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Enantioselective synthesis of the C14–C25 portion of the cytotoxic natural product, amphidinolide B1

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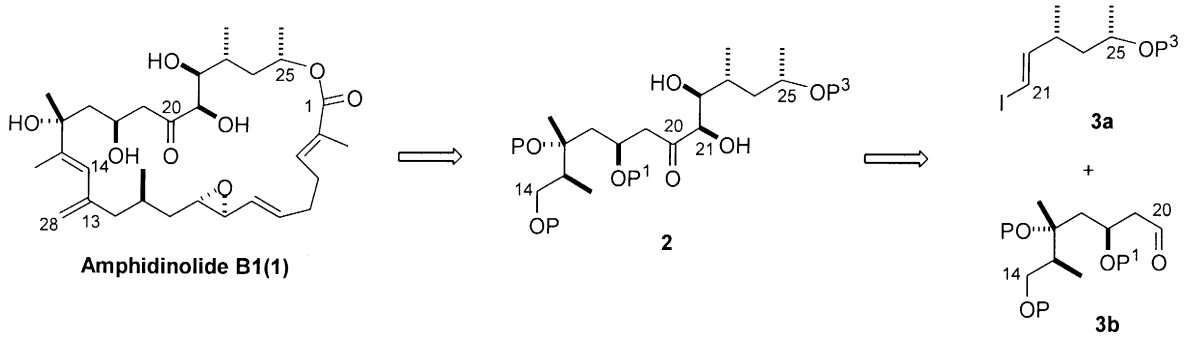
Abstract

The C14–C25 portion of the cytotoxic natural product, amphidinolide B1 (**1**), was synthesized enantioselectively using Myers asymmetric alkylation protocol, epoxide opening with higher order cuprate, Sharpless asymmetric epoxidation of allylic alcohol **17**, and Sharpless asymmetric dihydroxylation of **24** as key steps. © 2000 Elsevier Science Ltd. All rights reserved.

Amphidinolides A–S have recently been isolated from dinoflagellates, genus *Amphidinium*,[1] which is symbiotic with Okinawan marine flatworms of the genus *Amphiscolops* sp. and generally exhibited potent toxicities against cancer tumor cell lines.[2] This family has been a challenging target for synthetic chemists in recent years[3] and some synthesis of the segments has been reported, including amphidinolide B1 (**1**).[4] In our program toward the synthesis of the C14–C25 portion **2** of amphidinolide B1 (**1**), C1–C28 and C20–C25 fragments have already been synthesized in our laboratory[5] and we report herein the enantioselective synthesis of segments **3a**, **3b** and the coupling of these two components via a lithium–halogen exchange for the C14–C25 portion **2** of amphidinolide B1 (**1**). The features of the synthesis are: Myers asymmetric alkylation protocol for the chirality at C23; epoxide opening with higher order cuprate for the C18 asymmetric center; Sharpless asymmetric epoxidation for the chirality at C16; and Sharpless asymmetric dihydroxylation for the C21 and C22 asymmetric center.



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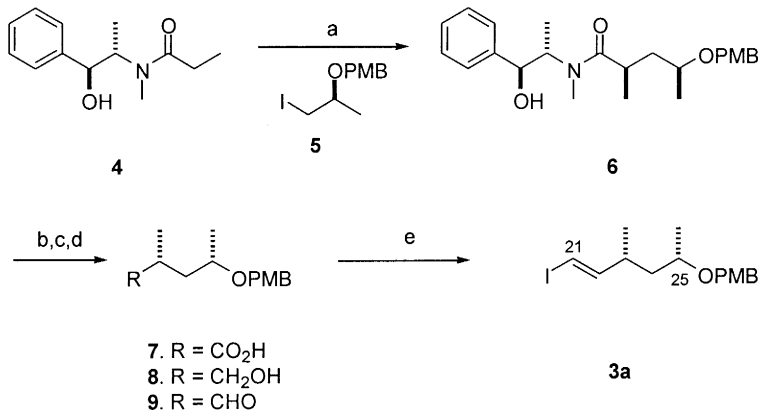
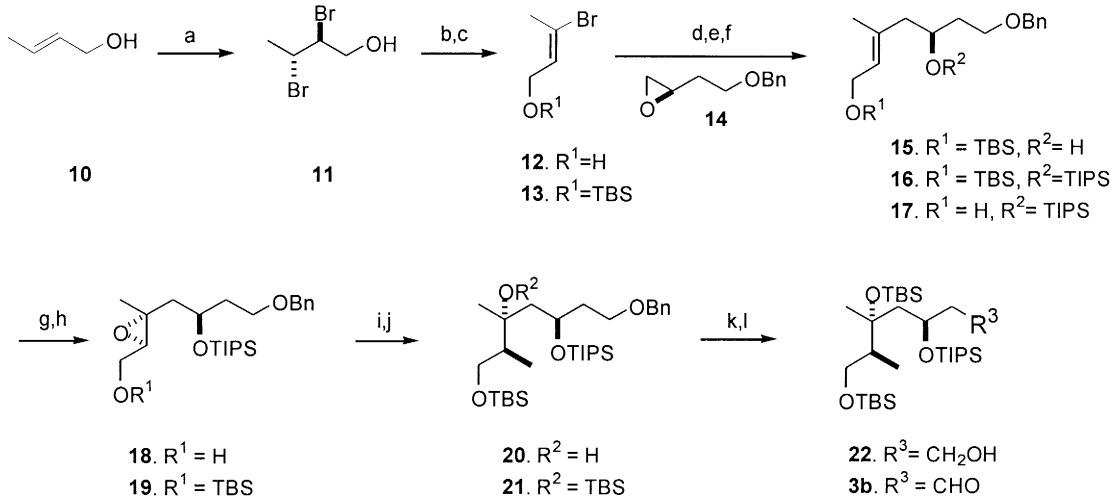
First, pseudoephedrin amide **4** was treated with alkyl iodide **5**, using the Myers protocol[6] to give the alkylation product **6** in 68% yield as a 12.8:1 ratio of diastereomers (determined by 500 MHz ^{1}H NMR) (Scheme 1). Alkyl iodide **5** was prepared in three steps from ethyl (*S*)-lactate via protection of a secondary alcohol with *p*-methoxybenzyl-2,2,2-trichloroacetimidate in the presence of TsOH, reduction of ester functionality with $LiAlH_4$ and iodination of the corresponding primary alcohol with triphenylphophine–iodine in a 56% overall yield. Amide **6** was hydrolyzed with a 3.2N aqueous NaOH solution at reflux for 24 h to the carboxylic acid **7** and the acid **7** was reduced with BH_3–DMS in THF at 0°C for 40 min to the primary alcohol **8** in a 58% two-step isolation yield. Swern oxidation of primary alcohol **8** afforded aldehyde **9** and then the aldehyde **9** was treated with $CrCl_2$ and CHI_3 in THF at rt for 7 h using the Takai protocol[7] to introduce the C21,C22 *trans*-vinyl iodide functionality of the C21–C25 fragment **3a** of amphidinolide B1 (**1**) in 21% overall yield from pseudoephedrine amide **4**. The synthetic route presented herein has several advantages over the previous one published in our laboratory,[5b] such as shorter reaction steps, more reliable results in multi-gram scale, and the purity of the product (almost pure versus 6:1 diastereomeric mixture).



Scheme 1. Synthesis of C21–C25 portion of amphidinolide B1 (**1**). (a) LDA, LiCl, THF, −78°C, 1 h, 0°C, 15 min, rt, 5 min; **5**, 0°C to rt, 3 days, 68%; (b) NaOH, MeOH, *t*-BuOH, reflux, 24 h, 71%; (c) BH_3–DMS, THF, 0°C, 40 min, 82%; (d) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C; DIPEA, −50°C, 1 h, quant.; (e) $CrCl_2$, CHI_3, THF, rt, 7 h, 53%

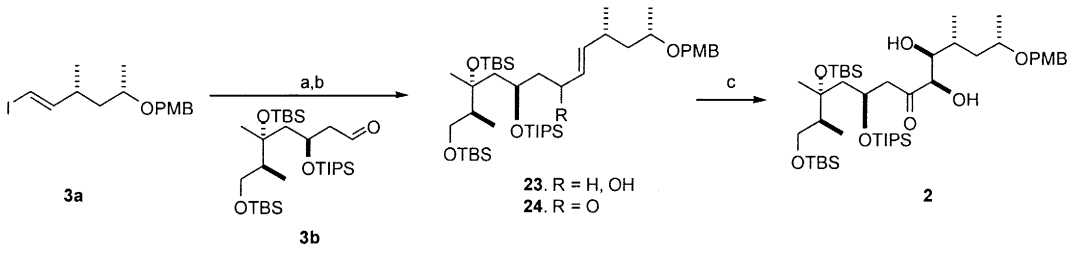
The other fragment **3b** was synthesized as described below (Scheme 2). Bromination of the crotyl alcohol **10** with Br_2 in CCl_4 at −5°C for 2 h and elimination of dibromide **11** with LDA and HMPA in THF at −78°C for 40 min were followed by protection of the corresponding primary alcohol **12** with TBSCl and TEA in CH_2Cl_2 in the presence of a catalytic amount of DMAP to give (*E*)-vinyl bromide **13** in a 57% three-step overall yield[8]. Treatment of vinyl bromide **13** with *t*-BuLi in ether and reaction of the corresponding vinyl lithium reagent with CuCN provided the higher order cuprate, which reacted smoothly with epoxide **14**[9] in diethyl ether at rt for 12 h to afford secondary alcohol **15** regioselectively in 91% yield. After protection of secondary alcohol **15** with TIPSOTf and TEA in CH_2Cl_2 at 0°C for 10 min, the compound **16** was subjected to selective desilylation with HF–Pyr leading to the corresponding allylic alcohol **17** in a 87% two-step yield. Sharpless asymmetric epoxidation[10] of allylic alcohol **17** using D-(−)-DET, Ti(O-*i*Pr)$_4$ and TBHP in CH_2Cl_2 at −20°C for 7 h afforded the epoxy alcohol **18** in 99% yield as a 11:1 ratio of diastereomers (determined by 500 MHz ^{1}H NMR). The epoxy alcohol **18** was treated with TBSCl and TEA in CH_2Cl_2 in the presence of DMAP at rt for 4 h, and the epoxide **19** was opened with the higher order cuprate derived from methyl lithium to give tertiary alcohol **20** regioselectively in a 73% two-step isolation yield. Protection of tertiary alcohol **20** with TBSOTf and TEA in CH_2Cl_2 at rt for 2 h (85% yield) was followed by hydrogenolysis of the benzyl ether **21** by the

use of hydrogen (1 atm) and 10% Pd/C in ethanol to afford alcohol **22** in 90% yield. Swern oxidation of primary alcohol **22** provided the C14–C20 portion **3b** of amphidinolide B1 (**1**) in quantitative yield.



Scheme 2. Synthesis of C14–C20 portion of amphidinolide B1 (**1**). (a) Br_2, CCl_4, −5°C, 2 h, 92%; (b) LDA, HMPA, THF, −78°C, 40 min, 67%; (c) TBSCl, DMAP, TEA, CH_2Cl_2, rt, 40 min, 92%; (d) *t*-BuLi, ether, −78°C, 1 h; CuCN, ether, 20 min; **14**, THF, −78°C to rt, 12 h, 91%; (e) TIPSOTf, TEA, CH_2Cl_2, 0°C, 10 min, quant.; (f) HF–Pyr, pyr, THF, 0°C to rt, 2 h, 87%; (g) $Ti(O\text{-}^iPr)_4$, D-(−)-DET, 4 Å MS, TBHP, CH_2Cl_2, −20°C, 7 h, 99%; (h) TBSCl, DMAP, TEA, CH_2Cl_2, 0°C to rt, 4 h, 73%; (i) $(CH_3)_2Cu(CN)Li_2$, ether, −78°C to rt, 12 h, quant.; (j) TBSOTf, TEA, CH_2Cl_2, 0°C to rt, 2 h, 85%; (k) H_2, Pd/C, EtOH, rt, 20 min, 90% (l) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C, 15 min; TEA, rt, 20 min, quant.

With two fragments **3a** and **3b** in hand, coupling reactions were followed (Scheme 3). Lithium–halogen exchange of vinyl iodide **3a** with *t*-BuLi at −78°C and addition of aldehyde **3b** to the resulting vinyl lithium reagent at −78°C for 15 min provided the allylic alcohol **23** in a 73% yield as a mixture of diastereomers at C20. Subsequent oxidation of allylic alcohol **23** with Dess–Martin periodinane[11] in Pyr:CH_2Cl_2 (ca. 1:4) at rt for 2 days gave a conjugated ketone **24** in a 86% isolation yield. Sharpless asymmetric dihydroxylation of conjugated ketone **24** with AD-mix-α in the presence of methanesulfonamide[12] in *t*-BuOH:H_2O (1:1) at 0°C afforded the diol **2**[13] in 35% yield as a 6:1 ratio of diastereomers (determined by 500 MHz ^{1}H NMR) along with the recovered starting material **24** (ca. 35%) after extensive investigations.



Scheme 3. Coupling of **3a** and **3b**. (a) **3a**, *t*-BuLi, −78°C, 15 min; **3b**, THF, −78°C, 20 min, 73%; (b) Dess–Martin periodinane, Pyr, CH_2Cl_2, rt, 2d, 86%; (c) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 1.5 days, 35%

Although further optimization might still be necessary, enantioselective synthesis of C14–C25 portion **2** of amphidinolide B1 (**1**) was completed in 5.5% overall yield via a 15-step sequence starting from (*E*)-crotyl alcohol **10**.

Acknowledgements

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13. Spectral data for **2**. R_f=0.49 (EtOAc:*n*-hexane, 1:20); $[\alpha]_D^{24}$ –7.692 (*c* 0.26, $CHCl_3$); FT-IR ($CDCl_3$) 3443.15 (OH), 2926.15, 2855.81, 1717.09; ^{1}H NMR (500 MHz) δ 7.260 (d, J=8.5 Hz, 2H), 6.865 (d, J=8.5 Hz, 2H), 4.614 (m, 1H), 4.553 (d, J=11 Hz, 1H), 4.337 (d, J=11.5 Hz, 1H), 4.157 (m, 1H), 3.798 (s, 3H), 3.762 (dd, J=9.5, 4 Hz, 1H), 3.729 (d, J=4.5 Hz, 1H), 3.389 (dd, J=9.5, 8 Hz, 1H), 2.950 (dd, J=16, 6 Hz 1H), 2.811 (dd, J=16, 5.5 Hz, 1H), 2.030 (m, 1H), 1.861–1.732 (m, 4H), 1.662–1.158 (m, 2H), 1.256 (s, 3H), 1.208 (d, J=6 Hz, 3H), 1.055 (s, 21H), 0.968 (d, J=7 Hz, 3H), 0.954 (d, J=7 Hz, 3H), 0.887 (s, 9H), 0.878 (s, 9H), 0.088 (s, 6H), 0.034, 0.030 (s, s, 6H); ^{13}C NMR (125 MHz) δ 209.506, 130.756, 129.325, 113.743, 77.890, 74.984, 72.143, 69.837, 66.707, 64.516, 55.249, 47.961, 46.803, 44.737, 40.826, 34.204, 27.052, 26.167, 20.037, 18.244, 15.633, 12.999, 12.715, −1.610, −1.659, −5.429; anal. calcd for $C_{45}H_{88}O_8Si_3$: C, 64.23; H, 10.54. Found: C, 64.27; H, 10.53.