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Synthetic Studies toward Potent Cytotoxic Agents Amphidinolides G and H: Synthesis of the Entire C_{15}-C_{26} Moiety of the Top Half

T. K. Chakraborty* and V. R. Suresh

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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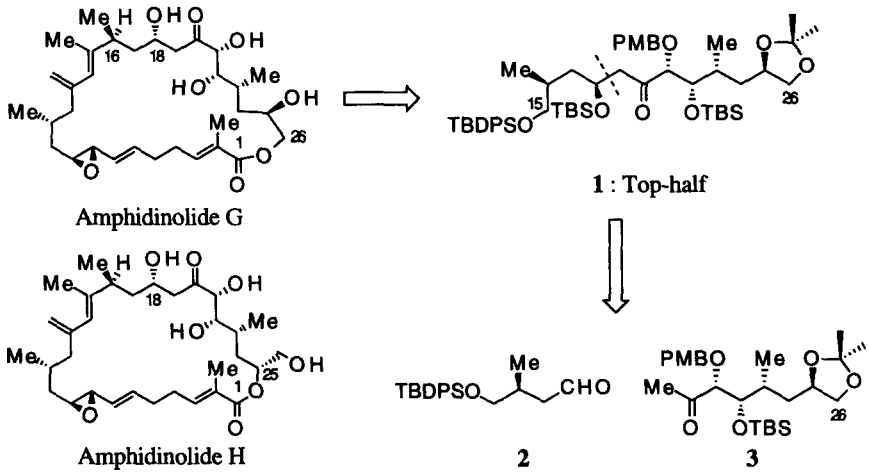
Abstract

Stereoselective synthesis of the entire (16*S*, 18*S*, 21*R*, 22*S*, 23*R*, 25*R*)-C_{15}-C_{26} segment **1** of amphidinolides G and H has been achieved for the first time following a highly efficient convergent strategy.

Keywords: amphidinolides; antitumor compounds; macrolides; aldol reactions.

Amphidinolides isolated from marine dinoflagellate of the genus Amphidinium have potent toxicity against various tumor cell lines [1,2]. Some of them also display activity toward rabbit skeletal muscle actomyosin ATPase. Many of these compounds are reported to be among the most potent of all substances tested to date in the NCI screen, and are attracting attention as potential cancer drugs. The cytotoxic activities of some structurally similar members of this family, like amphidinolides B, D, G, H, and L, are extremely strong making them challenging targets to synthetic organic chemists.



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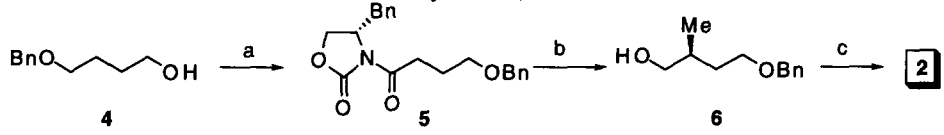
Whereas amphidinolides B, D, and H have 26-membered polyene macrolide skeleton, the other two have 27-membered rings. All of them have nine chiral centres, except amphidinolide L where a hemiketal moiety adds on one extra chiral centre. These chiral centres coupled with the presence of four double bonds with their respective geometric constraints have made the total synthesis of these molecules a formidable task.

The total synthesis of none of these compounds has so far been reported. The relative stereochemistry of amphidinolide B was established by a single crystal X-ray study [3] and its absolute stereochemistry was found to be in agreement with the absolute configuration of amphidinolide L [5] on the basis of enantioselective synthesis of a degradation product [4]. Other structurally similar members of the family may have similar absolute stereochemistries. Herein, we report the first stereoselective synthesis of (16*S*, 18*S*, 21*R*, 22*S*, 23*R*, 25*R*)-C_{15}-C_{26} moiety **1** of the entire top half of amphidinolides G and H.

Retrosynthetically, the C_{15}-C_{26} segment **1** can be dissected into two smaller units, the aldehyde **2** and the methylketone **3**, which can be combined together by a simple aldol process. Scheme 1 describes the construction of **2** [6,7]. The chiral *N*-acyloxazolidinone **5**[1] was prepared from monobenzyl-protected butane-1,4-diol **4**. Alkylation of the sodium enolate of **5** with MeI gave exclusively the required diastereomer [8] which was reduced by $LiBH_4$ in presence of water (molar equivalents of borohydride) [9] to remove the chiral auxiliary furnishing the chiral alcohol **6**[1] (53% yield from **4**). Subsequent functional group manipulations led to the formation of aldehyde **2**[2] (83% from **6**).



4 5 6

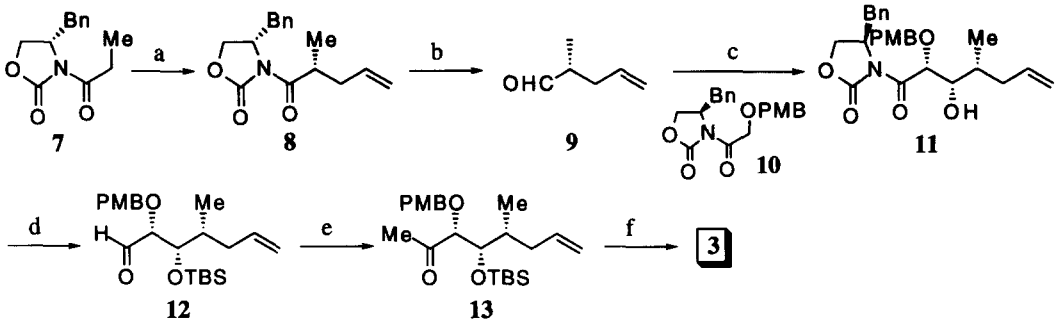
Scheme 1. Reagents and conditions. a) (i) Jones oxidation; (ii) Piv-Cl (1.1 eq.), Et_3N (3 eq.), THF, -20 °C, 2 h, then LiCl (1.5 eq.), (*S*)-4-benzyl-2-oxazolidinone (1 eq.), 25 °C, 6 h; b) (i) NaHMDS (1.2 eq.), MeI (3.0 eq.), THF, -78 °C, 3 h; (ii) $LiBH_4$ (3 eq.), H_2O (3 eq.), Et_2O, 0 to 25 °C, 0.5 h; c) TBDPSCl (1.2 eq.), Et_3N (2 eq.), DMAP (0.1 eq.), CH_2Cl_2, 25 °C, 2 h; (ii) Pd-C, H_2, MeOH; (iii) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h.

The synthesis of **3** started with the *N*-acyloxazolidinone **7** which on stereoselective allylation [8] gave intermediate **8**[1] as a single isomer in 81% yield (scheme 2). Removal of the chiral auxiliary followed by Swern oxidation provided the aldehyde **9**[1] (85% from **8**). Diastereoselective aldol condensation [10] between the aldehyde **9** and chiral oxazolidinone **10** led to the exclusive formation of all-*syn* aldol product **11**[1] in 84% yield. Protection of the hydroxy function as TBS-ether, reductive removal of the chiral auxiliary and oxidation gave the aldehyde **12** (85% from **11**) which was converted to the methylketone **13**[1] in 90% overall yield following standard methods. Finally, the terminal double bond was converted to the diol stereoselectively (3:1 ratio) by Sharpless asymmetric dihydroxylation method using AD-mix-β [11]. Acetonide protection of the diol gave the target intermediate **3**[1,3] (65% from **13**).

[1] Satisfactory NMR, IR and mass spectra were obtained for this compound.

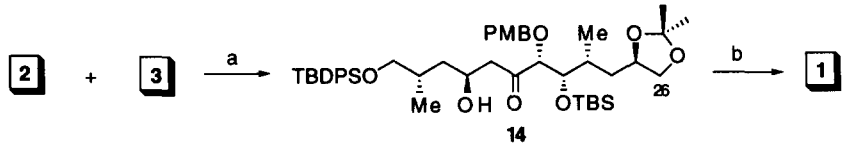
[2] **2**: ^1H NMR ($CDCl_3$, 200 MHz): δ 9.78 (s, 1 H, C*H*O), 7.65-7.35 (m, 10 H, aromatic), 3.58 (dd, *J* = 11.5, 5.7 Hz, 1 H, -C*H*OSi), 3.43 (dd, *J* = 11.5, 7.5 Hz, 1 H, C*H*'OSi), 2.7-2.2 (m, 3 H, CH_2, C*H*), 1.05 (s, 9 H, Si^{t}Bu), 0.96 (d, *J* = 6.5 Hz, 3 H, Me).

[3] **3**: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.2 and 6.82 (two d, *J* = 9 Hz, 4 H, aromatic), 4.38 (s, 2 H, OCH_2PMP), 3.98 (m, 1 H, C_{25}-*H*), 3.95 (m, 1 H, C_{26}-*H*), 3.86 (dd, *J* = 6 and 2 Hz, 1 H, C_{22}-*H*), 3.8 (s, 3 H, OCH_3), 3.65 (d, *J* = 6 Hz, 1 H, C_{21}-*H*), 3.4 (m, 1 H, C_{26}-*H*'), 2.12 (s, 3 H, CH_3CO), 1.65-1.2 (m, 3 H, CH_2, C*H*), 1.42 and 1.35 (two s, 6 H, acetonide CH_3), 0.9 (s, 9 H, Si^{t}Bu), 0.88 (d, *J* = 6.5 Hz, 3 H, C_{23}-CH_3), 0.08 and 0.01 (two s, 6 H, $SiMe_2$).



Scheme 2. Reagents and conditions. a) NaHMDS (1.2 eq.), allyl iodide (3 eq.), THF, -78 °C; b) (i) $LiBH_4$ (3 eq.), H_2O (3 eq.), Et_2O, 0 to 25 °C, 0.5 h; (ii) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h; c) **10**, n-Bu_2BOTf (1 eq.), Et_3N (1.05 eq.), toluene, - 50 °C, 1 h, then **9**, - 40 °C, 12 h; d) (i) TBSOTf (1.2 eq.), 2,6-lutidine (2 eq.), CH_2Cl_2, 0 °C,1 h; (ii) same as step b; e) (i) MeMgI (2 eq.), Et_2O, 0 °C, 0.5 h; (ii) same as step b (ii); f) (i) AD-mix-β (1.4 g per mmol of **13**), ^{t}BuOH:H_2O (1:1), 0 °C, 24 h; (ii) 2,2-dimethoxypropane, CSA (0.1 eq.), 0 °C, 0.5 h.

The stage was now set to couple **2** and **3**. Accordingly, the lithium enolate of **3** was reacted with aldehyde at -78 °C (scheme 3) to get selectively the required aldol adduct **14** as the only isomer. This is in accordance with earlier literature reports [12,13] on 1,3-chiral induction in the aldol reactions of β-alkyl aldehydes. Protection of the hydroxy function as TBS-ether furnished the target top half **1**[1,4] (80% in two steps).

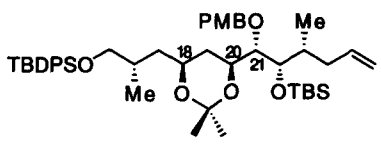


Scheme 3. Reagents and conditions. a) **3**, LDA (1 eq.), THF, -78 °C, 0.5 h, then **2**, 1 h; b) TBSOTf (1.2 eq.), 2,6-lutidine (2 eq.), CH_2Cl_2, 0 °C, 0.5 h.

The stereochemistry of the C_{18} center of **14** was assigned *S* on the basis of 18*S*, 20*S* stereochemistry of acetonide **15** determined by its ^{13}C methyl shifts (19.5 and 30.2 ppm) [14,15]. The acetonide **15**, which was chosen in order to make NMR assignments easier with only one acetonide ring, was prepared in three steps: a) stereoselective addition of Li-enolate of **13** to aldehyde **2** in the same way as described in scheme 3; b) diastereoselective reduction of C_{20}-ketone using $Zn(BH_4)_2$ [16-19]; and c) acetonide protection. It is well established in literature that $Zn(BH_4)_2$ reduces stereoselectively β-hydroxyketone to *syn*-1,3-diol [16,17] and α-hydroxyketone, hydroxy-protected [18] or -unprotected [19], to *anti*-1,2-product. In our case, the stereoselectivity of the ketone reduction was controlled by both the C_{18}-OH and C_{21}-OPMB giving the expected 20*S* product with 18,20-*syn*-20,21-*anti* relationship. Thus, the C_{21} center whose stereochemistry was fixed by diastereoselective aldol reaction (scheme 2) confirms, in turn, the *S*-configuration of C_{18} center.

[4] **1**: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.67 and 7.40 (m, 10 H, $SiPh_2$), 7.2 and 6.85 (two d, *J* = 9 Hz, 4 H, PMP), 4.4 (ABq, 2 H, OCH_2PMP), 4.3 (m, 1 H, C_{18}-*H*), 4.13 (dd, *J* = 15 and 7.5 Hz, 1 H, C_{26}-*H*), 3.95 (m, 2 H, C_{25}- *H* and C_{22}-*H*), 3.82 (s, 3 H, OCH_3), 3.7 (d, *J* = 6 Hz, 1 H, C_{21}-*H*), 3.48 (broad d, *J* = 5 Hz, 2 H, C_{15}-H_2), 3.4 (t, *J* = 7.5 Hz, 1 H, C_{26}-*H'*), 3.05 (dd, *J* = 18 and 7 Hz, 1 H, C_{19}-*H*), 2.44 (dd, *J* = 18 and 7 Hz, 1 H, C_{19}-*H'*), 1.7-1.2 (m, 6 H, CH_2, *CH*), 1.42 and 1.35 (two s, 6 H, acetonide CH_3), 1.1, 0.89 and 0.87 (three s and one d, 30 H, one Me and Si^{t}Bu), 1.0 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.1, 0.08, 0.03 and 0.01 (four s, 12 H, SiMe).

This was further proved by converting **14** into its (*R*)- and (*S*)-MTPA esters (**16**) and measuring $\Delta\delta$ [(δ_S - δ_R) × 1000] for the protons which show negative values for those on the left side of C_{18} center and positive values for those on its right side [20], confirming the assigned configuration of the center.



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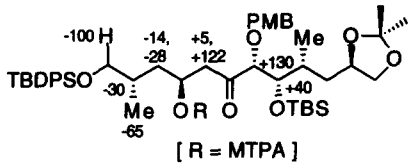

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In conclusion, an efficient convergent route presented here led to the first synthesis of the entire top half of amphidinolides G and H, which will not only help to achieve the total synthesis of these molecules but also other structurally similar congeners. Further work is under progress.

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