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Enantio- and Diastereoselective Synthesis of (*E*)-1,5-*syn*-Diols: Application to the Synthesis of the C(23)-C(40) Fragment of Tetrafibricin

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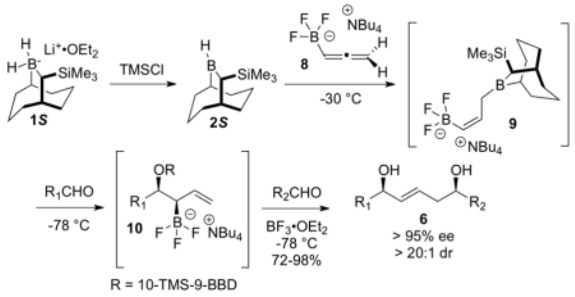
Abstract



A highly stereoselective synthesis of (*E*)-1,5-*syn*-diols 6 is described. The kinetically controlled hydroboration of allenyltrifluoroborate 8 with Soderquist borane 2 provides the (*Z*)-allylic trifluoroborate 9, which undergoes sequential allylboration with two different aldehydes to provide (*E*)-1,5-*syn*-diols 6 in 72–98% yields with > 95% ee. and > 20:1 dr. Application of this method to the synthesis of the tetrafibricin C(23)-C(40) fragment 19 is described.

The development of bifunctionalized allylmetal reagents is of considerable interest for use in the assembly of complex structures in a step-efficient, convergent manner.[1] Our laboratory has developed several 1,3-bifunctionalized chiral allylborane reagents[1c,i,j] for use in natural product synthesis.[2] In connection with an ongoing research problem, we required a method for the stereoselective synthesis of (*E*)-1,5-*syn*-diols **6**. This structural motif is present in many natural products,[3] but is not accessible by using our first-generation double allylboration reagents.[1c,i,j,4] Accordingly, we have developed and report herein a new double allylboration reagent for the enantio- and diastereoselective synthesis of (*E*)-1,5-*syn*-diols **6** (and its enantiomer *ent*-**6**), and apply this procedure to the highly stereoselective synthesis of the C(23)-C(40) fragment of tetrafibricin.

At the outset, we envisaged that the requisite double allylborating agent **4** could be prepared via kinetically controlled hydroboration of allene **3** with the Soderquist borane, 10-TMS-9-borabicyclo[3.3.2]decane [10-TMS-9-BBD-H, **2*R*]**, and that sequential treatment of **4** with two aldehydes would provide the targeted 1,5-diols **6** (Scheme 1).[2h,i] Successful implementation of this plan requires (1) that the hydroboration of **3** by the chiral borane reagent **2R** be highly stereoselective; (2) that *Z* to *E* isomerization of the (*Z*)-allylborane **4** be

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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.

slow, and (3) that the reaction of **5** with the second aldehyde, R_2CHO, proceed with high fidelity through transition state **TS-1** (Scheme 2). The first condition is established for allene hydroborations with the Soderquist borane, while the second is generally met with (*Z*)-γ-substituted allylboranes containing the 10-TMS-9-BBD auxiliary.[2h,i,5]

In the event, the double allylboration sequence performed with **3**, **2*R***, and two aldehydes proceeded in good yield and enantioselectivity, but ca. 4 : 1 mixtures of *ent*-**6** and **7** were obtained (Scheme 2).[6] These results indicated that second allylboration reaction (with **5**) proceeded with only a slight preference for the expected[1c] **TS-1** compared to **TS-2**. While the reasons for the poor stereoselectivity of this transformation are not certain, we speculated that non-bonded interactions between the (1,3,2)-dioxaborinane unit and the R_1 group might destabilize **TS-1** compared to **TS-2**. This prompted us to develop a new reagent as an alternate to **5** with a less sterically demanding set of substituents on the secondary allylic boron atom.

Batey reported allyl- and crotylation of aldehydes using potassium allyl- and crotyltrifluoroborate reagents and suggested that an allylboron difluoride intermediate is the reactive species.[7] Consequently, we imagined that allylic trifluoroborate **10** should be a viable precursor to allylboron difluoride **11** (Scheme 3). Moreover, we anticipated that **11** would undergo allylboration reactions of aldehydes with much higher stereoselectivity than with **5** owing to the smaller size of the difluoroborane unit of **11** compared to the (1,3,2)-dioxaborinane unit in **5** (e.g., compare **TS-3** with **TS-1**). Thus, we turned to the synthesis of **10** via the kinetically controlled hydroboration of allene **8** with borane **2*S*** (or **2*R*** in the enantiomeric series).

Allene **8** was synthesized as described in the Supporting Information. The tetrabutylammonium counterion was used to increase the solubility of **8**, **9**, and **10** in the non-polar solvents used in these experiments.

The hydroboration experiments commenced by treating a 0 °C solution **8** (1.3 equiv) in CH_2Cl_2 with 1 equiv of **2*S*** that was generated in situ by treatment of the borohydride **1*S*** with TMSCl (Table 1). After a 1 h reaction time, the solution was cooled to −78 °C and then benzaldehyde (0.7 equiv) was added. The reaction was worked up oxidatively to give 1,2-diol **12** as a 5.7: 1 mixture of syn and anti diastereomers, along with the unexpected (*E*)-1,5-*syn*-diol **13** (Table 1, entry 1). The mixture of 1,2-diol diastereomers **12** provides an indirect assessment of the isomeric purity of the initial hydroboration product, **9**, while the formation of **13** suggested that allylboron difluoride **11** was formed during the reaction. A significant improvement of the dr (16:1) for **12** was realized by performing the hydroboration at −10 °C for 1 h (entry 2), suggesting that the rate of boratropic isomerization of **9** can be controlled by keeping the reaction temperature below −10 °C. However, products **12** and **13** were still formed in a ca. 3:1 ratio. Addition of DIBAL to the reaction mixture to reduce any residual benzaldehyde prior to the oxidative workup did not eliminate the formation of **13** (entry 3). This experiment indicates that **13** must be formed during the reaction, and not during workup. The best dr for **12** (> 20:1) from experiments performed in CH_2Cl_2 was obtained when the hydroboration reaction was run at −30 °C (entries 5, 6). Evidently, under these conditions, the rate of the [1,3]-boratropic isomerization of **9** to the corresponding **(*E*)**-isomer is slow. We subsequently discovered that the competitive abstraction of fluoride ion from **10** (that generates **11** en route to **13**) was strongly influenced by the reaction solvent (entries 7, 8, and 9). Under optimal conditions (entry 9), the hydroboration/allylboration sequence performed in a mixture of toluene and CH_2Cl_2 (15:1) led to the chemo-, enantio- and diastereoselective formation of allylic trifluoroborate **10**, as evidenced by the isolation of *syn*-1,2-diol **12** in 87% yield, with 97% ee, and > 20:1 dr after oxidative workup.

With confidence that intermediate **10** could be generated with high efficiency and excellent stereochemical control, we turned the reactions of this species with a second aldehyde to give (*E*)-1,5-*syn*-diols **6** (Table 2). For these purposes, the reactive allylic boron difluoride **11** was generated in situ by treatment of the solution of **10** at −78 °C with $BF_3{\cdot}OEt_2$ in the presence of a slight excess of hydrocinnamaldehyde.[8]

The amount of the aldehyde used in the first allylboration leading to **10** proved to be critical for the selective formation of (*E*)-1,5-*syn*-diol **6a** (entries 1,2,3). Use of 0.75 equiv of benzaldehyde in the first allylation resulted in the formation of the 1,5-diol **14**, which indicated that the allylborane **9** was not fully consumed during the first step (entry 1). On the other hand, 1,5-diol **13** was produced when a larger amount of benzaldehyde (0.95 equiv) was used in the first allylation reaction (entry 3). However, use of 0.85 equiv of benzaldehyde in the first allylation, followed by addition of 1.2 equiv of the second aldehyde and 1.5 equiv of $BF_3{\cdot}OEt_2$ led to the isolation of (*E*)-1,5-*syn*-diol **6a** in 73% yield, with excellent enantioselectivity (97% ee), diastereoselectivity (dr > 20:1), and *E*/*Z* ratio (> 20:1) (entry 2). When the second allylation step was performed at higher temperatures (entries 4, 5), product **6a** was still obtained even in the absence of $BF_3{\cdot}OEt_2$, but with a significant decrease of the *E*/*Z* ratio. The high reactivity of allylboron difluoride **11**, allowing the second allylboration step to be run at −78 °C, was essential to achieve the selective *E* formation of 1,5-*syn*-diol **6a**.

Additional examples of this new double allylboration sequence are provided in Scheme 4. The optimal reaction conditions defined by entry 2 of Table 2 proved to be applicable to a variety of aldehydes (aromatic, aliphatic, α, β-unsaturated) and compatible with -OBn and -OTBS protecting groups. The (*E*)-1,5-*syn*-diols **6** were obtained in 72–98% yields, > 95% ee, dr > 20:1, and *E*/*Z* > 20:1 in all cases. To the best of our knowledge, **10** is the first chiral α-substituted allyltrifluoroborate reagent to exhibit such high *E*/*Z* olefin selectivity in reactions with aldehydes.[9] Both enantiomers of 1,5-diol **6** can be accessed by using either enantiomer of the borane **2*S*** or **2*R***, as exemplified by the syntheses of **6d** and *ent*-**6d**.

The stimulation to develop this new procedure for the synthesis of (*E*)-1,5-*syn*-diols was provided by the structure of tetrafibricin **15**, and especially the C(23)-C(40) fragment **16** (Figure 1). Tetrafibricin is a structurally unique fibrinogen receptor inhibitor isolated in 1993 from *Streptomyces neyagawaensis*.[10] Tetrafibricin displays potent anti-aggregation properties against human platelets by blocking the glycoprotein (GP)IIb/IIIa receptor on the platelet surface, which is important for blood clotting.[11] Unlike other fibrinogen receptor inhibitors (like snake venoms) **15** is non-peptidic. These features highlight **1** as a potential probe molecule for studying stroke and heart attack. The stereostructure of **15** was assigned by Kishi based on NMR database technology and NMR measurements in chiral solvents.[3b] Syntheses of fragments of tetrafibricin have been reported by Cossy,[12] Curran,[13] Friestad,[14] and our group.[15]

Our retrosynthetic analysis of the C(23)-C(40) fragment (**16**) of tetrafibricin is outlined in Figure 1. We were attracted to the possibility that **16** could be obtained in a highly convergent manner from aldehyde precursors **17** and **18**, by application of the new reagent *ent*-**9 (**deriving from **2*R***). Indeed, by using the optimized double allylboration procedure described above, the 29S,33S-diastereomer **19**, a synthetic precursor to **16** with stereochemistry identical to that proposed for tetrafibricin, was generated in 83% yield with > 20:1 diastereoselectivity and > 20:1 E/Z selectivity by the one-pot convergent coupling of **17** and **18** using *ent*-**9** (Scheme 5). Moreover, by using the enantiomeric reagent, **9**, deriving from **2*S***, the 29R,33R-diastereomer **20** was obtained in 78% yield, also with exceptional diastereoselectivity (dr > 20:1) and complete control of the *E*-olefin (> 20:1). The absolute

stereochemistry of the two new hydroxyl groups in **19** and **20** was assigned by using the Mosher method, as summarized in the SI.

In summary, we have developed an efficient and highly stereoselective double allylboration reaction leading to *syn*-1,5-diols **6** via a simple one-pot process. This method was successfully applied to the synthesis of the C(23)-C(40) tetrafibricin fragment **19** and its diastereoisomer **20**, which has inverted stereochemistry at C(29) and C(33). The ability to synthesize either **19** or **20** with excellent stereochemical control simply by changing the absolute configuration of the Soderquist borane, **2**, augurs well for application of this methodology for highly stereocontrolled, late stage fragment assembly reactions in the synthesis of natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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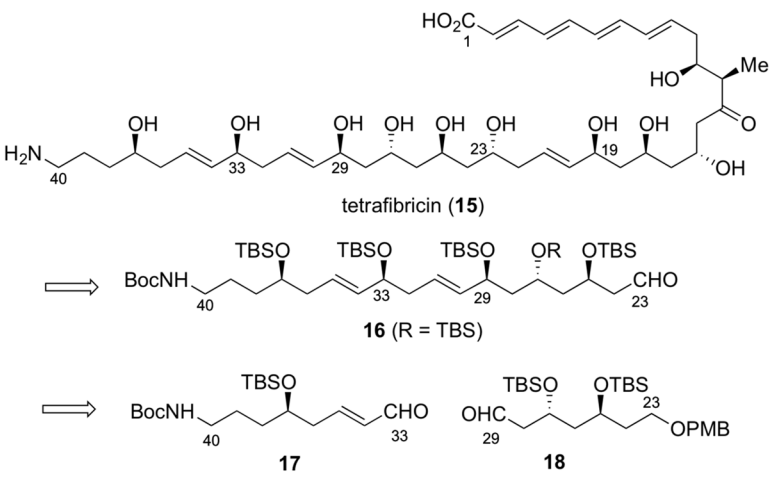
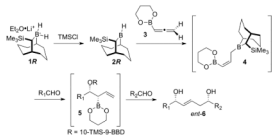
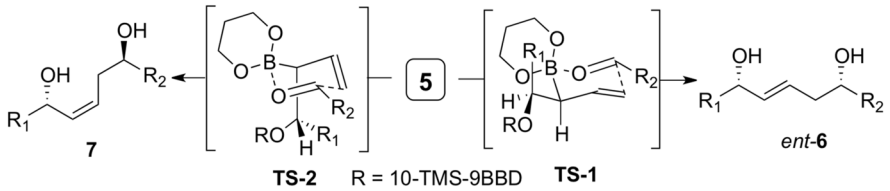


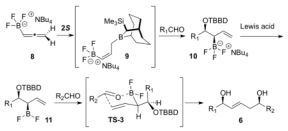
Figure 1.
Tetrafibricin (**15**) and retrosynthetic analysis of **16**



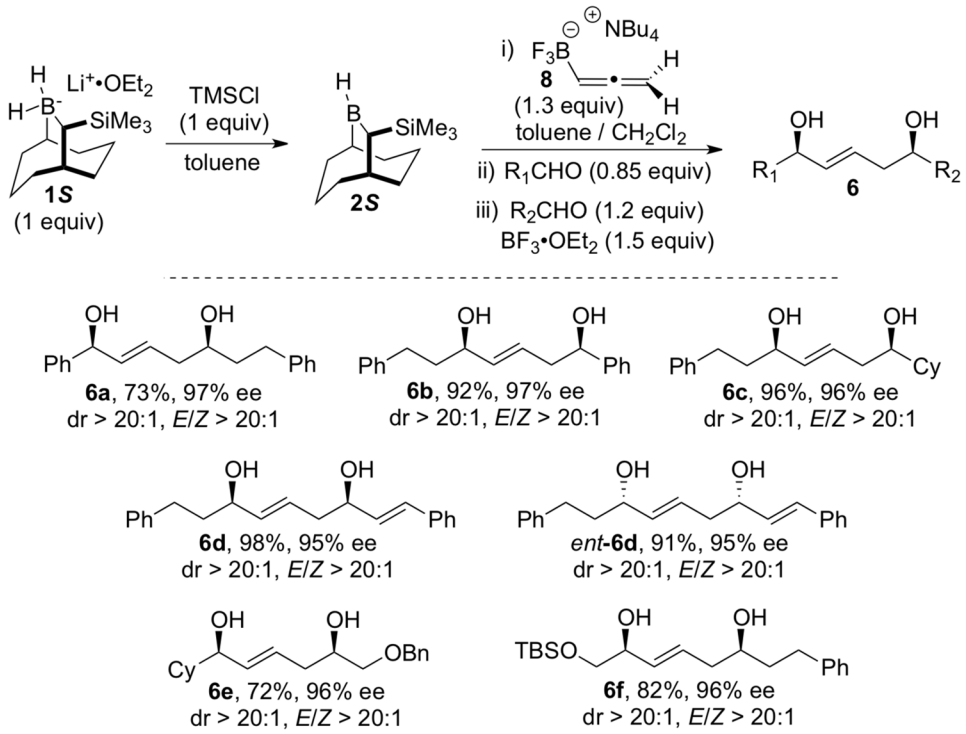
Scheme 1.
First generation strategy for synthesis of *ent*-**6**



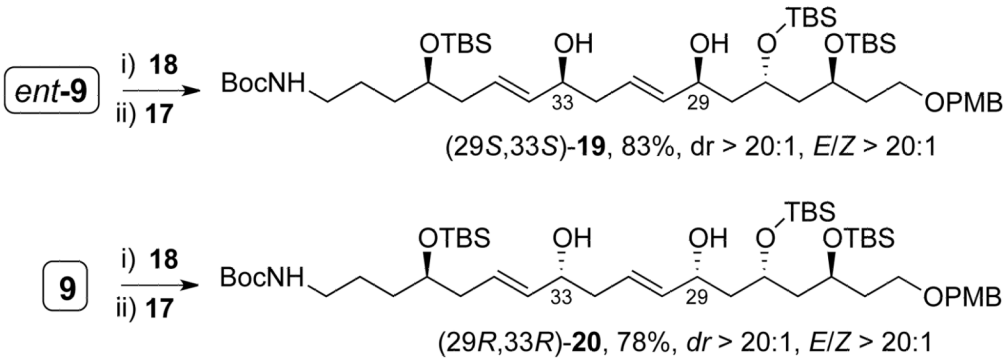
Scheme 2.
Competitive transition states leading to *ent*-**6** and **7**



Scheme 3.
Second generation strategy for synthesis of **6**



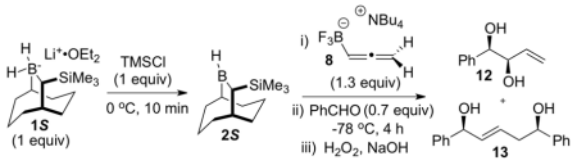
Scheme 4.
Stereoselective synthesis of (*E*)-1,5-syn-diol **6** [a]



Scheme 5.
Syntheses of tetrafibricin fragment **19** and **20**

Table 1

Optimization of the hydroboration/allylboration



entry	solvent	hydroboration temp/time	% yield of 12[a] (*syn*/*anti*)[b]	ratio 12:13[c]
1	CH_2Cl_2	0 °C/1 h	39 (5.7:1)	3.0:1
2	CH_2Cl_2	−10 °C/1 h	38 (16:1)	2.9:1
3[d]	CH_2Cl_2	−10 °C/1 h	39 (12:1)	3.3:1
4	CH_2Cl_2	−10 °C/3 h	41 (5.1:1)	3.2:1
5	CH_2Cl_2	−30 °C/1 h	52 (> 20:1)	3.7:1
6	CH_2Cl_2	−30 °C/3 h	52 (> 20:1)	4.3:1
7	Et_2O/CH_2Cl_2[e]	−30 °C/1 h	50 (> 20:1)	7.1:1
8	toluene/THF[f]	−30 °C/1 h	51 (> 20:1)	> 30:1
9	toluene/CH_2Cl_2[g]	−30 °C/1 h	87[h] (> 20:1)	> 30:1

[a] Isolated yields.

[b] Determined by ^{1}H NMR analysis.

[c] Determined after isolation of **12** and **13**.

[d] Dibal-H (2 equiv) added before the oxidation step.

[e] Et_2O/CH_2Cl_2 (2:1).

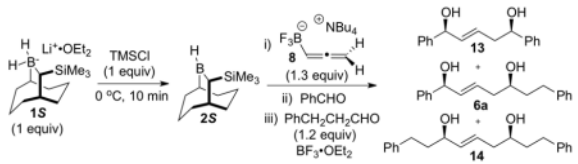
[f] Toluene/THF (2:1).

[g] Toluene/CH_2Cl_2 (15:1).

[h] **12** obtained in 97% ee, determined by Mosher ester analysis.

Table 2

Optimization of the double allylboration leading to **6**[a]



entry	PhCHO (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	% yield 6a[b]	ratio *E*/*Z*[c]	ratio 13/6a/14[c]
1	0.75	1.5	60	> 20:1	0:89:11
2	0.85	1.5	73	> 20:1	0:100[d]:0
3	0.95	1.5	51	> 20:1	8:92:0
4[e]	0.85	1.5	30	6:1	0:100:0
5[f]	0.85	-	77	6:1	0:100:0

[a] Reaction conditions: solvent: toluene/CH_2Cl_2; hydroboration: −30 °C, 1 h; first allylboration: −78 °C, 4 h; second allylboration: −78 °C, 4 h; workup: pH 7 buffer (KH_2PO_4/NaOH).

[b] Isolated yields.

[c] Determined by ^{1}H NMR analysis.

[d] **6a** obtained with > 20:1 dr and 97% ee, determined by Mosher ester analysis.

[e] Second allylboration: 0 °C, 2h.

[f] Second allylboration: −78 to 20 °C, 12 h.