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

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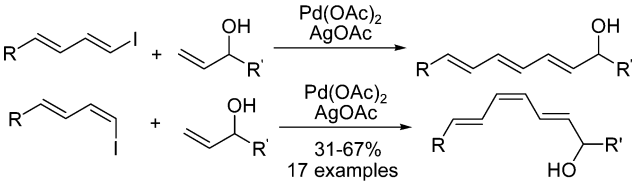
ABSTRACT



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 π-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

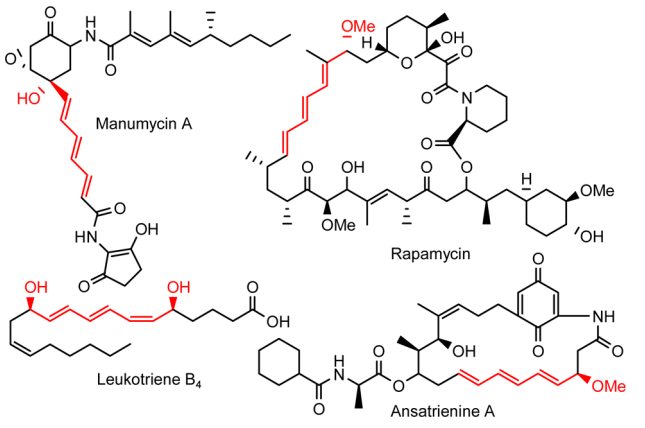


Figure 1. Examples of biologically active natural products containing conjugated trienol moieties.

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

(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.

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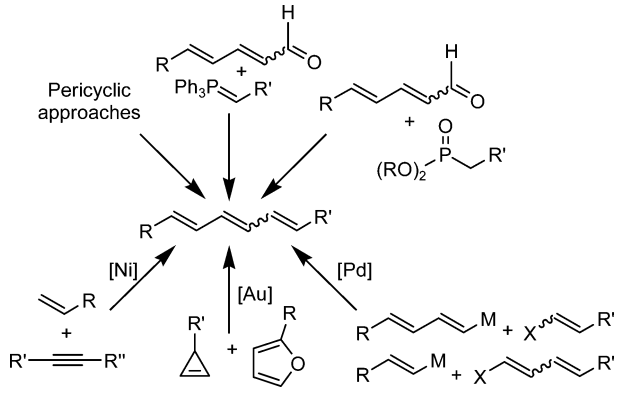
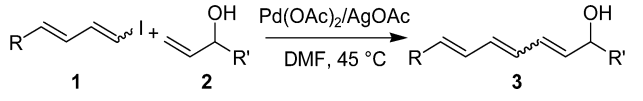
enough to be functional group tolerant. Pericyclic or biomimetic approaches to trienes can be used as well.[10,11] In addition, syntheses of π-conjugated systems through C−C bond formation, catalyzed by a transition metal such as palladium,[12] gold,[13] or nickel,[14] have been realized (Scheme 1).

Scheme 1. Synthesis of Trienic Units



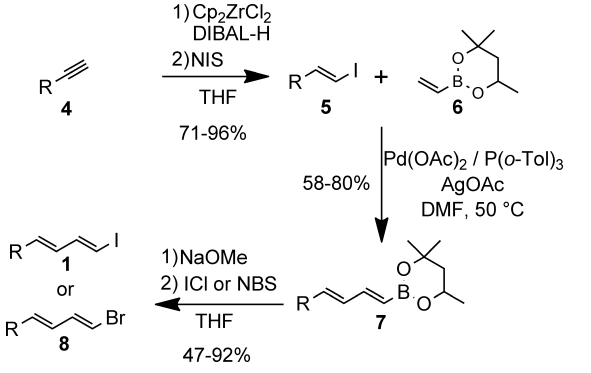
Herein, we would like to report a chemo-, regio-, and stereoselective method for the construction of conjugated trienols from 1-iodo-1,3-dienes **1** and nonprotected allylic alcohols **2** under Heck conditions[15] (Scheme 2).

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*-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.

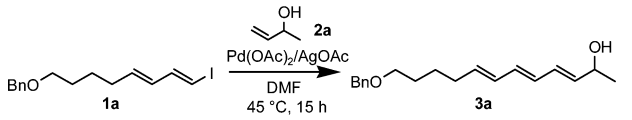
(15) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1991**, 324–325. (b) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133–1136.

(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.

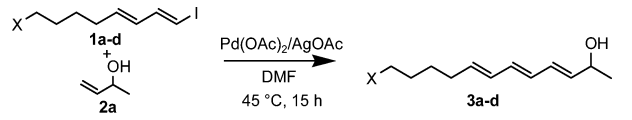
Table 1. Optimization of Allylic Alcohol and Palladium Quantity[a]



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.

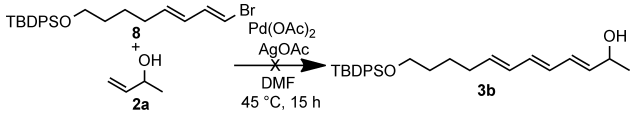
Table 2. Protecting Group Tolerance[a]



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



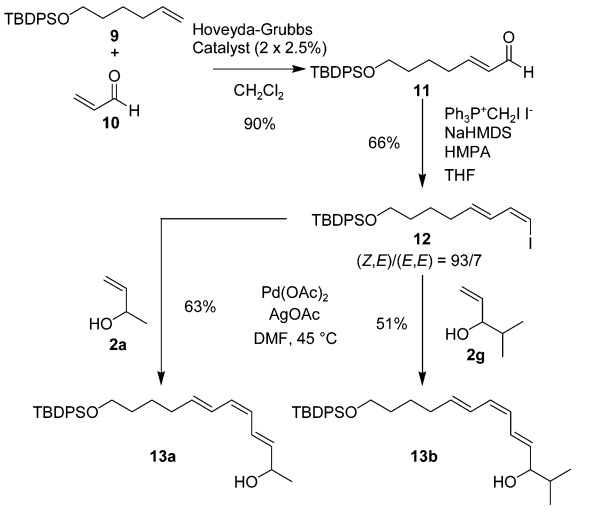
A diversity of allylic alcohols of type **2** were involved in the coupling reaction with 1-iodo-1,3-dienes **1a** and **1b**. The results are reported in Table 3. Prop-2-en-1-ol (**2b**) (Table 3, entry 1) as well as secondary alcohols such as **2c**–**2d** (Table 3, entries 2 and 3), 1-phenylprop-2-en-1-ol **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.

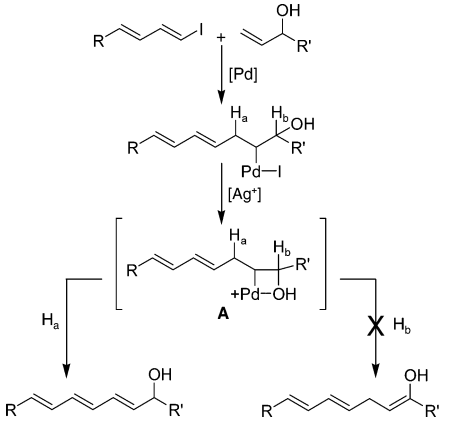
In addition, the coupling reaction between 1-iodo-1,3-dienes and allylic alcohols is stereoselective. Thus, when 1-iodo-1,3-diene **12** [(*Z*,*E*)/(*E*,*E*) = 93/7], prepared in two steps from olefin **9** (Scheme 5), was reacted with allylic alcohols **2a** and **2g**, under the previous conditions, **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 β-hydrogen elimination is

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

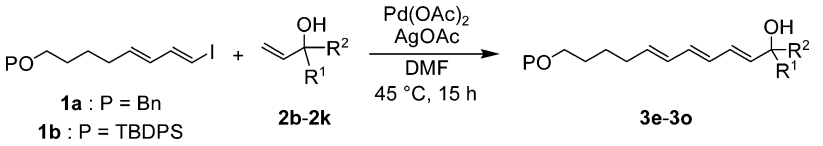


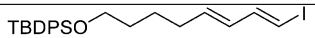
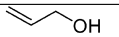
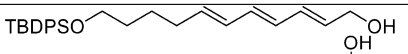
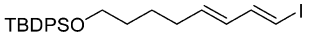
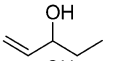
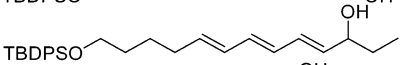
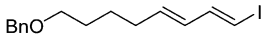
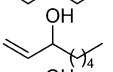
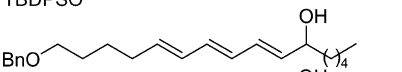
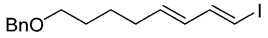
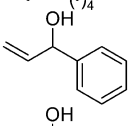
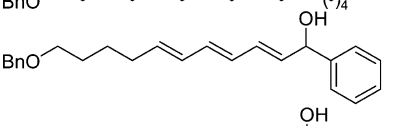
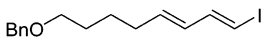
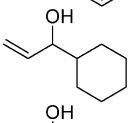
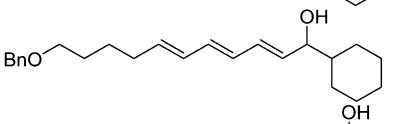
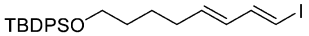
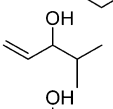
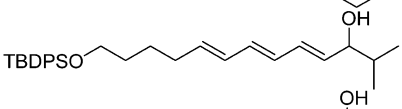
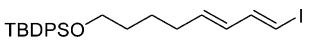
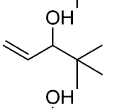
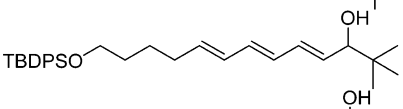
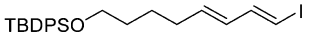
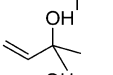
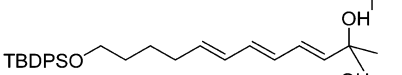
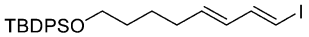
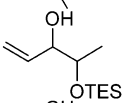
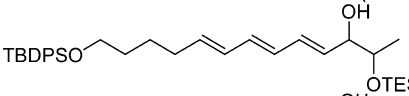
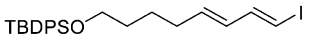
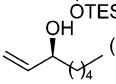
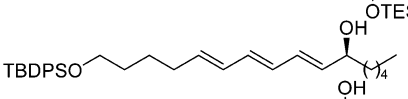
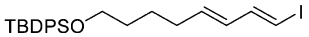
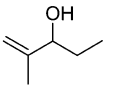
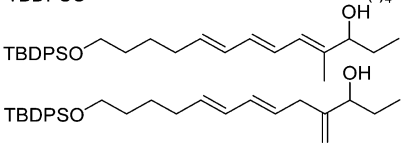
Scheme 6. Proposed Mechanism



(19) Enantiomeric excess was determined by ^{1}H 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



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% (ee > 92%)
11	 **1b**	 **2k**	 **3o** **3o'**	38% **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 β-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 ^1H 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.