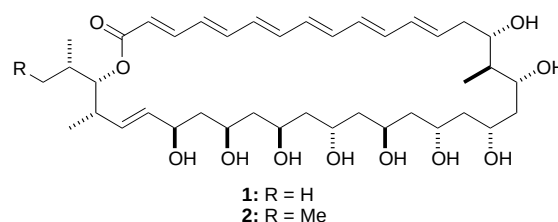


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Total Synthesis of Dermostatin A**

Christopher J. Sinz and Scott D. Rychnovsky*

By virtue of their biological activity and structural complexity, the polyene macrolides have attracted a great deal of interest from the synthetic community.^[1] We have been engaged in the development of broadly applicable methodology for the stereochemical elucidation and the total synthesis of highly oxygenated natural products. Pursuant to these goals, a recent report from our group described a new approach to the rapid stereochemical assignment of polyol-containing natural products in which 2D- ^{13}C acetamide analysis allowed for the stereochemical elucidation of dermostatin A (**1**) and B (**2**).^[2] Herein, we disclose studies which have culminated in the first total synthesis of dermostatin A (**1**).



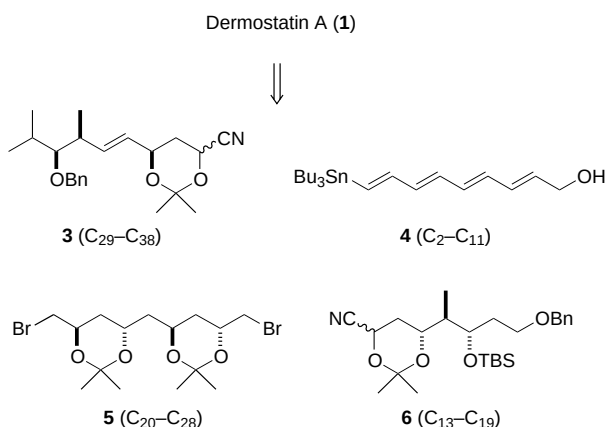
Dermostatin A (**1**) and B (**2**) are 36-membered macrolides that were isolated from the mycelium of *Streptomyces viridigriseus* Thirum.^[3] Their flat structures were determined by Rinehart and Pandey.^[4] The dermostatins show potent antifungal activity (comparable to amphotericin B) against a large number of human pathogens,^[5] and have been used clinically as a treatment for deep vein mycoses.^[6] Additionally, in an evaluation of a variety of polyene macrolides as potential HIV treatments, dermostatin A (**1**) and B (**2**) showed the highest antiproliferative activity against HIV in H9 cells.^[7] Although the dermostatins have demonstrated a broad range of biological activities, details of their mode of action remain unknown.

We set out to develop a highly convergent synthetic approach that would be sufficiently flexible to allow the facile generation of analogues for studies of the mode of action (Scheme 1). The central synthetic challenges posed by dermostatin A (**1**) are the complex polyol region and the conjugated hexaene. The acid- and light-sensitivity of the polyene necessitates delaying its introduction until a late stage. We intended to employ a palladium-mediated cross-coupling with vinyl stannane **4** as the penultimate carbon–carbon bond construction. Previous studies from our group have demonstrated the utility of cyanohydrin acetamide

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



Scheme 1. Retrosynthesis of dermostatin A (1).

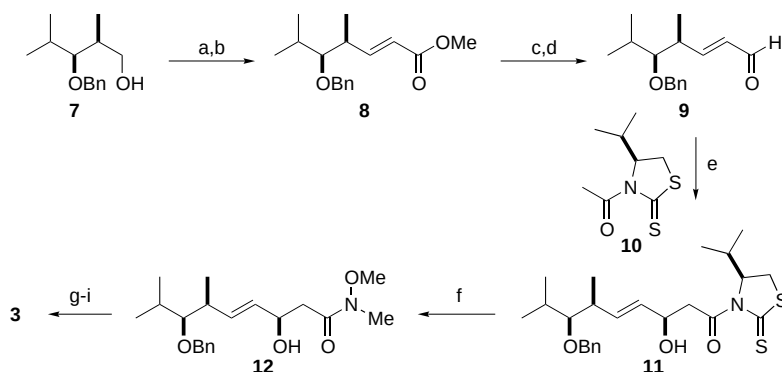
alkylations in the construction of complex 1,3-polyols.^[8] In the context of dermostatin A, the sequential connection of cyanohydrin acetonide fragments **3** and **6** with the C₂-symmetric dibromide **5** would provide the C₁₃–C₃₈ polyol region. Based on precedent from previous synthetic efforts, we anticipated that an intramolecular Horner–Wadsworth–Emmons macrolactonization would generate the macrolide under sufficiently mild conditions.^[9]

The synthesis of cyanohydrin acetonide **3** commenced with the oxidation and Wittig homologation of alcohol **7**,^[10] to provide enoate **8** (82%) (Scheme 2). Reduction with DIBAL-H (88%) and oxidation with *o*-iodoxybenzoic acid^[11] (99%) furnished enal **9**. Nagao's acetate aldol method^[12] has recently seen a resurgence in natural product synthesis.^[13] For our purposes, the addition of the tin enolate derived from *N*-acetyl thiazolidine-thione **10** to aldehyde **9** proceeded in excellent yield with 28:1 diastereoselectivity. The resulting compound **11** was converted into Weinreb amide **12** under mild conditions (90%). A three-step sequence (with no purification of intermediates required) provided cyanohydrin acetonide **3** in 80% yield.

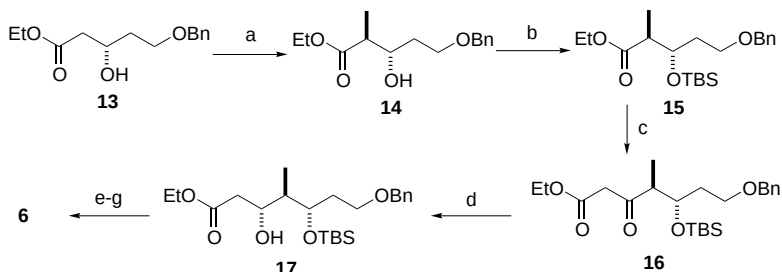
The Noyori hydrogenation product **13**^[10, 14] provided a convenient starting material for the synthesis of cyanohydrin acetonide **6** (Scheme 3). The required C₁₄–C₁₅ *anti* stereoarray was secured by a Frater–Seebach alkylation,^[15] to provide **14** in 78% yield with 14:1 diastereoselectivity. Silylation (TBSOTf, 2,6-lutidine) of **14** gave **15** in 94% yield. β -Keto ester **16** was procured by DIBAL-H reduction and Roskamp homologation^[16] of the intermediate aldehyde. Reduction with NaBH₄ in MeOH at –50 °C provided β -hydroxy ester **17** in 84% yield with 6.8:1 diastereoselectivity. Generation of the cyanohydrin acetonide proceeded without incident, providing **6** in 75% yield.

We recognized that carrying the C₂₀ and C₂₈ bromide substituents from the start of the syn-

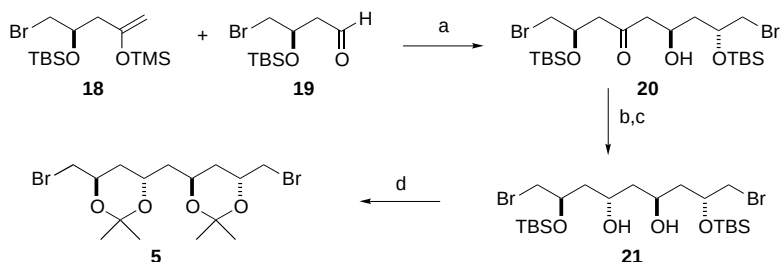
thetic sequence would constitute the most efficient approach to compound **5** (Scheme 4). To this end, a Mukaiyama aldol coupling of enol silane **18** and aldehyde **19**^[17] proceeded in 74% yield, with a modest preference^[18] for the desired 1,3-*anti* adduct **20** (3.3:1).^[19] We investigated a variety of protecting groups (e.g. the use of β -OBn- or β -OPMB-protected aldehydes), the use of cationic Lewis acids (Me₂AlCl) for chelation control,^[20] and reagent control with chiral Lewis acids.^[21] These modifications were not significantly more diastereoselective, and were much less practical than the original coupling. The conversion of **20** into *anti* 1,3-diol **21** was best accomplished by Evans–Tischenko reduction^[22]



Scheme 2. Reagents and conditions: a) DMSO, (COCl)₂, Et₃N, CH₂Cl₂; b) methyl(tri-phenylphosphoranylidene) acetate, CH₃CN, 90 °C, 82% over two steps; c) DIBAL-H, 88%; d) IBX, DMSO, 99%; e) **10**, Sn(OTf)₂, *N*-ethylpiperidine, CH₂Cl₂, –50 °C, 88%, 28:1 dr; f) MeNHOMe · HCl, imidazole, 90%; g) TMSCl, Et₃N; h) DIBAL-H; i) TMSCN, KCN/[18]crown-6; acetone, 2,2-dimethoxypropane, cat. $\pm$ -CSA, 80% over three steps. DMSO = dimethyl sulfoxide, DIBAL-H = diisobutylaluminum hydride, IBX = *o*-iodoxybenzoic acid, CSA = camphorsulfonic acid.



Scheme 3. Reagents and conditions: a) LDA, MeI, DMPU, THF, 78%, 14:1 dr; b) TBSOTf, 2,6-lutidine, 94%; c) DIBAL-H; ethyl diazoacetate, SnCl₂, 74%; d) NaBH₄, MeOH, –50 °C, 84%, 6.8:1 dr; e) TMSCl, Et₃N; f) DIBAL-H; g) TMSCN, KCN/[18]crown-6; acetone, 2,2-dimethoxypropane, cat. $\pm$ -CSA, 75% over three steps. LDA = lithium diisopropylamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.



Scheme 4. Reagents and conditions: a) BF₃ · OEt₂, CH₂Cl₂, –78 °C, 74%, 3.3:1 dr; b) cat. SmI₂, *i*PrCHO, THF, –20 °C; c) DIBAL-H, 75% over two steps, >95% de; d) Dowex-H⁺, MeOH, 75 °C; acetone, 2,2-dimethoxypropane, cat. $\pm$ -CSA, 50%.

followed by the reductive cleavage of the resultant ester (75 %, >95 % de). Desilylation under acidic conditions followed by protection of the crude tetraol gave bis-acetonide **5** in 50 % yield.

With the required fragments in hand, our attention turned to the coupling procedure (Scheme 5). Addition of LDA to a mixture of **5** (2.2 equivalents) and **6** in the presence of DMPU (5 equivalents) gave the monoalkylated adduct **22** in 65 % yield. Unreacted **5** could be readily recovered. Alkylation with the C₂₉–C₃₈ fragment **3** under the same conditions provided the protected polyol **23** in 70 % yield. Submission of **23** to a large excess of LiDBB (30 equivalents) at –78 °C effected reductive decyanation at C₁₃ and C₂₉ with concomitant deprotection of the C₁₃ and C₃₅ benzyl ethers, providing **24** in 75 % yield as a single diastereomer.^[23] Chemoselective oxidation with TEMPO under the conditions of Einhorn et al. gave aldehyde **25**, with no detectable oxidation of the C₃₅ secondary hydroxy group.^[24] Takai iodo-olefination of **25** gave vinyl iodide **26** in 88 % yield, with 11:1 *E/Z* selectivity.^[25] At

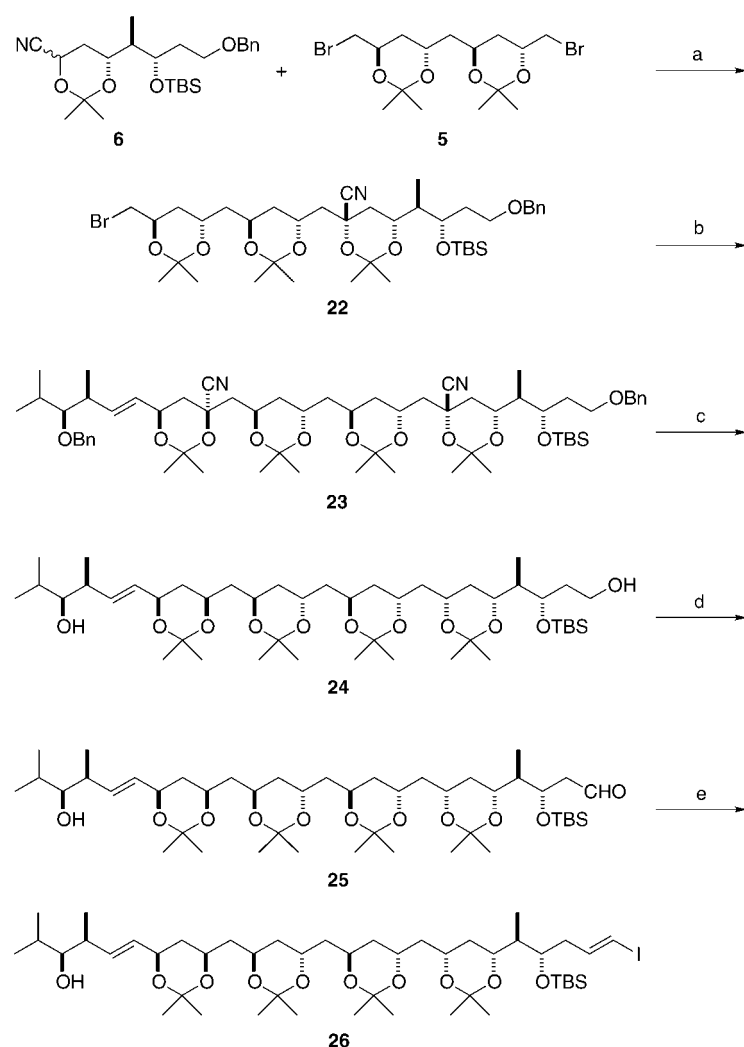
this point, the stage was set for installation of the polyene and subsequent macrocyclization.

In anticipation of the Horner–Wadsworth–Emmons macrocyclization, BOP/DMAP-promoted phosphonoesterification of **26** at C₃₅ gave **27** in quantitative yield (Scheme 6). The choice of a Stille coupling for the convergent introduction of the polyene^[26] was predicated on the belief that this transformation could be accomplished with highly functionalized substrates containing polar functional groups.^[27] In the event, palladium-mediated coupling of **27** with vinyl stannane **4**^[28] gave polyene **28** in 77 % yield, with no evidence of dimerization. Oxidation with the Dess–Martin periodinane to aldehyde **29** and submission to Masamune–Roush conditions^[9] provided macrolide **30** in 50 % yield over two steps. Deprotection proved to be surprisingly facile. Treatment of **30** with Dowex acidic resin in MeOH at ambient temperature effected the removal of the acetonide protecting groups and the partial deprotection of the C₁₅–TBS ether which could be driven to completion by gentle heating. Purification by HPLC

(high-pressure liquid chromatography) provided **1**, which was indistinguishable from natural dermostatin A by a variety of analytical methods (¹H NMR spectroscopic analysis in two solvents, high-resolution mass spectrometry, circular dichroism, HPLC).

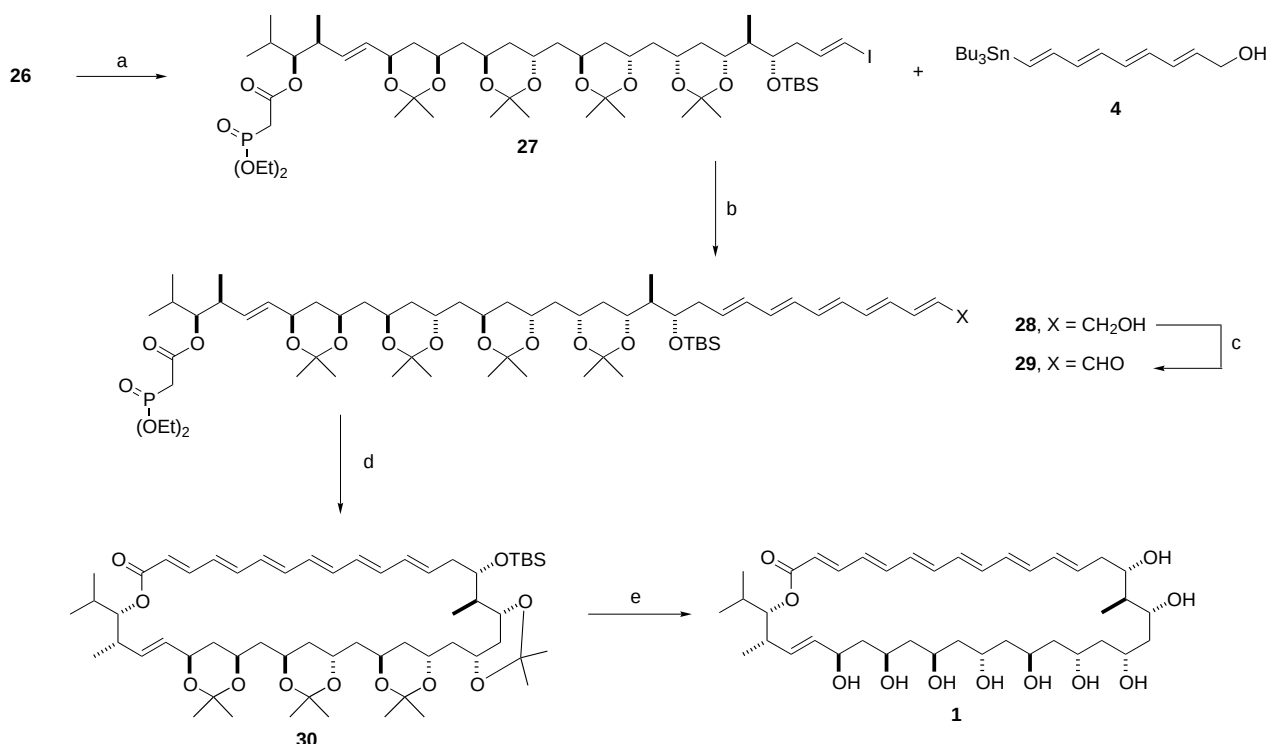
An efficient, convergent total synthesis of dermostatin A (**1**) has been achieved, thus confirming the reported stereostructure. The 1,3-polyol region was rapidly assembled by using the cyanohydrin acetonide method. The Stille cross coupling has been applied for the first time to the total synthesis of an oxo-polyene macrolide. The strategy and tactics described above should prove useful for the synthesis of analogues of dermostatin A as well as other polyene macrolides.

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Scheme 5. Reagents and conditions: a) LDA, DMPU, THF, –50 °C, 65 %; b) **3**, LDA, DMPU, THF, –50 °C, 70 %; c) LiDBB (30 equiv), THF, –78 °C, 75 %; d) TEMPO, Bu₄NCl, *N*-chlorosuccinimide, CH₂Cl₂, pH 8.6 buffer, 25 °C, 88 %; e) CrCl₂, CHI₃, dioxane/THF, 25 °C, 88 %, 11:1 *E/Z*. LiDBB = lithium di-*tert*-butylbiphenylide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

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Scheme 6. Reagents and conditions: a) (diethylphosphono)acetic acid, BOP, DMAP, CH₂Cl₂, 99 %; b) **4** (4 equiv), Pd₂(dba)₃·CHCl₃, iPr₂NEt, AsPh₃, THF, 77 %; c) Dess – Martin periodinane, NaHCO₃, CH₂Cl₂; d) LiCl, DBU, CH₃CN (c (**29**) = 0.002 M), 50 % over two steps; e) Dowex-H⁺, MeOH, 25 °C to 50 °C, 77 %. BOP = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, dba = (*E,E*)-dibenzylideneacetone, DMAP = 4-dimethylaminopyridine.

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