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

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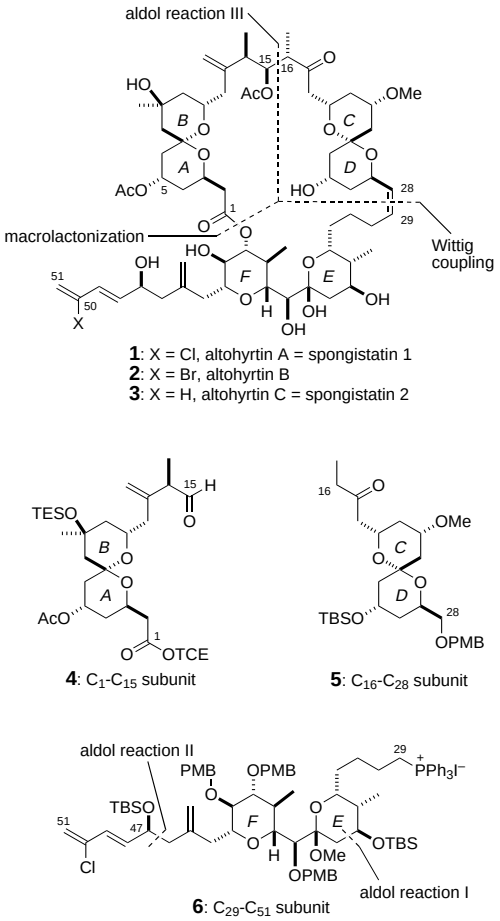
First reported in 1993 by three groups (Kobayashi and Kitagawa, Pettit, and Fusetani),[1] the altohyrtins/spongistatins/cinachyrolides are a unique family of antimitotic macrolides[2–5] which are obtained from marine sponges in trace amounts by bioassay-guided isolation and display exceptional potency against a wide variety of human cancer cell lines. They feature a highly substituted 42-membered macrolide ring which comprises two spiroacetals (*AB* and *CD* rings) and a bis(tetrahydropyran) unit (*E* and *F* rings), including a triene side chain, along with 24 stereogenic centers (Scheme 1, **1**–**3**). Initial discrepancies in the configurational assignments were resolved in 1997 by the first total synthesis of altohyrtin C (**3**) by the Evans group,[6] and soon after altohyrtin A (**1**) by the Kishi group,[7] which confirmed the full assignment proposed for the altohyrtins by Kobayashi and Kitagawa,[2d] and that they were identical to spongistatins 2 and 1, respectively, as isolated by Pettit et al.[3a,b] More recently, the Smith group has completed a second total synthesis of **3**.[8]

Spongistatin 1 (**1**) constitutes one of the most potent cytotoxic compounds tested by the US National Cancer Institute (NCI),[3a,b] having sub-nanomolar growth inhibitory activity (mean $GI_{50} = 0.03$ nM) against highly chemoresistant tumor types (including lung, colon and brain cancers), while in vivo human melanoma and ovarian carcinoma xenograft experiments showed curative responses at extremely low doses.[3g] It inhibits mitosis by binding to tubulin and blocking microtubule assembly.[3h] Despite this highly promising profile, the unreliable and extremely meagre supply (3.4×10^{-7}% isolation yield for **1**)[3a] 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.[9, 10] 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, and enables 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.[11]



Scheme 1. Representative structures of altohyrtins/spongistatins and key subunits employed for the synthesis of altohyrtin A/spongistatin 1 (**1**). TES = triethylsilyl, TCE = 2,2,2-trichloroethyl, TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl.

As shown in Scheme 1, our proposed synthetic route to **1**, which is based on a threefold disconnection of the 42-membered macrolide ring, employs macrolactonization as well as Wittig and aldol couplings. We planned[9] a modular route based on the late-stage, sequential connection of the fully functionalized spiroacetal subunits **4** and **5**, followed by the bis(tetrahydropyran) subunit **6**. 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 (aldol reactions I and III), along with the installation of the terminal chlorodiene and isolated C47 stereocenter in **6** (aldol reaction II).

As outlined in Scheme 2, the synthesis of the *F* ring subunit **7** began with a boron-mediated *anti* aldol reaction between the readily available[12] ketone (*R*)-**8** and acetaldehyde to give **9**, followed by reduction with $Me_4NBH(OAc)_3$[13] to the 1,3-

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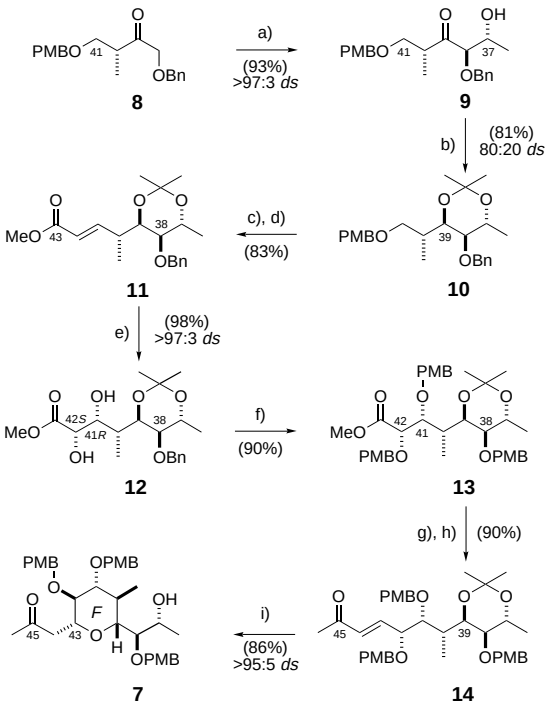
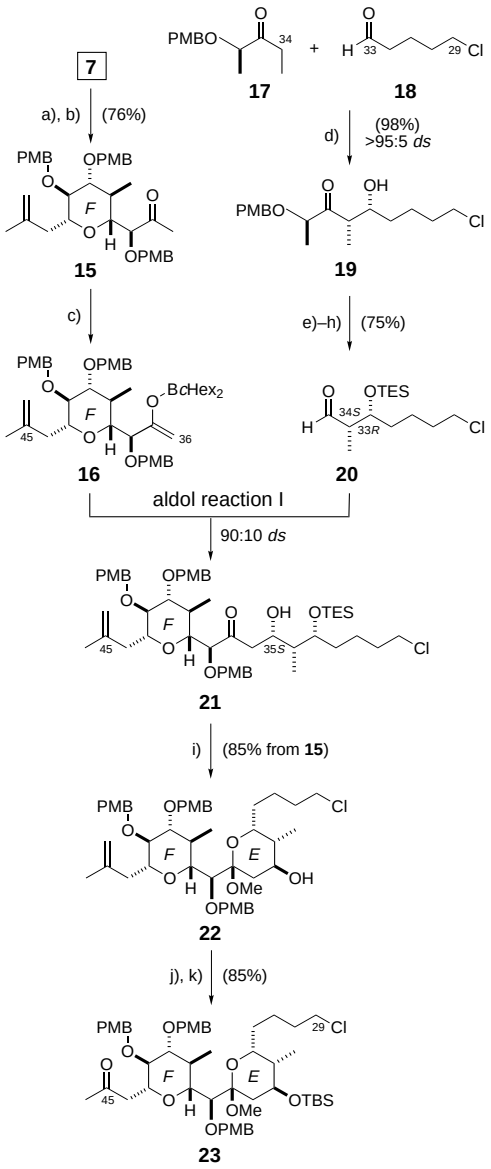
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



Scheme 2. Synthesis of the C36–C46 subunit **7**: a) *c*Hex$_2$BCl, Et$_3$N, Et$_2$O, −78 °C, 2 h; MeCHO, −78 → −20 °C, 16 h; H$_2$O$_2$, MeOH/pH 7 buffer, 0 →20 °C, 3 h; b) 1. Me$_4$NBH(OAc)$_3$, MeCN/AcOH, 4 °C, 60 h; 2. PPTS, Me$_2$C(OMe)$_2$, CH$_2$Cl$_2$, 20 °C, 16 h; c) 1. DDQ, CH$_2$Cl$_2$/pH 7 buffer, 0 °C, 90 min; 2. Dess–Martin periodinane, CH$_2$Cl$_2$, 20 °C, 3 h; d) (MeO)$_2$P(O)CH$_2$CO$_2$Me, LiCl, *i*Pr$_2$NEt, MeCN, 20 °C, 16 h; e) enriched AD-mix-β, MeSO$_2$NH$_2$, *t*BuOH/H$_2$O, 20 °C, 8 h; f) 1. H$_2$, Pd(OH)$_2$/C, NaHCO$_3$, MeOH, 20 °C, 20 h; 2. PMBO(C=NH)CCl$_3$, Ph$_3$CBF$_4$, THF, 0 °C, 2 h; g) DIBAL-H, CH$_2$Cl$_2$, −78 °C, 30 min; h) (MeO)$_2$P(O)CH$_2$COMe, Ba(OH)$_2$, THF/H$_2$O, 20 °C, 16 h; i) 1. AcOH, THF/H$_2$O, 20 °C, 48 h; 2. KOH, MeOH, 20 °C, 24 h. Bn = benzyl, PPTS = pyridinium *p*-toluenesulfonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride.

anti diol and formation of the acetonide **10**. Following 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 with a benzyloxy group at C38 proved to be an excellent substrate for Sharpless dihydroxylation[14] with enriched AD-mix-β to give solely the (41*R*,42*S*)-diol **12** in 98% yield.[15] For the remainder of the synthesis, we now chose to install PMB protecting groups at the C38, C41, and C42 hydroxy groups. Hydrogenolysis of **12** (Pd(OH)$_2$, NaHCO$_3$), followed by PMB protection with *p*-(methoxybenzyl)-trichloroacetimidate under mild catalysis[16] with Ph$_3$CBF$_4$ gave tris-PMB ether **13**. Reduction of **13** with DIBAL-H and HWE chain extension[17] with dimethyl (2-oxopropyl)-phosphonate and Ba(OH)$_2$ then provided the (*E*)-enone **14** exclusively (81% from **12**). Exposure of **14** to acetic acid in aqueous THF caused hetero-Michael cyclization by the C39 hydroxy group, to initially produce 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*)-stereocenter, as well as that at C35, turned out to be challenging; it proved best to first protect the C45 ketone then install the *E* ring before introducing the delicate side chain (Scheme 3). Thus, Petasis methylenation[19] of ketone **7** with [Cp$_2$TiMe$_2$] proceeded cleanly and was followed by TPAP/NMO oxidation[20] to afford the methyl ketone **15** (76% overall). For the introduction of the *E* ring, the aldehyde **20** having a chloride



Scheme 3. Synthesis of the C29–C46 subunit **23**: a) [Cp$_2$TiMe$_2$], PhMe, 120 °C, 2 h; b) TPAP, NMO, 4 Å-MS, CH$_2$Cl$_2$, 20 °C, 30 min; c) *c*Hex$_2$BBr, Et$_3$N, Et$_2$O, −78 °C, 2.5 h; **20**, −78 → −20 °C, 16 h; H$_2$O$_2$, MeOH/pH 7 buffer, 0 →20 °C, 2 h; d) *c*Hex$_2$BCl, Et$_3$N, Et$_2$O, −78 °C, 60 min; **18**, −78 → −20 °C, 16 h; H$_2$O$_2$, MeOH/pH 7 buffer, 0 →20 °C, 2 h; e) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 1 h; f) DDQ, CH$_2$Cl$_2$/pH 7 buffer, 20 °C, 16 h; g) LiAlH$_4$, THF, −78 °C, 30 min; h) Pb(OAc)$_4$, Na$_2$CO$_3$, CH$_2$Cl$_2$, 0 °C, 40 min; i) PPTS, (MeO)$_3$CH, MeOH, 20 °C, 1 h; j) TBSCl, Im, Et$_3$N, DMF, 20 °C, 16 h; k) 1. OsO$_4$, Me$_3$NO, acetone/H$_2$O, 20 °C, 16 h; 2. Pb(OAc)$_4$, Na$_2$CO$_3$, CH$_2$Cl$_2$, 0 °C, 40 min. Cp = cyclopentadienyl, TPAP = tetrapropylammonium perruthenate, TESOTf = triethylsilyl trifluoromethanesulfonate, Im = imidazole, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves.

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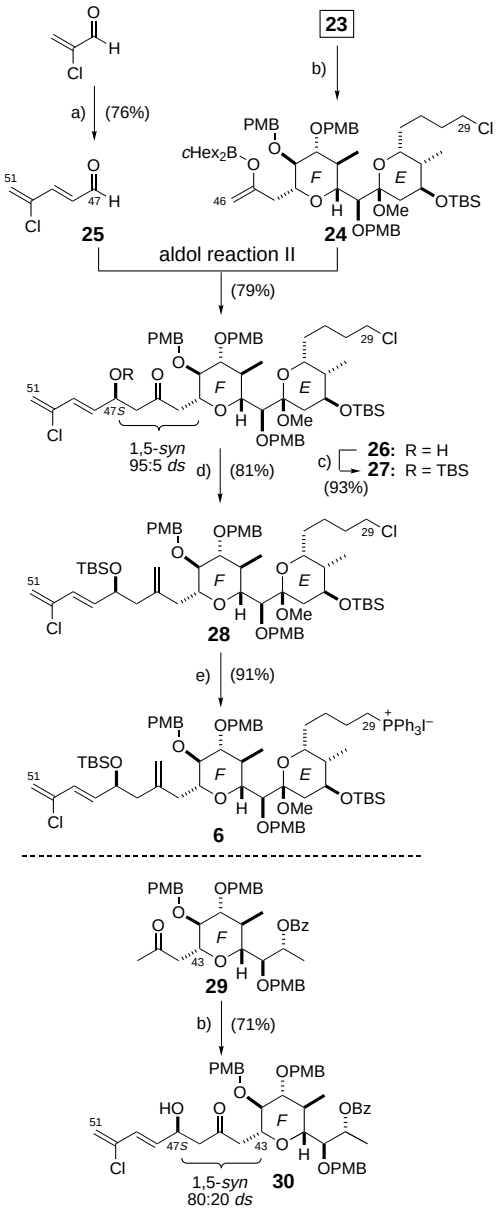
at C29 was selected to enable direct formation of the phosphonium salt for Wittig coupling. By using our lactate methodology,[18] a boron-mediated *syn* aldol reaction between the PMB-protected ketone **17** and the aldehyde **18** produced the adduct **19** (98%; >95:5 *ds*). Following a straightforward 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 reaction I) necessitated the use of freshly prepared *c*Hex_2BBr[21] as a more reactive enolizing reagent than the chloride. Exposure of **15** to *c*Hex_2BBr/Et_3N at $-78\,^{\circ}C$ in Et_2O, followed by addition of the aldehyde **20**, led to a 90:10 mixture of adducts with (35*S*)-alcohol **21** as the major isomer. Subjection to PPTS in $MeOH/CH(OMe)_3$ then induced TES removal and concomitant formation of the *E* ring as the methyl acetal **22**.[22] Following TBS protection of **22**, oxidative cleavage of the alkene by dihydroxylation and brief exposure to $Pb(OAc)_4$ regenerated the methyl ketone in **23**; this could be prepared on a gram scale in 72% yield over four steps from **15**.

Introduction of the chlorodiene terminus of altohyrtin A, with control of the isolated C47 stereocenter, was now required in aldol reaction II (Scheme 4). Ultimately, this proved remarkably effective using solely substrate control from the ketone component **23**. Here the addition of the dicyclohexylboron enolate **24** to the chlorodienal **25**[10h] (prepared in three steps from 2-chloroacrolein) proceeded selectively at $-78\,^{\circ}C$. After oxidative workup, the (47*S*)-adduct **26** was isolated in 80% yield with 95:5 *ds*.[23] Notably, this result is in the 1,5-*syn* sense, opposite to 1,5-*anti* stereoinduction observed for boron aldol reactions of simple β-alkoxy methyl ketones,[24] indicating the overriding contribution in this special case from the more remote stereocenters. A reinforcing effect from the *E* ring is apparent, as the analogous reaction with the ketone **29** proceeded with reduced 80:20 *ds* in favor 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 functionalized C45 ketone was achieved using a modified Takai procedure.[25] 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_3P in the presence of NaI. Thus, the fully functionalized C29–C51 subunit **6** was obtained efficiently in high overall yield (54% from **23**).

Scale up of our previously described aldol-based syntheses[9d–f] of the *AB* and *CD* spiroacetal units **4** and **5** led to multi-gram quantities,[26] in readiness for an *anti*-selective aldol coupling (aldol reaction III) to produce the *ABCD* segment **31** (Scheme 5). Notably, the *AB* spiroacetal ring is stabilized by a double anomeric effect, while the *CD* spiroacetal subunit benefits from only a single anomeric effect, and thus epimerizes readily at C23 such that acidic conditions must be avoided. While both boron[9d] and lithium-



Scheme 4. Synthesis of the C29–C51 phosphonium salt **6**: a) 1. $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, catechol, $-78 \rightarrow -20\,^{\circ}C$ 40 h; 2. DIBAL-H, CH_2Cl_2, $-78\,^{\circ}C$, 2 h; 3. oxalyl chloride, DMSO, $-78\,^{\circ}C$, 1 h; Et_3N, $-78\,^{\circ}C$, 1 h; b) *c*Hex_2BCl, Et_3N, Et_2O, $-78 \rightarrow -40\,^{\circ}C$, 90 min; **25**, $-78\,^{\circ}C$, 16 h; MeOH/pH 7 buffer then H_2O_2/pH 7 buffer, $0\,^{\circ}C$, 2.5 h; c) TBSCl, Im, DMF, $20\,^{\circ}C$, 3 h; d) Zn, CH_2I_2, $TiCl_4$, PbI_2, THF/CH_2Cl_2, $20\,^{\circ}C$, 4 h; e) PPh_3, NaI, *i*Pr_2NEt, MeCN/MeOH, Δ, 20 h. NaHMDS = sodium bis(trimethylsilyl)-amide, DMSO = dimethylsulfoxide, Bz = benzoyl.

mediated protocols[9f] were explored to produce the required (15*S*,16*S*)-adduct **31**, the former (as used independently by Evans et al.[6c,d]) proved superior on a larger scale. Controlled (*E*)-enolization of **5** with *c*Hex_2BCl/Et_3N in Et_2O and addition of aldehyde **4** led to the formation of **31** (90:10 *ds*) in 89% yield,[27] corresponding to preferential Felkin–Anh attack. A three-step sequence of acetylation of the C15 hydroxy group, PMB ether deprotection by DDQ (CH_2Cl_2, pH7 buffer), and TPAP oxidation then led to the fully functionalized C1–C28 aldehyde **32** (75% overall), without compromising the configurational integrity at C23 in the acid-labile *CD* spiroacetal.

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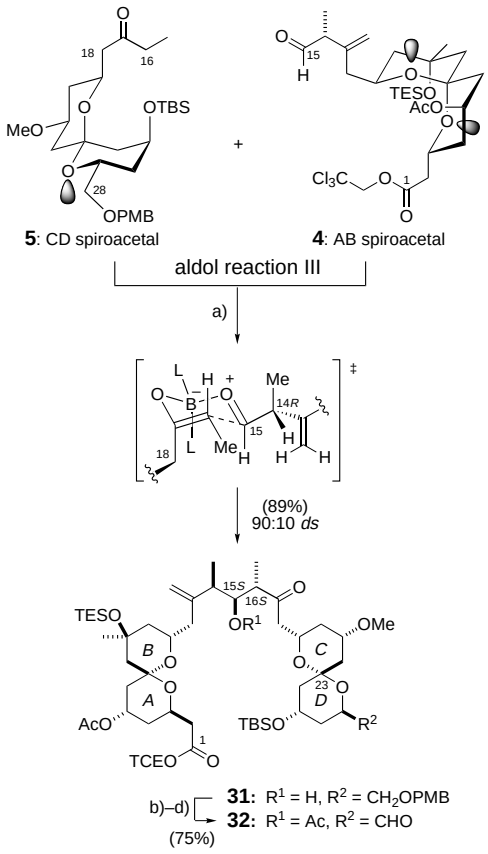
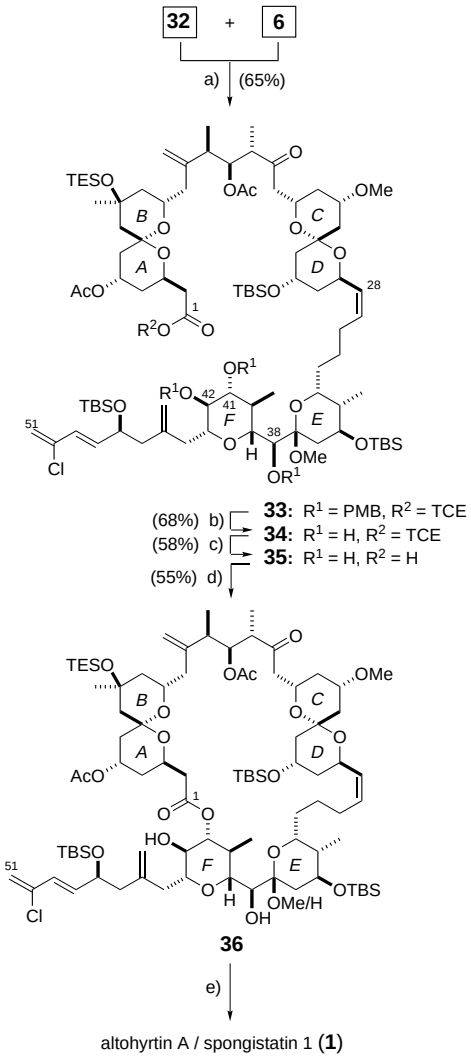


Scheme 5. Synthesis of C1–C28 aldehyde **32**: a) *c*Hex$_2$BCl, Et$_3$N, Et$_2$O, −78→0 °C, 20 min; **4**, −78 °C, 16 h; SiO$_2$, 20 °C, 40 min; b) Ac$_2$O, DMAP, pyr, 20 °C, 2 h; c) DDQ, CH$_2$Cl$_2$/pH 7 buffer, 0 °C, 90 min; d) TPAP, NMO, 4 Å-MS, CH$_2$Cl$_2$, 20 °C, 10 min. DMAP = 4-(dimethylamino)pyridine.



Scheme 6. Final steps of the 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$_2$Cl$_2$/pH 7 buffer, 0 °C, 60 min; c) Zn, THF/1 M NH$_4$OAc, 20 °C, 30 min; d) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF, 20 °C, 3 h; DMAP, PhMe, 100 °C, 20 h; e) HF, MeCN/H$_2$O, 0 °C, 4 h. LiHMDS = lithium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide. Compounds **34**, **35**, and **36** were mixtures of the methyl acetal and hemiacetal in ca. 1.3:1 ratio.

Realization of an efficient and reproducible Wittig coupling of the fully elaborated C1–C28 and C29–C51 subunits, **32** and **6**, was now crucial (Scheme 6).[28] Deprotonation of the phosphonium salt **6** with LiHMDS in THF/HMPA at −78 °C gave an intense orange-colored ylide solution, whereupon the aldehyde **32** was added, leading on warming to clean Wittig coupling and isolation of the (*Z*)-alkene **33** (*Z*:*E* > 97:3 by 800 MHz ^{1}H NMR) in 65 % yield, representing the fully protected *seco*-acid of altohyrtin A/spongistatin 1 (**1**).

In preparation for macrolactonization, rapid deprotection of the three PMB ethers was achieved in the presence of the potentially labile unsaturated side chain,[29] by exposure to excess DDQ in CH$_2$Cl$_2$/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).[30] Subjection of this mixture to Zn powder in THF/NH$_4$OAc induced deprotection[31] of the trichloroethyl (TCE) ester to give the *seco*-acid **35**. Regioselective macrolactonization[6c, 7b, 8b, 32] of the triol **35**, which engaged the C41 hydroxy group (in preference to those at C42 and C38), was performed under modified Yamaguchi conditions[33] to produce the 42-membered macrolide **36** in 55 % yield. Finally, exposure to HF/MeCN led to deprotection of the four silyl ethers and hydrolysis of the remaining methyl acetal to provide (+)-altohyrtin A/spongistatin 1 (**1**) in 36 % yield.[34] The spectroscopic data [^{1}H NMR (CD$_3$CN and CD$_3$OD, 500 and 800 MHz), ^{13}C NMR (CD$_3$CN), IR, HRMS],[35] along with specific rotation [[α]$_D^{20}$ = +21.0 (*c* = 0.44, MeOH); cf. Kobayashi[2a] [α]$_D^{20}$ = +21.7 (*c* = 1.20, MeOH) and Pettit[3a] [α]$_D^{20}$ = +26.2 (*c* = 0.32, MeOH)] of the synthetic material were in excellent agreement with that reported (and by comparison with the NMR spectra kindly provided by Professors Pettit and Kishi).[36]

Overall, this highly stereocontrolled total synthesis of altohyrtin A/spongistatin 1 proceeds in 33 steps and 1.0 % 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 stereoinduction. To date, this synthesis has already provided useful quantities of altohyrtin A/spongistatin 1 and thus contributes to replenishing the largely exhausted natural

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material from the initial isolation work[37] and enables more detailed biological evaluation.

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[1] The Kobayashi/Kitagawa group[2] obtained the altohyrtins from the Okinawan sponge *Hyrtios altum*, while the spongistatins were isolated from sponges of the genera *Spongia* and *Spirastrella*, and reported concurrently by the Pettit group.[3] Cinachyrolide A, isolated by the Fusetani group[4] from a sponge of genus *Cinachyra* is assumed to have the same structure as 15-desacetylaltohyrtin A and spongistatin 4.

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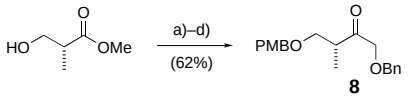

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[22] The minor C35 epimer could be inverted by oxidation/reduction to produce more of **22**. The stereochemistry in the *E* ring was assigned by supportive NOEs and coupling constants.

[23] The desired (47*S*)-configuration was determined by ^{1}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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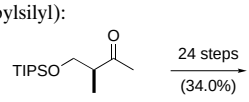
[26] On optimization, some improvements in yields were obtained as indicated below (TIPS = triisopropylsilyl):



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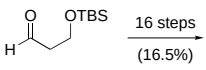

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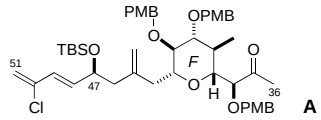
[27] As with some other sensitive systems, hydrolytic breakdown of the intermediate boron aldolate by direct exposure to silica gel was preferred over the usual oxidative workup.[11]

[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] I. Paterson, C. J. Cowden, V. S. Rahn, M. D. Woodrow, *Synlett* **1998**, 915. In the model tris-PMB ether system A, we encountered competing oxidation by DDQ of the side chain to the chlorodienone: However, a similar deprotection of a bis-PMB ether was achieved without difficulty in the Kishi synthesis.[7b]



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

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[34] Purity was determined by reverse-phase HPLC. Prodigy C_{18} 4.6 × 250 mm, 5 μm analytical column; 27.5% H_2O/MeOH; 1 mL min^{-1}.

[35] See Supporting information for tabulated ^{1}H and ^{13}C NMR data and copies of spectra.

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

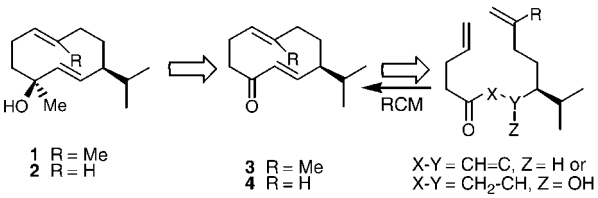
[37] Isolation from sponge sources: At present, we have synthesized 4.5 mg of **1** and 60 mg of its direct precursor **36**; optimum conditions for the final deprotection step are being developed. 13.8 mg from 400 kg of *Spongia* sp. by Pettit et al.[3a] + 7.6 mg from 112 kg of *Hyrtios altum.* by Kobayashi et al.[2c]

Synthesis of a 10-Membered Carbocycle By Olefin Metathesis**

Marta Nevalainen and Ari M. P. Koskinen*

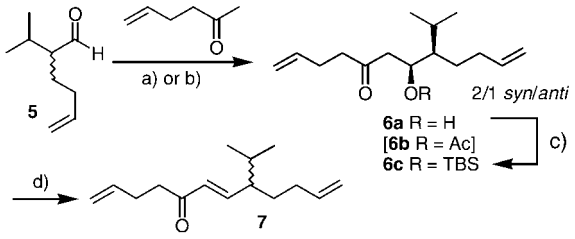
Dedicated to Professor Henry Rapoport

The pine sawfly *Neodiprion sertifer* is a common pest in pine trees of the northern hemisphere.[1] The population of larvae can cause extensive defoliation, resulting in serious economical damage. Therefore, great effort has recently been directed to monitor and control the population of sawfly species.[2] It was shown that the resin secreted by pines interferes with the development of larvae.[3] The main component of the sesquiterpene fraction of the resin of *Pinus sylvestris* is 1,6-germacradien-5-ol (**1**),[4] first isolated by Bohlmann et al.[5] from *Senecio phonolithicus.* On the other hand, 4α-hydroxygermacra-1(10),5-diene (4α-HDG, **2**) is a predominant foliage sesquiterpene in many pine trees (*Pinus radiata*).[6] To date, no synthesis for **1** or **2** has yet been reported.[7] Here we describe the synthesis of cyclodecenones (±)-**11** and (±)-**12**, which are direct precursors for (±)-**2** (Scheme 1), by ring-closing olefin metathesis (RCM). To the best of our knowledge, this is the first 10-membered carbocycle obtained by using the RCM methodology.[8] Only a few examples of the formation of ten-membered rings by RCM have been reported,[9] and all dealt with the synthesis of oxa- or azacycles.



Scheme 1. Retrosynthesis of 1,6-germacradien-5-ols **1** and **2**.

Among the many cyclization reactions, olefin metathesis has emerged as a very powerful tool for the formation of C=C bonds.[9, 10] However, as a result of inherent ring strain, the formation of 8- to 11-membered rings is particularly difficult,[9] and its success depends on the substitution pattern of the bis-olefin.[11] The importance of restricted chain mobility is clearly illustrated by **6a** (Scheme 2), in which the conformational-control element is the aldol moiety. Conversion of this functional group into an enone completely inhibits the cyclization, as described hereafter.



Scheme 2. Synthesis of bis-olefins **6** and **7**. a) LDA, THF, −78 °C (61%); b) LDA, THF, −78 °C; then Ac_2O (not isolated); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (96%); d) DBU, THF, 0 °C (56% from **5**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LDA = lithium diisopropylamide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Aldehyde **5** was synthesized in 72% overall yield from isovaleric acid. Condensation of **5** with 5-hexen-1-one delivered aldol **6a** with 3,4-*syn*/3,4-*anti* (Felkin) selectivity. In situ entrapment of **6a** with acetic anhydride followed by DBU-promoted elimination yielded enone **7** (Scheme 2).

The RCM reaction of enone **7** in the presence of the Grubbs catalyst provided only oligomers, along with unconverted starting material (Table 1, entry 1). In CH_2Cl_2 solution, enone **7** adopts a linear conformation in which the olefinic termini are located at a maximum distance from each other. Therefore, only acyclic diene metathesis polymerization takes place. We were thus pleased to observe that the aldol **6a** (*syn*/*anti* 2/1) underwent the RCM reaction to form 10-membered

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