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Total Syntheses of (+)-Zampanolide and (+)-Dactylolide Exploiting a Unified Strategy

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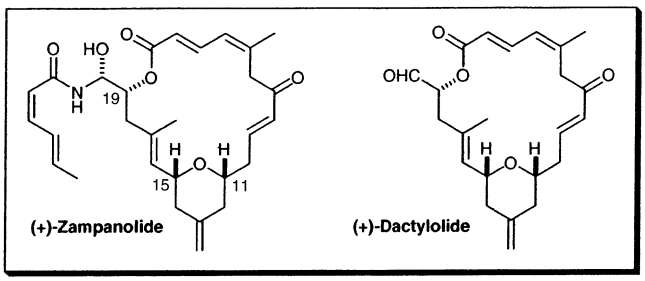
Abstract: The first total syntheses of (+)-zampanolide (**1**) and (+)-dactylolide (**2**), members of a new class of tumor cell growth inhibitory macrolides, have been achieved. Key features of the unified synthetic scheme included the stereocontrolled construction of the *cis*-2,6-disubstituted tetrahydropyran via a modified Petasis−Ferrier rearrangement, a highly convergent assembly of the macrocyclic domain, and, in the case of zampanolide, a Curtius rearrangement/acylation tactic to install the *N*-acyl hemiaminal. The complete relative and absolute stereochemistries for both (+)-zampanolide and (+)-dactylolide were also assigned, albeit tentatively in the case of (+)-zampanolide (**1**).

In 1996 Tanaka and Higa disclosed the isolation, partial structure elucidation, and biological activity of the architecturally novel macrolide (−)-zampanolide (**1**), obtained from *Fasciospongia rimosa*,[1] an Okinawan sponge that previously yielded significant quantities of (+)-latrunculin A and (−)-laulimalide,[2] as well as the related, but new metabolites (+)-latrunculin S and (−)-neolaulimalide.[3] The structure of (−)-zampanolide (**1**), including the relative stereochemistry between C(11), C(15), and C(19) stereogenic centers, was secured via extensive NMR analysis. The stereochemical disposition of the C(20) hydroxyl group and the absolute stereochemistry, however, were not defined.

The extreme scarcity of (−)-zampanolide and the impressive cytotoxicity displayed against the P388, HT29, A549, and MEL28 cell lines (IC_{50} 1−5 ng/mL), in conjunction with our longstanding interest in the construction of complex marine natural products, prompted us to launch a synthetic venture targeting this metabolite.[4] From the synthetic perspective, the challenging features of **1** include the highly unsaturated 20-membered macrolactone incorporating a *cis*-2,6-disubstituted tetrahydropyran and the unusual *N*-acyl hemiaminal side chain, a structural feature associated with several highly bioactive marine metabolites, such as the echinocandins B and C,[5] the mycalamides A and B,[6] spergualin,[7] and the recently reported upenamide.[8] Herein we describe, in full, an account of the design and execution of the first total synthesis and tentative stereochemical assignment of the non-naturally-occurring antipode, (+)-zampanolide (**1**). In addition, we will present the total synthesis and structure assignment of the related macrolide (+)-dactylolide (**2**) exploiting a unified synthetic strategy.[9]



Synthetic Analysis of Zampanolide. Our synthetic strategy for zampanolide (**1**) called for initial construction of the macrocyclic domain, with installation of the *N*-acyl hemiaminal structural unit late in the synthetic sequence, due to the anticipated fragile nature of this reactive moiety. Since neither the relative stereochemistry at C(20) nor the absolute configuration of zampanolide (**1**) had been defined, we arbitrarily set **1** as our initial target (Scheme 1). Disconnection at the amide linkage, followed by application of a Curtius rearrangement transform,[10] suggested an activated 2(*Z*),4(*E*)-hexadienoic acid (fragment **D**) and α-alkoxy acid **3**, wherein the C(7) ketone

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(1) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535.
(2) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159.
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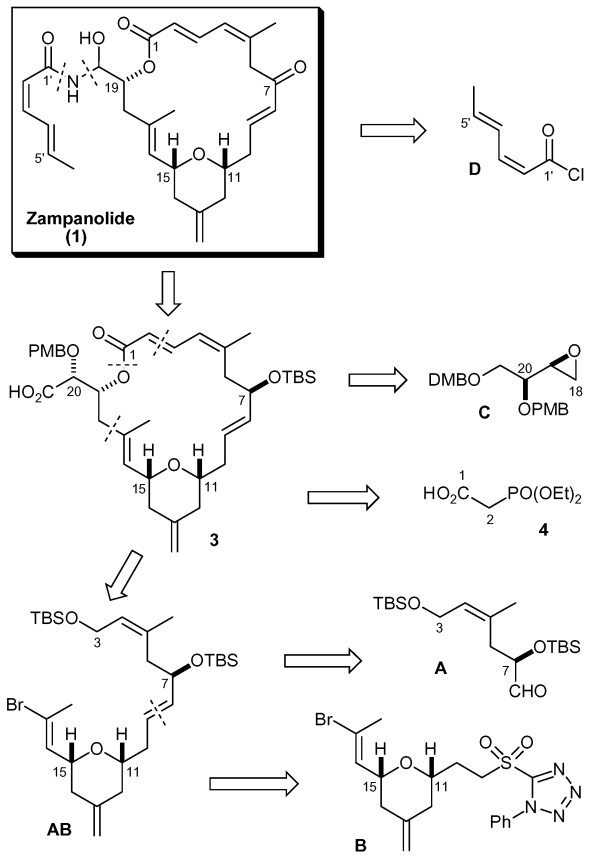
(4) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.
(5) (a) Benz, F.; Knüsel, F.; Nüesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459. (b) Traber, R.; Keller-Juslén, C.; Loosli, H.-R.; Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1979**, *62*, 1252.
(6) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K.. *J. Am. Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.
(7) Isolation: Takeuchi, T.; Iinuma, H.; Kunimoto, S.; Masada, T.; Ishizuka, M.; Takeuchi, M.; Hamada, M.; Naganawa, H.; Kondo, S.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1619. Structure: Umezawa, H.; Kondo, S.; Iinuma, H.; Kunimoto, S.; Ikeda, Y.; Iwazawa, H.; Ikeda, D.; Takeuchi, T. *J. Antibiot.* **1981**, *34*, 1622.
(8) Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465.
(9) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635.
(10) (a) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421. (b) Hoffmann, R. W.; Schlapbach, A. *Tetrahedron Lett.* **1993**, *34*, 7903.

10.1021/ja020635t CCC: $22.00

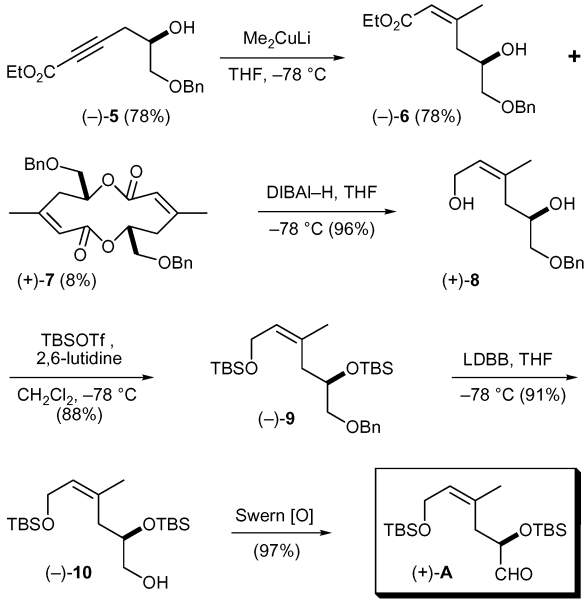
Scheme 1



would be masked as a TBS ether to forestall potential complications associated with the acidity of the C(6) position. Continuing with this analysis, three strategic disconnections of the macrolide ring led to fragments **A**, **B**, **C**, and the commercially available diethylphosphonoacetic acid (**4**). In the synthetic direction, we envisioned macrolide construction via a Kocienski−Julia olefination[11] of aldehyde **A** with sulfone **B**, followed in turn by nucleophilic opening of epoxide **C** with a mixed cyano-Gilman cuprate,[12] derived from vinyl bromide **AB**, incorporation of an acyl phosphonate via Mitsunobu inversion at C(19),[13] and a Horner−Wadsworth−Emmons (HWE) macrocyclization.[14] This highly convergent design would obviate the necessity to protect and then unmask the C(19) hydroxyl, a measure unavoidable involving approaches to the macrocycle via Mitsunobu macrolactonization.

Preparation of Aldehyde A: The C(3−8) Fragment. Our point of departure for construction of **A** was the known alkynoate (−)-**5**, prepared via the procedure of Ogasawara et al.[15] Michael addition of lithium dimethylcuprate (Me_2CuLi)[16] to the acetylenic ester furnished the expected enoate (−)-**6** and the unusual macrodiolide (+)-**7** in 78% and 8% yield, respectively (Scheme 2). Fortuitously, (+)-**7** also possessed the

Scheme 2

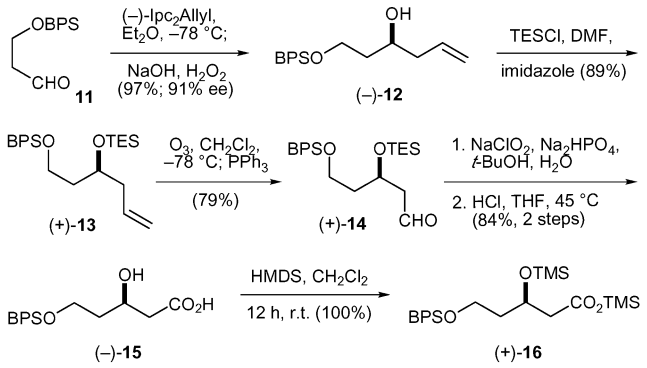


requisite olefin geometry needed for zampanolide. Thus, DIBAl−H reduction of (−)-**6** and (+)-**7**, either separately or as the mixture, gave diol (+)-**8** as a single product in near quantitative yield. Exhaustive silylation (TBSOTf, 2,6-lutidine) then proceeded smoothly, to provide the fully protected triol (−)-**9** in 88% yield. Reductive removal of the benzyl group with lithium di-*tert*-butylbiphenylide (LDBB),[17] followed by Swern oxidation[18] of the liberated hydroxyl [e.g., (−)-**10**], completed construction of aldehyde (+)-**A** in 88% yield for the final two steps. Fragment (+)-**A** was thus available in five steps and 58% overall yield from (−)-**5**.

Construction of Sulfone B: The C(9−17) Fragment. To assemble sulfone **B** we elected to utilize the Petasis−Ferrier rearrangement,[19] recently established in our laboratory as a powerful, stereocontrolled entry to *cis*-2,6-disubstituted tetrahydropyrans.[20] Success here would represent the first example of an α,β-unsaturated oxonium intermediate (e.g., **22a**; Scheme 4) in the Petasis−Ferrier rearrangement. Toward this end, Brown asymmetric allylation[21] of known aldehyde **11**[22] installed the C(11) stereogenic center (zampanolide numbering), both in high yield and with excellent enantiomeric excess, the latter determined by Mosher ester analysis (Scheme 3).[23] Protection of the derived homoallylic alcohol (−)-**12** (TESCl, imidazole) and ozonolysis of the terminal olefin delivered aldehyde (+)-**14** in 70% yield (two steps). Oxidation (buffered $NaClO_2$)[24] and

(11) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
(12) (a) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (b) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.
(13) Mitsunobu, O. *Synthesis* **1981**, 1.
(14) (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem.* **1977**, *89*, 608. (b) Burry, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.
(15) Oizumi, M.; Takahashi, M.; Ogasawara, K. *Synlett* **1997**, 1111.
(16) Corey, E. J.; Katzenellenbogen, J. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(17) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (b) Ireland, R. E.; Noreck, D. W.; Mandell, G. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285.
(18) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(19) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.
(20) (a) Smith, A. B., III; Verhoest, P. V.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. V.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913. (c) Smith, A. B., III; Verhoest, P. V.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834. (d) Smith, A. B., III; Verhoest, P. V.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942.
(21) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991**, *63*, 307.
(22) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.
(23) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(24) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.

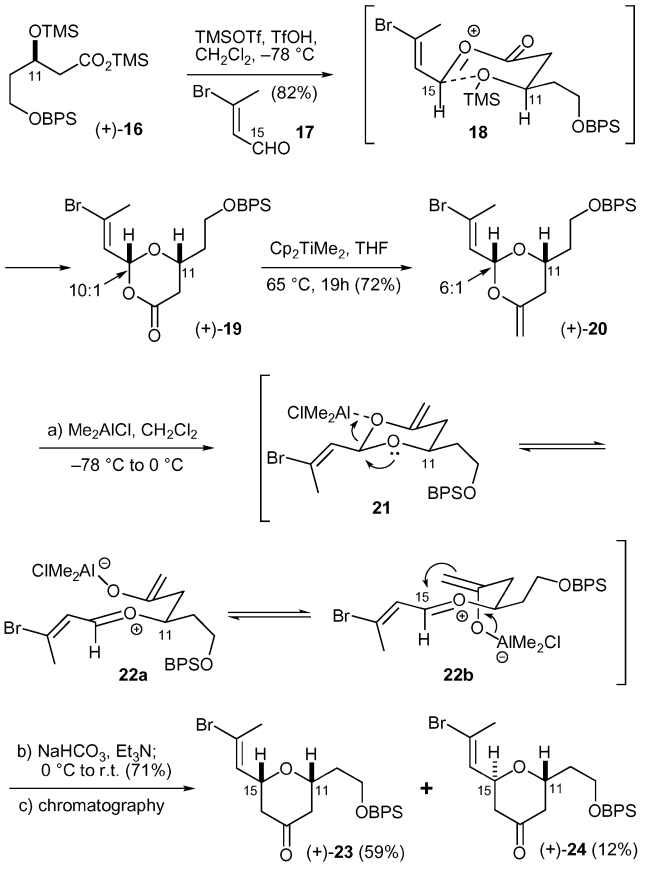
Scheme 3



removal of the TES group (aqueous HCl) then furnished the β-hydroxy acid (−)-**15**, which upon bis-silylation[25] (HMDS) provided (+)-**16**, the last acyclic intermediate required for sulfone **B**; the overall yield from (+)-**14** was 84% (three steps).

Condensation of (+)-**16** with 2(*E*)-3-bromobut-2-enal (**17**),[26] employing TMSOTf,[27] furnished an inseparable mixture of the corresponding dioxanones [10:1 at C(15)] in 82% combined yield, with the *cis* congener (+)-**19** as the major product (Scheme 4). Presumably, this transformation proceeds via

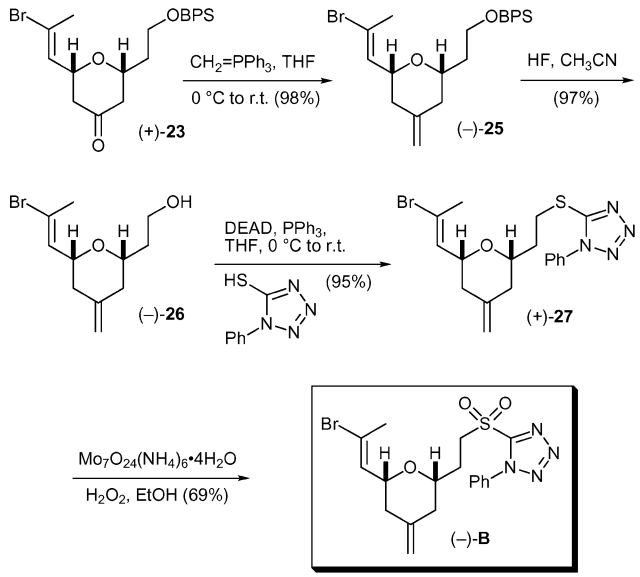
Scheme 4



transition state **18**, wherein the aldehyde side chain adopts a pseudoequatorial orientation to avoid unfavorable steric interactions with the C(11) axial hydrogen. Initial difficulties in the scale-up of this reaction suggested that triflic acid (TfOH) is the actual catalyst. Adventitious water, more pronounced on small scale, may generate TfOH in situ from TMSOTf, as well as TMS_2O. Large-scale reactions did not proceed until a catalytic amount (5−15 mol %) of TfOH was added (see the Supporting Information for details). Methylenation of (+)-**19** with the easily prepared and convenient to handle Petasis−Tebbe reagent (Cp_2TiMe_2)[28] furnished a difficultly separable mixture of enol ethers (+)-**20** [6:1 *cis*/*trans* at C(15); 72% yield].[29] The stage was thus set for the Petasis−Ferrier rearrangement,[19] the strategic transformation required for construction of sulfone **B**. In the event, treatment of the mixture with 1 equiv of dimethylaluminum chloride (Me_2AlCl)[20] at −78 °C effected the rearrangement to provide the desired *cis*-pyranone (+)-**23** in 59% isolated yield after chromatographic separation from the *trans* isomer (+)-**24** (12%).

Completion of sulfone **B** was then achieved in a straightforward fashion (Scheme 5); installation of the exo-methylene exploiting a standard Wittig reaction was followed by removal of the BPS group (HF, MeCN) to afford alcohol (−)-**26** in 95% yield for the two steps. Incorporation of the thiotetrazole via the Mitsunobu protocol,[13] employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol, followed by oxidation [H_2O_2, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$][30] of the derived sulfide (+)-**27**, proceeded smoothly to furnish sulfone (−)-**B** (66% yield, two steps). Subtarget (−)-**B** was thus available in 13 steps and in 12% overall yield from aldehyde **11**.

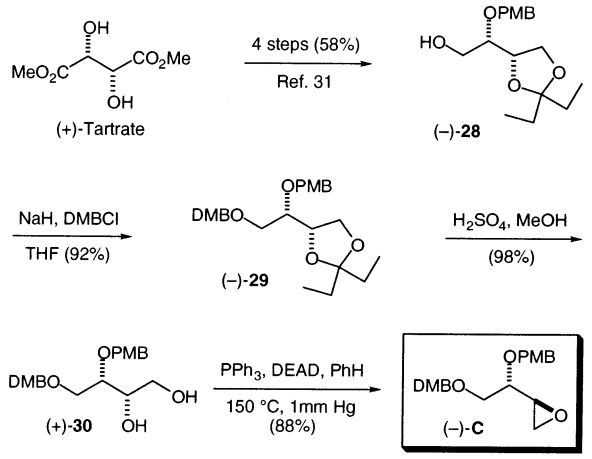
Scheme 5



Synthesis of Epoxide C: The C(18−20) Fragment. The two stereogenic centers in fragment **C** were envisioned to arise from the known diethyl ketal (−)-**28** (Scheme 6), conveniently prepared in four steps (50% overall yield) from (+)-dimethyl tartrate according to the protocols of Somfai and Yonemitsu.[31]

(25) Harada, T.; Yoshida, T.; Kagamihara, Y.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1367.
(26) Prepared by oxidation of 2(*E*)-3-bromobut-2-enol with PCC in 79% yield. For preparation of the latter, see: Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *19*, 1051.
(27) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.
(28) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(29) The observed decay in the *cis*/*trans* ratio for this transformation was partially attributed to the harsh reaction conditions.
(30) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

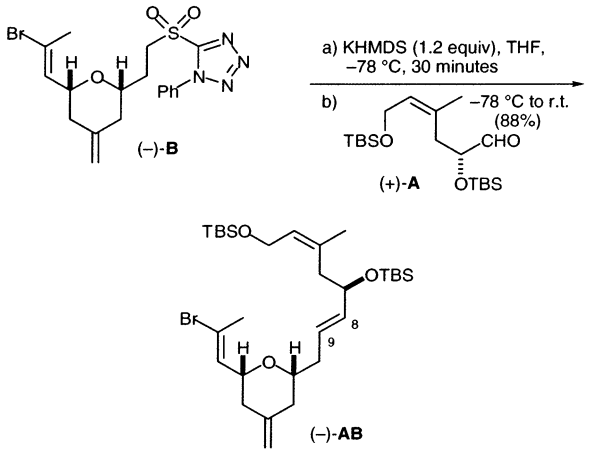
Scheme 6



Protection of the primary hydroxyl in (−)-**28** as the 3,4-dimethoxybenzyl (DMB) ether was then followed by proteolytic removal of the diethyl ketal to reveal diol (+)-**30** (90% yield, two steps). The best conditions to effect epoxide ring formation proved to be the modified Mitsunobu procedure of Abushanab et al.,[32] which effectively furnished epoxide (−)-**C**, with retention of the C(19) stereogenicity.[33] Fragment (−)-**C** was thus prepared in three steps and in 79% overall yield from diethyl ketal (−)-**28**.

Union of Fragments (+)-A and (−)-B. With multigram quantities of **A** and **B** in hand, we began assembly of the macrocyclic ring. The first step, the one-pot Kocienski-modified[11] Julia olefination[34] of aldehyde (+)-**A** with sulfone (−)-**B**, forged the *trans* C(8,9) double bond (Scheme 7). This tactic,

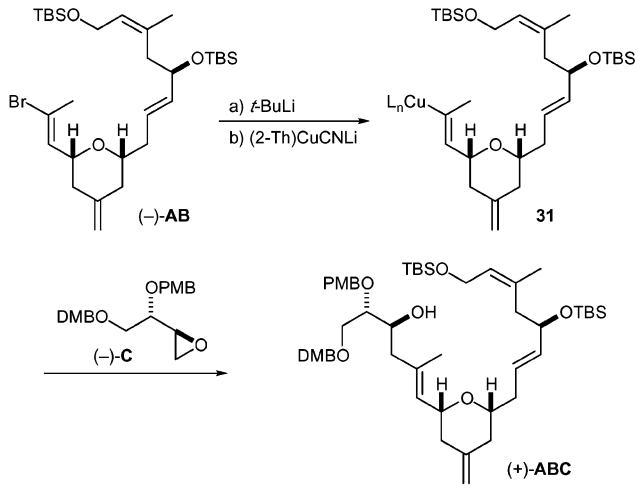
Scheme 7



particularly attractive since the reaction leads to high *trans* selectivity in the absence of such factors as α-branching or conjugation,[35] involved treatment of sulfone (−)-**B** with potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C, followed by addition of aldehyde (+)-**A** and warming to ambient temperature. Vinyl bromide (−)-**AB** was reproducibly obtained as the sole C(8,9) olefinic isomer, in 88% yield. The *E* geometry was confirmed by the large NMR coupling constant ($J_{H(8-9)}$ = 15.3 Hz) for the olefinic hydrogens.

Union of Fragments (−)-AB and (−)-C: A Difficult Maneuver. We next turned our attention to addition of the mixed cyano−Gilman cuprate (**31**), derived from vinyl bromide (−)-**AB** and lithium 2-thienylcyanocuprate,[36] to epoxide (−)-**C** (Scheme 8). Due to the high reactivity of alkenyl groups and the low transferability of the 2-thienyl group, cuprates of this type are extremely useful in organic synthesis, especially vis-à-vis reactions at sp^3 centers.[12,37]

Scheme 8

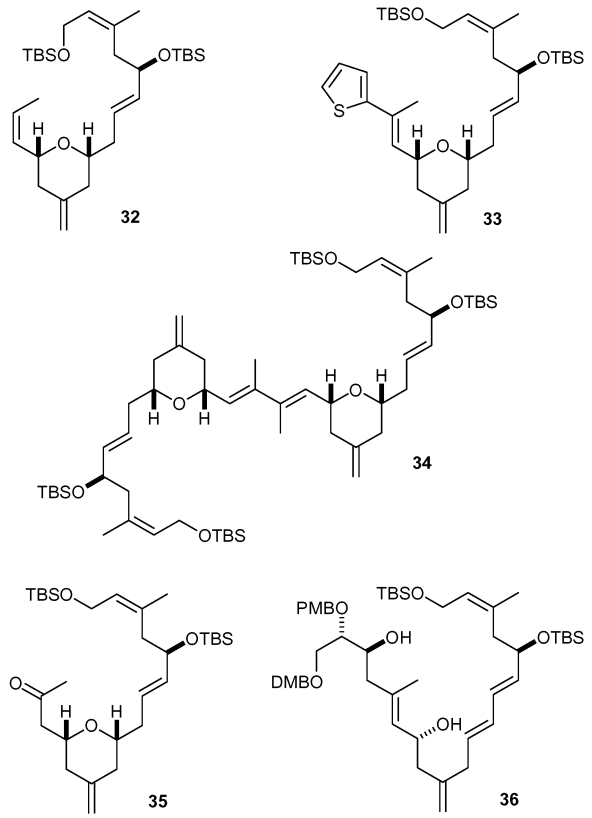


Initially, modest yields (16−38%) of the (+)-**ABC** adduct were obtained, leading us to conduct a detailed analysis of the coupling process. We first established that the initial lithium−halogen exchange occurs rapidly, even at −100 °C, and that the derived vinyllithium is stable at 0 °C for at least 15 min, as evidenced by reaction with benzaldehyde (81% yield). This study supported our conjecture that the coupling reaction proceeds poorly at the cuprate stage. Earlier observations by Bertz et al. indicated that THF can lead to a decrease in cuprate reactivity.[38] Performing the reaction in diethyl ether (Et_2O), however, had little or no effect on the yield of (+)-**ABC**. Eventually, identification of a series of byproducts **33**−**35** (Scheme 9), in addition to the expected side product **32** resulting from protonation of either the derived vinyllithium or cuprate **31**, suggested that the cuprate was extremely sensitive to adventitious oxygen.

Rigorous elimination of oxygen from the argon atmosphere via use of an OXICLEAR argon filter proved particularly

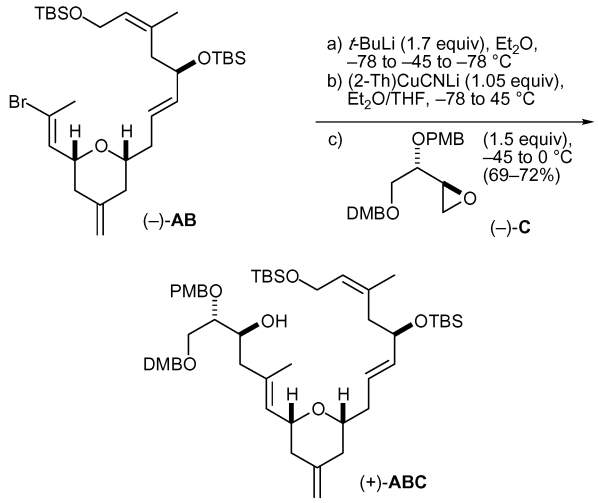
(31) (a) Somfai, P.; Olsson, R. *Tetrahedron* **1993**, *49*, 6645. (b) Horita, K.; Sakurai, Y.; Hachiya, S.; Nagasawa, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1994**, 683.
(32) Cichy, A. F.; Saibaba, R.; El Subbagh, H. I.; Panzica, R. P.; Abushanab, E. *J. Org. Chem.* **1991**, *56*, 4653.
(33) Interestingly, application of *N*-tosyl imidazole for epoxidation of (+)-**96** resulted in a 7:1 mixture of (−)-**C** and the C(19) epimer.
(34) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.
(35) For recent applications of the Kocienski−Julia olefination in total synthesis of complex natural products, see: (a) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924. (b) Smith, A. B., III; Wan, Z. *Org. Lett.* **1999**, *1*, 1491. (c) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612. (d) Smith, A. B., III; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685. (e) Mulzer, J.; Öhler, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3842. (f) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772. (g) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384.
(36) Lithium 2-thienylcyanocuprate was either purchased from Aldrich Chemicals or freshly prepared from commercially available 2-thienyllithium and CuCN according to the procedure of Lipshutz (see ref 12b).
(37) (a) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596. (b) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468.
(38) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

Scheme 9



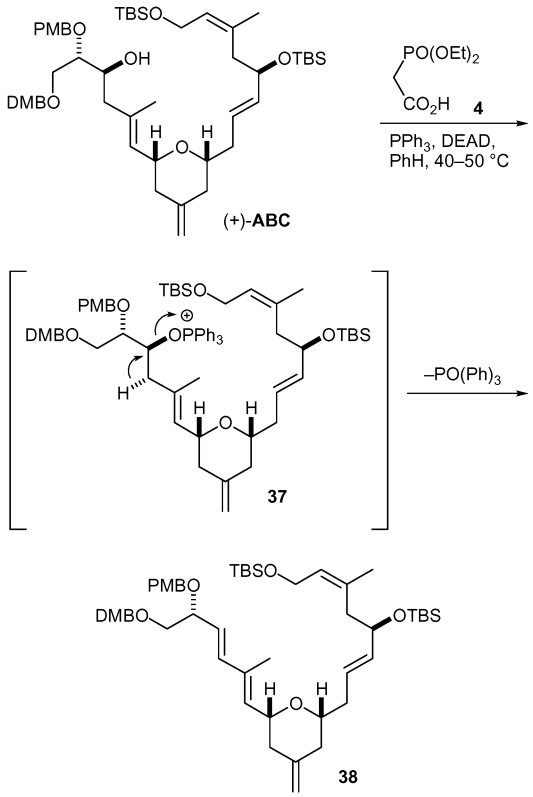
effective, not only reducing greatly byproduct formation (**33**−**35**) but also increasing the yield of the coupled (+)-**ABC** alcohol. A new byproduct **36**, involving ring opening of the tetrahydropyran ring, however, began to emerge (Scheme 9). Use of 2 equiv of *t*-BuLi for the lithium−halogen exchange led to the desired adduct (+)-**ABC** in 40−50% yield, with yields of **36** ranging from 6% to 27%. Best results, however, were obtained upon reducing the stoichiometry of *t*-BuLi to 1.7 equiv; the (+)-**ABC** fragment was thus produced in 69−72% yield, with only 3% of **36** (Scheme 10). The isolated yield (ca. 13−19%) of **32** remained rather constant in all cases.

Scheme 10



Esterification of (+)-ABC with Diethylphosphonoacetic Acid (4): An Anomalous Mitsunobu Reaction. With sufficient quantities of the (+)-**ABC** fragment in hand, the next step in the proposed synthetic sequence called for introduction of an acyl phosphonate at the C(19) secondary hydroxyl with inversion of configuration, employing the commercially available diethylphosphonoacetic acid (**4**).[13] The standard protocol for the Mitsunobu reaction calls for premixing the alcohol and acid,[13] followed by addition of triphenylphosphine (PPh_3) and diethylazodicarboxylate (DEAD). Surprisingly, incomplete consumption of (+)-**ABC** was observed even after prolonged stirring of this mixture at ambient temperature (12 h). Neither additional quantities of DEAD and PPh_3 nor reversing the order of reagent addition produced an effect on the reaction outcome. Heating the reaction mixture to 40−50 °C also proved unproductive, producing instead almost exclusively a side product (**38**), which results by elimination of the activated hydroxyl in the presumed (+)-**ABC**−PPh_3 complex **37** (Scheme 11).

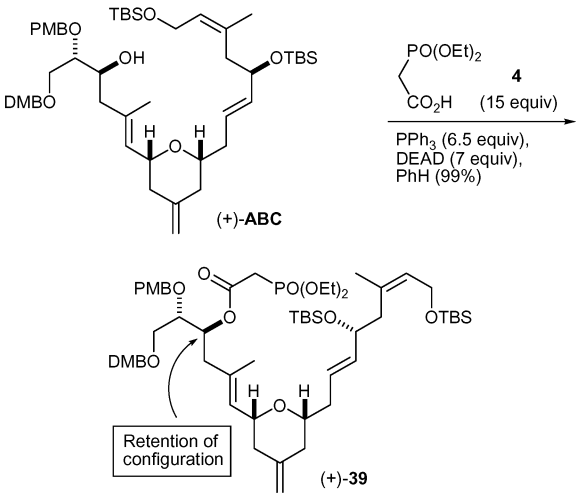
Scheme 11



Saturation of the reaction medium with a combination of **4** (15 equiv), PPh_3 (6.5 equiv), and DEAD (7 equiv) at ambient temperature eventually resulted in complete consumption of the starting material. The reaction now occurred in less than 3 h. To our chagrin, however, esterification of (+)-**ABC** had resulted in acyl phosphonate (+)-**39**, with complete *retention* of the C(19) stereogenicity (Scheme 12)! This stereochemical outcome, unrecognized at the time, will be addressed in detail later. To avoid confusion with what follows, the C(19) stereogenicity in all relevant compounds [from (+)-**39** to (−)-**53**] will be depicted with their correct (uninverted) configurations.

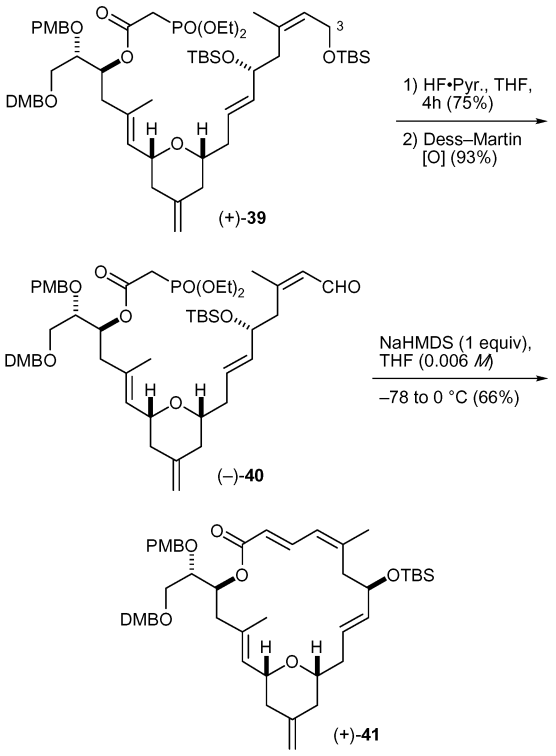
Completion of the Macrocycle. Selective removal of the TBS group at C(3) was next achieved with HF·pyridine in good yield (Scheme 13); oxidation of the derived allylic alcohol with Dess−Martin periodinane[39] then smoothly furnished aldehyde (−)-**40**, substrate for the intramolecular Horner−Wadsworth−

Scheme 12



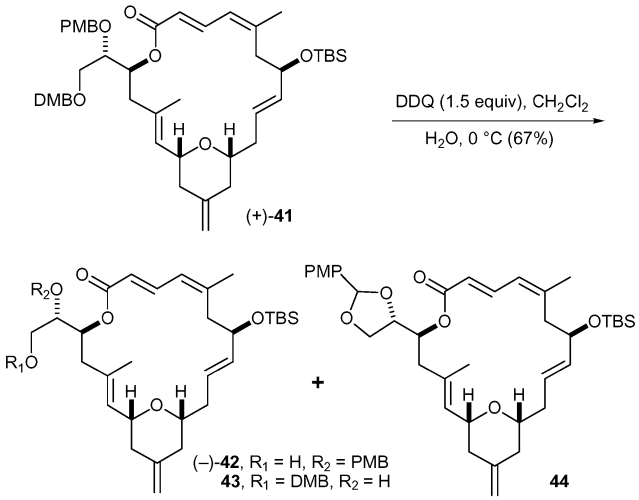
Emmons reaction.[14] At first, closure of the macrolactone under Masamune−Roush conditions (LiCl, DBU, MeCN)[40] led to the desired 20-membered macrolide [(+)-**41**], albeit in low yield, with little or no recovery of the starting material. However, treatment of a dilute solution (0.006 M) of (−)-**40** in THF with 1 equiv of sodium bis(trimethylsilyl)amide at −78 °C, followed by warming of the reaction mixture to 0 °C, furnished the desired macrolide (+)-**41** as a single olefinic isomer in 66% yield.[41]

Scheme 13



Installation of the *N*-Acyl Hemiaminal. With the assumption that the macrocyclic ring of zampanolide (**1**) was now in hand, we turned to elaboration of the C(20) *N*-acyl hemiaminal, followed by introduction of the unsaturated side chain. Selective removal of the primary DMB protecting group (DDQ)[42] in the presence of the C(20) PMB ether readily afforded primary alcohol (−)-**42**, albeit in a modest yield of 67% (Scheme 14). The major problem associated with this reaction was incomplete consumption of the staring material, (+)-**41**. Addition of more than 1 equiv of DDQ not only failed to force the reaction to completion but instead resulted in the generation of two prominent side products. Identified by ^{1}H NMR, one was the expected C(20) alcohol **43**, resulting from competitive removal of the PMB group; the other was the *p*-methoxybenzylidine acetal **44**, stemming presumably from intramolecular closure of the liberated primary hydroxyl onto the quinone methide intermediate derived from the activated PMB ether. In retrospect, the outcome of this transformation reveals the conceptual shortcoming of positioning two protecting groups susceptible to oxidative cleavage on vicinal hydroxyl groups.

Scheme 14

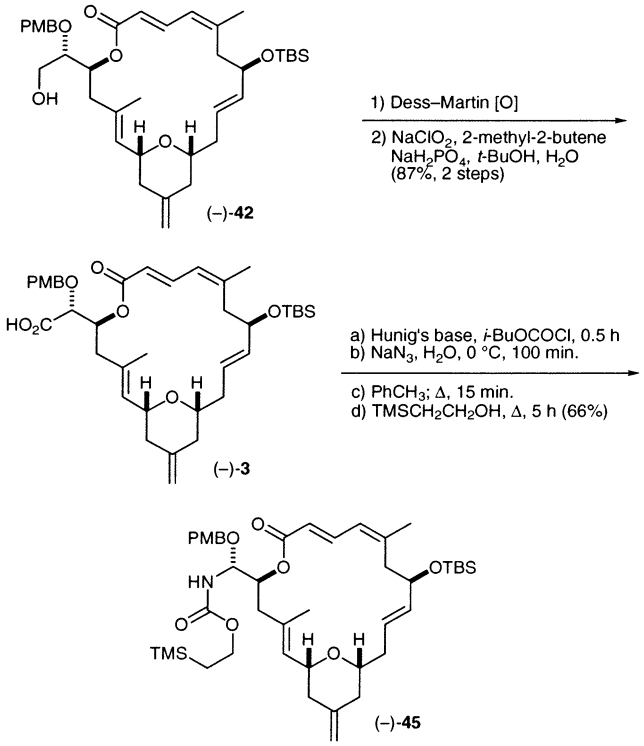


Conversion of alcohol (−)-**42** to the corresponding α-alkoxy acid (−)-**3** (Scheme 15) was next achieved in good yield via a two-step oxidation (Dess−Martin,[39] followed by buffered $NaClO_2$[24]). We were thus ready to install the *N*-acyl hemiaminal moiety via the proposed Curtius rearrangement.[10] Initially we explored the one-pot protocol of Yamada,[43] utilizing diphenylphosphoryl azide (DPPA). Unfortunately, this method proved unsatisfactory, leading to significant decomposition of the starting material. Attention was therefore shifted to the stepwise procedure of Weinstock.[44] Treatment of (−)-**3** in turn with excess Hünig's base, isobutyl chloroformate, and aqueous sodium azide, followed by thermal rearrangement[45] and capture of the isocyanate with 2-(trimethylsilyl)ethanol,[46] provided the desired α-alkoxy Teoc-carbamate (−)-**45** in 66% yield, with complete retention (vide infra) of the C(20) stereogenicity.[10]

Fragment D: 2(*Z*),4(*E*)-Hexadienoic Acid Chloride. The synthesis of fragment **D**, coupling partner for carbamate (−)-

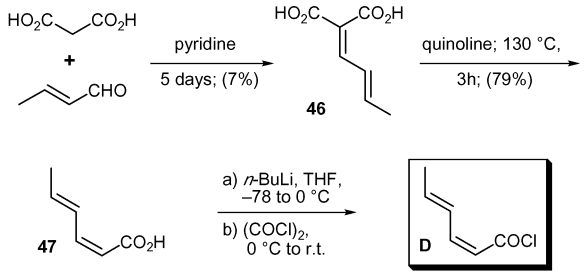
(39) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(40) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(41) Smith, A. B., III; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.
(42) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(43) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(44) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511. Also see: Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.
(45) This process was conveniently monitored by FT IR spectroscopy. The azide absorption band (ca. 2140 cm^{-1}) was no longer detectable after 15 min of refluxing. The corresponding isocyanate absorbed at ca. 2250 cm^{-1}.
(46) The 2250 cm^{-1} isocyanate absorption band disappeared 5 h after addition of 2-(trimethylsilyl)ethanol.

Scheme 15



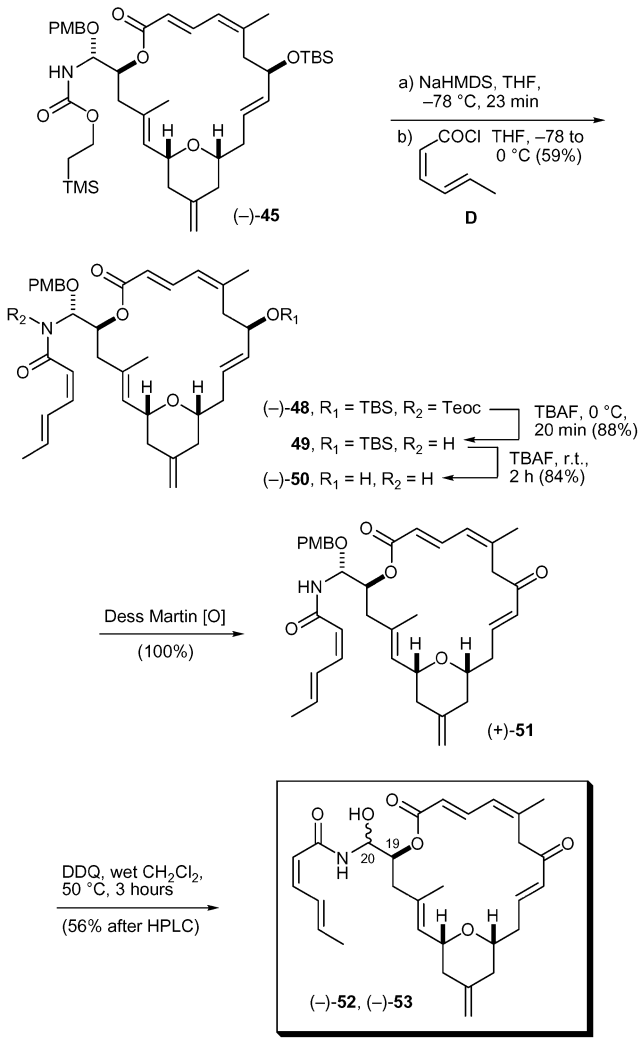
45, entailed three steps. Doebner condensation[47] of malonic acid with crotonaldehyde furnished the corresponding unsaturated diacid **46**, which was subjected to decarboxylation (quinoline, 130 °C) to afford 2(*Z*),4(*E*)-hexadienoic acid (**47**) as the sole isomer (Scheme 16).[48] Conversion to acid chloride **D** was then achieved with *n*-butyllithium (THF) and oxalyl chloride.[49] This procedure obviated the necessity to isolate the sensitive and volatile fragment **D**, since the byproducts [*n*-butane (g), CO_2 (g), CO (g), and LiCl (solubilized in THF)] would not be expected to interfere with the proposed carbamate acylation.

Scheme 16



Syntheses of C(19)-*epi*-Zampanolide and C(19,20)-Bis-*epi*-zampanolide. Having presumably successfully arrived at the macrocyclic framework of zampanolide, possessing the protected *N*-acyl hemiaminal moiety, we focused on completion of the synthesis. Introduction of the unsaturated amide side chain was achieved in 59% yield via acylation of carbamate (−)-**45** with fragment **D** (Scheme 17). On small scale, this transformation proved difficult, either failing to proceed in some cases or affording low yields, presumably due to adventitious water.[50]

Scheme 17



Best results (59%) were obtained by deprotonation of (−)-**45** with 1 equiv of sodium bis(trimethysilyl)amide at −78 °C, followed by careful addition of acid chloride **D** in THF.[49]

Attempted removal of the trimethylethoxycarbonyl (Teoc) and TBS protecting groups in one step with tetrabutylammonium fluoride (TBAF) afforded alcohol (−)-**50**, albeit in modest 42% yield, with substantial amounts of decomposition, ostensibly due to the basicity of TBAF. Exploiting the lower reactivity of the C(7) allylic TBS ether to TBAF at 0 °C, sequential desilylation via the intermediary amide **49** furnished (−)-**50** in 74% for the two steps. Oxidation with Dess−Martin periodinane[39] then provided the penultimate ketone (+)-**51**.

Removal of the PMB group in (+)-**51** under oxidative conditions also proved challenging. Initial treatment with DDQ or cerium ammonium nitrate in dichloromethane failed either at 0 °C or at ambient temperature. Other mild conditions, such as $SnCl_2$/TMSCl/anisole[51] and BCl_3·SMe_2,[52] led to major decomposition. The radical anion (LDBB)[17] also proved ineffective, even when used in large excess. Undaunted, we revisited the initial DDQ conditions, eventually discovering that exposure

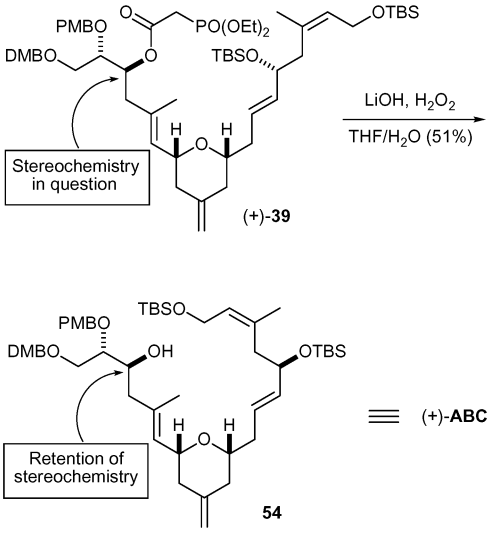
(47) Johnson, J. R. *Org. React.* **1942**, *1*, 210.
(48) Crombie, L.; Crombie, W. M. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1267.
(49) (a) Roush, W. R.; Pfeifer, L. A. *J. Org. Chem.* **1998**, *63*, 2062. (b) Roush, W. R.; Pfeifer, L. A.; Marron, T. G. *J. Org. Chem.* **1998**, *63*, 2064.
(50) In such cases, the starting material was recovered in essentially quantitative yield, with the C(20) stereogenicity remaining intact, as determined by ^{1}H NMR analysis.
(51) Akiyama, T.; Shima, H.; Shoichiro, O. *Synlett* **1992**, 415.
(52) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663.

of ketone (+)-**51** to 2 equiv of DDQ in wet CH_2Cl_2 at 50 °C yielded a mixture of two polar compounds (1.8:1), readily separable by HPLC, in a combined yield of 56%.

Initial ^{1}H NMR and HRMS analysis indicated removal of the PMB group in both products, suggesting that the two products were epimeric at C(20). However, detailed comparison of the ^{1}H NMR spectral data of the C(20) epimers with the literature data for (−)-zampanolide (**1**) clearly demonstrated that *neither* was zampanolide![53] Since no olefin migration and/or isomerization appeared to have occurred, we surmised that the lack of identity might have been due to the Mitsunobu reaction. Assuming this to be the case, we tentatively assigned the two products as (−)-**52** and (−)-**53**, both possessing the undesired stereogenicity at C(19).

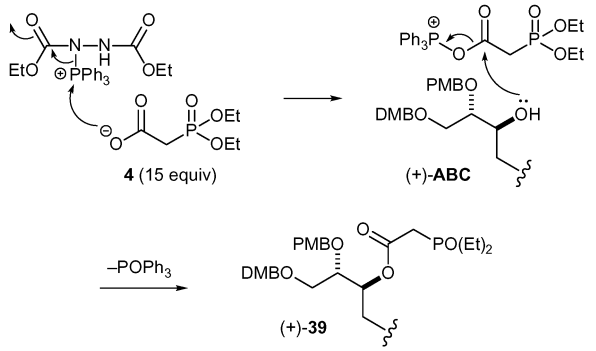
The Mitsunobu Reaction Revisited. To secure the stereochemical outcome of the Mitsunobu reaction, we subjected ester (+)-**39** to saponification (Scheme 18). The resulting product proved identical (500 MHz ^{1}H and 125 MHz ^{13}C NMR) with the (+)-**ABC** alcohol of known C(19) stereogenicity prepared earlier. Thus, inversion at C(19) had *not* occurred.

Scheme 18



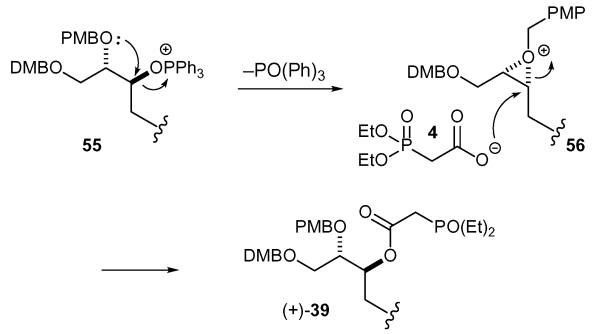
Two rationales could explain this unexpected result. The first, and the most likely scenario (Scheme 19), would entail failure of the PPh_3−DEAD complex to activate the C(19) hydroxyl due to steric inaccessibility. Consequently, diethylphosphonoacetic acid (**4**), present in large excess relative to (+)-**ABC**, would consume the DEAD and PPh_3; nucleophilic attack of the C(19) hydroxyl on the activated **4**−PPh_3 complex could then lead to (+)-**39**, the product with retention of C(19) configuration.

Scheme 19



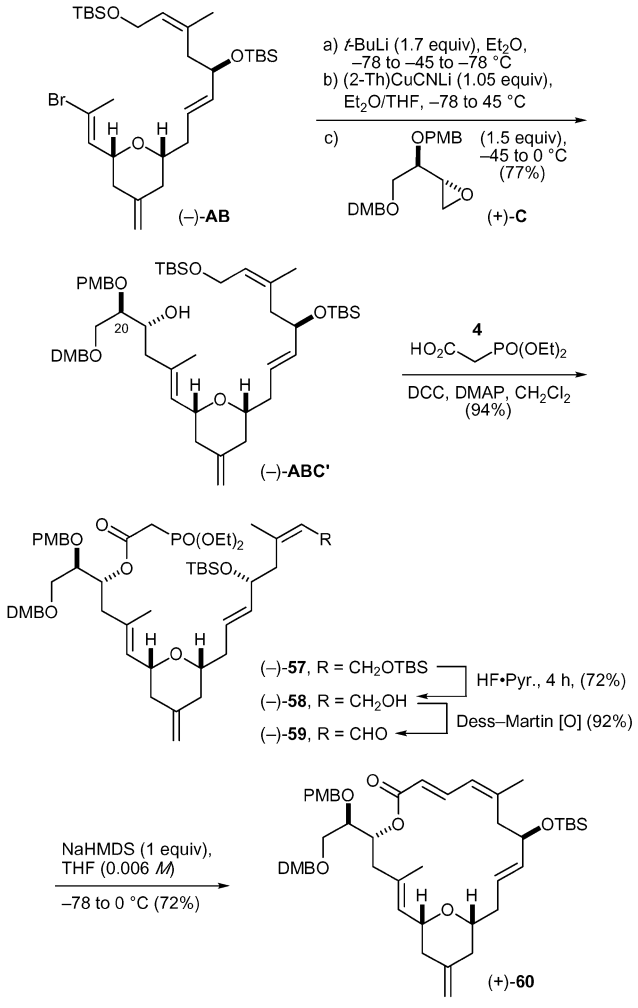
Alternatively, initial activation of (+)-**ABC** (i.e., **55**) does indeed occur (Scheme 20); however, due to the steric bulk surrounding the activated C(19) stereocenter, a more facile neighboring group participation may ensue, inverting the C(19) stereocenter and generating a highly electrophilic intermediate **56**, which in turn undergoes ring opening to furnish (+)-**39** with net retention of the stereochemistry at C(19). The high level of regioselectivity required in this proposal, however, leaves this explanation suspect.

Scheme 20



Construction of the Zampanolide Macrocycle: A Second Generation Strategy (Scheme 21). With the stereochemical outcome of the Mitsunobu reaction understood, all that would be required to arrive at the correct zampanolide macrolide would

Scheme 21

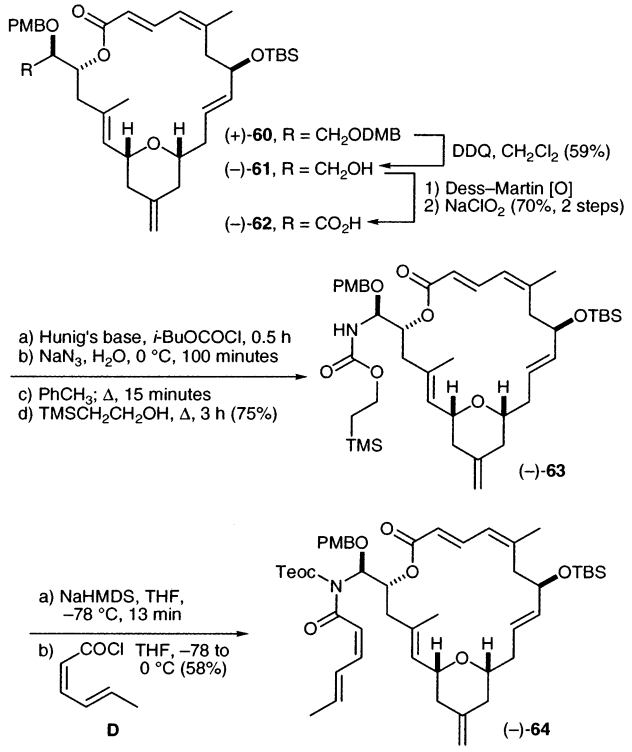


be access to the diastereomeric epoxide. We chose instead to employ the more readily available antipode of the epoxide [i.e., (+)-**C**]. Use of (+)-**C** would lead to the zampanolide macrolide possessing the β-C(20) relative configuration as our synthetic target. Importantly, this change would have no consequence vis-à-vis our overall strategy for construction of the zampanolide skeleton.

Toward this end, union of the mixed cyano−Gilman cuprate (**31**), derived from vinyl bromide (−)-**AB**, with epoxide (+)-**C**,[54] led, as expected, to alcohol (−)-**ABC′**, now possessing the desired relative C(19) stereogenicity (Scheme 21). Esterification with diethylphosphonoacetic acid (**4**) under the Steglich conditions (DCC, DMAP),[55] followed by selective removal of the C(3) silyl group and Dess−Martin oxidation,[39] furnished aldehyde (−)-**59**, substrate for the HWE macrocyclization.[14] Pleasingly, macrocycle (+)-**60** was produced in 72% yield.[41]

Total Syntheses of (+)-Zampanolide and (+)-C(20)-*epi*-Zampanolide. With ample quantities of the fully elaborated macrocycle (+)-**60** in hand, now possessing the requisite relative stereochemistry at C(19), we turned to complete the total synthesis. Oxidative removal of the DMB protecting group[42] in (+)-**60**, followed by a two-step oxidation[39,24] of the derived primary hydroxyl in (−)-**61**, produced (−)-**62**, substrate for Curtius rearrangement (Scheme 22); as before, rearrangement

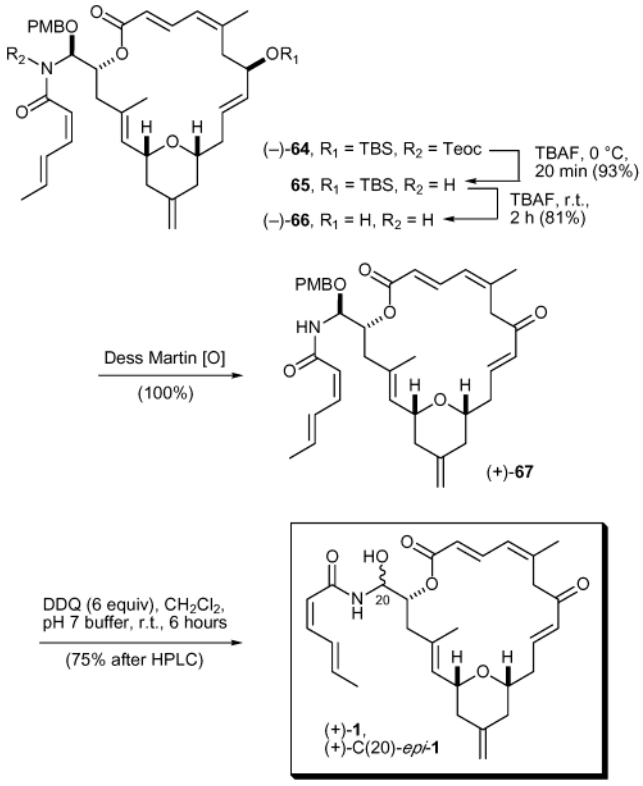
Scheme 22



afforded the desired α-alkoxy carbamate (−)-**63**, both in a highly stereospecific fashion and in good overall yield (75%). Acylation[49] with acid chloride **D** then gave the Teoc-protected amide (−)-**64**.

Iterative removal of the Teoc and TBS moieties, as before, followed by oxidation of the liberated C(7) hydroxyl, provided ketone (+)-**67**, a single compound in 75% overall yield for the three steps (Scheme 23). Oxidative removal of the PMB protecting group (DDQ, pH 7 buffer, CH_2Cl_2, ambient temperature) next produced a mixture (1.3:1) of two polar compounds epimeric at C(20). Best results (75% combined yield) were obtained with freshly recrystallized DDQ. Importantly, after HPLC separation, the major, less polar component possessed spectral data identical in all respects to the literature data for natural (−)-zampanolide (e.g., 500 MHz ^{1}H and 125 MHz ^{13}C NMR; 600 MHz COSY and HMQC; HRMS and IR),[53] except for chiroptic properties {natural **1**, $[\alpha]_D^{29} = -101°$ (*c* 0.12, CH_2Cl_2); synthetic **1**, $[\alpha]_D^{25} = +102.3°$ (*c* 0.09, CH_2Cl_2)}.[4] The structure of (+)-C(20)-*epi*-**1** was secured via extensive spectroscopic analysis. It should be emphasized that at this point the relative stereochemistry at C(20) in both (+)-**1** and (+)-C(20)-*epi*-**1** remained unknown.

Scheme 23

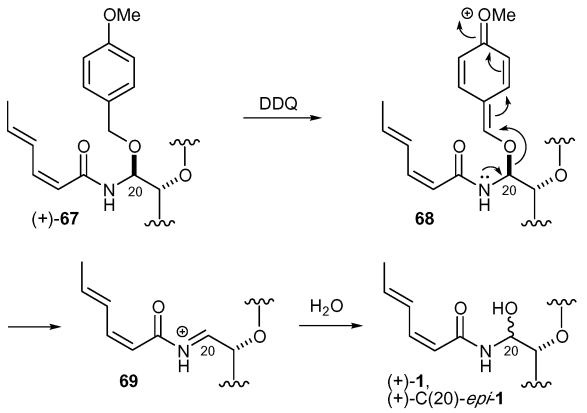


Comments on the Final Deprotection. Well aware of the potential instability of the *N*-acyl hemiaminal functionality, we had carefully selected the PMB protecting group, reasoning that acidic or basic conditions might be incompatible with the *N*-acyl hemiaminal group, as well as other functionality in the molecule. Protecting groups susceptible to hydrogenolysis were also excluded. The optimal choice thus appeared to be the *p*-methoxybenzyl group, known to release upon DDQ oxidation under essentially neutral conditions.[56] Nonetheless, epimerization at C(20) upon treatment with DDQ did occur presumably via an electrophilic acyliminium ion (i.e., **69**). Although the exact origin of **69** is unclear, the most plausible pathway would entail

(53) We thank Professors Tanaka and Higa for providing copies of the ^{1}H and ^{13}C NMR, COSY, HMQC, and IR spectra for natural (−)-zampanolide (**1**).
(54) Epoxide (+)-**C** was prepared in seven steps from commercially available (−)-dimethyl tartrate via a synthetic sequence analogous to that shown in Scheme 6; see the Supporting Information for details.
(55) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(56) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

either the facile elimination of *p*-anisaldehyde from the quinone methide intermediate **68** (Scheme 24) or an acid-promoted dehydration of the liberated *N*-acyl hemiaminal.

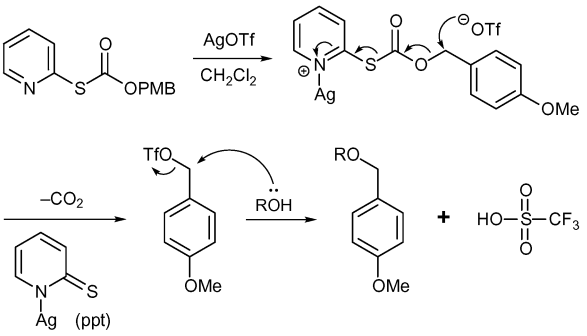
Scheme 24



To suppress the observed epimerization, we explored the use of a variety of organic buffers. Addition of bases such as 2,6-di-*tert*-butyl-4-methylpyridine did not prevent epimerization. Switching to a MeCN/pH 7 buffer system resulted only in recovery of starting material. Other conditions, such as cerium ammonium nitrate in MeCN/H_2O, were equally unsuccessful. Attempts to derivatize the C(20) stereocenter for Mosher ester analysis also met with failure.

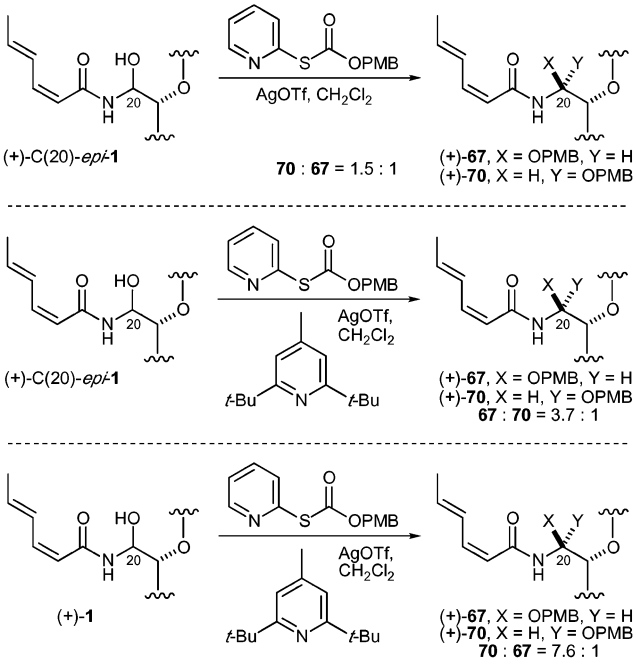
Tentative Assignment of the C(20) Relative Configuration. Unable to prevent erosion of the stereogenicity at C(20) upon deprotection of (+)-**67** and thereby assign with certainty the relative stereochemistry, we reasoned that reprotection of (+)-**1** and (+)-C(20)-*epi*-**1** as the PMB ether, in conjunction with spectroscopic correlation with (+)-**67**, possessing the known C(20) stereogenicity, would permit assignment of the C(20) configuration. After considerable experimentation, the PMB protection protocol of Hanessian[57] emerged as the method of choice, albeit not without difficulty (Scheme 25).

Scheme 25



Via this tactic, protection of (+)-C(20)-*epi*-**1** afforded a mixture of products (ca. 1.5:1), the minor component displaying spectroscopic properties (i.e., ^{1}H NMR) identical to those of ketone (+)-**67** (Scheme 26). Extensive spectroscopic analysis of the major product permitted assignment of structure (+)-**70**. Presumably, the trifluoromethanesulfonic acid, generated in the course of the reaction, promotes the epimerization at C(20). Buffering the reaction medium with 2,6-di-*tert*-butyl-4-methylpyridine abated epimerization. Under these conditions, the (+)-C(20)-*epi*-**1** congener afforded a 3.7:1 mixture of (+)-**67** and (+)-**70**; (+)-zampanolide (**1**), on the other hand, afforded (+)-**70** and (+)-**67** in a 7.6:1 ratio. Additional evidence for the structural assignments was provided by the various electronic spectra. Both (+)-**1** and (+)-**70** possessed UV absorption maxima (λ_{max}) at 259.2 nm, whereas (+)-C(20)-*epi*-**1** and (+)-**67** absorbed at 262.7 nm. Taken together, these results permit the tentative assignment of the relative and absolute stereochemistry of (+)-zampanolide (**1**) as 11*R*, 15*R*, 19*R*, and 20*R*.[4]

Scheme 26



Total Synthesis of (+)-Dactylolide (2). Shortly after completion of the synthesis of (+)-**1**, we became aware of the isolation, partial structure assignment, and biological activity of (+)-dactylolide (**2**), a new cytotoxic natural product derived from a marine sponge of the genus *Dactylospongia*, collected off the coast of the Vanuatu islands (Scheme 27).[58] In addition to (+)-dactylolide (**2**), the sponge also yielded the known marine metabolites (−)-mycothiazole, (−)-isolaulimalide, (+)-latrunculin A, and (−)-laulimalide. Interestingly, the latter two metabolites were also isolated from the Okinawan sponge *F. rimosa*, the source of (−)-zampanolide (**1**).[1]

The structure of **2** comprises the macrocyclic domain of zampanolide (**1**), with *cis* relative stereochemistry between the C(11) and C(15) stereogenic centers, and undefined, but configurationally stable stereogenicity at C(19);[59] the absolute stereochemistry was not assigned.[58] Interestingly, (+)-dactylolide (**2**) displayed modest tumor cell growth inhibitory activity in a number of cell lines [i.e., 63% inhibition of L1210 (lymphatic leukemia of mice) and 40% inhibition of SK-OV-3 (carcinoma of the ovaries) tumor cell lines at 3.2 μg/mL].[58] The mode of action, however, was not reported.

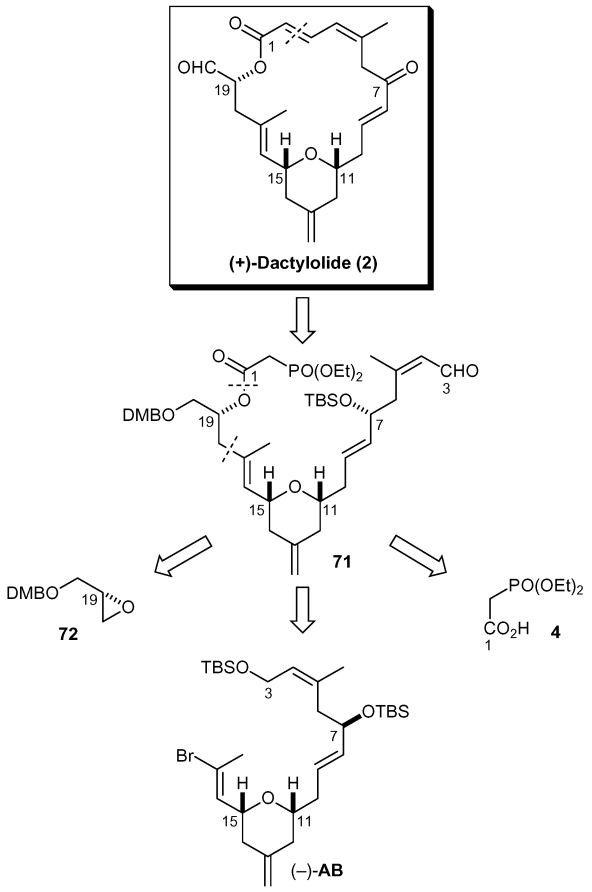
Since (+)-**2** can be viewed as a simplified analogue of (−)-**1**, parallel biological screening of both metabolites would provide data on the significance of the *N*-acyl hemiaminal moiety in zampanolide. With this goal, and with the desire to

(57) Hanessian, S.; Huynh, H. K. *Tetrahedron Lett.* **1999**, *40*, 671.

(58) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775.

(59) Apparently, Riccio and co-workers were unaware of (−)-zampanolide (**1**).

Scheme 27

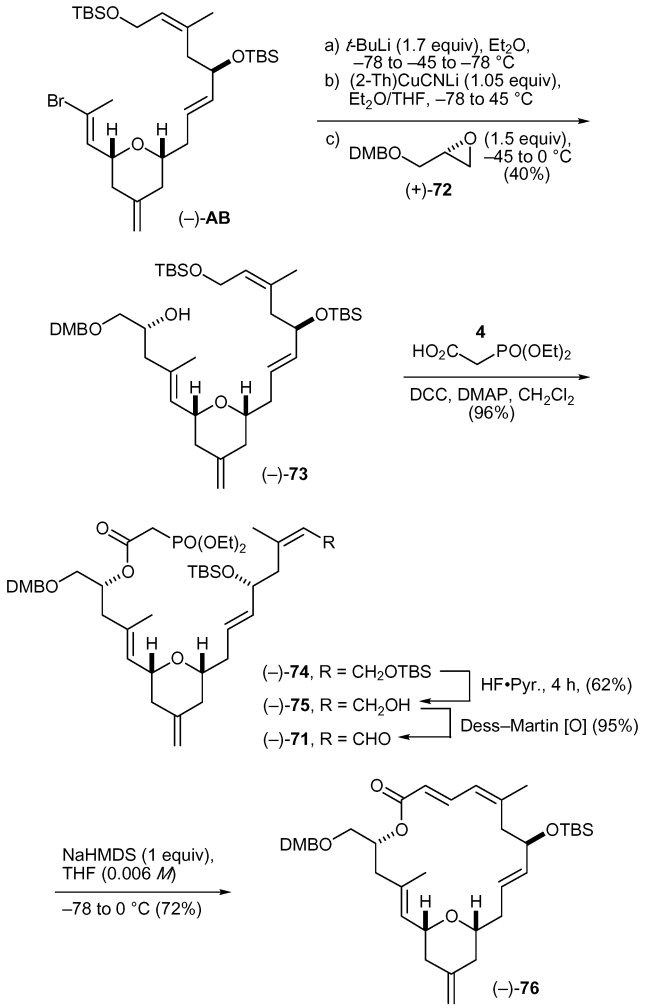


define the complete stereostructure in mind, we embarked on the total synthesis of (+)-dactylolide (**2**), exploiting the same antithetic analysis as employed in the zampanolide synthesis (Scheme 27). Given the close structural relationship, we envisioned (+)-dactylolide to possess the same relative [i.e., at C(19)] and absolute stereochemistries; thus, our synthetic target was set at **2**, with the clear expectation that the use of (−)-**AB** from the synthesis of (+)-zampanolide (**1**) would, if successful, lead to the unnatural enantiomer of **2**.

Assembly of the (+)-Dactylolide Macrocycle. As with (+)-zampanolide (**1**), union of the mixed cyano−Gilman cuprate (**31**),[12] derived from vinyl bromide (−)-**AB**, now with epoxide (+)-**72**, the latter prepared in one step (NaH, DMBCl) from commercially available (*S*)-(−)-glycidol, furnished alcohol (−)-**73** in an unoptimized yield of 40% (Scheme 28). Acylation[55] with **4** next gave phosphonoester (−)-**74** in near quantitative yield. Selective desilylation (HF•pyridine) at C(3), and Dess−Martin oxidation[39] then afforded aldehyde (−)-**71** (57% yield, three steps), which was subjected to Horner−Wadsworth−Emmons macrocyclization[14] [NaHMDS (1 equiv), −78 °C, with subsequent warming to 0 °C] to produce (−)-**76** in 72% yield.[41]

Completion of the (+)-dactylolide (**2**) synthesis was then achieved in four steps; unmasking the C(7) hydroxyl (TBAF), followed by Dess−Martin oxidation,[39] furnished ketone (+)-**77** in 50% yield for the two steps (Scheme 29). Oxidative removal of the DMB protecting group (DDQ)[56] and oxidation with Dess−Martin periodinane[39] then afforded (+)-dactylolide (**2**) in 69% yield for the two steps. The spectral and chiroptic data for synthetic (+)-**2** proved identical in all respects with the spectral data derived from the natural product {e.g., ^{1}H (500

Scheme 28



and 600 MHz) and HSQC (600 MHz) NMR and HRMS; natural **2**, $[\alpha]_D^{25} = +30°$ (*c* 1.0, MeOH); synthetic **2**, $[\alpha]_D^{25} = +235°$ (*c* 0.52, MeOH)}.[60]

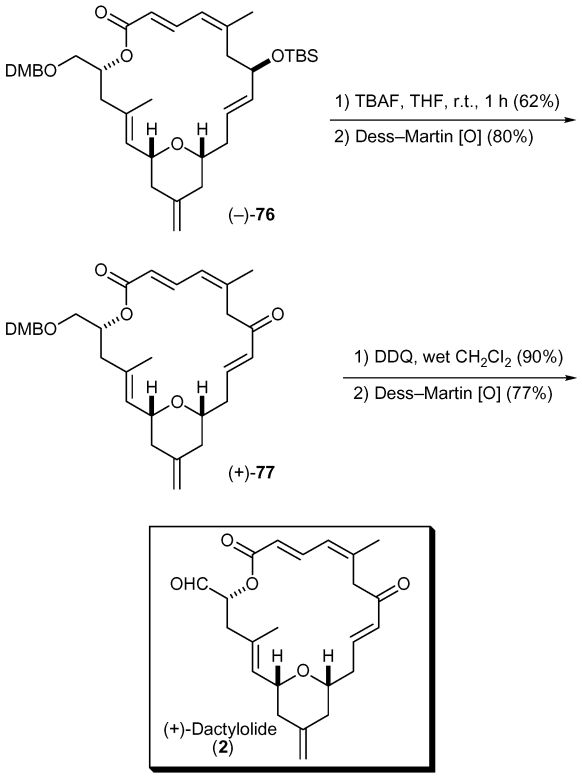
Completion of the total synthesis of (+)-dactylolide (**2**) provided an interesting observation: vinyl bromide (−)-**AB** gives rise both to natural dactylolide [(+)-**2**] and to the non-naturally-occurring antipode of zampanolide, (+)-**1**. Thus, assuming that the published chiroptic data for the two natural products are correct, the macrocyclic domain of natural zampanolide is enantiomeric with that of natural dactylolide.[61]

Although (−)-**1** and (+)-**2** were isolated from two geographically widely separated, taxonomically different sponge species, the structural similarity of the two metabolites would seem to imply that both arise from genetically related symbiotic

(60) We thank Professor Raffaele Riccio for the 600 MHz ^{1}H and HSQC NMR spectra of natural (+)-dactylolide (**2**). Interestingly, the 125 MHz ^{13}C NMR data for synthetic (+)-dactylolide revealed small shifts ($\Delta\delta = \pm 0.1-0.9$ ppm) for most carbon signals relative to the corresponding signals reported, and presumably derived from the HSQC NMR spectrum of natural (+)-dactylolide; the ^{1}H NMR (i.e., 500 and 600 MHz) spectra of the synthetic and natural materials were completely superimposable.

(61) We have verified with Professor Riccio that the observed sign of the optical rotation of natural dactylolide is plus. For examples of enantiomeric natural products of plant origin, see: (a) Ashworth, D. M.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1983**, 1327. (b) Spavold, Z. M.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 4. (c) Zhang, Y.; Zheng, L.; Woo, M.-H.; Gu, Z.-M.; Ye, Q.; Wu, F.-E.; McLaughlin, J. L. *Heterocycles* **1995**, *41*, 1743 and references cited therein. (d) Melching, S.; Bülow, N.; Wihstutz, K.; Jung, S.; König, W. A. *Phytochemistry* **1997**, *44*, 1291. (e) Fukuyama, Y.; Yokoyama, R.; Ohsaki, A.; Takahashi, H.; Minami, H. *Chem. Pharm. Bull.* **1999**, *47*, 454 and references cited therein.

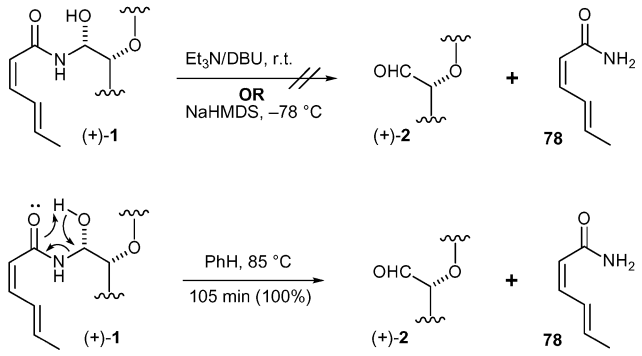
Scheme 29



microorganisms. That is, (+)-dactylolide might be the biosynthetic precursor of (+)-zampanolide, if the latter exists in nature, or perhaps comprises a degradation product thereof.

Chemical Correlation of (+)-Zampanolide (1) with (+)-Dactylolide (2). To achieve a chemical correlation between the two natural products, we reasoned that exposure of (+)-zampanolide (**1**) either to base or to thermolysis in an inert solvent would lead to elimination of the side chain by cleavage of the C(20)−N bond, presumably via a retro-ene-like reaction, to afford (+)-dactylolide (**2**) and 2(*Z*),4(*E*)-hexadienoic acid amide (**78**). Initially, all attempts to promote a base-induced fragmentation of (+)-**1** either with triethylamine or 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) at room temperature or with sodium bis(trimethylsilyl)amide at −78 °C met with failure (Scheme 30). Heating (+)-zampanolide (**1**) in benzene at 85 °C for 105 min, however, cleanly furnished (+)-dactylolide (**2**) and amide **78**, as evidenced by the ^{1}H NMR of the reaction mixture. Subsequent chromatographic purification furnished (+)-dactylolide (**2**), which displayed spectral and physical data

Scheme 30



identical in all respects to those of (+)-**2**, prepared from vinyl bromide (−)-**AB**. Similarly, exposure of a 1.3:1 mixture of (+)-**1** and (+)-C(20)-*epi*-**1** to the aforementioned thermal reaction conditions afforded (+)-**2** and **78** as the only products detectable by ^{1}H NMR. Interestingly, permitting the reaction mixture to stand in deuterated chloroform either at room temperature or at 60 °C did not lead to re-formation of either (+)-zampanolide (**1**) or (+)-C(20)-*epi*-**1**, as evidenced by ^{1}H NMR.

Summary. The first total syntheses of (+)-zampanolide (**1**) and (+)-dactylolide (**2**) have been achieved. Key features of the unified synthetic scheme included the stereocontrolled construction of the *cis*-2,6-disubstituted tetrahydropyran via a modified Petasis−Ferrier rearrangement and a highly convergent assembly of the macrocyclic domain. Installation of the *N*-acyl hemiaminal in (+)-zampanolide (**1**) was then achieved via a stereospecific Curtius rearrangement. The complete relative and absolute stereochemistries for both (+)-zampanolide and (+)-dactylolide were also assigned, albeit tentatively in the case of (+)-zampanolide (**1**).

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Supporting Information Available: Experimental procedures and analytical data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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