Total Syntheses of Amphidinolide T1, T3, T4, and T5

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Abstract: A concise, flexible, and high yielding entry into the family of amphidinolide T macrolides, a series of cytotoxic natural products of marine origin, has been developed. All individual members, except amphidinolide T3 (**3**), derive from compound **39** as a common synthetic intermediate which is formed from three building blocks of similar size and complexity. The fragment coupling steps involve a highly diastereoselective $SnCl_4$ mediated reaction of the furanosyl sulfone derivative **11** with the silyl enol ether **18** and a palladium-catalyzed Negishi type coupling reaction between the polyfunctional organozinc reagent derived from iodide **32a** and the enantiopure acid chloride **24b**. The 19-membered macrocyclic ring is then formed by a high yielding ring closing metathesis (RCM) reaction of diene **33** catalyzed by the "second generation" ruthenium carbene complex **34**. The efficiency of the RCM transformation stems, to a large extent, from the conformational bias introduced by the *syn−syn*-configured stereotriad at C12−C14 of the substrate which constitutes a key design element of the synthesis plan. The use of Nysted's reagent **38** in combination with $TiCl_4$ was required for the olefination of the sterically hindered ketone group in **36**, whereas more conventional alkene formations were unsuccessful for this elaboration. Finally, it is shown that the inversion of a single and seemingly remote stereocenter (C12) in one of the building blocks not only affects the efficiency and stereochemical outcome of the RCM step but also exerts a significant influence on the course of the acyl-Negishi reaction, allowing a radical manifold to compete with productive cross coupling.

Introduction

The amphidinolides are a rapidly growing family of macrolides produced by marine dinoflagellates of the genus *Amphidinium* which live in symbiosis with the Okinawan acoel flatworm *Amphiscolops* sp.[1] Though structurally quite diverse, all members are distinguished by a pronounced cytotoxicity against various cancer cell lines, with some of them reaching potencies comparable to those of the most cytotoxic compounds known to date.[2] In contrast to macrolide antibiotics derived from terrestrial microorganisms, however, the majority of amphidinolides features an *odd*-numbered macrolactone ring which is biosynthesized by a complex, nonsuccessive mixed polyketide pathway.[3]

The five members belonging to the amphidinolide T subgroup feature these characteristics.[4] These extremely scarce secondary metabolites[5] differ only in the oxygenation pattern and stereo-chemistry of the C12−C14 region displayed on a uniform 19-membered macrolide core. Amphidinolide T2 is the only exception as it incorporates an additional $CH_2−OH$ group in the alkyl side chain. Structures were elucidated by careful NMR investigations and chemical degradation studies and subsequently confirmed by the X-ray analysis of compound **1** as a prototype member of this series. Because of the significant cytotoxicity against human epidermoid carcinoma KB and murine lymphoma L1210 cell lines[4] and unusual structural characteristics, these marine natural products constitute highly relevant target structures for total synthesis. Outlined below is a full account of our work which led to amphidinolide T1, T3, T4, and T5 by a highly convergent and flexible approach.[6−8]

Results and Discussion

Strategic Considerations and Retrosynthetic Analysis. Our retrosynthetic analysis was guided by the perception that all

(1) Reviews: (a) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543−575. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131−149. (c) Kobayashi, J.; Ishibashi, M. In *Comprehensive Natural Products Chemistry*; Mori, K., Ed.; Elsevier: New York, 1999; Vol. 8, pp 415−649.

(2) Notably, 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*, 117−131. (b) For representative studies, see: Kobayashi, J.; Takahashi, M.; Ishibashi, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1639−1640. (c) Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 7827−7832. (d) Sato, M.; Shimbo, K.; Tsuda, M.; Kobayashi, J. *Tetrahedron Lett.* **2000**, *41*, 503−506.

(4) (a) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134−142. See also: (b) Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 1349−1352. (c) Kubota, T.; Endo, T.; Tsuda, M.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 6175−6179.

(5) They only make up for 0.0001−0.005% of the algae's wet weight.

(6) For a preliminary communication on the synthesis of amphidinolide T4, see: Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *Angew. Chem.* **2002**, *114*, 4958−4960; *Angew. Chem., Int. Ed.* **2002**, *41*, 4763−4766.

(7) Shortly after our preliminary communication (ref 6) had been published, a total synthesis of amphidinolide T1 was communicated following a similar retrosynthetic logic; cf. Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374−2375.

(8) For total syntheses of other amphidinolides, see: (a) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198−11199. (b) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945−948. (c) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765−766. (d) Lam, H. W.; Pattenden, G. *Angew. Chem.* **2002**, *114*, 526−529; *Angew. Chem., Int. Ed.* **2002**, *41*, 508−511. (e) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 3387−3390. (f) Maleczka, R. E.; Terrell, L. R.; Geng, F.; Ward, J. S. *Org. Lett.* **2002**, *4*, 2841−2844. (g) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420−12421.

Amphidinolide T1 (**1**)

Amphidinolide T2 (**2**)

Amphidinolide T3 (**3**)

Amphidinolide T4 (**4**)

Amphidinolide T5 (**5**)
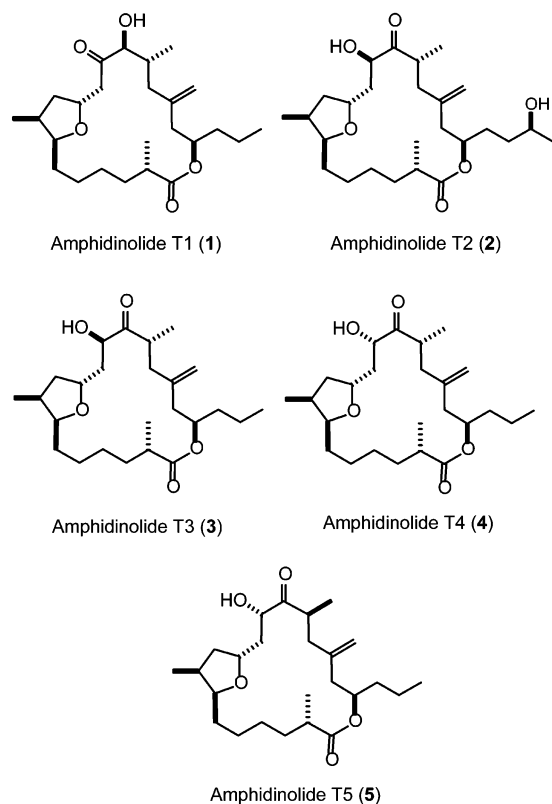
members of this family (except T2) are accessible from a common advanced intermediate **A** by simple permutations of the final deprotection/oxidation steps, followed by stereochemical adjustments where necessary (Scheme 1). This strategy relies on a judicious choice of orthogonal protecting groups R^1 and R^2 for the vicinal hydroxyl groups of the key intermediate.

For the sake of convergency, compound **A** itself should be assembled from the building blocks **C**–**E** of similar size and complexity, using a ring closing metathesis (RCM) reaction for the formation of the macrocyclic scaffold.[9] The 19-membered lactone ring of amphidinolide T1 (**1**) is known to be very compact (as evident from transannular interactions between the C3–C5 and the C14–C25 domains observed from NOESY spectra in solution as well as from X-ray diffraction studies) and features a methyl branch (C24) that is oriented in toward the macrocycle.[4c] Thus, it seems advisable to preorganize the substrate **B** in a cyclization friendly conformation to ensure high efficiency in this maneuver. A *syn–syn* stereotriad at C12–C14 should be able to shape **B** in a proper way and might therefore be preferred over other possible stereochemical alignments in this part of the molecule.[10,11] Under this premise, we envisaged that amphidinolide T3 (**3**) might be more accessible by inversion of the hydroxy group at C12 rather than by cyclization of a precursor with the correct configuration at that center. Moreover, one has to take into account that the efficiency of macrocyclizations by RCM is strongly affected by heteroelements in proximity to the reacting alkenes which can attenuate the reactivity of the emerging metal carbene

(9) Reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (d) Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1–36. (e) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037–2056. (f) Fürstner, A. *Top. Catal.* **1997**, *4*, 285–299.

Scheme 1
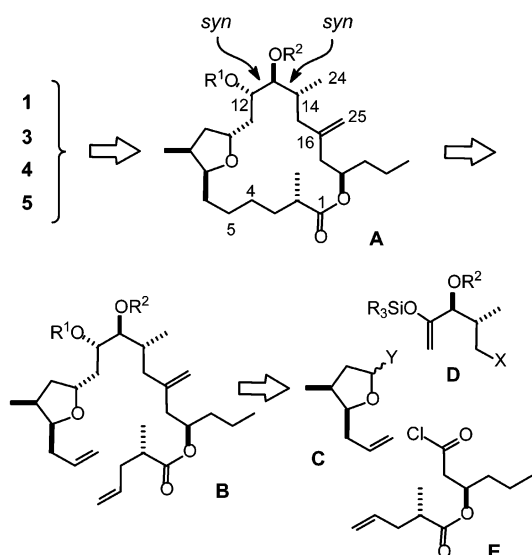
species by formation of chelate complexes.[12,13] From that perspective, the C4–C5 bond appeared to be the best compromise as the site for the retrosynthetic disconnection, leading back to the precursor **B** which we sought to assemble by a diastereoselective Lewis acid mediated alkylation of a silyl enol ether **D** with an oxocarbenium cation derived from lactol **C**, and a palladium catalyzed acylation of an organometallic reagent with an enantiomerically pure acid chloride **E**.

Preparation of the Building Blocks. The tetrahydrofuran derivative **11** as a synthetic equivalent of synthon **C** was derived from commercial hydroxyester **6** which was tosylated prior to reduction with Dibal-H. Reaction of the resulting aldehyde with $(-)$-Ipc$_2$B-allyl[14] at low temperature afforded alcohol **8** in diastereomerically pure form on a multigram scale. While the tosylate is sufficiently stable and serves as a protecting group for the primary alcohol during the hydride reduction and the allylation steps, it can be directly used as an appropriate leaving group in the subsequent reaction with KCN. The resulting nitrile **9** was reduced with Dibal-H to afford hemiacetal **10** after acidic workup, which was converted into sulfone **11** upon treatment with an excess of PhSO$_2$H in the presence of CaCl$_2$ as the dehydrating agent (Scheme 2).[15] The 2,5-trans orientation of the allyl and the PhSO$_2$ group on the tetrahydrofuran ring were confirmed by the X-ray structure analysis of this compound (Figure 1).

The required coupling partner (synthon **D**) was obtained from *N*-propionyl oxazolidinone **12**[17] by a sequence of high yielding

(10) This expectation is based on molecular modeling studies, the careful inspection of Dreiding models, as well as on an analysis of the dihedral angles of amphidinolide T1 in the solid state; cf. ref 4c. Although we have not performed a full analysis of the entire conformational space of various derivatives differing in their individual substitution pattern, the models suggest that the conformational bias should be enhanced by increasing the steric demand of the protecting groups R^1 and R^2.

(11) For reviews on the control of the conformational space populated by acyclic compounds, see: (a) Hoffmann, R. W. *Angew. Chem.* **2000**, *112*, 2134–2150; *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070. (b) Göttlich, R.; Kahrs, B. C.; Krüger, J.; Hoffmann, R. W. *Chem. Commun.* **1997**, 247–252.

(12) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.

(13) Fürstner, A.; Thiel, O. R.; Lehmann, C. W. *Organometallics* **2002**, *21*, 331–335.

(14) (a) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614–6617. (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093.

(15) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293–4308.

Scheme 2 [a]
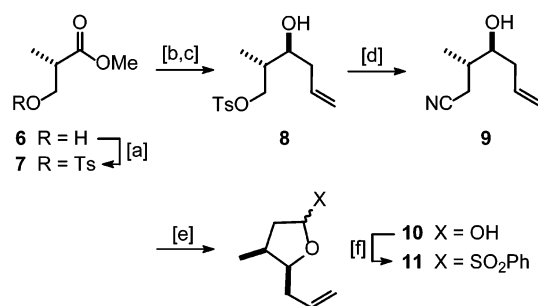
[a] Synthesis of segment **C**: [a] TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 94%; [b] Dibal-H, toluene, −95 °C; [c] (−)-Ipc$_2$B-allyl, Et$_2$O, −100 °C, 70% (over both steps); [d] KCN, DMSO, 99%; [e] Dibal-H, CH$_2$Cl$_2$, −78 °C, 91%; [f] PhSO$_2$H, CaCl$_2$, CH$_2$Cl$_2$, 0 °C, 87%.
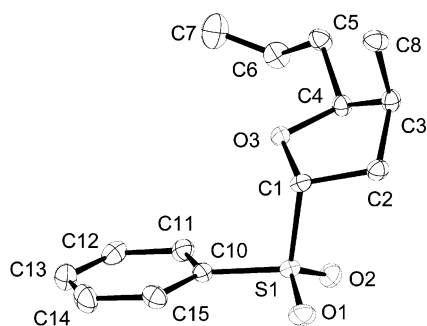

Figure 1. Molecular crystal structure of compound **11**. Anisotropic displacement parameters are drawn at the 50% probability level.[16]

steps. Specifically, an aldol reaction of the (*Z*)-boron enolate of **12** with methacrolein provided *syn*-aldol **13**[18] on a multi-gram scale for subsequent O-protection by an MOM group prior to reduction with LiBH$_4$. Primary alcohol **15** was converted to the TBS ether **16** which was ozonized to provide methyl ketone **17** in excellent overall yield (Scheme 3).[19] Treatment with TBSOTf and Et$_3$N delivered silyl enol ether **18** as the nucleophilic reaction partner for the envisaged coupling reaction. This compound can be conveniently purified by flash chromatography without noticeable decomposition, whereas the corresponding Me$_3$Si- and Et$_3$Si-enol ethers were too labile for practical use.

(16) Crystal data for compound **11**: C$_{14}$H$_{18}$O$_3$S, $M = 266.34$ g mol^{-1}, colorless, crystal dimensions $0.31 \times 0.28 \times 0.08$ mm^3, orthorhombic $P2_12_12_1$ (no. 19), at 100 K, $a = 8.6145(2)$ Å, $b = 8.85250(10)$ Å, $c = 18.0214(2)$ Å, $U = 1374.31(4)$ Å^3, $Z = 4$, $\rho = 1.287$ mg m^{-3}, $\mu = 0.233$ mm^{-1}, $\lambda = 0.710$ 73 Å. X-ray diffraction data were collected using a Nonius Kappa CCD diffractometer employing CCD scans to cover reciprocal space up to 27.50° with 98.0% completeness; integration of raw data yielded a total of 5201 reflections, merged into 2996 unique reflections with $R_{int} = 0.0233$ after applying Lorentz, polarization, and absorption correction. The structure was solved by direct method using SHELXS-97 (Sheldrick, 1997), and atomic positions and displacement parameters were refined using full matrix least-squares based on F^2 using SHELXL-97 (Sheldrick, 1997). Refinement of 163 parameters using all reflections converged at R = 0.025, wR = 0.076, highest residual electron density peak 0.3 Å^3. Complete lists of atom coordinates and anisotropic displacement parameters as well as tables of bond lengths and bond angles are available as Supporting Information. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre and can be obtained free of charge by applying to the following: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, United Kingdom, quoting the reference no. CCDC-213618.
(17) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83−91.
(18) For leading references on Evans-aldol reactions with methacrolein, see: (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151−7157. (b) Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454−455. (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747−5750. (d) Smith, A. B.; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777−10778.
(19) For a similar sequence, see: Makino, K.; Kimura, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9073−9076.

Scheme 3 [a]
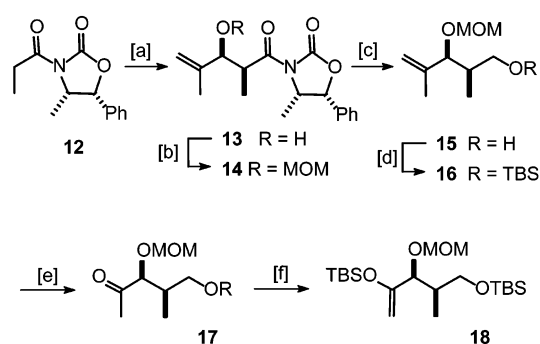
[a] Synthesis of segment **D**: [a] (i) Bu$_2$BOTf, Et$_3$N; (ii) methacrolein, 90%; [b] MOMCl, (^{i}Pr)$_2$NEt, CH$_2$Cl$_2$, 93%; [c] LiBH$_4$, Et$_2$O, 92%; [d] TBSCl, imidazole, DMF, 90%; [e] O$_3$, then PPh$_3$, CH$_2$Cl$_2$, 86%; [f] TBSOTf, Et$_3$N, Et$_2$O, 0 °C → rt, 91%.

Scheme 4 [a]
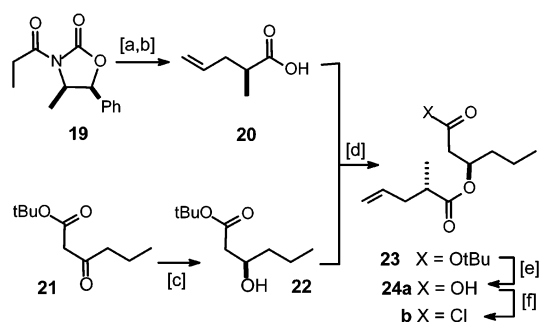
[a] Synthesis of segment **E**: [a] NaHMDS, THF, −78 °C, then allyl bromide, 60%; [b] LiOH, H$_2$O$_2$, THF/H$_2$O, 93%; [c] [((*R*)-Binap)-RuCl$_2$]$_2$(NEt$_3$) catalyst, H$_2$ (10 atm), MeOH, 95 °C, 84%; [d] EDCI, DMAP, CH$_2$Cl$_2$, 93%; [e] F$_3$CCOOH, Et$_3$SiH, CH$_2$Cl$_2$, quantitative; [f] (COCl)$_2$, CH$_2$Cl$_2$/DMF catalyst, quantitative.
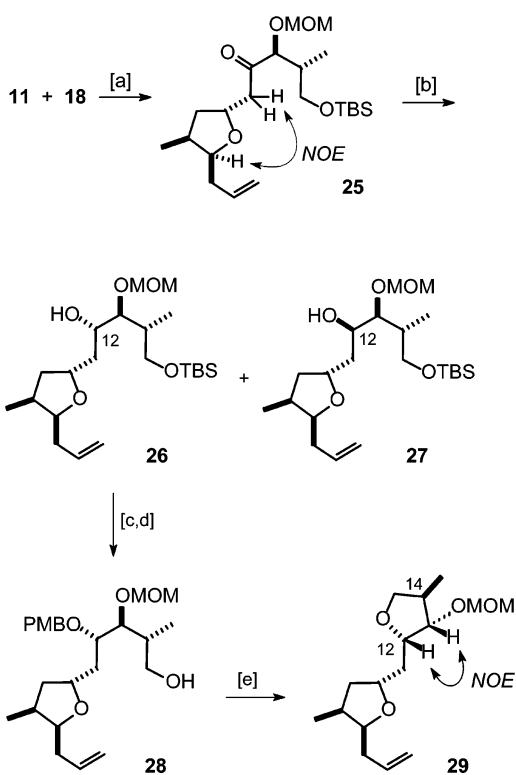
The last segment was accessible on a large scale by the route shown in Scheme 4. Thus, β-keto ester **21** was hydrogenated in the presence of [((*R*)-Binap)RuCl$_2$]$_2$(NEt$_3$) as the catalyst to give product **22** in excellent enantiomeric purity (98% ee).[20] This alcohol was then esterified with acid **20** which in turn was derived from the *N*-acyl oxazolidinone **19** by an asymmetric allylation reaction following known procedures.[21] Deprotection of the *tert*-butyl ester in **23** with F$_3$CCOOH in the presence of Et$_3$SiH and subsequent conversion of the resulting acid **24a** into the corresponding acid chloride **24b** furnished the remaining building block **E** for the planned total synthesis effort.

Assembly. With the required building blocks in hand, the assembly of the metathesis precursor was investigated. For this purpose, sulfone **11** was activated with a variety of Lewis acids and the resulting oxocarbenium ion was trapped by admixed silyl enol ether **18** (Scheme 5).[15] Careful optimization of the individual reaction parameters showed that the use of SnCl$_4$ in CH$_2$Cl$_2$ at −78 °C afforded the best results, furnishing the desired ketone **25** in 86% yield after hydrolytic workup. Other Lewis acids (AlCl$_3$, BF$_3$·Et$_2$O, TMSOTf, HgCl$_2$) gave significantly lower yields in this reaction.

Importantly, compound **25** was obtained with excellent diastereoselectivity in favor of the desired *trans* isomer (*trans*/

(20) 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.
(21) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

Scheme 5 [a]

Table 1. Diastereoselective Reduction of Ketone **25** in THF

			isolated yield, %	
entry	reducing agent	T, °C	26	27
1	L-Selectride	−78	72	3
2	LiHBEt$_3$	−78 → rt	19	32
3	LiAlH$_4$ (5 equiv) + LiI (10 equiv)	−100	11	70

numbering) with the desired *syn−syn* stereotriad at the three contiguous chiral centers, whereas the use of LiAlH$_4$ in combination with excess LiI[24] inverts the stereochemical bias and leads to the preferential formation of the corresponding (12*R*)-isomer **27** (Table 1). This outcome is best explained by invoking chelate complexes such as **H** or **I** in the Li^{+}-rich medium, either of which should favor the formation of alcohol **27** upon attack of an external hydride.[24c] This ability to control the course of the reduction of the ketone group by the proper choice of the reducing agent was ultimately decisive for the success of this total synthesis project (see below).

[a] Coupling of compounds **11** and **18**: [a] SnCl$_4$, CH$_2$Cl$_2$, −78 °C, 86%; [b] see Table 1; [c] PMBBr, KHMDS, THF, 77%; [d] TBAF, THF, 93%; [e] I$_2$, PPh$_3$, imidazole, CH$_2$Cl$_2$, 34%.
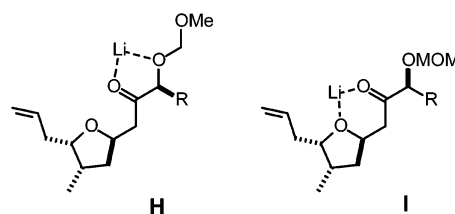
Scheme 6
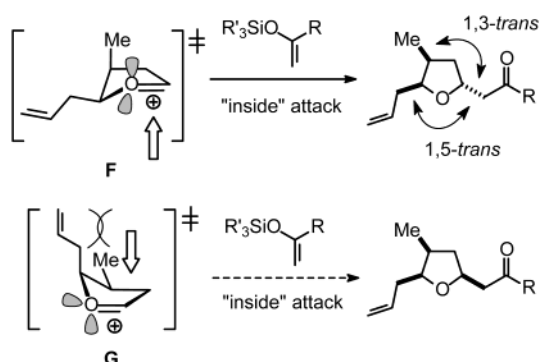
cis ≥ 26:1) as can be deduced from the strong NOE effect indicated in Scheme 5. This stereochemical outcome is in accord with previous observations, showing that a substituent as small as a methyl group at C3 of a furanoid oxocarbenium cation suffices to bias nucleophilic attack with high 1,3-*anti* selectivity.[22,23] This pattern is explained by assuming that the carbocation prefers an envelope conformation where the [C=O]$^+$ unit resides in the flattened portion of the ring, which is attacked by the nucleophile from "inside" for stereoelectronic reasons.[22] When applied to the present case (Scheme 6), it is rather obvious that transition state **F** should be favored over **G** because of the equatorial orientation of the larger substituent and the more open "inside" trajectory for the incoming silyl enol ether.

Reduction of ketone **25** with L-Selectride affords the (12*S*)-configured alcohol **26** as the major product (amphidinolide

The stereochemistry of alcohols **26** and **27** was rigorously established during an unintended deviation from the projected course of the synthesis. After protection of compound **26** as the corresponding PMB ether and cleavage of the terminal silyl group, we had planned to convert the resulting primary alcohol **28** into the corresponding iodide under standard conditions.[25] However, the only product isolated from the reaction mixture was the tetrahydrofuran **29**, which was formed by an intramolecular attack of the PMB ether oxygen onto the transient iodide.[26] NOE effects in combination with the pertinent coupling constants ($^3J_{H12,H13}$ = 4.5 Hz, $^3J_{H13,H14}$ = 2.0 Hz) revealed the *cis* orientation of the hydrogen atoms H12 and H13 in this compound and therefore permitted deduction of the (12*S*)-configuration of alcohol **26** (Scheme 5, amphidinolide numbering). This assignment was ultimately corroborated by the successful completion of the total synthesis project.

The ease of formation of tetrahydrofuran **29** makes clear that the O12-protecting group not only must be orthogonal to the terminal −OTBS function but also has to attenuate the nucleophilicity of the ether oxygen. The TBDPS group fulfills these criteria,[27] although its introduction was efficient only when KHMDS was used as the base. Compound **30** thus obtained can be selectively transformed into the primary alcohol **31** on exposure to TsOH in aq MeOH, which behaved properly and

(22) Larsen, C. H.; Ridway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.

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(24) (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419−5422. (b) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem.−Eur. J.* **1995**, *1*, 318−333. (c) For a comprehensive discussion of chelation controlled hydride reductions of carbonyl compounds, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

(25) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866−2869. (b) Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem.* **1991**, *56*, 2213−2217.

(26) For similar cyclizations, see: (a) Martin, O. R.; Yang, F.; Xie, F. *Tetrahedron Lett.* **1995**, *36*, 47−50. (b) Désiré, J.; Prandi, J. *Eur. J. Org. Chem.* **2000**, 3075−3084.

(27) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975−2977.

Scheme 7 [a]
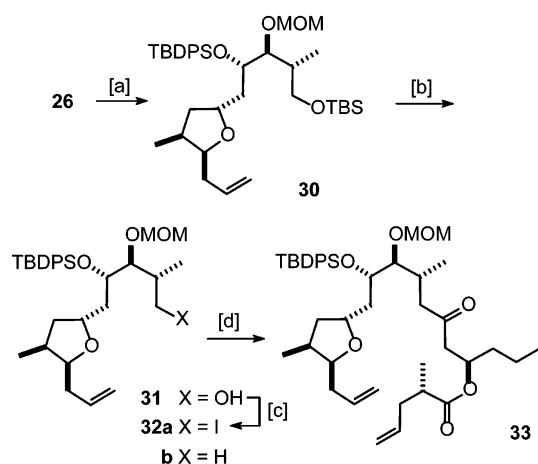
[a] Assembly of the RCM precursor: [a] KHMDS, TBDPSCl, THF, 77%; [b] TsOH, aq MeOH, 75%; [c] I₂, PPh₃, imidazole, toluene, 80%; [d] (i) Zn/Cu couple, TMSCl, toluene, DMA; (ii) **24b**, Pd₂(dba)₃ catalyst, P(2-furyl)₃ catalyst, 40–50% (**33**) + 20–30% (**32b**).

converted into the required iodide **32a** without interference of a neighboring group (Scheme 7).

With this compound in hand, the remaining coupling was achieved by a palladium catalyzed acyl-Negishi reaction.[28,29] Thus, exposure of **32a** to a Zn/Cu couple, which was activated in situ with TMSCl immediately prior to use, gave the corresponding organozinc reagent. This intermediate reacted with the enantiomerically pure acid chloride **24b** in the presence of Pd₂(dba)₃ catalyst and tris(2-furyl)phosphine as the ligand to give the desired ketone **33**, together with the reduced product **32b**. The reaction must be carried out in toluene in the presence of DMA as a cosolvent, since THF is cleaved under these conditions. Attempts to perform this coupling with nucleophiles other than the organozinc reagent and/or different catalysts and ligand sets were unrewarding.[30] Notably, this reaction constitutes one of the most advanced examples of an acyl-Negishi coupling reported to date[31] and sets the stage for the envisaged macrocyclization via RCM.

Completion of the Total Synthesis of Amphidinolides T1, T4, and T5. In line with our expectations,[32] the formation of the macrocyclic ring by RCM of diene **33** worked exquisitely well when carried out under standard conditions in the presence of the "second generation" ruthenium carbene complex **34** as the precatalyst bearing an imidazol-2-ylidene ligand (Scheme 8).[33] Hydrogenation of the resulting cycloalkene **35** (E:Z = 6:1) delivers compound **36** in high yield ready for the introduction of the exo-methylene group of the final target.

However, the seemingly routine transformation of **36** into **39** turned out to be quite problematic. Specifically, Ph₃P=CH₂

Scheme 8 [a]
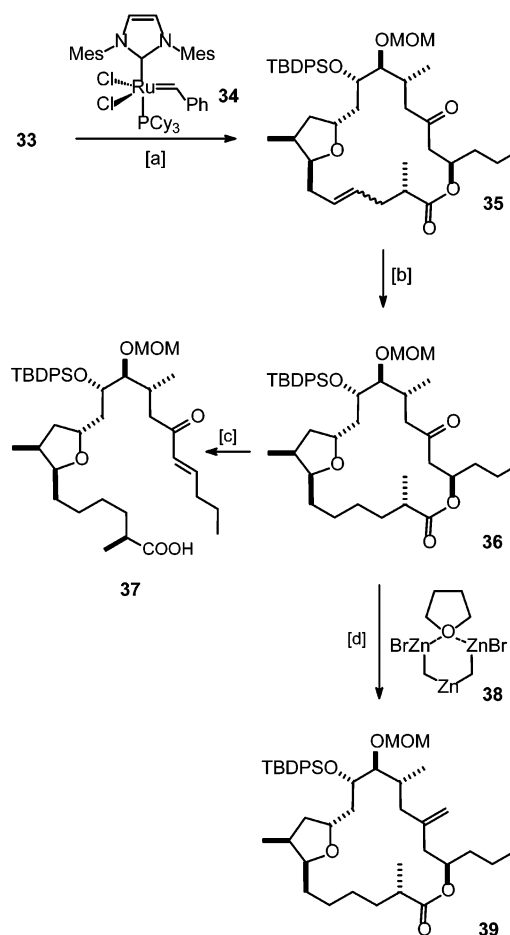
[a] Macrocyclization and olefination: [a] catalyst **34**, CH₂Cl₂, reflux, 86%; [b] H₂ (1 atm), Pd/C, EtOAc, 86%; [c] PH₃P=CH₂, THF, quantitative; [d] Nysted's reagent **38** (excess), TiCl₄, THF, reflux, 64%.

proved to be too basic and led only to a β-elimination of the aldol with concomitant opening of the macrocycle to give acid **37**. The use of a modified Peterson reagent for this olefination met with complete failure.[34] Semiempirical calculations[35] showed that the difficulties encountered in the attempted olefinations are likely steric in origin. In line with the results reported by Kobayashi et al. concerning the conformational compression of the macrocycle in amphidinolide T1,[4c] the

(28) (a) Negishi, E.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 1–47. (b) Sugihara, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 1, pp 635–647.

(29) (a) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181–5184. (b) Tamaru, Y.; Ochiai, H.; Sanda, F.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5529–5532.

(30) This includes (i) the use of Pd(0) in combination with tri-*o*-tolylphosphine, dppf, or tri-(*p*-methoxyphenyl)phosphine as the ligands; (ii) the use of CoBr₂ or (PPh₃)₂Rh(CO)Cl as catalysts instead of Pd(0); and (iii) attempts to transmetalate the organozinc species with CuCN·2LiCl, CuBr·Me₂S, PhSCuLi, MnI₂, or MnCl₂·2LiCl prior to cross coupling.

(31) For another advanced example, see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603.

(32) These expectations derive from our experiences gained in the following total syntheses: (a) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005–7008. (b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (c) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424–425. (d) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361–2366. (e) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215–8230. (f) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814–7821. (g) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275–8280. (h) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990–7995. (i) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671–672. (j) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. *Chem.—Eur. J.* **2002**, *8*, 1856–1871. (k) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem.* **2002**, *114*, 2203–2206; *Angew. Chem., Int. Ed.* **2002**, *41*, 2097–2101. (l) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem.—Eur. J.* **2003**, *9*, 320–326. (m) Fürstner, A.; Leitner, A. *Angew. Chem.* **2003**, *115*, 320–323; *Angew. Chem., Int. Ed.* **2003**, *42*, 308–311.

(33) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250. (c) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787–4790. (d) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207.

(34) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281–283.
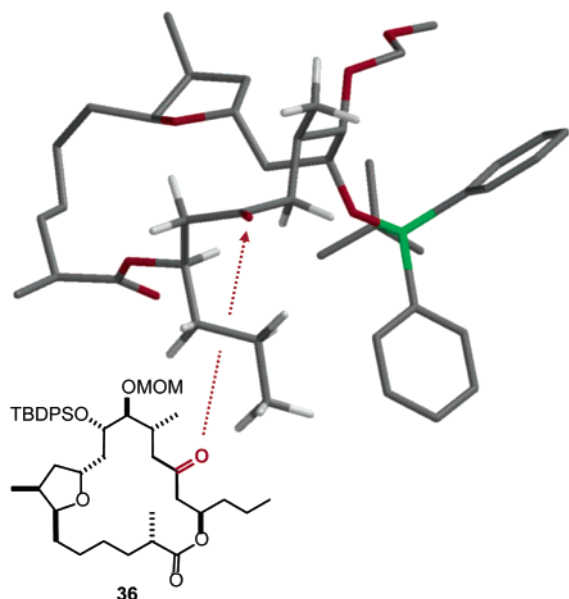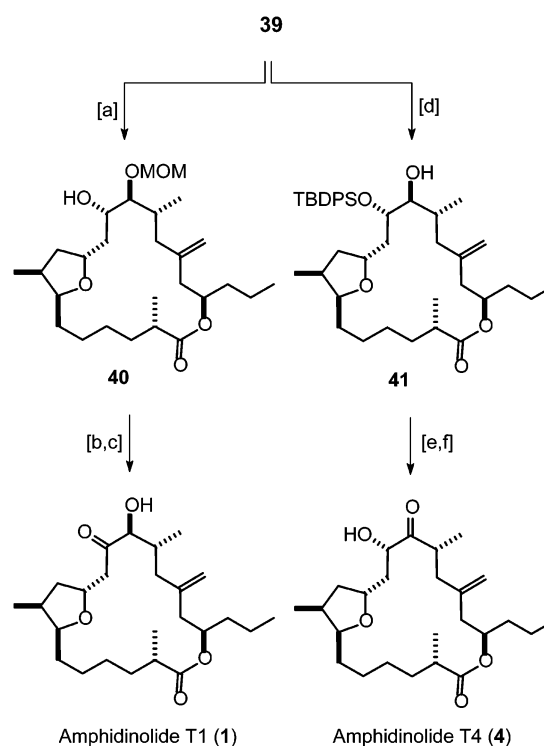
(35) Using Spartan 02, 2001, software at the PM3 level.

Figure 2. Lowest energy conformation of compound **36**, illustrating the steric shielding of the carbonyl group at C16.

overall structure of ketone **36** was found to be very compact. As can be seen from the representation depicted in Figure 2, one side of the ketone group is strongly shielded by the macrocycle which is locked in an unfavorable conformation by the large −OTBDPS group, while the trajectory to the other π-face is severely hindered by the propyl side chain.

It should be possible to improve the access to this hidden carbonyl group by increasing the conformational flexibility of the macrocycle. This can be done either by cleavage of the bulky TBDPS ether or by increasing the reaction temperature. Since we were unable to find conditions allowing to remove the TBDPS group without concomitant opening of the macrocyclic ring to give acid,[37] we searched for a reagent with strictly nonbasic characteristics to avoid the destructive retro-Michael pathway; ideally, this reagent should operate at higher temperatures. The Takai olefination using CH_2Br_2 in the presence of TiX_4 (X = Cl, OiPr)/Zn fulfilled these stringent criteria and gave the desired olefin, but the yields were rather variable.[36] Consistent results, however, were obtained by applying Nysted's reagent **38** (cyclo-dibromo-di-μ-methylene-[μ-(tetrahydrofuran)]-trizinc) which delivered product **39** in 64% yield when applied in refluxing THF in the presence of $TiCl_4$ as the promoter (Scheme 8).[37]

Compound **39** represents the common precursor "**A**" to all amphidinolides of the T series (except T2). In fact, a selective cleavage of its TBDPS group can be achieved by means of $[(Me_2N)_3S][Me_3SiF_2]$ in MeCN.[38,39] Subsequent oxidation of
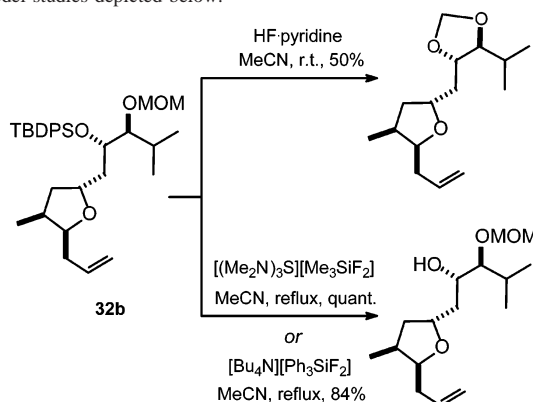
(36) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417−2420. (b) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H.; *Tetrahedron Lett.* **1985**, *26*, 5581−5584. (c) For a highly successful application in a case where the Wittig reaction had also failed, see: Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.−Eur. J.* **2001**, *7*, 4811−4820.

(37) (a) Tochtermann, W.; Bruhn, S.; Meints, M.; Wolff, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Tetrahedron* **1995**, *51*, 1623−1630. (b) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313−315. For recent applications, see: (c) Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett.* **2003**, *5*, 89−92. (d) Tarraga, A.; Molina, P.; Lopez, J. L.; Velasco, M. D. *Tetrahedron Lett.* **2001**, *42*, 8989−8992. (e) Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806−5816.

Scheme 9 [a]

a Completion of the total synthesis of compounds **1** and **4**: [a] $[(Me_2N)_3S][Me_3SiF_2]$, MeCN, 84%; [b] Dess−Martin periodinane, CH_2Cl_2, 93%; [c] Dowex AG 50W-X4, MeOH, 52%; [d] TMSCl, $^nBu_4NBr$, CH_2Cl_2, 0 °C, 85%; [e] Dess−Martin periodinane, CH_2Cl_2, 83%; [f] HF·pyridine, MeCN, 87%.

the resulting alcohol **40** with Dess−Martin periodinane[40] and removal of the remaining MOM acetal under slightly acidic conditions using Dowex AG 50W-X4 resin in MeOH readily afforded amphidinolide T1 (**1**) in good overall yield (Scheme 9). We were pleased to find that it was possible to gain access

(38) (a) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6237. (b) For the preparation and properties of the reagent, see: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598−1608.

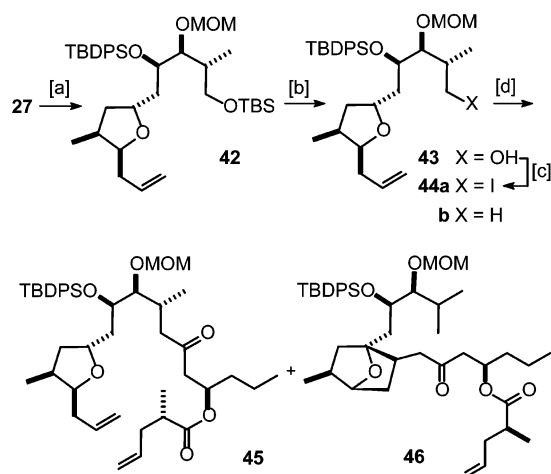(39) The choice of the desilylating agent followed the results obtained in the model studies depicted below:

While the use of Bu$_4$NF or BF$_3$·Et$_2$O in combination with salicylaldehyde (Mabic, S.; Lepoittevin, J. P. *Synlett* **1994**, 851) led to the decomposition of the starting material, HF·pyridine resulted in formation of the shown cyclic acetal by participation of the adjacent MOM group. Only the complex fluorosilicates $[(Me_2N)_3S][Me_3SiF_2]$ or $[Bu_4N][Ph_3SiF_2]$ in MeCN gave the desired alcohol in high yields.

(40) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552. (c) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141−152.

Scheme 10 *a*

a Assembly of the RCM precursor for the synthesis of amphidinolide T3: [a] KHMDS, TBDPSCl, THF, 82%; [b] TsOH, aq MeOH, 87%; [c] I$_2$, PPh$_3$, imidazole, toluene, 89%; [d] (i) Zn/Cu couple, TMSCl, toluene, DMA; (ii) **24b**, Pd$_2$(dba)$_3$ catalyst, P(2-furyl)$_3$ catalyst, 64% (**45:46** = 3:2).

to amphidinolide T4 (**4**) by changing the order of events, although slightly different reagents were necessary in this case. Specifically, the use of TMSBr (generated in situ from TMSCl and *n*-Bu$_4$NBr) led to a selective and high yielding cleavage of the MOM group without compromising the adjacent silyl ether. Alcohol **41** (Scheme 9) was oxidized with Dess−Martin periodinane, and the resulting ketone was desilylated by means of HF·pyridine in MeCN to furnish amphidinolide T4 (**4**). The analytical and spectroscopic data of the synthetic samples of **1** and **4** are in excellent agreement with those of the natural products as reported in the literature.[4] Since it has previously been shown that amphidinolide T4 undergoes epimerization at C14 on treatment with K$_2$CO$_3$ in MeOH to give amphidinolide T5 (**5**),[4c] a formal total synthesis of this only recently discovered congener has also been achieved.

Total Synthesis of Amphidinolide T3: The Impact of a Seemingly Minor Change. As outlined in the discussion of our retrosynthetic plan, a modification of the end game strategy should lead to the remaining congener amphidinolide T3 (**3**) from the common synthetic intermediate **39**. Specifically, this required inversion of the free hydroxyl group in compound **40** to set the proper configuration at C12 followed by a sequence of oxidation/deprotection steps similar to those outlined above. Despite considerable efforts, however, we were unable to find appropriate conditions for the seemingly trivial inversion step.

As a consequence, access to this particular target had to be secured by a different route. The ease with which the reduction of ketone **25** can be controlled to give either the (12*S*)- or the (12*R*)-configured alcohols **26** and **27** (cf. Scheme 5 and Table 1) helped to solve this problem. Therefore, we repeated the assembly of the metathesis precursor using the epimeric series as shown in Scheme 10. While the elaboration of compound **27** to the corresponding iodide **44a** proceeded uneventfully, the crucial acyl-Negishi coupling[28,29] led to a rather surprising outcome. In addition to the desired ketone **45** and minor amounts of the reduction product **44b**, an additional compound was isolated from the crude reaction mixture by HPLC. Extensive NMR investigations allowed us to assign its structure as **46**. This rearranged skeleton is thought to derive from the radical

Scheme 11
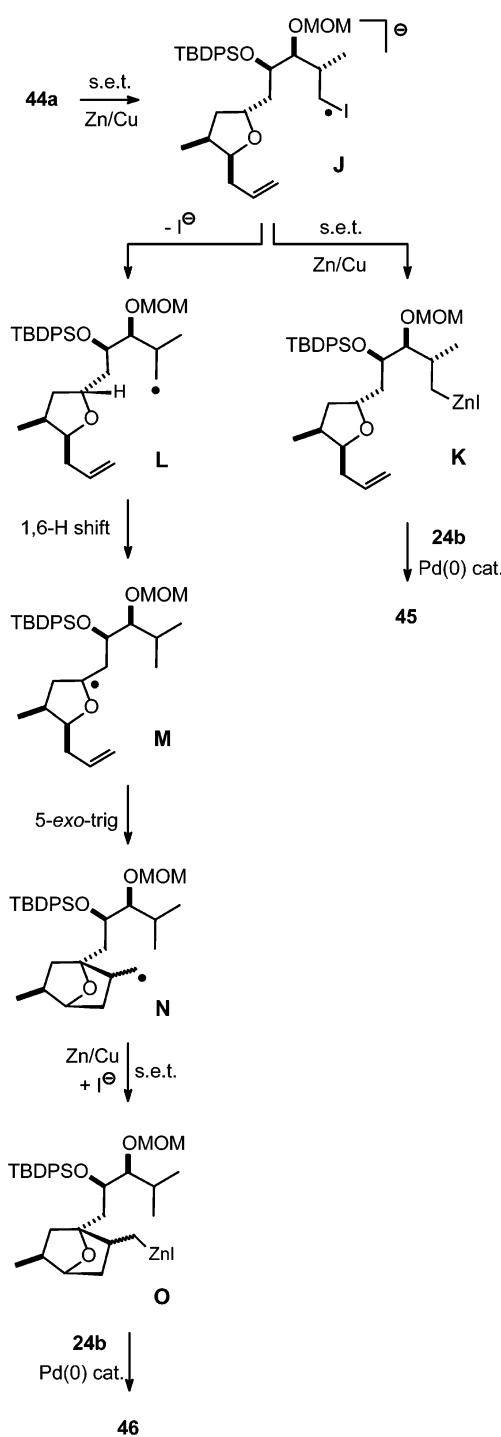
cascade shown in Scheme 11, triggered by single electron transfer (s.e.t.) from the Zn/Cu couple to iodide **44a** and likely reflects the conformational peculiarities of this compound.

The radical anion **J** initially formed on exposure of **44a** to Zn/Cu can evolve along two competing pathways (Scheme 11). If a rapid second s.e.t. occurs, the desired organozinc derivative **K** will be formed which undergoes the palladium catalyzed acyl-Negishi reaction leading to the expected cross coupling product **45**. However, if **J** expells I$^-$ prior to the second s.e.t., the resulting primary carbon radical **L** can abstract an anomeric hydrogen atom from the tetrahydrofuran ring via a formal 1,6-H shift. The substituents on the carbon backbone obviously enforce
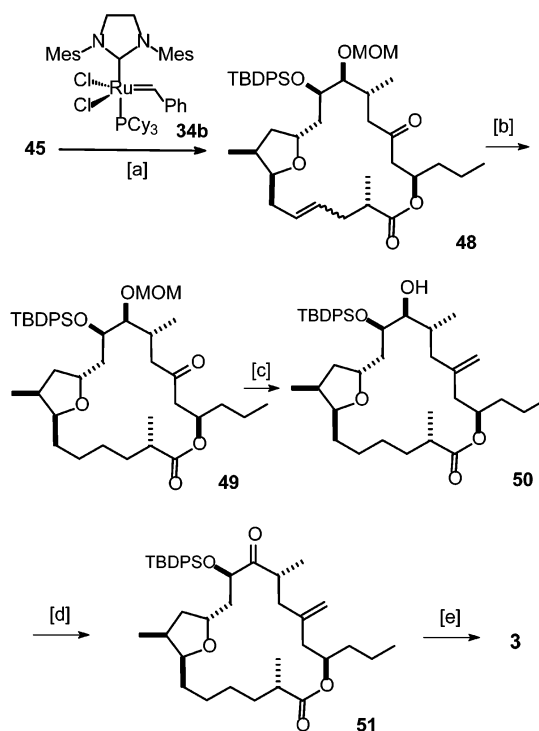
Scheme 12 *a*
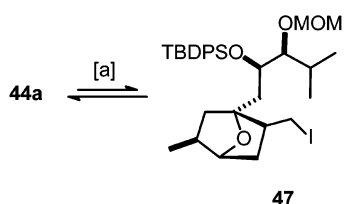
a [a] (Me$_3$Sn)$_2$ (0.3 equiv), AIBN (0.1 equiv), benzene, reflux, 16 h, **44a:47** = 3:1; see text.

a conformation in which these sites are brought into close vicinity. The resulting radical **M** undergoes a rapid 5-*exo-trig* cyclization leading to the bicyclic intermediate **N** which delivers the transposed organozinc derivative **O** after a second s.e.t.. Interception of this compound by the acid chloride **24b** in the presence of Pd(0) as the catalyst affords the two epimers of product **46** (diastereomeric ratio, d.r. = 8:3) which were unambiguously identified by 2D NMR experiments at 600 MHz.

To lend credence to this scenario, iodide **44a** was reacted with hexamethylditin in the presence of AIBN (Scheme 12). Under free radical conditions,[41] an equilibrium between **44a** and the transposed bicyclic iodide **47** formed by iodine transfer is established. The latter compound was isolated by preparative HPLC as a 1:1 mixture of isomers. This control experiment strongly advocates a radical process triggered by an s.e.t. from Zn/Cu to the substrate[42] as the origin for the observed formation of compound **46** during the acyl-Negishi coupling step.

The unexpected results of the zinc-induced fragment coupling process augured for possible difficulties during the ring closure of diene **45** by RCM. In line with the notion that the *anti–syn* stereotriad in the C12–C14 region of this compound might be far from optimal for the macrocyclization, this compound was found to react much more reluctantly than its *syn–syn* configured counterpart **33**.[43] Good conversion could only be attained by exchanging the solvent from CH$_2$Cl$_2$ to toluene[44] and increasing the reaction temperature to 110 °C.[45] Although ruthenium carbene complexes are known to be fairly labile under such forcing conditions,[46] the desired ring closure was faster than the decomposition of the catalyst, thus delivering

(41) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265–6276.

(42) It has been previously shown that the formation of organozinc derivatives under similar reaction conditions likely involves radical intermediates; cf.: (a) Crandall, J. K.; Ayers, T. A. *Organometallics* **1992**, *11*, 473–477. (b) Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373–5374. (c) Pradhan, S. K.; Kolhe, J. N.; Mistry, J. S. *Tetrahedron Lett.* **1982**, *23*, 4481–4484. (d) Samat, A.; Vacher, B.; Chanon, M. *J. Org. Chem.* **1991**, *56*, 3524–3530 and literature cited therein.

(43) For previous examples showing that small changes at remote sites of a given substrate can have a strong impact on the outcome of RCM-based macrocyclizations, see ref 12 and the following: (a) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731–3734. (b) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem.–Eur. J.* **2001**, *7*, 5286–5298. (c) Fürstner, A.; Schlede, M. *Adv. Synth. Catal.* **2002**, *344*, 657–665. (d) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zeng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.

(44) The "second generation" catalyst **34** is known to be inherently more reactive in toluene than in CH$_2$Cl$_2$. This effect is not merely a consequence of the higher reaction temperature that can be reached but reflects a real solvent effect. For a discussion see ref 33d and the following reference: Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem.–Eur. J.* **2001**, *7*, 3236–3253.

(45) For recent precedence on the use of very high temperatures in RCM, see: Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299.

(46) For studies on the decomposition of ruthenium carbene complexes, see: (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554. (b) Amoroso, D.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2002**, *21*, 3335–3343.

Scheme 13 *a*

a Completion of the total synthesis of amphidinolide T3 (**3**). [a] catalyst **34b** (20 mol %), toluene, 110 °C, 82%; [b] H$_2$ (1 atm), Pd/C, EtOAc, 99%; [c] Nysted's reagent **38**, TiCl$_4$, THF, reflux, 54%; [d] Dess–Martin periodinane, CH$_2$Cl$_2$, 88%; [e] HF·pyridine, MeCN, 55%.

cycloalkene **48** in a respectable 82% isolated yield. The mixture of isomers (*E:Z* = 2:1) was hydrogenated under standard conditions to give product **49** (Scheme 13).

The conformational constraints imposed on all compounds of this series by the −OTBDPS group at C12 and the eclipsed MOM acetal in an *anti* arrangement at C13 are particularly pronounced in cycloalkene **48** and the saturated derivative **49** derived thereof. Specifically, the NMR spectra of **48** and **49** show exceptional line broadening due to severely restricted rotations in this part of the molecule when recorded using the programs of the standard NMR pulse library at ambient temperature. This effect is so strong that the −OCH$_2$O− entity of the MOM group is *seemingly* absent, and even its −OMe part is very strongly affected; the corresponding signals are clearly visible only upon recording the spectra at +80 °C (cf. the Supporting Information). All other spectroscopic data (IR, MS, HRMS) confirm that the MOM acetal is fully intact and preserved until after the olefination step.

Furthermore, it is noteworthy that the relative configuration at C12/C13 of the cyclization precursor determines the stereo-chemical course of the RCM reaction. This can be deduced from a comparison of the *E/Z* ratios produced in the cyclizations of dienes **33** and **45**, which differ only in the configuration of the remote C12 chiral center. While cycloalkene **35** derived from **33** is formed with an appreciable selectivity in favor of the (*E*)-isomer (*E:Z* = 6:1), the corresponding *E:Z* ratio for its congener **48** was only 2:1. Assuming that the reactions using the highly active "second generation" catalyst **34** at elevated temperatures are reversible and therefore likely under thermodynamic control as previously shown in other cases,[47] this outcome should reflect the relative stability of the geometrical isomers.[48] In fact,

semiempirical calculations indicate that (*E*)-**35** is considerably more stable than its (*Z*)-counterpart ($\sim$8 kcal mol^{-1}), whereas the geometrical isomers of **48** are much closer in energy, favoring the (*E*)-cycloalkene by only $\sim$1.2 kcal mol^{-1}.[35]

Product **49** was then subjected to olefination using Nysted's reagent **38** in combination with TiCl$_4$.[37] Not only did this reaction install the *exo*-methylene group but also was accompanied by a cleavage of the MOM acetal during the workup. Since this protecting group had to be removed anyway, product **50** was directly amenable to oxidation with Dess−Martin periodinane.[40] Cleavage of the remaining silyl group in **51** completed the total synthesis of amphidinolide T3 (**3**) in excellent overall yield.

Conclusions

A concise, modular, and high yielding entry into the amphidinolide T family has been described. The syntheses of these bioactive macrolides of marine origin highlight the outstanding performance and excellent application profile of modern organometallic chemistry and catalysis. At the same time, however, they showcase how seemingly small changes in the substrates can have a major impact on the course and efficiency of a given transformation. This is evident from the RCM experiments which are strongly affected by the chosen stereochemical setting of the substrate. Likewise, the configuration of a remote stereocenter determines whether a radical manifold can effectively compete with the organometallic pathway during an acyl-Negishi reaction used for fragment coupling. Therefore, these results bear witness to the eminent importance of controlling the conformational space populated by *acyclic* molecules, an aspect that is likely gaining further relevance as the complexity of the target structures continues to increase.

Supporting Information Available: Full experimental details, spectroscopic and analytical data of all new compounds, and copies of the spectra of compounds **1**, **3**, **4**, **39**, **46**, **47**, and **49** as well as crystallographic data concerning compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA038216Z

(47) See the following for leading references: (a) Smith, A. B.; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990−991. (b) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449−451. (c) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302−10316. (d) Paquette, L. A.; Basu, K.; Eppich, J. C.; Hofferberth, J. E. *Helv. Chim. Acta* **2002**, *85*, 3033−3051.

(48) For a detailed discussion and an example showing how to use kinetic versus thermodynamic control over RCM in synthesis, see: Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069.