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Enantioselective Synthesis of the C1-C28 Portion of the Cytotoxic Natural Product, Amphidinolide B1

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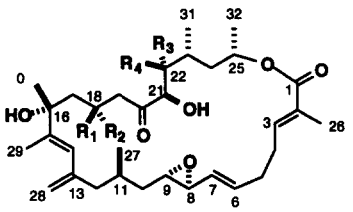
***Abstract** : The C1-C28 portion of the cytotoxic natural product, amphidinolide B1 (**1a**), was synthesized enantioselectively using as key steps Evans chiral oxazolidinone chemistry, Sharpless asymmetric epoxidation, and the orthoester Claisen rearrangement. The overall yield is 3.6% in 13 step sequence starting from propionyl oxazolidinone **2**.*

Amphidinolides A-Q have recently been isolated from dinoflagellates, genus *amphidinium*, symbiotic with the Okinawan marine flatworms and generally exhibited potent toxicities against cancer tumor cell lines.[1,2] Although the chemical structures of them were elucidated mainly on the basis of extensive spectroscopic studies including 2D NMR experiments, their configurations still remain unclear except for amphidinolides B, J, and L.[3,4]

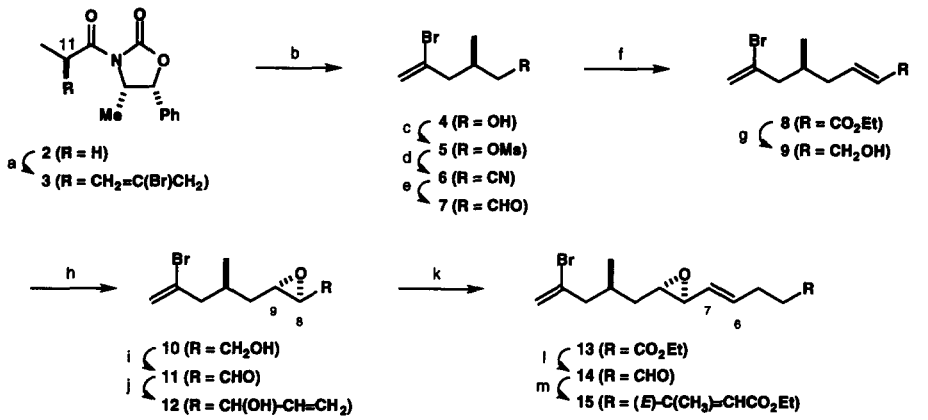


1a : Amphidinolide B1 (R_1=R_4=OH, R_2=R_3=H)
1b : Amphidinolide B2 (R_2=R_4=OH, R_1=R_3=H)
1c : Amphidinolide B3 (R_1=R_3=OH, R_2=R_4=H)

In a program toward the total synthesis of amphidinolide B1 (**1a**), we report herein the first enantioselective synthesis of the C1-C28 fragment of amphidinolide B1 (**1a**). The features of the synthesis (Scheme I) are Evans oxazolidinone chemistry for the chirality at C11, Sharpless asymmetric epoxidation for the C8,C9-epoxide moiety, and the orthoester Claisen rearrangement for the introduction of C6,C7-trans double bond and an ester functionality at C3, which would be used in the final functional group transformations.

First, oxazolidinone **2** was treated with 2,3-dibromopropene using Evan's protocol[5] to give the alkylation product **3** in 70% yield as a 96:4 mixture of diastereomers (determined by capillary GC). Oxazolidinone **3** was reduced to the primary alcohol **4** and the alcohol **4**, after filtration to recover chiral oxazolidinone, was converted into the mesylate **5** in 85% two step isolation yield. The mesylate **5** was then treated with potassium cyanide to provide the nitrile **6** in 78% yield. After the nitrile **6** was reduced by DIBAL, the crude aldehyde **7** was treated with (carbethoxymethylene)triphenylphosphorane to yield the thermodynamically more stable trans conjugate ester **8** in 80% two step isolation yield. The ester **8** was then transformed to an allylic alcohol **9**, a key intermediate in the synthesis, in 72% yield. Sharpless asymmetric epoxidation of the allylic alcohol **9** using L-(+)-DIPT and TBHP[6] afforded the epoxy alcohol **10** in 90% yield as a 90 : 10 ratio of diastereomers (determined by capillary GC). Swern oxidation of primary alcohol **10** and subsequent reaction of the crude aldehyde **11** with vinylmagnesium bromide provided a mixture of diastereomeric allylic epoxy alcohol **12** in 68% yield. The diastereomeric ratio of **12** was not analyzed. Orthoester Claisen rearrangement of **12**[7] (66% isolation yield) and DIBAL reduction (1.1 equiv)

of the γ,δ-unsaturated ester **13** afforded a mixture of products consisting of aldehyde **14** as a major component. The crude aldehyde **14** was sequentially treated with [1-(carbethoxy)ethylene]triphenylphosphorane to provide the conjugate ester **15**[8] in 40% two step isolation yield.



Scheme I. Synthesis of C1-C28 Portion 15 of Amphidinolide B1.

(a) LDA, THF, -78°C, 30 min; 2,3-dibromopropene, -45°C, 10 h, 70 %. (b) LAH, ether, 0°C ; warmed to rt, 1 h. (c) MsCl, TEA, CH_2Cl_2, 0°C, 1 h, 85% overall. (d) KCN, DMSO, 55°C, 5 h, 78%. (e) DIBAL, CH_2Cl_2, 0°C, 3h. (f) (carbethoxymethylene)triphenylphosphorane, benzene, 50°C, 4h, 80% overall. (g) DIBAL, THF, -78°C,3h, 72%. (h) Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, 4Å MS, *t*-BuOOH, CH_2Cl_2, -20°C, 2day, 90%. (i) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C; TEA, -78°C to warm up, 81%. (j) vinylmagnesium bromide, ether, 0°C, 1h, 68%. (k) $CH_3C(OEt)_3$, cat. propionic acid, 90°C, 12 h, 66%. (l) DIBAL, THF, -78°C, 1h. (m) [1-(carbethoxy)ethylene]triphenylphosphorane, toluene, 50°C, 5h, 40% overall.

In summary, enantioselective synthesis of the C1-C28 portion of the cytotoxic natural product, amphidinolide B1, was efficiently completed in 3.6% overall yield *via* 13 step sequence starting from propionyl oxazolidinone **2**.

Acknowledgment

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(8) Spectroscopic data for **15** : R_f: 0.55 (hexane : EtOAc = 3 : 1). $[\alpha]_D$ = -52.0 (c 0.02, CH_2Cl_2). ^{1}H-NMR (200MHz, $CDCl_3$) : δ 6.74 (m, 1H), 5.92 (m, 1H), 5.85 (s, 1H), 5.46 (s, 1H), 5.23 (dd, 1H, J=5Hz), 4.25 (m, 4H), 3.09 (d, 1H, J=5Hz), 2.87 (m, 1H), 2.00-2.61 (m, 7H), 1.52-1.77 (m, 2H), 1.20-1.50 (m, 4H), 1.01 (d, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) : δ 140.9, 135.2, 133.3, 128.5, 128.7, 118.2, 60.8, 60.4, 58.8, 48.7, 48.5, 38.2, 31,0, 29.2, 27,9,18.7, 14.0, 12.2. FTIR(neat, cm^{-1}) : 2960, 1709, 1267, 1114. LRMS (CI) : 372.29 (MH^+).

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