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# Enantioselective Synthesis of the Protein Phosphatase Inhibitor (−)-Motuporin

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***Abstract:*** A highly convergent asymmetric synthesis of the protein phosphatase inhibitor motuporin **1a** is described. Synthesis and coupling of the individual peptide fragments [**34** + **35** → **51**] followed by macrocyclization afforded the fully protected motuporin precursor **33**, which is converted to the natural product by dehydration and ester hydrolysis. Six of the eight stereogenic centers associated with the natural product were introduced using asymmetric crotylsilane bond construction methodology. Our approach features an efficient Pd(0)-catalyzed cross-coupling reaction between a configurationally well-defined vinyl zinc intermediate **22** and an (*E*)-vinyl iodide **7**, which afforded compound **43**, resulting in the construction of the trisubstituted (*E,E*)-diene system of the motuporin side chain. Improved reaction conditions for macrocyclization in the formation of **33** are also detailed.

## Introduction

It is now widely accepted that modulation of the reversible phosphorylation of proteins, as catalyzed by protein kinases (PKs) and protein phosphatases (PPs), is the principal mechanism by which eukaryotic cells respond to external stimuli.[1] The balance between phosphorylated and dephosphorylated proteins, which is controlled by the protein kinase and phosphatase activities, is crucial to maintaining proper cellular function.[2] Excessive protein phosphorylation, whether through the activation of kinases or through the inhibition of phosphatases, can lead to uncontrolled cellular proliferation, suggesting the possibility of an active role for the phosphatases in tumor suppression.[3] The controlled disruption of this balance through the use of PPs inhibitors is a method by which one can dissect this complex system.

There is a diverse group of structurally interesting natural products that act by inhibiting certain phosphatases, thereby disrupting the normal biochemical pathway. Examples include okadaic acid,[4] tautomycin,[5] calyculin,[6] cantharidine,[7] microcystins,[8] nodularins,[9] and motuporin,[10] all of which are potent competitive inhibitors of two major classes of phosphatases, protein phosphatase 1 (PP1), and protein phosphatase 2A (PP2A).[11] In vivo, these compounds have been reported to promote tumor formation,[12] suppress cell transformation,[13] or induce apoptosis,[14] depending on length of exposure and the cell type.

Motuporin (**1a**) is a cyclic pentapeptide isolated in 1992 by Andersen and co-workers from the marine sponge *Theonella swinhoei* Gray collected in Papua New Guinea.[10] This molecule is one of the most potent PP1 inhibitors known, inhibiting at sub-nanomolar concentrations ($IC_{50}$ < 1.0 nM) and showing strong in vitro cytotoxicity against a variety of human cancer cells. The structures of motuporin and cyanobacterial derived natural product nodularin (**1b**) show remarkable resemblance to each other. Specifically, these cyclic peptides contain the unusual $\beta$-amino acid (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda),[9b] an $\alpha,\beta$-unsaturated amino acid *N*-methyldehydrobutyrine (N-Me$\Delta$But), an isolinked D-glutamate, and a $\beta$-methyl D-aspartate ($\beta$-MeAsp) residue (Figure 1).

Motuporin was isolated later than other members of its class and is derived from a much less readily accessible source.

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**10.1021/ja0206700 CCC: $22.00** 

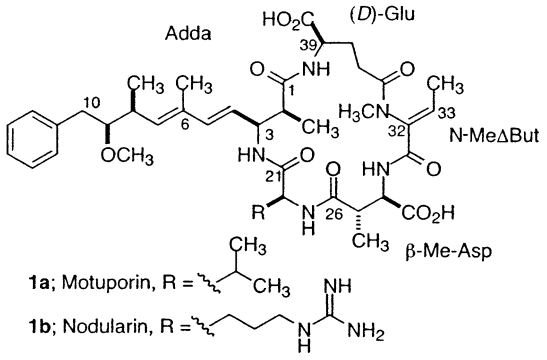



***Figure 1.***

Consequently much of the information concerning its biology and chemistry is extrapolated from data on nodularin and the structurally related heptapeptide microcystins. Of the nanomolar-binding agents of small molecule protein phosphatase inhibitors, **1a** is an especially attractive target for total synthesis for several reasons, including its relative scarcity, its reported high potency, and its unique structure.

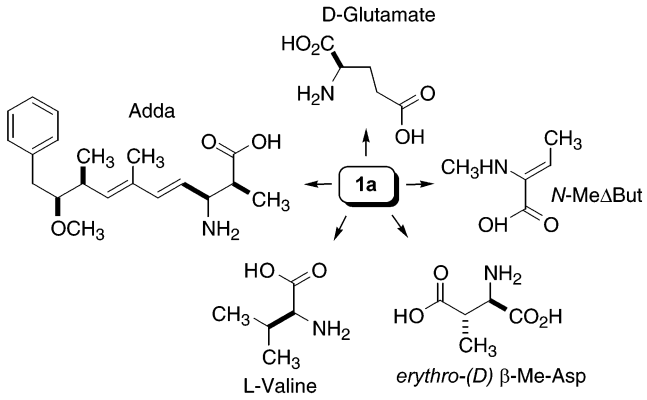
The biological activity and the structural complexity exhibited by the cyclic peptide PPs inhibitors have stimulated much activity within the synthetic community. Thus far, four asymmetric syntheses of motuporin have been accomplished independently, with the first total synthesis being reported in 1995 from Schreiber's group.[15] In addition, Chamberlin and co-workers have recently accomplished a total synthesis of structural related natural product microcystin.[16] Here we describe, in full, the design and execution of a convergent and flexible synthetic strategy for motuporin.

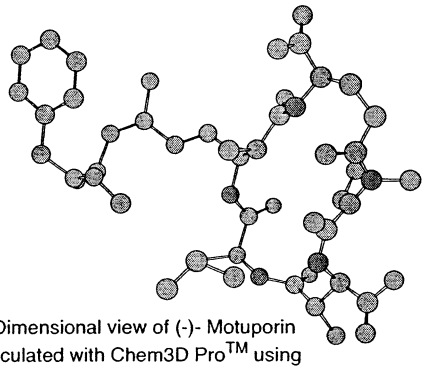
## Results and Discussion

After a careful analysis of the amino acid constituents of motuporin, one recognizes a pair of common α-amino acids and three unusual residues (Scheme 1). Our approach to the synthesis of **1a** would necessarily employ L-valine and D-glutamate as starting materials and require development of efficient syntheses of three unnatural amino acids, Adda, $\beta$-MeAsp, and N-MeΔBut.

We envisioned that the Adda fragment, possessing *syn*-related methyl−oxygen stereogenic centers at C8−C9, could be constructed using asymmetric crotylation methodology (Scheme 2).[17] In addition, the crotylation to the dimethyl acetal allows the direct introduction of the C9-methyl ether. Further examination of the Adda and $\beta$-MeAsp residues identified a common stereochemical triad; a pair of carbon atoms bearing vicinal amino and methyl groups in an anti relationship is shared by both $\beta$-amino acids. Utilizing a chiral silane reagent bearing an azide alpha to the ester,[18] the $\beta$-methyl aspartate equivalent could also be synthesized with high selectivity.

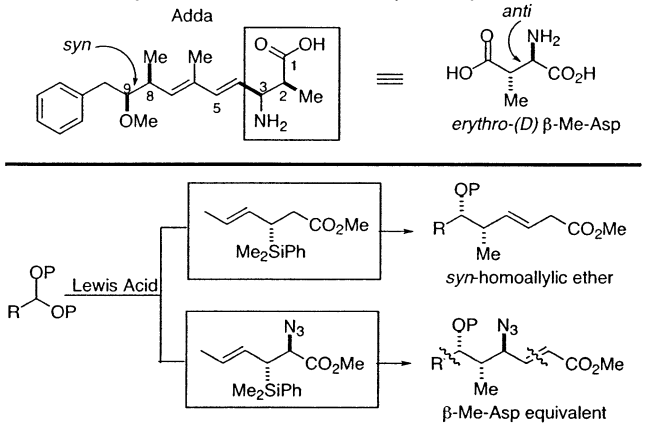
***Scheme 1***



3-Dimensional view of (-)- Motuporin calculated with Chem3D Pro™ using MM2 energy minimization protocol

***Scheme 2.*** Synthetic Plan for Adda and $\beta$-MeAsp Residues




**Retrosynthetic Analysis.** On the basis of isolation and biosynthetic predictions of the natural product,[19] we anticipated that cyclization of the 19-membered macrocycle could be effected at the C21 of the valine−Adda amide bond (Scheme 3). With further disconnection of the linear pentapeptide **2** at the C1-carboxyl of the Adda residue, a convergent approach was then developed which involved the fragment coupling of two advanced intermediates, the *N*-Boc Adda **3** and C21−C40 tetrapeptide fragments **4**. This plan allowed the incorporation of the valuable Adda residue late in the synthesis. The orthogonal protecting group scheme of the tetrapeptide **4** was composed of a N−Boc group, 2-trimethylsilylethyl ester (TMSE), and the dehydroamino acid moiety (N-MeΔBut), which was masked as a $\beta$-hydroxy amide until late in the synthesis. In the

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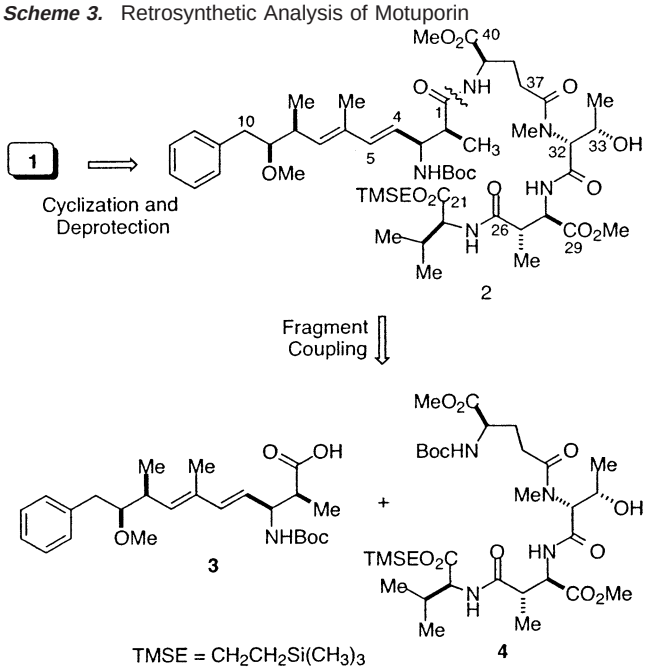
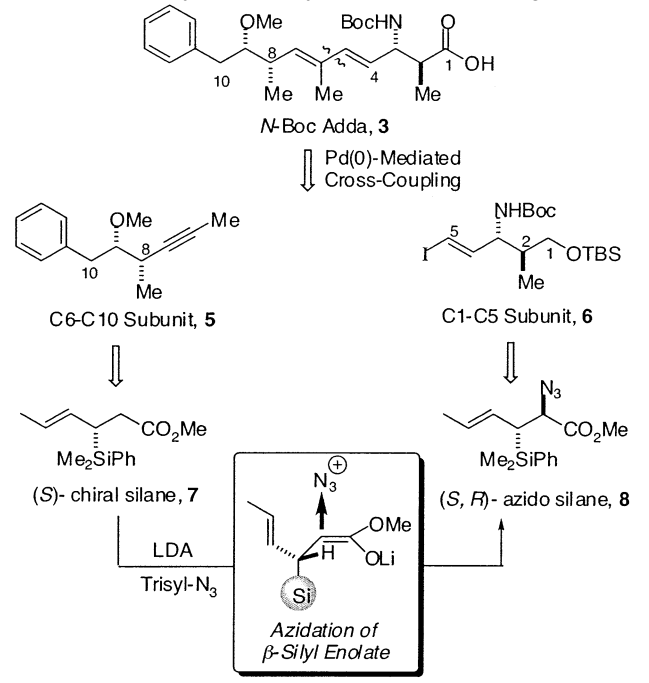
***Scheme 3.*** Retrosynthetic Analysis of Motuporin




***Scheme 4.*** Retrosynthetic Analysis of *N*-Boc Adda Fragment

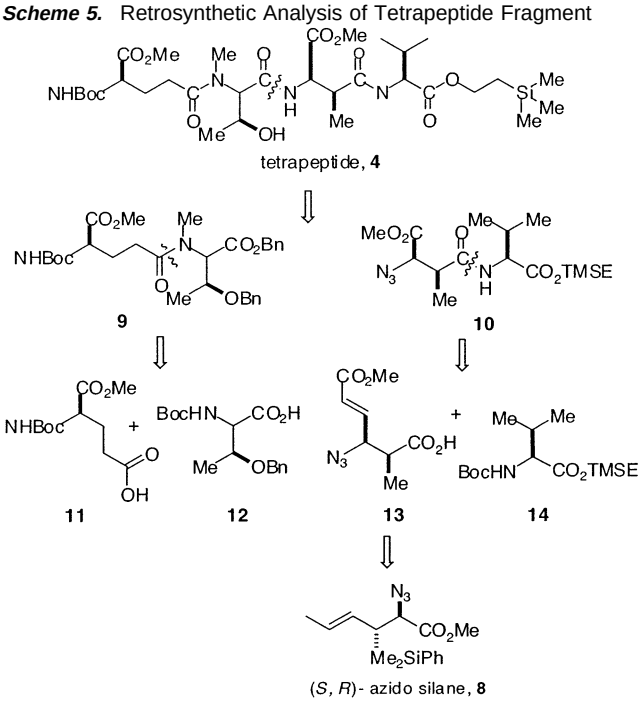



synthesis reported by Schreiber and Valentekovich it was shown that a $Ba(OH)_2$ catalyzed saponification of the C29 and C40 methyl esters also resulted in stereoselective dehydration of the threonine residue to afford the natural product motuporin.[15a] The stereochemical course of the dehydration is consistent with NMR studies on the solution structure of motuporin which, suggested that the (*Z*)-geometry of the olefin is preferred on thermodynamic considerations.[20]

The retrosynthesis of *N*-Boc protected Adda fragment **3** is shown in Scheme 4. The first disconnection at the C5−C6 bond produced two subunits including the *syn*-homopropargylic ether **5** (C6−C10 subunit) and secondary allylic amine bearing an

(20) See ref 15 for detailed discussion.

***Scheme 5.*** Retrosynthetic Analysis of Tetrapeptide Fragment




(*E*)-vinyl iodide **6** (C1−C5 Subunit). A palladium(0)-mediated cross-coupling reaction could be used to construct the (*E,E*)-diene employed a vinylmetal intermediate derived from acetylene **5**. Further analysis of the individual subunits produced two silane reagents, of which the more functionalized *anti*-azido silane **8** was obtained from the (*S*)-silane reagent **7** through the stereoselective azidation of a derived $\beta$-silyl enolate.[18] In this approach, the C1−C5 and C6−C10 subunits were ultimately derived from the same chiral silane reagent **7**.

The retrosynthesis of the C21−C40 tetrapeptide **4** is shown in Scheme 5. Amide bond cleavage at C31 carbonyl afforded two dipeptide segments **9** and **10**, which can be further disconnected to give four protected amino acids or their equivalents **11**−**14.** As described earlier in Scheme 2, the *erythro*-(D)-$\beta$-Me-Asp equivalency **13** would be derived from the azido silane **8**.

**Synthesis of *N*-Boc Adda Fragment 3.** During the course of our studies, several reports had appeared describing the synthesis of Adda.[21] The majority of these approaches rely on the use of phosphorus-based olefination procedures to assemble the trisubstituted (*E,E*)-diene, which often produces mixtures of isomers. To complement that strategy, we have designed a highly convergent and stereocontrolled synthesis of Adda which is based on a Pd(0) cross-coupling strategy.[22] The preparation of the C6−C10 subunit **5** relied on a *syn*-crotylation for the installation of the C8−C9 stereochemical relationship. The synthesis was initiated with a $BF_3{\cdot}OEt_2$ (1.2 equiv) promoted condensation of silane (*S*)-**7** with phenyl acetaldehyde dimethyl

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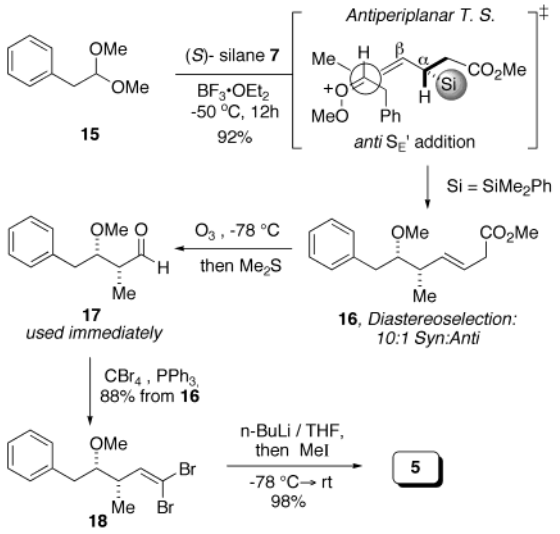
(22) Preliminary communication on the synthesis of **3**, see: Panek, J.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914−4915.

***Scheme 6.*** Synthesis of the C6−C10 Subunit




acetal **15** (−78 °C → −50 °C) to afford the homoallylic ether **16** in 92% yield, with 10:1 (*syn/anti*) diastereoselectivity. The stereochemical course of the crotylation is based on an anti $S_{E'}$-open transition state model illustrated in Scheme 6.[23] Two important features that may account for the useful level of diastereo- and enantioselectivty bear mention. First, the large silicon group is positioned anti-periplanar to the $\pi$-orbital of the oxonium ion, so maximum stabilization of the emerging secondary carbocation ($\beta$ to the silyl group) could be achieved. Second, the proper orientation of the vinyl methyl group is required to minimize steric destabilization among the diastereomeric transition states. Oxidative cleavage of the trans-double bond of **16** gave the desired aldehyde **17**, which was found to be prone to epimerization when subjected to purification on $SiO_2$ (Scheme 6). Accordingly, this material was used directly without purification in the next reaction after extractive isolation. The dibromoolefination[24] of the aldehyde **17** gave the desired acetylene precursor **18** in 88% yield (two steps from **16**). Exposure of the **18** to Corey−Fuchs conditions[24] (2.2 equiv of nBuLi, THF, −78 °C) followed by trapping of the intermediate acetylenic anion with MeI (5.0 equiv) led to the substituted acetylene **5** in 98% yield.

The major challenge in the synthesis of C1−C5 subunit **6** was to control the stereochemistry of the adjacent methyl and amine groups. We had anticipated that a crotylation using **8** to formaldehyde would produce allylic azide **19**. This initial intermediate was anticipated to undergo a facile, and stereoselective allylic azide isomerization[25] to generate 1,3-azido alcohol **20** (Scheme 7), bearing a vicinal anti methyl−azide relationship.[26] This transformation was especially attractive since the stereocontrolled allylic azide isomerization is a highly underdeveloped reaction and capable of rapidly building molecular complexity. Further transformation of intermediate **20** into the requisite C1−C5 subunit **6** would follow a straightforward sequence.

With the first synthetic plan established, the Lewis acid promoted condensation reaction of silane **8** with (*s*)-trioxane

***Scheme 7.*** Strategy for Introducing the C4, C5 Stereocenters

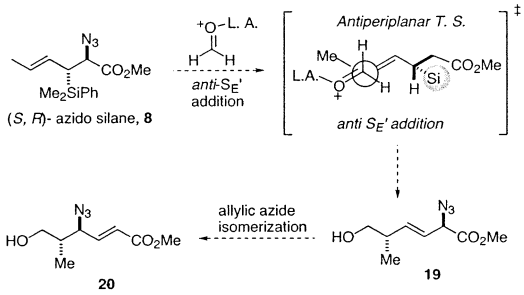
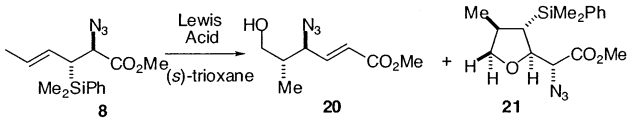



***Table 1.*** Lewis Acid Promoted Azide-Silane Addition to (*s*)-Trioxane (eq 1)




| Lewis acid | time (h)/temp (°C) | dr of **20**[a] | yield of **20**[b] (%) | yield of **21**[b] (%) |
|---|---|---|---|---|
| $SbCl_5$ | 2/−78 | >30:1 | 34 | 0 |
| $TiCl_4$ | 14/−35 | >30:1 | 56 | 33 |
| $SnCl_4$ | 14/−35 | >30:1 | 38 | 25 |
| $AlCl_3$ | 14/−35 | >30:1 | 30 | 48 |
| TMSOTf | 14/−50 | >30:1 | 0 | 83 |
| $BF_3$•$OEt_2$ | 14/−50 | >30:1 | 0 | 91 |

[a] Ratio of diastereomers was determined by $^1$H NMR (400 MHz) analysis of the crude products. [b] Yield refer to pure materials isolated after chromatography on $SiO_2$.

was evaluated for its feasibility to access **20** (Table 1). In the presence of $BF_3$•$OEt_2$, or TMSOTf, this reaction produced stereochemically pure tetrahydrofuran **21** as sole product; while **20** or a mixture of **20/21** was obtained when $AlCl_3$, $TiCl_4$, $SnCl_4$, or $SbCl_5$ was used to catalyze the reaction. The formation of tetrahydrofuran **21** exists as the major competing reaction pathway with elimination of the silyl group to form homoallylic alcohol **19** after initial condensation with the carbonyl carbon. In the case examined, the allylic azide group of **19** underwent a stereoselective 1,3-allylic azide rearrangement to give the desired 1,3-azido alcohol **20** bearing an $\alpha,\beta$-unsaturated ester.

For this reaction, the stereochemistry of the Me-bearing center of **20** is determined by the configuration of the C−Si bond of **8** and is rationalized through an anti $S_{E'}$ open TS model. The relative stereochemistry of tetrahydrofuran **21** was assigned by $^1$H NMR experiments, 2D COSY, and difference NOE measurements and by analogy with closely related structures obtained from earlier experiments.[27] The absolute stereochemistry is consistent with the stepwise mechanism proposed to rationalize the previously reported [3 + 2]- and [4 + 2]-annulations resulting in the production of tetrahydrofurans,[27] cyclopentanes,[28] $\Delta^2$-isoxazoline,[29] and dihydropyrans.[30] As illustrated in Scheme 7, the initial C−C bond construction occurs by an *anti*-$S_{E'}$-mode of addition and the emerging $\beta$-silyl carbocation is stabilized through the $\sigma \rightarrow \pi$ conjugation of the adjacent C−Si bond. A 1,2-cationic silyl migration then proceeds through a bridged carbocation, followed by heterocyclization producing the tetrahydrofuran **21**. A synclinal or antiperiplanar transition

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(27) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *26*, 9868−9870. (b) Beresis, R. T.; Panek, J. S. *Bioorg. Med. Chem. Lett.* **1993**, *1* (3), 1609−1613.
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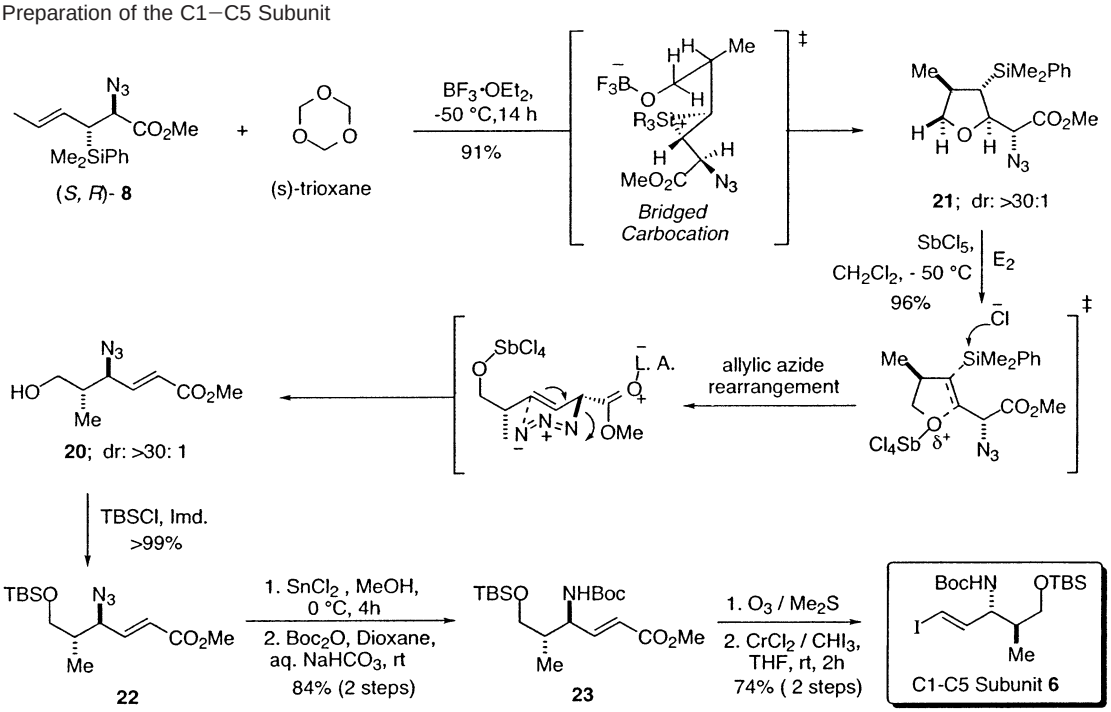
(29) Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898−7899.
(30) (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837. (b) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693−1696.

***Scheme 8.*** Preparation of the C1−C5 Subunit




state can be invoked for the furan formation, but the proximity of the oxygen functionality to the silylcarbocation prior to cyclization in the synclinal orientation lends support to the former.

Although the furan was produced in 91% yield in the presence of $BF_3$·$OEt_2$ the desired 1,3-azido alcohol **20** could only be isolated in yields ranging from 30 to 56%. We then explored conditions for transforming the tetrahydrofuran **21** to the key 1,3-azido alcohol **20**. After considerable effort,[31] we had learned that clean tetrahydrofuran ring opening and subsequent suprafacial allylic azide isomerization could be effected by treatment of **21** with $SbCl_5$ (1.3 equiv, −50 °C, 14 h) in dilute $CH_2Cl_2$ (0.05 M). This action resulted in formation of alcohol **20** as a single diastereomer with an isolated yield of 96%. A proposed mechanism for the $SbCl_5$ promoted ring opening may involve coordination of the Lewis acid to the furan oxygen facilitating an $E_2$-like elimination process followed by azide isomerization. This *one-pot* process delivered the thermodynamically more stable $\alpha,\beta$-unsaturated (*E*)-olefin **20** as the only observed product (Scheme 7). Several attempts to convert **20** back to **19** by treatment with a range of conventional Lewis acids were unsuccessful.

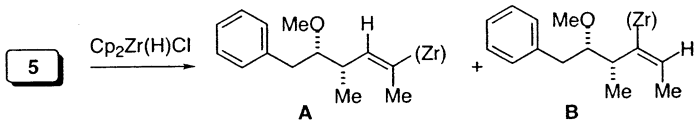
With the establishment of an anti-relationship between the methyl and azide groups, the transformation of the primary alcohol to the 1,3-azido alcohol and eventually to a vinyl iodide for coupling with the C6−C10 subunit **5** was addressed. Accordingly, the primary hydroxyl was first protected using TBSCl/imidazole to give TBS ether **22** in nearly quantitative yield. The azide functional group of **22** was reduced with $SnCl_2$ in anhydrous methanol (0 °C → room temperature, 4 h), and the resulting primary amine was then acylated with $(Boc)_2O$ in dioxane−aqueous sodium bicarbonate[32] to give the Boc protected amine **23** in 84% yield over two steps (Scheme 8). Oxidative cleavage ($O_3$/$Me_2S$) of the trans double bond of **23** gave the corresponding unstable aldehyde, which was immediately transformed into vinyl iodide **6** using Takai's $CrCl_2$-mediated homologation procedure[33] to afford exclusively the (*E*)-alkene in 74% yield (two steps), completing the preparation of the C1−C5 subunit.

**Hydrozirconation of Internal Alkyne 5.** To establish palladium(0)-mediated cross-coupling to assemble the trisubstituted (*E*,*E*)-diene of the Adda fragment, the unsymmetrical acetylene **5** was to be converted to a terminal (*E*)-vinylmetal species. Literature precedent regarding hydrometalation of substrates similar to **5** suggested that a hydroboration[34] or hydrozirconation[35] might be the best options for this cross-coupling reaction. Our initial efforts were directed on the hydroboration of alkyne **5** using conventional hydroborating reagents such as 9-BBN,[36] dibromoborane dimethyl sulfide ($Br_2$-BH·$SMe_2$),[37] and catecholborane:[38] all gave high conversion of the starting alkyne; however, poor regioselectivity in the range of a 2−4:1 ratio was not acceptable. Accordingly, we began to explore conditions for regioselective hydrozirconation of unsymmetrical acetylene **5**, with the anticipation that the resulting

(31) Furan ring opening proved unsuccessful with Lewis acids such as $TiCl_4$, $ZnCl_2$, $MgBr_2$, and $SnCl_4$ at various reaction temperatures. After the $BF_3$·$OEt_2$ promoted furan reaction went to completion, attempts to effect ring opening by reaction with $SbCl_5$ failed. Reaction under basic conditions with TBAF/THF was also carried out, but no reaction ensued.

(32) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030.
(33) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.
(34) (a) Brown, H. C.; Campbell, J. B. *Aldrichim. Acta* **1981**, *14*, 3−11. (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagent*; Academic Press: London, 1988; p 98. (c) Smith, K.; Pelter, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 8, p 703.
(35) For recent reviews on hydrozirconation, see: (a) Labinger, J. A. In *Comprehensive Organic Synthesis: Hydrozirconation of C=C and C≡C and Hydrometalation by Other Metals*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 8; p 667−702. (b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12910.
(36) Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96−99.
(37) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 389−395.
(38) (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249−5255. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370−4371.

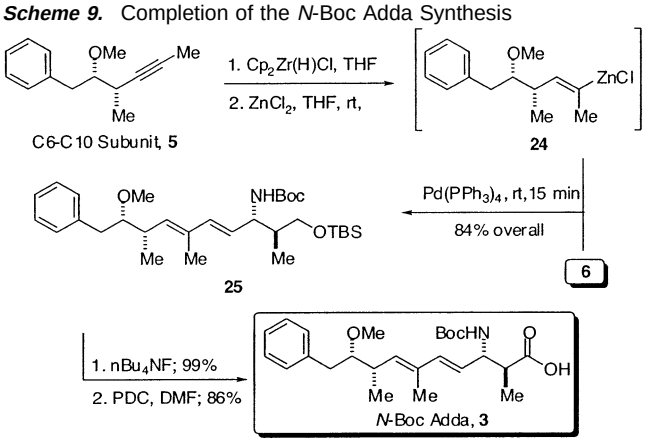
***Table 2.*** Regioselective Hydrozirconation of Unsymmetrical Internal Alkyne **5**



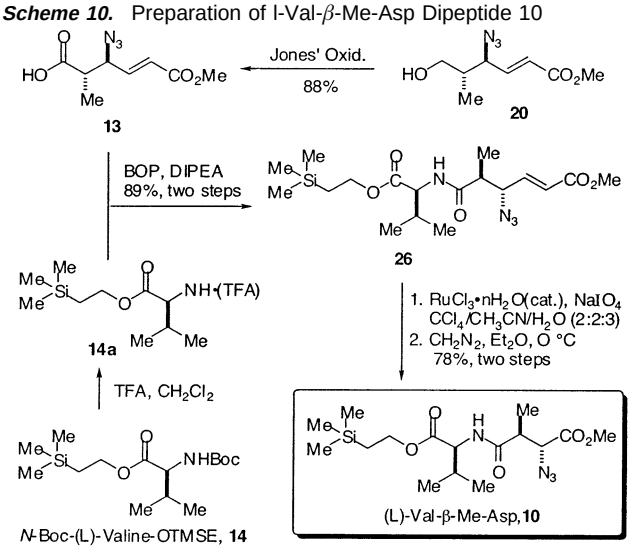

| entry | solvent | $Cp_2ZrHCl$ (equiv)[a] | temp (°C) | time (h) | conversion[b] | A/B[c] (%) |
|---|---|---|---|---|---|---|
| 1 | toluene | 1.2 | 45 | 2.0 | 92 | 63:37 |
| 2 | toluene | 2.0 | 45 | 3.0 | 100 | 92:8 |
| 3 | benzene | 1.5 | 45 | 0.3 | 90 | 75:25 |
| 4 | benzene | 2.0 | 50 | 4.0 | 100 | 100:0 |
| 5 | $CH_2Cl_2$ | 2.0 | room temp | 5.0 | 100 | 85:15 |
| 6 | $CH_2Cl_2$ | 2.0 | 40 | 3.0 | 100 | 91:9 |
| 7 | $(CH_2)_2Cl_2$ | 2.0 | 60 | 2.0 | 100 | 87:13 |
| 8 | THF | 1.3 | 50 | 0.5 | 87 | 63:37 |
| 9 | THF | 2.0 | 50 | 0.4 | 100 | 87:13 |
| 10 | THF | 2.0 | 50 | 1.0 | 100 | 100:0 |

[a] For the preparation of Schwartz's reagent, see ref 40b. [b] Percent conversion was measured by $^1$H NMR analysis of the crude reaction mixtures and is based on remaining alkyne. [c] Regioselectivity (A/B ratio) was determined by $^1$H NMR analysis.

***Scheme 9.*** Completion of the *N*-Boc Adda Synthesis




***Scheme 10.*** Preparation of l-Val-$\beta$-Me-Asp Dipeptide 10




vinylmetal species (or its derivatives) could participate in Pd(0)-catalyzed cross-coupling reaction with the C1−C5 vinyl iodide subunit.[39]

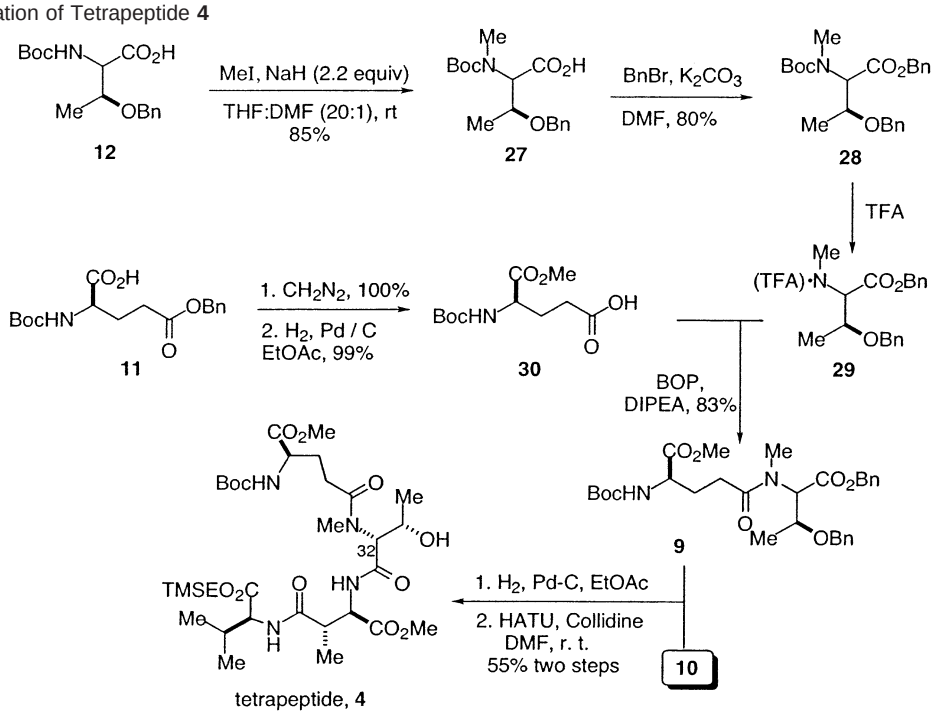
In 1975 Schwartz documented the syn-addition of zirconocene hydrochloride ($Cp_2Zr(H)Cl$, Schwartz's reagent)[40] to terminal or internal alkynes followed by treatment with electrophiles provided *trans*-alkenes with a high selectivity (>98%).[41] Although useful levels of regio- and stereoselectivity can be achieved on unfunctionalized alkynes, the hydrozirconation of branched internal alkynes reveals a more complex picture for regioselective product formation and is highly underdeveloped.[34] Experimental results aimed at optimizing the regioselectivity of the hydrozirconation with $\alpha,\beta$-branched alkyne **5** are summarized in Table 2.

In agreement with literature precedent,[35] our experiments have also shown that excess Schwartz's reagent is necessary to achieve useful selectivity in the generation of the vinylmetal species. Using conventional solvents for hydrozirconation such as benzene or dichloromethane, high selectivity could be obtained (entries 4 and 6, Table 2); however, neither is suitable for the subsequent cross-coupling reaction. Quantitative conversion of alkyne **5** to the desired vinyl zirconium product **A** could be achieved when the reaction was conducted in THF at 50 °C (entry 10). *This crucial result would allow one to execute the hydrozirconation and subsequent cross-coupling reaction in THF as a one-pot reaction sequence thereby simplifying the operational aspects*. Our experiments have shown that the hydrozirconation of alkyne **5** was governed by the amount of Schwartz's reagent employed. With 1 equiv, the kinetic product was obtained as a mixture of regioisomers **A** and **B**, and with an excess of reagent the thermodynamic product **A** was obtained. This may be rationalized by the reversible addition of a second equivalent of reagent to the initially formed vinylzirconium adduct.[39] Having achieved complete conversion and regioselectivity in the hydrozirconation of **5**, the vinylzirconium intermediate was used for the subsequent cross-coupling reaction with the vinyl iodide fragment to access the diene.

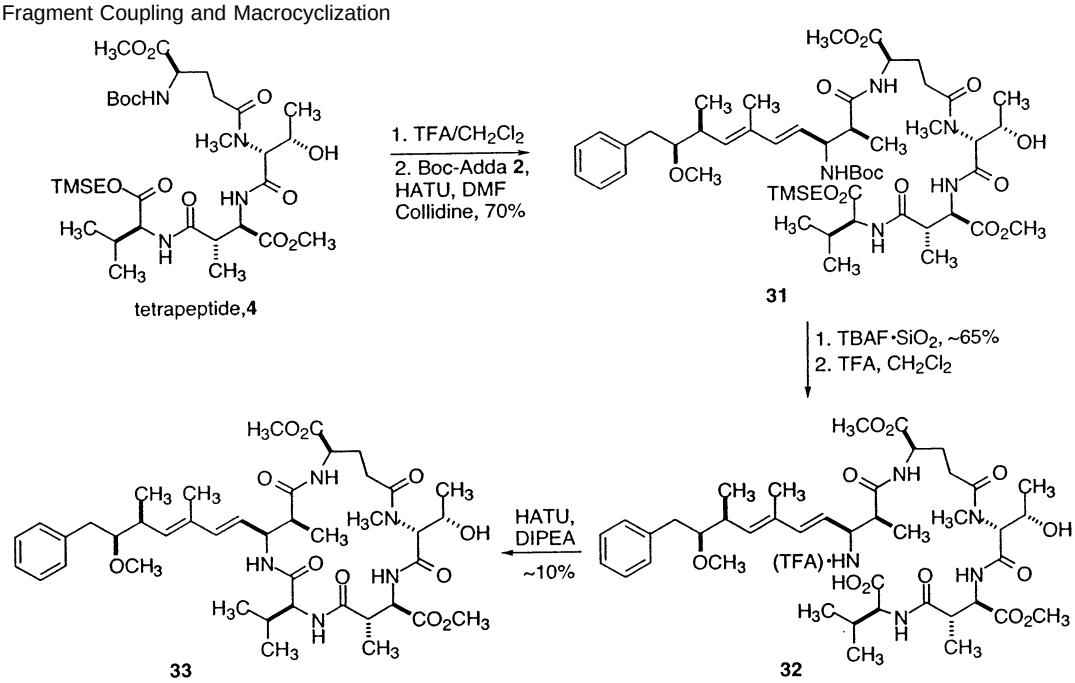
**Completion of the *N*-Boc Adda Synthesis (3).** The key sp2−sp2 bond construction was carried out using a modified Negishi type coupling and involved the reaction of a vinylzinc intermediate with branched (*E*)- and (*Z*)-vinyl halides, catalyzed with $Pd(PPh_3)_4$. The feasibility of this method was tested in our stereoselective synthesis of Adda (Scheme 9).[42] The coupling process was initiated with the regioselective formation of the (*E*)-vinylzinc intermediate. Alkyne **5** was hydrozirconated using Schwartz's reagent (2.0 equiv of $Cp_2Zr(H)Cl$, THF, 50 °C, 1.0

(39) Negish, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254−2256.
(40) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115−8116. For preparation of Schwatz's reagent, see: (b) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1992**, *71*, 77−80. (c) Buchwald, S. L.; La Maire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895−3898.
(41) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679−680.

***Scheme 11.*** Preparation of Tetrapeptide **4**




***Scheme 12.*** Fragment Coupling and Macrocyclization




h) to produce the (*E*)-zirconate as a single regioisomer. Subsequent transmetalation with anhydrous $ZnCl_2$ (3.0 equiv, room temperature, 2.0 min) afforded the vinylzinc species **24**, which was used directly in the coupling with (*E*)-vinyl iodide **6** in the presence of $Pd(Ph_3P)_4$ (0.05 equiv, THF, room temperature, 5 min), completing the assembly of the configurationally pure (*E*,*E*)-diene (84% yield). This one-pot sequence gave the fully functionalized precursor to Adda **25**, which was converted to *N*-Boc Adda **3**. Treatment of a solution of the silyl ether **25** in THF with $nBu_4NF$ (1.0 equiv, THF, room temperature, 30 min) resulted in clean conversion to the primary alcohol, which was oxidized to the corresponding carboxylic acid by treatment with PDC (7.0 equiv, DMF, 22 h, 86%), completing the synthesis of *N*-Boc Adda **3**. The spectroscopic and physical properties of this material were identical in all respects ($^1H$, $^{13}C$, IR, $[\alpha]_D$, and HRMS) with those previously reported.[21]

**Synthesis of Tetrapeptide Fragment 4.** Preparation of dipeptide **10** began with the modification of 1,3-amino alcohol **20**, as illustrated in Scheme 10. This intermediate was oxidized with Jones' reagent (1.9 M, acetone/$H_2O$, 0 °C) to provide the $\beta$-azido acid **13** in 88% yield. It was coupled directly to compound **14a**, the Boc-deprotected TFA salt of amine **14**[43]

(42) Our preliminary results of the hydrozirconation and subsequent cross-coupling strategy have been published. See: Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912−4913.

(43) Compound **14** was prepare by DCC mediated coupling between commecially available *N*-Boc-(L)-Val and trimethylsilyl ethanol in the presence of catalytic amount of DMAP.

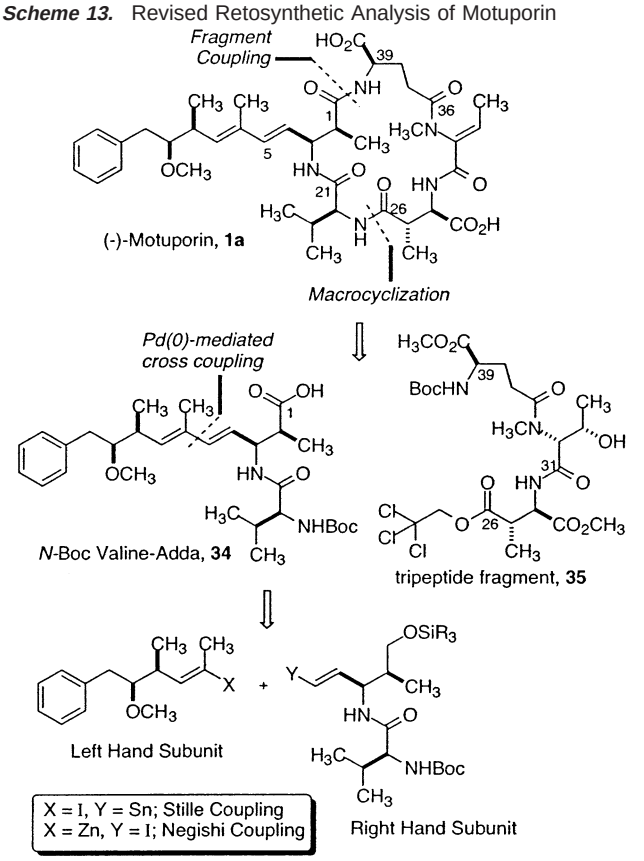
(1.1 equiv) by treatment with excess DIPEA (3.0 equiv) and BOP reagent (1.1 equiv) to afford dipeptide **26** in 89% overall yield. The trans double bond in **26** was oxidized by using a catalytic amount of $RuCl_3$ with $NaIO_4$ (4.0 equiv) as cooxidant,[44] and the resulting crude carboxylic acid was immediately converted to its methyl ester by treatment with $CH_2N_2$, affording **10** in 78% yield over two steps.

Selective *N*-methylation of commercially available *N*-Boc-*O*-benzyl-D-threonine **12**, under conditions developed by Benoiton,[45] gave *N*-methylated product **27** in 85% yield (Scheme 11). The carboxylic acid **27** was protected as its benzyl ester **28**, followed by removal of the Boc group to generate the TFA salt of amine **29**. This residue was used directly in peptide coupling with carboxylic acid **30**, which was prepared in two steps from *N*-Boc-D-Glu α-methyl ester **11**. The acylation of *N*-terminal *N*-methyl amino acids is generally a sluggish process,[46] and in the present case, the reaction rate was enhanced by the fact that the acylating carbonyl of **30** is unhindered. The coupling between **29** and **30** was carried out under standard peptide coupling conditions (1.1 equiv of **30**, 1.0 equiv of BOP, 3.0 equiv of DIPEA) afforded **9** in 83% yield over two steps.

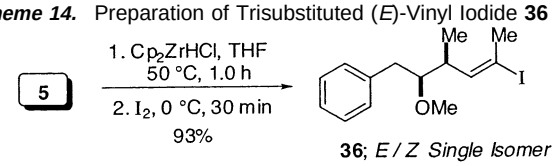
Coupling of the dipeptides **9** and **10** was carried out using Carpino's racemization-supressing reagent HATU.[47] Accordingly, dipeptides **9** and **10** (1:1 mole ratio) were dissolved in EtOAc and exposed to an atmosphere of $H_2$ in the presence of catalytic amounts of Pd/C effected simultaneous debenzylation of compound **9** and reduction of the azide group of **10** (Scheme 11). The resulting reaction intermediates were then subjected to peptide coupling conditions as described by Carpino (1.3 equiv of HATU, 3.0 equiv of collidine, DMF) for 15 h at room temperature. This reaction afforded the fully protected tetrapeptide fragment **4** as a 2.5:1 mixture of diastereomers as determined by $^1H$ NMR analysis of the crude reaction mixtures. Presumably, epimerization at the threonyl α-center (C32) is responsible for the resulting mixture.[46] After separation from the minor isomer, the desired tetrapeptide **4** was obtained in 55% yield.[48] This one-pot deprotection−reduction−coupling sequence completed the synthesis of fragment **4** and produced the material to be used in subsequent fragment coupling with Boc−Adda fragment **3**.

**Fragment Coupling and Macrocyclization.** The *N*-Boc Adda intermediate was activated by HATU (1.5 equiv) and coupled with the Boc-deprotected tetrapeptide of **4** in the presence of collidine (3.0 equiv), affording the desired pentapeptide **31** in 70% yield with no trace of epimerization (Scheme 12). Surprisingly, sequential removal of the TMSE ester of **31** proved troublesome. After surveying a variety of reaction conditions (TBAF, HF·Py, TBAF/AcOH, KF/$nBu_4NCl$, and TAS−F), the most effective reagent was TBAF·$SiO_2$. Under these reaction conditions (TBAF·$SiO_2$ 2.0 equiv, 5:1 THF/DMF), the desired TMSE-deprotected product was obtained in 50−65% yield. After removal of the Boc group, the resulting crude residue **32** was subjected to the cyclization conditions by slow addition to a $CH_2Cl_2$ solution of HATU/DIPEA. Unfortunately, only 8−12% of the desired macrocycle **33** was obtained under these cyclization conditions, as well as extensive epimerization at the valine α-carbon was observed. When the cyclization was performed in the presence of pentafluorophenyl diphenylphosphinate (FDPP),[49] a slightly higher yield of the macrocycle was achieved. However, due to epimerization and the slow rate of cyclization, we were unable to obtain useful amounts of the macrocycle for transformation to motuporin. At this point several concerning issues had arisen that caused us to abandon the present route. [At this point we chose to modify our route by selecting an alternative cyclization site along with minor alterations in the protecting group strategy.]

***Scheme 13.*** Revised Retosynthetic Analysis of Motuporin




***Scheme 14.*** Preparation of Trisubstituted (*E*)-Vinyl Iodide **36**




**Revised Retrosynthetic Analysis.** In the revised synthetic plan, we anticipated that the macrocyclization could be carried out at C26 that contains a carboxylate group and also lacks a deactivating α-amide substituent. In addition, fragment coupling would still be conducted at C1−C39 amide bond (Scheme 13).

In our original plan, the deprotection step for the trimethylsilylethyl ester (TMSE) had become unmanageable, we then chose to protect the C26 carboxylic acid as a trichloroethyl (Tce) ester whose removal would be carried out under mild reductive

(44) Carlsen, Per H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.
(45) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906−910.
(46) For review on peptide coupling strategy, see: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243−2266.
(47) (a) Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1994**, *59*, 695−698. (b) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398. (c) Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1995**, *60*, 3561.
(48) Although other peptide coupling conditions were also attempted, similar levels of racemization were observed in this segment coupling reaction.
(49) (a) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711−6714. (b) Dudash, J., Jr.; Jiang, J.; Mayer, S. C.; Joullie, M. M. *Synth. Commun.* **1993**, *23*, 349.

***Scheme 15.*** Preparation of (*E*)-Vinylstannane for Stille Coupling

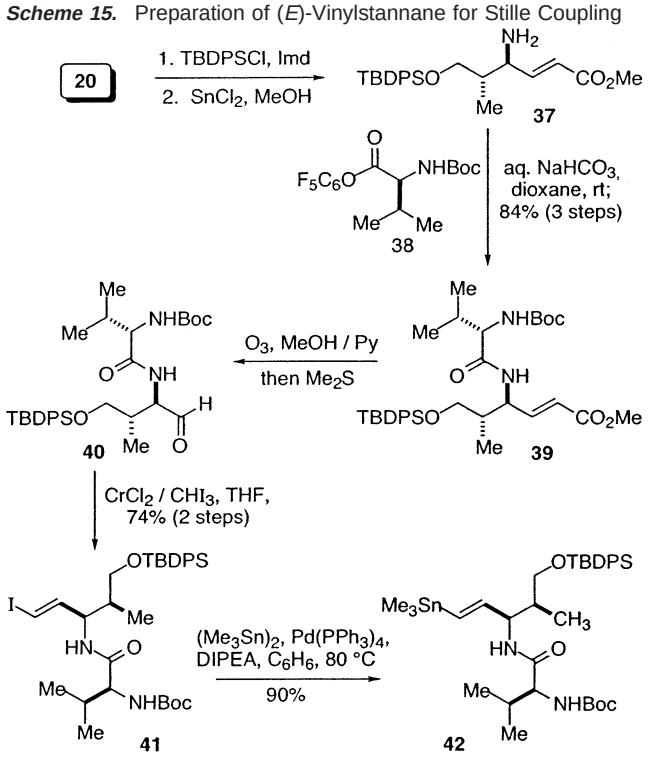
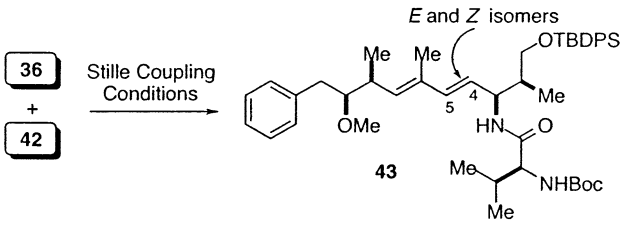



***Table 3.*** Summary of the Stille Coupling Reaction between **36** and **42**



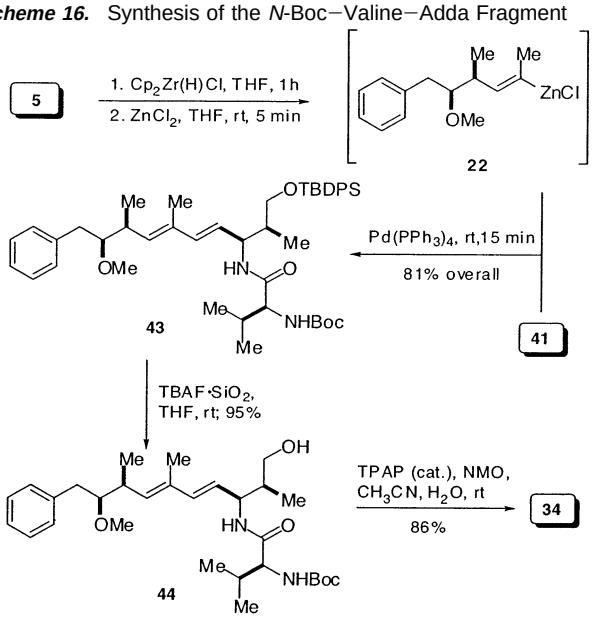

| catalyst | solvent/temp (°C) | base | additives | *E*/*Z*[a] | yield[b] (%) |
|---|---|---|---|---|---|
| $Pd(PPh_3)_4$ | DMF/50 | | | 1:1 | 22 |
| $Pd(MeCN)_2Cl_2$ | THF/room temp | | $CdCl_2$ | 2:1 | 39 |
| $Pd(PPh_3)_4$ | THF/50 | | $ZnCl_2$ | 2:1 | 45 |
| $Pd(PPh_3)Cl_2$ | DMF/room temp | DIPEA | | 2:1 | 30 |
| $Pd_2(dba)_3$ | THF/50 | DIPEA | $AsPh_3$ | 3:2 | 46 |
| $Pd_2(dba)_3$ | DMF/room temp | DIPEA | TFP | 2:1 | 35 |
| $Pd(PPh_3)_4$ | DMF/room temp | DIPEA | CuI/CsF | 4:1 | 50 |
| $Pd(PPh_3)_4$ | NMP/room temp | DIPEA | CuI (0.1 equiv) | 4:1 | 55 |

[a] Ratio was determined by $^1H$ NMR (400 MHz) analysis of the crude products. [b] Yield refer to combined yields of *E*- and *Z*-isomers isolated after chromatography on $SiO_2$.

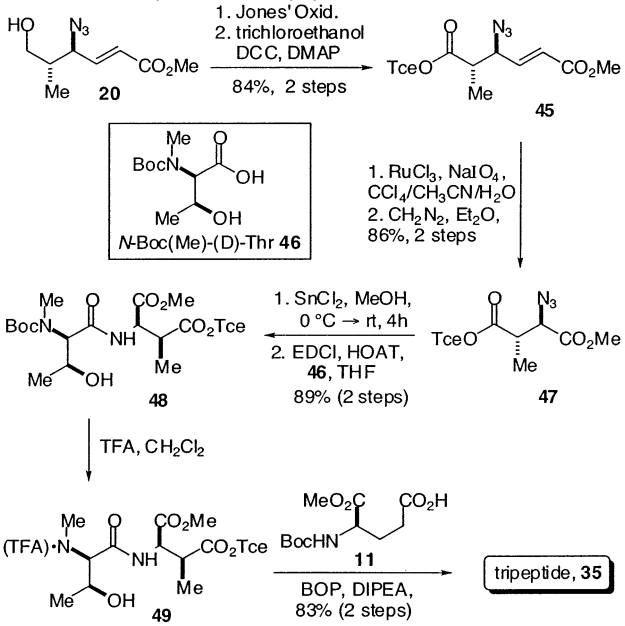
conditions using activated zinc dust. Literature precedence has documented that similar conditions have been routinely used in structurally complex peptide syntheses. By dividing motuporin into two advanced intermediates, the fragment **34** and the tripeptide fragment **35**, the level of convergence is maintained. As illustrated in Scheme 13, the fragment **34** could, in principle, be assembled through two different sets of coupling conditions: the conventional Stille coupling or a modified Negishi coupling.

**Stille Coupling Strategy.** The construction of the (*E*,*E*)-trisubstituted diene using Stille coupling conditions required the preparation of a trisubstituted (*E*)-vinyl iodide and a (*E*)-vinylstannane coupling partner. The (*E*)-vinyl iodide **36** was readily prepared through regioselective hydrozirconation of

***Scheme 16.*** Synthesis of the *N*-Boc−Valine−Adda Fragment




***Scheme 17.*** Preparation of Tripeptide **35**

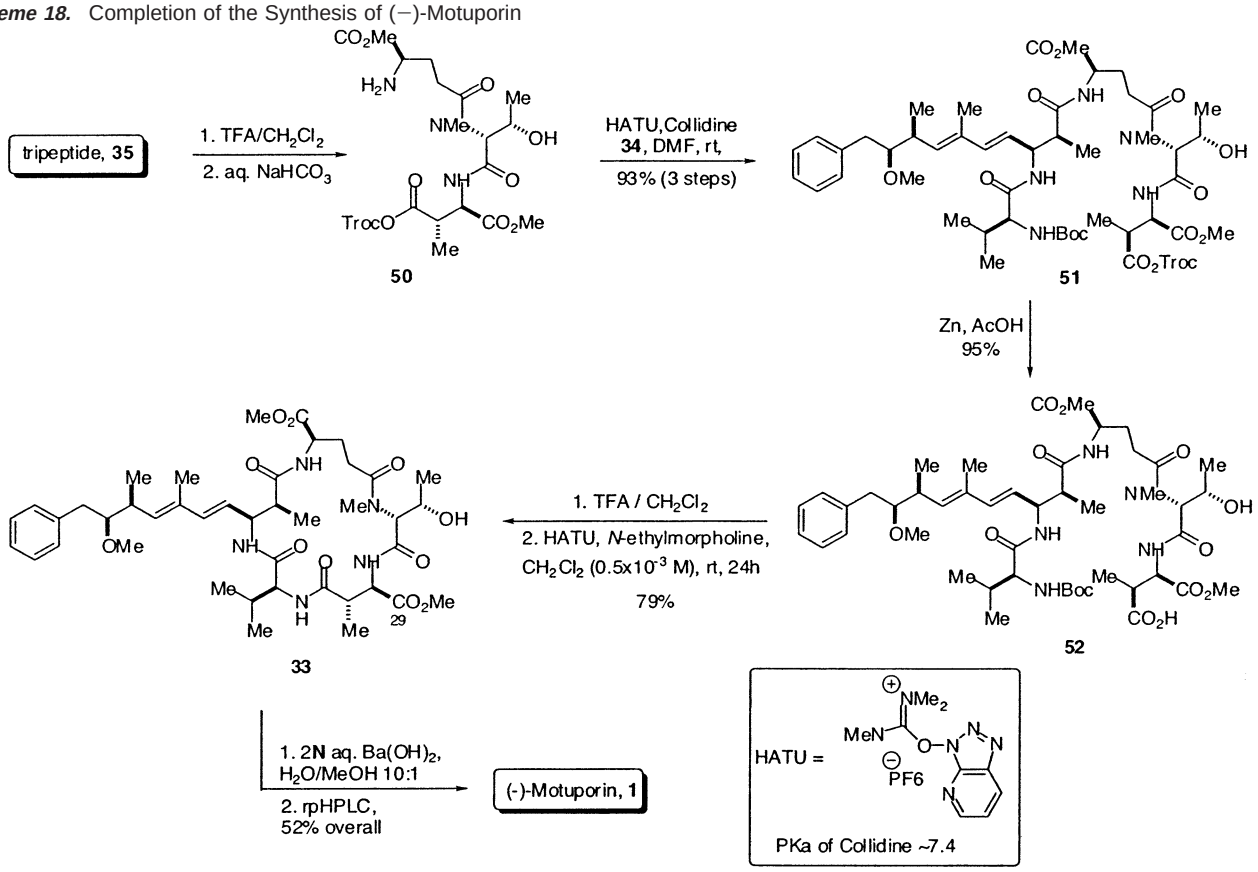



alkyne **5**, followed by iodination of the alkenyl zirconium intermediate (Scheme 14).

The primary hydroxyl of **20** was protected as TBDPS ether, and the azide reduced using $SnCl_2$ (1.5 equiv) in anhydrous methanol (0 °C → room temperature, 4 h) to provide primary amine **37**, which was condensed with pentafluorophenyl ester activated *N*-Boc L-valine **38** in dioxane/aqueous $NaHCO_3$ using a biphasic reaction system to afford dipeptide **39** in 84% yield over three steps (Scheme 14). Oxidative cleavage of the olefin gave the aldehyde **40**, which was immediately subjected to Takai's homologation protocol[32] to afford the pure (*E*)-vinyl iodide **41** (74%, Scheme 15). This material was transformed to the corresponding stannane by reaction with bis(trimethyltin) in the presence of catalytic $Pd(PPh_3)_4$, cleanly generating the (*E*)-vinylstannane **42** in 90% yield, ready for the subsequent Stille coupling.[50]

The Stille coupling between **36** and **42** was evaluated, and those results are summarized in Table 3. Despite extensive

***Scheme 18.*** Completion of the Synthesis of (−)-Motuporin




efforts to optimize this reaction, it remained plagued by poor double bond ratios at C4−C5 (1−4:1, *E*/*Z*), protodestannylation, and homocoupling byproducts.

The addition of a noncoordinating base, diisopropylethylamine (DIPEA), markedly reduced the amount of protodestannylation.[51] However, we were unable to prevent double bond isomerization and the formation of products from homocoupling that might be attributed to the slow transmetalation of the vinylstannane to the Pd(II) intermediate. Working under the assumption that the transmetalation was the rate-determining step in the catalytic cycle, the addition of facilitators, such as $AsPh_3$,[52] $CdCl_2$,[53] or $ZnCl_2$[38] were also explored; however, only slight improvements were achieved.

Best results for this Stille coupling were achieved using Liebeskind's procedure.[54] In the presence of a catalytic amount of CuI and $Pd(PPh_3)_4$, using NMP (*N*-methylpyrrolidinone) as the solvent, this Stille coupling went to completion in 30 min at room temperature, providing the coupling product **43** in 55% yield with a 4:1 *E*/*Z* ratio at the C4−C5 double bond. Reaching only moderate yield and poor stereoselectivity in the olefination, we then focused on the modified Negishi coupling strategy.

**Modified Negishi Coupling Strategy.** The establishment of an efficient method for the formation of the trisubstituted (*E*,*E*)-diene of *N*-Boc Adda **2** using a one-pot $sp^2-sp^2$ Pd(0)-catalyzed coupling has provided the basis for a highly convergent synthesis of Adda. When the identical reaction conditions were applied to the cross-coupling between alkyne **7** and dipeptide vinyl iodide **41**, configurationally pure (*E*,*E*)-diene **43** was produced in 81% yield (Scheme 16). The overall efficiency of the Negishi coupling process may be attributed to the enhanced electrophilicity and accessibility of the vinyl iodide in combination with good nucleophilicity of the vinyl zinc species (facile transmetalation). The success of this cross-coupling relied on the use of a double transmetalation process (Zr → Zn → Pd) of low kinetic barrier that replaced a single transmetalation process (Zr → Pd) of high activation energy, which leads to an overall rate enhancement.[38]

With the cross-coupling chemistry established as an efficient approach to the diene, the final stage of the valine−Adda synthesis was carried out. Deprotection of the silyl group using TBAF·$SiO_2$ (2.5 equiv, room temperature, 4 h) afforded the primary alcohol **44** in 95% yield. With the presence of stoichiometric amount of $H_2O$ this material was directly oxidized to carboxylic acid **34** using Ley's oxidation protocol (TPAP/NMO, $CH_3CN$, 1 h; then $H_2O$, room temperature, 18 h), completing the synthesis of valine−Adda dipeptide.[55]

**Preparation of Tripeptide 35.** The preparation of the tripeptide fragment once again began with the oxidation of 1,3-azido alcohol **20** followed by protection of the carboxylic acid as a trichloroethyl ester gave **45** in 84% yield in two steps. Olefin oxidation (catalyst $RuCl_3 \cdot nH_2O$, $NaIO_4$) of **45**, followed by exposure of the resulting α-azido acid to diazomethane ($Et_2O$, 0 °C) afforded methyl ester **47** in 86% yield (two steps) as

(50) For reviews on Stille coupling reaction, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1−652.
(51) Evans, D. A.; Gage, J. R.; leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.
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(53) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513.
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described in Scheme 17. The azide group could be selectively reduced with $SnCl_2$ (1.5 equiv) to provide the free amine, without effecting the trichloroethyl ester. The crude amine was used without purification and coupled with *N*-Boc(Me)−D-threonine **46**[56] (1.1 equiv) under standard conditions to give dipeptide **49** in 89% yield. After the removal of Boc protecting group, the resulting TFA salt of **49** underwent BOP induced amide bond formation with **11**, completing the formation of tripeptide **35** in 83% yield.

**Fragment Coupling and Completion of the Synthesis.** With the tripeptide **35** and *N*-Boc−valine−Adda fragments **34** in our possession, the crucial fragment coupling reaction was effectively carried out using Carpino's protocol.[46] First, the Boc protecting group was removed with TFA and the resulting salt was washed with aqueous $Na_2CO_3$ to give free amine **50**. Without purification, the crude amine was treated with **34** in the presence of HATU/collidine in DMF to provide the protected pentapeptide **51** in 93% yield (Scheme 18). In contrast to the lower yields and epimerization problems with the BOP reagent, reaction using HOBt/EDCI, or the pentaflurophenol activated ester proceeded without any detectable amounts of epimerization.[57]

In the final stage of the synthesis, removal of the trichloroethyl group of **51** was accomplished under reductive conditions using zinc dust/acetic acid (room temperature, 4 h) which gave the carboxylic acid **52** in 95% yield. Removal of the *N*-Boc protecting group of **52** was carried out using TFA/$CH_2Cl_2$ (0 °C, 30 min) to afford the amine 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 **33** in 79% yield.[58] Treatment of **33** with barium hydroxide (2 N $Ba(OH)_2$, $H_2O$/MeOH, 10:1) resulted in simultaneous hydrolysis of both methyl esters and a complete in situ dehydration of *N*-methylthreonine.[15a] The resulting (*Z*)-olefin geometry is thermodynamically controlled, which was previously observed by Schreiber and Valentekovich (Scheme 18).[15a] Upon acidification with 1 N HCl to pH 2 and reverse-phase HPLC purification, synthetic motuporin (**1**) was obtained as its free dicarboxylic acid form in 52% yield. The spectroscopic and analytical properties of this material were identical in all respects with the reported data.[59] Treatment of **1** with $NaHCO_3$ /MeOH followed by gel filtration using Sephadex LH-20 provided the disodium salt of motuporin, which agreed in all respects ($^1H$ and $^{13}C$ NMR, $[\alpha]_D$, IR, FAB−HRMS, rpHPLC) with the data reported earlier.

## Conclusion

We have described a highly convergent, enantioselective synthesis of the (−)-motuporin based on the use of chiral organosilane reagents. Six of the eight stereogenic centers were established utilizing asymmetric crotylsilane bond construction methodology. An efficient Pd(0)-catalyzed cross-coupling reaction for the construction of the trisubstituted (*E*,*E*)-diene system of the (−)-motuporin side chain is also featured in this synthesis. The route was completed in a total of 31 steps with the longest linear sequence of 16 steps (from chiral crotylsilane reagents) commencing with an overall yield of 15.8%.

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**Supporting Information Available:** Complete experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(56) This compound was prepared through hydrogenolysis of substrate **27** using $H_2$/Pd−C/EtOH at room temperature for 15 h.
(57) 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) analysis on crude reaction mixtures.
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