Communications

1,3-Stereocontrol with Bromoallenes. Synthesis of *N*-Boc-ADDA, the Unique Amino Acid Present in Several Inhibitors of Serine/Threonine Phosphatases

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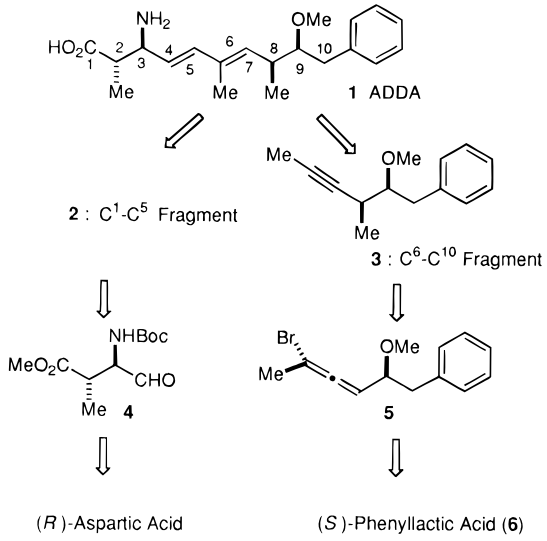
Mycrocystins, nodularin and motuporin, both cyclic peptides from cyanobacteria, have a common feature, a unique C_{20} amino acid ADDA (**1**) that seems to be essential for their biological functions.[1] In the reported syntheses of ADDA, the *E*,*E*-dienic system present in **1** was prepared *via* Julia−Wittig-type chemistry, which did not allow for the complete control of the stereochemistry of the double bonds.[2−5]

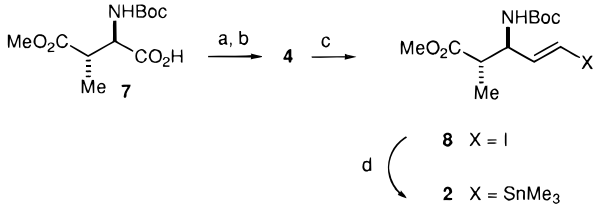
We designed an alternative strategy to **1**, which is depicted in retrosynthetic Scheme 1. In this strategy, the disconnection of the C^5-C^6 bond of **1** suggested two fragments, C^1-C^5 (**2**) and C^6-C^{10} (**3**), which, in a forward synthetic direction, could be coupled together under Stille conditions to give ADDA (**1**).[6] We envisioned that the C^1-C^5 fragment (**2**) could be derived from the β alkylated α-amino aldehyde **4**, which in turn could originate from (*R*)-aspartic acid. For fragment C^6-C^{10} (**3**), a disubstituted chiral alkyne, we believed the stereochemistry of the stereogenic center at carbon C-8 could be controlled via S_N2' alkylation of chiral bromoallene **5**, derived from enantiomerically pure phenyllactic acid (**6**) (Scheme 1). A similar diastereoselectivity has been demonstrated in our recent work.[7]

Scheme 2 outlines the elaboration of C^1-C^5 fragment.[4,8,9] To selectively reduce the carboxylic group to an aldehyde in the presence of a methyl ester, we decided to convert acid **7** into the corresponding ethylthioester. Subsequent reduction with triethylsilane in the presence of catalytic amounts of Pd/C gave aldehyde **4** in 66% yield over the two steps.[10] Further elaboration of aldehyde **4** into vinylstannane **2** was done using the following sequence: reaction with CHI_3 in the presence of $CrCl_2$ gave *trans* vinyl iodide **8**,[11] and stannylation with hexamethyldistannane in the presence of freshly prepared Pd(PPh_3)$_4$, yielded *trans* vinylstannane **2** (56% yield over the two steps).[6] The geometry of the vinylic hydrogens

Scheme 1



Scheme 2[a]



[a] Key: (a) EtSH, DCC, DMAP, CH_2Cl_2, rt (81%); (b) Et_3SiH, Pd/C, acetone, rt (82%); (c) CHI_3, $CrCl_2$, THF (75%); (d) $Me_3SnSnMe_3$, Pd(PPh_3)$_4$, THF, 50 °C (74%).

in **2** was exclusively *trans* as suggested by the coupling constant of the two vinylic protons (J = 19 Hz).

The preparation of the C^6-C^{10} fragment is depicted in Scheme 3.[8] Commercially available (*S*)-phenyllactic acid (**6**) was transformed into the Weinreb amide **9** using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (py-BOP) as a coupling reagent (72% yield over the two steps).[12] The *N*-methyl-*N*-methoxy group worked first as a protecting group during the methylation

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(8) Physical data for **2**, **3**, **5**, and **12**: **2**: ^{1}H NMR (200 MHz, $CDCl_3$, 50 °C, TMS) δ = 0.09 (s, J = 27 Hz, 9 H, coupling with ^{119}Sn), 1.19 (d, J = 7.1 Hz, 3 H), 1.42 (s, 9 H), 2.69−2.79 (m, 1 H), 3.62 (s, 3 H), 4.29−4.33 (m, 1 H), 5.30 (d, J = 9.2 Hz, 1 H), 5.85 (dd, J = 19, 4.2 Hz, 1 H), 6.15 (d, J = 19 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$, 50 °C, TMS) δ = −9.7 (t, J = 173 Hz), 14.2, 28.2, 43.1, 51.4, 56.2, 79.2, 130.7, 145.2, 155.5, 175.2. **3**: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS) δ = 1.19 (d, J = 7 Hz, 3 H), 1.84 (d, J = 2.4 Hz, 3 H), 2.52−2.60 (m, 1 H), 2.80−3.04 (m, 2 H), 3.21−3.33 (m, 1 H), 3.28 (s, 3 H), 7.20−7.30 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 3.6, 17.4, 30.1, 37.8, 58.4, 65.8, 81.1, 85.8, 126.0, 128.1, 129.5, 139.1; IR (CCl_4) ν = 3034, 2926, 1939, 1453, 1119 cm^{-1}; MS (EI) m/z 202 (3) [M$^+$], 170 (7), 155 (4), 135 (100), 111 (56), 103 (30), 91 (29), 77 (10); $[\alpha]^{20}_D$ = −60.2 (c = 1, $CHCl_3$). **5**: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS) δ = 2.25 (d, J = 3 Hz, 3 H), 2.82−3.03 (m, 2 H), 3.34 (s, 3 H), 3.93−4.04 (m, 1 H), 5.10−5.18 (m, 1 H), 7.18−7.35 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS) δ = 25.1, 41.8, 56.8, 65.8, 79.8, 97.8, 126.3, 128.2, 129.4, 137.5, 203.3; IR (CCl_4) ν 3069, 2928, 1958, 1604, 1454, 1105 cm^{-1}; MS (IE) m/z 268 (0.3) [MH$^+$], 186 (13), 175 (74), 155 (77), 135 (100), 103 (31), 91 (63), 77 (13). **12**: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS) δ = 1.05 (d, J = 6.8 Hz, 3 H), 2.26 (d, J = 1.4 Hz, 3 H), 2.43−2.55 (m, 1 H), 2.66−2.89 (m, 2 H), 3.15−3.25 (m, 1 H), 3.28 (s, 3 H), 6.11 (dd, J = 1.4, 10 Hz, 1 H), 7.18−7.35 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS) δ = 15.4, 27.7, 37.7, 39.0, 58.5, 85.9, 94.1, 126.0, 128.2, 129.3, 138.8, 143.7; IR (CCl_4) ν = 3033, 2933, 1635, 1454, 1100 cm^{-1}; $[\alpha]^{20}_D$ = −48 (c = 1, $CHCl_3$).

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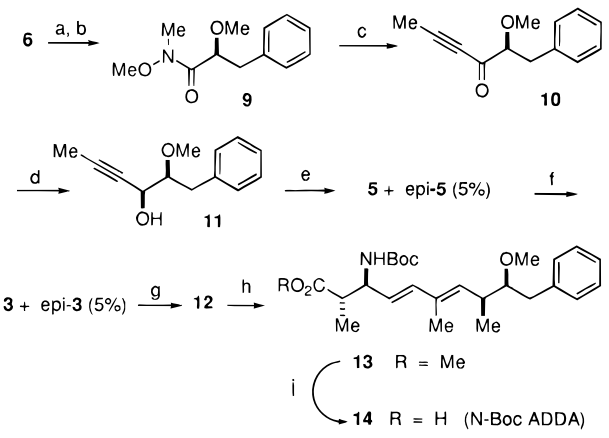
Scheme 3[a]



[a] Key: *N*,*O*-dimethylhydroxylamine·HCl, triethylamine, pyBOP, CH_2Cl_2, rt (81%); (b) CH_3I, Ag_2O, DMF, rt (88%); (c) MeC≡CLi, THF, −78 °C, (89%); (d) K-Selectride, THF, −100 °C (72%); (e) BuLi, LiBr, TosCl, THF, then CuBr·DMS, LiBr, −60 °C (75%: **5** and *epi*-**5**); (f) MeCuCNLi, THF, −78 °C (76% of **3** and 4% of *epi*-**3**); (g) $Cp_2ZrCl(H)$, C_6H_6, 43 °C, then I_2 in CCl_4 (70%); (h) **2**, $PdCl_2(CH_3CN)_2$, DMF, rt (58%); (i) LiOH, dimethoxyethane−H_2O 1/1, rt (70%).

of the secondary alcohol using silver oxide and methyl iodide and after as a carbonyl activating group for the preparation of propargylic ketone **10**.

Compound **9** was reacted with lithium propyne (obtained by reaction of 1-bromopropene and 2.2 equiv of BuLi)[13] to give **10** in 89% yield. *Syn* stereoselective reduction of the carbonyl group of **10** was performed with potassium tri-*sec*-butyl borohydride (K-Selectride, Aldrich) at −100 °C in THF.[14] The resulting propargylic alcohol **11** was isolated isomerically pure after column chromatography in 72% yield. The stereochemistry of this product was confirmed by analyzing the value of the coupling constant between the protons attached to the stereogenic centres (J = 5.8 Hz), typical for a *syn* arrangement. Propargylic alcohol **11** was transformed into the bromoallene **5** through reaction of LiBr and CuBr in THF at −60 °C with the corresponding tosylate.[15,16] This reaction is highly regio- and stereoselective, giving the desired compound **5** with 90% de. The epimeric bromoallene (*epi*-**5**), present in *ca.* 5%, was detected by ^{1}H NMR (200 MHz) and could not be separated by TLC. We suspect that to some extent direct substitution of the transient tosylate by bromine occurred, producing a propargylic bromide that in turn was converted into the bromoallene identified as *epi*-**5** (see below). Alkylation of the mixture of **5** and its *anti* isomer *epi*-**5** was performed with the organocopper reagent MeCuCNLi in THF and afforded a separable mixture of two compounds identified as **3** (*syn*: J = 6 Hz, 76%) and its *anti* isomer *epi*-**3** (*anti*: J = 3.5 Hz, 5%). The reaction with the copper reagent proceeded through a pure S_N2' mechanism introducing the methyl group on the side of the allene opposite to that of the bromine, producing alkylalkyne **3** as the sole adduct.[7] No trace of the direct substitution product resulting from attack of the copper reagent was detected by ^{1}H and ^{13}C NMR.

For the selective formation of the *E* iodide **12**, the triple bond in **3** was subjected to hydrozirconation followed by quenching with iodine.[17] This sequence installed the halogen at the less hindered side of the triple bond in **3** and defined the geometry of the double bond for Stille coupling with compound **2**. The protected ADDA fragment **13** with the correct *E*,*E* stereochemistry was finally obtained by reaction of iodide **12** and vinyl stannnane **2** in dry DMF in the presence of $Pd(CH_3CN)_2Cl_2$ (5%) in an acceptable yield (60%).[6,18] During the cross coupling reaction, 5% of the corresponding *E*,*Z* isomer was formed but subsequently separated from **13** by column chromatography. Finally, saponification of the methyl ester in **13** with LiOH afforded the *N*-Boc amino acid **14** ready to be used for the synthesis of the phosphatase inhibitors mentioned above. Compound **14**, obtained in this way, was fully characterized and found to have the same physical and spectroscopic properties previously described for *N*-Boc ADDA.[4,19,20] In conclusion, we have demonstrated that homochiral bromoallenes are reliable intermediates for the regio- and diastereocontrolled preparation of disubstituted alkylalkynes.

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Supporting Information Available: Experimental procedures and characterization data for all compounds (8 pages).

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