Total Synthesis of (-)-Motuporin

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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 [(2S,3S,8S,9S)-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 righthand 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

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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 SnCl₂ in anhydrous methanol (0 °C \rightarrow rt, 4 h). The resulting crude amine was directly condensed with the pentafluorophenyl ester activated N-Boc-L-valine in a dioxane/aqueous NaHCO₃ 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 protocol⁸ to afford the geometrically pure (*E*)-vinyl iodide **5** in 74% yield, completing the synthesis of the right-hand fragment.

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Coupling of **4** and **5** utilized a modified Negishi protocol,⁹ catalyzed by Pd(Ph₃P)₄. Hydrozirconation of alkyne 12⁶ using Schwartz's reagent¹⁰ [Cp₂Zr(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(PPh₃)₄ (5 mol %), affording the configurationally pure (E, E)-diene in 81% yield (Scheme 2).¹¹ This one-pot sequence involving a bimetallicmediated 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· SiO₂ (2.5 equiv, rt, 4 h, 95%) and (ii) oxidation of the derived primary alcohol with a modified Ley's oxidation protocol (TPAP/NMO, CH₃CN, 1 h; then H₂O, 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 (RuCl₃, NaIO₄) of **14**, followed by exposure of the resulting α -azido acid to diazomethane (Et₂O, 0 °C), afforded methyl ester **15**. Reduction of the azido group of **15** using SnCl₂ (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, $[\mathbf{2} + \mathbf{3}]$, 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

(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

(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.



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 NaHCO₃/MeOH provided the disodium salt of motuporin, which agreed in all respects (¹H and ¹³C NMR, [α]_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.

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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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