ORGANIC LETTERS

2000
Vol. 2, No. 1
65−67

An Efficient and Stereoselective Synthesis of Xerulin *via* Pd-Catalyzed Cross Coupling and Lactonization Featuring (*E*)-Iodobromoethylene as a Novel Two-Carbon Synthon

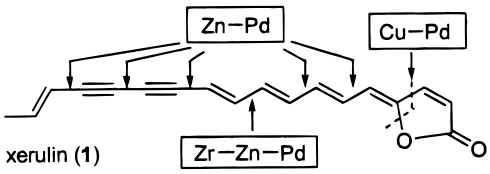
Ei-ichi Negishi,*,† Asaf Alimardanov, and Caiding Xu

Herbert C. Brown Laboratories, Purdue University, West Lafayette, Indiana 47907

negishi@purdue.edu

Received November 1, 1999

ABSTRACT



Xerulin, an inhibitor of cholesterol biosynthesis, has been synthesized from commercially available (*E*)-1-bromopropene, acetylene, and propynoic acid in five steps (longest linear sequence) in 30% overall yield and >96% stereoselectivity. The preparation of (*E*)-iodobromoethylene and its use in the Pd-catalyzed cross coupling are two of the novel aspects of the synthesis reported herein.

Xerulin (**1**), isolated from *Xerula melanotricha* Dörfelt as an inseparable mixture containing a minor amount of dihydroxerulin,[1] is an inhibitor of cholesterol biosynthesis. As a polyenynyl (*Z*)-γ-butenolide containing six C=C and two C≡C bonds in conjugation, it provides an interesting synthetic challenge and an opportunity for testing and comparing new synthetic procedures. Herein, we report an efficient and stereoselective total synthesis of xerulin (**1**) requiring only five steps (longest linear sequence) in 30% overall yield and >96% stereoselectivity (Scheme 1).[2] Ten total steps starting from commercially available (*E*)-1-bromopropene, acetylene, and propynoic acid are required to complete the synthesis including the preparation of HC≡CTBS and that of (*Z*)-ICH=CHCOOH.[3]

All seven C−C single bonds linking the six acetylene-derived C=C and C≡C units were formed via Pd-catalyzed cross coupling. Some notable steps include (i) direct terminal alkyne synthesis using ethynylzinc bromide without silyl protection−deprotection,[4] (ii) double metal-catalyzed alkenyl−alkenyl coupling with in situ generated alkenylzirconium derivatives catalyzed by Pd and Zn,[5] (iii) Pd-catalyzed conjugated diyne synthesis via 1-haloenynes,[6] and (iv) a recently developed Pd-catalyzed ene−yne cross coupling−carboxymetalation tandem process.[7,8] Additionally, the synthesis reported herein features (i) a substantially improved and satisfactory preparation of (*E*)-iodobromoethylene[9] and

† FAX: +1-765-494-0239.

(1) Kuhnt, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; Steffan, B.; Steglich, W. *J. Antibiot.* **1990**, *43*, 1413.

(2) During the course of our study, the first synthesis of xerulin employing a much different synthetic strategy and lacking stereoselectivity in the critical final step (Wittig olefination) was published [Siegel, K.; Brückner, R. *Synlett* **1999**, 1227]. The same group has also published a total synthesis of dihydroxerulin [Siegel, K.; Brückner, R. *Chem. Eur. J.* **1998**, *3*, 1116].

(3) Stolz, R. *Chem. Ber.* **1886**, *19*, 536.

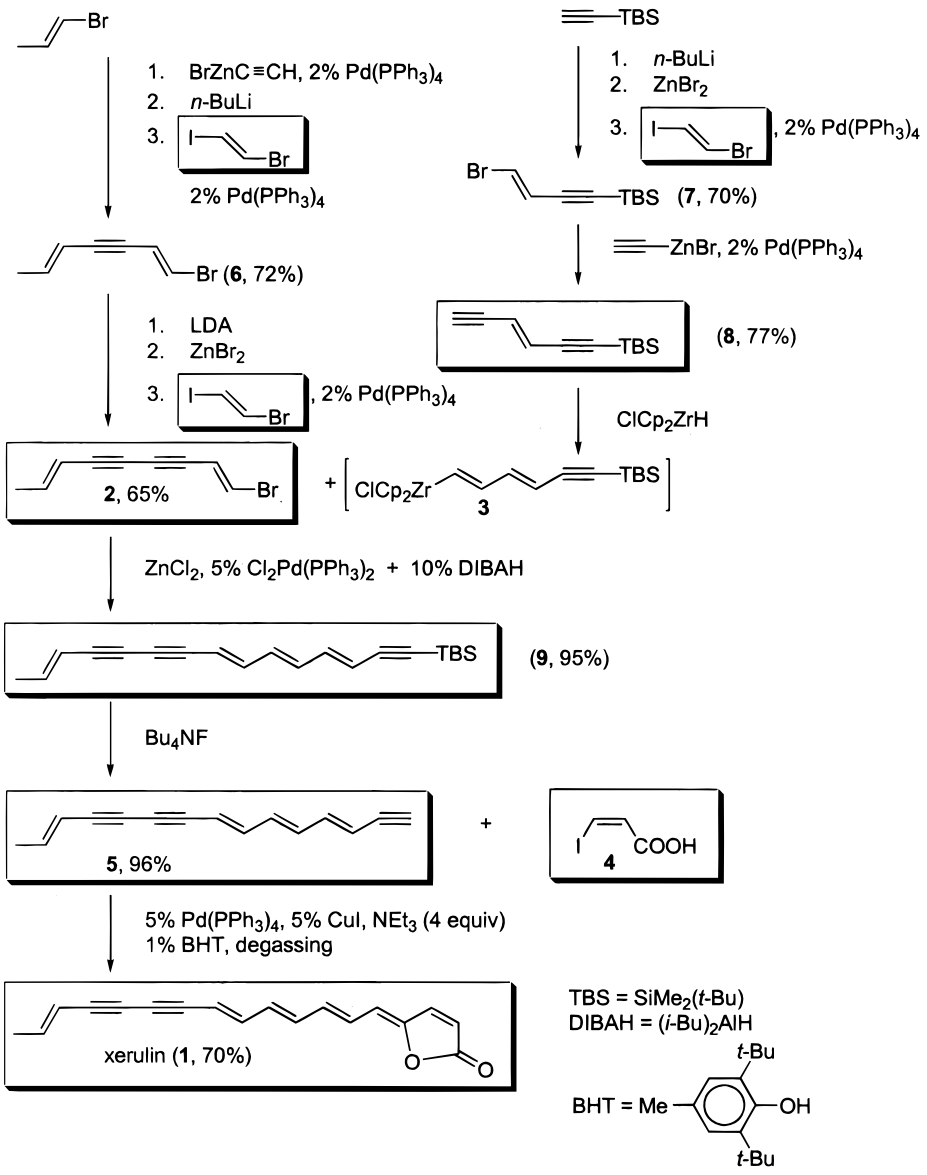
(4) (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) King, A. O.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 1027. (c) Negishi, E. In *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J. H., Ed.; Plenum Press: New York, 1978; p 287. (d) Negishi, E.; Xu, C.; Tan, Z.; Kotora, M. *Heterocycles* **1997**, *46*, 209. (e) Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957.

(5) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. J. *J. Am. Chem. Soc.* **1978**, *100*, 2254.

(6) (a) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629. (b) Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.

10.1021/ol990336h CCC: $19.00
Published on Web 12/15/1999

Scheme 1



(ii) its selective and stepwise mono- and disubstitution. We believe that (*E*)-iodobromoethylene[10] promises to be the most convenient, generally applicable, and selective (*E*)-C=C synthon of the six possible (*E*)-1,2-dihaloethylenes containing Cl, Br, and/or I. Of the various alternative routes to xerulin tested in this study, the one involving **2**−**4** as three key intermediates, i.e., **2** + **3** → **5** and then **5** + **4** → **1** (Scheme 1), has proved to be the most satisfactory. The noteworthy aspects of the synthesis are further elaborated below.

First, there have been two distinct groups of reactions for the Pd-catalyzed alkyne synthesis. One is the Heck-type alkyne C−H substitution reactions[11] represented by the Sonogashira protocol.[11a] The other is the Pd-catalyzed reaction of preformed alkynylmetals containing Zn, B, Sn, and Mg originally reported by us.[4a−c] One of the limitations of the Sonogashira and Heck protocols is that they cannot be applied to the direct synthesis of terminal alkynes. In contrast, our protocol with commercially available ethynylmagnesium halides or ethynylzincs in particular cleanly provided (*E*)-3-penten-1-yne and **8** in high yields without the need for protection−deprotection.

Second, attractive opportunities for a one-pot tandem process consisting of hydrometalation and Pd-catlayzed alkenyl−alkenyl coupling were sought. However, hydro-

(7) (a) Kotora, M.; Negishi, E. *Tetrahedron Lett.* **1996**, *37*, 9041. (b) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121. (c) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591. (d) For a review containing pertinent references, see: Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707.

(8) For related studies leading to the development of this procedure, see: (a) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1993**, *34*, 5963. (b) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86.

(9) Viehe, H. G.; Franchimont, E. *Chem. Ber.* **1963**, *96*, 3153.

(10) Bartlome, A.; Stampfli, U.; Neuschwander, M. *Chimia* **1991**, *45*, 346.

(11) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259.

metalation reactions of conjugated enynes and diynes including those with B,[12] Al,[13] and Zr[14] are generally complicated by placement of metals in internal positions. Fortunately, favorable results were obtained in the hydrozirconation−cross coupling tandem reaction of **8**. Thus, its hydrozirconation generated **3** in 80% yield by NMR. The reaction of **3**, generated in situ from **8**, with **2** in the presence of a Pd catalyst prepared from 5 mol % of $Cl_2Pd(PPh_3)_2$ and 10 mol % of DIBAH as well as $ZnCl_2$ (0.6 equiv) afforded, after chromatographic purification, 97% pure **9** in 95% yield based on **2**.

Third, unsymmetrically substituted conjugated diynes are commonly synthesized by the Cadiot−Chodkiewicz reaction[15a] and its modification with Pd catalysts.[15b] These methods, however, are often complicated by homocoupling leading to diminished yields of the desired cross-coupling products. We earlier introduced a strictly "pair-selective" alternative procedure using (*E*)-ICH═CHCl.[6] Although expected, the feasibility of attaching the second carbon group to the butadiyne unit via Pd-catalyzed cross coupling has not been reported. The synthesis of **2** from **6** demonstrates not only the feasibility of such transformations but also the interchangeability between (*E*)-ICH═CHBr and (*E*)-ICH═CHCl. The scope of this method for the synthesis of conjugated diynes needs to be further delineated. Nonetheless, we believe it is a significantly more selective and potentially more general method of comparable overall efficiency, as compared with the widely used procedures mentioned above.[15]

Fourth, complications associated with the regiochemistry and some other aspects of hydrometalation of conjugated enynes and diynes have prompted us to develop highly stereoselective modular approaches to the synthesis of oligoenes and oligoenynes using (*E*)-1,2-dihaloethylenes. Of three such compounds used thus far, Cl-containing compounds, i.e., (*E*)-ClCH═CHCl[16] and (*E*)-ICH═CHCl,[6] suffer from the generally low reactivity of the C−Cl bond in the Pd-catalyzed cross coupling except for those cases where alkynes are used as nucleophiles. On the other hand, BrCH═CHBr used as *E* and *Z* mixtures has been associated with chemo- and/or stereoselectivity problems as well as modest product yields.[17] We therefore chose (*E*)-ICH═CHBr as a potentially superior alternative. The reported synthesis[9] of (*E*)-ICH═CHBr in 44% crude yield by treatment of acetylene with I_2 and Br_2 in $CHCl_3$ was improved by treatment of acetylene with commercially available IBr at 0 °C over 48 h to provide pure (*E*)-ICH═CHBr in 73% yield. As expected, its Pd-catalyzed selective monoalkynylation has proved to be facile and high-yielding, as exemplified by the synthesis of **2**, **6**, and **7**, shown in Scheme 1. Furthermore, the second Pd-catalyzed substitution with alkynyl- and alkenylmetals can also be satisfactory, as shown in the synthesis of **8** and **9**.

Finally, the Pd-catalyzed cross coupling−lactonization tandem procedure[7] involving the use of 1 mol % of BHT and several cycles of freeze−thaw degassing[7c] was high-yielding, stereoselective, and regioselective. Xerulin (**1**) was formed in 70% yield as a >96% stereoisomerically pure compound. The ^1H and ^{13}C NMR spectral data[18] are in excellent agreement with those reported in the literature.[1,2] The extent of homocoupling of **5** was <5%. Neither the formation of the corresponding pyrone nor other side reactions,[7b] such as conjugate substitution of **1**, were detectable.

Acknowledgment. We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research and Johnson-Matthey for palladium compounds.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **4**, **5**, and **7**−**9** as well as spectroscopic data for **2** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990336H

(12) (a) Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 4068. (b) For a review, see: Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988; p 503.

(13) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.

(14) (a) For a review, see: Labinger, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 667−702. (b) Fryzuk, M. D.; Bates, G. S.; Stone, C. *Tetrahedron Lett.* **1986**, *27*, 1537. (c) Crombie, L.; Hobbs, A. J. W.; Horsham, M. A.; Blade, R. J. *Tetrahedron Lett.* **1987**, *28*, 4875.

(15) (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; p 597. (b) See, for example: Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 2053.

(16) (a) Rotovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315. (b) Alami, M.; Gueugnot, S.; Domingues, E.; Linstrumelle, G. *Tetrahedron* **1995**, *51*, 1209. (c) Ramaiandrasoa, P.; Bréhon, B.; Thivet, A.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 2447.

(17) (a) Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 4351. (b) Andreini, B. P.; Benetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **1987**, *43*, 4591.

(18) Xerulin (**1**): ^1H NMR (500 MHz, $CDCl_3$) 1.84 (dd, J = 6.8 and 1.9 Hz, 3 H), 5.61 (dqd, J = 15.6, 1.9, and 1.1 Hz, 1 H), 5.76 (d, J = 15.6 Hz, 1 H), 5.90 (d, J = 11.8 Hz, 1 H), 6.18 (d, J = 5.4 Hz, 1 H), 6.34 (dq, J = 15.8 and 7.0 Hz, 1 H), 6.4−6.55 (m, 3 H), 6.74−6.85 (m, 2 H), 7.37 (d, J = 5.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 18.99, 72.55, 79.40, 80.66, 83.36, 109.91, 112.15, 114.69, 118.89, 127.73, 135.07, 135.54, 137.81, 142.53, 143.79, 143.95, 149.46, 169.31.