Hidden Symmetry

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Enantioselective Total Synthesis of Amphidinolide F**

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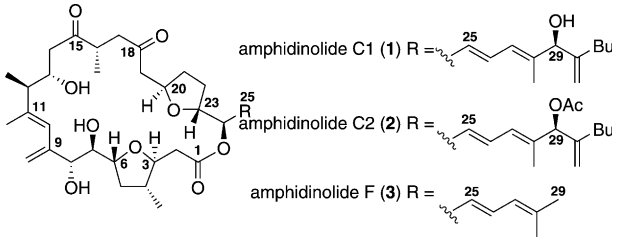
Over 30 members of the diverse amphidinolide family of biologically active macrolides have been isolated from the dinoflagellate *Amphidinium* sp.[1] From this family, amphidinolides C (**1**–**2**)[2] and F(**3**)[3] are among the most complex and densely functionalized members (Scheme 1).[4] These natural

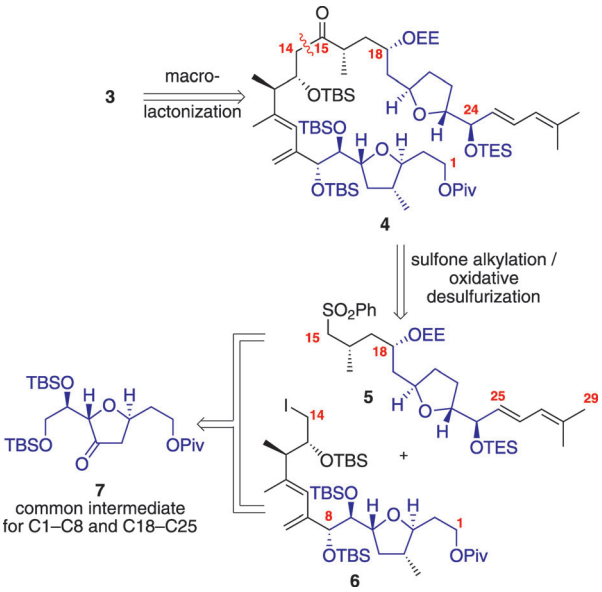


Scheme 1. Structurally complex amphidinolide natural products.

products **1**–**3** contain eleven stereogenic centers embedded within a 25-membered macrolactone including two *trans*-disposed tetrahydrofuran ring systems, a 1,4-diketone motif, and a highly substituted diene moiety at C9–C11. In addition to the sizable structural challenges present in **1**–**3**, these macrolides have shown significant cytotoxic activity.[2,3] Consequently, compounds **1**–**3** have attracted considerable synthetic attention from numerous laboratories,[5] including our own.[6] Despite these sizable endeavors,[5,6] neither amphidinolide C nor amphidinolide F have been successfully synthesized in the more than 20 years since their isolation. It should be noted that the stereochemical assignment of compound **3** is based on analogy to compound **1** and isolation from the same organism. Herein, we disclose the first total synthesis of amphidinolide F (**3**), and thus confirm both the absolute and relative stereochemistry of the natural product.

Our initial disconnection in the retrosynthesis involved cleavage of the macrolactone linkage at C1 to provide ketone **4** (Scheme 2). This ketone **4** should be accessible from sulfone **5** and iodide **6** through an umpolung strategy,[7] involving a sulfone alkylation/oxidative desulfurization sequence,[6a,8] which would mask the otherwise challenging 1,4-dicarbonyl functionality. We noticed considerable "hidden" symmetry within the tetrahydrofuran (THF) portions of fragments **5** and **6**. Specifically, the C1–C8 and the C18–C25 portions contain nearly identical functionalization, oxidation states, and stereochemistry. This observation led us to propose that compounds **5** and **6** might be accessible via common intermediate **7**. Ketone **7** should provide access to over half of the carbon backbone of the macrocycle as well as the majority of the stereochemistry present in amphidinolide F.

Synthesis of common intermediate **7** is shown in Scheme 3. Starting from known alcohol **8**,[9] oxidation and Ohira–Bestmann reaction[10] cleanly provided alkyne **10**. Removal of the benzylidine acetal under acidic conditions followed by protection and Sonogashira cross-coupling provided enyne **13**. Sharpless asymmetric dihydroxylation gave diol **14** in excellent yield and diastereoselectivity.[11] Building on the work from Gagosz[12] and Krause,[13] we had hoped to use a gold-catalyzed cyclization to generate enol ether **16**. The presence of the 1,2-diol moiety complicates any cyclization conditions, as both furan and pyran formation might be possible. Unfortunately, all attempts to facilitate this transformation under Au catalysis failed to generate the desired product. Fortunately, we found that $AgBF_4$[14] nicely provided desired dihydrofuran **16** in good yield and complete stereoselectivity (d.r. > 20:1). This transformation was routinely performed on 5-gram scale and provided sufficient quantities



Scheme 2. Retrosynthetic analysis of amphidinolide F. EE = ethoxyethyl, Piv = pivaloyl, TBS = *tert*-butyldimethylsily, TES = triethylsilyl.

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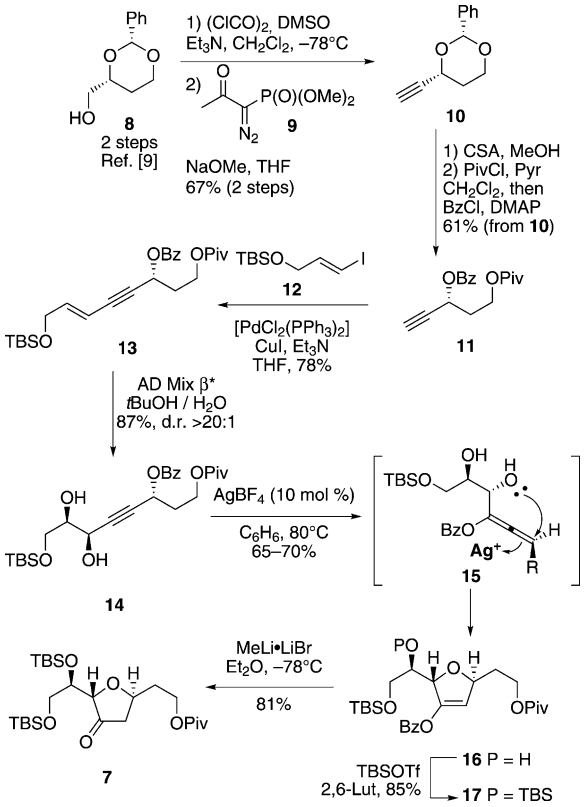
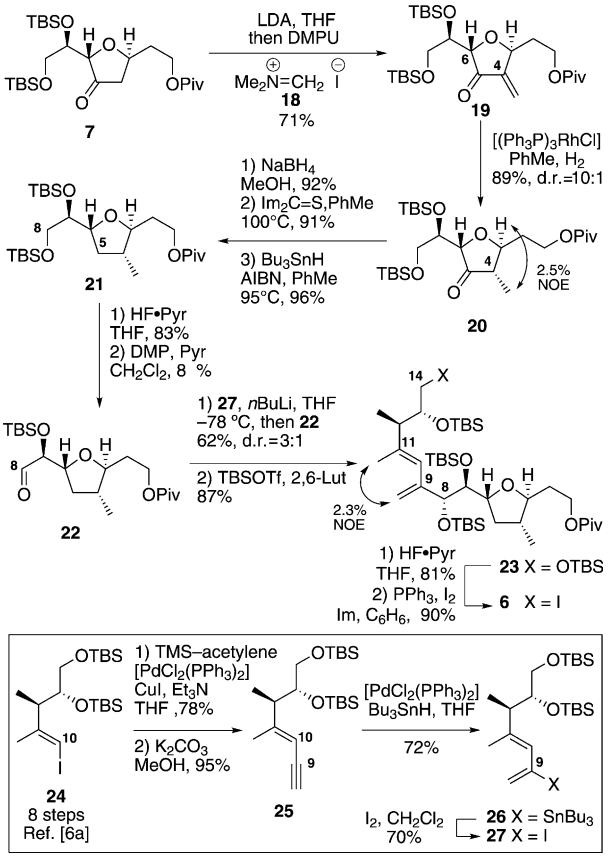


Scheme 3. Synthesis of common intermediate. Bz = benzyl, CSA = 10-camphorsulfonic acid, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, 2,6-Lut = 2,6-lutidine, Pyr = pyridine, Tf = trifluoromethylsulfonyl.

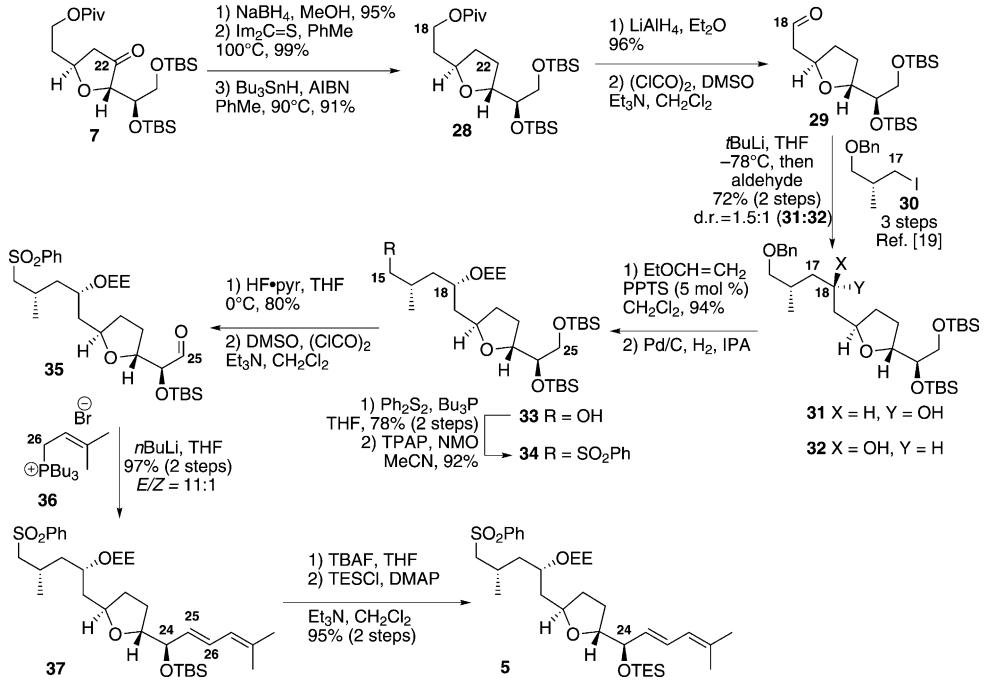


Scheme 4. Synthesis of the C1–C14 subunit. AIBN = azobisisobutyronitrile, DMP = Dess–Martin periodinane, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, Im = imidazole, LDA = lithium diisopropylamide, TMS = trimethylsilyl.

of **16**, which might serve as a building block for a variety of *trans*-disposed furan-containing natural products. Subsequent silyl protection and removal of the enol benzoate with MeLi·LiBr[15] produced common intermediate **7**.

Synthesis of the C1–C14 subunit is shown in Scheme 4. We had hoped to directly trap the enolate derived from ketone **7** with methyl iodide to generate the C4-methyl derivative **20**; however, the stereochemistry at C6 appeared to be the dominant stereocontrolling element in the alkylation and resulted in the undesired C_4-methyl stereochemistry. Fortunately, we were able to exploit this directing effect to our advantage through hydrogenation of the *exo*-methylene compound **19** using Wilkinson's catalyst to provide the correct stereochemical combination **20**. Deoxygenation of the carbonyl group at C5 followed by deprotection and oxidation at C8 generated aldehyde **22**. Next, we required the stereoselective addition of a 2-metallo-1,3-diene species to α-silyloxy aldehyde **22**. Precursor **27** was prepared in four steps from previously reported iodide **24**[6a] through a regioselective hydrostannylation of enyne **25**. This regiochemistry is counter to what is typically observed with most Pd-catalyzed hydrostannylations.[16] Treatment of iodide **27** with *n*BuLi followed by addition to aldehyde **22** provided the C8–C9 coupled material in good yield and reasonable diastereoselectivity (d.r. = 3:1).[17] We had been concerned that the organolithium species might undergo 1,3-metallotropic shifts[18] to generate allenyl metallo species as well as scramble the *E*/*Z* olefin geometry at C10–C11; however, we did not see evidence of this rearrangement occurring under the reaction conditions. Generation of a related vinyllithium species via a hydrazone using Shapiro conditions led to extensive decomposition. After silylation at C8, incorporation of the iodide at C14 through a two-step sequence provided fragment **6**.

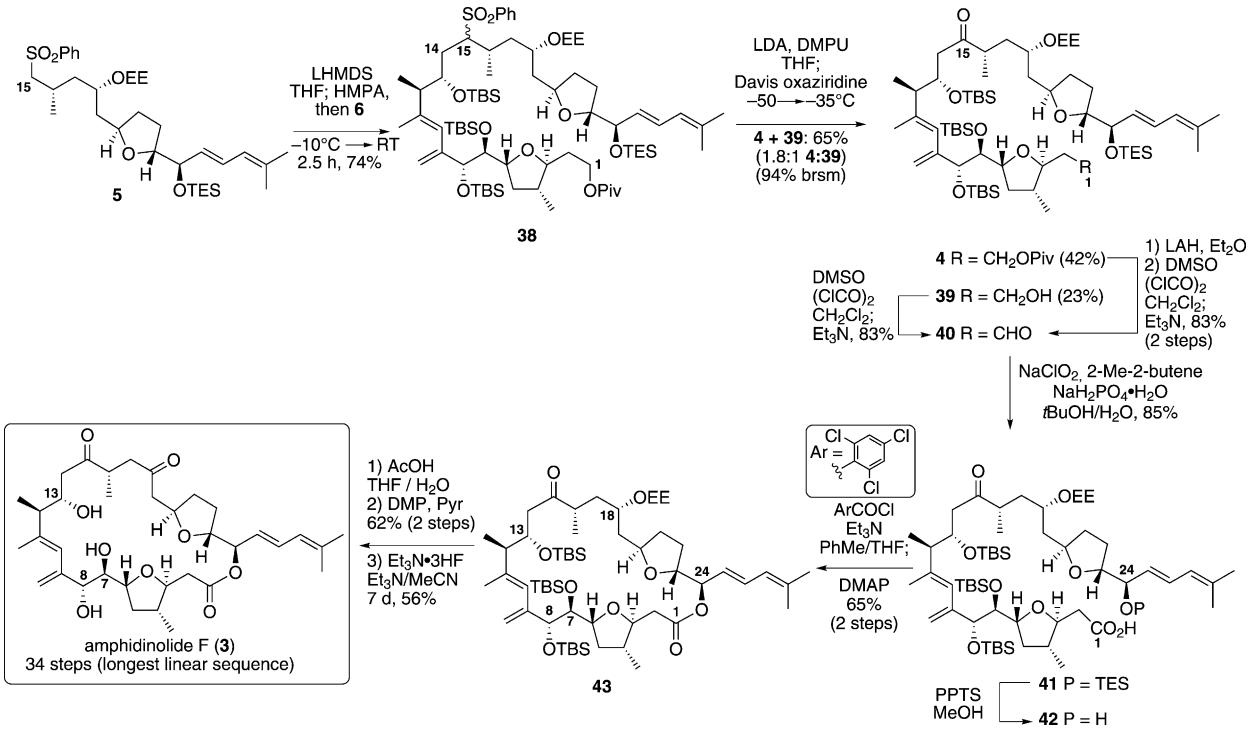
The construction of the second major fragment was also accomplished with common intermediate **7** (Scheme 5). As before, deoxygenation at C22 easily provided tetrahydrofuran **28**. Removal of the pivolate at C18 followed by oxidation generated aldehyde **29**. Addition of the organolithium species derived from known iodide **30**[19] provided secondary alcohols **31** and **32** as an inseparable mixture of stereoisomers. We initially had hoped to convert the alcohol at C18 into its corresponding dimethyl ketal by oxidation followed by ketalization under Noyori conditions. This approach had proven productive in our prior model system.[6] While the oxidation was effective, we were never able to ketalize the corresponding ketone under a diverse array of conditions. Consequently, we chose protection of alcohol(s) **31** and/or **32** as its/their ethoxyethyl (EE) ether as a viable alternative. While we believe that both C18 alcohols **31** and **32** are viable compounds for the synthetic sequence, we proceeded forward with C18-*S* isomer **31**[17] for practicality reasons, including simplification of NMR spectra. Oxidation of the mixture of **31** and **32** with TPAP and NMO followed by reduction with lithium tri-sec-butylborohydride (L-Selectride) gave C18-*S*



Scheme 5. Synthesis of the C15–C29 subunit. Bn = benzyl, IPA = isopropyl alcohol, NMO = 4-methylmorpholine-*N*-oxide, TPAP = tetra-*n*-propylammonium perruthenate, PPTS = pyridinium toluene-*p*-sulfonate, TBAF = tetra-*n*-butylammonium fluoride.

isomer **31** in high distereoselectivity (**31:32** = 15:1, 85% yield over two steps). After EE protection of alcohol **31**, debenzylation, and incorporation of the sulfone moiety at C15 provided compound **34**. Selective deprotection of the primary TBS ether using HF·Pyr followed by Swern oxidation gave key α-oxy aldehyde **35**. We had initially planned to exploit Julia–Kocienski–Blakemore olefination[20] of this aldehyde with the known PT sulfone;[21] however, this reaction showed a preference for the undesired *cis* alkene. While alternate, multi-step solutions have been developed to circumvent this problem,[5c,j] we continued to look for a direct solution. Fortunately, use of the Vedejs-type tributyl phosphonium salt **36**[22] cleanly generated desired *E* alkene **37** in good selectivity (97% yield, *E*:*Z* = 11:1). Exchange of the silyl protecting groups at C24 provided C15–C29 fragment **5**.

The completion of the total synthesis of amphidinolide F is shown in Scheme 6. The key coupling of the major fragments was accomplished by treatment of sulfone **5** with LHMDS and HMPA followed by the addition of alkyl halide **6**, smoothly forming C14–C15 coupled material **38**.[6a] The nucleophilicity of sulfone carbanions was instrumental in the success of this challenging coupling between an α-branched alkyl iodide and an α-branched nucleophile.[23] Next, oxida-



Scheme 6. Total synthesis of amphidinolide F. brsm = based on recovered starting material, HMPA = hexamethylphosphoramide, LAH = lithium aluminum hydride, LHMDS = lithium hexamethyldisilazanide.

tive desulfurization was accomplished using LDA/DMPU followed by treatment with Davis' oxaziridine to provide desired ketone **4** along with the Piv-deprotected ketone **39** in a combined 65% yield (94% brsm). While this type of oxidation has been known for some time,[24] it is only recently starting to gain attention as a viable method for the incorporation of carbonyl moieties in synthesis.[6,8] Interestingly, the Davis oxaziridine proved superior to our previous TMSOOTMS conditions.[6a,8a] Both compounds **4** and **39** were easily converted to seco acid **42**. In contrast to our synthesis of amphidinolide B,[25] macrolactonization proved to be an effective way for construction of cyclized product **43**, with Yamaguchi conditions[26] being optimum. Next, careful deprotection at C18 under aqueous acidic conditions followed by oxidation resulted in the sensitive C15,C18 diketone. Finally, global desilylation using $Et_3N{\cdot}3HF$[27] provided synthetic amphidindolide F (**3**), which matched the reported isolation data (^1H NMR, ^{13}C NMR, $[\alpha]_D$).[3]

In summary, the total synthesis of amphidinolide F has been accomplished in 34 steps (longest linear sequence). Highlights of the synthetic sequence include a silver-catalyzed dihydrofuran formation, use of common intermediate **7** to access both the C1–C8 and C18–C25 fragments, regioselective hydrostannylation of enyne **25**, diasteroselective addition of a 2-lithio-1,3-diene species to aldehyde **22**, and the sulfone alkylation/oxidative desulfurization sequence to couple the major subunits and incorporate the carbonyl moiety at C15.

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[1] a) J. Kobayashi, M. Tsuda, *Nat. Prod. Rep.* **2004**, *21*, 77–93; b) J. Kobayashi, *J. Antibiot.* **2008**, *61*, 271–284.
[2] a) J. Kobayashi, M. Ishibashi, N. R. Wälchli, H. Nakamura, T. Yamasu, Y. Hirata, T. Sasaki, Y. Ohizumi, *J. Am. Chem. Soc.* **1988**, *110*, 490–494; b) T. Kubota, M. Tsuda, J. Kobayashi, *Org. Lett.* **2001**, *3*, 1363–1366; c) T. Kubota, Y. Sakuma, M. Tsuda, J. Kobayashi, *Mar. Drugs* **2004**, *2*, 83–87; d) T. Kubota, A. Suzuki, M. Yamada, S. Baba, J. Kobayashi, *Heterocycles* **2010**, *82*, 333–338.
[3] J. Kobayashi, M. Tsuda, M. Ishibashi, H. Shigemori, T. Yamasu, H. Hirota, T. Sasaki, *J. Antibiot.* **1991**, *44*, 1259–1261.
[4] T. Kubota, J. Kobayashi, *J. Nat. Prod.* **2007**, *70*, 451–460.
[5] a) H. Ishiyama, M. Ishibashi, J. Kobayashi, *Chem. Pharm. Bull.* **1996**, *44*, 1819–1822; b) T. Kubota, M. Tsuda, J. Kobayashi, *Tetrahedron* **2003**, *59*, 1613–1625; c) J. B. Shotwell, W. R. Roush, *Org. Lett.* **2004**, *6*, 3865–3868; d) D. K. Mohapatra, H. Rahaman, M. S. Chorghade, M. K. Gurjar, *Synlett* **2007**, 567–570; e) R. H. Bates, J. B. Shotwell, W. R. Roush, *Org. Lett.* **2008**, *10*, 4343–4346; f) A. Armstrong, C. Pyrkotis, *Tetrahedron Lett.* **2009**, *50*, 3325–3328; g) M. P. Paudyal, N. P. Rath, C. D. Spilling, *Org. Lett.* **2010**, *12*, 2954–2957; h) L. Ferrié, B. Figadère, *Org. Lett.* **2010**, *12*, 4976–4979; i) S. Roy, C. D. Spilling, *Org. Lett.* **2010**, *12*, 5326–5329; j) N. A. Morra, B. L. Pagenkopf, *Org. Lett.* **2011**, *13*, 572–575; k) D. A. Fischer, D. R. Williams, R. De, R. M. Fultz, A. Morales-Ramos, D. Rodriguez-Reyes, 243st National American Chemical Society Meeting, San Diego, CA, March 25–29, **2012**, ORGN-756.
[6] a) S. Mahapatra, R. G. Carter, *Org. Biomol. Chem.* **2009**, *7*, 4582–4585; b) S. Mahapatra, R. G. Carter, 241st National American Chemical Society Meeting, Anaheim, CA, March 27–31, **2011**, ORGN-295; c) S. Mahapatra, R. G. Carter, 2011 Northwest Regional American Chemical Society Meeting, Portland, OR, June 26–30, **2011**, NORM-261.
[7] D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[8] a) X.-T. Zhou, R. G. Carter, *Angew. Chem.* **2006**, *118*, 1819–1822; *Angew. Chem. Int. Ed.* **2006**, *45*, 1787–1790; b) A. C. Bonaparte, M. P. Betush, B. M. Panseri, D. J. Mastarone, R. K. Murphy, S. S. Murphree, *Org. Lett.* **2011**, *13*, 1447–1449.
[9] a) O. Flögel, M. G. O. Amombo, H.-U. Reißig, G. Zahn, I. Brüdgam, H. Hartl, *Chem. Eur. J.* **2003**, *9*, 1405–1415; b) B. Herradon, *Tetrahedron: Asymmetry* **1991**, *2*, 191–194.
[10] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564; b) S. Müller, B. Liepold, G. J. Roth, J. Bestmann, *Synlett* **1996**, 521–522; See also: c) W. R. F. Goundry, J. E. Baldwin, V. Lee, *Tetrehedron* **2003**, *59*, 1719–1729; d) M. Kitamura, M. Tokynaga, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2931–2932.
[11] Diastereoselectivity was determined by ^1H NMR analysis of compounds **14**, **16**, and **17**, which showed a single diastereomer (d.r. > 20:1).
[12] A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957–1959.
[13] F. Volz, N. Krause, *Org. Biomol. Chem.* **2007**, *5*, 1519–1521.
[14] Y. Shigemasa, M. Yasui, S. Ohrai, M. Sakaki, H. Sashiwa, H. Saimoto, *J. Org. Chem.* **1991**, *56*, 910–912.
[15] M. Turks, P. Vogel, *J. Org. Chem.* **2009**, *74*, 435–437.
[16] a) This reactivity was first noted by Smith et al. as an unwanted side reaction in their synthesis of rapamycin: A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. W. Leahy, R. E. Maleczka, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 962–973; for alternative routes to similar stannanes, see: b) A. C. Oehlschlager, M. W. Hutzinger, R. Aksela, S. Sharma, S. M. Singh, *Tetrahedron Lett.* **1990**, *31*, 165–168; c) F. Suzenet, E. Blart, J.-P. Quintard, *Synlett* **1998**, 879–881; d) A. K. Mandal, J. R. Schneekloth, Jr., K. Kuramochi, C. M. Crews, *Org. Lett.* **2006**, *8*, 427–430.
[17] The stereochemistry was established by advanced Mosher ester method. See the Supporting Information for details. I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
[18] R. W. Hoffmann, A. Polachowski, *Chem. Eur. J.* **1998**, *4*, 1724–1730.
[19] a) J. D. White, M. Kawaski, *J. Org. Chem.* **1992**, *57*, 5292–5300; b) B. G. Vong, S. Abraham, A. X. Xiang, E. A. Theodorakis, *Org. Lett.* **2003**, *5*, 1617–1620; c) D. J. Kopecky, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421.
[20] a) P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* **2000**, 365–366; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.
[21] D. Takano, T. Nagamitsu, H. Ui, K. Shiomi, Y. Yamaguchi, R. Masuma, I. Kuwajima, S. Omura, *Org. Lett.* **2001**, *3*, 2289–2291.
[22] a) E. Vedejs, C. F. Marth, R. Ruggeri, *J. Am. Chem. Soc.* **1988**, *110*, 3940–3948; b) R. Tamura, K. Saegusa, M. Kakihana, D. Oda, *J. Org. Chem.* **1998**, *63*, 2723–2728.
[23] H. Fuwa, Y. Okamura, H. Natsugari, *Tetrahedron* **2004**, *60*, 5341–5352.
[24] J. R. Hwu, *J. Org. Chem.* **1983**, *48*, 4432–4433.
[25] L. Lu, W. Zhang, R. G. Carter, *J. Am. Chem. Soc.* **2008**, *130*, 7253–7255.
[26] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[27] J. R. Dunetz, L. D. Julian, J. S. Newcom, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 16407–16416.

