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Total Syntheses of Amphidinolide X and Y

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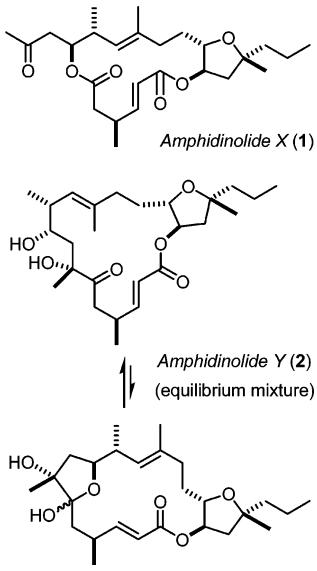
Abstract: Concise total syntheses of the cytotoxic marine natural products amphidinolide X (**1**) and amphidinolide Y (**2**) as well as of the nonnatural analogue 19-*epi*-amphidinolide X (**47**) are described. A pivotal step of the highly convergent routes to these structurally rather unusual secondary metabolites consists of a *syn*-selective formation of allenol **17** by an iron-catalyzed ring opening reaction of the enantioenriched propargyl epoxide **16** (derived from a Sharpless epoxidation) with a Grignard reagent. Allenol **17** was then cyclized with the aid of Ag(I) to give dihydrofuran **19** containing the (*R*)-configured tetrasubstituted sp^3 chiral center at C.19, which was further elaborated into tetrahydrofuran **25** representing the common heterocyclic motif of **1** and **2**. The aliphatic chain of amphidinolide X featuring an *anti*-configured stereodiad at C.10 and C.11 was generated by a palladium-catalyzed, Et_2Zn-promoted addition of the enantiopure propargyl mesylate **29** to the functionalized aldehyde **28**. The preparation of the corresponding C.1−C.12 segment of amphidinolide Y relies on asymmetric hydrogenation of an α-ketoester, a diastereoselective boron aldol reaction, and a chelate-controlled addition of MeMgBr in combination with suitable oxidation state management for the elaboration of the tertiary acyloin motif. Importantly, the end games of both total syntheses follow similar blueprints, involving key fragment coupling processes via the "9-MeO-9-BBN" variant of the alkyl-Suzuki reaction and final Yamaguchi esterifications to forge the 16-membered macrodiolide ring of amphidinolide X and the 17-membered macrolide frame of amphidinolide Y, respectively. This methodological convergence ensures high efficiency and an excellent overall economy of steps for the entire synthesis campaign.

Introduction

Marine dinoflagellates of the genus *Amphidinium* sp. living in symbiosis with the Okinawan flatworm *Amphiscolops* spp. have turned out to be exceptionally rich sources of bioactive natural products with previously unknown structural characteristics.[1] To date, they have given rise to more than 30 novel metabolites belonging to the "amphidinolide" class, all of which exhibit potent cytotoxic properties against various cancer cell lines in the standard assays.[2] Despite their common origin and this uniform activity profile, the individual members of the series are quite dissimilar in structural terms. This diversity is the result of a complex nonsuccessive polyketide biosynthesis pathway that generates a host of frequently *odd*-numbered macrocyclic skeletons of largely varying ring size that are decorated with *exo*-methylene groups, vicinal one-carbon branches, and 1,3-diene units.[1,3] However, even these distinctive features are not preserved throughout the family, as can be seen from amphidinolide X (**1**), which displays none of these structural elements on its *even*-numbered macrocycle.[4] Moreover, **1** was the first example of a natural product containing a macrodiolide ring that embodies a diacid and a diol subunit rather than two hydroxyacid entities.[5]



Yet another glimpse of the complex biochemical machinery producing the individual amphidinolides was caught during a

(1) (a) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (b) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543. (c) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131. (d) Kobayashi, J.; Ishibashi, M. In *Comprehensive Natural Products Chemistry*; Mori, K., Ed.; Elsevier: Amsterdam, 1999; Vol. 8; pp 415−649.

(2) IC_{50} values as low as 0.00014 μg/mL were reported; hence, amphidinolides H and N exhibit potencies similar to that of the spongistatins, cf. ref 1.

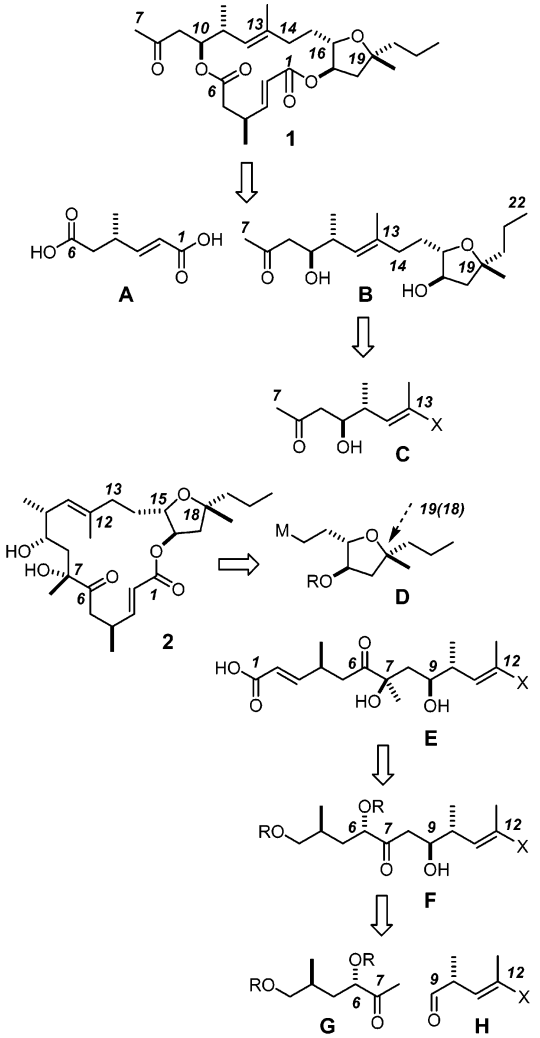
(3) (a) Review: Rein, K. S.; Borrone, J. *Comp. Biochem. Physiol., B* **1999**, *124*, 117. (b) For representative studies on the biosynthesis of the amphidinolides see: Kobayashi, J.; Takahashi, M.; Ishibashi, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1639. (c) Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 7827. (d) Sato, M.; Shimbo, K.; Tsuda, M.; Kobayashi, J. *Tetrahedron Lett.* **2000**, *41*, 503.

10.1021/ja061918e CCC: $33.50

recent recollection of the *Amphidinium* Y-42 strain, which not only provided **1** together with three other known amphidinolides but also afforded tiny amounts of a novel congener, designated amphidinolide Y (**2**); this product exists as an equilibrium mixture of the dominant C.6-keto- and the minor C.6(9)-hemiacetal form.[6] Although **2** contains a 17-membered lactone rather than the conspicuous 16-membered macrodiolide core of its companion amphidinolide X (**1**), it is obviously closely related to the latter and is thought to be its biogenetic precursor. In line with this notion, oxidative cleavage of the α-hydroxyketone moiety with lead tetraacetate followed by spontaneous lactonization of the resulting acid with the hydroxyl group in vicinity converted compound **2** into **1** in fair yield.[6]

During our studies on the total synthesis[7] and biological evaluation[8] of various natural products of marine or terrestrial origin, a strong interest arose in the amphidinolide class.[9,10] These compounds constitute obvious targets for an exploratory program at the chemistry/biology interface because of their challenging and diverse molecular architectures and because they are extremely scare, thus rendering a detailed assessment of their promising anticancer activities difficult if one relies on extraction from the producing dinoflagellates only. As part of this program, we now present the first total syntheses of amphidinolide X,[11] its nonnatural stereomer **47**, as well as of its biosynthetic precursor amphidinolide Y. Moreover, from the purely chemical perspective, this endeavor provided an excellent opportunity to scrutinize methodology for catalytic C−C-bond formation previously developed in this laboratory.

Scheme 1. Retrosynthetic Analysis of Amphidinolide X (**1**) and Y (**2**), Converging to the Common Synthon D[a]



[a] Note the "shift" in the numbering scheme for the two natural products caused by their different ring sizes and connectivities.

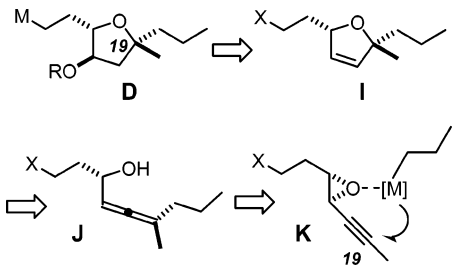
Results and Discussion

General Retrosynthetic Considerations. Because of the identity of the tetrahydrofuran segments in **1** and **2**, it should be possible to use a common building block for both syntheses. While the ester linkages forming the macrodiolide ring of amphidinolide X constitute obvious sites for disconnection of this target, it was envisaged to assemble the required C.7−C.22 diol entity **B** by metal-catalyzed cross coupling at the C.13−C.14 bond (Scheme 1). This strategy employs building blocks **A**, **C**, and **D** of similar size and ultimately ensures high flexibility; more importantly, however, it allows one to address the critical formation of the tetrasubstituted chiral center C.19 residing at the ether bridge in **D** in an early stage of the synthesis campaign. Because **D** can be directly used for the envisaged total synthesis of amphidinolide Y (**2**) as well by a similar fragment-coupling process at the corresponding C.12−C.13 bond, an excellent overall "economy of steps",[12] a favorable methodological redundancy, and hence a significant convergence of the entire program should be secured. The C.1−C.12 fragment **E** to be embedded into **2**, which carries another

(4) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 5339.
(5) For a recent review on macrodiolides see: Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348.
(6) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 9109.
(7) Recent examples: (a) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620. (b) Fürstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462. (c) Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2777. (d) Scheiper, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11960. (e) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2097. (f) Fürstner, A.; Müller, C. *Chem. Commun.* **2005**, 5583. (g) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061. (h) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112. (i) Fürstner, A.; Wuchrer, M. *Chem. Eur. J.* **2006**, *12*, 76. (j) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006.
(8) (a) Fürstner, A.; Kirk, D.; Fenster, M. D. B.; Aïssa, C.; De Souza, D.; Müller, O. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (c) Fürstner, A. *Eur. J. Org. Chem.* **2004**, 943. (d) Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Tetrahedron* **2004**, *60*, 9543.
(9) (a) Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512. (b) Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4763.
(10) For total syntheses of amphidinolides reported by other groups, see: (a) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198. (b) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945. (c) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765. (d) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508. (e) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S. *Org. Lett.* **2002**, *4*, 2841. (f) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374. (g) Trost, B. M.; Harrington, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 5028. (h) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704. (i) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998. (j) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618. (k) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420. (l) Ghosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085. (m) Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921. (n) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wrobleski, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 13598. (o) Colby, E. A.; Jamison, T. F. *Org. Biomol. Chem.* **2005**, *3*, 2675. (p) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297.
(11) Preliminary communication: Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970.

(12) For a discussion see: Fürstner, A. *Synlett* **1999**, 1523.

Scheme 2. Use of an Axially Chiral Allene J as a Relay for the Envisaged Chirality Transfer from a Propargyl Epoxide K to Fragment D Embodying the Tetrasubstituted Chiral Center C.19.



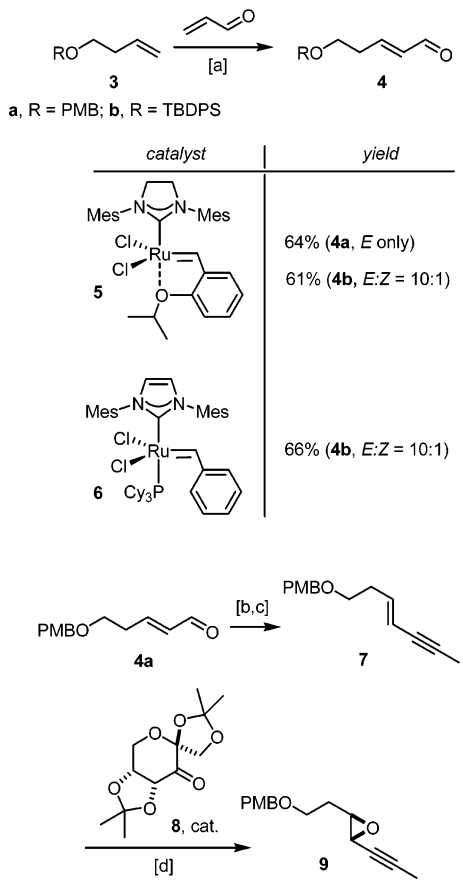
tetrasubstituted chiral center at C.7, should be accessible by aldol chemistry joining segments **G** and **H**, followed by elaboration of the C.6/C.7 acyloin motif through suitable oxidation-state management and a chelate-controlled addition of a methyl donor to an adequately protected α-hydroxy ketone at C.7.

Preparation of the Common Tetrahydrofuran Segment. Control over the absolute configuration of the tertiary ether residing at C.19 of the tetrahydrofuran segment **D** (amphidinolide X numbering) deemed crucial for the entire synthesis campaign and was therefore addressed in an early stage.

The chosen route to this key structural element hinges upon methodology recently developed in our laboratory (Scheme 2).[13,14] Specifically, it was planned to use a chiral allene **J** as latent progenitor of the tetrahydrofuran ring, which can be formed stereoselectively by an iron-catalyzed reaction of a propargyl epoxide **K** with a suitable Grignard reagent.[13] This sequence should enable an efficient chirality transfer from a readily accessible epoxide to the quaternary chiral sp^3 center C.19 in **D** via the axial chirality of an allene relay.

To reduce this plan to practice, we initially pursued a cross metathesis approach[15] using complexes **5**[16] or **6**[17] as appropriate catalysts (Scheme 3). Since only aldehyde **4a** (R = PMB) could be obtained in isomerically pure form, this compound was chosen for further elaboration into enyne **7** as the substrate for a chemo- and enantioselective oxidation with Oxone mediated by the D-fructose derivative **8**.[18] Although significant levels of enantiocontrol could be reached, the conversion remained unsatisfactory despite considerable experimentation. Since catalyst **8** also leads to the wrong enantiomer of **9** and would ultimately have to be replaced by (a surrogate for) nonnatural L-fructose, we decided to abandon this very short entry and to pursue a somewhat more conservative route to the required building block.

Scheme 3 [a]

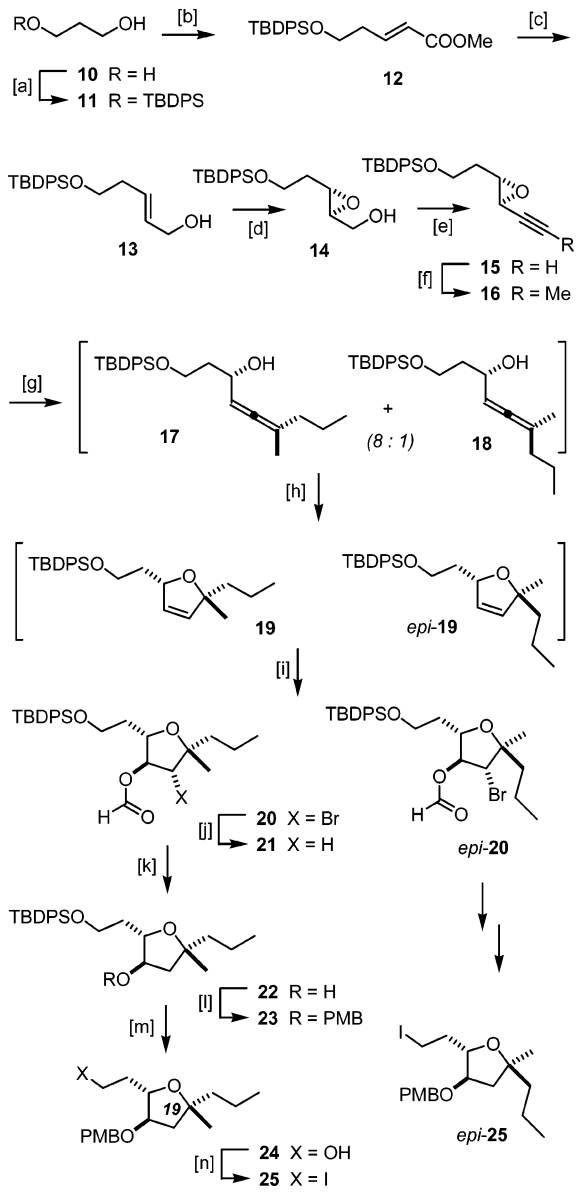


[a] Reagents and conditions: [a] Catalyst **5** or **6** (5 mol %), CH_2Cl_2, rt; [b] CBr_4, PPh_3; CH_2Cl_2, 0 °C; [c] *n*-BuLi, THF, −78 °C, then MeI, 0 °C, 66% (over both steps); [d] ketone **8** (25 mol %), MeCN/DMM, Bu_4NHSO_4 cat., aq K_2CO_3, Oxone, Na_2ETDA, −10 °C, 33% (ee = 83%).

To this end, monosilylation of propane-1,3-diol **10** followed by oxidation and standard olefination of the resulting aldehyde ensured the exclusive formation of (*E*)-**12**, which was reduced with Dibal-H (Scheme 4).[19] The allylic alcohol **13** thus obtained was epoxidized by the Sharpless method[20] to give product **14**[19] in excellent yield and decent optical purity (ee = 83%). Swern oxidation followed by treatment of the resulting aldehyde with the Ohira−Bestmann reagent[21] gave alkyne **15**, which could be methylated on treatment with LiHMDS/MeOTf at −78°C. Gratifyingly, reaction of the resulting propargyl epoxide **16** with *n*-PrMgCl in the presence of cheap and benign $Fe(acac)_3$ as the precatalyst furnished allenes **17** and **18** as an 8:1 mixture in favor of the required *syn* isomer.[13] The reaction is exceptionally fast, requiring less than 5 min to go to completion. In contrast to our original protocol, the iron salt was added to the substrate as a solution in toluene. This simple modification avoids some uncontrolled degradation of the labile oxirane during the time it takes to dissolve the catalyst when added in solid form, and therefore ensures good reproducibility and respectable yields in this crucial step. The pronounced diastereoselectivity favoring the *syn*-isomer **17** likely results from a directed delivery of the nucleophile enforced by the preco-

(13) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355.
(14) (a) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (b) See also: Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (d) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (e) Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950. (f) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (g) Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236.
(15) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.
(16) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8.
(17) (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (b) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.
(18) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.
(19) Nacro, K.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1999**, *55*, 14013.
(20) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 231−280.
(21) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

Scheme 4 [a]



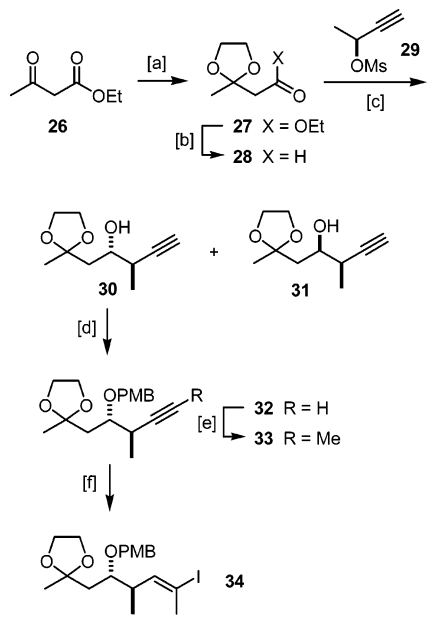
[a] Reagents and conditions: [a] TBDPSCl, Et_3N, CH_2Cl_2, 92%; [b] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $MeOOCCH_2P(O)(OEt)_2$, NaH, THF, 85% (over two steps); [c] Dibal-H, Et_2O, 86%; [d] $Ti(OiPr)_4$ cat., L-(+)-DET cat., *t*-BuOOH, MS 4 Å, CH_2Cl_2, 97% (ee = 83%); [e] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH, 67%; [f] LiHMDS, MeOTf, THF, 95%; [g] *n*-PrMgCl, $Fe(acac)_3$ cat., toluene, 62% (*syn*:*anti* = 8:1); [h] $AgNO_3$, $CaCO_3$, aq acetone, 90%; [i] NBS, DMF/H_2O (15/1), 65%; [j] AIBN, $(TMS)_3SiH$, toluene; [k] $NaHCO_3$, MeOH, 90% (over both steps); [l] $PMBOC(=NH)CCl_3$, PPTS, CH_2Cl_2/C_6H_{12}, 76%; [m] TBAF, THF, 97%; [n] I_2, PPh_3, imidazole, MeCN/Et_2O, 92%.

ordination of the oxophilic catalyst and/or reagent to the epoxide ring (Scheme 2) and hence nicely complements the *anti*-selectivity of the standard copper-based methods for allenol formation.[13]

Because the allene isomers **17** and **18**, however, were not readily separable, the mixture was treated with $AgNO_3/CaCO_3$ in aqueous acetone[22] to afford the corresponding dihydrofurans **19** and *epi*-**19** with strict chirality transfer. Subsequent bromoesterification with NBS in aqueous DMF[23] gave the bromohydrines **20** and *epi*-**20** as single stereomers each,[24] which could be separated by flash chromatography. Removal of the bromide in **20** using $(Me_3Si)_3SiH$[25] and AIBN followed by standard protecting-group manipulations furnished product **25** as functional surrogate of synthon **D**.[26] The minor product *epi*-**20** was processed analogously to give *epi*-**25** which was ultimately converted into the first fully synthetic analogue of amphidinolide X as outlined below.

(22) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

Scheme 5 [a]

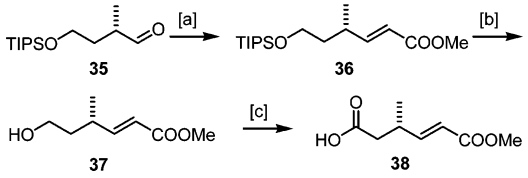


[a] Reagents and conditions: [a] Ethylene glycol, PTSA cat., benzene; [b] Dibal-H, Et_2O, 54% (over two steps); [c] Et_2Zn, $Pd(OAc)_2$ cat., PPh_3 cat., THF, 65% (*anti*:*syn* = 4.5:1); [d] PMBCl, NaH, TBAI, DMF, 94%; [e] LiHMDS, MeI, THF, 95%; [f] (i) Cp_2ZrHCl, C_6H_6; (ii) I_2, CH_2Cl_2, 61%.

Total Synthesis of Amphidinolide X. The preparation of the second building block required for the total synthesis of amphidinolide X started from acetoacetate **26**, which was transformed into acetal **27**[27] prior to reduction with Dibal-H (Scheme 5). The resulting aldehyde **28**[28] was subjected to a Et_2Zn-mediated, palladium-catalyzed reaction with propargyl mesylate **29**,[29,30] furnishing the desired *anti*-configured alcohol **30** in good yield, decent diastereoselectivity (dr = 4.5:1) and excellent optical purity (ee = 94%); the fact that the minor *syn*-isomer **31** could be readily separated by routine chromatography turned out to be an additional bonus. Elaboration of alkyne **30** into product **33** followed by a hydrozirconation/iodination in

(23) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Eur. J. Org. Chem.* **1998**, 1675.
(24) Originally, it had been envisaged to install the missing −OH group at C.17 via hydroboration/oxidation or, alternatively, by a Wacker oxidation of the olefin in **19** followed by reduction of the resulting ketone; however, both sequences turned out to be unsatisfactory.
(25) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.
(26) For a recent alternative synthesis of a **D**-synthon surrogate see: Chen, Y.; Jin, J.; Wu, J.; Dai, W.-M., *Synlett* **2006**, 1177.
(27) Toluene should not be used as substitute for benzene in the acetalization reaction because the separation of the volatile product is then much more difficult and results in significantly lower yields.
(28) The literature reports that this Dibal-H reduction affords the corresponding alcohol, cf: Langer, P.; Freifeld, I. *Synlett* **2001**, 523; in our hands, however, the reduction reproducibly stopped at the aldehyde stage even if an excess Dibal-H was used.
(29) (a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201. (c) Marshall J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.
(30) For a recent application see: Beşev, M.; Brehm, C.; Fürstner, A. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1696.

Scheme 6 [a]



[a] Reagents and conditions: [a] $(EtO)_2P(O)CH_2COOMe$, LiCl, DBU, MeCN, 94%; [b] HF·pyridine, MeCN, quant.; [c] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}CHCH_3$, *t*-BuOH, 92%.

benzene as the solvent of choice[31,32] gave vinyl iodide **34** in well reproducible 65% yield as the only regioisomer.[33]

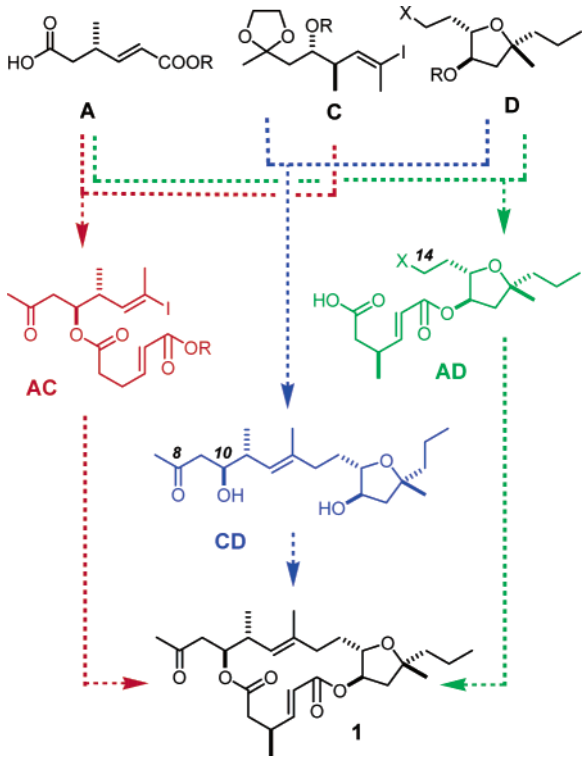
The third fragment (Scheme 6) was obtained by olefination of the known aldehyde **35** (ee = 95%)[34] under Masamune–Roush conditions,[35] providing ester (*E*)-**36** in 85% yield. Desilylation with HF·pyridine gave alcohol **37** which was converted to acid **38** by stepwise oxidation[36] that was more productive than the one-step protocol using PDC in DMF.[37]

With all required fragments in suitably protected form in hand, the stage was set for the completion of the first total synthesis of amphidinolide X (**1**). The assembly process itself, however, deserves careful consideration.

Due to the "bifunctional" nature of each building block, various scenarios for the assembly of **1** can be envisaged (Scheme 7). Among them, the sequence **AD** + **C** (green line) was ruled out because it implies rather severe selectivity issues during the conversion of the leaving group X at C.14 of the **AD** part into a suitable nucleophile as required for the envisaged cross coupling with the alkenyl iodide residing on segment **C**.[38] In contrast, the choice between the remaining two options, **AC** + **D** (red line) or **CD** + **A** (blue line), seemed less obvious.

Some exploratory studies, however, provided clear guidance. Thus, it was found that the unprotected aldol substructure extending from the keto group at C.8 to the −OH group at C.10 is fairly labile to acid as well as base, suffering from elimination even under mild conditions. This observation spoke against a late-stage manipulation of this site as required in the **CD** + **A** scenario and certainly against attempted formation of the macrocycle by lactonization at the fragile aldolic −OH. Since the sequence **AC** + **D** projects formation of the crucial ester linkage at C.10 in an early stage, it seemed less risky overall. Furthermore, this particular assembly process has the subtle advantage of introducing the most valuable building block, **D**, last in the linear sequence and might therefore engender optimal productivity. As a consequence, our attempts to complete the first total synthesis of amphidinolide X gravitated toward this option, which could in fact be successfully reduced to practice as shown in Scheme 8.

Scheme 7. Possible Scenarios for the End Game

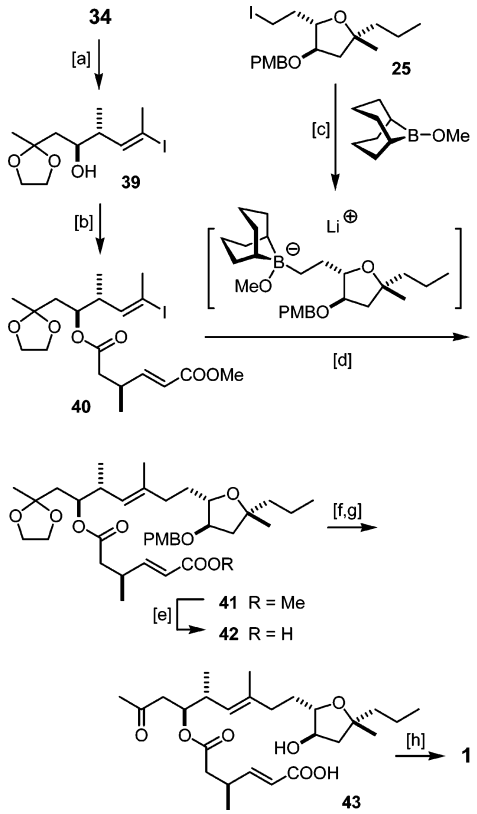


To this end, the PMB-ether in **34** was cleaved with DDQ,[39] and the resulting alcohol **39** was subjected to a Yamaguchi esterification[40,41] with acid **38**, delivering the desired product **40** in excellent yield. The crucial coupling of this elaborate alkenyl iodide with the tetrahydrofuran segment **25** was achieved by recourse to the "9-MeO-9-BBN variant" of the Suzuki reaction previously developed in this laboratory (Scheme 9).[42] Rather than generating the required borate nucleophile by complexation of an organoborane precursor with base (e.g., MeOM),[43] the reactive species is formed from 9-MeO-9-BBN on treatment with a suitable organolithium- or other polar organometallic reagent RM,[42] which can also be generated in situ, e.g., by metal–halogen exchange.[44]

Application of this method to the present case resulted in efficient alkyl–alkenyl cross coupling[45] of the highly function-

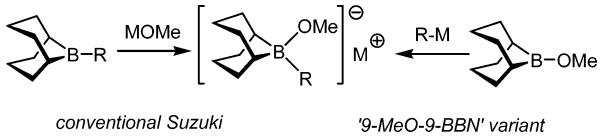
(31) (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (b) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115
(32) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11368.
(33) Thereby it was essential to dilute the mixture with CH_2Cl_2 prior to the addition of iodine at low temperature (−15°C) to avoid freezing of the reaction medium. Moreover, it is important to treat the mixture with aq $Na_2S_2O_3$ once the color of iodine starts to persist in order to ensure high and reproducible yields, cf. Supporting Information.
(34) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410.
(35) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(36) (a) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.
(37) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
(38) Such a transformation could be achieved via zinc insertion into the C–X bond in the **AD** fragment followed by Negishi cross coupling. Exploratory studies, however, invariably resulted in low yields and were abandoned in favor of the Suzuki route.
(39) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(40) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.
(41) (a) Review: Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911. (b) For a recent application from this laboratory, see: Mlynarski, J.; Ruiz-Caro, J.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 2214.
(42) (a) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (b) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107. (d) Fürstner, A.; Seidel, G. *Synlett* **1998**, 161. (e) The method was also independently reported by: Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401.
(43) For general reviews on the Suzuki reaction see, inter alia: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(44) (a) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (b) Mickel, S. J. et al. *Org. Process Res. Dev.* **2004**, *8*, 113–121.(c) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720.
(45) Reviews on the alkyl-Suzuki reaction and applications to total synthesis: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (c) For early applications of the alkyl-Suzuki reaction from this laboratory, see: Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (d) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071. (e) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332. (f) Fürstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krüger, C.; Mynott, R. *Tetrahedron* **1995**, *51*, 8875.

Scheme 8 [a]



[a] Reagents and conditions: [a] DDQ, CH_2Cl_2, pH 7 buffer, 89%; [b] acid **38**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; then **39**, DMAP, 96%; [c] *t*-BuLi, Et_2O/THF, then 9-MeO−9-BBN; [d] (dppf)$PdCl_2$, Ph_3As, K_3PO_4, aq DMF, 74%; [e] LiI, pyridine, 125 °C; [f] aq HOAc, 53% (over both steps); [g] DDQ, CH_2Cl_2, pH 7 buffer, 84%; [h] 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, toluene, 62%.

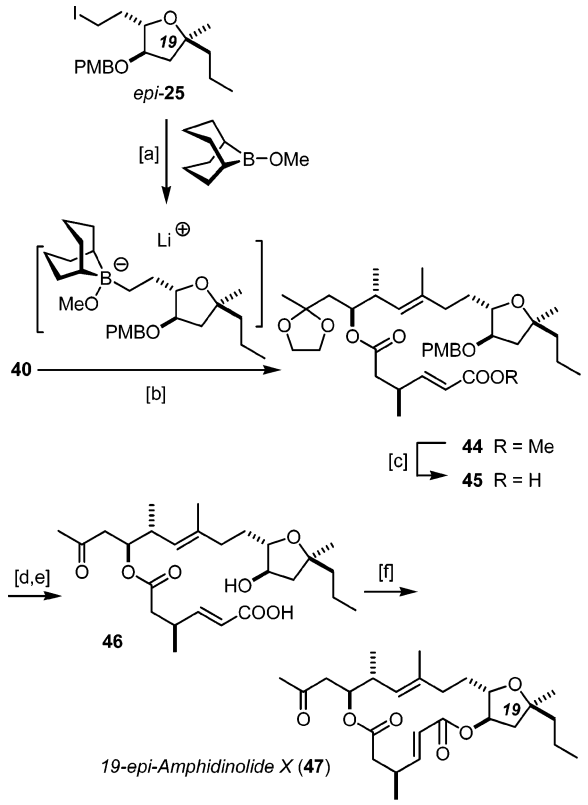
Scheme 9. Preparation of the Borate Donor Necessary for Suzuki Cross-Coupling Reactions Either via the Conventional Route or by the "9-MeO-9-BBN" Variant[42]



alized segments **40** and **25**. Specifically, alkyl iodide **25** was treated with *t*-BuLi at −78°C followed by addition of excess 9-MeO-9-BBN to give the corresponding borate which transfers its functionalized alkyl group to the organopalladium species derived from alkenyl iodide **40** and (dppf)$PdCl_2$/$AsPh_3$, thus delivering product **41** in 74% isolated yield. Selective cleavage of the methyl ester in diester **41** with LiI in pyridine[46] followed by successive removal of the remaining dioxolane moiety and the PMB ether gave *seco*-acid **43**. Not unexpectedly, the acetal cleavage in **42** was somewhat delicate due to the lability of the released aldol subunit (see above). The use of dilute AcOH, however, furnished the desired product **43** in 53% over two steps. The final macrocyclization of *seco*-acid **43** under Yamaguchi conditions[40,41] gave amphidinolide X **1** in 62% yield, thus completing the first total synthesis of this unusual macrodiolide.[11,47] The analytical and spectroscopic data of the synthetic samples are in excellent agreement with those reported for the natural product.[4]

(46) Hunter, T. J.; O'Doherty, G. A. *Org. Lett*. **2002**, *4*, 4447.

Scheme 10. Preparation of 19-*epi*-Amphidinolide X[a]



[a] Reagents and conditions: [a] *t*-BuLi, Et_2O/THF, then 9-MeO-9-BBN; [b] (dppf)$PdCl_2$, Ph_3As, K_3PO_4, aq DMF, 43%; [c] LiI, pyridine, 125 °C; [d] aq HOAc, 57% (over both steps); [e] DDQ, CH_2Cl_2, pH 7 buffer; [f] 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, toluene, 39% over both steps.

19-*epi*-Amphidinolide X. As outlined above, our total synthesis of amphidinolide X is based on the assembly of three building blocks of similar size. With a reliable protocol for the coupling of these subunits at hand, a first attempt to exploit the flexibility inherent to this synthesis blueprint was made as a prelude for more detailed future investigations of the structure/activity relationships of this particular target.

The epimeric tetrahydrofuran *epi*-**25** derived from the iron-catalyzed allenol formation/cyclization strategy shown in Scheme 4 was chosen for this exploratory study (Scheme 10). Metal−halogen exchange with excess *t*-BuLi and interception of the resulting organolithium species with 9-MeO-9-BBN[42] delivered the required borate which underwent productive alkyl-Suzuki cross coupling[45] with iodide **40**. The subsequent elaboration of the resulting product **44** could also be performed in close analogy to the amphidinolide X case and proceeded in similar yields, thus affording 19-*epi*-amphidinolide X **47** as a first example of a fully synthetic analogue of the natural lead. Further investigations on the synthesis and biological evaluation of congeners and isomers of this cytotoxic macrolide antibiotic are in progress and will be disclosed in due course.

Amphidinolide Y: Preparation of the Building Blocks. The reliability and excellent chemoselectivity profile of the "9-

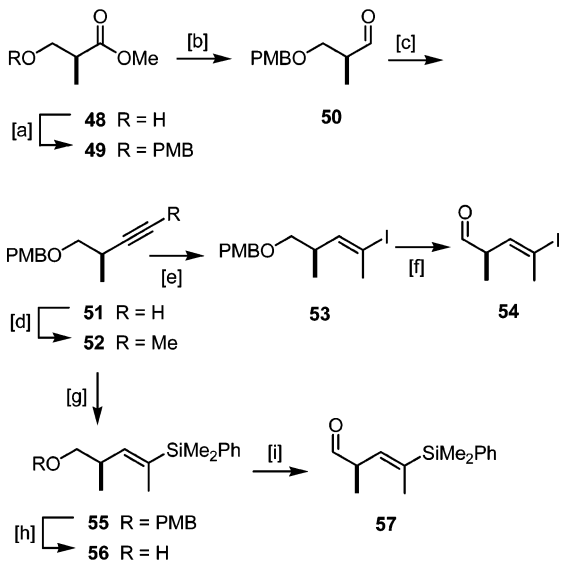
(47) For other macrodiolide syntheses from this laboratory see: (a) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc*. **2003**, *125*, 13132. (b) Fürstner, A.; Ruiz-Caro, J.; Prinz, H.; Waldmann, H. *J. Org. Chem*. **2004**, *69*, 459. (c) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett*. **2001**, *3*, 449. (d) Fürstner, A.; Mlynarski, J.; Albert, M. *J. Am. Chem. Soc*. **2002**, *124*, 10274. (e) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M. *J. Am. Chem. Soc*. **2002**, *124*, 1168.

MeO-9-BBN variant" of the alkyl-Suzuki reaction experienced in the amphidinolide X and 19-*epi*-amphidinolide X series recommend the use of this transformation as a late-stage maneuver for the projected synthesis of amphidinolide Y (**2**) as well. As already mentioned, the tetrahydrofuran embedded into **2** is identical to that of **1**, which makes any adaptation of the corresponding synthon **D** unnecessary. The required coupling partner **E**, however, is entirely different because of the macrolidic rather than macrodiolidic nature of the target. For the sake of convergence, it was desirable to generate **E** bearing the complementary vinyl iodide motif from two subunits, **G** and **H**, of similar size and complexity (Scheme 1). Although various transformations can be envisaged for such a purpose, an aldol strategy seemed highly appropriate, not least because it allows for control over the stereochemistry of the emerging chiral center, and because the carbonyl group of the resulting product **F** also provides a handle for the installation of the tertiary alcohol group residing at C.7 of the chain. We therefore set out to prepare surrogates of synthons **G** and **H** in adequately functionalized form.

Our synthesis started from Roche ester **48**, which was protected as O-PMB ether **49**. Subsequent reduction with Dibal-H delivered aldehyde **50** which was homologated in excellent overall yield to alkyne **51** using the Corey−Fuchs protocol[48] followed by C-methylation with *n*-BuLi/MeI.[49] In a first run, alkyne **52** was converted into alkenyl iodide **53** by hydrozirconation/iodination. Unfortunately, however, **53** and aldehyde **54** derived thereof turned out to be difficult to work with, as they were found to be highly sensitive as well as rather volatile. Therefore a more appropriate substitute was searched for and found in the corresponding vinylsilane **57**, which was accessible on a multigram scale, by regioselective silylcupration[50] of alkyne **52** followed by cleavage of the PMB group in **55** with DDQ[39] and oxidation of the resulting alcohol **56** to aldehyde **57** with Dess−Martin periodinane.[51] Although **57** is also somewhat sensitive, it can be stored in the freezer for extended periods of time if care is taken to avoid any residual traces of acid or base (Scheme 11).

The preparation of the ketone building block commenced with the enantiomeric Roche ester *ent*-**48**, which was converted to the known O-TBDPS-protected aldehyde **59**[52] by routine manipulations. Reaction of the latter with phosphonate **60**[53] readily afforded the α-acetoxy-enoate **61** which could be hydrolyzed to give α-ketoester **62** in high yield, provided that the cleavage of the acetate group was performed at low temperature; more conventional conditions for this saponification led to significantly poorer results. Although the catalytic hydrogenation of α-ketoesters is less common than that of their *β*-ketoester analogues,[54,55] we were pleased by the outcome of this transformation: thus, reduction of **62** in the presence of $[((S)\text{-binap})_2Ru_2Cl_5]^-\ [Et_2NH_2]^+$ (**67**)[56] as the catalyst in MeOH under H_2 atmosphere (20 bar) worked exquisitely well, delivering the desired alcohol **63** in 92% isolated yield with a diastereomeric ratio of ≥23:1 (NMR) (Scheme 12).[57] Mosher analysis provided an independent and unambiguous proof for the configuration assigned to the newly created stereocenter (cf. Supporting Information). This excellent selectivity was decisive for the further course of the total synthesis because the secondary alcohol at C.6 set by asymmetric hydrogenation was planned to serve as a crucial relay, transferring stereochemical information to the chiral centers to be generated at C.7 (via chelate-controlled addition) as well as C.9 (via diastereoselective aldolization), before it will ultimately be oxidized to the ketone group residing on the aliphatic chain of amphidinolide Y (Scheme 13). This concept also dictated the choice of the protecting group for this secondary alcohol, which must impart donor properties yet withstand basic conditions and organometallic reagents. A PMB-ether seemed optimal, which was installed in the usual fashion prior to conversion of the ester moiety in the resulting product **64** to methyl ketone **66** via the Weinreb amide intermediate **65**.

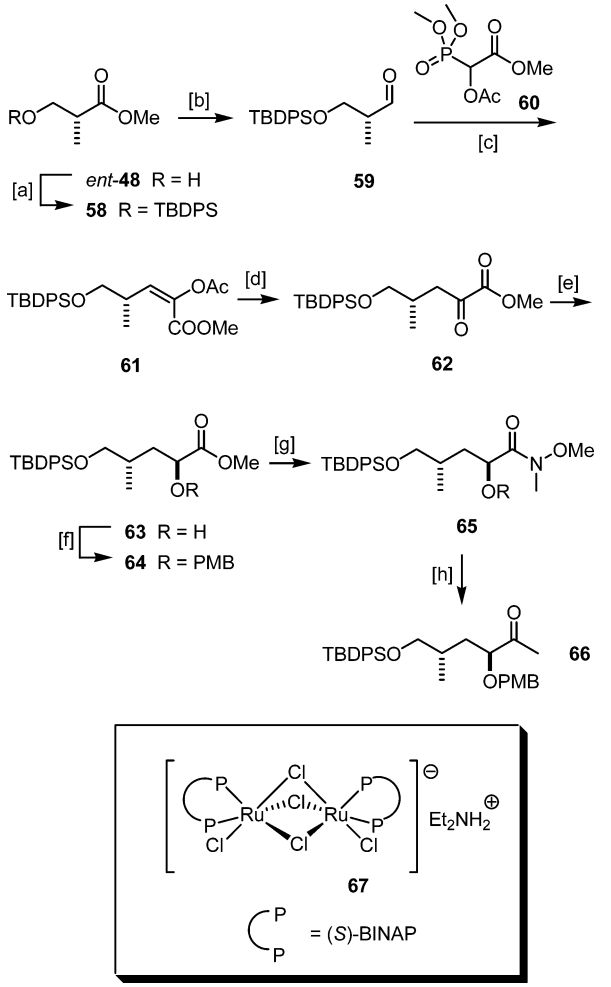
Scheme 11 [a]



[a] Reagents and conditions: [a] PMBOC(=NH)CCl_3, PPTS cat., CH_2Cl_2, 84%; [b] Dibal-H, CH_2Cl_2, −78 °C, 78%; [c] CBr_4, PPh_3, CH_2Cl_2, −78 °C, 90%; [d] *n*-BuLi, MeI, THF, −78 °C → rt, 91%; [e] $Cp_2Zr(H)Cl$, THF, I_2, 66%; [f] (i) DDQ, CH_2Cl_2/pH 7 buffer (10/1), 0 °C → rt; (ii) Dess−Martin periodinane, CH_2Cl_2, 0°C, cf. text; [g] $(Me_2PhSi)_2Cu(CN)Li_2$, THF, −78 °C → 0 °C, 92%; [h] DDQ, CH_2Cl_2/pH 7 buffer (10/1), then $NaBH_4$, MeOH, 0 °C → rt, 92%; [i] Dess−Martin periodinane, CH_2Cl_2, 0 °C, 92%.

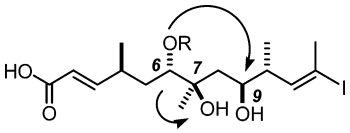
(48) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(49) The enantiomer of **52** is known, see: Organ, M. G.; Wang, J. *J. Org. Chem.* **2003**, *68*, 5568.
(50) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
(51) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549. (c) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.
(52) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(53) (a) Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663. (b) Schmidt, U.; Langner, J.; Kirschbaum, B.; Braun, C. *Synthesis* **1994**, 1138.
(54) Reviews: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1; pp 199−246. (c) Noyori, R. *Angew. Chem,. Int. Ed.* **2002**, *41*, 2008. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
(55) For precedence on enantioselective hydrogenations of α-ketoesters with Ru-based catalysts, see the following for leading references and literature cited therein: (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (b) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064. (c) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U. S.A.* **2004**, *101*, 5799. (d) Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 8340. (e) Transfer hydrogenation: Sterk, D.; Stephan, M. S.; Mohar, B. *Tetrahedron Lett.* **2004**, *45*, 535.
(56) The catalyst was prepared as described in: King, S. A.; Keller, J. *Org. Synth.* **2005**, *81*, 178.
(57) For precedence on the diastereoselective hydrogenation of a chiral α-ketoester see: Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133.

Scheme 12 [a]



[a] Reagents and conditions: [a] TBDPSCl, imidazole, DMAP cat., CH_2Cl_2, 90%; [b] Dibal-H, hexanes, −78 °C, 79%; [c] phosphonate **60**, LiHMDS, THF, −78 °C → rt, 91% (*E*:*Z* = 6:1); [d] NaOMe, MeOH, −40 °C, 86%; [e] catalyst **67**, HCl cat., H_2 (20 bar), MeOH, 92% (dr ≥ 23:1); [f] PMBOC(=NH)CCl_3, $BF_3{\cdot}Et_2O$ cat., CH_2Cl_2/cyclohexane (1:2), 0 °C, 84%; [g] (i) LiOH, MeOH/THF/H_2O (4:1:1); (ii) HN(OMe)Me hydrochloride, DCC, EtN(^{i}Pr)$_2$, DMAP cat., CH_2Cl_2, 0 °C → rt, 86% (over both steps); [h] MeMgBr, THF, 0 °C, 91%.

Scheme 13. Envisaged Stereochemical Relay



Amphidinolide Y: Elaboration of the Western Domain. With the two required components in hand, the crucial fragment coupling by an aldol reaction was investigated. Encouraged by a report by Evans et al. describing high levels of 1,4-*anti*-selectivity in the addition of boron enolates derived from *methyl* ketones bearing alkoxy substituents at the nonreacting α-position,[58−60] compound **66** was treated with Cy_2BCl, EtN(^{i}Pr)$_2$ and aldehyde **57** (Scheme 14, Table 1). Although good yields could be obtained when CH_2Cl_2 was chosen as the solvent (entry 3), the observed diastereoselectivity was low. Attempts to improve on this outcome by recourse to chiral IPC enolates[61] was only partly successful, as the improved selectivity in the matched case was overcompensated by low conversions when (+)-DIPCl was used as the reagent or by significant decomposition in the case of the more reactive (+)-DIPOTf (entries 4−6). A satisfactory solution, however, was found by changing the size of the spectator alkyl groups on boron.[62] Thus, replacement of Cy_2BCl by (n-Bu)$_2$BOTf or, preferably, Et_2BOTf resulted in improved levels of stereochemical communication. In the latter case, an isolated yield of 84% and a dr ≥ 4:1 in favor of the 1,4-*anti*-isomer could be reproducibly achieved on a >2 g scale, provided that the reaction was performed in toluene at −90°C (entry 10). Although the individual isomers were not separable at this stage, a Mosher analysis unequivocally indicated the required (*S*)-configuration of the newly created secondary

Scheme 14. Fragment Coupling by Aldol Reaction; for the Conditions and Results, See Table 1

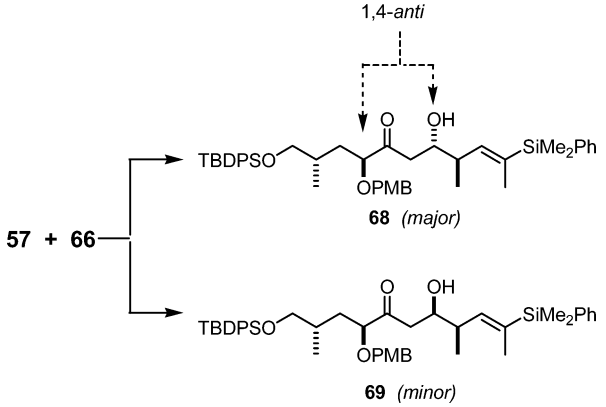


Table 1. Aldol Reaction According to Scheme 14

entry	reagents	solvent	*T* (C°)	dr	yield (%)
1	Cy_2BCl, EtN(iPr)$_2$	Et_2O	−78	2.0:1	46
2		toluene	−78	2.4:1	41
3		CH_2Cl_2	−78	2.0:1	71
4	(−)-DIPCl, EtN(iPr)$_2$	CH_2Cl_2	−78	1:3.0	18[a]
5	(+)-DIPCl, EtN(iPr)$_2$	CH_2Cl_2	−78	4.3:1	41[a]
6	(+)-DIPOTf, EtN(iPr)$_2$	toluene	−78	b	44
7	Bu_2BOTf, EtN(iPr)$_2$	toluene	−78	3.0:1	38
8	Et_2BOTf, EtN(iPr)$_2$	pentane	−110	5.5:1	32[a]
9		toluene	−78	3.3:1	69
10		toluene	−90	4.0:1	84
11	LiHMDS	THF	−78	1.5:1	75
12	TMSCl, Et_3N, LiHMDS; then $BF_3.Et_2O$	THF	−78	1:30[c]	65

[a] Incomplete conversion. [b] Partial decomposition makes an accurate determination of the dr difficult. [c] The crude NMR seems to indicate formation of an additional product, which was not characterized any further.

(58) (a) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc*. **1999**, *121*, 7540. To the best of our knowledge, this is the only report showing 1,4-induction by α-alkoxy substitutents in methyl ketones without any superimposed 1,5-induction and/or directing effects exerted by substituents in the aldehyde component. For further examples in which such effects might be operative in addition to 1,4-induction see: (b) Crimmins, M. T.; Katz, J. D.; McAtee, L. C.; Tabet, E. A.; Kirincich, S. J. *Org. Lett*. **2001**, *3*, 949. (c) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Aceña, J. L.; Bach, J.; Keown, L. E.; Trieselmann, T. *Org. Biomol. Chem*. **2005**, *3*, 2420.

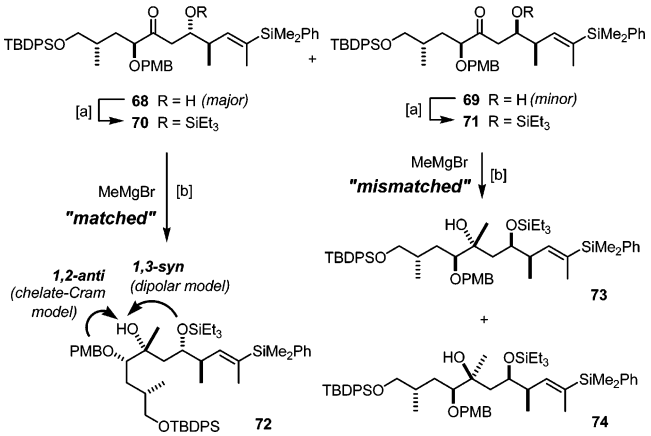
(59) For pertinent discussions on the related 1,5-induction observed in reactions of β-alkoxy substituted methyl ketone enolates with (chiral) aldehydes see the following for leading references: (a) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett*. **1995**, *36*, 3443. (b) Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc*. **2003**, *125*, 10893. (c) Paterson, I.; Collett, L. A. *Tetrahedron Lett*. **2001**, *42*, 1187. (d) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem*. **2002**, *67*, 4275 and literature cited therein.

(60) Review: Cowden, C. J.; Paterson, I. *Org. React*. **1997**, *51*, 1.

(61) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, 46, 4663. (b) Ramachandran, P. V.; Xu, W.; Brown, H. C. *Tetrahedron Lett*. **1996**, *37*, 4911.

(62) For precedence see: Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett*. **2002**, *4*, 481.

Scheme 15 [a]



[a] Reagents and condtions: [a] TESCl, imidazole, CH_2Cl_2, 0 °C → rt, 91%; [b] MeMgBr, Et_2O, −78 °C, 96% (dr = 15:2.6:1, NMR), cf. text.

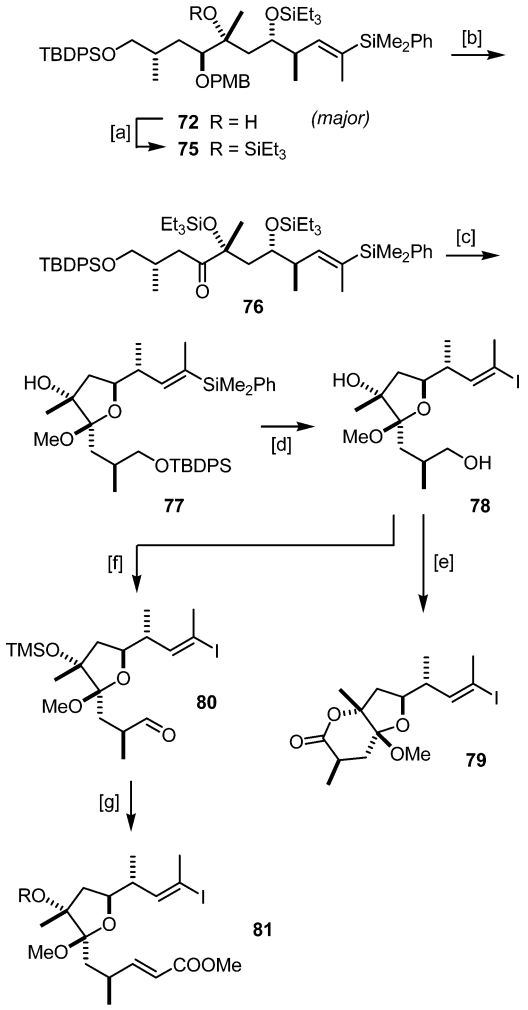
alcohol in the major product **68** (cf. Supporting Information). As expected, the use of the lithium enolate derived from **66** displayed poor selectivity (entry 11), while application of the Mukaiyama conditions afforded the 1,4-*syn* product preferentially (entry 12).

Next, the aldol products were reacted with TESCl and imidazole (Scheme 15). This particular protecting group was chosen under the premise that bulky silyl ethers at the β-position to a carbonyl group are known to be poor ligands to Lewis acidic metal cations and hence "nonchelating" substituents, exerting directing effects in carbonyl addition reactions via 1,3-dipol minimization in the transition state.[63] In contrast, −OPMB groups α to a ketone readily engage in chelation in carbonyl addition reactions of, e.g., methylmagnesium halide, strongly favoring the formation of the corresponding "chelate-Cram" products.[64] With these established patterns in mind, one may forecast a matched situation for the major product **70**, whereas the companion minor isomer, **71**, should experience opposing effects and therefore constitute a mismatched case.

In line with this analysis,[65] treatment of the inseparable 1,4-*anti*/1,4-*syn* aldol mixture with MeMgBr in Et_2O at −78°C furnished only three of the four possible tertiary alcohols in a 15/2.6/1 ratio. This outcome parallels the diastereomeric purity of the starting material (dr ≥ 4/1; 15:3.6 ≈ 4.2:1), lending credence to the notion that the major isomer **70** affords the desired chelate-Cram product **72** diastereoselectively, whereas the minor aldol **71** furnishes a mixture of both possible addition products **73** and **74** due to the mismatched influences of its substituents.

However, no attempt was made to rigorously confirm this tentative stereochemical assignment at this stage; rather, priority was given to find a practical method for the separation of the major isomer to keep the synthesis workable. After testing several conceivable options, it was found that the mixture can be processed into furanoside **77** by temporary protection of the

Scheme 16 [a]



[a] Reagents and conditions: [a] TESOTf, 2,6-lutidine, −78 °C → rt, 92%; [b] (i) DDQ, CH_2Cl_2/pH 7 buffer (1:1), 0 °C, 92%; (ii) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C → rt., 93%; [c] camphorsulfonic acid (cat.), MeOH/THF (5:1), 0 °C, 65% (α:β = 3:1); separation of the major isomer followed by reequilibration of the minor β-isomer with *p*-toluenesulfonic acid (cat.), MeOH, 86%; [d] (i) NIS, MeCN, 0 °C; (ii) TBAF, THF, 72% (over both steps); [e] Dess−Martin periodinane, pyridine, CH_2Cl_2; [f] (i) TMSCl, imidazole, CH_2Cl_2, 0 °C → rt, 94%; (ii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C → 0 °C; [g] LiHMDS, $(EtO)_2P(=O)CH_2COOMe$, THF, −78 °C → 0 °C, 76% (over both steps).

tertiary alcohol, subsequent cleavage of the PMB-group in **75** with DDQ in buffered medium, oxidation of the liberated hydroxyl group to the corresponding ketone **76**, and cyclization with formation of methyl glycoside **77** (Scheme 16). Importantly, *the major product* **77** *could be separated without difficulties at this level by routine flash chromatography* and was obtained in a satisfactory overall yield over five routine steps, starting from the aldol products.

With a pure isomer in hand, it was possible to investigate the stereochemical pattern of the product by extensive NOESY spectroscopy which clearly supported the assignments made above (cf. Supporting Information); the final proof then came by the successful completion of the total synthesis. From the strategic point of view it is worth mentioning that the "internal protection" of the ketone in form of a glycoside also seems highly advantageous, given the known lability of the α-hydroxyketone entity embedded into the amphidinolide Y frame under oxidative conditions. As will be outlined below, the final stages

(63) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(64) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
(65) For pertinent examples in the ketone (rather than much more closely investigated aldehyde series) see: (a) "chelate controlled" MeMgI addition to α-alkoxyketone: Nakamura, S.; Inagaki, J.; Sugimoto, T.; Kudo, M.; Nakajima, M.; Hashimoto, S. *Org. Lett.* **2001**, *3*, 4075. (b) "Dipole controlled" addition of MeMgBr to β-silyloxy ketones: Ukaji, Y.; Kanda, H.; Yamamoto, K.; Fujisawa, T. *Chem. Lett.* **1990**, *19*, 597.

of the synthesis confirmed the notion that the chosen "glycoside strategy" is preferable over other conceivable protecting-group regimens.[66]

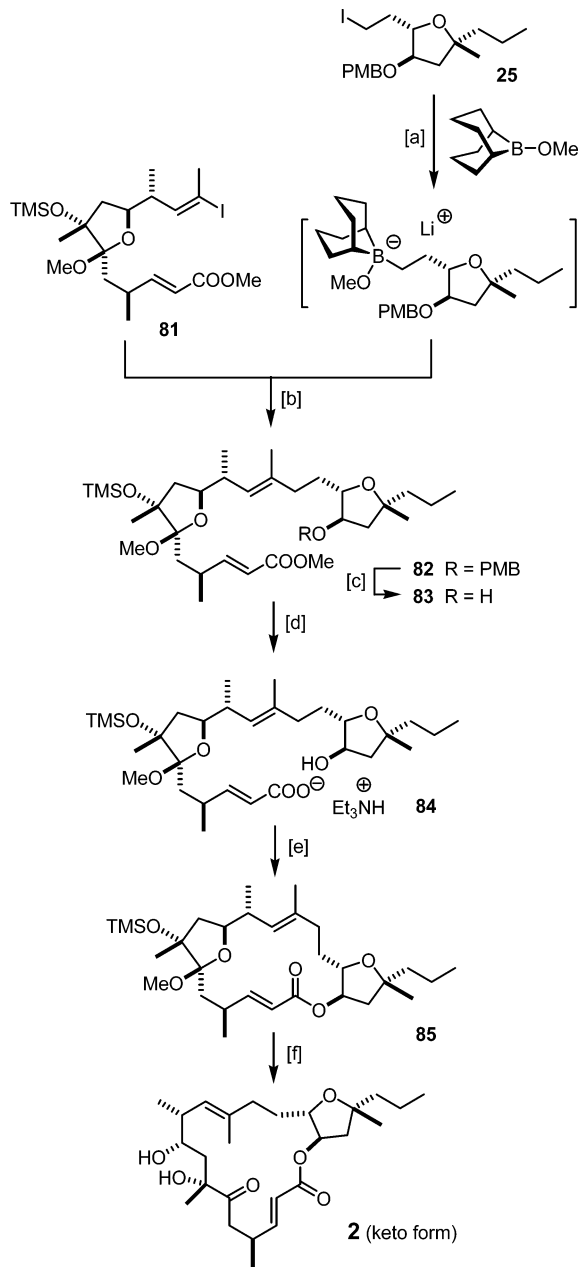
With the supply, constitution, and stereochemistry of this key synthetic intermediate being secured, the conversion of the vinylsilane into the alkenyl iodide moiety as required for the envisaged fragment coupling via the Suzuki protocol was performed on exposure of **77** to NIS in MeCN in the dark;[67] cleavage of the remaining silyl ether of the crude product then afforded diol **78** in 72% isolated yield over two steps. Unfortunately, attempted conversion of this compound into enoate **81** (R = H) by selective oxidation of the primary alcohol followed by olefination met with failure due to spontaneous hemiacetal formation at the aldehyde level[68] and further oxidation to the corresponding lactone **79**, which was of no avail for the synthesis.

This unproductive path, however, could be avoided by silylation of **78** with TMSCl and imidazole followed by oxidation of the resulting bis-silyl ether with formation of aldehyde **80**. Horner−Wadsworth−Emmons reaction then gave enoate **81** as the fully functional building block required for the ensuing end game of the total synthesis.

Amphidinolide Y: Completion of the Total Synthesis. In line with our expectations, the coupling between the highly functionalized alkenyl iodide **81** and the tetrahydrofuran segment via the "9-MeO-9-BBN variant"[42] of the alkyl-Suzuki reaction proceeded smoothly under the conditions worked out in the amphidinolide X series, affording product **82** in 79% isolated yield (Scheme 17). Although an excess of *t*-BuLi and 9-MeO-9-BBN has to be used, it is noteworthy that this reaction employs both valuable components **25** and **81** exactly in a 1:1 ratio and is therefore highly adequate as a late-stage maneuver. The subsequent removal of the PMB-group with DDQ occurred readily, but the isolated yields of the resulting alcohol **83** were somewhat variable, ranging between 51 and 75%. This outcome is deemed to reflect the sensitivity of the product toward uncontrolled over-oxidation in case of adventitious opening of the tertiary methyl glycoside locking the furanose ring; since this functional group is somewhat labile, however, the DDQ oxidation must be carried out in buffered medium to keep such uncontrolled oxidative degradations to a minimum.

This sensitivity must also be taken into consideration during the very end game. While the saponification of the methyl ester in **83** with LiOH in aqueous THF/MeOH per se poses no problem, the extractive work up is a critical phase because the medium has to be made weakly acidic to allow for the isolation of the resulting *seco*-acid. This very fragile product should be immediately transformed into the corresponding triethylammonium salt **84** to avoid self destruction and, as such, should be subjected to cyclization under modified Yamaguchi conditions[69] without delay. The resulting crude lactone **85** was finally deprotected with dilute HOAc in aqueous THF. This sequence

Scheme 17 [a]



[a] Reagents and conditions: [a] *t*-BuLi, Et_2O/THF, then 9-MeO-9-BBN; [b] (dppf)$PdCl_2$, Ph_3As, K_3PO_4, aq DMF, 79%; [c] DDQ, CH_2Cl_2/pH 7 buffer (1:1), 0 °C, 51−75%, cf. text; [d] LiOH, MeOH/THF/H_2O (4:1:1), then Et_3N; [e] 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, toluene; [f] HOAc/THF/H_2O (4:1:1), 56% (over three steps).

avoids flash chromatography of any of the labile intermediates and afforded amphidinolide Y (**2**) in well reproducible 56% over three steps as a 5:1 mixture of the keto- and the corresponding hemiacetal form. The spectra of the synthetic samples are superimposable with those of the natural product isolated from the *Amphidinium* Y-42 strain, and their analytical properties, including the $[\alpha]_D$, are also in excellent agreement with the literature data (cf. Supporting Information).[6]

With the first total synthesis of this bioactive marine natural product completed, some additional comments on the final stages of the successful route seem appropriate. As mentioned above, the methyl glycoside plays a crucial role, providing proper "internal protection" of the sensitive α-hydroxyketone

(66) For a related example see: Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc*. **2005**, *127*, 10028.
(67) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647.
(68) Note that this spontaneous cyclization provides further evidence for the *cis*-orientation of the alkyl group at the anomeric center and the tertiary alcohol group generated through chelate-Cram addition.
(69) In this modification, the slightly acidic Et_3NH^+ salts formed as byproducts in the generation of the mixed anhydride are filtered off prior to concentration of the solution and subsequent macrocyclization. This protocol is highly advisable for very acid-sensitive compounds, cf: Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc*. **2003**, *125*, 10899.

motif of the synthesis intermediates against undue oxidative degradation. It should be mentioned, however, that the adjacent TMS-ether at C.7 was also indispensable. Although this group had originally been introduced only because no direct way for the elaboration of the primary alcohol in **78** to the required enoate of type **81** (R = H) could be found, we noticed later that this silyl ether is more than just a quiet bystander. Specifically, samples of **84** devoid of the protecting groups were *not* amenable to regular Yamaguchi lactonization;[70] even though the tertiary −OH at C.7 is sterically encumbered, it interferes by 1,4-additon to the α,β-unsaturated acid segment of the starting material, its activated mixed anhydride form, and/or the resulting lactone under the basic reaction conditions, thus leading to a dreadful mixture of which the desired product is only a minor component. Hence, the silylation of **78**, originally regarded as a detour, unintentionally turned out to be key to success.

Conclusions

Concise, modular, and efficient total syntheses of the biogenetically related marine natural product amphidinolide X (**1**), and its ring-expanded congener, amphidinolide Y (**2**), have been developed which unravel many chemical characteristics of these structurally unique macrolides. The flexibility inherent to the chosen route is illustrated by the efficient preparation of 19-*epi*-amphidinolide X **47** as a first fully synthetic analogue, thus encouraging further synthesis-driven explorations of these cytotoxic agents. The robustness and excellent chemoselectivity profile recommends the chosen assembly process based upon the "9-MeO-9-BBN" variant of the Suzuki coupling for a more detailed mapping of the structure/activity relationships through "diverted total synthesis". Finally, these investigations constitute the first application of the iron-catalyzed formation of allenol derivatives[13,14] to natural product chemistry. This benign procedure not only complements existing methodologies in stereochemical terms and allows for substantial structural variations if desirable, but also provides a convenient solution for the problem posed by the delicate tetrasubstituted chiral ether bridge embedded into **1** and **2** via a straightforward relay strategy. We are currently in the stage of further optimizing the underlying synthesis blueprints, trying to expand our studies in the field beyond the total synthesis stage, and intending to cover other members of the amphidinolide family as well. Progress along these lines and on the accompanying biochemical investigations will be reported in due course.

(70) Unprotected samples of the crude *seco*-acid were obtained by lowering the pH during the extractive work to <5.

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Supporting Information Available: Full experimental details, complete ref 44b, spectroscopic and analytical data of all new compounds, and copies of the NMR spectra of key synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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