[3] G. Smith, R. R. Schrock, M. R. Churchill, W. J. Youngs, *Inorg. Chem.* **1981**, *20*, 387.

[4] D. Kwon, M. D. Curtis, *Organometallics* **1990**, *9*, 1.

[5] a) Crystal structure data of **1** (173 K) with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å): $M_r = 487.16$, crystal dimensions $0.40 \times 0.35 \times 0.35$ mm, triclinic, space group $P\bar{1}$, $a = 7.555(2)$, $b = 9.712(2)$, $c = 13.263(4)$ Å, $\alpha = 68.626(4)$, $\beta = 80.968(5)$, $\gamma = 77.277(4)^\circ$, $Z = 2$, $\rho_{calcd} = 1.837$ g cm^{-3}, $R1 = 0.057$ for 3340 data ($I > 4\sigma I_o$). b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-160698 (**1**) and -160699 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[6] J. L. Templeton, *Adv. Organomet. Chem.* **1989**, *29*, 1.

[7] P. Binger, B. Biedenbach, A. T. Herrmann, F. Langhauser, P. Betz, R. Goddard, C. Krüger, *Chem. Ber.* **1990**, *123*, 1617.

[8] EHMO calculations were performed with the CACAO 98 program: C. Mealli, D. M. Prosierpio, *J. Chem. Educ.* **1990**, *67*, 399.

[9] Note that the orbitals for **1** corresponding to the phosphaalkyne $\pi_\parallel$, $\pi_\parallel^*$ $\pi_\perp$, and $\pi_\perp^*$ sets also showed some electron density on the *t*Bu group, but in each case the orbital comprised at least 70% carbon and phosphorus p orbitals of suitable symmetry. Hence the populations of the P–C π bond contributions will be slightly lower than the figures quoted above.

[10] M. D. Curtis, J. Real, D. Kwon, *Organometallics* **1989**, *8*, 1644.

[11] The NMR data of **A** and **B** were calculated with a DFT/ECP geometry optimization by using the Vosko–Wilk–Nusair[12] functional and the 6-31G(d,p) basis set for all atoms except Ta, which was described by the Dolg–Stoll–Preuss–Pitzer effective core potential.[13] Geometry and magnetic shielding data have been deposited at the CCC Erlangen at http://www.ccc.uni-erlangen.de/sharc with the registry numbers alk,2000-05-27GMT081407 (**A**) and alk,1999-11-28GMT133322 (**B**) and are also available as Supporting Information. We are currently investigating the bonding in these phosphaalkyne and alkyne complexes more thoroughly in a DFT study.

[12] S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200.

[13] M. Dolg, H. Stoll, H. Preuss, R. M. Pitzer, *J. Phys. Chem.* **1993**, *97*, 5852.

[14] At the applied level of theory the isotropic magnetic shielding of $^{13}C(TMS)$ is 191.8 and of $^{31}P(PH_3)$ is 606.3. The experimental values $\delta^{31}P(PH_3, \text{liquid}) = -240$ and $\delta^{13}C(TMS) = 0$ were used to convert shieldings into chemical shifts.

[15] A similar approach to the calculation of ^{31}P NMR chemical shifts in transition metal complexes has been reported: M. Kaupp, *Chem. Ber.* **1996**, *129*, 535.

[16] G. Brauers, M. Green, C. Jones, J. F. Nixon, *J. Chem. Soc. Chem. Commun.* **1995**, 1125.

[17] J. C. T. R. Burckett-St. Laurent, P. B. Hitchcock, H. W. Kroto, J. F. Nixon, *J. Chem. Soc. Chem. Commun.* **1981**, 1141.

[18] G. Brauers, Ph.D. Thesis, University of Bath, **1995**.

[19] Crystal structure data of **4** (173 K) with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å): crystal dimensions $0.50 \times 0.40 \times 0.10$ mm, monoclinic, space group $P2_1/n$, $a = 9.085(2)$, $b = 15.400(4)$, $c = 16.560(2)$ Å, $\beta = 102.71(1)^\circ$, $Z = 4$, $\rho_{calcd} = 1.726$ g cm^{-3}, $R1 = 0.030$ for 5147 data ($I > 2\sigma I_o$).[5b]

[20] P. Binger, G. Glaser, S. Albus, C. Krüger, *Chem. Ber.* **1995**, *128*, 1261.

[21] M. T. Nguyen, M. T. Landuyt, L. G. Vanquickenborne, *J. Org. Chem.* **1993**, *58*, 2817.

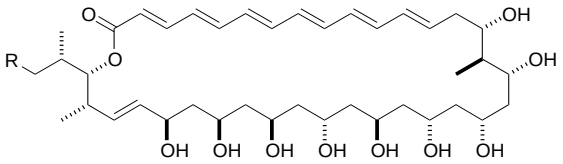
[22] S. Creve, M. T. Nguyen, L. G. Vanquickenborne, *Eur. J. Inorg. Chem.* **1999**, 1281.

[23] P. Binger, T. Wettling, R. Schneider, F. Zurmühlen, U. Bergsträsser, J. Hoffmann, G. Maas, M. Regitz, *Angew. Chem.* **1991**, *103*, 208; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 207.

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 acetonide 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**).



1: R = H
2: R = Me

Dermostatin A (**1**) and B (**2**) are 36-membered macrolides that were isolated from the mycelium of *Streptomyces viridogriseus* 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 acetonide

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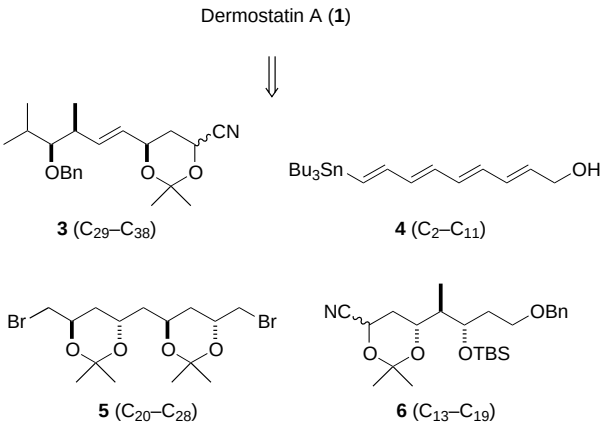


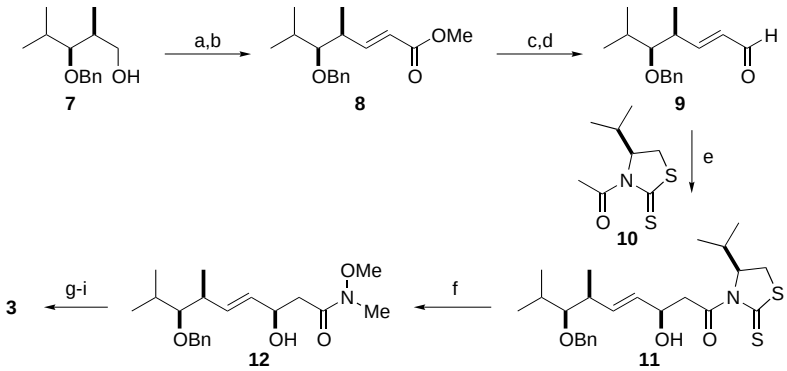
Scheme 1. Retrosynthesis of dermostatin A (**1**).

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 C_2-symmetric dibromide **5** would provide the $C_{13}-C_{38}$ 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]

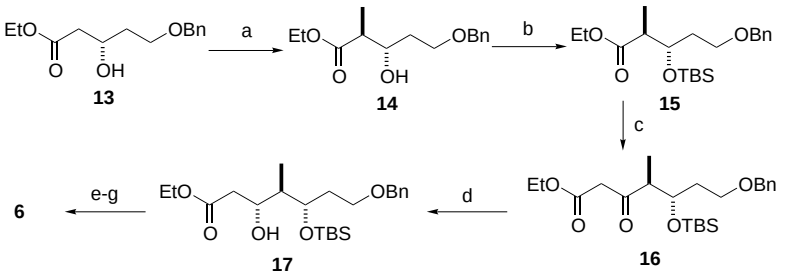
The synthesis of cyanohydrin acetonide **3** commenced with the oxidation and Wittig homologation of alcohol **7**,[10] to provide enoate **8** (82%) (Scheme 2). Reduction with DIBAL-H (88%) and oxidation with *o*-iodoxybenzoic acid[11] (99%) furnished enal **9**. Nagao's acetate aldol method[12] has recently seen a resurgence in natural product synthesis.[13] For our purposes, the addition of the tin enolate derived from *N*-acetyl thiazolidinethione **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 C_{14}–C_{15} *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 $NaBH_4$ in MeOH at $-50\,^{\circ}C$ 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.

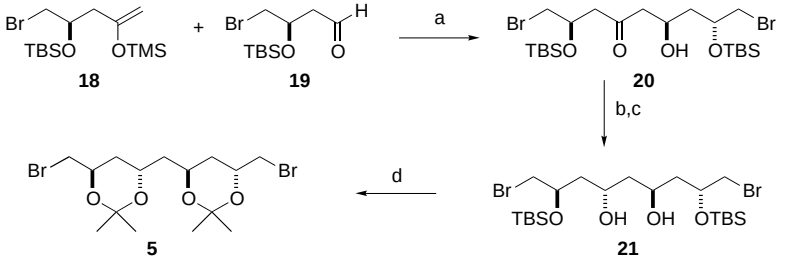
We recognized that carrying the C_{20} and C_{28} bromide substituents from the start of the synthetic sequence would constitute the most efficient approach to compound **5** (Scheme 4). To this end, a Mukaiyama aldol coupling of enol silane **18** and aldehyde **19**[17] proceeded in 74% yield, with 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 (Me_2AlCl) 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, $(COCl)_2$, Et_3N, CH_2Cl_2; b) methyl(triphenylphosphoranylidene) acetate, CH_3CN, 90 °C, 82% over two steps; c) DIBAL-H, 88%; d) IBX, DMSO, 99%; e) **10**, $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, $-50\,^{\circ}C$, 88%, 28:1 dr; f) MeNHOMe · HCl, imidazole, 90%; g) TMSCl, Et_3N; h) DIBAL-H; i) TMSCN, KCN/[18]crown-6; acetone, 2,2-dimethoxypropane, cat. ±-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, $SnCl_2$, 74%; d) $NaBH_4$, MeOH, $-50\,^{\circ}C$, 84%, 6.8:1 dr; e) TMSCl, Et_3N; f) DIBAL-H; g) TMSCN, KCN/[18]crown-6; acetone, 2,2-dimethoxypropane, cat. ±-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) $BF_3 \cdot OEt_2$, CH_2Cl_2, $-78\,^{\circ}C$, 74%, 3.3:1 dr; b) cat. SmI_2, *i*PrCHO, THF, $-20\,^{\circ}C$; c) DIBAL-H, 75% over two steps, >95% de; d) Dowex-H^+, MeOH, 75 °C; acetone, 2,2-dimethoxypropane, cat. ±-CSA, 50%.

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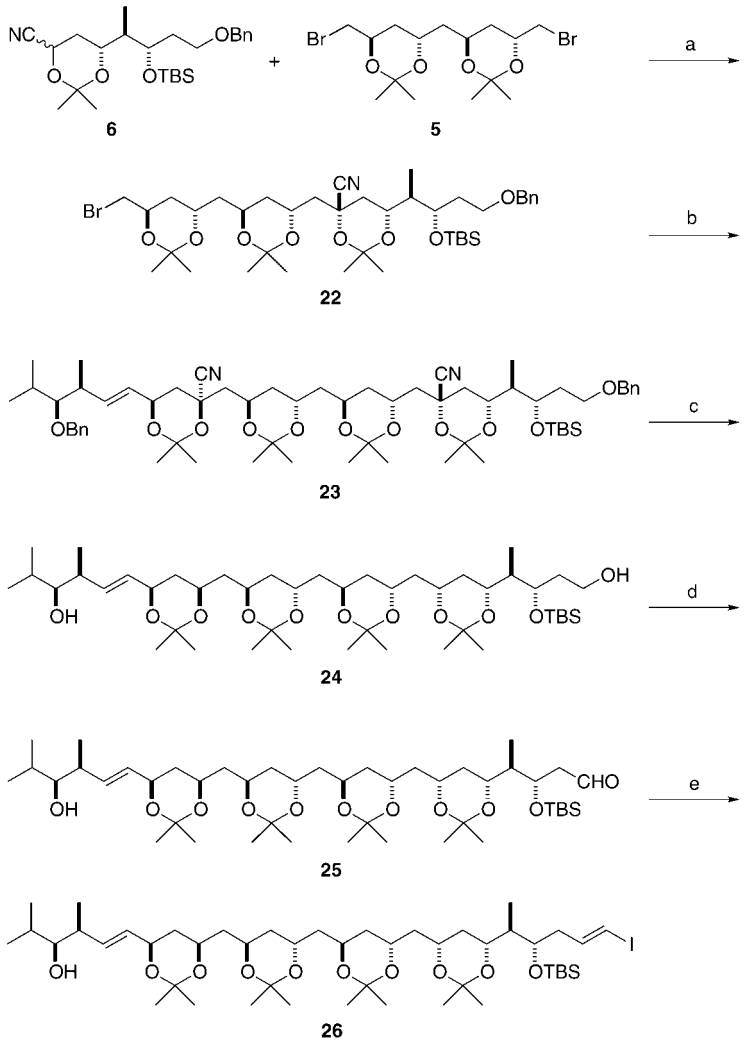
followed by the reductive cleavage of the resultant ester (75%, >95% de). Desilylation under acidic conditions followed by protection of the crude tetraol gave bis-acetonide **5** in 50% yield.

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 $C_{29}-C_{38}$ 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 $-78\,^{\circ}C$ effected reductive decyanation at C_{13} and C_{29} with concomitant deprotection of the C_{13} and C_{35} 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 C_{35} 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 C_{35} 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 C_{15}-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 (^{1}H 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.



Scheme 5. Reagents and conditions: a) LDA, DMPU, THF, $-50\,^{\circ}C$, 65%; b) **3**, LDA, DMPU, THF, $-50\,^{\circ}C$, 70%; c) LiDBB (30 equiv), THF, $-78\,^{\circ}C$, 75%; d) TEMPO, Bu_4NCl, *N*-chlorosuccinimide, CH_2Cl_2, pH 8.6 buffer, $25\,^{\circ}C$, 88%; e) $CrCl_2$, CHI_3, dioxane/THF, $25\,^{\circ}C$, 88%, 11:1 *E*/*Z*. LiDBB = lithium di-*tert*-butylbiphenylide, TEMPO = 2,2,6,6,tetramethyl-1-piperidinyloxy, free radical.

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[1] Reviews: a) S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021–2040; b) C. Schneider, *Angew. Chem.* **1998**, *110*, 1445–1448; *Angew. Chem. Int. Ed.* **1998**, *37*, 1375–1378; for recent studies on oxo-polyene macrolides, see: c) S. D. Dreher, J. L. Leighton, *J. Am. Chem. Soc.* **2001**, *123*, 341–342; d) I. Paterson, L. A. Collett, *Tetrahedron Lett.* **2001**, *42*, 1187–1191; e) S.-I. Kiyooka, M. A. Hena, T. Yabukami, K. Murai, F. Goto, *Tetrahedron Lett.* **2000**, *41*, 7511–7516; f) A. B. Smith III, S. M. Pitram, *Org. Lett.* **1999**, *1*, 2001–2004.

[2] S. D. Rychnovsky, T. I. Richardson, B. N. Rogers, *J. Org. Chem.* **1997**, *62*, 2925–2934.

[3] D. S. Bhate, G. R. Ambekar, K. K. Bhatnagar, *Hind. Antibiot. Bull.* **1962**, *4*, 159–162.

[4] R. C. Pandey, K. L. Rinehart Jr., D. S. Millington, M. B. Swami, *J. Antibiot.* **1973**, *26*, 475–477.

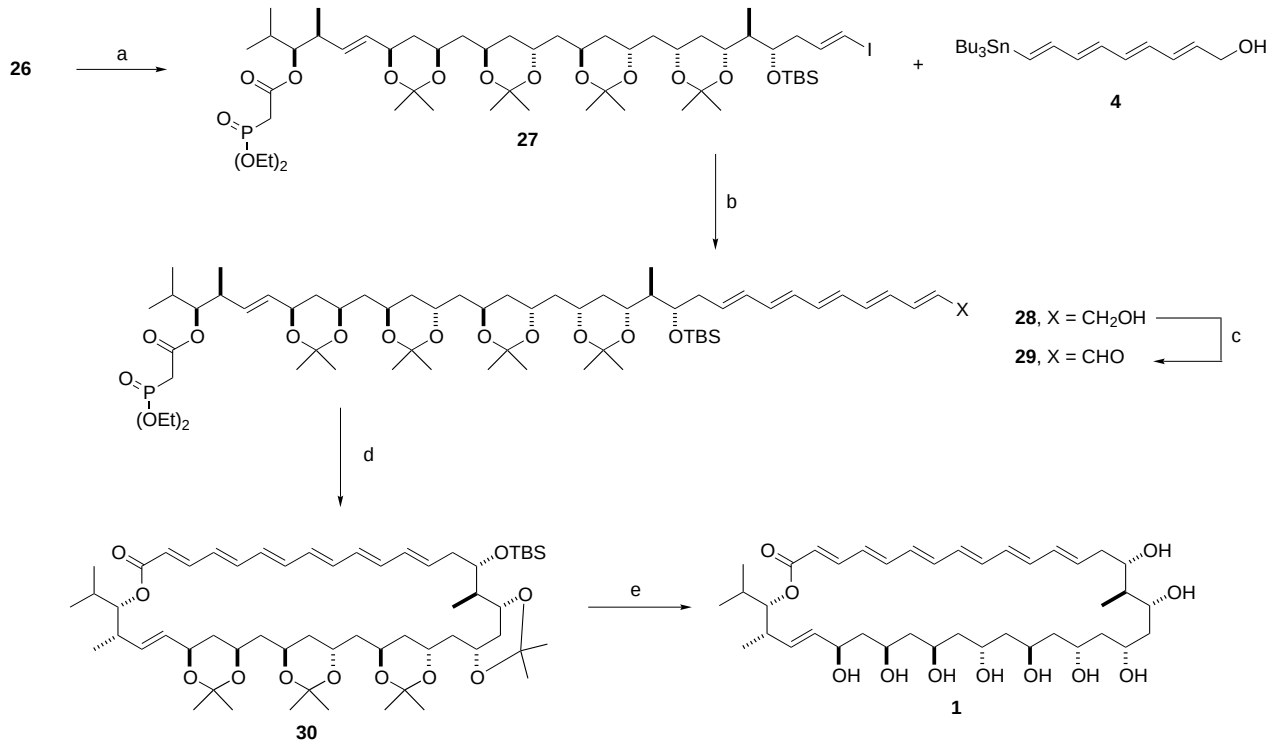
[5] a) B. B. Gokhale, M. V. Joglekar, A. A. Padhye, M. J. Thirumalachar, *Hind. Antibiot. Bull.* **1962**, *4*, 127–129; b) M. J. Thirumalachar, S. K. Menon, *Hind. Antibiot. Bull.* **1962**, *4*, 106–108.

[6] A. A. Padhye, B. B. Gokhale, M. J. Thirumalchar, *Hind. Antibiot. Bull.* **1963**, *5*, 74–77.

[7] R. C. Pandey (Xechem, Inc), US Patent 5159002, **1992**.

[8] Alkylation of 4-cyano-1,3-dioxanes: a) S. D. Rychnovsky, S. S. Swenson, *J. Org. Chem.* **1997**, *62*, 1333–1340; total

  0044-8249/01/11317-3326 $ 17.50+.50/0



Scheme 6. Reagents and conditions: a) (diethylphosphono)acetic acid, BOP, DMAP, CH_2Cl_2, 99%; b) **4** (4 equiv), $Pd_2(dba)_3 \cdot CHCl_3$, iPr_2NEt, $AsPh_3$, THF, 77%; c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; d) LiCl, DBU, CH_3CN (*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.

syntheses: b) T. I. Richardson, S. D. Rychnovsky, *Tetrahedron* **1999**, *55*, 8977–8996; c) S. D. Rychnovsky, U. R. Khire, G. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 2058–2059; d) S. D. Rychnovsky, R. C. Hoye, *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.

[9] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

[10] S. D. Rychnovsky, C. Rodriguez, *J. Org. Chem.* **1992**, *57*, 4793–4795.

[11] M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

[12] Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto, E. Fujita, *J. Org. Chem.* **1986**, *51*, 2391–2393.

[13] For recent examples, see: a) A. B. Smith III, P. R. Verhoest, K. P. Minbiole, J. J. Lim, *Org. Lett.* **1999**, *1*, 909–912; b) D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, J. O. Liu, *J. Am. Chem. Soc.* **1998**, *120*, 12337–12254.

[14] M. M. Claffey, C. J. Hayes, C. H. Heathcock, *J. Org. Chem.* **1999**, *64*, 8267–8274.

[15] a) G. Frater, *Helv. Chim. Acta* **1979**, *62*, 2825–2828; b) D. Seebach, D. Wasmuth, *Helv. Chim. Acta* **1980**, *63*, 197–200.

[16] C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258–3260.

[17] Compounds **18** and **19** were synthesized from commercially available (*S*)-ethyl-4-bromo-3-hydroxybutyrate. Compound **18**: MeNHOMe·HCl, Me_3Al; TBSOTf, 2,6-lutidine; MeMgBr; LDA, TMSCl, 68% overall yield. Compound **19**: TBSOTf, 2,6-lutidine; DIBAL-H, 78% overall yield.

[18] For a detailed study of 1,3-selectivity in Mukaiyama aldol reactions, see: D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

[19] The aldol diastereomers were readily separable by medium-pressure liquid chromatography (MPLC).

[20] D. A. Evans, B. D. Allison, M. G. Yang, *Tetrahedron Lett.* **1999**, *40*, 4457–4460.

[21] a) K. Furuta, T. Maruyama, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042; b) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, *33*, 6907–6910.

[22] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

[23] The mass balance is comprised mainly of the C_{35}-benzyl ether of **24** (15–25% yield). This material could be recycled.

[24] J. Einhorn, C. Einhorn, F. Ratajczak, J.-L. Pierre, *J. Org. Chem.* **1996**, *61*, 7452–7454.

[25] a) K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410; b) D. A. Evans, W. C. Black, *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.

[26] For an alternative approach, see: B. H. Lipshutz, B. Ullman, C. Lindsley, S. Pecchi, D. J. Buzard, D. Dickson, *J. Org. Chem.* **1998**, *63*, 6092–6093.

[27] Recent examples of Stille couplings in complex molecule synthesis: a) Y. Kim, R. A. Singer, E. M. Carreira, *Angew. Chem.* **1998**, *110*, 1321–1323; *Angew. Chem. Int. Ed.* **1998**, *37*, 1261–1263; b) A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, *119*, 962–973.

[28] Prepared by DIBAL-H reduction of the corresponding known ester: B. Dominguez, B. Iglesias, A. R. de Lera, *Tetrahedron* **1999**, *55*, 15071–15098.