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Enantioselective Synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-Triol Monosilyl Ethers Using a Cross-Metathesis Allylboration Sequence

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Abstract

The enantioselective synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-triol monosilyl ethers via a two-step sequence involving olefin cross-metathesis of β -alkoxyallylboronate **4** and subsequent allylboration of the derived bisboronate intermediate **6** provides triol monoethers **7** with good to excellent diastereoselectivity.

Stereodefined 1,2,5-triol subunits are present in many biologically active natural products. The zooxanthellamides, stagonolides, and annonaceous acetogenins are three classes of natural products in which this moiety is found.¹

The boron-mediated allylation reaction has proven to be an important method for carbon-carbon bond formation.² This reaction proceeds with predictable control of stereochemistry via cyclic, chair-like transition states, and has been widely applied in the synthesis of natural products. In recent years, our laboratory has focused on developing higher-order applications of the allylboration reaction in which two C—C bond forming events are performed in a single operation with a bifunctionalized allylboron reagent (i.e., the double allylboration reaction).^{3,4} One limitation to this methodology, which provides 1,5-diols with excellent stereochemical control, is the general difficulty of synthesizing reagents that enable placement of additional substituents on the 1,5-diol scaffold as a direct result of the double allylboration event.

In an effort to expand the utility of the double allylboration reaction, we imagined that manipulation of the terminal olefin of boronate ester **3** via cross metathesis might provide a means to introduce additional functionality (Scheme 1).⁵ Owing to our long-standing interest in the synthesis of polyhydroxylated natural products,⁶ we concentrated on metathesis partners that would enable us to access 1,2-*anti*-2,5-*anti* triols of type **7**. Specifically, we studied the cross metathesis reactions of silyl ether protected allylboronates **4** and pinacol vinyl boronate (**5**), which is a well-established metathesis coupling partner.⁷ Accordingly, we report herein a highly diastereoselective synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-1,2,5-triols **7** by the sequence summarized in Scheme 1.

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Supporting Information Available. Experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Allylboronate **3a** ($R_1 = \text{CH}_2\text{CH}_2\text{Ph}$, $X = \text{H}$) was synthesized via the hydroboration of allene **1a** ($X = \text{H}$) with $^t\text{Ipc}_2\text{BH}$ followed by treatment of allylboronate **2** with hydrocinnamaldehyde at -78°C .^{3a,8} Initial attempts to effect cross metathesis reactions of silyl ethers **4a** (derived from **3a**) with pinacol vinylboronate **5** using Grubbs' 2nd generation catalyst were unsuccessful.⁹ The lack of reactivity was attributed to the steric bulk associated with the tetraphenyl-substituted dioxaborolane unit of **4a** ($R_1 = \text{CH}_2\text{CH}_2\text{Ph}$, $X = \text{H}$), along with the bulky pinacol boronate ester of the coupling partner **5**. Therefore, we turned to use of the more robust Hoveyda-Grubbs' 2nd generation catalyst¹⁰ in order to accommodate the increase in reaction temperature necessary to effect the cross metathesis reaction. However, treating a mixture of **4a** ($R_1 = \text{CH}_2\text{CH}_2\text{Ph}$, $X = \text{H}$, $-\text{SiR}_3 = \text{TBS}$), **5** and the second generation Grubbs-Hoveyda catalyst in toluene at 80°C led to olefin 14–24% isomerization of **4a** to the corresponding vinylboronate after 24 h, presumably due to a Ru-H species generated in situ upon decomposition of the ruthenium catalyst.¹¹ Following an extensive screening of additives to suppress the olefin isomerization, tetrafluoro-1,4-benzoquinone was selected as the most effective reagent to prevent this side reaction.¹²

A third variable that had to be optimized to maximize selectivity for the (*E*)-olefin geometry in the cross metathesis product **6** is the size of the alcohol protecting group. Because it is known that steric bulk at the allylic position generally enhances selectivity for the (*E*)-olefinic metathesis product,¹³ we studied the cross metathesis of a series of silyl ethers generated from **3a** ($R_1 = \text{PhCH}_2\text{CH}_2$, $X = \text{H}$) (Table 1). These experiments led to the identification of the TIPS ether as the alcohol protecting group that gives greatest selectivity for (*E*)-**6**.

The results of cross-metathesis reactions of a range of allylboronate substrates are summarized in Table 2. In all cases, the selectivity for the (*E*)-olefinic product was excellent ($\geq 20 : 1$). Most of these reactions provided the vinylboronate products **6a–k** in 60–75% yield, along with some recovered **4a–k**. Presumably, these reactions did not proceed to completion owing to the high steric of use demands of the cross coupling partners—a consequence of the TIPS ether to maximize selectivity for the (*E*)-olefin product in the metathesis reaction.

At the outset, we anticipated that the allylboration reactions of **6** would proceed via the chair-like transition state **TS-A** (see Scheme 1) with the α -silyloxy carbon chain residing in an axial position to avoid non-bonded steric interactions with the tetraphenyl-1,3,2-dioxaborolane unit of the reagent, which become quite significant in the alternative (disfavored) transition state **TS-B**.^{3a} Accordingly, it was anticipated that this allylboration sequence would provide (*Z*)-1,2-*anti*-2,5-*anti*-1,2,5-triol monoethers **7** with excellent selectivity following oxidative workup. However, we recognized that a third allylboronate, **9**, would be produced in the allylboration of reactions of **6**, and that **9** could, in principle, react with a second equivalent of the aldehyde partner to provide double allylboration products of type **10** or **11** (Scheme 2). Indeed, in experiments performed using **6a** (with the para substituent $X = \text{H}$), mixtures of **7** (major) and **10/11** were obtained when **6a** was treated with 1.0 equiv. of aldehydes at various reaction temperatures and concentrations (data not shown). These results indicated that the reactivities of **6a** and **9a** ($X = \text{H}$) towards aldehydes are comparable.

Consequently, we directed our attention to adjusting the reactivity of the allylboronate functional group in **6** relative to that of the intermediate allylboronate species **9**. Based on earlier studies in which we observed that a *p*-nitrophenyl substituent on a 1,3,2-dioxaborolane increased the Lewis acidity of the allylboronate and correspondingly increased the rate of its reaction with aldehydes, compared to the parent allylboronate with a phenyl-substituted dioxaborolane,¹⁴ we synthesized the tetra-*p*-fluorophenyl substituted allylboronate **6b** ($X = \text{F}$) by a sequence paralleling that used for the synthesis of **6a** ($X = \text{H}$). Treatment of **6b** with hydrocinnamaldehyde in CH_2Cl_2 (0.1 M) for 24 h, and subsequent workup with H_2O_2 and NaOH afforded triol **7a** in 67% yield with $\geq 20 : 1$ d.s. Increasing the allylboration reaction

period to 36 h provided **7a** in 71% yield, and while after 48 h the yield of **7a** was 77% (see Scheme 3). In all cases, the double allylboration products **10/11** were not observed. Thus, this proof of principle experiment established that the inductive effect of the *p*-fluoro substituents increased the reactivity of **6b** such that allylboration reactions of intermediate **9** were no longer competitive.

The scope of allylboration reactions of **6b** with additional aldehydes is presented in Scheme 3, and results of allylboration reactions of **6c**, **d**, **f**, **g** and **j** with hydrocinnamaldehyde are presented in Scheme 4. In the vast majority of cases (the one exception being the reaction of **6b** with hydrocinnamaldehyde in Scheme 3), the reactions were performed at ambient temperature for 36 h. The triol monoethers **7** were obtained in 52–89% yield, 82–93% e.e., and ≥ 14 : 1 d.s. for all examples except **7g** (10 : 1 d.s., Scheme 3) and **7n** (9 : 1 d.s., Scheme 4).

The relative and absolute stereochemistry of the triol monoethers presented in Schemes 3 and 4 were assigned via advanced Mosher ester analysis of the corresponding MPTA esters.^{15,16}

In summary, the allylboration-cross metathesis-allylboration sequence presented in Scheme 1 constitutes a convergent and highly enantio- and diastereoselective method for synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-triol monosilyl ethers **7** with synthetically useful efficiency. This new method represents an expansion of our double allylboration methodology,³ and defines a strategy for introduction of substituents at positions internal to the 1,5-diol motif. Applications of this new method in the synthesis of natural products, along with further extensions of the double allylboration methodology, are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. (a) Onodera K, Nakamura H, Oba Y, Ohizumi Y. J. Am. Chem. Soc 2005;127:10406. [PubMed: 16028954] (b) Giri AG, Mondal MA, Puranik VG, Ramana CV. Org. Biomol. Chem 2010;8:398. [PubMed: 20066276] (c) Zeng L, Zhang Y, Ye Q, Shi G, He K, McLaughlin JL. Bioorg. Med. Chem 1996;4:1271. [PubMed: 8879548]
2. For reviews of allylboration reactions, see: (a) Roush, WR. Comprehensive Organic Synthesis. Trost, BM., editor. Vol. 2. Oxford: Pergamon Press; 1991. p. 1 (b) Yamamoto Y, Asao N. Chem. Rev 1993;93:2207. (c) Denmark, SE.; Almstead, NG. Modern Carbonyl Chemistry. Otera, J., editor. Weinheim: Wiley-VCH; 2000. p. 299 (d) Chemler, SR.; Roush, WR. Modern Carbonyl Chemistry. Otera, J., editor. Weinheim: Wiley-VCH; 2000. p. 403 (e) Denmark SE, Fu J. Chem. Rev 2003;103:2763. [PubMed: 12914480] (f) Lachance H, Hall DG. Org. React 2008;73:1..
3. (a) Flamme EM, Roush WR. J. Am. Chem. Soc 2002;124:13644. [PubMed: 12431072] (b) Kister J, DeBaillie AC, Lira R, Roush WR. J. Am. Chem. Soc 2009;131:14174. [PubMed: 19775159]
4. For other recent contributions to the double allylmethylation reaction: (a) Peng F, Hall DG. J. Am. Chem. Soc 2007;129:3070. [PubMed: 17315879] (b) González AZ, Román JG, Alicea E, Canales E, Soderquist JA. J. Am. Chem. Soc 2009;131:1269. [PubMed: 19117388] .
5. For reviews of olefin metathesis: (a) Grubbs, RH. Handbook of Metathesis. Weinheim Germany: Wiley-VCH; 2003. (b) Nicolaou KC, Bulger PG, Sarlah D. Angew. Chem. Int. Ed 2005;44:4490. (c)

- Connon SJ, Blechert S. *Angew. Chem. Int. Ed* 2003;42:1900. (d) Schuster M, Blechert S. *Angew. Chem. Int. Ed* 1997;36:2036..
6. For representative examples, see: (a) Roush WR, Straub JA, VanNieuwenhze MS. *J. Org. Chem* 1991;56:1636. (b) Roush WR, Grover PT. *Tetrahedron* 1992;48:1981. (c) Hunt JA, Roush WR. *J. Org. Chem* 1997;62:1112. (d) Roush WR, Hartz RA, Gustin DJ. *J. Am. Chem. Soc* 1999;121:1990. (e) Heo J-N, Holson EB, Roush WR. *Org. Lett* 2003;5:1697. [PubMed: 12735755] .
7. (a) Morrill C, Grubbs RH. *J. Org. Chem* 2003;68:6031. [PubMed: 12868943] (b) Blackwell HE, O'Leary DJ, Chatterjee AK, Washenfelder RA, Bussman DA, Grubbs RH. *J. Am. Chem. Soc* 2000;122:58. (c) Esteban J, Costa AM, Vilarrasa J. *Org. Lett* 2008;10:4843. [PubMed: 18837554] (d) White BH, Snapper ML. *J. Am. Chem. Soc* 2003;125:14901. [PubMed: 14640667] (e) Nicolaou KC, Li A, Edmonds DJ, Tria GS, Ellery SP. *J. Am. Chem. Soc* 2009;131:16905. [PubMed: 19874023]
8. (a) Flamme EM, Roush WR. *Org. Lett* 2005;7:1411. [PubMed: 15787519] (b) Hicks JD, Flamme EM, Roush WR. *Org. Lett* 2005;7:5509. [PubMed: 16288543]
9. Scholl M, Ding S, Lee CW, Grubbs RH. *Org. Lett* 1999;38:2416.
10. Garber SB, Kingsbury JS, Gray BL, Hoveyda AH. *J. Am. Chem* 2000;122:8168.
11. (a) Hong SH, Wenzel AG, Salguero TT, Day MW, Grubbs RH. *J. Am. Chem. Soc* 2007;129:7961. [PubMed: 17547403] (b) Hong SH, Day MW, Grubbs RH. *J. Am. Chem. Soc* 2004;126:7414. [PubMed: 15198568]
12. Hong SH, Sanders DP, Lee CW, Grubbs RH. *J. Am. Chem. Soc* 2005;127:17160. [PubMed: 16332044]
14. Roush WR, Banfi L, Park JC, Hoong LK. *Tetrahedron Lett* 1989;30:6457.
15. (a) Hoye TR, Jeffrey CS, Feng S. *Nature Prot* 2007;2:2451. (b) Ohtani I, Kusumi T, Kashman Y, Kakisawa H. *J. Am. Chem. Soc* 1991;113:4092. (c) Dale JA, Mosher HS. *J. Am. Chem. Soc* 1968;90:3732.
16. See Supporting Information for data.

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Scheme 2.
Allylboronate Intermediate **9** May Undergo a Second Allylboration.

Scheme 3.

 Allylboration Reactions of **6b**—Scope of Aldehyde Substrates.^a
^aUnless indicated otherwise, all allylboration reactions were performed for 36 h at ambient temperature. ^bDetermined by advanced Mosher ester analysis. ^cDiastereomer ratio determined by ¹H NMR analysis of the crude product.

Scheme 4.

Allylboration Reactions of **6c**, **6d**, **6f**, **6g** and **6j** with Hydrocinnamaldehyde.

^aDetermined by advanced Mosher ester analysis. ^bDiastereomer ratio determined by ¹H NMR analysis of the crude reaction product.

Table 1*(E)*-Selectivity in the Cross-Metathesis Reactions of Silyl Ether Derivatives of Allylboronate **3a**

entry ^a	R ₃ Si	<i>E/Z</i> ratio in 5 ^b
1	TMS	3:1
2	TES	6:1
3	TBS	8:1
4	TBDPS	16:1
5	TIPS	≥ 20:1

^a Reactions were performed by treating silyl ethers derived from allylboronate **3a** (R₁ = CH₂CH₂Ph, X=H; 1.0 equiv) and pinacol vinyl boronate **5** (1.5 equiv) with the 2nd generation Hoveyda-Grubbs catalyst in toluene (0.5 M) at 80 ° C for 24 h in the presence of tetrafluoro-1,4-benzoquinone (0.10 equiv).

^b Olefin geometry in **6** was determined by ¹H NMR analysis of the crude product.

Table 2

Cross-Metathesis Reactions of Allylboronates **4a-k**.

entry	R_1			product	catalyst (mol %)	additive ^c (mol %)	yield ^d (%) / brsm ^e (%)	
1				6a^d	10	10	56 / (90)	
					10	none	51 / (—)	
2				6b^b	10	10	61 / (82)	
					12	none	74 / (—)	
				6c^b	10	10	50 / (57)	

entry	R ₁			product	catalyst (mol %)	additive ^c (mol %)	yield ^d (%) / brsm ^e (%)	
		4a-k (1.0 equiv)	5 (1.5 equiv)					
3				6d ^b	10	10	69	(87)
4				6e ^b	10	10	67	(80)

entry	R ₁	product	catalyst (mol %)	additive ^c (mol %)	yield ^d (%) / brsm ^e (%)
5		6f ^b	10	none	52 / (—)

entry	R ₁						product	catalyst (mol %)	additive ^c (mol %)	yield ^d (%) / brsm ^e (%)	
6							6g ^b	10	8	55 / (71)	
7							6h ^b	10	none	67 / (–)	
8							6i ^b	10	10	46 / (61)	
9							6j ^b	10	none	88 / (–)	
							6k ^b	15	10	74 / (83)	
							6l ^b	10	none	75 / (–)	
							6m ^b	10	10	45 / (54)	
							6n ^b	10	none	43 / (–)	

entry	R ₁	product	catalyst (mol %)	additive ^c (mol %)	yield ^d (%) / brsm ^e (%)
10			10	none	67 / (—)

^aX = H.^bX = F.^cTetrafluorobenzoquinone was added to prevent olefin isomerization.^dIsolated yields of **6a-k**.^eYield based on recovered starting material.^fOlefin geometry determined by ¹H NMR analysis of the crude reaction products.