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Stereoselective transformation of easily available (2*Z*,4*E*)-2,4-alkadien-1-ols into (*E*)-3-alkene-1,2,5-triol derivatives

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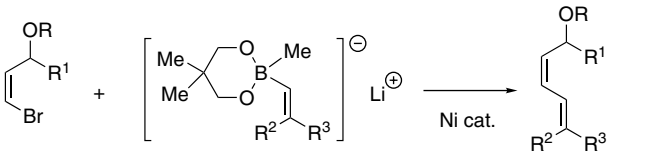
Abstract—Synthesis of 3-alkenyl-1,2,5-triol derivatives, potentially useful intermediates in organic synthesis, is established, which constitutes stereoselective epoxidation of the hitherto hardly accessible dienyl alcohols of the *cis*,*trans* stereochemistry followed by Pd-catalyzed reaction with AcOH.

Previously, we reported the synthesis of dienyl alcohol derivatives **4** by a coupling reaction shown in Scheme 1 (**1**+**3**→**4**).[1] The high reactivity of lithium borates **3** in combination with a nickel catalyst compensates the poor reactivity of the (*Z*)-1-halo alkenes **1**, which stems from the congestion by the OR group at the proximal position.[2] In addition to the high efficiency, ready availability of **1** in optically active form by several methods[3] is another synthetic advantage of the reaction. We then applied this reaction to the synthesis of biologically active compounds, such as dihydro-leukotrienes B_4[4] and korormicin,[5] both of which possess the dienyl alcohol unit in its core. As the coupling reaction has been proved to be highly productive through these applications, we turned our attention to the transformation of these dienyl alcohol products to highly functionalized compounds that are useful in organic synthesis.

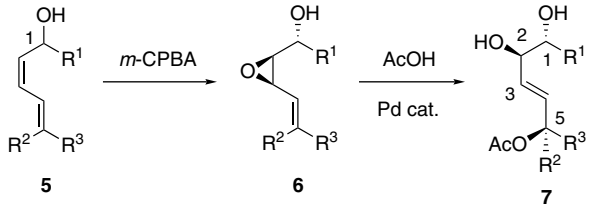


1, R = TBS, R^1 = alkyl
2, R = H, R^1 = alkyl

(*E*)-**3**, R^2 = H, R^3 = alkyl
(*Z*)-**3**, R^2 = alkyl, R^3 = H

4, R = TBS
5, R = H

Scheme 1.



5 **6** **7**

for **5**–**7**
a, $R^1 = R^3 = C_5H_{11}$, R^2 = H;
b, $R^1 = R^2 = C_5H_{11}$, R^3 = H;
c–**e**, see Table 1.

Scheme 2. Key transformation.

Delineated in Scheme 2 is one such transformation to afford triol derivatives **7**. The stereochemistry newly created by this transformation was predicted as depicted in the structure on the basis of the reactions in the literature: the first step is a chelation-controlled epoxidation of **5** with *m*-CPBA,[6] and the second step is a stereocontrolled formation of the π-allyl palladium intermediate from epoxide **6**, followed by the reaction with acetate anion.[7] Consequently, we were much interested in the efficiency of these steps. The triol derivatives of the type **7** as such would be intermediates for the synthesis of trioxillin A_3,[8] decarestrictine D,[9,10] and acetogenins,[11] while oxidation(s) of **7** at the olefin moiety would furnish carbohydrates.

Keywords: Palladium catalyst; Lithium borate; Coupling; Epoxidation; Triol derivative.
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Table 1. Results of the transformations

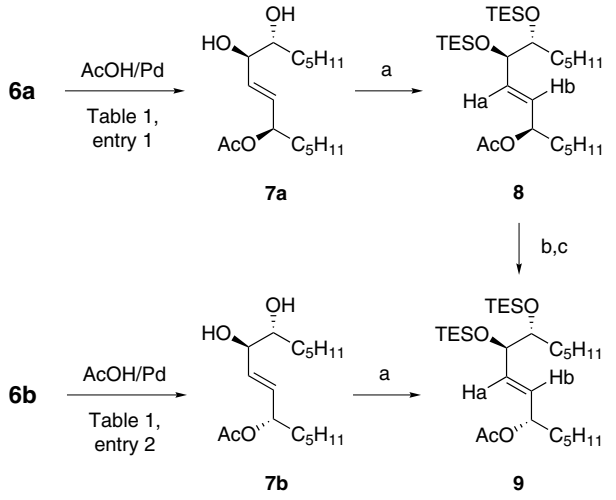
Entry	Substituents for **5**–**7**			Compound number, yield[a], and stereoselectivity		
	R^1	R^2	R^3	Diene **5**	Epoxide **6**	Acetate **7**
1	C_5H_{11}	H	C_5H_{11}	**5a**, 72%, 95% ss[b]	**6a**, 77%, >95% ds[c]	**7a**, 71%, 93% ds[d]
2	C_5H_{11}	C_5H_{11}	H	**5b**, 95%, 92% ss	**6b**, 6%, >95% ds	**7b**, 88%, 93% ds
3	*c*-C_6H_{11}	H	C_5H_{11}	**5c**, 63%, 93% ss	**6c**, 63%, >95% ds	**7c**, 77%, 95% ds
4	*t*-Bu	H	C_5H_{11}	**5d**, 83%, 90% ss	**6d**, 62%, 80% ds	**7d**, 49%, 91% ds
5	C_5H_{11}	H	$CH(n\text{-}Bu)_2$	**5e**, 71%, 95% ss	**6e**, 82%, >95% ds	**7e**, 52%, 93% ds

[a] Isolated yields.
[b] Stereoselectivity of *cis*,*trans* diene **5** over *trans*,*trans* isomer.
[c] Diastereoselectivity at the epoxy moiety.
[d] Diastereoselectivity at C(5).

In the original coupling reaction (**1**+**3**→**4**),[1] (*Z*)-1-bromoalkenes with a *protected* hydroxyl group at the γ position were used as substrates for the coupling, while the presence of the *free* hydroxyl group is crucial for the stereoselective epoxidation. Thus, the coupling reaction of unprotected alcohol **2** with borate **3** was investigated again. The reaction of racemic alcohol **2a** ($R^1 = C_5H_{11}$) with 1.5 equiv of borate **3a** ($R^2 = H$, $R^3 = C_5H_{11}$) under the original conditions ($NiCl_2(PPh_3)_2$, THF/Et_2O (5:1), rt, overnight) produced *cis*,*trans* dienyl alcohol **5a** ($R^1 = R^3 = C_5H_{11}$, $R^2 = H$) only in 49% yield. To improve the efficiency, ligands for the nickel catalyst and solvents were studied without changing the molar ratio of **3a**:**2a**. When $NiCl_2$(dppf) was employed as a catalyst in an Et_2O-rich solvent (Et_2O/THF, 5:1), the yield of **5a** was improved to 72% with 95% stereoselectivity (ss) over the *trans*,*trans* isomer (Table 1, entry 1). Interestingly, the hydroxyl group in alcohol **2a** did not quench the borate **3a** under the conditions.[12] In a similar way, *cis*,*cis* isomer **5b** and other *cis*,*trans* dienyl alcohols **5c**–**e** possessing various alkyl groups as R^1, R^2, or R^3 were synthesized efficiently under the modified conditions (Table 1, entries 2–5). Among the entries, noteworthy is the success with the highly congested *t*-Bu substrate **2** ($R^1 = t$-Bu). The minor *trans*,*trans* isomers produced in the entries 1–5 were separated by chromatography on silica gel.

Epoxidation of **5a** was carried out with *m*-CPBA under the literature conditions[6] ($NaHCO_3$, CH_2Cl_2, 0 °C) to furnish **6a** in 77% isolated yield with >95% diastereoselectivity (ds) (Table 1, entry 1). *cis*,*cis* Dienyl alcohol **5b** and other *cis*,*trans* dienyl alcohols **5c**–**e** were also converted into the corresponding epoxides **6b** and **6c**–**e** in good yields, respectively. The stereoselectivity of **6b**, **6c**, and **6e** was >95%, and that of **6d** ($R^1 = t$-Bu) was 80%, respectively, by ^{1}H NMR spectroscopy. The stereochemistry of epoxides **6a** and **6b** was determined later as depicted in Scheme 2, while the stereochemistry of other epoxides **6c**–**e** is a speculation on the basis of that observed for **6a** and **6b**.

Palladium-catalyzed reaction of epoxide **6a** with AcOH in the presence of $Pd(PPh_3)_4$ (10 mol %) at 0 °C for 30 min provided acetate **7a** in 71% yield with 93% ds at C(5) (Table 1, entry 1). The *trans* stereochemistry was assigned to the olefin by the coupling constant ($J_{Ha\text{-}Hb} = 16$ Hz) of the bis-TES ether **8** (TES = $SiEt_3$) (Scheme 3), while the ds was calculated by using the

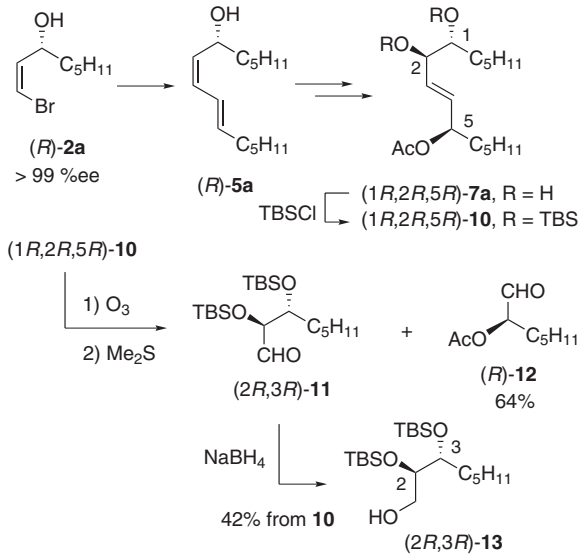


Scheme 3. Products **7a** and **7b** were converted into compounds **8** and **9** for calculation of the diastereoselectivity and for determination of the olefin geometry. Reagents and conditions: (a) TESCl, imidazole, 90% for **8**, 82% for **9**; (b) K_2CO_3, MeOH, 72%; (c) AcOH, DEAD, PPh_3, THF, 60%.

height of the ^{13}C signals for **8** and its diastereomer **9** at 74.9 and 75.2 ppm, respectively, since the signals in their ^{1}H NMR spectra were superimposed on each other. The latter isomer was synthesized from **8** by Mitsunobu inversion.[13]

To assign the relative stereochemistry of **7a** unambiguously, the homochiral alcohol (*R*)-**2a** (>99% ee)[3a] was subjected to the above transformation (Scheme 4). The product **7a** was then converted to bis-TBS ether **10**, which upon ozonolysis afforded two aldehydes **11** and **12**. The former aldehyde after separation was reduced to alcohol **13**, which was identical with that of the known *syn* isomer by the ^{1}H NMR spectroscopy.[14] The observed specific rotations of **12** ($[\alpha]_D^{26}$ +31 (*c* 0.10, $CHCl_3$)) and **13** ($[\alpha]_D^{26}$ +33 (*c* 0.48, $CHCl_3$)) were opposite to those reported for (*S*)-**12** ($[\alpha]_D^{20}$ −37.8 (*c* 0.5, $CHCl_3$))[15] and (2*S*,3*S*)-**13** ($[\alpha]_D^{25}$ −33.2 (*c* 1.0, $CHCl_3$)),[14] respectively, thus allowing assignment of the relative configuration of **7a** to be 1*R**,2*R**,5*R**, which is depicted in the structure.

Palladium-catalyzed reaction of **6b** with AcOH proceeded as well under the reaction conditions applied to **6a**, thus producing the C(5) diastereomer **7b** in 88% yield

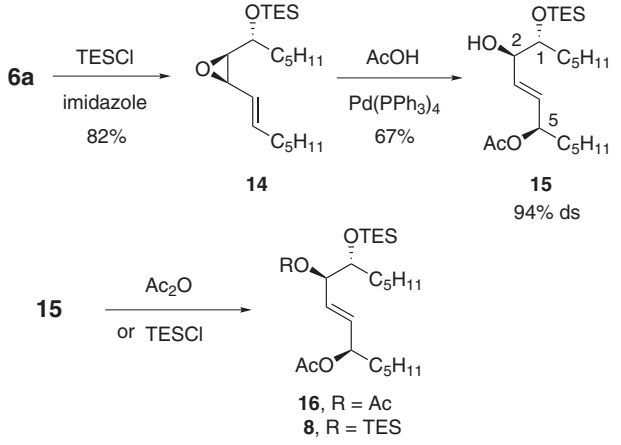


Scheme 4. Transformation for determination of the stereochemistry of **7a**.

with 93% ds (Scheme 3; Table 1, entry 2). The product **7b** was converted to silyl ether **9** to determine the *trans* olefin geometry and the relative stereochemsitry as depicted by NMR spectroscopy. Thus, the coupling constant between olefinic protons was calculated to be 16 Hz, while the carbon signal at the 75 ppm area was identical with **9** derived from **8**.

Palladium-catalyzed transformation was also examined with epoxides **6c–e** in order to establish the generality of the reaction. Epoxides **6c** and **6e** with a *sec*-alkyl group as R^1 or R^2 produced **7c** and **7e** in moderate to good yields with similarly good efficiency (Table 1, entries 3 and 5), while **6d** with the *t*-Bu group afforded **7d** in moderate yield with a slightly less stereoselectivity than that of **5a** (entry 4).

In order to discriminate the three hydroxyl groups in **7**, the epoxy alcohol **6a** was converted into TES ether **14**, which upon palladium-catalyzed reaction with AcOH furnished **15** in 67% yield with 94% ds (Scheme 5). No migration of the TES group onto the C(2)-oxygen was confirmed by ^{1}H NMR spectroscopy and also by the sole production of acetate **16** from **15** in 93% yield.[16] The differentiated hydroxyl groups will provide wider opportunity for further elaboration of the product. It should be emphasized that synthesis of *trans* 3-alkenyl-1,2,5-triols with different hydroxyl protections such as **15** would be hardly accomplished by using the well-known Sharpless asymmetric dihydroxylation of the corresponding diene with the AD-mix reagent.[17]



Scheme 5. Synthesis of 1,2,5-triol derivative **15**, in which the three hydroxyl groups are differentiated.

In summary, we have presented an efficient transformation of dienyl alcohols **5** to *trans* 3-alkenyl-1,2,5-triol derivatives **7**. The core structure of **7** is seen in some of the biologically important natural products. Moreover, the transformation is successfully applied to the synthesis of *trans* 3-alkenyl-1,2,5-triol derivatives, in which the three hydroxyl groups are discriminated for further transformation.

Acknowledgments

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