ORGANIC LETTERS

2012
Vol. 14, No. 21
5594–5597

# Stereoselective Synthesis of Conjugated Trienols from Allylic Alcohols and 1-Iodo-1,3-dienes

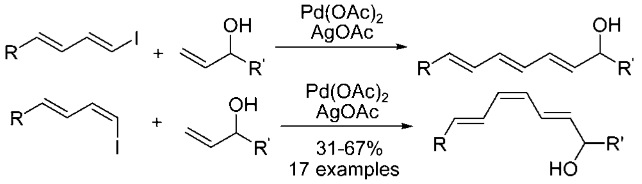
**Damien Brandt, Véronique Bellosta, and Janine Cossy***

*Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin,*
*75231 Paris Cedex 05, France*

*janine.cossy@espci.fr*

**Received October 2, 2012**

## ABSTRACT



**The stereoselective synthesis of conjugated trienes has been achieved from allylic alcohols and 1-iodo-1,3-dienes using Pd(OAc)$_2$/AgOAc.**

Conjugated trienes are present in a great variety of biologically active polyenic natural products such as macrolides with antitumor, antifungal, or antibiotic properties.[1] For example, trienic units are present in ansatrienine A[2] (antitumor), manumycin A[3] (antifungal, antibacterial, and antitumor agent against leukemia stem cells), and rapamycin[4] (antibacterial and immunosuppressive agent). Furthermore, trienes are present in retinoids,[5] in eicosanoids such as leukotriene $B_4$,[6] an antitumor agent, and in $\pi$-conjugated materials[7] (Figure 1).

Due to the importance of trienic units, new synthetic methods toward these building blocks are of importance. The existing approaches toward functionalized substituted trienes, such as the Wittig[8] and the Horner–Wadsworth–Emmons[9] olefinations, are not step and/or atom economical processes, as the reagents have to be used in stoichiometric amounts. In addition, the conditions are not mild

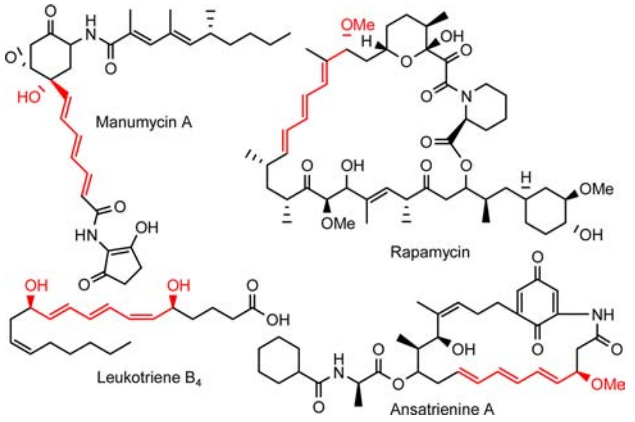


**Figure 1.** Examples of biologically active natural products containing conjugated trienol moieties.

---

(1) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999–1023.

(2) (a) Damberg, M.; Russ, P.; Zeeck, A. *Tetrahedron Lett.* **1982**, *23*, 59–62. (b) Sugita, M.; Natori, Y.; Sueda, N.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1474–1479.

(3) (a) Sattler, I.; Thiericke, R.; Zeeck, A. *Nat. Prod. Rep.* **1998**, *15*, 221–240. (b) Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707–3716.

(4) Belshaw, P. J.; Meyer, S. D.; Johnson, D. D.; Romo, D.; Ikeda, Y.; Andrus, M.; Alberg, D. G.; Schultz, L. W.; Clardy, J.; Schreiber, S. L. *Synlett* **1994**, *1994*, 381–392.

(5) (a) Sporn, M. B.; Roberts, A. B.; Goodman, D. S. *The Retinoids*; Academic Press Inc.: 1984. (b) Sporn, M. B.; Roberts, A. B. *The Retinoids: Biology, Chemistry, and Medicine*; Raven Press: 1994. (c) Dawson, M. I.; Okamura, W. H. *Chemistry and Biology of Synthetic Retinoids*; CRC Press: 1990.

(6) Green, R. H.; Lambeth, P. F. *Tetrahedron* **1983**, *39*, 1687–1721.

(7) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350–1377.

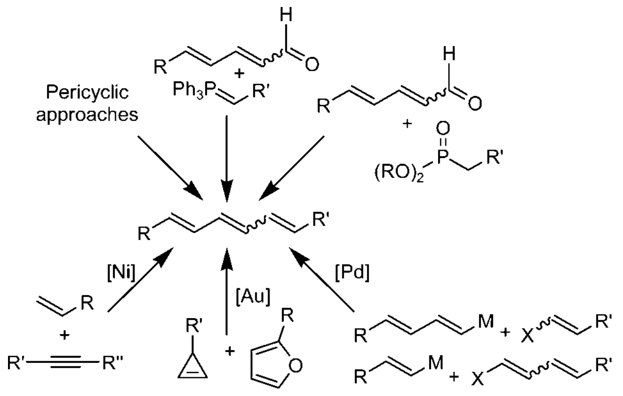
(8) For a review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

(9) For reviews, see: (a) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73–253. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; pp 729–817.

10.1021/ol302719e

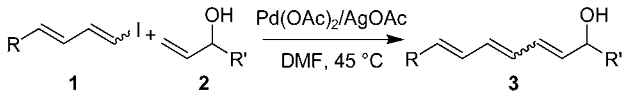
enough to be functional group tolerant. Pericyclic or biomimetic approaches to trienes can be used as well.[10,11] In addition, syntheses of $\pi$-conjugated systems through C−C bond formation, catalyzed by a transition metal such as palladium,[12] gold,[13] or nickel,[14] have been realized (Scheme 1).

**Scheme 1.** Synthesis of Trienic Units



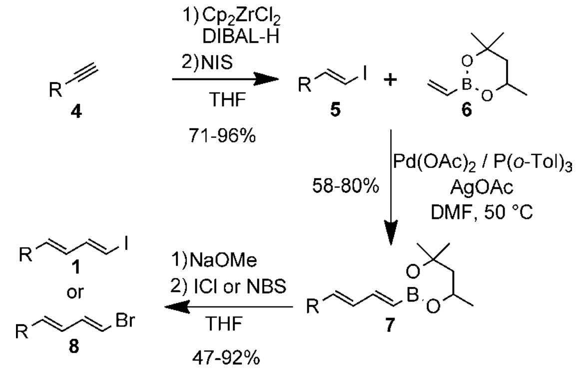
Herein, we would like to report a chemo-, regio-, and stereoselective method for the construction of conjugated trienols from 1-iodo-1,3-dienes **1** and nonprotected allylic alcohols **2** under Heck conditions[15] (Scheme 2).

**Scheme 2.** General Scheme



We initiated our investigation with (*E*,*E*)-1-iodo-1,3-dienes **1** and (*E*,*E*)-1-bromo-1,3-diene **8** in the presence of but-2-en-3-ol (**2a**). The synthesis of 1-halogeno-1,3-dienes was realized in three steps from acetylenic derivatives **4**. After hydrozirconation−iodation ($Cp_2ZrCl_2$, DIBAL-H, NIS, THF),[16] the corresponding (*E*)-vinyl iodides **5** were obtained and coupled with vinylboronate **6** under Heck conditions [$Pd(OAc)_2$, $P(o\text{-}Tol)_3$, AgOAc, DMF, 50 °C] to produce **7**.[17] The obtained conjugated dienyl boronates **7** were then treated with NIS or NBS under basic conditions (NaOMe, THF) to furnish the desired (*E*,*E*)-1-iodo-1,3-dienes **1** and (*E*,*E*)-1-bromo-1,3-dienes **8** respectively in good to excellent yields (47−92%) (Scheme 3).[18]

**Scheme 3.** Preparation of 1-Halogeno-1,3-dienes



At first, 1-iodo-1,3-diene **1a** was examined. When this diene was treated under Heck conditions [$Pd(OAc)_2$ (10 mol %), AgOAc (1.1 equiv)] in DMF at 45 °C for 15 h in the presence of but-3-en-2-ol (**2a**) (3 equiv), the coupling product **3a** was obtained in 72% yield (Table 1, entry 1). The use of 2 equiv of alcohol **2a** gave a similar result (Table 1, entry 2). It is worth pointing out that it was also possible to reduce the quantity of palladium acetate to 5 mol % to produce **3a** with an identical yield (Table 1, entry 3). However, when the quantity of alcohol **2a** was reduced to 1.2 equiv, only traces of the coupling product **3a** were observed (Table 1, entry 4). The best conditions appeared to be the use of 2 equiv of the allylic alcohol, 5 mol % of $Pd(OAc)_2$, and 1.1 equiv of AgOAc (Table 1, entry 3).

Benzyl-, *p*-methoxybenzyl-, and *tert*-butyldiphenylsilyl ethers were tolerated as well as protected amines, as 1-iodo-1,3-dienes **1a**−**1d** were transformed to conjugated (*E*,*E*,*E*)-trienols **3a**−**3d** in good yields (54%−72%) (Table 2).

It is worth noting that the reaction of but-3-en-2-ol (**2a**) with 1-bromo-1,3-diene **8** under the previously developed conditions [2 equiv of **2a**, 5 mol % of $Pd(OAc)_2$, and 1.1 equiv of AgOAc in DMF at 45 °C] did not lead to triene **3b** and that 1-bromo-1,3-diene **8** was recovered (Scheme 4) indicating that the conditions used were chemoselective.

---

[10] Vogel, P.; Turks, M.; Bouchez, L.; Marković, D.; Varela-Álvarez, A.; Sordo, J. Á. *Acc. Chem. Res.* **2007**, *40*, 931–942.

[11] (a) Leblanc, Y.; Fitzsimmons, B. J.; Zamboni, R.; Rokach, J. *J. Org. Chem.* **1988**, *53*, 265–267. (b) Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755–3762. (c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2004**, *6*, 3469–3472.

[12] For selected examples, see: Stille coupling: (a) Crombie, L.; Horsham, M. A.; Jarrett, S. R. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1511–1524. (b) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem.—Eur. J.* **1995**, *1*, 318–333. (c) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407–5408. Sonogashira coupling: (d) Avignon-Tropis, M.; Berjeaud, J. M.; Pougny, J. R.; Fréchard-Ortuno, I.; Guillerm, D.; Linstrumelle, G. *J. Org. Chem.* **1992**, *57*, 651–654. Suzuki coupling: (e) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435–2454. (f) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318. (g) Fuwa, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 584–587. Hiyama coupling: (h) Denmark, S. E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127*, 8971–8973.

[13] Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2011**, *47*, 1333–1335.

[14] Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2010**, *46*, 7229–7231.

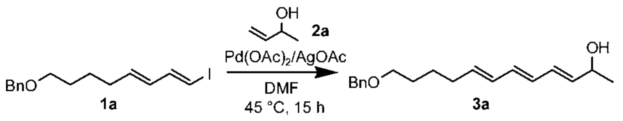
[15] (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1991**, 324–325. (b) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133–1136.

[16] Huang, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 3675–3678.

[17] (a) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3925–3928. (b) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645–7648.

[18] (a) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3929–3932. (b) Knowles, J. P.; O'Connor, V. E.; Whiting, A. *Org. Biomol. Chem.* **2011**, *9*, 1876–1886.

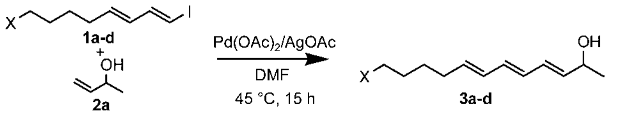
**Table 1.** Optimization of Allylic Alcohol and Palladium Quantity[a]



| entry | **2a** (equiv) | $Pd(OAc)_2$ (mol %) | yield in **3a** (%)[b] |
|---|---|---|---|
| 1 | 3 | 10 | 72 |
| 2 | 2 | 10 | 69 |
| 3 | 2 | 5 | 69 |
| 4 | 1.2 | 5 | traces |

[a] All experiments were performed with 1.1 equiv of AgOAc. [b] Isolated yield.

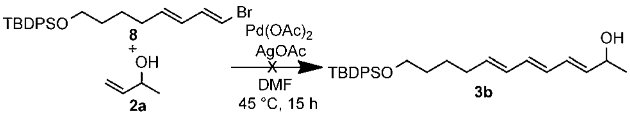
**Table 2.** Protecting Group Tolerance[a]



| entry | 1 | X | 3 | yield in **3**[b] |
|---|---|---|---|---|
| 1 | **1a** | BnO | **3a** | 69% |
| 2 | **1b** | TBDPSO | **3b** | 54% |
| 3 | **1c** | PMBO | **3c** | 59% |
| 4 | **1d** | Boc(Ts)N | **3d** | 58% |

[a] All reaction were performed with 2 equiv of **2a**, 5 mol % of $Pd(OAc)_2$, and 1.1 equiv of AgOAc. [b] Isolated yield.

**Scheme 4**



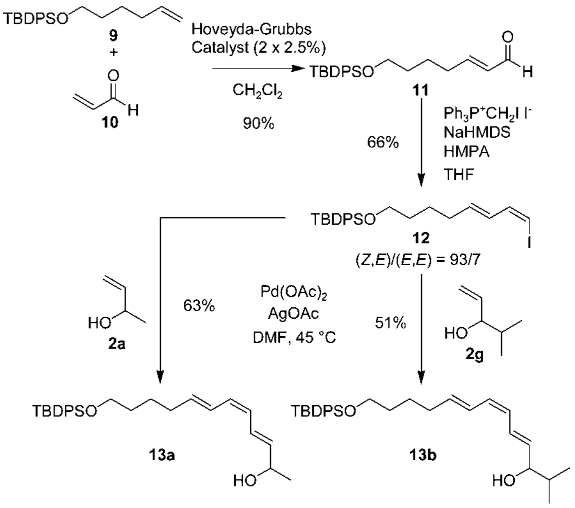
A diversity of allylic alcohols of type **2** were involved in the coupling reaction with 1-iodo-1,3-dienes **1a** and **1b**. The results are reported in Table 3. Prop-2-en-1-ol (**2b**) (Table 3, entry 1) as well as secondary alcohols such as **2c**–**2d** (Table 3, entries 2 and 3), 1-phenylprop-2-en-1-ol **2e** (Table 3, entry 4), sterically hindered alcohols such as **2f**–**2h** (Table 3, entries 5 to 7), and tertiary alcohol **2i** (Table 3, entry 8) led to the corresponding trienols **3e**–**3l** in good yields. When monoprotected diol **2j** was involved in the coupling reaction with **1b**, trienol **3m** was formed in 46% yield (Table 3, entry 9). In addition, optically active trienols can be synthesized using optically active allylic alcohols. Thus, **3n** was formed in 65% yield with an enantiomeric excess superior to 92%[19] when (*S*)-**2d** (ee = 99%) was involved in the coupling reaction with **1a** (Table 3, entry 10).

With alcohol **2k**, in which a disubstituted double bond is present, two trienols **3o** and **3o′** were formed, in a 55/45 ratio in favor of the conjugated triene **3o**, with a moderate yield of 38% (Table 3, entry 11). It is worth noting that all the coupling products **3e**–**3o** were obtained as pure (*E*,*E*,*E*)-trienols.

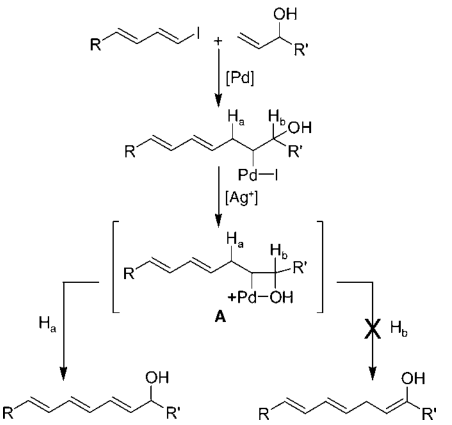
In addition, the coupling reaction between 1-iodo-1,3-dienes and allylic alcohols is stereoselective. Thus, when 1-iodo-1,3-diene **12** [(*Z*,*E*)/(*E*,*E*) = 93/7], prepared in two steps from olefin **9** (Scheme 5), was reacted with allylic alcohols **2a** and **2g**, under the previous conditions, **13a** and **13b** were obtained in 66% and 51% yield respectively in an (*E*,*Z*,*E*)/(*E*,*E*,*E*) ratio of 90/10 (Scheme 5).

In considering the retention of configuration in trienol **3n**, we can suppose that the $H_b$ $\beta$-hydrogen elimination is

**Scheme 5.** Coupling with (*E*,*Z*)-Trienols



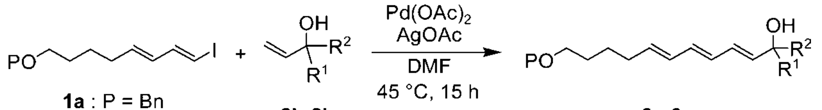
**Scheme 6.** Proposed Mechanism



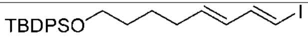
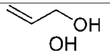
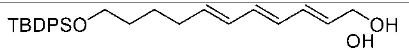
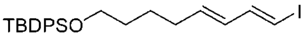
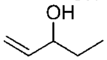
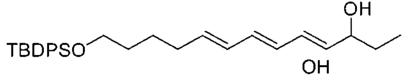
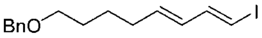
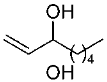
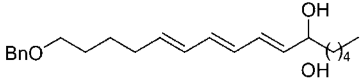
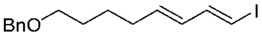
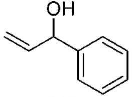
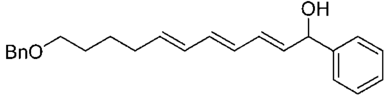
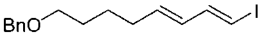
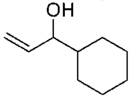
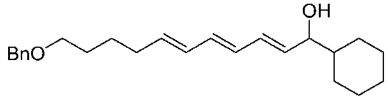
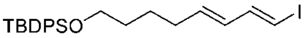
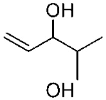
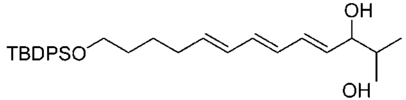
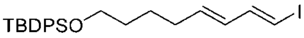
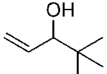
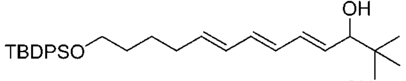
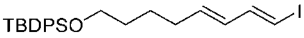
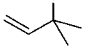
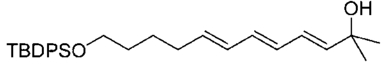
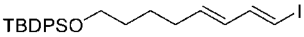
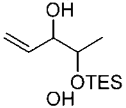
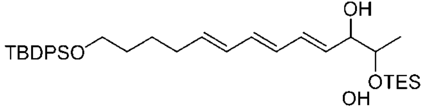
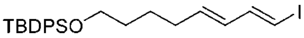
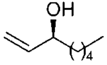
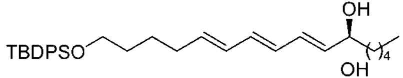
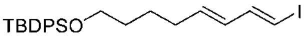
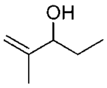
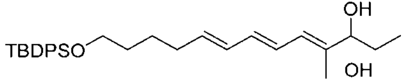
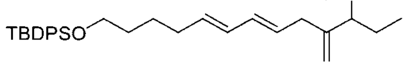
---

(19) Enantiomeric excess was determined by $^1H$ NMR spectroscopy by addition of $Eu(hfc)_3$ to the NMR tube. No traces of the other enantiomer were observed.

**Table 3.** Comparison of Different Allylic Alcohols



**1a** : P = Bn
**1b** : P = TBDPS
**2b-2k**
**3e-3o**

| entry | 1 | | 2 | | 3 | | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **1b** |  | **2b** |  | **3e** | 37% |
| 2 |  | **1b** |  | **2c** |  | **3f** | 62% |
| 3 |  | **1a** |  | **2d** |  | **3g** | 64% |
| 4 |  | **1a** |  | **2e** |  | **3h** | 51% |
| 5 |  | **1a** |  | **2f** |  | **3i** | 61% |
| 6 |  | **1b** |  | **2g** |  | **3j** | 49% |
| 7 |  | **1b** |  | **2h** |  | **3k** | 53% |
| 8 |  | **1b** |  | **2i** |  | **3l** | 43% |
| 9 |  | **1b** |  | **2j** |  | **3m** | 46% |
| 10 |  | **1b** |  | (*S*)-**2d** |  | **3n** | 65%<br>(ee > 92%) |
| 11 |  | **1b** |  | **2k** | <br> | **3o**<br>**3o'** | 38%<br>**3o**/**3o'** = 55/45 |

not proceeding. Intermediate **A** is probably formed in which a coordination of palladium with the hydroxy group is occurring, preventing the $\beta$-hydrogen elimination of $H_b$, as a *syn*-relationship between Pd and H is required for palladium hydride elimination. In contrast, the palladium hydride elimination can occur with $H_a$ (Scheme 6).

In conclusion, we have demonstrated that (*E*,*E*,*E*)-trienols and (*E*,*Z*,*E*)-trienols can be obtained from allylic alcohols in good yields by using the Pd(OAc)$_2$/AgOAc system.

**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.

---

The authors declare no competing financial interest.