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

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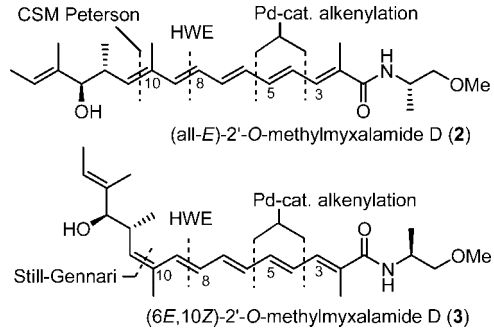
ABSTRACT



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 ≥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-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 (≥98%). Much more widely applicable and

(1) Kundim, B. A.; Itou, Y.; Sakagami, Y.; Fudou, R.; Yamanaka, S.; Ojika, M. *Tetrahedron* **2004**, *60*, 10217–10221.

(2) Jansen, R.; Reifenstahl, G.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1983**, 1081–1095.

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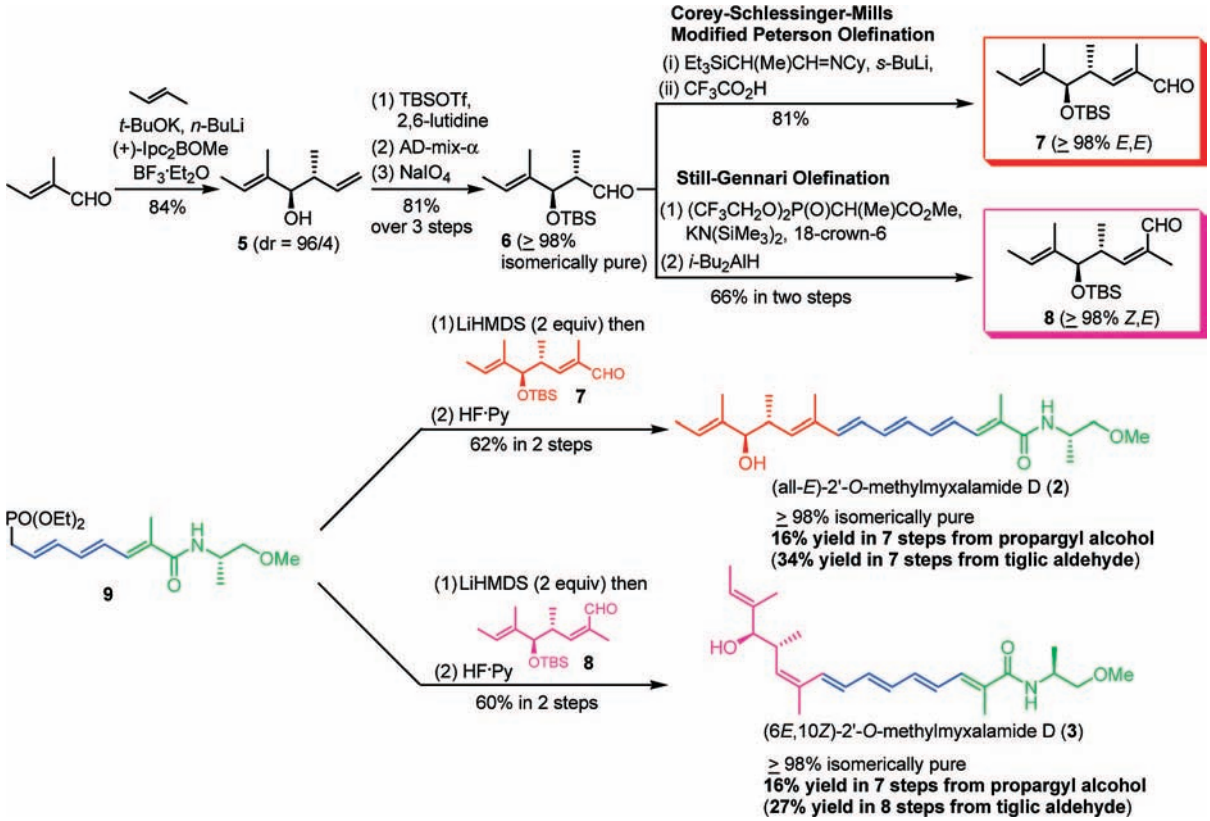
Scheme 1



strictly stereoselective (≥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]

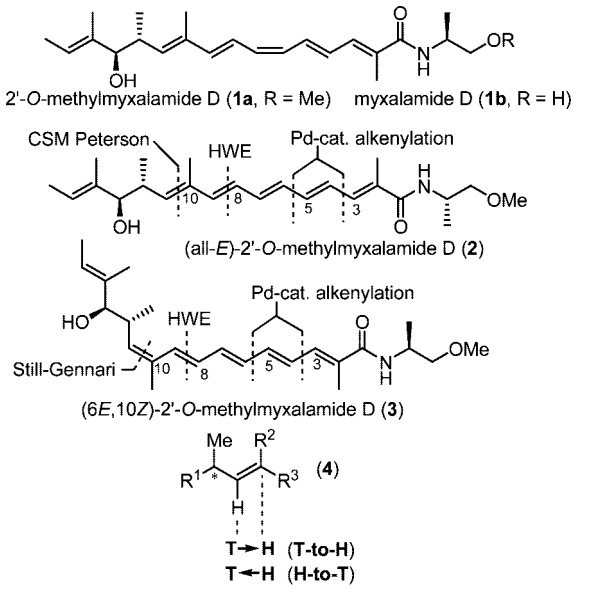


Figure 1. Myxalamide D and its derivatives.

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]

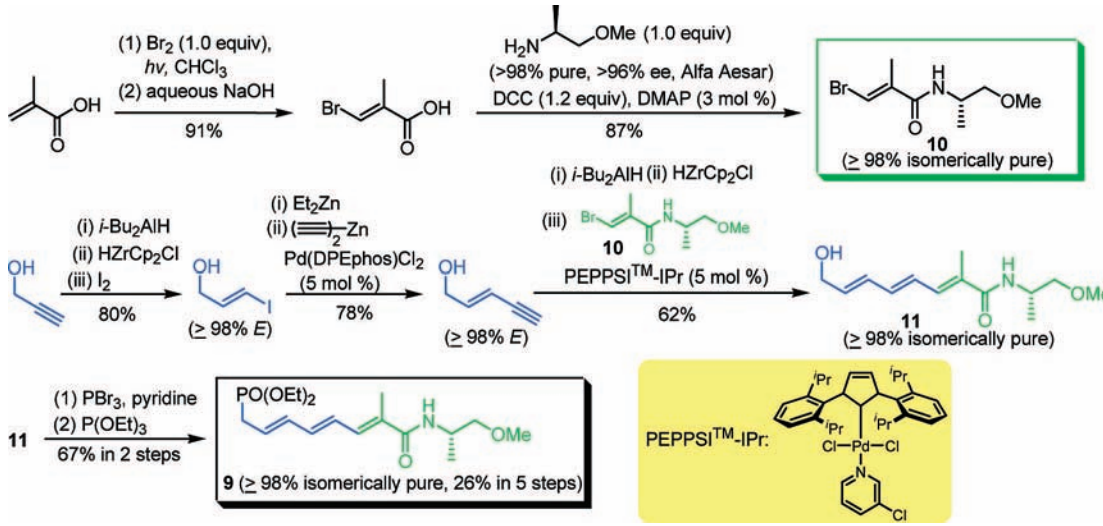
Herein, we report highly efficient and selective syntheses of both (all-*E*) and (6*E*,10*Z*)-isomers of 2′-*O*-methylmyxalamide D (**2** and **3**), in which the crucial conjugated pentaene moieties are assembled in ≥98% stereoselectivity through the use of two Pd-catalyzed alkenylation reactions for 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

(4) For a review of the Wittig and related olefinations, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (b) Horner, L.; Hoffmann, H.; Wippel, J. H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505. (c) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Soc. Chem.* **1961**, *83*, 1733–1738. (d) For a seminal work on the Still−Gennari olefination, see: Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408. (e) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7–10. (f) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391–2394. (g) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 3895–3898.

(5) For reviews on Pd-catalyzed alkenylation, see: (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; 2 Vols., pp 3279; 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.

Scheme 2



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 tigilic aldehyde (≥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 (≥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 ≥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 crotylboration[7] 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*-methoxydiisopinocamphenylborane (Aldrich) according to the literature procedure[7] 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 $NaIO_4$ provided **6**, which was purified by chromatography (Silica gel, 5% EtOAc in hexanes). The yield of ≥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 ≥98% *E*,*E* by ^{13}C NMR after simple chromatographic purification, and ≥98% pure **7** was obtained in 81% yield (55% yield in five steps from tiglic aldehyde). The Still−Gennari olefination of **6** with $(CF_3CH_2O)_2P(O)CH(Me)CO_2Me$, $KN(SiMe_3)_2$, and 18-crown-6 (1.5 equiv)[4d] proved to be ≥98% *Z*-selective. After reduction with *i*-Bu_2AlH, **8** was obtained as a ≥98% pure compound in 66% yield over two steps (Scheme 1).

In view of the current high cost of $(CF_3CH_2O)_2P(O)CH(Me)CO_2Me$ 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 $TBDPSOCH_2CH{=}CH_2$ to **14** via **13**[14] was achieved in 30% yield in seven steps, its application to the conversion of **6** to

(7) For the Brown crotylboration, see: (a) Brown, H. C.; Bhatt, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923. (b) Brown, H. C.; Jadhav, P. K.; Bhatt, K. S. *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. (b) Zeng, X.; Zeng, F.; Negishi, E. *Org. Lett.* **2004**, *6*, 3245–3248.

(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.

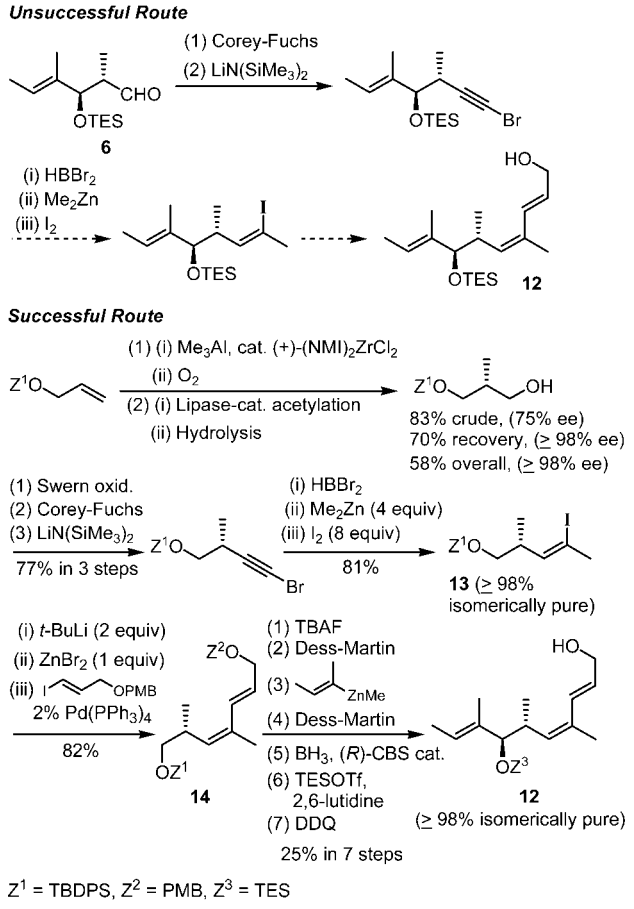
(10) For the H-to-T (head-to tail) construction of (*E*)-**4**, see: Hoye, T. R.; Temakoon, M. A. *Org. Lett.* **2000**, *2*, 1481–1483.

(11) For the T-to-H (tail-to-head) construction of (*Z*)-**4**, see: (a) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912–4913. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914–4915. (c) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397–2400. (d) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960–8961. (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.

(12) (a) AD-mix-α: Sharpless asymmetric dihydroxylation agent containing hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$], $K_3Fe(CN)_6$, K_2CO_3, and $K_2OsO_4{\cdot}2H_2O$. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; 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, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

Scheme 3



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 C7 epimers of **12** which was converted to **12** of ≥98% purity via Dess−Martin oxidation[15] 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 ≥99% *E* in 80% yield via (i) in situ OH protection with *i*-Bu_2AlH, (ii) hydrozirconation with $HZrCp_2Cl$-$ClAl(i\text{-}Bu)_2$ generated in situ from *i*-Bu_2AlH-$ZrCp_2Cl_2$,[17] and (iii) iodinolysis all in one pot. Ethynylation[18] of (*E*)-3-iodoallyl alcohol was performed in 78% yield by (i) OH protection with Et_2Zn and (ii) ethynylation with $(HC{\equiv}C)_2Zn$ in the presence of 5 mol % of $Pd(DPEphos)Cl_2$. 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 PEPPSI-IPr (98%, Aldrich)[19] provided **11** of ≥98% isomeric purity in 62% yield. The required intermediate **10** was prepared in three steps in 79% yield by β-bromination of methacrylic acid[20] and amidation with (*S*)-$H_2NCH(Me)CH_2OMe$ (98% pure, Alpha Aesar). As detailed in an upcoming publication, an *N*-heterocyclic carbene-containing PEPPSI-IPr proved to be distinctly superior to $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, or $Pd(DPEphos)Cl_2$. Thus, **11** was prepared as a ≥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 $P(OEt)_3$ according to the literature[21] proceeded in 67% yield over two steps (26% from propargyl alcohol or 33% from methacrylic acid in five steps). All isolated compounds were ≥98% isomerically pure by ^{13}C 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**).

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

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(20) Dzierba, C. D.; Zandi, K. S.; Möllers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 4711–4712.
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