ORGANIC LETTERS

2009
Vol. 11, No. 4
935−938

A Convergent Approach toward the C1−C11 Subunit of Phoslactomycins and Formal Synthesis of Phoslactomycin B

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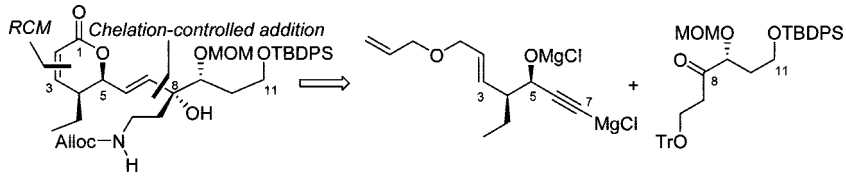
Received December 18, 2008

ABSTRACT



The preparation of the C1−C11 subunit of phoslactomycins, and a formal synthesis of phoslactomycin B, were achieved by a convergent strategy involving the chelation-controlled addition of an alkynyl Grignard reagent to an α-alkoxy ketone. Catalytic enantioselective reductions of acetylenic ketones and a [2,3]-Wittig rearrangement were utilized as key steps to control the configuration of the C4, C5, and C9 stereocenters.

Phoslactomycins (PLMs) A−F, isolated in 1989 from the culture broth of a strain of *Streptomyces nigrescens*, were found to exhibit potent activity against phytopathogenic fungi.[1] These compounds share a common backbone including a α,β-unsaturated δ-lactone, a disubstituted alkene of (*E*) configuration (C6−C7), a tertiary alcohol at C8 substituted by a 2-aminoethyl chain, a phosphate at C9, a secondary alcohol at C11, and a conjugated (*Z*,*Z*)-diene (C12−C15) with a cyclohexyl group at C15 but differ by the substituent at C18 on the latter cyclohexane ring. Phospholine (PLM B) was isolated from the fermentation broth of a strain of *Streptomyces hygroscopicus* and potent activities against L1210, P388 and EL4 murine cancer cell lines were reported for this compound.[2] In 1993, the structurally related leustroducsins (LSNs) A−C, isolated from the culture broth of *Streptomyces platensii* (SANK 60191), were found to possess colony-stimulating factors inducing activity.[3] The mode of action of PLMs and LSNs[4] seems to derive from the selective inhibition of serine-threonine phosphatase 2A,[5] an enzyme involved in the regulation of many crucial biological events (Figure 1).[6]

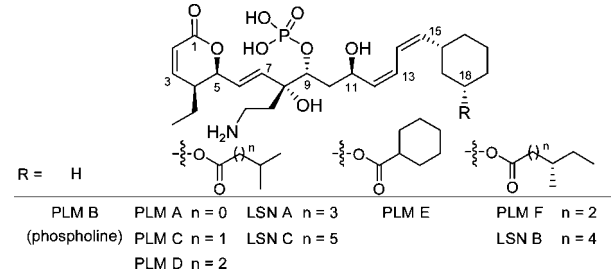


Figure 1. Phoslactomycins (PLMs) and Leustroducsins (LSNs).

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[‡] Syngenta Crop Protection.

(1) (a) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019–1025. (b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot. Chem.* **1989**, *42*, 1026–1036.

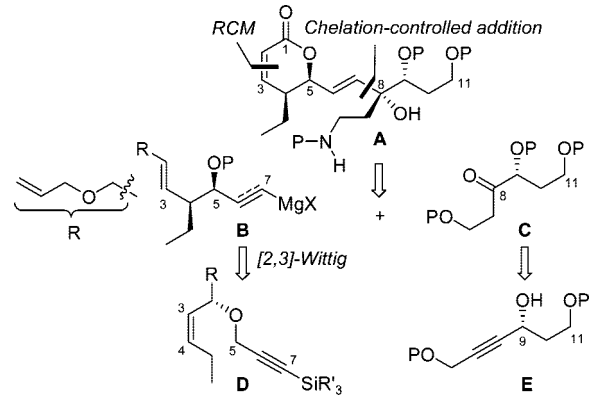
10.1021/ol8029142 CCC: $40.75
Published on Web 01/26/2009

To date, two total syntheses of PLM B[7,8] and LSN B[9,10] as well as one formal synthesis of the latter compound have been reported.[11] Evans aldol reactions[7,9] or Brown-type pentenylation[8,11] have essentially been used to control the configuration of the C4 and C5 stereocenters. Alternatively, a Sharpless asymmetric epoxidation followed by ring-opening of the resulting epoxide with an alkynylalane has also been described.[10] The 1,2-diol at C8−C9 has often been installed by a Sharpless asymmetric dihydroxylation,[8,10,11] and an interesting enzymatic desymmetrization of a *meso*-1,3-diol has also been used to control the absolute configuration of C8.[9] Interestingly, in one total synthesis of PLM B, the chelation-controlled addition of vinylmagnesium bromide to a ketone at C8 was described. However, several steps were subsequently required to create the C4 and C5 stereocenters and elaborate the disubstituted unsaturated lactone from the introduced vinyl group.[7a,12]

Herein, we report a new convergent approach toward the C1−C11 subunit of PLMs and a formal synthesis of PLM B, relying on the formation of the C7−C8 bond.

In our retrosynthetic analysis, the C1−C11 fragment of the PLMs **A** was disconnected at the C7−C8 bond and the construction of the unsaturated lactone was envisaged by ring-closing metathesis (RCM). The goal was to achieve the chelation-controlled addition of an alkenyl or an alkynyl Grignard reagent of type **B**, precursor of the C1−C7 segment and already containing the C4 and C5 stereocenters, to a suitably protected α-alkoxy ketone **C** in order to control the configuration of the C8 stereocenter.[13] Additionally, the use of new key steps was considered to create the C4, C5, and C9 stereocenters in this family of natural products. A [2,3]-Wittig rearrangement of the allylic and propargylic ether of type **D**, operating with chirality tranfer, would be used to control the configuration of C4 and C5.[14] Although any R substituent could in principle be used, an allyloxymethyl group was selected in order to act as a relay during the RCM.[15] Ketone **C** would be prepared from the propargylic alcohol **E** by regioselective copper-catalyzed cyclo-functionalization using tosyl isocyanate. Thus, the configurations of C4, C5, and C9 would all be controlled, either in an indirect or a direct manner, respectively, by catalytic enantioselective reductions of acetylenic ketones (Scheme 1).

Scheme 1. Retrosynthetic Analysis of the C1−C11 Subunit



The synthesis of the C3−C7 subunit was carried out from the readily available α-allyloxyacetic acid **1**,[16] which was converted to a Weinreb amide,[17] and subsequent addition of but-1-ynyllithium led to the acetylenic ketone **2** (71%, two steps from **1**). The chirality was introduced through an enantioselective reduction of ketone **2**, catalyzed by ruthenium complex (*S*,*S*)-Ru-**I** (5 mol %) in *i*-PrOH,[18] to provide the optically active propargylic alcohol **3** (97%, ee = 91%).[19] Stereoselective reduction of the alkyne using a zinc−copper couple (THF/*i*-PrOH, reflux)[20] generated the corresponding (*Z*)-allylic alcohol which was alkylated with (triisopropyl-

(2) (a) Ozasa, T.; Suzuki, K.; Sasamata, M.; Tanaka, K.; Kobori, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. *J. Antibiot. Chem.* **1989**, *42*, 1331–1338. (b) Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwa, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. *J. Antibiot. Chem.* **1989**, *42*, 1339–1343.

(3) (a) Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki, T.; Sakaida, Y.; Satoh, A.; Shiraishi, A. *J. Antibiot. Chem.* **1993**, *46*, 1503–1511. (b) Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot. Chem.* **1993**, *46*, 1512–1519. (c) Shibata, T.; Kurihara, S.; Yoda, K.; Haruyama, H. *Tetrahedron* **1995**, *51*, 11999–12012.

(4) Shibata, T.; Kurihara, S.; Oikawa, T.; Ohkawa, N.; Shimazaki, N.; Sasagawa, K.; Kobayashi, T.; Kohama, T.; Asai, F.; Shiraishi, A.; Sugimura, Y. *J. Antibiot. Chem.* **1995**, *48*, 1518–1520.

(5) (a) Usui, T.; Marriott, G.; Inagaki, M.; Swarup, G.; Osada, H. *J. Biochem.* **1999**, *125*, 960–965. (b) Kawada, M.; Kawatsu, M.; Masuda, T.; Ohba, S.; Amemiya, M.; Kohama, T.; Ishizuka, M.; Takeuchi, T. *Int. Immunopharmcol.* **2003**, *3*, 179–188.

(6) Lawhorn, B. G.; Boga, S. B.; Wolkenberg, S. E.; Colby, D. A.; Gauss, C.-M.; Swingle, M. R.; Amable, L.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 16720–16732, and references therein. .

(7) (a) Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320–3323. (b) Nonaka, H.; Maeda, N.; Kobayashi, Y. *Tetrahedron Lett.* **2007**, *48*, 5601–5604.

(8) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139–2142.

(9) Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048–4049.

(10) (a) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *Tetrahedron Lett.* **2007**, *48*, 3829–3833. (b) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *J. Org. Chem.* **2008**, *73*, 5360–5370.

(11) Moïse, J.; Sonawane, R. P.; Corsi, C.; Wendeborn, S. V.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 2617–2620.

(12) The chelation-controlled addition of an alkenyl Grignard reagent to a methyl ketone has been used in several convergent syntheses of the structurally related natural product fostriecin, see: (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667–3670. (b) Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615–4618. (c) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666–3667.

(13) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031–1034.

(14) (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885–902. (b) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 3, pp 975−908.

(15) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (b) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915.

(16) Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472–4490.

(17) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (b) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913–3916.

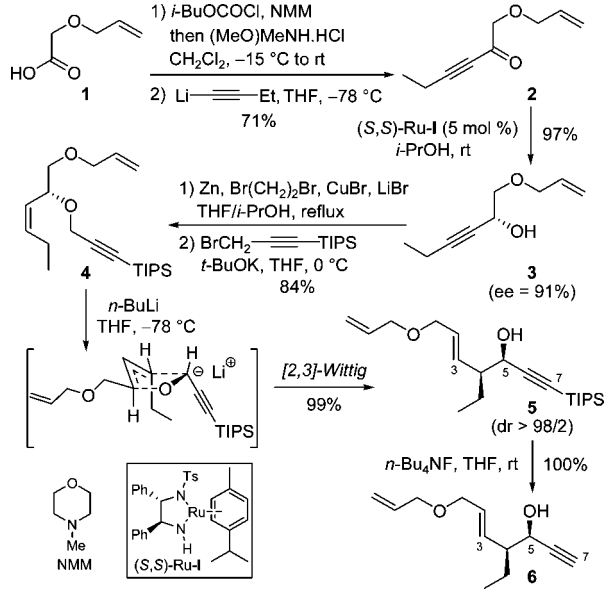
(18) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

(19) The ee was determined by super-critical fluid chromatography analysis (chiral phase), see the Supporting Information.

(20) Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 735–736.

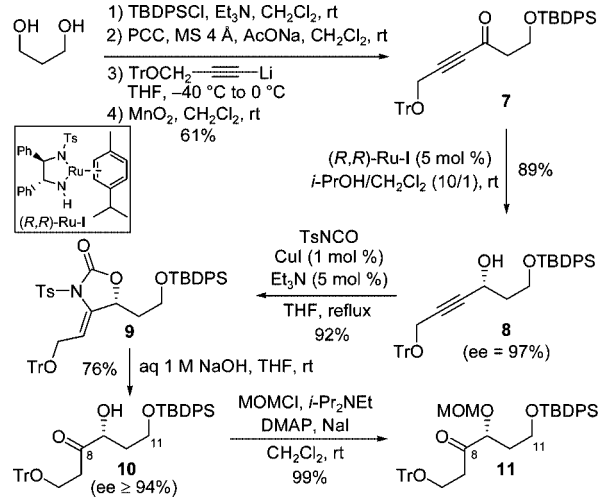
silyl)propargyl bromide[21] to afford propargylic ether **4** (84%, two steps from **3**). The C4 and C5 stereocenters were then created by the [2,3]-Wittig rearrangement of the optically active allylic and propargylic ether **4** (*n*-BuLi, THF, −78 °C). The propargylic and homoallylic alcohol **5** was isolated as a single diastereomer in almost quantitative yield.[22] The observed stereochemical outcome is in agreement with a five-membered-ring transition state of envelope conformation wherein the allyloxymethyl chain preferentially occupies a pseudoequatorial position, while an *exo* orientation is favored for the π-donating stabilizing alkynyl group.[23] Desilylation of the terminal alkyne provided compound **6** (100%), which corresponds to the C3−C7 subunit of the PLMs. Its preparation has thus been achieved in seven steps from α-allyloxyacetic acid (57% overall yield) (Scheme 2).

Scheme 2. Synthesis of the C3−C7 Subunit



The preparation of the C8−C11 fragment was carried out from ketone **7**, which is readily available from propane-1,3-diol through a series of straightforward operations (four steps, 61% overall yield). Enantioselective reduction of the acetylenic ketone **7**, catalyzed by ruthenium complex (*R*,*R*)-Ru-**I** (5 mol %) [*i*-PrOH/CH_2Cl_2 (10/1), rt], afforded the optically active propargylic alcohol **8** (89%, ee = 97%).[18] The formal regioselective hydration of the disubstituted alkyne, required to convert compound **8** into an α-alkoxy ketone of type **C**, was achieved through cyclofunctionalization. Alcohol **8** was treated with tosyl isocyanate in the presence of a catalytic amount of CuI and Et_3N (THF, reflux) to produce the *N*-tosyl-4-(alkylidene)oxazolidin-2-one **9** (92%) as a single geometric isomer.[24] Hydrolysis of compound **9** under carefully controlled alkaline conditions (1 M NaOH/THF) led to the desired α-hydroxy ketone **10** in good yield (76%, ee ≥ 94%).[19,25] Finally, protection of the hydroxyl group as a MOM ether afforded the α-alkoxy ketone **11** in almost quantitative yield.[26] This compound, which corresponds to the C8−C11 subunit, has been prepared in eight steps from propane-1,3-diol (38% overall yield) (Scheme 3).

Scheme 3. Synthesis of the C8−C11 Subunit



The coupling of the two fragments was then investigated. Initial efforts to couple alkenyl Grignard reagents, incorporating a precursor of the C1−C7 subunit, with α-alkoxy ketones bearing a 2-alkoxyethyl chain were discouraging. Little addition occurred, and enolization was observed as a side reaction.

For this reason, the use of a less hindered (and less basic) alkynyl Grignard reagent was considered. Thus, treatment of propargylic alcohol **6** with *i*-PrMgCl (2 equiv) generated an alkynyl Grignard reagent which smoothly reacted with ketone **11** to afford the tertiary alcohol **12** (84% yield based on **11**) with good diastereoselectivity (dr = 92/8), as a result of a chelate control exerted by the alkoxy (OMOM)-substituted C9 stereocenter.[13] An excess of the Grignard reagent was conveniently used (3.5 equiv) to ensure complete conversion of ketone **11**, and the excess of terminal alkyne **6** could be quantitatively recovered and recycled. Stereoselective hydroalumination of the alkyne with Red-Al[27] and

(21) Wright, J. M.; Jones, G. B. *Tetrahedron Lett.* **1999**, *40*, 7605–7609.

(22) For recent applications of [2,3]-Wittig rearrangements to the preparation of polypropionate subunits, see: (a) Parker, K. A.; Xie, Q. *Org. Lett.* **2008**, *10*, 1349–1352. (b) Cao, H.; Parker, K. A. *Org. Lett.* **2008**, *10*, 1353–1356.

(23) (a) Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421–1423. (b) Mikami, K.; Uchida, T.; Hirano, T.; Wu, Y.-D.; Houk, K. N. *Tetrahedron* **1994**, *50*, 5917–5926.

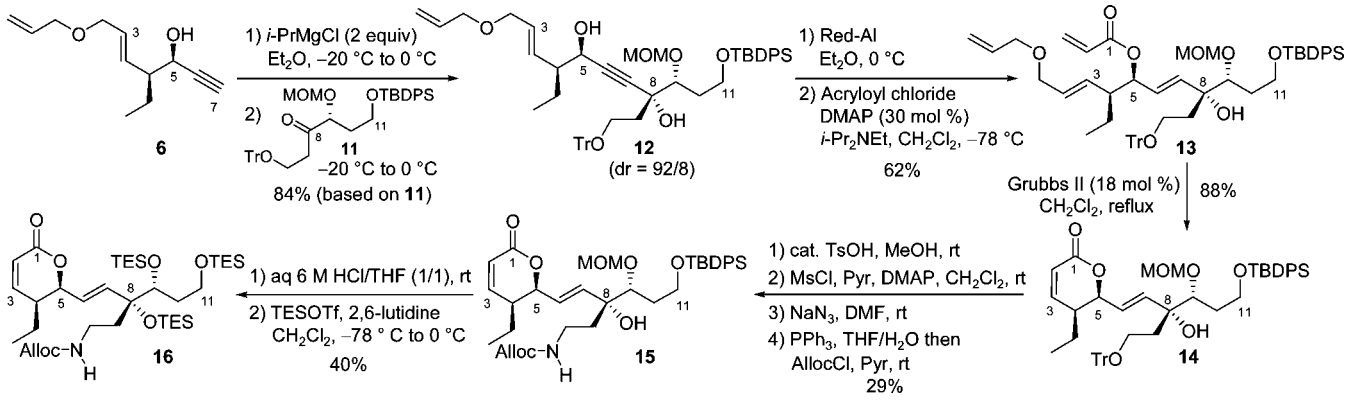
(24) Ohe, K.; Ishihara, T.; Chatani, N.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1991**, *56*, 2267–2268.

(25) For the use of this strategy to prepare an α-hydroxy ketone bearing a tertiary alcohol, see: Matsuura, T.; Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1993**, 1503–1504.

(26) Protection as a PMB ether was unsuccessful under various reaction conditions.

(27) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–3505. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595–4597.

Scheme 4. Preparation of the C1−C11 Fragment of the Phoslactomycins. Formal Synthesis of Phoslactomycin B



subsequent condensation of the secondary allylic alcohol at C5 with acryloyl chloride provided acrylate **13** (62%, two steps from **12**). The formation of the unsaturated lactone was next achieved by a relay ring-closing metathesis,[15] catalyzed by Grubbs second-generation catalyst,[28] during which dihydrofuran was expelled and the α,β-unsaturated lactone **14** was produced in 88% yield.[29,30] Conversion of lactone **14** into the target C1−C11 subunit of PLMs was achieved in four steps by cleavage of the trityl group, mesylation of the resulting primary alcohol, and displacement of the mesylate with sodium azide. Subsequent Staudinger reaction followed by in situ acylation of the primary amine with allyl chloroformate finally led to compound **15** (29% overall yield from **14**), which constitutes the C1−C11 subunit of PLMs in our convergent synthetic approach toward this family of natural products. To confirm the structural and stereochemical assignments made for compound **15**, the secondary and primary hydroxyl groups in the latter compound were deprotected (aq 6 M HCl/THF, rt), and protection of the three alcohols as a triethylsilyl ethers led to compound **16** (40%), whose spectroscopic data matched with those previously reported for the same advanced intermediate in Hatakeyama's total synthesis of PLM B (Scheme 4).[8]

In conclusion, we have reported the synthesis of the C1−C11 subunit of the PLMs by a convergent route involving the diastereoselective addition of an alkynyl Grignard reagent, incorporating an elaborate precursor of the C1−C7 fragment, to an α-alkoxy ketone. The key steps involved in the control of the configuration of the C4, C5, and C9 stereocenters are ruthenium-catalyzed enantioselective reductions of acetylenic ketones and a highly diastereoselective [2,3]-Wittig rearrangement. Also noteworthy is the use of a copper-catalyzed cyclofunctionalization of a chiral propargylic alcohol since, to our knowledge, it is the first report on the use of this strategy to generate an optically active α-hydroxy ketone bearing a secondary alcohol.[25]

Acknowledgment. Syngenta Crop Protection is gratefully acknowledged for financial support. V.D. thanks the MRES for a grant.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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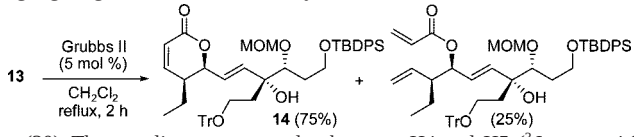
(28) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *6*, 953–956.

(29) Treatment of **13** with Grubbs II (5 mol %, CH_2Cl_2, reflux 2 h) led the desired lactone **14** (75%) and the corresponding terminal alkene at C3 (25%). The RCM of the latter compound subsquently proceeded at a much slower rate and required a higher catalyst loading to reach completion, thus highlighting the interest of the relay RCM.



(30) The coupling constant value between H4 and H5 ($^{3}J_{H4\text{-}H5}$ = 4.6 Hz) confirmed the relative configuration of C4 and C5; see ref 6 and: (a) Bialy, L.; Lopez-Canet, M.; Waldmann, H. *Synthesis* **2002**, 2096–2104. (b) Salit, A.-F.; Meyer, C.; Cossy, J.; Delouvrié, B.; Hennequin, L. *Tetrahedron* **2008**, *64*, 6684–6697.