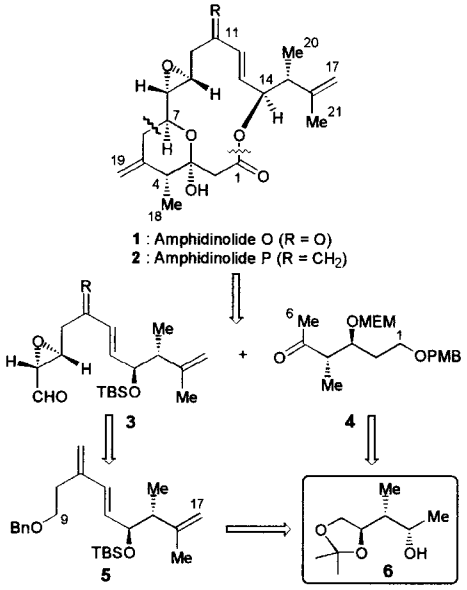
Synthetic Studies toward Potent Cytotoxic Agents Amphidinolides: Synthesis of the C_1-C_6 and C_9-C_{17} Moieties of Amphidinolides O and P

T. K. Chakraborty* and Sanjib Das
Indian Institute of Chemical Technology, Hyderabad 500 007, India

(Received Septmber 14, 1999; CL-990789)

Stereoselective synthesis of the (4*R*)-C_1-C_6 and (14*R*, 15*R*)-C_9-C_{17} segments, **4** and **5** respectively, of amphidinolides O and P have been achieved starting from a common chiral precursor **6** which was obtained by radical-mediated opening of a trisubstituted epoxy alcohol using Cp_2TiCl-cyclohexa-1,4-diene.

Amphidinolides O (**1**) and P (**2**), two novel cytotoxic 15-membered macrolides with unprecedented structural frameworks, were isolated from the cultured marine dinoflagellate *Amphidinium sp*.[1-3] They may be biogenetically related to each other with one of them likely to be the precursor of the other. The planned total synthesis of these macrolides will not only provide an access to larger quantities of them necessary for further biological studies, but also help to establish their absolute stereochemistries.



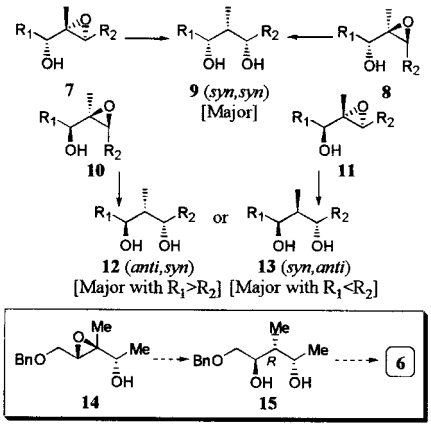
Scheme 1. Retrosynthetic analysis of **1** and **2**.

Retrosynthetically, these molecules can be divided into two halves (Scheme 1): the C_7-C_{17} unit **3** bearing the epoxyaldehyde moiety and the C_1-C_6 methylketo unit **4**, the enolate of the latter being planned to add stereoselectively to the aldehyde group of the former followed by functional group manipulations before carrying out the crucial cyclization reaction. The epoxyaldehyde **3**, in turn, can be prepared from precursor **5**. In this paper, we describe the stereoselective syntheses of two key fragments, the (4*R*)-C_1-C_6 unit **4** and the (14*R*, 15*R*)-C_9-C_{17} unit **5** having the "1,3-diene" moiety.

The salient feature of our synthesis is that both the fragments, **4** and **5**, originate from a single chiral precursor **6**, which was prepared following a method developed by us[4] recently for the synthesis of chiral 2-methyl-1,3-diol by radical-mediated anti-Markovnikov opening of trisubstituted epoxy alcohols at the more substituted carbon using Cp_2TiCl-cyclohexa-1,4-diene, thus, highlighting the applicability of our process in multi-step synthesis of natural products.

According to our study as shown in Scheme 2, both *syn* and *anti* epoxy alcohols, **7** and **8** respectively, on epoxide ring opening with Cp_2TiCl-cyclohexa-1,4-diene give *syn,syn* diol **9** as the major product, whereas the products from epoxy alcohols **10** and **11** depend on the relative sizes of R_1 and R_2. When R_1 is bigger than R_2, the major product is *anti,syn* diol **12**. With smaller R_1, the *syn,anti* product **13** predominates.

This study prompted us to use the *anti* epoxy alcohol **14** (Scheme 2) as the precursor for the synthesis of **6**, the common starting material for fragments **4** and **5**. The $BnOCH_2$ substituent being bigger than the Me, the epoxy alcohol **14** was



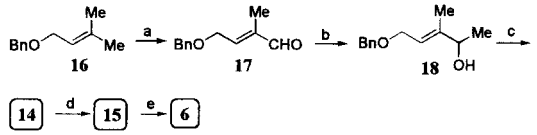
Scheme 2. Radical-mediated opening of trisubstituted epoxy alcohols.

expected to deliver the *anti,syn* stereoisomer **15** on ring opening.

Scheme 3 delineates the synthesis of **6**. Selenium dioxide oxidation[5] of the benzyl-protected 3-methyl-2-buten-1-ol (**16**) gave the aldehyde **17** which on Grignard addition led to the formation of allylic alcohol **18**. Sharpless kinetic resolution[6] of **18** gave the expected epoxy alcohol **14**.[6d] The unbranched substituents on **18**, allowed a very fast reaction.[6a-c] Stage was now set to carry out our epoxide opening reaction. When **14** was subjected to Cp_2TiCl-cyclohexa-1,4-diene, according to the procedure reported by us earlier,[4] the desired diastereomer **15** was formed as the major product in 7.5:1 ratio determined by ^1H NMR of the mixture.[7] The minor isomer with *S*-methyl could be separated easily by standard silica gel column chromatography after two steps. By allowing the reaction mixture to warm up very slowly to room temperature over a period of 4 h and following a longer reaction time of 8 h, the diastereoselectvity was improved as compared to our earlier report.[4] Debenzylation of **15**, followed by acetonide protection of the resulting product, gave selectively the 5-membered acetonide **6**. The purified major isomer **6** was used to prepare the frag-

ments **4** and **5**.

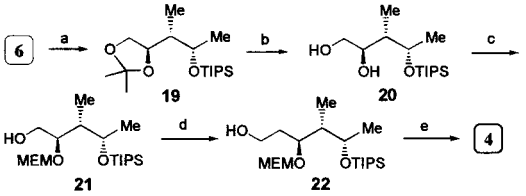
Conversion of **6** to **4** is outlined in Scheme 4. Silylation of **6** with TIPSOTf and 2,6-lutidine gave **19**. Acetonide of **19** was then removed under mild conditions using silica supported $FeCl_3$.[8] Selective acetylation[9] of the primary hydroxyl of the resulting diol **20** was followed by MEM-protection of the secondary hydroxyl and deacylation to give the intermediate **21**. A standard 3-step protocol was carried out next to make one



Scheme 3. Synthesis of chiral precursor **6**. Reagents and conditions. a) SeO_2 (0.5 eq.), TBHP (70% aq. sol., 3.5 eq.), CH_2Cl_2, 25 °C, 8 h, 58%; b) MeMgI (1 M in Et_2O, 1.5 eq.), Et_2O, 0 to 5 °C, 0.5 h, 94%; c) $Ti(^iPrO)_4$ (0.1 eq.), (+)-DIPT (0.12 eq.), TBHP (3 M in toluene, 1 eq.), 4 A MS (20 wt%), CH_2Cl_2, -20 °C, 25 min., 90% (based on ~48% conversion); d) Cp_2TiCl_2 (5 eq.), Zn (10 eq.), $ZnCl_2$ (5 eq.), cyclohexa-1,4-diene (10 eq.), THF, - 15 to 25 °C, 8 h, 80% (7.5:1); e) i) H_2, Pd-C, MeOH, 25 °C, 0.5 h; ii) 2,2-dimethoxypropane (2 eq.), CSA (0.1 eq.), acetone, 0 °C, 1 h, 92% from **15**.

carbon extension: oxidation, Wittig olefination and hydroboration, to give **22**. PMB-protection of **22** was followed by desilylation and oxidation to furnish the desired fragment **4**.[10]

Synthesis of **5** is described in Scheme 5. Oxidation of **6** was followed by Wittig methylenation to give the intermediate **23**. Removal of the acetonide, disilylation, and then selective deprotection of the primary hydroxyl gave alcohol **24**. Swern oxidation of **24** was followed by Horner-Wadsworth-Emmons olefination with the ketophosphonate **25**[11] to furnish the *E*-enone **26** with complete selectivity and no *Z*-olefin was detect-

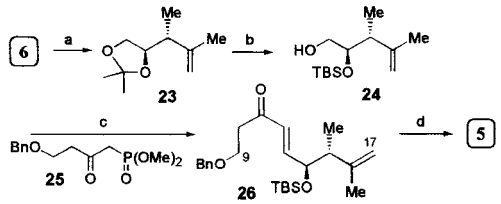


Scheme 4. Stereoselective synthesis of **4**. Reagents and conditions. a) TIPSOTf (1.2 eq.), 2,6-lutidine (2 eq.), CH_2Cl_2, 0 °C, 0.5 h, 95%; b) $FeCl_3$-SiO_2 (10 mg/mmol), $CHCl_3$, 25 °C, 12 h, 72% (based on recovered starting material); c) i) AcCl (1.2 eq.), 2,4,6-collidine (2 eq.), CH_2Cl_2, -78 °C, 3 h, then - 40 °C, 6 h; ii) MEM-Cl (1.5 eq.), DIPEA (2.0 eq.), CH_2Cl_2, 0 to 25 °C, 36 h; iii) K_2CO_3 (5 eq.), MeOH, 25 °C, 1 h, 90% from **20**; d) i) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h; ii) $Ph_3P{=}CH_2$ (2 eq.), ether, 0 °C, 0.5 h; iii) BH_3-DMS (6 eq.), THF, 0 to 25 °C, 1.5 h, then MeOH (12 eq.), NaOH (3 N aq. sol., 9 eq.), H_2O_2 (50% w/v, 21 eq.), 50 °C, 1 h, 50% from **21**; e) i) PMB-Br (1.5 eq.), NaHMDS (1 M in THF, 1.5 eq.), THF-DMF (2:1), 0 °C, 0.5 h; ii) TBAF (3eq.), THF, 25 °C, 4 h; iii) same as step d(i), 82% from **22**.

ed. Finally, Wittig methylenation converted the enone **26** to the desired 1,3-diene intermediate **5**.[12]

In conclusion, two major fragments of amphidinolides O and P have been synthesized from a common chiral intermediate **6**, which was obtained using a method developed by us recently involving radical-mediated opening of a trisubstituted epoxy alcohol, thus, demonstrating its practical utility. Further work on the total synthesis is presently under progress.

We thank Drs. A. C. Kunwar and M. Vairamani for NMR and mass spectroscopic assistance, respectively; UGC, New Delhi for research fellowship (S.D.) and Young Scientist Award Research Grant (T.K.C.).



Scheme 5. Stereoselective synthesis of **5**. Reagents and conditions. a) i) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, - 78 to 0 °C, 1.5 h; ii) $Ph_3P{=}CH_2$ (2 eq.), ether, 0 °C, 0.5 h, 80% from **6**; b) i) PTSA (0.5 eq.), MeOH, 25 °C, 0.5 h; ii) TBSOTf (2.5 eq.), 2,6-lutidine (4 eq.), CH_2Cl_2, 0 °C, 0.5 h; iii) CSA (0.5 eq.), MeOH-CH_2Cl_2, 0 to 10 °C, 0.5 h, 75% from **23**; c) i) same as step a(i); ii) **25** (1 eq.), nBuLi (0.8 eq.), THF - 78 °C, 0.5 h, then aldehyde (0.5 eq.) from step i, - 78 to 25 °C, 3 h, 75% from **24**; d) same as step a(ii), 85%.

2 J. Kobayashi and M. Ishibashi, *Chem. Rev.*, **93**, 1753 (1993).

3 M. Ishibashi, M. Takahashi, and J. Kobayashi, *J. Org. Chem.*, **60**, 6062 (1995).

4 T. K. Chakraborty and S. Dutta, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1257.

5 B. B. Snider and J. V. Duncia, *J. Org. Chem.*, **45**, 3461 (1980).

6 (a) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987); (b) T. Katsuki and V. S. Martin, *Org. React.*, **48**, 1 (1996); (c) Sharpless kinetic resolution of a similar substrate is reported: A. R. Chamberlin, M. Dezube, S. H. Reich, and D. J. Sall, *J. Am. Chem. Soc.*, **111**, 6247 (1989); (d) Sharpless kinetic resolution of **18** was done following standard procedure (ref. 6a-c) using $Ti(^iPrO)_4$ (0.1 eq.), (+)-DIPT (0.12 eq.) and TBHP (1.0 eq.) at – 20 °C. After 25 min., the reaction was quenched by adding an aqueous solution of tartaric acid (30%) and after usual work-up, the residue was purified by silica gel column chromatography to get the unreacted allylic alcohol (52%), followed by the desired product **14** (43%). A small amount of the *syn* diastereomer (ca. 2-3%) was also formed which could be separated easily. While the diastereomeric purity of **14** was ascertained by ^1H NMR spectroscopy, its ee (85%) was determined by Mosher's ester method. Selected physical data for **14**: $[\alpha]_D^{22}$ 2.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4-7.25 (m, 5 H, Ar*H*), 4.65 and 4.52 (ABq, 2 H, PhCH_2O-), 3.75 (q, *J* = 6.7 Hz, 1 H, CH_3CHOH), 3.68 (dd, *J* = 10.5, 4.5 Hz, 1 H, C*H*-O), 3.57 (dd, *J* = 10.5, 6 Hz, 1 H, C*H'*-O), 3.28 (dd, *J* = 6, 4.5 Hz, 1 H, epoxy *H*), 2.05 (br s, 1 H, O*H*), 1.25 (s, 3 H, epoxy Me), 1.22 (d, *J* = 6.7 Hz, 3 H, CH_3CHOH).

7 The stereochemistry of **15** and its minor diastereomer were determined, as described earlier (ref. 4), by converting them to 6-membered acetonides and studying their proton coupling constants (4-5 Hz for *syn*-protons and 8-9 Hz for *anti*-protons).

8 K. S. Kim, Y. S. Song, B. H. Lee, and C. S. Hahn, *J. Org. Chem.*, **51**, 404 (1986).

9 K. Ishihara, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, **58**, 3791 (1993).

10 Selected physical data for **4**: ^1H NMR ($CDCl_3$, 200 MHz, amphidinolide numberings): δ 7.4 and 6.82 (two d, *J* = 8.5 Hz, 4 H, aromatic), 4.65 (s , 2 H, O-CH_2-O), 4.38 (s, 2 H, O-CH_2-Ar), 4.0 (m, 1 H, C_3-H), 3.8 (s, 3 H, PMB: -OMe), 3.65-3.45 (m, 6 H, O-CH_2-CH_2-O, C_1-H_2), 3.35 (s, 3 H, MEM: -OMe), 2.86 (dq, *J* = 6.4 Hz, 1 H, C_4-H), 2.15 (s, 3 H, $COCH_3$), 1.72 (m, 2 H, C_2-H_2), 1.05 (d, *J* = 6.4 Hz, 3 H, C_4-CH_3); MS (LSIMS): *m/z* 353 (M^+-H), 377 (M^++Na).

11 The ketophosphonate **25** was prepared in two steps from mono-benzyl-protected propane-1,3-diol as follows: i) Jones' oxidation – CH_2N_2 (to give ester); ii) $CH_3P(O)(OCH_3)_2$ – *n*BuLi (Li-phosphonate addition to the ester to give the ketophosphonate).

12 Selected physical data for **5**: ^1H NMR ($CDCl_3$, 200 MHz, amphidinolide numberings): δ 7.35 (m, 5 H, aromatic), 6.15 (d, *J* = 16.5 Hz, 1 H, C_{12}-H), 5.62 (dd, *J* = 16.5, 7 Hz, 1 H, C_{13}-H), 5.02 (two s, 2 H, $C_{11}{=}CH_2$), 4.75 (two s , 2 H, $C_{16}{=}CH_2$), 4.55 (s, 2 H, OCH_2Ph), 4.12 (t, *J* = 7 Hz, 1 H, C_{14}-H), 3.62 (t, *J* = 7 Hz, 2 H, C_9-H_2), 2.55 (t, *J* = 7 Hz, 2 H, C_{10}-H_2), 2.28 (dq, *J* = 7 Hz, 1 H, C_{13}-H), 1.75 (s, 3 H, C_{16}-CH_3), 0.95 (d, *J* = 7 Hz, 3 H, C_{15}-CH_3), 0.9 (s, 9 H, Si^{t}Bu), 0.05 and 0.0 (two s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 147.2, 142.4, 138.5, 132.1, 131.2, 128.3, 127.8, 127.3, 118.5, 111.5, 76.2, 73, 69, 47.8, 32.7, 25.4, 21.8, 18.2, 14.5, -4.3, -4.8; MS (LSIMS): *m/z* 399 (M^+-H).

References and Notes

1 M. Ishibashi and J. Kobayashi, *Heterocycles*, **44**, 543 (1997).