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SYNTHESIS OF THE 1,2-ANTI TYPE OF 3*E*-ALKENE-1,2,5-TRIOL DERIVATIVES[†]

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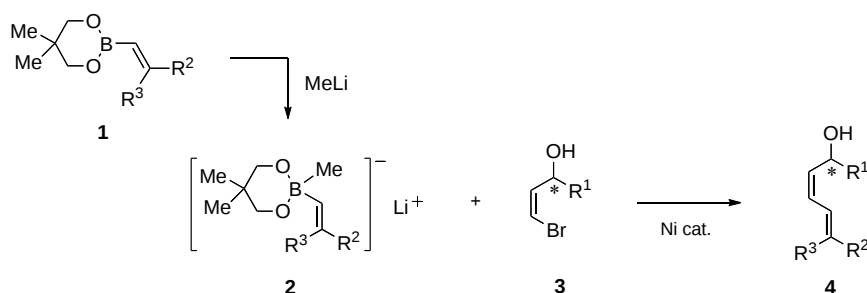
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Abstract – We invented an efficient method to obtain 3*E*-alkene-1,2,5-triol derivatives with 1,2-*anti* stereochemistry from the 2*Z*,4*E*-alkadienyl alcohol derivatives, which were synthesized by using nickel-catalyzed coupling between lithium 1*E*-alkenyl borates and 1-halo-1*Z*-alken-3-ols. The method involves (1) asymmetric dihydroxylation at the *E* olefin moiety of the dienyl alcohol derivatives followed by formation of a cyclic carbonates; (2) palladium-catalyzed reaction with AcOH in the presence of Et₃N. The method was applied successfully to the synthesis of the C6–C20 part of trioxilin A₃.

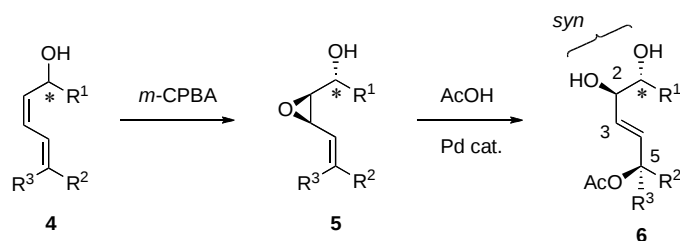
Previously, we reported a nickel-catalyzed coupling reaction of alkenyl lithium borates **2** with less reactive 1-halo-1*Z*-alken-3-ols **3** and their silyl ethers (Scheme 1) to produce 2*Z*,4*E*-alkadien-1-ols **4** and their silyl ethers effectively.¹ The high reactivity promoted by a nickel catalyst compensates for the low reactivity of alkenyl halides **3**. Furthermore, the almost neutral character of the borates **2** is compatible with the hydroxyl group,^{2,3} while the halides **3** are available easily in enantiomerically enriched forms.⁴ Later, the reaction was applied for the synthesis of 10,11-dihydroleukotriene B₄ and korormicin, both of which possess the structural unit of **4**.^{5,6} Since then, we reported functionalization of **4** to 3*E*-alkene-1,2,5-triols **6** (Scheme 2), and the method was applied to the stereoselective synthesis of decarestrictine D (Figure 1).⁷ The *syn* diol unit in it was stereoselectively introduced through epoxidation of alcohol **4** with *m*-CPBA. However, the method is hardly extended to the 1,2-*anti* isomers, which is seen in several biologically active compounds such as those delineated in Figure 1. To overcome this

[†] This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

limitation, we envisioned a sequence consisting of asymmetric dihydroxylation⁸ (AD) with AD-mix- β , cyclic carbonate formation, and palladium-catalyzed reaction of the resultant carbonates with AcOH. This transformation is illustrated in Scheme 3 with the MOM ethers **7** with the *S* chirality to produce diol derivatives **9**. To realize the scheme, isomerization of the π -allylpalladium intermediate **11** to thermodynamically more stable **12** should precede the reaction with acetate anion, and the latter reaction from the B side should be stereoselective and regioselective. However, the electronic and steric effects on dictating the regiochemistry conflict each other, whereas extend of the effects was out of prediction.⁹ The same discussion would be applicable to the conversion of diastereomeric carbonates **13**, giving *anti* diol derivatives **14**. Herein, we present the results of this investigation and a preliminary study toward synthesis of trioxilin A₃.



Scheme 1. Nickel-catalyzed coupling between lithium alkenyl borates and 1-bromo-1*Z*-alken-3-ols



Scheme 2. Transformation to the 1,2-*syn*-3*E*-alkene-1,2,5-triols

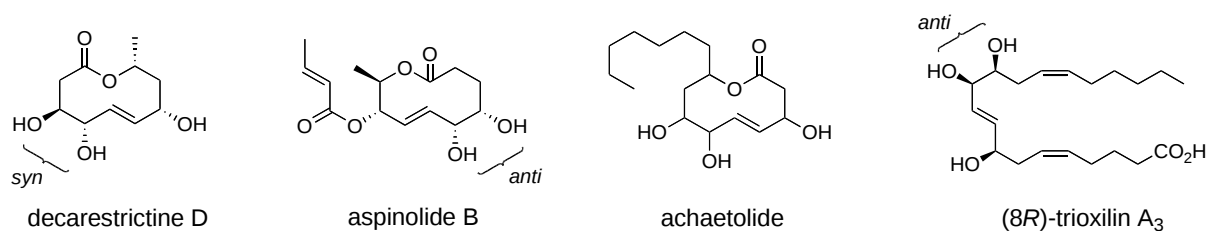
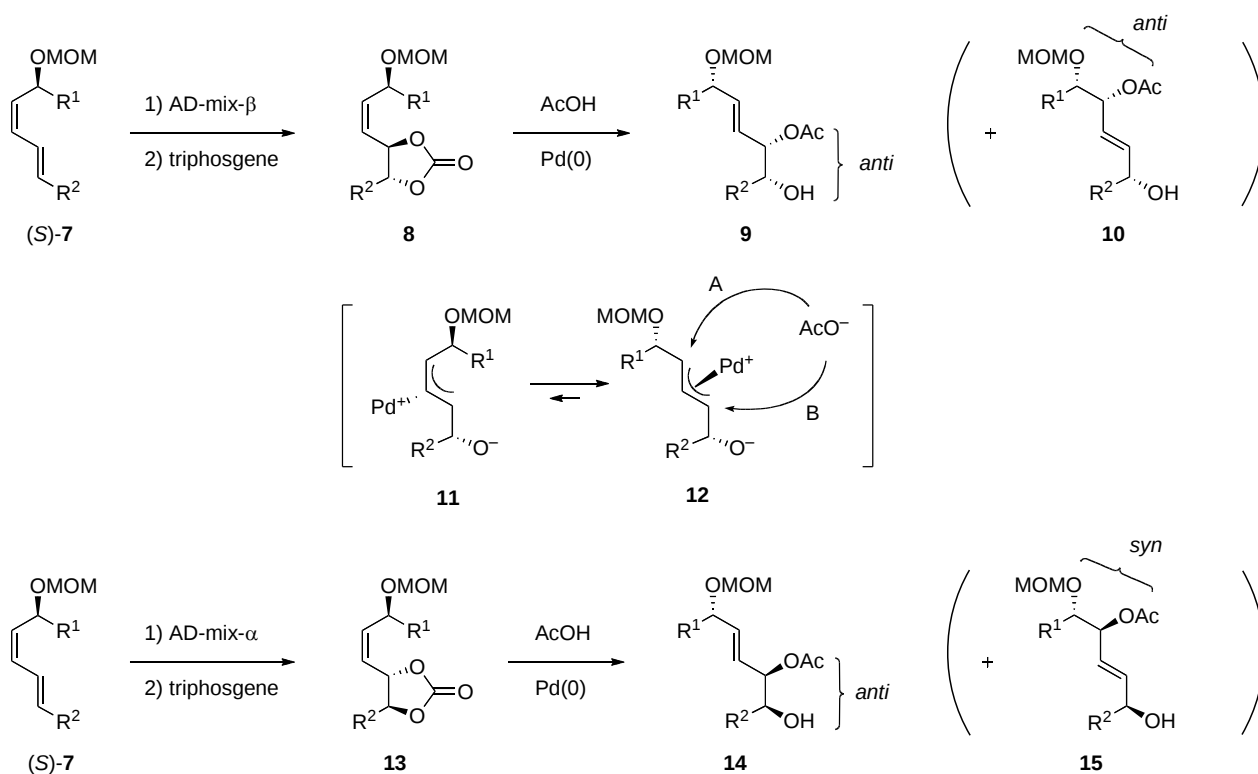


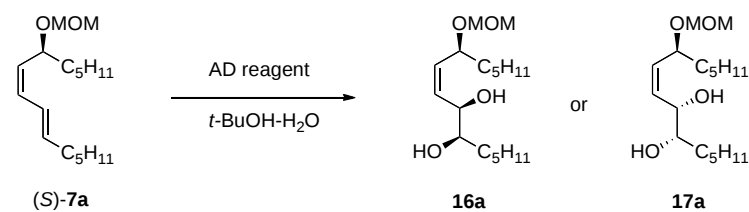
Figure 1. Biologically active compounds with a 3*E*-alkene-1,2,5-triol structure



Scheme 3. Strategy to the 1,2-*anti* type of 3*E*-alkene-1,2,5-triol derivatives **9** and **14**

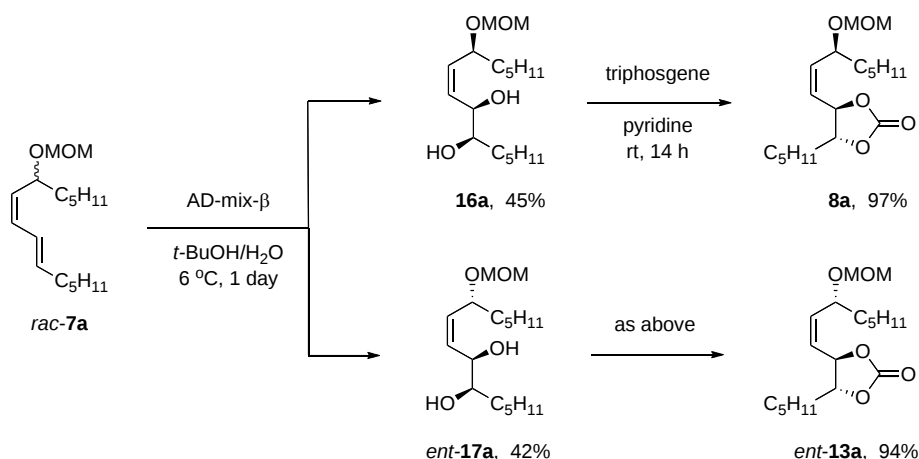
First, the MOM ether (*S*)-**7a** ($R^1 = R^2 = \text{C}_5\text{H}_{11}$) was prepared by the coupling reaction between borate **2** ($R^2 = \text{C}_5\text{H}_{11}$, $R^3 = \text{H}$) and the enantiomerically enriched alcohol **3** ($R^1 = \text{C}_5\text{H}_{11}$) of >99% ee followed by protection with MOMCl and *i*-Pr₂NEt in 72% yield based on the alcohol. AD reaction of (*S*)-**7a** with AD-mix- β run at 0 °C produced, after one day, diol **16a** highly stereoselectively (Table 1, entry 1), whereas that with AD-mix- α took three days to afford **17a** with somewhat low stereoselectivity (entry 3). The latter result indicates a mismatched pair of the substrate and the α reagent. To save reaction time, the reaction was examined at 6 °C (run in a refrigerator) to complete reaction after 1 day, giving **17a** in good yield though the stereoselectivity dropped a little (entry 4). Similarly, AD reaction with the β reagent at 6 °C resulted in a little drop in stereoselectivity (entry 2), though the selectivity was still in high level.

To our surprise, R_f values of the diols **16a** and **17a** were sufficiently different each other ($\Delta R_f = 0.2$), suggesting easy separation by chromatography on silica gel. With the result in mind, racemic dienyl alcohol *rac*-**7a** was subjected to AD reaction with AD-mix- β and the resulting diastereomeric mixture of diols was separated, indeed easily, by chromatography to afford **16a** and *ent*-**17a** in 45% and 42% yields, respectively (Scheme 4). Each diol was converted to carbonate **8a** or *ent*-**13a** in good yields.

Table 1. Asymmetric dihydroxylation of (*S*)-**7a**


Entry	AD reagent	Temp., °C	Time, day	Isolated yield, % ^a	Ratio ^b of 16a : 17a
1	AD-mix-β	0	1	83	64 : 1
2	AD-mix-β	6	1	99	53 : 1
3	AD-mix-α	0	3	89	1 : 13
4	AD-mix-α	6	1	89	1 : 10

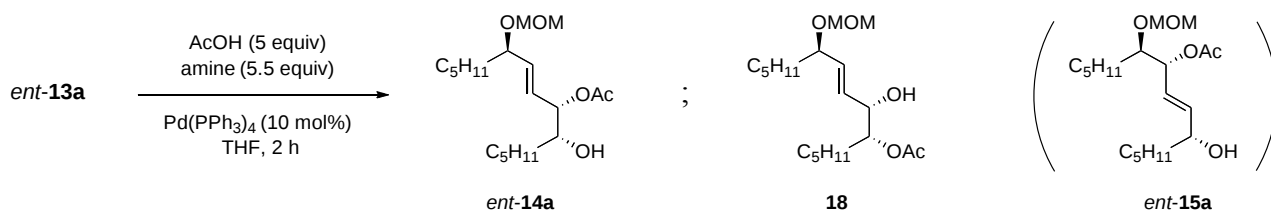
^a Of the major product. ^b Ratio was determined by ¹H NMR.

**Scheme 4.** AD reaction of racemic diene *rac*-**7a**

Palladium-catalyzed reaction of *ent*-**13a** with AcOH (5 equiv) was examined in THF at 40 °C for 2 h. However, the reaction was unsuccessful (Table 2, entry 1), while decomposition took place at higher temperatures, giving a mixture of unidentified products. In contrast, addition of Et₃N (5.5 equiv) was found to accelerate the reaction especially at 40 °C to afford *ent*-**14a** in high yield (entry 3). Other isomers that were expected in advance (such as *ent*-**15a**) were not detected by ¹H NMR spectroscopy. Although the reaction afforded *ent*-**14a**, migration of the Ac group to the next oxygen atom took place during chromatography on silica gel to afford a mixture of *ent*-**14a** and **18** in a 1 : 1 ratio (entry 3). We think that this migration is not a synthetic problem because removal of the Ac group from the mixture

affords the corresponding diol, which would be useful for further transformation. A successful resolution of this issue along this way is seen in the synthesis of C6–C20 part of trioxilin A₃ (vide infra). In addition, attempted reactions with other amines such as *i*-Pr₂NEt and pyridine resulted in incomplete reaction giving a mixture of *ent*-**14a** and the substrate.

Table 2. Palladium-catalyzed reaction of *ent*-**13a** with AcOH

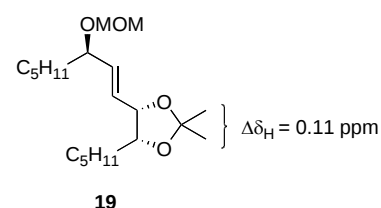


Entry	Temp., °C	Amine	Calculated yield ^a	Isolated yield and ratio
			of <i>ent</i> - 14a , %	of <i>ent</i> - 14a and 18 , %
1	40	–	1 ^b	nd ^c
2	rt	NEt ₃	22 ^b	nd ^c
3	40	NEt ₃	83	83 (1 : 1)
4	40	<i>i</i> -Pr ₂ NEt	48 ^b	nd ^c
5	40	pyridine	45 ^b	nd ^c

^a Yields were determined by ¹H NMR spectroscopy using pyridine as an internal standard.

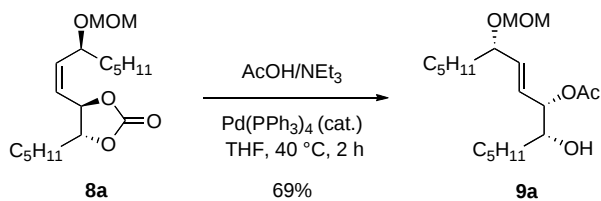
^b The substrate was recovered. ^c Not determined.

The *trans* stereochemistry of the newly created olefin of *ent*-**14a** (and **18**) was easily confirmed by the coupling constant of the olefinic protons of the derived diol (*J* = 16 Hz) (structure not shown), while the *anti* stereochemistry of the diol portion was determined by Δδ_H of 0.11 ppm

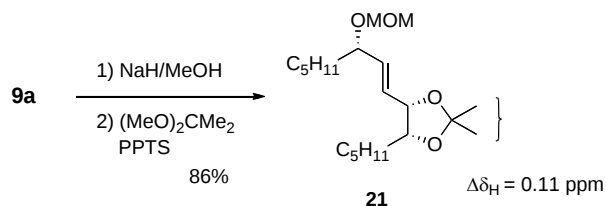


for the acetonide methyl groups of **19**, which is almost equal to the characteristic value for *anti* isomers (cf. Δδ for *syn* isomers is ca. 0.03 ppm).¹⁰

Next, the above reaction conditions, when applied to carbonate **8a**, produced **9a** regio- and stereoselectively in 69% yield (Scheme 5). The product was converted to acetonide **21**, which showed 0.11 ppm for Δδ_H of the acetonide methyl groups, indicating the *anti* stereochemistry as well¹⁰ (Scheme 6).

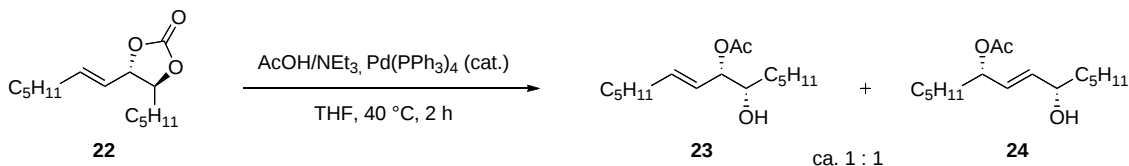


Scheme 5. Palladium-catalyzed reaction of carbonate **8a** with AcOH



Scheme 6. Conversion of **9a** to **21**

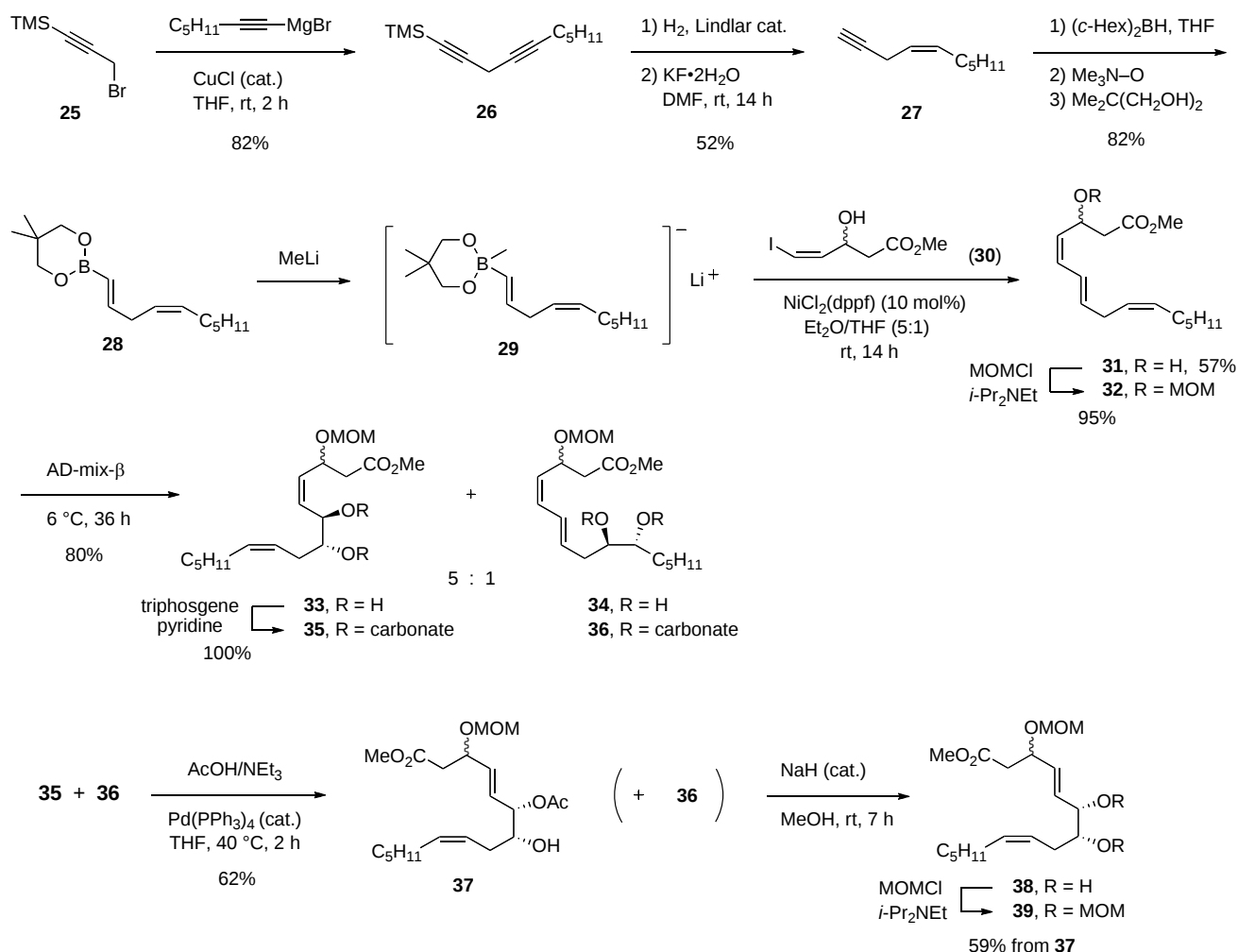
These results clearly indicate that the regiochemistry is controlled predominantly by the steric factor provided by the MOM-oxy group (see the introduction for difficulty of predicting the regioselectivity). The steric effect by the MOM-oxy group was supported by another reaction of carbonate **22** that lacks the group, producing a mixture of regioisomers **23** and **24** (Scheme 7).



Scheme 7. Palladium-catalyzed reaction of a simple carbonate with AcOH

With the above results in mind, we studied a synthesis of **39**, which corresponds to the C6–C20 portion of trioxilin A₃ (Figure 1), a lipoxygenase metabolite of arachidonic acid.¹¹ The elements for nickel-catalyzed coupling were borate **29** and vinyl iodide **30**. The iodide **30** was prepared by the method published,¹² while the boronate ester **28**, a precursor of borate **29**, was synthesized as delineated in Scheme 8. Copper-assisted coupling of propargyl bromide **25** with C₅H₁₁C≡CMgBr afforded **26** in 82% yield. Lindlar reduction of **26** was followed by removal of the TMS group with KF to furnish acetylene **27** in 52% yield. Hydroboration of **27** with (*c*-Hex)₂BH proceeded cleanly and the resulting borane was transformed to the boronate ester **28** by oxidation with Me₃NO followed by transesterification with Me₂C(CH₂OH)₂. For the nickel-catalyzed coupling reaction, the ester was converted to borate **29** with MeLi, and the resulting borate was subjected to coupling with vinyl iodide **30** at room temperature for 14 h to deliver dienyl alcohol **31** in 57% yield, which was converted to the MOM ether **32**. AD reaction with AD-mix-β produced a mixture of diol **33** and regioisomer **34** in a 5 : 1 ratio by ¹H NMR spectroscopy. Since the products were eluted without separation, the mixture was converted to the cyclic carbonates **35** and **36** quantitatively. The mixture was subjected to palladium-catalyzed reaction with AcOH under the same conditions established above to afford a mixture of **37** and the unreacted carbonate **36**. The products

were separated easily by chromatography on silica gel. Finally, the monoacetate **37** was converted to the MOM ether **39** in 59% yield.



Scheme 8. Preliminary study of the synthesis of trioxilin A₃

In summary, the 2*Z*,4*E*-alkadienyl alcohol derivatives **7**, synthesized by the nickel-catalyzed coupling between borates and alkenyl halides (Scheme 1), were converted to the 1,2-*anti* type of 3*E*-alkene-1,2,5-triol derivatives **9** and **14** (Scheme 3). The transformation was applied to the synthesis of the C6–C20 part of trioxilin A₃ successfully (Scheme 8).

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