Asymmetric Synthesis of (2*S*,3*S*,8*S*,9*S*)-*N*-Boc ADDA: Application of a Palladium(0)-Catalyzed Cross-Coupling Reaction of Trisubstituted Olefins

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Received April 11, 1997

In the preceeding paper, we described the regio- and stereocontrolled preparation of branched trisubstituted conjugated dienes by a palladium(0)-catalyzed cross-coupling reaction.[1] Here, we report the convergent, asymmetric synthesis of the C21 β-amino acid Adda associated with the bioactive marine natural products motuporin (**1a**)[2] and nodularin (**1b**). Motuporin, recently identified through an enzyme assay-guided screening of crude extracts from the marine sponge *Theonella swinhoei* Gray,[3] and the related agent nodularin, isolated from the cyanophyte *Nodularin spumigena*,[4] have displayed potent inhibitory activity against a number of protein phosphatases. Members of a related family of hepatotoxic heptapeptides, the mycrocystins, have displayed inhibitory activity against protein phosphatases.[5] The crucial biochemical role that the protein serine and threonine phosphatases (PSPs) play in intracellular signaling processes has generated much interest in the ability of peptides bearing Adda to inhibit the activity of these phosphatases.[4] As a consequence, several research groups have reported approaches to these natural products, and a number of syntheses of Adda and derivatives have recently been published.[5]

Our synthesis makes use of chiral allylsilane bond construction methodology[6] for the introduction of the four stereogenic centers. The synthesis also features an efficient palladium-catalyzed cross-coupling reaction for the construction of the (*E*,*E*)-trisubstituted double bond. The first disconnection at the C5−C6 bond produced two subunits including the *syn*-homopropargylic ether (**3**, C6−C10 subunit) and secondary allylic amine bearing an (*E*)-vinyl iodide **4** (Figure 1). Further analysis of the individual subunits produced two synthons in the form of silane reagents **5** and **6**, of which the *anti*-azido silane **6** was derived from (*S*)-**5** through the azidation of β-silyl enolate.[7] Therefore, in the synthetic analysis, subunits **3** and **4** are ultimately derived from the same starting silane **5**.

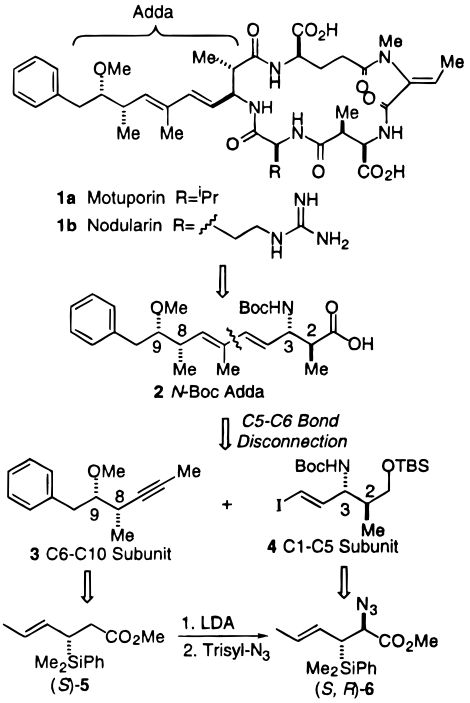
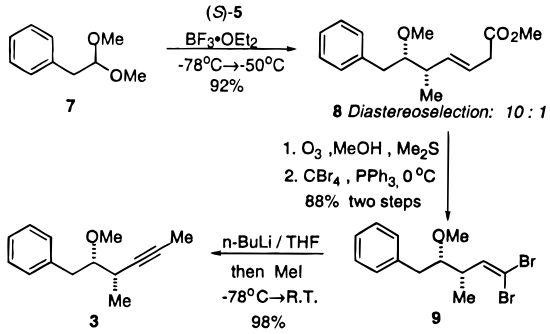


Figure 1.

Scheme 1

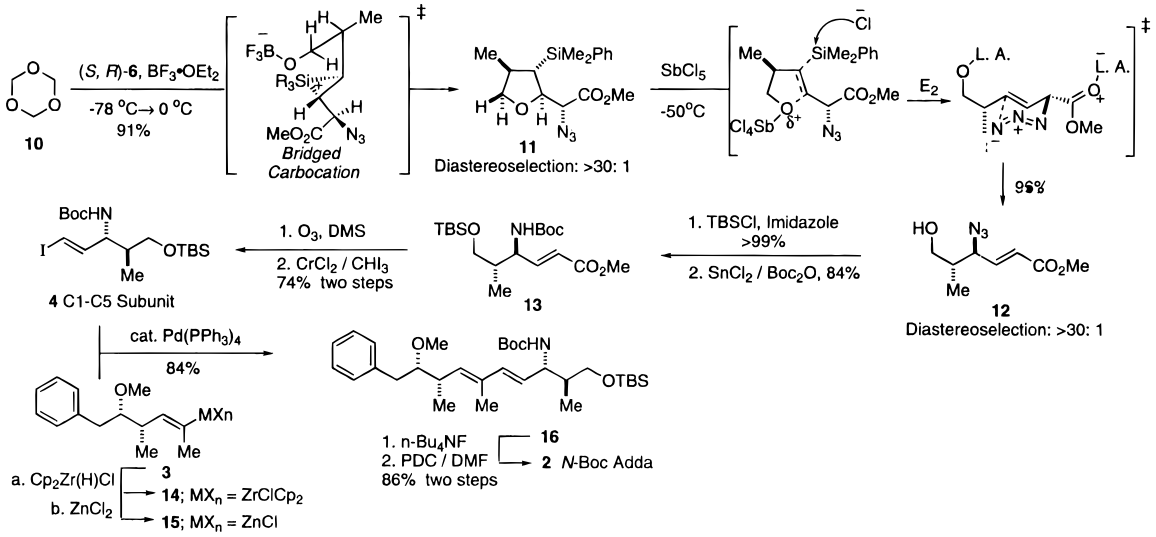


C6−C10 Subunit. The preparation of this material relied on the installation of the C8−C9 stereochemical relationship through a *syn*-selective crotylation reaction. This short sequence was initiated with a Lewis acid-promoted condensation of silane (*S*)-**5**[8] with phenyl acetaldehyde dimethyl acetal **7** (Scheme 1). In the presence of $BF_3{\cdot}OEt_2$ (1.2 equiv), this *syn*-selective crotylation (10:1 *syn*/*anti*) proceeds through an open transition state involving an intermediate oxonium ion to give the homoallylic ether **8** in 92% yield.[9] Cleavage of the *trans*-double bond of **8** by ozonolysis and direct dibromoolefination[10] of the intermediate aldehyde gave the desired acetylene precursor **9** in 88% yield (two steps). Exposure of the dibromoolefin **9** to Corey−Fuchs conditions (*n*-BuLi, THF, −78 °C) followed by trapping of the intermediate acetylenic anion with MeI led to the methyl-substituted acetylene **3** in 98% yield. This sequence completed the synthesis of the C6−C10 subunit and produced the material to be used in the cross-coupling reaction.[11]

(1) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912.
(2) (a) Dilip de Silva, E.; Williams, D. E.; Anderson, R. J.; Klix, H.; Holmes, C. F. B.; Allen, T. M. *Tetrahedron Lett.* **1992**, *33*, 1561−1564. (b) Total synthesis of motuporin: Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 9069−9070.
(3) (a) Rinehart, K. L.; Harada, K.; Namikoshi, M.; Chen, C.; Harvis, C. A.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasley, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, *110*, 8557−8558. (b) Namikoshi, M.; Choi, B. W.; Sakai, R.; Sun, F.; Rinehart, K. L.; Carmichael, W. W.; Evans, W. R.; Cruz, P.; Munro, M. H. G.; Blunt, J. W. *J. Org. Chem.* **1994**, *59*, 2349−2357.
(4) (a) Goldberg, J.; Huang, H.; Kwon, Y.; Greengard, P.; Nairn, A. C.; Kuriyan, J. *Nature* **1995**, *376*, 745−753 and references cited therein. (b) Fujiki, H.; Suganuma, M. *Adv. Cancer Res.* **1993**, *61*, 143−194.
(5) (a) Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. *Tetrahedron Lett.* **1989**, *30*, 4349−4352. (b) Chakraborty, T. K.; Joshi, S. P. *Tetrahedron Lett.* **1990**, *31*, 2043−2046. (c) Beatty, M. F.; White, C. J.; Avery, M. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1637−1641. (d) Kim, H. Y.; Toogood, P. L. *Tetrahedron Lett.* **1996**, *37*, 2349−2352. (e) D'Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870−4871. (f) Sin, N.; Kallmerten, J. *Tetrahedron Lett.* **1996**, *37*, 5645−5648. (g) For the total synthesis of microcystin, see: Humphrey, J. M.; Aggen, J. B.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1996**, *118*, 11759−11770.
(6) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.
(7) Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341−7344.
(8) Panek, J. S.; Yang, M. G.; Solomon, J. *J. Org. Chem.* **1993**, *58*, 1003−1010.
(9) Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755−5758.
(10) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3772.
(11) Satisfactory spectroscopic data (^{1}H and ^{13}C NMR, IR, CIMS, CIHRMS) were obtained for all new compounds. Ratios of diastereomers were determined by 400 Hz 1H NMR.

S0022-3263(97)00648-8 CCC: $14.00

Scheme 2



C1−C5 Subunit and *N*-Boc Adda. We were interested in the possibility of establishing the C3-nitrogen-bearing stereocenter through a sequential diastereoselective crotylation and allylic azide isomerization reaction. This option seemed quite attractive, given that literature precedent for transformations of this type have been established together with the notion that the use of the allylic azide isomerization would provide access to a stereochemically well-defined 1,3-azido alcohol. This intermediate would serve as a precursor to the vinyl iodide bearing the chiral secondary amine. The synthesis of this subunit was initiated with a $BF_3{\cdot}OEt_2$-promoted addition of the (*S*,*R*)-**6** silane to an *in situ* generated oxonium ion of formaldehyde derived from (*S*)-trioxane **10**. The reaction afforded the azidofuran **11** as a single diastereomer (>30:1, *syn*/*anti*) in 91% yield (Scheme 2) and installed the C2 Me-bearing stereocenter.[12] The isolation of the 2,5-*cis* tetrahydrofuran is consistent with the stepwise mechanism proposed to rationalize the formation of related tetrahydrofurans, cyclopentanes, and Δ^2-isoxazolines; initial C−C bond construction occurs by an *anti*-S_E' addition.[6] The stabilized β-silyl carbocation is illustrated as rearranging through a bridged carbocation; this migration promotes the cyclization step, as it proceeds with inversion at the C5 position.

Subsequent opening of the intermediate furan by treatment with $SbCl_5$ (1.3 equiv) followed by a suprafacial allylic azide isomerization afforded the 1,3-azido alcohol **12** as a single diastereomer (96% overall yield).[12] With the establishment of an *anti*-stereochemical relationship set between the methyl and azide groups, the 1,3-azido alcohol was prepared for the Negishi-type coupling.[1] Accordingly, the primary hydroxyl group was protected as its TBS ether, the azide was reduced with $SnCl_2$ in anhydrous methanol (0 °C → rt, 4 h), and the primary amine was then acylated with $(Boc)_2O$ in dioxane−aqueous sodium bicarbonate[13] to give the protected amine **13.** This material was converted to the (*E*)-vinyl iodide **4** in two steps: ozonolysis of the double bond followed by iodoolefination with iodoform (CHI_3) in the presence of $CrCl_2$,[14] which completed the preparation of the C1−C5 subunit. The sequence installed the (*E*)-vinyl iodide **4**[11] and defined the configuration of the double bond for the palladium-catalyzed subunit coupling.

The coupling process was initiated with the regioselective and stereospecific formation of the (*E*)-trisubstituted zirconate. The alkyne **3** was hydrozirconated using the Schwartz reagent[1] $Cp_2Zr(H)Cl$ (2.0 equiv, THF, 50 °C, 1.0 h) to produce the (*E*)-trisubstituted zirconate **14** as a single regioisomer.[1] An *in situ* transmetalation with anhydrous $ZnCl_2$ (3.0 equiv, rt, 2.0 min) afforded the vinyl zinc species **15**. This material was used directly in the subunit coupling with the (*E*)-vinyl iodide **4** in the presence of $Pd(Ph_3P)_4$ (0.05 equiv, THF, rt, 5 min), completing the assembly of the configurationally pure (*E*,*E*)-diene in 84% yield.[15] This one-pot sequence of bimetallic mediated transformations gave the fully functionalized Adda precursor **16**, which was now set for final conversion to *N*-Boc Adda. The following two-step deprotection/oxidation sequence was completed through the intermediate amino alcohol derived from desilation with fluoride ion. Treatment of a solution of the silyl ether **16** in THF with *n*-Bu_4NF (1.0 equiv, THF, rt, 30 min) resulted in clean conversion to the primary alcohol. This material was oxidized to the carboxylic acid by treatment with PDC (7.0 equiv, DMF, 22 h, 86%, two steps), completing the synthesis of *N*-Boc Adda. Its spectroscopic and physical properties were identical in all respects (^1H, ^{13}C, IR, $[\alpha]_D$, and MS) with those previously reported.

In summary, the asymmetric synthesis of *N*-Boc Adda was accomplished in a highly convergent manner using 11 steps in 27% overall yield. The synthesis and coupling of the associated amino acids and completion of the total synthesis of motuporin will be reported at a later time.

Acknowledgment. We are grateful to Professor Peter Toogood (University of Michigan) for providing copies of ^1H and ^{13}C NMR spectra of **2** for comparison. Financial support was obtained from the NIH (RO1 CA56304).

Supporting Information Available: General experimental procedures and spectral data for all intermediates and the final product (30 pages).

JO9706483

(12) (a) Beresis, R. T.; Panek, J. S. *Bioorg. Med. Chem. Lett.* **1993**, *13*, 1609−1613. (b) Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063−4064.

(13) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030.

(14) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(15) Recently, French and Italian groups reported the synthesis of Adda and that a similar Negishi-type coupling failed; see: D'Aniello, F.; Mann, A.; Schonfelder, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447−1456.