Asymmetric Synthesis of Syn 1,2-Diols via the Reaction of Aldehydes with Chiral γ-(Tetrahydropyranyloxy)allylstannanes

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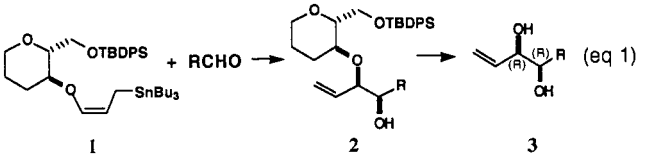
Summary: Asymmetric synthesis of syn 1,2-diols **3** has been accomplished via the reaction of the chiral γ-alkoxy-substituted allylstannane **1** with aldehydes in the presence of $AlCl_3$ or $AlCl_3$·OEt_2, followed by a five-step operation to remove the chiral auxiliary.

Asymmetric synthesis of syn and/or anti 1,2-diols via the "α-alkoxyallylation"[1p] of aldehydes with γ-alkoxyallylmetal reagents has received considerable attention in recent years.[1] Enantioselective synthesis of syn and anti 1,2-diols[1p] has been accomplished by using allylboranes having chiral auxiliaries directly bonded to the boron atom (BL_n*). Allylboranes having a chiral auxiliary at the allyl terminus have been used for the asymmetric synthesis of syn 1,2-diols.[1i] Although allylboranes are useful reagents for allylation of electrophiles, they are less air- and moisture-stable than allylstannanes. This characteristic of the borane reagents becomes a significant drawback when they are used for intramolecular reactions, since the starting materials including the borane group are often exposed to air and/or moisture before the cyclization. We needed a stable γ-alkoxy-substituted allylstannane having a chiral alkoxy auxiliary. Syn 1,2-diols have been prepared with high ee via the intermolecular reaction of allylstannanes having an asymmetric center at the α-position.[1h] We wish to report another approach to the enantioselective synthesis of syn 1,2-diols: the reaction of the γ-(tetrahydropyranyloxy)allylstannane **1** with aldehydes in the presence of $AlCl_3$·OEt_2 or $AlCl_3$. The syn adducts **2** were formed with high diasteroeselectivities and were converted to syn diols **3** upon removal of the chiral alkoxy group (eq 1).

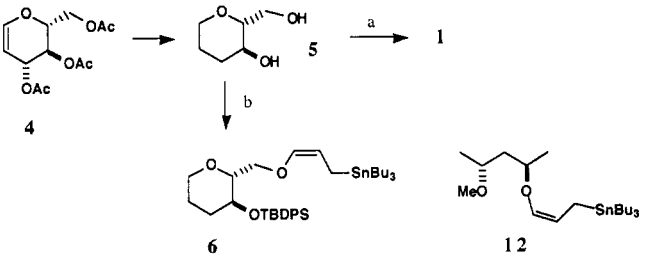


1 2 3

Tri-*O*-acetyl-D-glucal (**4**), an easily available and cheap chiral starting material, was converted to diol **5** according to the literature procedure.[2] As shown in Scheme I, selective protection of the primary OH of **5** by tritylation, conversion of the secondary OH to allyl ether, removal of the trityl group, protection of the primary OH as the *tert*-butyldiphenylsilyl (TBDPS) ether, and subsequent lithiation and trapping with Bu_3SnCl[3] gave **1** in 54% overall yield from **4**. γ-Alkoxyallylstannane **6** was also prepared from **5** via procedures similar to those used for the synthesis of **1** (see Scheme I, b). The reaction of **1** with aldehydes proceeded smoothly in the presence of BF_3·OEt_2, $AlCl_3$, or $AlCl_3$·OEt_2 in CH_2Cl_2. The results are summarized in Table I.

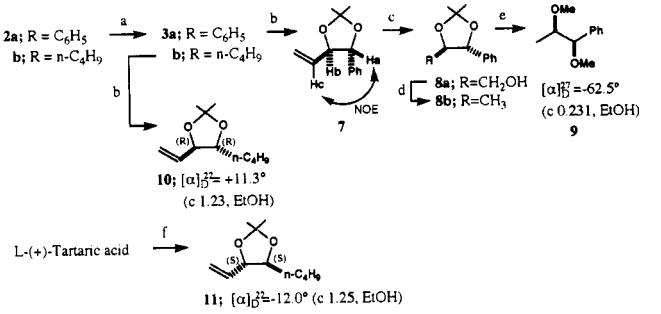
Both aromatic and aliphatic aldehydes afforded the syn adducts **2** with very high diastereoselectivities upon treatment with BF_3·OEt_2, $AlCl_3$, or $AlCl_3$·OEt_2. The ratio of **2** to its anti isomer was greater than 97:3; the use of $TiCl_4$ and $SnCl_4$ gave unsatisfactory results (entries 4 and 5). Reactive aldehydes such as benzaldehyde and *p*-nitrobenzaldehyde gave **2** in high to good chemical yields (entries 1–3, 6), but the reaction of *p*-tolualdehyde and

Scheme I[a]



[a] Key: (a) (1) TrCl, DMAP, DMF; (2) allyl bromide, KH; (3) HCl, MeOH; (4) TBDPSCl, imidazole, DMF; (5) *sec*-BuLi, TMEDA, Bu_3SnCl; (b) (1) TrCl, DMAP, DMF; (2) TBDPSCl, imidazole; (3) TsOH, MeOH; (4) allyl bromide, KH; (5) *sec*-BuLi, TMEDA, Bu_3SnCl.

Scheme II.[a] **Determination of Absolute Configuration**



[a] Key: (a) MOMCl, *i*-Pr_2NEt; (2) Bu_4NF; (3) $(COCl)_2$, DMSO, Et_3N; (4) K_2CO_3; (5) HCl; (b) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2; (c) (1) O_3/MeOH, Me_2S, (2) $LiAlH_4$; (d) (1) MsCl, pyridine, (2) $LiAlH_4$; (e) (1) TsOH/MeOH, (2) MeI/NaH; (f) (1) MeOH, HCl; (2) $Me_2C(OMe)_2$, TsOH; (3) LAH; (4) KH, TsCl; (5) *n*-Pr_2CuLi; (6) $(COCl)_2$, DMSO, Et_3N; (7) Ph_3PCH_3Br, *n*-BuLi.

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Table I. Asymmetric Synthesis of 1,2-Diol Derivatives[a]

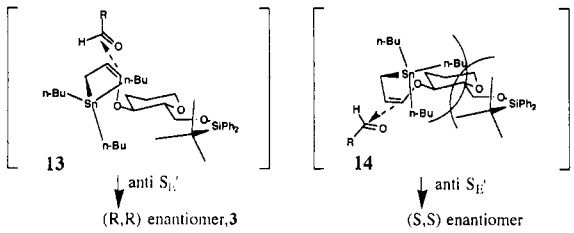
entry	aldehyde (RCHO) R	Lewis acid	reaction time at −78 °C, h	product 2 yield, %	isomer ratio syn(2):anti	de of 2, % (abs confign at C-1, C-2)
1	C_6H_5	$BF_3{\cdot}OEt_2$	1	82	97:3	67 (*R*,*R*)
2	C_6H_5	$AlCl_3{\cdot}OEt_2$	1	68	97:3	88 (*R*,*R*)
3	C_6H_5	$AlCl_3$	0.17	52	97:3	92 (*R*,*R*)
4	C_6H_5	$TiCl_4$	1	48	73:27	73 (*R*,*R*)
5	C_6H_5	$SnCl_4$	1	no reaction		
6	*p*-$NO_2C_6H_4$	$AlCl_3{\cdot}OEt_2$	3	80	100:3	76
7	*p*-MeC_6H_4	$AlCl_3{\cdot}OEt_2$	3	47	98:2	90
8	*n*-C_7H_{15}	$BF_3{\cdot}OEt_2$	3	17	100:0	63
9	*n*-C_7H_{15}	$AlCl_3{\cdot}OEt_2$	2	26	93:7	63
10	*n*-C_7H_{15}	$AlCl_3$	0.25	47	98:2	85
11	*n*-C_4H_9	$AlCl_3{\cdot}OEt_2$	2	21	96:4	65 (*R*,*R*)
12	*n*-C_4H_9	$AlCl_3$	0.67	53	98:2	89 (*R*,*R*)
13	CH_3	$AlCl_3$	0.17	47	100:0	94

[a] The reaction was carried out, in general, with the following molar ratios: Lewis acid:aldehyde:1 = 1.2:1:1. However, in entries 3, 10, 12, and 13, 2 equiv of the aldehydes was used. The isomer ratios and de in entries 1–7 were determined by ^1H NMR; the coupling constants of the syn-isomers were 7.5 Hz whereas those of the anti-isomers were 4.0 Hz. The aldehydes were recovered when the addition resulted in low yields. The ratios and de in entries 8–13 were determined by HPLC. (Shimazu LC-6A); **2b** (R = *n*-Bu), column Merck Hibar RT 250-4, hexane:EtOAc = 5:1, flow rate 1.5 mL/min, t_R/min 6.80 (*RR*), 9.50 (*SS*), 9.75 (anti), 10.47 (anti); **2c** (R = *n*-C_7H_{15}), column YMC R-SIL S-5 60A, hexane:EtOAc = 10:1, flow rate 1.5 mL/min, t_R/min 8.03 (*RR*), 11.13 (*SS* + anti), 12.11 (anti); **2d** (R = Me), column YMC R-SIL-5-06 S-5 60A, hexane:EtOAc = 5:1, flow rate 1.5 mL/min, t_R/min 9.62 (*RR*), 12.57 (*SS*).

some aliphatic aldehydes resulted in moderate to low yields (entries 7–13). The diastereomeric excess of **2** (the ratio of **2**:(**2** + its (*S*,*S*) isomer)) was high when $AlCl_3{\cdot}OEt_2$ or $AlCl_3$ was used as Lewis acid (entries 2, 3, 7, 10, 12, and 13), while $BF_3{\cdot}OEt_2$ led to decreased de ratios. For aliphatic aldehydes the use of $AlCl_3$ gave higher stereoselectivity than $AlCl_3{\cdot}OEt_2$, whereas both Lewis acids produced high de ratios with aromatic aldehydes. Aluminum chloride–etherate complex is soluble in CH_2Cl_2, but $AlCl_3$ itself is insoluble. The aldehydes and $AlCl_3$ (solid) were first combined in a 2:1.2 ratio, and the resulting mixture, upon stirring, became homogeneous and finally soluble in CH_2Cl_2.

The absolute configurations of **2a** and **2b** were determined in the following manner (Scheme II). The hydroxyl groups of **2a** (obtained in entry 1, 67% de) and **2b** (obtained in entry 12, 89% de) were protected as MOM ethers, and the TBDPS group was removed by treatment with Bu_4NF. The resulting primary OH was oxidized to give the corresponding aldehyde. Retro-Michael reaction in the presence of base, followed by removal of the MOM protecting group, afforded **3a** in 64% overall yield. Diol **3a** was converted to acetonide **7** in 80% yield. NOE enhancement was observed between the Ha and Hc protons of **7**, but not between the Ha and Hb protons, indicating the syn stereochemistry of **3a**. Ozonolysis of **7** (O_3/MeOH/Me_2S) followed by $LiAlH_4$ reduction gave alcohol **8a** in 87% yield. The conversion of the alcohol to methanesulfonate followed by reduction gave **8b** in 83% yield. Hydrolysis of the acetonide followed by methylation afforded **9** in 56% yield; $[\alpha]^{27}_D$ = −62.5° (*c* 0.23, EtOH). This rotation was compared with that of authentic *R*,*R* enantiomer; $[\alpha]^{24}_D$ = −83.8° (*c* 0.370, EtOH).[4] Similarly, **2b** was converted to **3b**, which was transformed to **10** by standard procedures; $[\alpha]^{22}_D$ = +11.3° (*c* 1.23, EtOH). Authentic **11** was obtained in 6% overall yield; $[\alpha]^{22}_D$ = −12.0° (*c* 1.25, EtOH).[5] Accordingly, it is clear that the absolute configurations of **2a** and **2b** are 1*R*,2*R* and 3*R*,4*R*, respectively.

Scheme III



Reaction of **6** with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ gave the corresponding syn adducts exclusively in high yield, but the diastereomer excess was only 24%. This lower de is presumably attributable to the fact that the asymmetric center of **6** is three bond lengths away from the γ-carbon at which the carbon-carbon bond formation takes place, whereas alkylation of **1** occurs only two bond lengths from the nearest chiral center. The $BF_3{\cdot}OEt_2$-mediated reaction of benzaldehyde with **12**, in which the asymmetric center is separated by two bond lengths from the γ-carbon, produced the corresponding syn adducts with 28% de. Although the chiral center of **12** is close to the reactive carbon, efficient blocking of one face of the double bond is not accomplished with this chiral auxiliary.

The enantioselective formation of the *R*,*R* isomer via **1** may be accounted for by transition state **13** shown in Scheme III. The front side of the plane, consisting of the γ-oxygen and the three carbon atoms at the α, β, and γ-positions, is blocked by the sterically bulky TBDPS groups, forcing the aldehyde to approach the γ-carbon from the back side of the plane. Although antiperiplanar approach of the aldehyde is shown in both **13** and **14**, synclinal orientation of the aldehyde is also conceivable; both approaches lead to the same result. An important question is why **13** is favored over **14**. It is well accepted that the Lewis acid-mediated allylstannane–aldehyde condensation proceeds in an anti S_E' manner;[6] the tributylstannyl group has to be located on the front side of the allyl plane. A molecular model of **14** clearly indicates

(4) Yamada, J.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118. This number of rotations corresponds to 74.5% ee of **9**.

(5) L-(+)-Tartaric acid was treated with MeOH/HCl to give the corresponding methyl ester and the two hydroxyl groups were protected with acetonide. $LiAlH_4$ reduction of the ester groups afforded the corresponding diol, which was converted to monotosylate upon treatment with KH/TsCl. Substitution of the tosylate with *n*-Pr_2CuLi gave the carbon-chain elongated product. The remaining primary OH was oxidized to the corresponding aldehyde, which was converted to **11** by a Wittig reaction.

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severe steric repulsion between Bu_3Sn and TBDPS groups, whereas such steric hindrance is significantly diminished in **13**.

It was seemed likely that the steric size of the 2-(hydroxymethyl) substituent on the tetrahydropyran ring would play an important role in the asymmetric induction of these allylstannane–aldehyde condensations. To test this hypothesis, we prepared the corresponding OCH_3 (**15**, 2-[(methoxymethyl)oxy] THP) and CH_3 (**16**, 2-methyl THP) derivatives of the γ-alkoxyallylstannane. The Lewis acid-mediated reaction of **15** and **16** with benzaldehyde gave the syn adducts in good yields, but the diastereomer ratios of *RR*:*RS* were 2.5:1 and 1:1, respectively. Therefore, it is now clear that steric bulk of the alkoxy group is important to obtain high enantio- and diastereoselection.

Synthesis of **2a** is representative (entry 3 of Table I). In a 50-mL two-necked flask under Ar were placed dry CH_2Cl_2 (1 mL) and anhyd $AlCl_3$ (35 mg, 0.26 mmol), purified by sublimation of commercially available material. Benzaldehyde (45 μL, 0.44 mmol) was slowly added at −78 °C, and the resulting mixture was stirred for 30 min. To the resulting homogeneous solution was added slowly a dry CH_2Cl_2 (1 mL) solution of **1** (158 mg, 0.22 mmol), cooled at −78 °C. The reaction was continued for 10 min and quenched with MeOH. The mixture was allowed to warm to rt. Extraction with ether, concentration in vacuo, treatment with aqueous KF solution at rt for 1 h, extraction with ether, washing with brine, drying ($MgSO_4$), concentration in vacuo, and purification by flash column chromatography 15 cm × 17 mm; hexane, 50 mL and then hexane:AcOEt = 10:1) gave **2a** (58.9 mg, 0.114 mmol) in 52% yield.

Supplementary Material Available: Synthetic methods, characterization data, and NMR spectra (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of an Acylphosphate Driven by a Proton Gradient. A Model for H^+-ATPase

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Summary: We describe the first model for a proton pump, H^+-ATPase. This model uses the energy from an indirect transfer of two protons from a solution at pH 0.3 to a solution at pH 10 to drive the synthesis of a high-energy phosphate, citraconyl phosphate.

H^+-ATPases link proton transfer across cell membranes to the synthesis or hydrolysis of ATP. Some H^+-ATPases synthesize ATP using a proton gradient as the driving force (e.g., F_oF_1-ATPase in mitochondria); others create a proton gradient using the hydrolysis of ATP as the driving force (e.g., H^+/K^+-ATPase in the mucosa of the stomach).[1] While some mechanistic features of these enzymes are known,[2] the molecular-level mechanism of coupling is not. Other models of active transport have shown how proton transport can drive the transport of other cations;[3] this is the first model that shows how proton transport can drive the synthesis of a high-energy phosphate, citraconyl phosphate.

To model a proton gradient across a lipid bilayer, we separated solutions of pH 0.3 and pH 10 with a layer of chloroform in a concentric ring cell, Figure 1a. When the acidic compartment contained citraconic acid (1.0 M), protons (detected by pH stat) and citraconate dianion (detected by ^{1}H-NMR) were transferred to the basic compartment.

Citraconic acid did not pass directly from the acidic to the basic compartment. Instead, citraconic acid dehydrated to the anhydride, which then diffused to the basic compartment, hydrolyzed, and generated two protons, Figure 1b. We call this mechanism of proton transfer indirect because the protons that appeared in the basic compartment upon hydrolysis of anhydride came from water, not from the acidic compartment. It is a true proton transfer since a molecule of citraconic acid has been removed from the acidic compartment and the citraconate dianion and two protons generated in the basic compartment. In support of this mechanism, citraconic anhydride (0.6 mol %) was detected in an acidic aqueous solution of citraconic acid by ^{1}H-NMR. This facile formation of anhydride is due to the high effective molarity of the neighboring carboxylic acid group.[4] The equilibrium constant for dehydration of citraconic acid is larger than that for maleic acid (<0.2 mol %) and succinic acid (10^{-4} mol %) but smaller than that for dimethylmaleic acid (84 mol %).[5] In a parallel experiment involving only two phases, a ^{1}H-NMR of a $CDCl_3$ phase, equilibrated with acidic aqueous citraconic acid (1.0 M, 0.5 M HCl), showed only citraconic anhydride (65 ± 10 mM, <2 mM citraconic acid). More anhydride formed in the chloroform phase because there was less water in the chloroform (50 mM H_2O) and because the anhydride was more soluble in the chloroform than the acid. Thus, protons were indirectly transferred across the chloroform layer via citraconic anhydride.

Transfer of two protons from pH 0.3 to pH 10 released 26.5 kcal, while formation of citraconic anhydride at pH 10 ($-\Delta G°_{hyd}$) required 18.8 kcal/mol, based on K_{hyd} = 167 for uncharged citraconic acid and pK_1 = 2.29 and pK_2 = 6.15.[6] Thus, indirect proton transfer provided a thermodynamic driving force of 7.7 kcal/mol for the formation of citraconic anhydride.

The high free energy of hydrolysis of citraconic anhydride indicates that it is thermodynamically capable of making high-energy phosphates such as acyl phosphates.

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