Diastereoselective Synthesis of 2,3-*anti*-5-Benzyloxy-2,4-dimethyl-1,3-pentanediols via Cyclic Hydroboration

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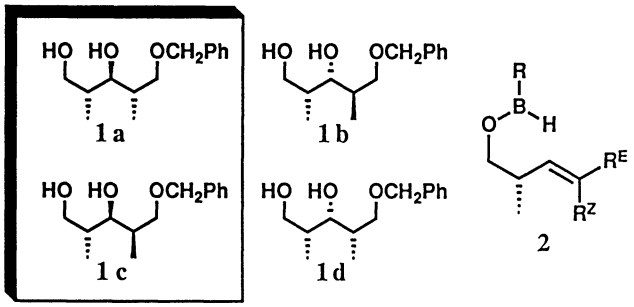
Synopsis. The treatment of (2*E*,4*S*)- and (2*Z*,4*S*)-1-benzyloxy-5-ethenyloxy-2,4-dimethyl-2-pentene with borane both with and without a catalytic amount of $Rh(Ph_3P)_3Cl$ gave 2,3-*anti*-3,4-*anti*-(2*R*,3*R*,4*S*)- and 2,3-*anti*-3,4-*syn*-(2*R*,3*R*,4*R*)-5-benzyloxy-2,4-dimethyl-1,3-pentanediols, respectively, with fair to good diastereoselectivity.

The enantioselective preparation of polypropionate antibiotics, particularly macrolides, has attracted the strong attention of a large number of synthetic organic chemists.[1] As the synthon of polypropionates, 2,4-dimethyl-1,3,5-pentanetriol derivatives **1a**—**d** and the related compounds are very useful, and have been used in the synthesis of biologically important natural compounds.[2—4] An excellent review concerning these compounds has already appeared.[5]

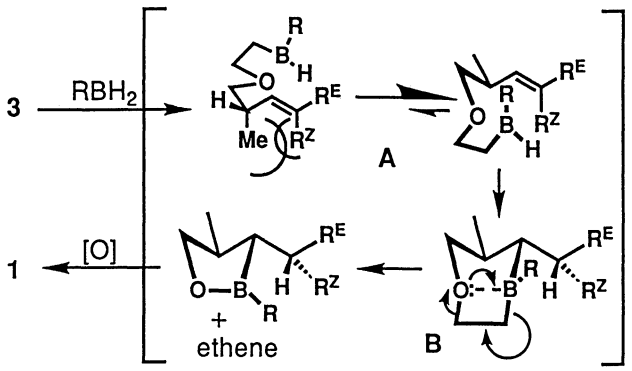
We have recently reported an allylic 1,3-strain-controlled cyclic hydroboration, used to produce acyclic compounds possessing a 1,2-*anti*-2-methyl-1,4-diol unit.[6] In this article we would like to report on the diastereoselective construction of 2,3-*anti*-2,4-dimethyl-1,3,5-pentanetriol derivatives via the cyclic hydroboration method.



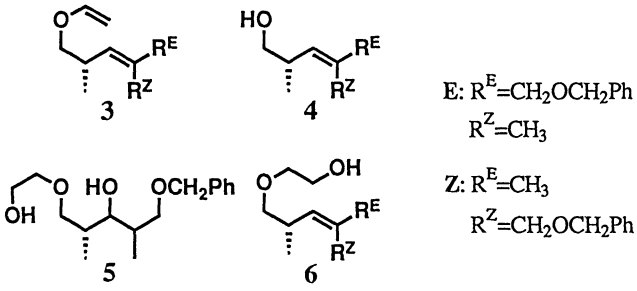
Our target molecules to prepare were **1a** and **1c**. Since species **2** was known not to afford intramolecular hydroboration products (because of its low reactivity toward olefins[7]), we had to find a new reaction system. We chose ethenyl ethers as the intramolecular borane carrier. The advantage of using ethenyl ethers is that this C_2 unit is known to fall off as an ethene molecule during the intramolecular hydroboration reaction;[8] therefore, no ether cleavage reaction, (which is sometimes difficult[9]) was necessary for a further chemical transformation (Scheme 1).

Ethenyl ethers **3E** and **3Z** were prepared from the corresponding optically active alcohols, **4E** and **4Z**, respectively, with almost complete control of the double-bond geometry (>98 : <2)[6b] without any loss of chirality.[2]

The reaction of *E* isomer **3E** with borane in THF at



Scheme 1.



−70 °C to room temperature, followed by an alkaline hydrogen peroxide treatment, gave an inseparable mixture of two triol monobenzyl ethers (**1a** and **1b**, 56%), together with 2-hydroxyethyl ether **5** (15%). The diastereomeric ratio, **1a**/**1b**, was determined to be 80/20 by comparing the ^1H NMR data with that described in the literature.[2,3] In a low-Lewis-basic solvent, CH_2Cl_2, which might accelerate ethene extrusion by avoiding solvent coordination to the boron atom of cyclic intermediate **B** in Scheme 1, no hydroxyethyl ether **5** was detected, though a smaller amount of a mixture of diols (75/25, 36%) was obtained with homoallylic ether **6E** (10%).

It was found that (1,1,2-trimethylpropyl)borane (thexylborane) is not effective in this reaction. The steric bulkiness interfered not only a stereoselective reaction, but even cyclic hydroboration, itself.

Similar results were obtained for ethenyl ether **3Z** (Table 1).

The diastereoselectivity of this reaction was lower than that of 1,4-dienes.[6] Although Harada et al. observed that boranes reacted with the electron-rich, sterically-uncongested ethenyloxy moiety faster than with the trisubstituted double bond,[8] the low reactivity of **A** in Scheme 1 might have allowed a reversely diaster-

Table 1. Cyclic Hydroboration of Ethenyl Ethers **3E** and **3Z**

Substrate	Borane	Solvent	Time/h[a]	**1** Yield/% (*anti*/*syn*)		**5** Yield/%	**6** Yield/%
3E	BH_3	THF	16.5	56	(80/20)	15	0
3E	BH_3	Ether	12.5	60	(75/25)	9	0
3E	BH_3	CH_2Cl_2	20	36	(75/25)	0	10
3E	$ThexBH_2$[b]	THF	14(5)	33	(50/50)	7	25
3Z	BH_3	THF	15	77	(70/30)	17	4
3Z	BH_3	Ether	18	71	(70/30)	8	0
3Z	BH_3	CH_2Cl_2	20.5	53	(70/30)	0	0
3Z	$ThexBH_2$[b]	THF	15(3.5)	44	(75/25)	42	6

a) Reaction time at room temperature. Additional refluxing time before quenching, if done, is in the parenthesis. b) $ThexBH_2$ stands for (1,1,2-trimethylpropyl)borane.

Table 2. Cyclic Hydroboration of Ethenyl Ethers **3E** and **3Z** with Borane in THF in the Presence of $Rh(PPh_3)_3Cl$

Substrate	Rh(I)/mol%	Time/h	**1** Yield/% (*anti*/*syn*)		**5** Yield/%	**6** Yield/%
3E	2.1	18	53	(60/40)	22	0
3Z	4.6	17.5	53	(90/10)	0	10

eoselective *intermolecular* hydroboration of a borane species toward the trisubstituted double bond of **A** to give isomers **1b** or **1d**.

In 1985 Männig and Nöth reported that hydroboration reactions using 1,3,2-benzodioxaborole (catecholborane) were greatly accelerated by a catalytic amount of $Rh(PPh_3)_3Cl$.[10] Recently, further developments and applications of this reaction have been reported.[11–14] Pt-catalyzed hydrosilylation, closely related to Rh-catalyzed hydroboration, was also reported by Tamao et al.[15] Since the intramolecular hydroboration of intermediate **A** in Scheme 1 was not very fast at −78 °C, it would be accelerated by the Rh(I) catalyst. While hoping to improve the *anti*/*syn* selectivity of the diols, we next carried out a reaction (borane, THF, −78 °C to room temperature) with 2—5 mol% of $Rh(PPh_3)_3Cl$. The results are given in Table 2.

Although ethenyl ether **3E** gave a 60/40 mixture of diols **1a** and **1b** in 53%, **3Z** gave a mixture of **1c**/**1d** with a 90/10 ratio in 53% yield. A similar observation, that the selectivity of the Pt-catalyzed hydrosilylation reaction of (*Z*)-olefin was better than that of (*E*)-olefin, has been reported by Tamao et al. According to them, the hydrosilylation-oxidation reaction of **3E** gives **1a** in a 3.5/1 ratio, while **3Z** gives **1c** in >10/1.[15]

Experimental

The IR spectra were measured using a JASCO A-202 IR spectrometer. The ^1H NMR spectra were recorded with a JEOL JNM-FX-90Q or JEOL JNM-PMX-60 spectrometer in $CDCl_3$, unless otherwise noted. The low- and high-resolution mass spectra were taken with a JEOL JMS D-300 mass spectrometer. All reactions were carried out in dry solvents under a nitrogen atmosphere.

(2*E*,4*R*)-1-Benzyloxy-2,4-dimethyl-5-ethenyloxy-2-pentene (3E). To a mixture of mercury(II) acetate (287 mg, 0.90 mmol, 1.53 equiv) and ethenyl ethyl ether (2 ml) at room temperature was added a solution of (2*R*,3*E*)-5-benzyloxy-2,4-dimethyl-3-penten-1-ol (**4E**) (130 mg, 0.59 mmol) in 3.5 ml ethenyl ethyl ether; the resulting mixture was refluxed for 17.5 h. During that period, another 5 ml of ethenyl ethyl ether was added. At the end of the reaction, 5 ml of ether and 6 ml of 5% aqueous potassium hydroxide solution were successively added. Extraction with ether followed by the usual work up and purification with silica gel flash column chromatography (hexane–ethyl acetate, 95:5) gave 131 mg (90%) of ethenyl ether (**3E**). ^1H NMR (CCl_4, 60 MHz) δ=1.03 (3H, d, J=7.0 Hz), 1.69 (3H, s), 2.8 (1H, m), 3.47 (2H, d, J=6.3 Hz), 3.80 (2H, s), 3.88 (1H, dd, J=6.7, 2.0 Hz), 4.31 (1H, dd, J=14.2, 2.0 Hz), 4.39 (2H, s), 5.21 (1H, d, J=9.2 Hz), 6.39 (1H, dd, J=14.2, 6.7 Hz), 7.23 (5H, s); IR (neat) 1630 (sh), 1610, 1200, 700 cm^{-1}; MS m/z (rel intensity) 246 (M^+; 0.1), 138 (M^+−$PhCH_2OH$; 100). Found: m/z 138.1052. Calcd for $C_9H_{14}O$ (M−$PhCH_2OH$): 138.1045.

(2*Z*,4*R*)-1-Benzyloxy-2,4-dimethyl-5-ethenyloxy-2-pentene (3Z). Essentially the same procedure described above using mercury(II) acetate (450 mg, 1.41 mmol, 1.19 equiv), ethenyl ethyl ether (9 ml), and (2*R*,3*Z*)-5-benzyloxy-2,4-dimethyl-3-penten-1-ol (**4Z**) (262 mg, 1.19 mmol) gave 283 mg (97%) of ethenyl ether (**3Z**). ^1H NMR (CCl_4, 60 MHz) δ=0.94 (3H, d, J=7.0 Hz), 1.80 (3H, s), 2.8 (1H, m), 3.46 (2H, d, J=6.3 Hz), 3.93 (1H, dd, J=7.0, 2.0 Hz), 4.01 (2H, s), 4.34 (1H, dd, J=14.1, 2.0 Hz), 4.44 (2H, s), 5.18 (1H, d, J=9.2 Hz), 6.37 (1H, dd, J=14.1, 7.0 Hz), 7.29 (5H, s); IR (neat) 1630 (sh), 1607, 1200, 700 cm^{-1}; MS m/z (rel intensity) 246 (M^+; 0.1), 138 (M^+−$PhCH_2OH$; 100). Found: m/z 138.1046. Calcd for $C_9H_{14}O$ (M−$PhCH_2OH$): 138.1045.

Typical Procedure of Cyclic Hydroboration. Ethenyl ether **3Z** (112 mg, 0.454 mmol) was dissolved in ether (5 ml); the solution was then cooled to −74 °C, to which was added (dropwise over a period of 2 h) a mixture of a 2.0 mol dm^{-3} ethereal solution of borane–dimethyl sulfide complex (1/1) (0.25 ml, 0.5 mmol, 1.1 equiv) and ether (5 ml). After the addition was completed, the cooling bath was removed, and the reaction mixture was stirred for 18 h at room temperature. To it was added 1 ml water, 1 ml 1 mol dm^{-3} aq sodium hydroxide, and 0.3 ml 35% aq hydrogen peroxide successively; the mixture was then stirred at 60 °C for 2 h. Extraction with ethyl acetate followed by the usual work up and silica-gel flash column chromatography (hexane–ethyl acetate, 70:30 to 50:50) gave a mixture of **1c** and **1d** (61 mg, 0.258 mmol, 57%), **1d** (15 mg, 0.063 mmol, 14%), and 2-hydroxyethyl ether **5** (11

Table 3. Selected ^{1}H NMR Data of Diol **1d**[a)]

In C_6D_6			
Data from Ref. 2	0.55 (3H, d, J=6.9 Hz)	0.93 (3H, d, J=6.9 Hz)	4.22 (2H, s)
Our data	1.03 (3H, d, J=7.4 Hz)	1.11 (3H, d, J=7.1 Hz)	4.26 (2H, s)
In $CDCl_3$			
Data from Ref. 3	1.01 (3H, d, J=7.0 Hz)	1.05 (3H, d, J=7.0 Hz)	4.50 (2H, s)
Our data	1.00 (3H, d, J=6.8 Hz)	1.05 (3H, d, J=6.8 Hz)	4.49 (2H, s)

a) Given in δ (ppm) downfield from tetramethylsilane as an internal standard.

mg, 0.037 mmol, 8%). The **1c**/**1d** ratio of the diol mixture was analyzed by ^{1}H NMR to be 90/10.

Typical Procedure of Cyclic Hydroboration with Rh(PPh$_3$)$_3$Cl. Ethenyl ether **3E** (133 mg, 0.538 mmol) was dissolved in THF (6 ml), and the solution was cooled to −74 °C. To it was added (dropwise over a period of 2 h) a mixture of a 2.0 mol dm^{-3} ethereal solution of borane–dimethyl sulfide complex (1/1) (0.30 ml, 0.6 mmol, 1.1 equiv) and THF (6 ml). To this was added (at that temperature) a solution of Rh(PPh$_3$)$_3$Cl (11 mg, 0.011 mmol, 2.1 mol%) in THF (4 ml). After the addition was completed, the cooling bath was removed, and the reaction mixture was stirred for 18 h at room temperature. To it was added 1 ml water, 1 ml 1 mol dm^{-3} aq sodium hydroxide, and 0.6 ml 35% aq hydrogen peroxide, successively; the mixture was then stirred at 60 °C for 2 h. Extraction with ethyl acetate followed by the usual work up and silica-gel flash column chromatography (hexane–ethyl acetate, 70 : 30 to 50 : 50) gave a mixture of **1a** and **1b** (68 mg, 0.285 mmol, 53%) and 2-hydroxyethyl ether **5** (33 mg, 0.116 mmol, 22%). The **1a**/**1b** ratio was analyzed by ^{1}H NMR to be 60/40.

Assignment of the Product Stereochemistry. The product ratio was determined by ^{1}H NMR. Namely, the chemical shift values of two doublet methyls were compared with the values reported in the Refs. 2 and 3; the ratio was calculated from the integration values. It should be noted that the chemical shift values of the diol **1d** in C_6D_6 reported by Nagaoka and Kishi in Ref. 2 are not in good accordance with those of ours. However, ours were identical with the data of **1d** in $CDCl_3$ reported by Oikawa et al. in Ref. 3. The chemical shift data of **1d** are listed in Table 3.

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