Total Synthesis of (−)-Motuporin

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Received March 15, 1999

Motuporin **1a** is a cyclic pentapeptide recently identified through an enzyme assay-guided screening of crude extracts from the marine sponge *Theonella swinhoei* Gray (Figure 1).[1] Motuporin and the structurally related agent nodularin **1b**, isolated from the cyanophyte *Nodularin spumogena*,[2] have displayed potent inhibitory activity against a number of protein phosphatases. Members of a related family of hepatotoxic heptapeptides, the mycrocystins, have also displayed inhibitory activity against protein phosphatases.[3] 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 [(2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid] to inhibit the activity of these phosphatases.[4−6] The first total synthesis of motuporin was reported in 1995 from Schreiber's group, and the synthesis of microcystin was recently achieved by Chamberlin and co-workers.[5] This Communication reports a highly convergent, asymmetric synthesis of **1a** and documents an efficient Pd(0)-mediated cross-coupling reaction for the construction of the trisubstituted (*E*,*E*)-diene in a peptide system.

Our approach, outlined in Figure 1, utilized asymmetric crotylation methodology for the introduction of the stereogenic centers. Motuporin (**1a**) is divided into two principal fragments, *N*-Boc-valine-Adda fragment **2** and the remaining tripeptide fragment **3**. Disconnection of **2** at the C5−C6 bond produces two subunits, the vinyl metal species (**4**, C6−C10 subunit) and the (*E*)-vinyl iodide dipeptide **5**. Both the right-hand subunit **5** and the α-azido ester **6** are conveniently derived from azido alcohol **7**. Further retrosynthetic disconnection of the individual subunits produced two chiral silane reagents, of which the *anti*-azido silane **9** is derived from the unsubstituted silane reagent (*S*)-**8** through the stereoselective azidation of its *β*-silyl enolate.[7]

Synthesis of **2** required the construction of the right-hand subunit **5** and the C6−C10 subunit **4** which were joined together through a Pd(0)-catalyzed cross-coupling reaction to construct the carbon framework of this valine-Adda dipeptide fragment. The preparation of the left-hand subunit **4** has been previously reported in our synthesis of Adda

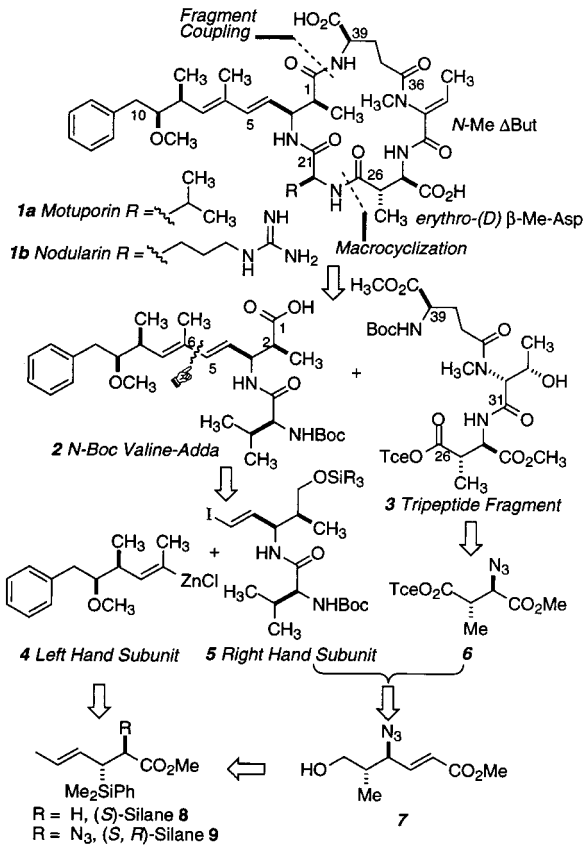
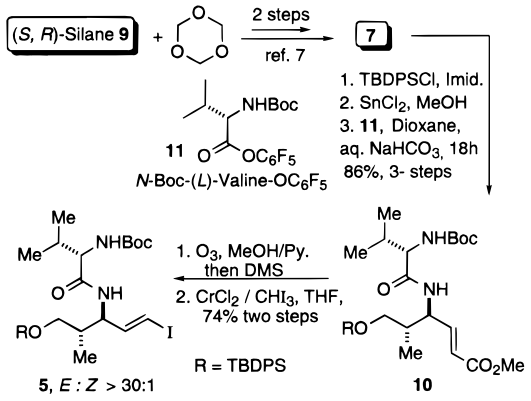


Figure 1.

Scheme 1



utilizing asymmetric crotylation methodology.[6] The 1,3-azido alcohol **7**, obtained via a sequential diastereoselective crotylation and allylic azide isomerization reaction,[6] was protected as its TBDPS ether, at which point the azide group was subsequently reduced with $SnCl_2$ in anhydrous methanol (0 °C → rt, 4 h). The resulting crude amine was directly condensed with the pentafluorophenyl ester activated *N*-Boc-L-valine in a dioxane/aqueous $NaHCO_3$ biphasic reaction system at rt to afford dipeptide **10** in high yield (86%, three steps, Scheme 1). Oxidative cleavage of the (*E*)-olefin of **10** gave a sensitive aldehyde which was immediately subjected to Takai's homologation protocol[8] to afford the geometrically pure (*E*)-vinyl iodide **5** in 74% yield, completing the synthesis of the right-hand fragment.

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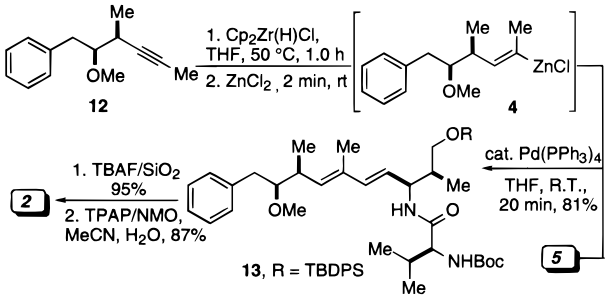
10.1021/jo9904617 CCC: $18.00
Published on Web 04/14/1999

Scheme 2

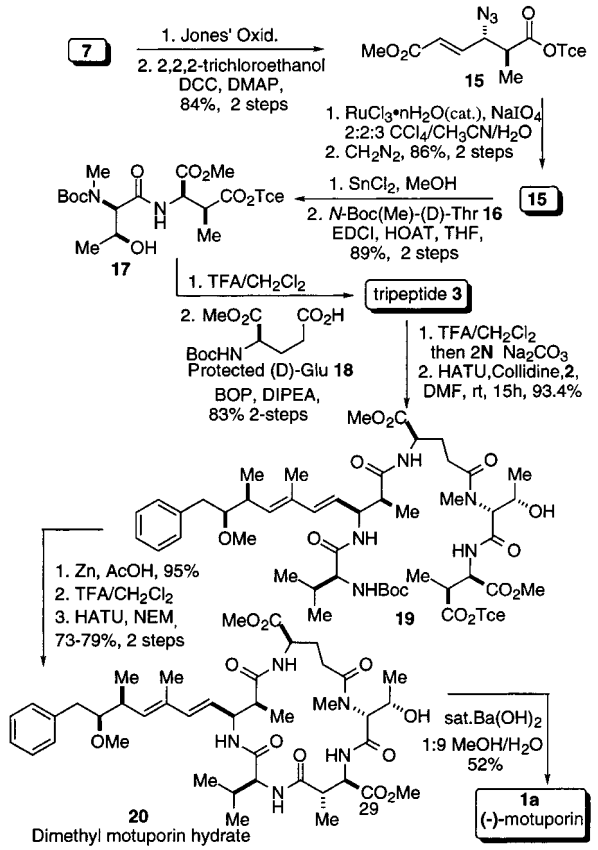


Coupling of **4** and **5** utilized a modified Negishi protocol,[9] catalyzed by $Pd(Ph_3P)_4$. Hydrozirconation of alkyne **12**[6] using Schwartz's reagent[10] [$Cp_2Zr(H)Cl$] (2.0 equiv, THF, 50 °C, 1.0 h) produced the (*E*)-trisubstituted zirconate as a single isomer.[9a] This was followed by an in situ transmetalation with anhydrous $ZnCl_2$ (3.0 equiv, rt, 2.0 min) to afford the vinyl zinc species **4**. This material was immediately treated with vinyl iodide **5** (1.0 equiv) and $Pd(PPh_3)_4$ (5 mol %), affording the configurationally pure (*E*,*E*)-diene in 81% yield (Scheme 2).[11] This one-pot sequence involving a bimetallic-mediated transformation gave the fully functionalized valine-Adda precursor **13**.[12] This intermediate was readied for fragment coupling by conversion to the carboxylic acid via a two-step sequence: (i) silyl group deprotection with TBAF·SiO_2 (2.5 equiv, rt, 4 h, 95%) and (ii) oxidation of the derived primary alcohol with a modified Ley's oxidation protocol (TPAP/NMO, CH_3CN, 1 h; then H_2O, rt, 18 h),[13] afforded the *N*-Boc-valine-Adda fragment **2** in 87% yield.

The preparation of tripeptide **3** began with the elaboration of intermediate **7** (Scheme 3). Oxidation of 1,3-azido alcohol **7** followed by protection of the carboxylic acid as a trichloroethyl ester gave **14** in 84% yield (two steps). Olefin oxidation ($RuCl_3$, $NaIO_4$) of **14**, followed by exposure of the resulting α-azido acid to diazomethane (Et_2O, 0 °C), afforded methyl ester **15**. Reduction of the azido group of **15** using $SnCl_2$ (1.5 equiv) produced the free amine, which was coupled with *N*-Boc(Me)-D-threonine **16**[14] (1.1 equiv) under standard peptide coupling conditions to give dipeptide **17** (89%, two steps). Deprotection of the Boc group in **17**, followed by BOP-induced amide bond formation with the protected D-glutamate **18**,[14] completed the formation of tripeptide **3**.

The crucial fragment coupling reaction, [**2** + **3**], which provides the cyclization precursor **19**, was based on Carpino's procedure using HATU.[15] Deprotection of tripeptide **3**, followed by treatment with **2** in the presence of HATU/collidine in DMF, gave the protected pentapeptide **19** in 93.4% yield (Scheme 3). This coupling proceeded without any detectable level of epimerization.[16] Reductive removal of the trichloroethyl group using zinc/acetic acid (rt, 4 h, 95%) was followed by *N*-terminal Boc deprotection to afford the amine

Scheme 3



as its TFA salt which was set for macrocyclization. This intermediate underwent an efficient cyclization in the presence of HATU and *N*-ethylmorpholine yielding macrocycle **20** in 79% yield.[17] Treatment of **20** with $Ba(OH)_2$ resulted in the simultaneous hydrolysis of both methyl esters together with the in situ dehydration of *N*-methylthreonine.[5a] Upon acidification with 1 N HCl to pH 2 and reverse phase HPLC purification, synthetic motuporin **1a** was obtained as its diacid form in 52% yield. The spectroscopic and analytical properties of this material were identical in all respects with the reported data.[1,5a,18] Treatment of **1a** with $NaHCO_3$/MeOH provided the disodium salt of motuporin, which agreed in all respects (^1H and ^{13}C NMR, $[\alpha]_D$, IR, FAB-HRMS, rp-HPLC) with the data reported earlier.[1,5a]

In closing, the total synthesis of motuporin was completed in 28 steps, with a longest linear sequence of 16 steps (15.8% overall). The synthesis emphasized emerging synthetic methodology: an efficient Pd(0)-catalyzed cross-coupling reaction of a configurationally well-defined vinyl zinc intermediate with an (*E*)-vinyl iodide for the construction of the trisubstituted (*E*,*E*)-diene in a peptidic system. Six of the eight stereogenic centers associated with motuporin were introduced using asymmetric crotylsilane bond construction methodology.

Acknowledgment. Financial support was obtained from NIH/NCI (RO1 CA56304).

Supporting Information Available: Experimental procedures, spectral data for all new compounds, and copies of proton and carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) More conventional cross-coupling protocols such as the Stille coupling reaction proved to be less efficient, as only modest yield (20−50%) was achieved. In addition, considerable levels of double bond isomerization occurred during the cross-coupling reactions.

(12) To our knowledge, this is the first documentation of a Negishi-type coupling reaction performed with a peptide system. It is notable that this strategy may be suitable for the preparation of structurally diverse cyclicpeptides for the SAR study of the motuporin family.

(13) For a review of Ley's oxidation, see: Ley, S.; Norman, J.; Griffith, W.; Marsden, S. *Synthesis* **1994**, 639−666.

(14) For preparation of this compound, see Supporting Information.

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(16) Satisfactory spectroscopic and analytic data (^1H and ^{13}C NMR, IR, $[\alpha]_D$, MS, HRMS) were obtained for all new compounds. Ratios of diastereomers were determined by ^1H NMR (400 MHz).

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