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2. Synthesis of the C.14-C.26 hydrophilic domain of amphidinolide B1 and formation of the (*E*)-1,1',3-trisubstituted diene sector

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Abstract: In the preceding letter, we described a synthesis of the conserved C.1-C.13 hydrophobic domain common to the potent B-type amphidinolides. In this letter, we present syntheses of the C.14-C.26 hydrophilic domain specific to amphidinolide B1 and a model for uniting the hydrophobic and hydrophilic domains to form the (*E*)-1,1',3-trisubstituted diene. © 1999 Published by Elsevier Science Ltd. All rights reserved.

A retrosynthetic outline for a unified synthesis of the highly cytotoxic B-type amphidinolides is shown in Figure 1.[2] We have reported the synthesis of a methyl ketone precursor to vinyl anion **2** in the preceding letter.[3] In this letter, we describe the synthesis of the hydrophilic domain aldehyde **1** specific to amphidinolide B1. Finally, we present a model allylic alcohol that examines the coupling of the two domains for the synthesis of the critical (*E*)-1,1',3-trisubstituted diene moiety found in the B-type amphidinolides.

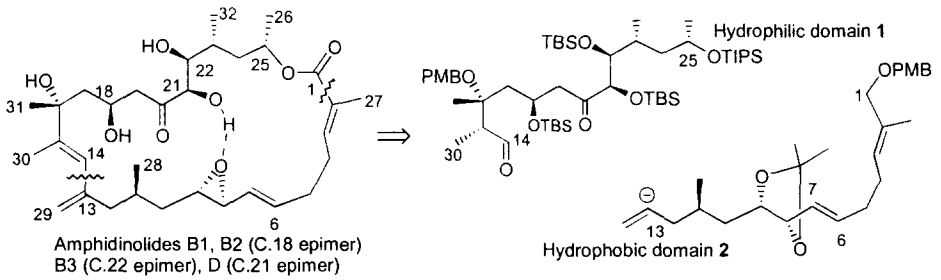

Figure 1. Retrosynthesis of the B-type amphidinolides.

The synthesis of aldehyde **1** begins with geraniol epoxide **3**, available in 97% e.e. from a Sharpless asymmetric epoxidation (Scheme 1).[4] The latent C.30 vinyl methyl group was introduced regioselectively with lithium dimethyl cuprate to give diol **4**. Installation of the PMB ether *via* a two-step procedure gave primary alcohol **5**. Alcohol **5** was protected as its silyl ether, and the trisubstituted olefin moiety was oxidatively cleaved and converted to an aryl selenide. *In situ* oxidation of the selenide with H_2O_2 gave terminal olefin **6**.[5] Installation of the C.18 stereocenter was accomplished by a Sharpless asymmetric dihydroxylation using

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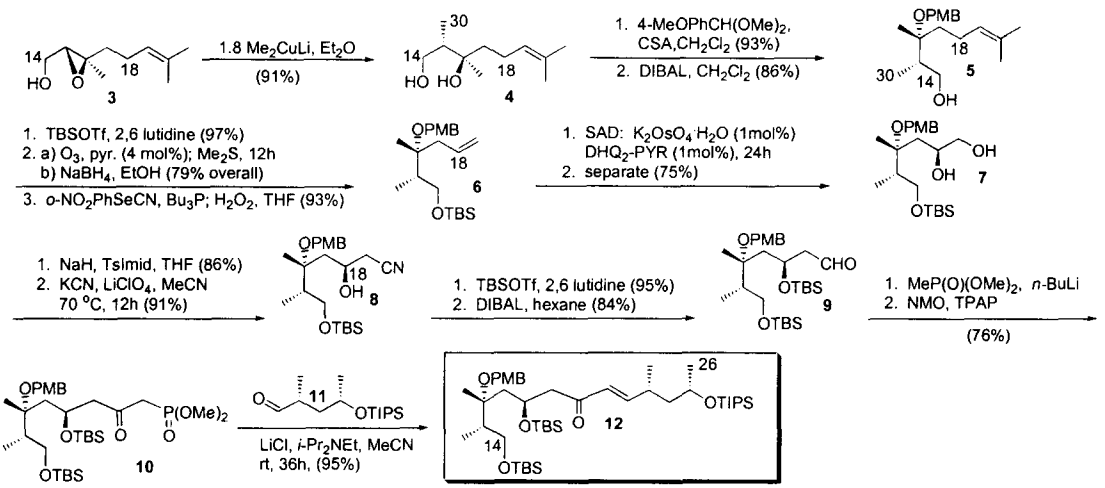
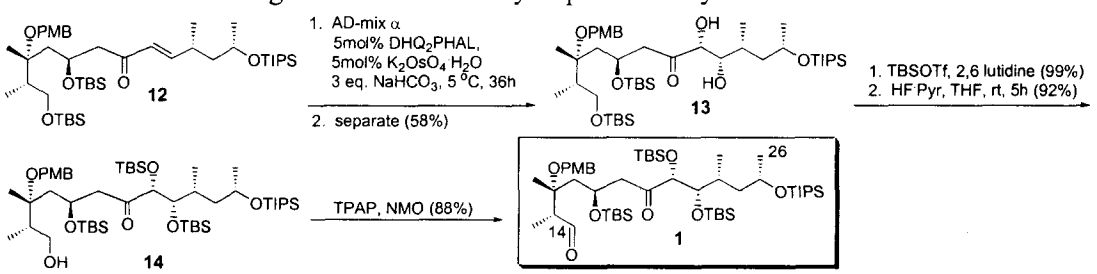
Sharpless' DHQ_2PYR ligand to give a >3:1 mixture of diastereomers.[6] Careful silica gel chromatography (30% EtOAc/30% CH_2Cl_2/40% Hx) gave the desired diol **7** in 75% overall yield. Conversion of the diol to the epoxide was cleanly accomplished with NaH/tosyl imidazole and the resulting epoxide was homologated regioselectively with $KCN/LiClO_4$ in near refluxing MeCN to give C.18 alcohol **8**.[7,8] Following protection of the free alcohol, the nitrile was reduced and hydrolyzed to the stable aldehyde **9**.[9] Addition of the lithium anion of dimethyl methyl phosphonate and TPAP oxidation of the resulting crude mixture gave the ketophosphonate **10**. Aldehyde **11** was synthesized by a Parikh-Doering oxidation (SO_3·pyr, Et_3N, 84%) of the universal alcohol described in the preceding paper.[10] Coupling of the two pieces under Roush-Masamune conditions smoothly led to ketone **12**.[11]



Scheme 1. Synthesis of C.14-C.26 carbon framework.

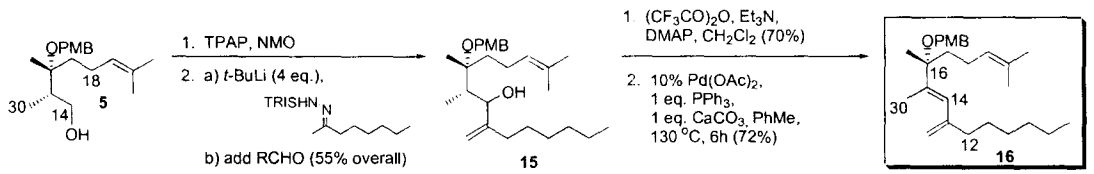
The remaining two stereocenters were installed under modified Sharpless conditions (5 mol% Os, 5 mol% DHQ_2PHAL) since ketone **12** proved to be a slow-reacting substrate.[12] The resulting 6:1 mixture of diastereomers was easily separated by normal silica gel chromatography and the desired diol **13** was isolated in 58% yield. Persilylation of the diol with TBSOTf and selective removal of the primary C.14 silyl group gave primary alcohol **14**. Oxidation of **14** with TPAP/NMO then gave the C.14-C.26 hydrophilic aldehyde **1**.[13]



Scheme 2. Synthesis of the fully functionalized C.14-C.26 hydrophilic domain.

The novel (*E*)-1,1',3-trisubstituted diene sector is not unique to the amphidinolides and interestingly occurs in the fungal extract galbonolide B, for which synthetic studies, including a total synthesis, have been reported.[14-15] However, since we were interested in a unified synthesis of the B-type amphidinolides wherein the diene would ultimately be formed as a result of a coupling between the common and variable domains, we sought strategies that would be compatible with this requirement. Hauser has shown that simple racemic allylic acetates containing an *exo*-methylene group can eliminate to form an (*E*)-1,3-disubstituted diene exclusively when treated with Pd(0) generated *in situ*.[16] Since formation of the overall *E*-alkene geometry was found to be independent of the stereochemistry of the starting acetate, we wondered whether a similar level of specificity could be expected in the construction of the more complex (*E*)-1,1',3-trisubstituted diene found in the B-type amphidinolides.

Toward that end, alcohol **5** was oxidized and added to a vinyl anion generated from the trisylhydrazone of 2-octanone to give alcohol **15** as a single, undetermined diastereomer (Scheme 3).[17] Conversion of the resulting allylic alcohol **15** to the corresponding acetate (Ac_2O, Et_3N, CH_2Cl_2) and elimination under Hauser conditions (10% $Pd(OAc)_2$, Ph_3P, $CaCO_3$, dioxane) typically gave low yields of the desired diene. However, activation of alcohol **15** as its trifluoroacetate ester and treatment with 10% $Pd(OAc)_2$, 1 eq. PPh_3, and 1 eq. $CaCO_3$ to scavenge the eliminated acid was found to be the most reliable sequence in securing diene **16**. The *E*-alkene geometry was assigned based on comparison of its spectroscopic data to that of the known B-type amphidinolides.[2] In particular, the vinyl C.30 methyl group of diene **16** exhibited a high upfield ^{13}C resonance (14.0 ppm) as would be expected for methyl groups of *E*-olefins and compared favorably to the C.30 methyl resonances found in amphidinolides B1, B2, B3, and D (15.0 ppm-15.8 ppm).[18] We have found diene **16** to be stable and can be stored in untreated $CDCl_3$ for months at room temperature without any noticeable decomposition.



Scheme 3. Synthesis of the model diene.

In summary, an (*E*)-1,1',3-trisubstituted diene similar to the C.12-C.17 sector of the B-type amphidinolides was synthesized in good yield from allylic alcohol **15** upon activation as its trifluoroacetate ester and elimination with Pd(0). An efficient and practical synthesis of the hydrophilic domain aldehyde **1** of amphidinolide B1 is presented and represents a potential precursor to a more advanced and useful allylic alcohol. Critical to the synthesis of **1** is the late stage dihydroxylation of the fully coupled C.14-C.26 β-silyloxy enone **12**. The successful timing of such an event enabled the assembly of the complete carbon skeleton of the hydrophilic domain without simultaneous generation of a stereocenter, thereby avoiding potential problems in separation and identification. Finally, the six carbon universal alcohol described in the

preceding letter is used as a precursor to the C.22-C.26 portion of the hydrophilic domain. Since the parent alcohol of aldehyde **11** is used in both syntheses of the hydrophilic and hydrophobic domains, it accounts for 12 of the 32 amphidinolide B1 carbons and provides an atom-economical solution to the large number of isolated stereocenters found in the B-type amphidinolides.

References and Notes

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(2) (a) Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R. W.; Cornell, L.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 2657-2658. (b) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J. Nat. Prod.* **1989**, *52*, 1036-1041. (c) Tsuda, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1994**, *59*, 3734-3737. (d) Kobayashi, J.; Shigemori, H.; Ishibashi, M.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Org. Chem.* **1991**, *56*, 5221-5224. (b) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543-572.

(3) Preceding letter in this issue.

(4) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976. (b) Gao, Y.; Hanson, R. M.; Kunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

(5) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.

(6) Crispino, G. A.; Jeong, K.; Kolb, H. C.; Wang, Z.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785-3786.

(7) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.

(8) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *36*, 4775-4778.

(9) Baasov, T.; Sheves, M. *J. Am. Chem. Soc.* **1985**, *107*, 7524-7533.

(10) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

(11) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

(13) Satisfactory spectroscopic data was obtained for all intermediates. Aldehyde **1**: ^{1}H NMR (360.1 MHz, $CDCl_3$) δ 10.05 (d, 1H, J = 1.1 Hz), 7.31 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 4.60 (m, 2H), 4.43 (d, 1H, J = 10.5 Hz), 4.08 (d, 1H, J = 4.8 Hz), 4.00 (m, 1H), 3.81 (s, 3H), 3.64 (m, 1H), 3.11 (m, 1H), 2.85 (m, 2H), 2.07 (m, 1H), 1.80 (m, 1H), 1.62 (m, 3H), 1.18 (m, 6H), 1.05 (m, 27H), 0.95 (m, 9H), 0.91 (m, 9H), 0.82 (m, 9H), 0.08-0.07 (m, 9H), 0.01- -0.02 (m, 9H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 208.6, 207.0, 158.8, 131.4, 129.0, 113.6, 81.4, 79.2, 78.9, 66.6, 65.1, 63.2, 55.2, 52.6, 50.3, 45.5, 42.3, 30.6, 26.0, 25.8, 24.4, 21.2, 18.3, 18.2, 17.7, 15.1, 12.7, 9.4, -3.8, -4.2, -4.4, -4.5, -4.6, -4.9. IR (thin film) 2951, 1719, 1252, 837 cm^{-1}. HRMS (FAB NaI/NBA) *m/z* 975.6418, $(M+Na)^+$ calcd for $C_{51}H_{100}NaO_8Si_4$: 975.6393. $[\alpha]_D^{20}$ = -57.4 (*c* = 0.018 g/mL, $CHCl_3$).

(14) Tse, B. *J. Am. Chem. Soc.* **1996**, *118*, 7094-7100.

(15) Smith, P. M.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3541-3556.

(16) Hauser, F. M.; Tommasi, R.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1988**, *53*, 4886-4887.

(17) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147-154.

(18) Diene **16**: ^{1}H NMR (360.1 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.6 Hz), 5.84 (s, 1H), 5.14 (m, 1H), 5.12 (s, 1H), 5.04 (s, 1H), 4.19 (ABq, 2H, Δν = 38.7 Hz, J = 10.9 Hz), 3.80 (s, 3H), 2.10 (m, 2H), 1.95 (m, 2H), 1.80 (s, 3H), 1.70 (m, 5H), 1.59 (s, 3H), 1.40 (s, 3H), 1.29 (m, 8H), 0.87 (t, 3H, J = 6.4 Hz). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 158.8, 146.5, 140.0, 131.8, 131.3, 128.8, 128.1, 124.5, 113.7, 113.2, 80.4, 63.8, 55.3, 38.9, 37.9, 31.8, 28.9, 28.3, 25.7, 22.9, 22.6, 21.8, 17.6, 14.1, 14.0. HRMS (FAB NaI/NBA) *m/z* 421.3089, $(M+Na)^+$ calcd for $C_{27}H_{42}O_2Na$: 421.3082.