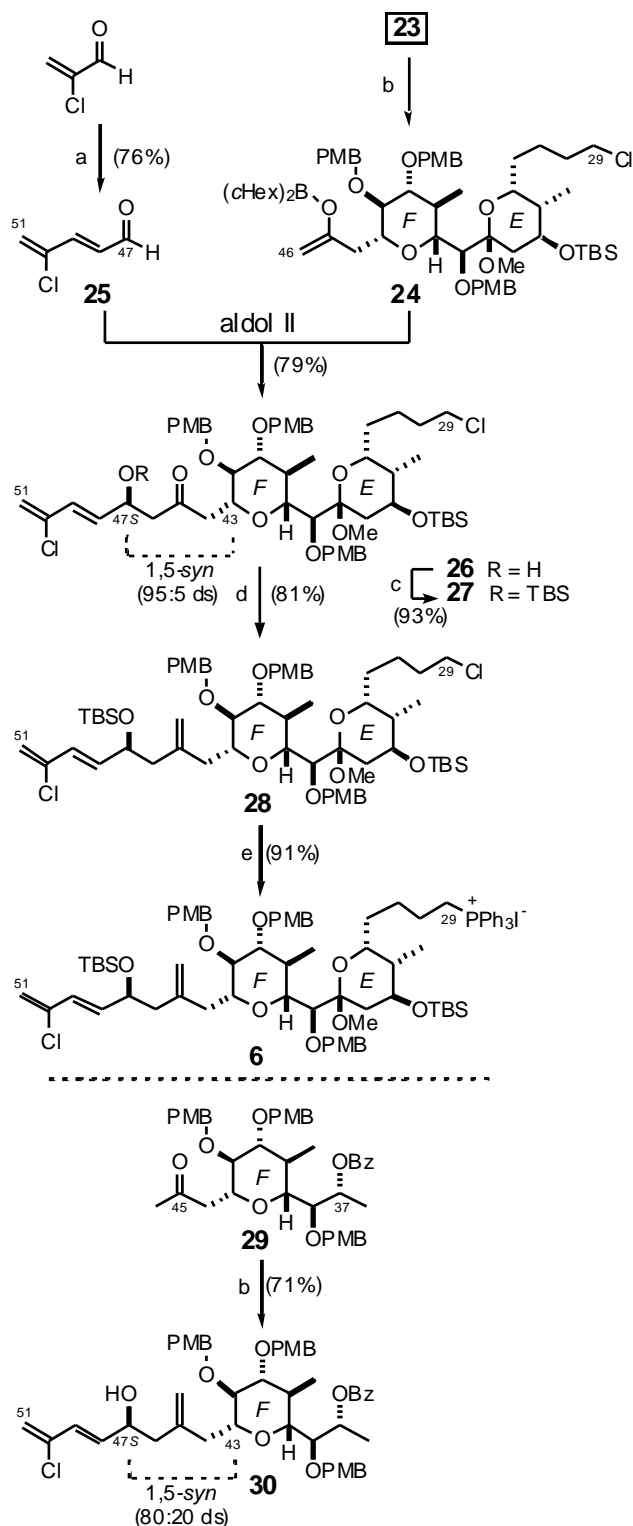
Ba(OH)<sub>2</sub> then provided the (*E*)-enone **14** exclusively (81% from **12**). Exposure of **14** to acetic acid in aqueous THF, caused hetero-Michael cyclisation by the C39 hydroxyl, initially producing a mixture (ca 1:1 at C43) of tetrahydropyrans. On treatment with KOH in MeOH, clean equilibration (>95:5) led to the desired F ring ketone **7** (86%), having all the substituents equatorial. This efficient 9-step sequence could be performed on a multigram scale and proceeded in high overall yield (34%).

Introduction of the *E* ring and chlorodiene side-chain were now required to reach the fully elaborated C29-C51 segment **6** of altohyrtin A. The control of the remote (47*S*)-stereocentre, as well as that at C35, proved challenging; where it proved best to first protect the C45 ketone then install the *E* ring before introducing the delicate side-chain (Scheme 2). Thus, Petasis methylenation<sup>[19]</sup> of ketone **7** using Cp<sub>2</sub>TiMe<sub>2</sub> proceeded cleanly, followed by TPAP/NMO oxidation<sup>[20]</sup> to afford the methyl ketone **15** (76% overall). For the introduction of the *E* ring, the aldehyde **20** having a chloride at C29 was selected to enable direct formation of the phosphonium salt for Wittig coupling. Using our lactate methodology,<sup>[18]</sup> a boron-mediated *syn* aldol using the PMB-protected ketone **17** with the aldehyde **18** produced the adduct **19** (98%; >95:5 ds). Following a straightforward four-step sequence, the (33*R*,34*S*)-aldehyde **20** was obtained cleanly (75%).

The successful boron aldol coupling between ketone **15** and aldehyde **20** (aldol I) necessitated the use of freshly prepared *c*Hex<sub>2</sub>BBr<sup>[21]</sup> as a more reactive enolising reagent than the chloride. Exposure of **15** to *c*Hex<sub>2</sub>BBr/Et<sub>3</sub>N at low temperature in Et<sub>2</sub>O, followed by addition of the aldehyde **20**, led to a 90:10 mixture of adducts favouring the (35*S*)-isomer **21**. Subjection to PPTS in MeOH/CH(OMe)<sub>3</sub> then induced TES removal and concomitant formation of the *E* ring as the methyl acetal **22**.<sup>[22]</sup> Following TBS protection of **22**, oxidative cleavage of the alkene by dihydroxylation and brief exposure to Pb(OAc)<sub>4</sub> regenerated the methyl ketone in **23**; this could be prepared on a gram scale in 72% yield over 4 steps from **15**.

Introduction of the chlorodiene terminus of altohyrtin A, with control of the isolated C47 stereocentre, was now required in aldol II (Scheme 3). Ultimately, this proved remarkably effective using solely substrate control from the ketone component **23**. Here the addition of the dicyclohexylboron enolate **24** to the chlorodialdehyde **25** (prepared in 3 steps from 2-chloroacrolein) proceeded selectively at -78 °C. After oxidative work-up, the (47*S*)-adduct **26** was isolated in 80% yield with 95:5 ds.<sup>[23]</sup> Notably, this result is in the 1,5-*syn* sense, opposite to that observed for boron aldol reactions of simple β-alkoxy methyl ketones (*i.e.* 1,5-*anti* stereoinduction),<sup>[24]</sup> indicating the overriding contribution in this special case from the more remote stereocentres. A reinforcing effect from the *E* ring is apparent, as the analogous reaction with the ketone **29** proceeded with reduced 80:20 ds in favour of **30**. In both these cases, the corresponding lithium aldol reaction (LiHMDS) gave no measurable induction. To complete the fully elaborated EF segment **6**, TBS protection gave **27** and methylenation of the highly functionalised C45 ketone was achieved using a modified Takai procedure.<sup>[25]</sup> Overall, this

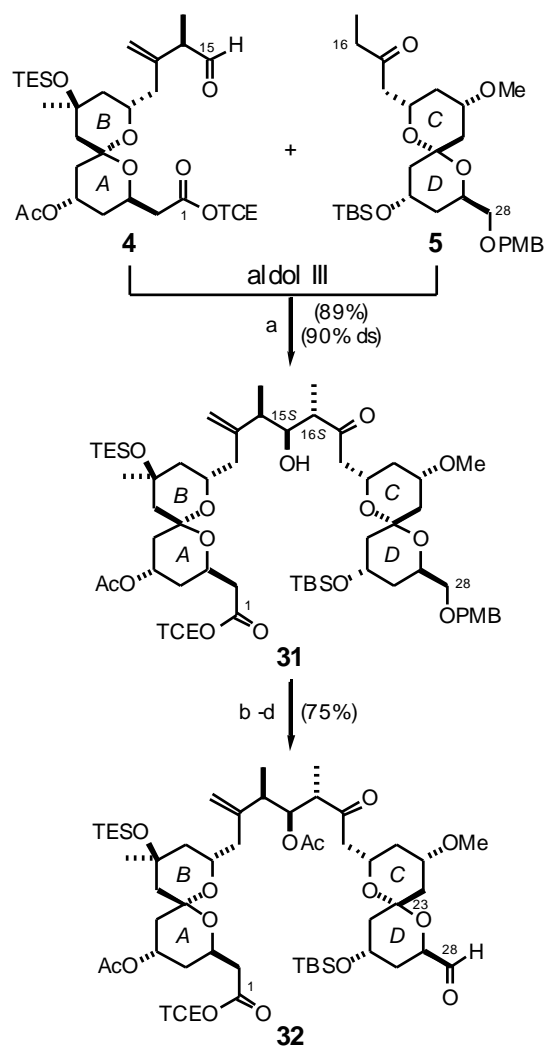
new method for introducing the altohyrtin/spongistatin side chain proceeds in high overall yield (60% for **23** → **28**) and should be applicable to other congeners, as in altohyrtins B and C (**2** and **3**), simply by changing the aldehyde. In preparation for the final Wittig coupling, direct conversion of **28** into the phosphonium salt **6** was achieved in 91% yield by heating with Ph<sub>3</sub>P in the presence of NaI. Thus the fully functionalised C29-C51 subunit **6** was obtained efficiently in high overall yield (54% from **23**).



Scheme 3. Synthesis of the C<sub>29</sub>-C<sub>51</sub> phosphonium salt **6**: a) *i*) (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, NaHMDS, catechol, -78 → -20 °C 40 h; *ii*) Dibal-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 h; *iii*) oxalyl chloride, DMSO, -78 °C, 1 h; Et<sub>3</sub>N, -78 °C, 1 h; b) *i*) *c*Hex<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, -78 → -40 °C, 90 min; **25**, -78 °C, 16

h; ii) MeOH/pH 7 buffer then H<sub>2</sub>O<sub>2</sub>/pH 7 buffer, 0 °C, 2.5 h; c) TBSCl, Im, DMF, 20 °C, 3 h; d) Zn, CH<sub>2</sub>I<sub>2</sub>, TiCl<sub>4</sub>, PbI<sub>2</sub>, THF/CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 4 h; e) PPh<sub>3</sub>, NaI, *i*Pr<sub>2</sub>NEt, MeCN/MeOH, Δ, 20 h. NaHMDS = sodium bis(trimethylsilyl)amide, DMSO = dimethylsulfoxide, Bz = benzoyl.

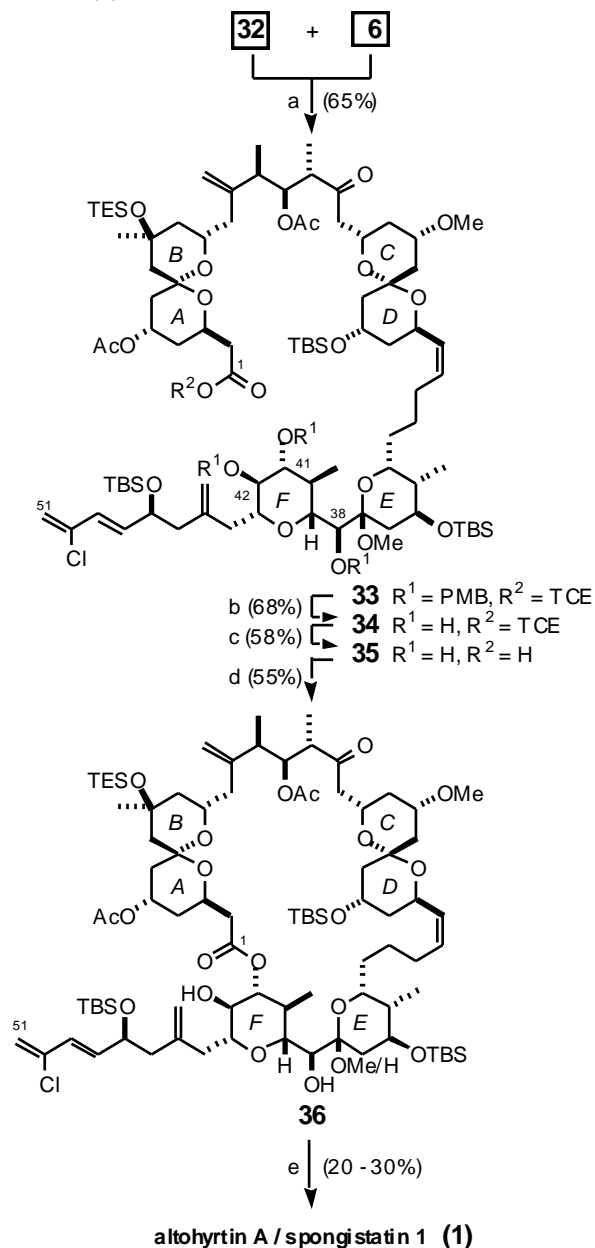
Scale up of our previously described aldol-based syntheses<sup>[9d-f]</sup> of the AB and CD spiroacetal units **4** and **5** led to multi-gram quantities,<sup>[26]</sup> in readiness for an *anti*-selective aldol coupling (aldol III) to produce the ABCD segment **31** (Scheme 4). While both boron<sup>[9d]</sup> and lithium-mediated protocols<sup>[9f]</sup> were explored to produce the required (1*S*,16*S*)-adduct **31**, the former (as used independently by Evans<sup>[6c,d]</sup>) proved superior on a larger scale. Controlled (*E*)-enolisation of **5** with *c*Hex<sub>2</sub>BCl/Et<sub>3</sub>N in Et<sub>2</sub>O and addition of aldehyde **4** led to the formation of **31** (90:10 ds) in 89% yield.<sup>[27]</sup> A three-step sequence of acetylation of the C15 hydroxyl, PMB ether deprotection by DDQ (CH<sub>2</sub>Cl<sub>2</sub>, pH7 buffer), and TPAP oxidation then led to the fully functionalised C1–C28 aldehyde **32** (75% overall), without compromising the configurational integrity at C23 in the (acid-labile) CD spiroacetal.



Scheme 4. Synthesis of C<sub>1</sub>–C<sub>28</sub> aldehyde **32**: a) *i*) *c*Hex<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, -78 → 0 °C, 20 min; **4**, -78 °C, 16 h; ii) SiO<sub>2</sub>, 20 °C, 40 min; b) Ac<sub>2</sub>O, DMAP, pyr, 20 °C, 2 h; c) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer, 0 °C, 90 min; d) TPAP, NMO, 4Å mol. sieves, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 10 min, DMAP = *N,N*-dimethylaminopyridine.

Realisation of an efficient and reproducible Wittig coupling of the fully elaborated C<sub>1</sub>–C<sub>28</sub> and C<sub>29</sub>–C<sub>51</sub>

subunits, **32** and **6**, was now crucial (Scheme 5).<sup>[28]</sup> Deprotonation of the phosphonium salt **6** with LiHMDS in THF/HMPA at -78 °C gave an intense orange-coloured ylide solution, whereupon the aldehyde **32** was added, leading on warming to clean Wittig coupling and isolation of the (*Z*)-alkene **33** (>97:3 *Z*:*E* by 800 MHz NMR) in 65% yield, representing the fully protected *seco*-acid of altohyrtin A/spongistatin **1** (**1**).



Scheme 5. Total synthesis of altohyrtin A/spongistatin **1** (**1**): a) LiHMDS, THF/HMPA, -78 °C, 10 min; **32**, -78 → 20 °C, 40 min; b) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer, 0 °C, 60 min; c) Zn, THF/1 M NH<sub>4</sub>OAc, 20 °C, 30 min; d) 2,4,6-trichlorobenzoyl chloride, Et<sub>3</sub>N, THF, 20 °C, 3 h; DMAP, PhMe, 100 °C, 20 h; e) HF, MeCN/H<sub>2</sub>O, 0 °C, 4 h. LiHMDS = lithium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide. Compounds **33**, **34** and **35** were mixtures of methylacetal and hemiacetal in *ca.* 1.3:1 ratio.

In preparation for macrolactonisation, rapid deprotection of the three PMB ethers was achieved in the presence of the potentially labile unsaturated side-chain,<sup>[29]</sup> by exposure to excess DDQ in CH<sub>2</sub>Cl<sub>2</sub>/pH7 buffer, to give the triol **34** (68%; obtained as a *ca.* 1.3:1 mixture of the E ring methyl acetal and its hemiacetal hydrolysis product).<sup>[30]</sup>

Subjection of this mixture to Zn powder in THF/NH<sub>4</sub>OAc induced deprotection<sup>[31]</sup> of the trichloroethyl (TCE) ester to give the *seco*-acid **35**. Regioselective macrolactonisation<sup>[6c,7b,32]</sup> of the triol **35**, engaging the C41 hydroxyl (in preference to those at C42 and C38), was performed under Yamaguchi conditions<sup>[33]</sup> to produce the 42-membered macrolide **36** in 55% yield. Finally, exposure to HF/MeCN led to deprotection of the four silyl ethers to provide althoyrtin A/spongistatin 1 (**1**), isolated in 22% yield after purification by reverse phase HPLC.<sup>[30,34]</sup> The spectroscopic data [<sup>1</sup>H NMR (CD<sub>3</sub>CN and CD<sub>3</sub>OD, recorded at 500 and 800 MHz), IR, HRMS], including <sup>13</sup>C NMR (CD<sub>3</sub>CN),<sup>[35]</sup> along with specific rotation [ $[\alpha]_D^{20} +21.0$  (*c* 0.44, MeOH)] (cf. Pettit<sup>[3a]</sup> [ $[\alpha]_D^{20} +26.2$  (*c* 0.32, MeOH) and Kitagawa/Kobayashi<sup>[2a]</sup> [ $[\alpha]_D^{20} +21.7$  (*c* 1.20, MeOH)]), of the synthetic material were in excellent agreement with that reported (and by comparison with the <sup>1</sup>H and <sup>13</sup>C NMR spectra kindly provided by Professors Pettit and Kishi).<sup>[36]</sup>

Overall, this highly stereocontrolled total synthesis of althoyrtin A/spongistatin 1 proceeds in 33 steps and 0.63% overall yield for the longest linear sequence (based on the AB subunit). Altogether, this constitutes one of the most testing applications of boron-mediated aldol methodology for polyketide synthesis, including its use for the side chain installation (as in **23** → **26**) which benefits from a remarkable level of remote 1,5-stereoiduction. To date, this synthesis has already provided useful quantities (4.4 mg) of althoyrtin A (spongistatin 1), thus contributing to replenishing the largely exhausted natural material from the initial isolation work<sup>[37]</sup> and enabling more detailed biological evaluation.

**Keywords:** aldol chemistry, boron, cancer, macrolide, total synthesis

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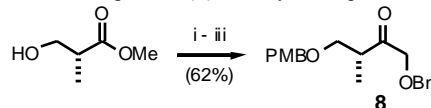
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[12] Prepared in three steps from (*R*)-ester by the sequence:



MeONHMe•HCl, AlMe<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 18 h; ii) PMBTCA, TfOH, Et<sub>2</sub>O, 0 → 20 °C, 3.5 h; iii) BnOCH<sub>2</sub>SnBu<sub>3</sub>, *n*BuLi, THF, -78 °C, 20 min.

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[22] The minor epimer could be inverted by oxidation/reduction to produce more of **22**. The stereochemistry in the E ring was assigned by supportive NOEs and coupling constants.

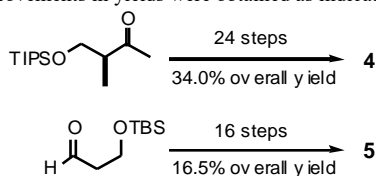
[23] The desired (4*S*)-configuration was determined by <sup>1</sup>H NMR analysis of the (*R*)- and (*S*)-MTPA esters. I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

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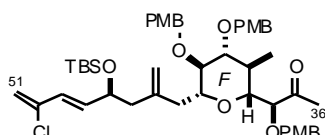
[26] Some improvements in yields were obtained as indicated below:



[27] As with some other sensitive systems, hydrolytic breakdown of the intermediate boron aldolate by direct exposure to silica gel was preferred over the usual oxidative work-up (ref 11).

[28] A range of yields have been reported for this challenging Wittig step (Evans - 64%; Kishi - 40%; Smith - 34%) under a variety of reaction conditions.

[29] In a model *tris*-PMB ether system, we encountered competing oxidation by DDQ of the side-chain to the chlorodienone:



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[30] A similar result was observed by the Kishi group (ref 7b).

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[34] Prodigy C<sub>18</sub> 4.6 x 250 mm, 5 μm analytical column; 27.5% H<sub>2</sub>O/MeOH; 1 mL/min.

[35] See the supporting information for tabulated <sup>1</sup>H and <sup>13</sup>C NMR data and copies of spectra.

[36] We thank Professors Pettit and Kishi for providing comparison NMR spectra.

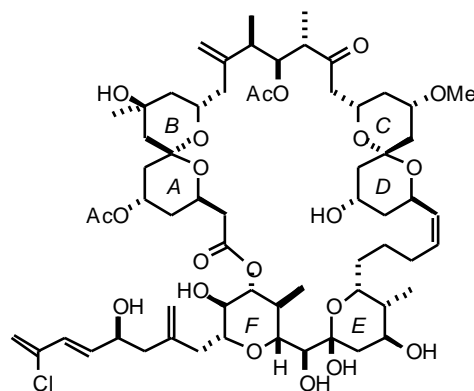
[37] Isolation from sponge sources: 13.8 mg from 400 kg of *Spongia* sp. by Pettit *et al.* + 7.6 mg from 112 kg of *Hyrtios altum*. by Kobayashi *et al.*

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I. Paterson,\* D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross.

## Stereocontrolled Total Synthesis of (+)-Altohyrtin A (Spongistatin 1)

As an exceptionally potent antimitotic macrolide, altohyrtin A (spongistatin 1) shows great promise in cancer chemotherapy but the extreme scarcity from the sponge sources has halted its further preclinical development. A highly stereocontrolled total synthesis, which exploits inter alia boron-mediated aldol bond constructions, has been realised to provide, for the first time, a useful amount of synthetic altohyrtin A.



altohyrtin A (spongistatin 1)