Published in final edited form as:

Org Lett. 2008 August 7; 10(15): 3223–3226. doi:10.1021/ol801115s.

Efficient and Selective Syntheses of (all-*E*)- and (6*E*,10*Z*)-2'-*O*-Methylmyxalamides D via Pd-Catalyzed Alkenylation—Carbonyl Olefination Synergy

Guangwei Wang, Zhihong Huang, and Ei-ichi Negishi

Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

Abstract

Highly efficient and selective syntheses of both (all-*E*) and (6*E*,10*Z*)-isomers of 2'-*O*-methylmyxalamide D (**2** and **3**), in which the crucial conjugated pentaene moieties were assembled in $\geq 98\%$ stereoselectivity through the use of two Pd-catalyzed alkenylation reactions, the Horner—Wadsworth—Emmons (HWE) olefination, and either the Corey—Schlessinger—Mills modified (CSM-modified) Peterson olefination for **2** or the Still—Gennari olefination for **3**, are reported. Either **2** or **3** was prepared in 16% yield in seven steps from propargyl alcohol.

Ojika and co-workers reported in 2004 the isolation and identification of three polyene antifungal agents **1**—**3** from the myxobacterium *Cystobacter fuscus*.¹ 2'-*O*-Methylmyxalamide D (**1a**) is an O-methylated derivative of the previously known myxalamide D (**1b**),² and the other two are its (6*E*)-isomer (**2**) and (6*E*,10*Z*)-isomer (**3**) (Figure 1). Myxalamide D (**1b**), 2'-*O*-methylmyxalamide D (**1a**) and its (6*E*)-isomer (**2**) have recently been synthesized by using the Pd-catalyzed cross-coupling with (all-*E*)-1-stanna-6-bora-1,3,5-

negishi@purdue.edu

Supporting Information Available: Detailed experimental procedures and ¹H and ¹³C NMR spectra of isolated pure compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL801115S

hexatriene.³ To the best of our knowledge, however, the (6*E*,10*Z*)-isomer (**3**) does not appear to have been synthesized.

Over the past few decades, two methodologically discrete routes to regio- and stereodefined alkenes have been developed as widely applicable and selective methods. *Carbonyl olefination*,⁴ especially variants of the Wittig reaction^{4a} including the *E*-selective Horner-Wadsworth-Emmons (HWE hereafter) reaction^{4b,c} and its *Z*-selective Still-Gennari modification,^{4d} as well as the Corey-Schlessinger-Mills modified Peterson olefination (CSM—modified Peterson olefination hereafter),^{4e-g} can in some cases be highly stereoselective ($\geq 98\%$). Much more widely applicable and strictly stereoselective ($\geq 98-99\%$) in most cases is the *Pd*-catalyzed *alkenylation*.⁵ Nevertheless, other synthetic requirements and restrictions have made it desirable to use both methods, i.e., *alkenylation-carbonyl olefination synergy*.⁶ A case in point is the synthesis of allylically Me-branched trisubstituted alkenes (**4**) that can be most readily and selectively prepared by either the CSM-modified Peterson olefination (*E*-isomers)^{4e-g} or the Still—Gennari-modified HWE reaction (*Z*-isomer).^{4d}

Herein, we report highly efficient and selective syntheses of both (all-*E*) and (6*E*,10*Z*)-isomers of 2'-*O*-methylmyxalamide D (**2** and **3**), in which the crucial conjugated pentaene moieties are assembled in $\geq 98\%$ stereoselectivity through the use of two Pd-catalyzed alkenylation reactions for the formation of the C3-C4 and C5-C6 bonds, the HWE olefination for the C8-C9 double bond, and either the CSM-modified Peterson olefination (for **2**) or the Still—Gennari olefination (for **3**) for the formation of the C10—C11 double bond. As summarized in Schemes 1 and 2, either **2** or **3** was prepared in 16% overall yield in just seven steps from propargyl alcohol. In fact, the overall yield of **2** in the same seven steps from tiglic aldehyde ($\geq 96\%$, Aldrich) is significantly higher at 34%, while the overall yield of **3** in eight steps in the longest linear sequence is 27%. Except in the Brown crotylboration of tiglic aldehyde ($\geq 96\%$) producing a 96/4 diastereomeric mixture of **5** and requiring chromatographic isomer separation after the conversion of **5** into **6**, no isomer formation was detectable throughout either of the two syntheses. The ready availability of **5** in one step, its high yielding three-step conversion to **6**, and one- or two-step conversion of **6** into isomerically $\geq 98\%$ pure **7** or **8** dictated their HWE olefination with the trienoic amide containing phosphonate (**9**) prepared in 26% yield in five steps from propargyl alcohol (or in 33% yield in five steps from methacrylic acid) via a series of two Pd-catalyzed alkenylation reactions followed by phosphonation, as detailed in Scheme 2.

Of various selective and asymmetric routes^{3,7-11} to two key intermediates **7** and **8** tested and/or considered, the one via the Brown crotylboration⁷ of tiglic aldehyde proved to be the most efficient and selective, albeit noncatalytic (Scheme 1). Thus, the reaction of tiglic aldehyde with a crotylborane reagent generated from *trans*-2-butene and (+)-*B*-methoxydiisopinocampheylborane (Aldrich) according to the literature procedure⁷ afforded **5** in 84% yield. The observed diastereomeric ratio of 96/4 indicates the overall enantiomeric purity to be $>99.9\%$ by virtue of kinetic resolution operative in the crotylboration. After protection of the hydroxyl group with TBSOTf and 2,6-lutidine, the Sharpless dihydroxylation with AD-mix- α ¹² (Aldrich) followed by oxidation with NaIO₄ provided **6**, which was purified by chromatography (Silica gel, 5% EtOAc in hexanes). The yield of $\geq 98\%$ pure **6** was 81% over three steps. For the conversion of **6** to **7**, the CSM-modified Peterson olefination proved to be both efficient requiring just one step and highly stereoselective. The crudely isolated **7** was $\geq 98\%$ *E,E* by ¹³C NMR after simple chromatographic purification, and $\geq 98\%$ pure **7** was obtained in 81% yield (55% yield in five steps from tiglic aldehyde). The Still—Gennari olefination of **6** with (CF₃CH₂O)₂P(O)CH(Me)CO₂Me, KN(SiMe₃)₂, and 18-crown-6 (1.5 equiv)^{4d} proved to be $\geq 98\%$ *Z*-selective. After reduction with *i*-Bu₂AlH, **8** was obtained as a $\geq 98\%$ pure compound in 66% yield over two steps (Scheme 1).

In view of the current high cost of $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}(\text{Me})\text{CO}_2\text{Me}$ and the variable *Z*-selectivity of the Still-Gennari olefination, we initially considered the conversion of **6** to **12** via Corey-Fuchs reaction,¹³ bromoalkyne hydroboration-migratory insertion, zincation-iodinolysis, and Pd-catalyzed alkenylation,^{11e} as depicted in Scheme 3. Even though a model transformation for converting $\text{TBDPSOCH}_2\text{CH}=\text{CH}_2$ to **14** via **13**¹⁴ was achieved in 30% yield in seven steps, its application to the conversion of **6** to **12** encountered an unexpected and as yet unsolved difficulty in the attempted conversion of the bromoalkyne intermediate to the corresponding iodoalkene. We therefore opted for the conversion of **14** to **12**, which was achieved in 25% yield in seven steps. In the absence of external chiral reagents, the reaction of α -methylaldehyde derived from **14** with (*E*)-2-butenylmethylzinc gave nearly 1:1 *C*₇ epimers of **12** which was converted to **12** of $\geq 98\%$ purity via Dess—Martin oxidation¹⁵ and Corey—Bakshi—Shibata reduction.¹⁶ At this point, however, it became unmistakably clear that the route summarized in Scheme 1 would be superior to that shown in Scheme 3.

For the construction of the C1-C8 fragment **9**, propargyl alcohol was converted to 3-iodoallyl alcohol of $\geq 99\%$ *E* in 80% yield via (i) in situ OH protection with *i*-Bu₂AlH, (ii) hydrozirconation with $\text{HZrCp}_2\text{Cl}-\text{ClAl}(\text{i-Bu})_2$ generated in situ from *i*-Bu₂AlH-ZrCp₂,¹⁷ and (iii) iodinolysis all in one pot. Ethynylation¹⁸ of (*E*)-3-iodoallyl alcohol was performed in 78% yield by (i) OH protection with Et₂Zn and (ii) ethynylation with $(\text{HC}\equiv\text{C})_2\text{Zn}$ in the presence of 5 mol % of $\text{Pd}(\text{DPEphos})\text{Cl}_2$. Hydrozirconation of (*E*)-2-penten-4-yn-1-ol performed as in the first step followed by Pd-catalyzed cross-coupling with **10** and 5 mol % of PEPPSIIPr (98%, Aldrich)¹⁹ provided **11** of $\geq 98\%$ isomeric purity in 62% yield. The required intermediate **10** was prepared in three steps in 79% yield by β -bromination of methacrylic acid²⁰ and amidation with (*S*)-H₂NCH(Me)CH₂OMe (98% pure, Alpha Aesar). As detailed in an upcoming publication, an *N*-heterocyclic carbene-containing PEPPSI-IPr proved to be distinctly superior to $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, or $\text{Pd}(\text{DPEphos})\text{Cl}_2$. Thus, **11** was prepared as a $\geq 98\%$ isomerically pure compound in just three steps either from propargyl alcohol (39% overall yield) or from methacrylic acid (49% overall yield) via a series of two Pd-catalyzed alkenylation reactions. Conversion of **11** to **9** via bromination with PBr_3 and pyridine followed by phosphonation with $\text{P}(\text{OEt})_3$ according to the literature²¹ proceeded in 67% yield over two steps (26% from propargyl alcohol or 33% from methacrylic acid in five steps). All isolated compounds were $\geq 98\%$ isomerically pure by ¹³C NMR either as crude products or as purified compounds. With **7**, **8**, and **9** in hand, the final assembly of **2** and **3** proceeded smoothly as shown in Scheme 1 and described earlier. The spectral data for **2** and **3** are in excellent agreement with those reported in the literature.^{1,3}

In summary, combined use of the Pd-catalyzed alkenylation and carbonyl olefination reactions, such as the HWE olefination, its Still-Gennari modification, and the CSM-modified Peterson olefination, permits efficient and selective synthesis of various oligoenes containing *E*- and/or *Z*-trisubstituted alkenes. This protocol has been applied to the synthesis of (all-*E*)- and (6*E*, 10*Z*)-2'-*O*-methylmyxalamides **D** (**2** and **3**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research. We also thank Sigma-Aldrich for samples of PEPPSI-IPr and Albemarle for organoaluminum compounds.

References

- (1). Kundim BA, Itou Y, Sakagami Y, Fudou R, Yamanaka S, Ojika M. *Tetrahedron* 2004;60:10217–10221.
- (2). Jansen R, Reifensahl G, Gerth K, Reichenbach H, Höfle G. *Liebigs Ann. Chem* 1983;1081–1095.
- (3). Coleman RS, Lu X, Modolo I. *J. Am. Chem. Soc* 2007;129:3826–3827. [PubMed: 17358066]
- (4). For a review of the Wittig and related olefinations, see (a) Maryanoff BE, Reitz AB. *Chem. Rev* 1989;89:863–927.. (b) Horner L, Hoffmann H, Wippel JHG, Klahre G. *Chem. Ber* 1959;92:2499–2505.. (c) Wadsworth WS Jr, Emmons WD. *J. Am. Soc. Chem* 1961;83:1733–1738. For a seminal work on the Still-Gennari olefination, see: (d) Still WC, Gennari C. *Tetrahedron Lett* 1983;24:4405–4408.. (e) Corey EJ, Enders D, Bock MG. *Tetrahedron Lett* 1976:7–10.. (f) Schlessinger RH, Poss MA, Richardson S, Lin P. *Tetrahedron Lett* 1985;26:2391–2394.. (g) Desmond R, Mills SG, Volante RP, Shinkai I. *Tetrahedron Lett* 1988;29:3895–3898.
- (5). For reviews on Pd-catalyzed alkenylation, see: (a) Negishi E 20022 Vols. 3279 *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience New York Chap. III.2.6, pp 335–408; Chap. III.2.14.2, pp 721–766; Chap. III.2.15, pp 767–789; Chap. III.2.17, pp 807–823; Chap. III.2.18, pp 863–942. (b) Negishi E, Hu Q, Huang Z, Qian M, Wang G. *Aldrichimica Acta* 2005;38:71–88.
- (6). Negishi E, Huang Z, Wang G, Mohan S, Wang C, Hattori H. *Acc. Chem. Res.* submitted
- (7). For the Brown crotylboration, see: (a) Brown HC, Bhatt KS. *J. Am. Chem. Soc* 1986;108:5919–5923.. (b) Brown HC, Jadhav PK, Bhatt KS. *J. Am. Chem. Soc* 1988;110:1535–1538.
- (8). For the T-to-H (tail-to-head) construction of natural products containing (*E*)-**4** via the CSM-modified Peterson olefination, see: (a) Magnin-Lachaux M, Tan Z, Liang B, Negishi E. *Org. Lett* 2004;6:1425–1427. [PubMed: 15101758]. (b) Zeng X, Zeng F, Negishi E. *Org. Lett* 2004;6:3245–3248. [PubMed: 15355023]
- (9). For other T-to-H (tail-to-head) routes to (*E*)-**4**, see: (a) Tan Z, Negishi E. *Angew. Chem., Int. Ed* 2004;43:2911–2914.. (b) Zhu G, Negishi E. *Chem.-Eur. J* 2008;14:311–318.
- (10). For the H-to-T (head-to tail) construction of (*E*)-**4**, see: Hoye TR, Temakoon MA. *Org. Lett* 2000;2:1481–1483. [PubMed: 10814478]
- (11). For the T-to-H (tail-to-head) construction of (*Z*)-**4**, see: (a) Panek JS, Hu T. *J. Org. Chem* 1997;62:4912–4913.. (b) Panek JS, Hu T. *J. Org. Chem* 1997;62:4914–4915.. (c) Arefolov A, Panek JS. *Org. Lett* 2002;4:2397–2400. [PubMed: 12098256]. (d) Roethle PA, Chen IT, Trauner D. *J. Am. Chem. Soc* 2007;129:8960–8961. [PubMed: 17595091]. (e) Tanino K, Arakawa K, Satoh M, Iwata Y, Miyashita M. *Tetrahedron Lett* 2006;47:861–864.. (f) Tan Z, Negishi E. *Angew. Chem., Int. Ed* 2006;45:762–765.. (g) Huang Z, Negishi E. *J. Am. Chem. Soc* 2007;129:14788–14792. [PubMed: 17985915]
- (12). (a) AD-mix- α : Sharpless asymmetric dihydroxylation agent containing hydroquinine 1,4-phthalazinediyl diether [(DHQ)₂PHAL], K₃Fe(CN)₆, K₂CO₃, and K₂OsO₄·2H₂O. Sharpless KB, Amberg W, Bennani YL, Crispino GA, Hartung J, Jeong K-S, Kwong H-L, Morikawa K, Wang Z-M, Xu D, Zhang X-L. *J. Org. Chem* 1992;57:2768–2771.. (b) Kolb HC, VanNieuwenhze MS, Sharpless KB. *Chem. Rev* 1994;94:2483–2547.
- (13). Corey EJ, Fuchs PL. *Tetrahedron Lett* 1972;13:3769–3772.
- (14). Liang B, Novak T, Tan Z, Negishi E. *J. Am. Chem. Soc* 2006;128:2770–2771. [PubMed: 16506734]
- (15). Dess DB, Martin JC. *J. Org. Chem* 1983;48:4155–4156.
- (16). Corey EJ, Shibata S, Bakshi RK. *J. Org. Chem* 1988;53:2861–2863.
- (17). Huang Z, Negishi E. *Org. Lett* 2006;8:3675–3678. [PubMed: 16898789]
- (18). Negishi E, Anastasia L. *Chem. Rev* 2003;103:1979–2017. [PubMed: 12744698]
- (19). Kantchev EAB, O'Brien CJ, Organ MG. *Angew. Chem., Int. Ed* 2007;46:2768–2813.
- (20). Dzierba CD, Zandi KS, Möllers T, Shea KJ. *J. Am. Chem. Soc* 1996;118:4711–4712.
- (21). Lira R, Roush WR. *Org. Lett* 2007;9:533–536. [PubMed: 17249805]

Fig. 1.
Myxalamide D and its derivatives.

Scheme 1.

Scheme 2.

Unsuccessful Route **Successful Route**

$\text{Z}^1 = \text{TBDPS}$, $\text{Z}^2 = \text{PMB}$, $\text{Z}^3 = \text{TES}$

Scheme 3.