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SYNTHETIC STUDIES TOWARD AMPHIDINOLIDE A: SYNTHESIS OF FULLY FUNCTIONALIZED SUBUNITS

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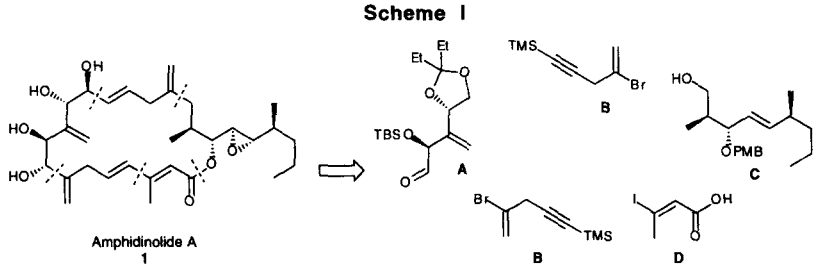
Abstract A retrosynthetic breakdown of amphidinolide A affords four fragments **A-D** and illustrates the main synthetic challenges of this molecule. A concise stereoselective synthesis of the four appropriately functionalized subtargets is described.

Keywords: *amphidinolide A, antitumour compounds, macrolides.*

Marine microalgae are of considerable interest as new promising sources of bioactive substances. The amphidinolides[1] represent a novel and significant class of natural products which originate from such algae. Amphidinolide A (**1**), isolated from the marine dinoflagellate *Amphidinum sp*, was the first polyolefinic macrolide of this unique series of compounds to be identified.[2] Amphidinolide A displays marked biological properties, especially *in vitro* activity against L1210 marine leukemia cells[1] and human epidermoid carcinoma KB cells. In addition to its impressive anti-cancer activity, the 20-membered lactone, has several striking structural features, including the presence of lipophilic and hydrophilic moieties as well as the presence of exocyclic olefins and both conjugated and non-conjugated dienes. It is for these structural and biological features that amphidinolide A is a current target for total synthesis.[3]

Scheme I



Our retrosynthetic breakdown of amphidinolide A (Scheme I) affords four fragments **A-D**. Several issues guided our retrosynthetic plan. These included the formation of multiple stereocenters early in the synthesis, the development and evaluation of new synthetic methods,[4] and maintaining a flexible approach to the target molecule. Furthermore, the successful construction of subunits **A-D** would allow us to simultaneously investigate multiple coupling strategies, providing valuable information as to which coupling sequence will be employed in our final elaboration of amphidinolide A. Herein we report the synthesis of these key building blocks.

The synthesis of fragment **A** (Scheme II), began with the conversion of the bisisopentylidene of D-mannitol into allylic alcohol (+)-**4**[5] via an approach which largely paralleled procedures[6] previously established for the preparation of the less stable isopropylidene analog of **4**. As such, bisisopentylidene **3** was oxidatively cleaved by KIO_4 and then sub-

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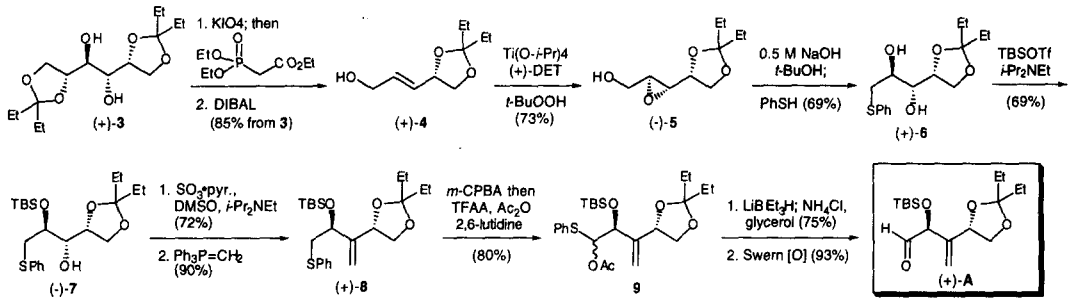
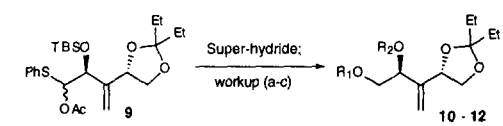
Scheme II



jected to an *in situ* Wittig olefination. Dibal reduction of the resultant ester provided allylic alcohol (+)-**4**[7] in 85% yield over the three steps. Asymmetric epoxidation[8] of (+)-**4** gave 2,3-epoxy-1-ol (-)-**5** with complete stereocontrol. Sharpless had already shown[9] that exposure of 2,3-epoxy-1-ols to the equilibrating conditions of the Payne[10] rearrangement can result in selective opening of the terminal epoxide upon the addition of *t*-butylthiol. Therefore, we decided to follow a similar approach, substituting thiophenol for *t*-butylthiol as this would set up the molecule for an ensuing Pummerer rearrangement. In practice, this tactic provided sulfide (+)-**6**, which could be mono protected at the C-2 hydroxyl affording TBS ether (-)-**7**[11] in 69% yield along with the disilylated (10%) material and unreacted diol (17%). A Doering-Parikh oxidation[12] of (-)-**7**, followed by reaction with $Ph_3P{=}CH_2$ efficiently installed the exo olefin of (+)-**8**. *m*-CPBA converted the sulfide of (+)-**8** into its sulfoxide which was immediately made to undergo a Pummerer rearrangement.[13] This allowed the isolation of acetoxy sulfide **9** in 80% yield as a mixture of diastereomers. Unmasking of the aldehyde was accomplished in 70% yield by a lithium triethylborohydride (Super-Hydride®) reduction and subsequent Swern oxidation, providing target aldehyde (+)-**A**.[5]

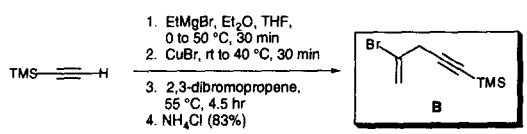
It is worth noting that during the initial experiments (Scheme III) on the Super-Hydride® reduction of **9**, aqueous NH_4Cl workup led soley to the isolation of an unhydrolyzed organoborane species (**11**) as indicated by a green flame test.[14] Given the resiliency of the organoborane to mildly acidic conditions, we attempted a basic workup. While treatment with aqueuos NaOH did bring about complete removal of the boron, it also resulted in partial migration of the TBS group to the primary alcohol (+)-**12**. In the end, we found that a combined NH_4Cl/glycerol[15] workup afforded high yields of alcohol (+)-**10** without movement of the silyl ether.

Scheme III



(a) aqueous NH_4Cl: **11** [R_1=BR_2, R_2=TBS (95% crude yield)]
(b) aqueous NaOH: (+)-**10** [R_1=H, R_2=TBS (49%)] + (+)-**12** [R_1=TBS, R_2=H (25%)]
(c) aqueous NH_4Cl, the glycerol: (+)-**10** [R_1=H, R_2=TBS (75%)]

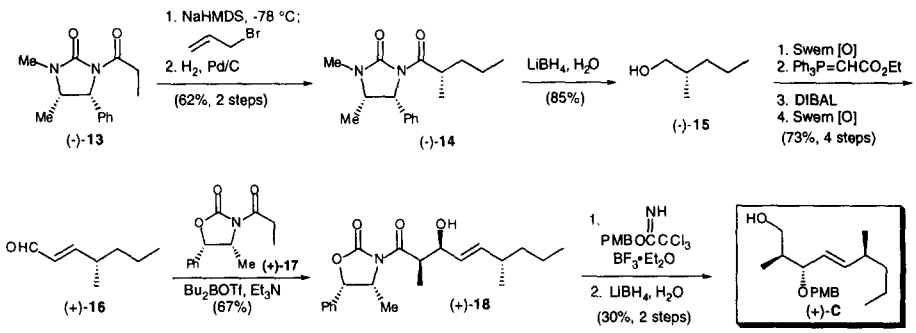
Scheme IV



Having produced the requisite aldehyde **A**, we turned to the preparation of fragment **B** (Scheme IV). We anticipated the need for multigram quantities of subunit **B** as it is a common building block for both the upper and lower hemispheres of amphidinolide A. Somewhat surprisingly, this relatively simple molecule had yet to be described in the literature. Nonetheless, we were convinced it could be prepared by the addition of trimethylsilylacetylide to 2,3-dibrompropene under phase transfer conditions. Our confidence was quickly shattered as these two reactants,

which individually have been successfully employed in similar reactions, failed to couple. Furthermore, straightforward displacements of both 2,3-dibromo- or 2-bromo-3-iodopropene by either the lithium, sodium, or potassium TMS-acetylides also failed. Finally, after considerable experimentation, we discovered cuprate conditions which ultimately provided us with gram quantities of **B**[5] in 83% yield.

Scheme V

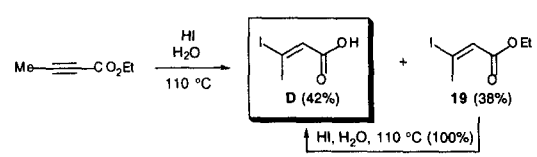


Prior to our synthesis of fragment **C**, (*S*)-2-methylpentan-1-ol ((-)-**15**)[16] and the racemate of aldehyde **16**[17] were known. However, as we planned to employ an Evans[18] aldol reaction to generate what would ultimately become the C-18 and C-19 asymmetric centers of amphidinolide A, it was decided that an iterative chiral auxiliary based approach to all the stereogenic carbons in **C** would make for the most efficient synthesis of that fragment (Scheme V). Therefore the synthesis of fragment **C** began with the need to allylate imidazolidin-2-one (-)-**13**.[19] Literature reports suggest the lithium enolate of chiral imidazolidinones such as (-)-**13** which possess a phenyl group in the C-4 position often do not alkylate with efficient stereocontrol.[19] However, we found that by using NaHMDS as the base coupled with a slow addition of the electrophile,[20] the allylated product could be isolated as a single observable isomer. Furthermore in our hands the imidazolidinones proved much more amenable to scale-up than did the corresponding oxazolidinones.

Once the allyl group was in place, hydrogenation of this side chain gave (-)-**14** in 62% overall yield from (-)-**13**. The chiral auxiliary of (-)-**14** was then reductively cleaved[21] to afford optically pure (*S*)-2-methylpentan-1-ol (-)-**15**.[22] Subjecting this alcohol to a one-pot Swern oxidation/Wittig olefination protocol,[23] followed by a DIBAL/Swern sequence provided (+)-**16** in the desired aldehydic oxidation state (4 steps, 73% yield). Compound (+)-**16** was then reacted with the boron enolate of *N*-acyloxazolidinone (+)-**17** affording the desired Evans[18] aldol product (+)-**18** which could be isolated in 67% yield. Lewis acid catalyzed para-methoxybenzyl (PMB) ether formation[24] followed by reductive cleavage of the chiral auxiliary liberated fragment (+)-**C**[5] in a 30% yield over two steps.

The known iodo acid **D** is readily available from ethyl 2-butynoate (Scheme VI).[25] The alkyne was added to a sealed tube containing hydriodic acid (48% aq) and heated to 110 °C. After 12 h the crystalline carboxylic acid (**D**)[5] which had fallen out of solution was filtered off and the remaining solution which contained approximately 38% unhydrolyzed ester **19** was resubjected to the reaction conditions where the ester hydrolysis was nearly quantitative. This recycling protocol afforded fragment **D** in an 80% combined overall yield and in terms of throughput turned out to be more efficient than running the reaction to completion in a single pass.

Scheme VI



With the stereoselective syntheses of all subtargets in hand, we are now in the coupling phase of our synthetic venture. The results of these studies and the final elaboration of amphidinolide A will be reported as they develop.

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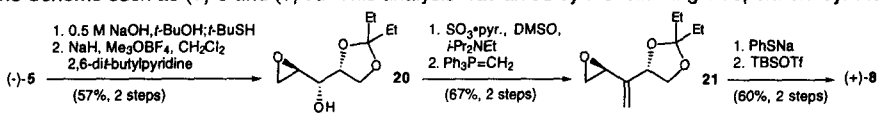
REFERENCES AND NOTES

1. (a) For a review of amphidinolides A-Q see Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543-572. (b) For the first total synthesis of an amphidinolide (J) see Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198-11199.
2. (a) Kobayashi, J.; Ishibashi, M.; Hirota, H. *J. Nat. Prod.* **1991**, *54*, 1435-1439. (b) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5755-5758.
3. (a) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 703-706. (b) Boden, C.; Pattenden, G. *Synlett* **1994**, 181-182. (c) O'Connor, S. J.; Williard, P. G. *Tetrahedron Lett.* **1989**, *30*, 4637-4640.
4. Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, 63, 9622-9623.
5. All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 300-MHz ^1H NMR and 75-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.
6. (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373-1378. (b) Ko, S.Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245-264.
7. Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391-402.
8. (a) Hill, J. G.; Sharpless, K. B.; Exon, C. M. *Org. Synth.* **1985**, *63*, 66-78. (b) Scheuplein, S. W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 917-925.
9. Behrens, C. H.; Ko, Y. S.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687-5696.
10. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819-3822.
11. The regiochemistry of TBS ether (-)-**7** was made obvious through the spectroscopic analysis of compounds later in the Scheme such as (+)-**8** and (+)-**A**. This analysis was aided by the following independent synthesis of (+)-**8**.



12. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
13. Tanikaga, R.; Yabuki, Y.; Ono, N.; Kaji, A. *Tetrahedron Lett.* **1976**, 2257-2258.
14. Hall, J. A.; Keyworth, D. A. In *Brief Chemistry of the Elements with Qualitative Analysis*, Benjamin: Meleno Park, 1971, p.119.
15. Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1-12.
16 (a) Mori, K.; Murata, N. *Liebigs Ann. Chem.* **1994**, 1153-1160. (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081-1084. (c) Desrut, M.; Kergomard, A.; Renard, M. F.; Veschambre, H. *Tetrahedron* **1981**, *37*, 3825-3829.
17. Syper, L. *Tetrahedron* **1987**, *43*, 2853-2871.
18. (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83-90. (c) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.
19. Drewes, S. E; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663-2673.
20. Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260-6268.
21. Penning, T. D.; Djuric, S. W; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307-312.
22. $[\alpha]_{578}^{23}$ -13.0 (c 1.08, $CHCl_3$); literature[16c] $[\alpha]_{578}^{25}$ -12.9 to -14 (c 0.104, $CHCl_3$).
23. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198-2200.
24. Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240-1241.
25. Le Noble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897-3899.