HETEROCYCLES, Vol. 80, No. 2, 2010, pp. 811 - 818. © The Japan Institute of Heterocyclic Chemistry
Received, 30th July, 2009, Accepted, 18th September, 2009, Published online, 18th September, 2009
DOI: 10.3987/COM-09-S(S)89

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

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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 Et_3N. The method was applied successfully to the synthesis of the C6–C20 part of trioxilin A_3.

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 B_4 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

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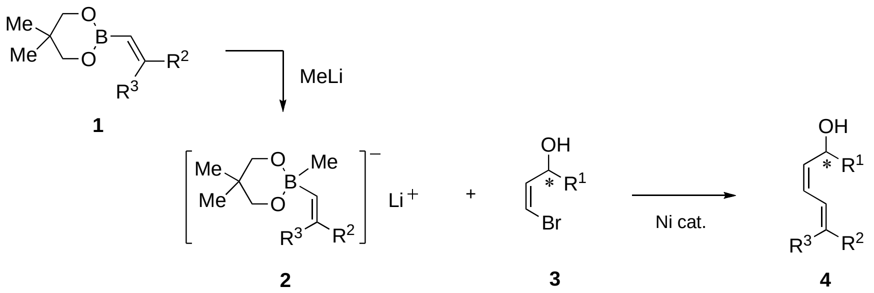
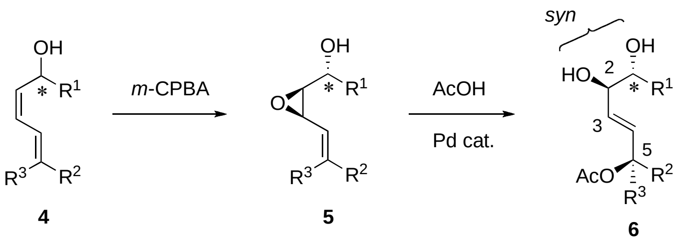
† This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

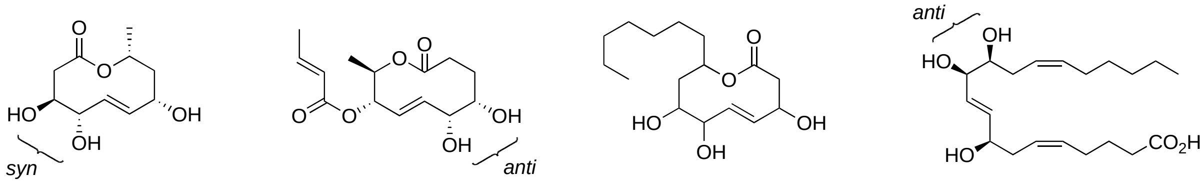
limitation, we envisioned a sequence consisting of asymmetric dihydroxylation[8] (AD) with AD-mix-β, cyclic carbonate formation, and palladium-catalyzed reaction of the resultant carbonates with AcOH. This transformation is illustrated in Scheme 3 with the MOM ethers **7** with the *S* chirality to produce 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 preliminarly study toward synthesis of trioxilin A_3.



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

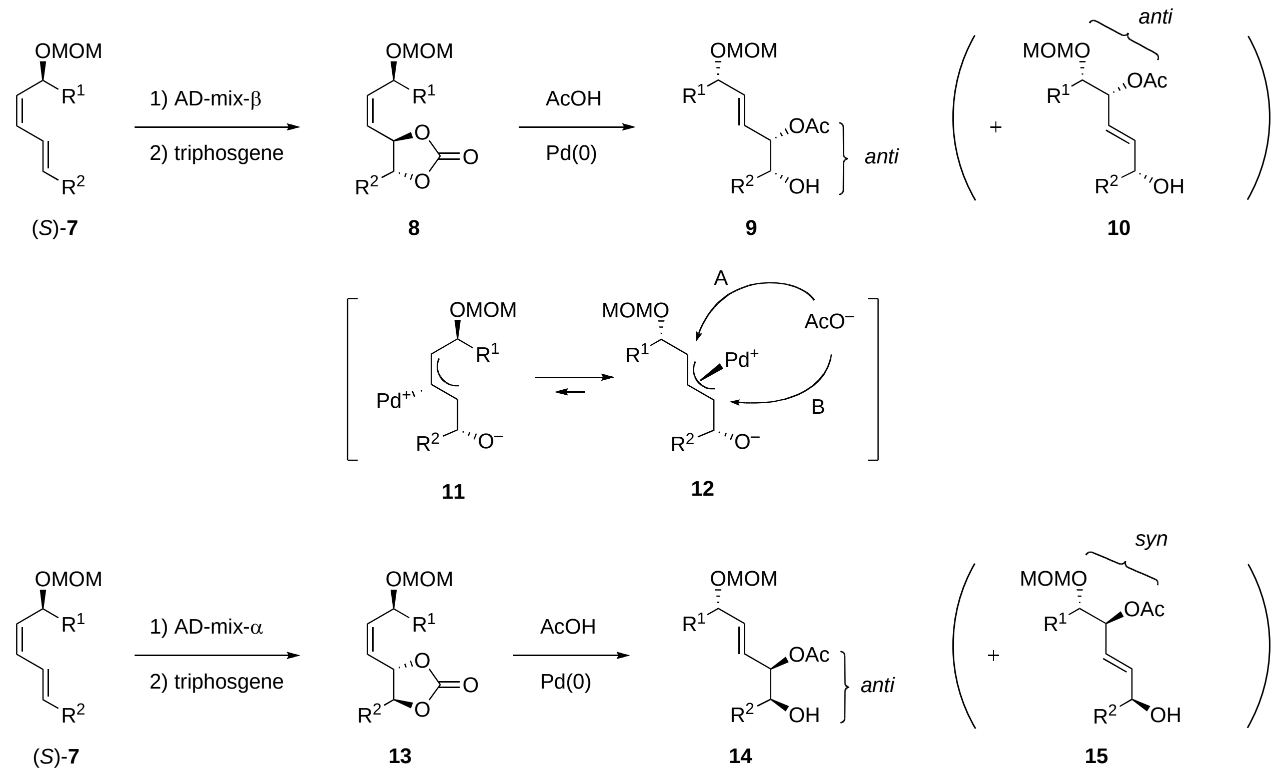


Scheme 2. Transformation to the 1,2-*syn*-3*E*-alkene-1,2,5-triols



decarestrictine D aspinolide B achaetolide (8*R*)-trioxilin A_3

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

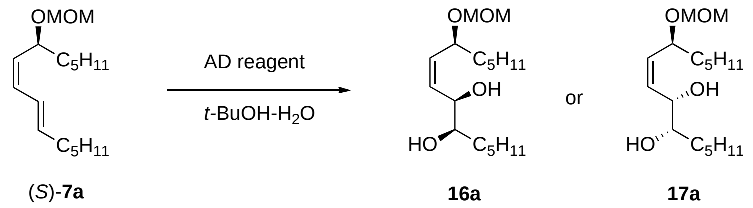


Scheme 3. Strategy to the 1,2-*anti* type of 3*E*-alkene-1,2,5-triol derivatives **9** and **14**

First, the MOM ether (*S*)-**7a** ($R^1 = R^2 = C_5H_{11}$) was prepared by the coupling reaction between borate **2** ($R^2 = C_5H_{11}$, $R^3 = H$) and the enantiomerically enriched alcohol **3** ($R^1 = C_5H_{11}$) of >99% ee followed by protection with MOMCl and *i*-Pr$_2$NEt 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.

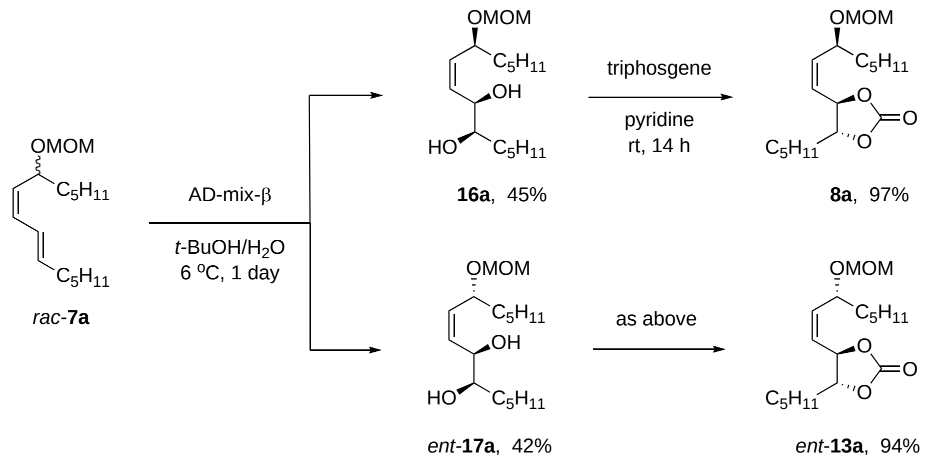
To our surprise, R_f values of the diols **16a** and **17a** were sufficiently different each other ($\Delta R_f = 0.2$), suggesting easy separation by chromatography on silica gel. With the result in mind, racemic dienyl alcohol *rac*-**7a** was subjected to AD reaction with AD-mix-β and the resulting 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

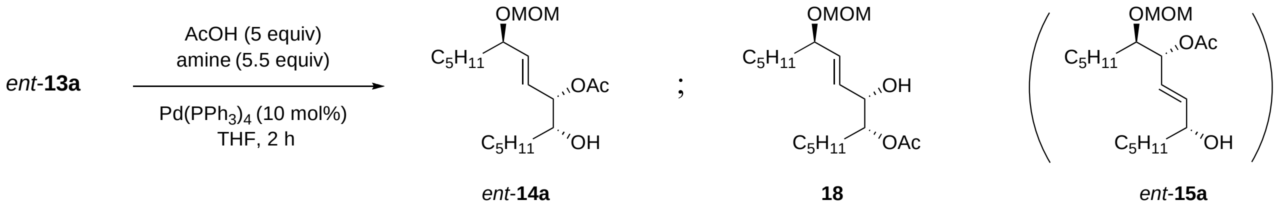
[a] Of the major product. [b] Ratio was determined by ^{1}H NMR.



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 Et_3N (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 ^{1}H 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 A_3 (vide infra). In addition, attempted reactions with other amines such as *i*-Pr_2NEt and pyridine resulted in incomplete reaction giving a mixture of *ent*-**14a** and the substrate.

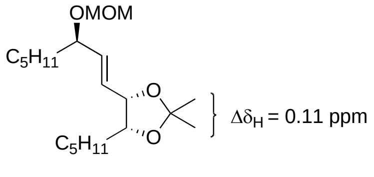
Table 2. Palladium-catalyzed reaction of *ent*-**13a** with AcOH



Entry	Temp., °C	Amine	Calculated yield[a] of *ent*-**14a**, %	Isolated yield and ratio of *ent*-**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*-Pr_2NEt	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.



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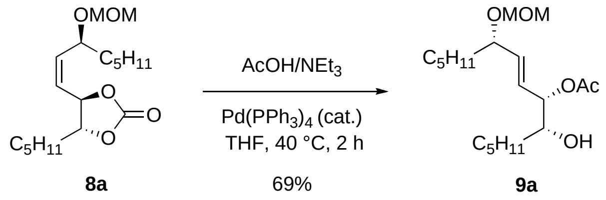
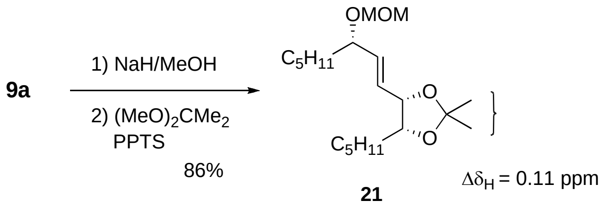
The *trans* stereochemistry of the newly created olefin of *ent*-**14a** (and **18**) was easily confirmed by the coupling constant of the olefinic protons of the derived diol (J = 16 Hz) (structure not shown), while the *anti* stereochemistry of the diol portion was determined by $\Delta\delta_H$ of 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 $\Delta\delta_H$ of the acetonide methyl groups, indicating the *anti* stereochemistry as well[10] (Scheme 6).

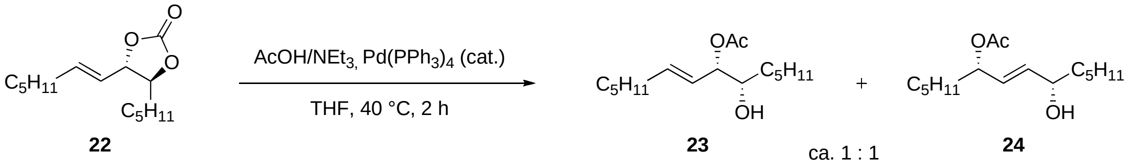


Scheme 5. Palladium-catalyzed reaction of carbonate **8a** with AcOH



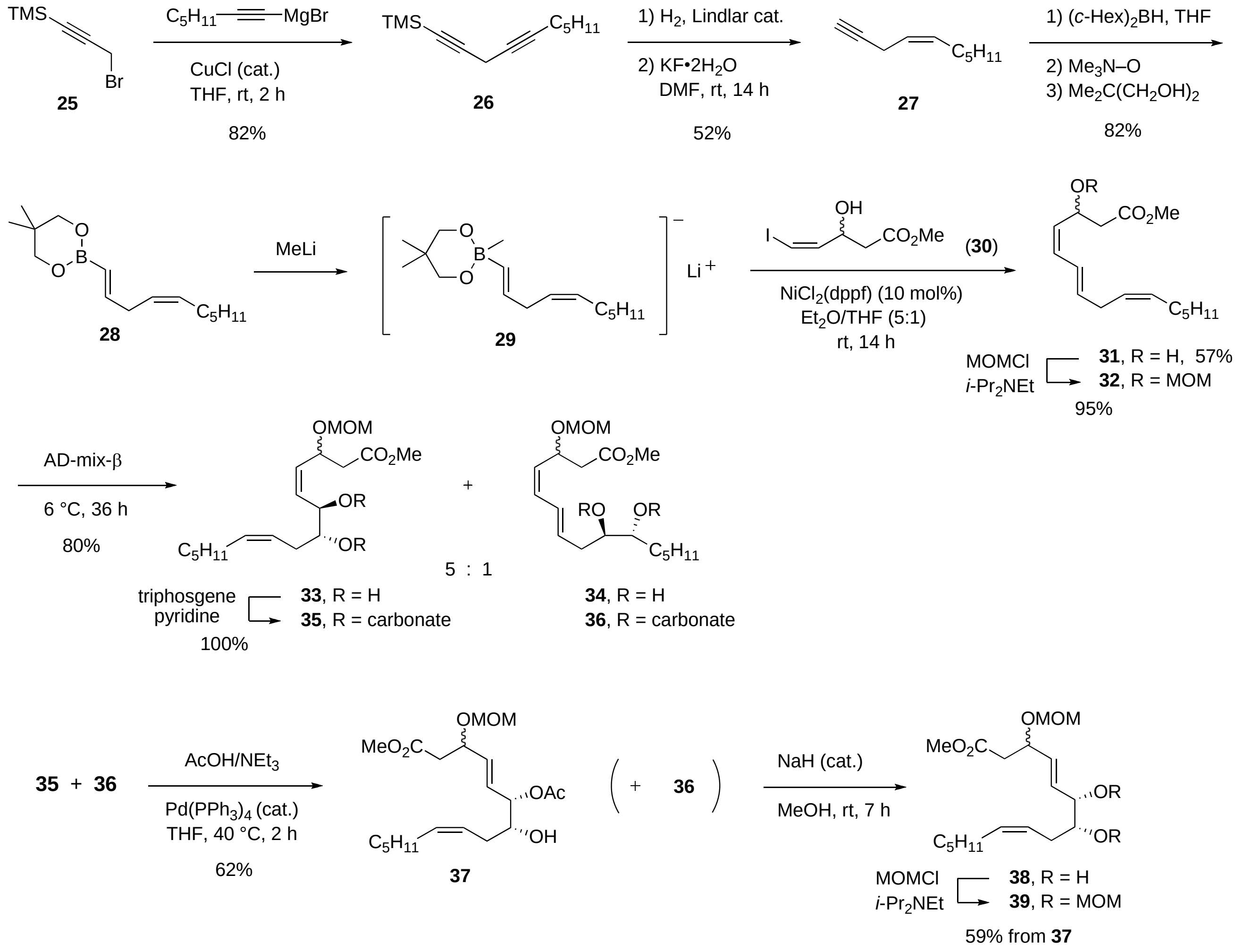
Scheme 6. Conversion of **9a** to **21**

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 A_3 (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 $C_5H_{11}C{\equiv}CMgBr$ 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)$_2$BH proceeded cleanly and the resulting borane was transformed to the boronate ester **28** by oxidation with Me_3NO followed by transesterification with $Me_2C(CH_2OH)_2$. 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 ^{1}H 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 A_3

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 A_3 successfully (Scheme 8).

ACKNOWLEDGEMENT

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

REFERENCES AND NOTES

1. Y. Kobayashi, Y. Nakayama, and R. Mizojiri, *Tetrahedron*, 1998, **54**, 1053.
2. Y. Kobayashi, R. Mizojiri, and E. Ikeda, *J. Org. Chem*., 1996, **61**, 5391.
3. Reviews: (a) Y. Kobayashi, *Trends in Org. Chem*., 1998, **7**, 27; (b) Y. Kobayashi, *J. Synth. Org. Chem. Jpn*., 1999, **57**, 845.
4. Y. Kitano, T. Matsumoto, and F. Sato, *Tetrahedron*, 1988, **44**, 4073.
5. Y. Nakayama, G. B. Kumar, and Y. Kobayashi, *J. Org. Chem*., 2000, **65**, 707.
6. Y. Kobayashi, S. Yoshida, and Y. Nakayama, *Eur. J. Org. Chem*., 2001, 1873.
7. Y. Kobayashi, S. Yoshida, M. Asano, A. Takeuchi, and Hukum P. Acharya, *J. Org. Chem*., 2007, **72**, 1707.
8. H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev*., 1994, **94**, 2483.
9. J. Tsuji, H. Kataoka, and Y. Kobayashi, *Tetrahedron Lett*., 1981, **22**, 2575.
10. P. Allevi, F. Cajone, P. Ciuffreda, and M. Anastasia, *Tetrahedron Lett*., 1995, **36**, 1347.
11. (a) C. R. Pace-Asciak, E. Granstrom, and B. Samuelsson, *J. Biol. Chem*., 1983, **258**, 6835; (b) S. Lumin and J. R. Falk, *Tetrahedron Lett*., 1992, **33**, 2091; (c) J. S. Yadav and V. Prahlad, *Tetrahedron Lett*., 1994, **35**, 641.
12. Y. Kitano, S. Okamoto, and F. Sato, *Chem. Lett*., 1989, 2163.