

## Prins Cyclization of 4-Allyl-1,3-Dioxanes Prepared from 1,3-Diol Synthons. A Rapid Entry into Functionalized Tetrahydropyrans

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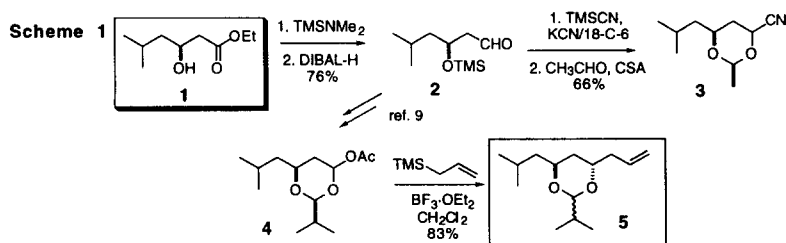
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*Key Words:* Prins cyclization, 1,3-diols, tetrahydropyrans.

**Abstract:** A variety of 4-allyl-1,3-dioxanes were prepared and cyclized to give 4-chloro or 4-acetoxy tetrahydropyrans in good yields and with high stereoselectivity.  
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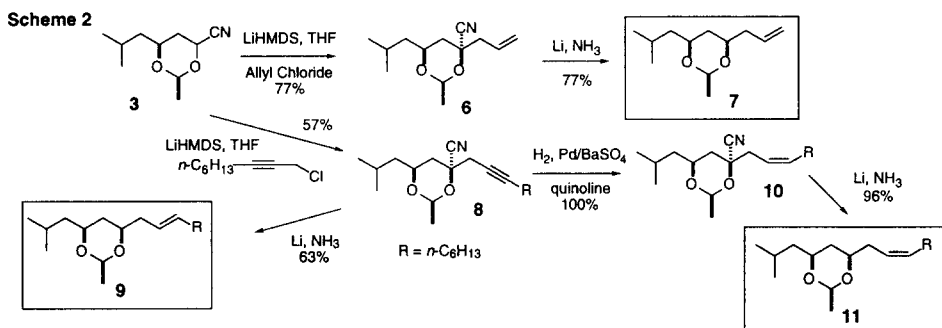
Prins cyclizations have been used to prepare a variety of monoxygenated rings.<sup>1</sup> Cyclizations of mixed acetals to tetrahydrofurans were among the early examples of this reaction,<sup>2,3</sup> which has since been extended to the preparations of oxepanes<sup>4</sup> and oxocanes.<sup>5</sup> Mixed acetals derived from unsaturated alcohols are the most common precursors, although there are isolated examples using acetals of unsaturated diols.<sup>6</sup> We became interested in Prins cyclizations as an approach to oxygenated tetrahydropyran rings found in natural products such as althohyrin (spongistatin).<sup>7</sup> The cyclization substrates were envisioned to arise from straightforward extensions of our 1,3-diol synthon chemistry.<sup>8,9</sup> Allylation of 1,3-diol synthons followed by Prins cyclization provide a rapid entry into functionalized tetrahydropyrans in which three new stereogenic centers are introduced stereoselectively.

The 1,3-diol synthons **3** and **4** were prepared from 3-hydroxy ester **1** as illustrated in Scheme 1.<sup>10</sup> The 4-cyano-1,3-dioxane **3** was prepared via aldehyde **2** by cyanohydrin formation and protection as an acetaldehyde acetal. This procedure is directly analogous to our synthesis of cyanohydrin acetonides.<sup>8</sup> Conversion of aldehyde **2** to acetate **4** has been previously reported, and involves equilibration of the 3-hydroxy aldehyde with excess isobutyraldehyde followed by acetylation of the intermediate 4-hydroxy-1,3-dioxane.<sup>9</sup> The coupling of acetate **4** with allyltrimethylsilane was promoted by  $\text{BF}_3 \cdot \text{OEt}_2$ , and produced the trans adduct **5** with >95:5 selectivity.<sup>9</sup>



The cis adducts **7**, **9**, and **11** were prepared by alkylation and reductive decyanation of 4-cyano-1,3-dioxane **3** as shown in Scheme 2. Deprotonation of **3** with  $\text{LiHMDS}$  and alkylation with allyl

chloride gave **6** as a single stereoisomer, and reductive decyanation with  $\text{Li}/\text{NH}_3$  produced the all-equatorial adduct **7** with >99:1 selectivity. The stereoselectivity of the reductive decyanation route complements that of the  $\text{BF}_3\cdot\text{OEt}_2$ -promoted allylation. More complex unsaturated side chains can be introduced by direct alkylation, but geometrically defined *E* and *Z* allyl chlorides can be difficult to prepare. The route we developed begins with alkylation of **3** with 1-chloro-2-nonyne. Standard conditions for the reductive decyanation of **8** lead to concomitant reduction of the alkyne to the syn *E*-alkene **9**. The *Z*-alkene **11** was prepared by Lindlar's hydrogenation followed by reductive decyanation. Each of the Prins cyclization substrates was prepared as single diastereomer from 1,3-diol synthon **3** or **4**.



Prins cyclizations were initially investigated using  $\text{TiCl}_4$ .<sup>3</sup> Entries 1,5,6, and 9 in Table 1 show that each of these cyclizations proceed in high yield, and with the exception of the *Z*-alkene **11**, the stereoselectivity is better than 93:7 in each case. Alkene **11** leads to a 2:1 mixture of stereoisomers where the major and minor isomers have equatorial and axial chlorides, respectively. These cyclizations are related to the oxonium-ion initiated polyene cyclizations developed by Johnson.<sup>11</sup> The synthetic targets of interest have oxygen rather than halogen substitution at the 4-position of the tetrahydropyran, so cyclization and trapping with various oxygen nucleophiles was investigated.<sup>6</sup> The best general conditions are C in Table 1 and involve cyclization with 4 equiv.  $\text{BF}_3\cdot\text{OEt}_2$ , 10 equiv. HOAc, and 2 equiv. TMSOAc in cyclohexane at 25 °C.<sup>12</sup> The reaction products were acetylated to simplify analysis. The TMSOAc leads to a modest increase in yield, and the nonpolar cyclohexane solvent reduces the amount of fluoride trapping<sup>13</sup> (compare entries 3 & 4). Cyclizations of **5** and **7** produce the equatorial acetate products **16** and **15** in ca. 85% yield with > 90% diastereoselectivity. The cyclization and trapping with acetate were further investigated using substrates **12** and **13**, which were prepared in a route analogous to the preparation of **5**.<sup>9</sup> These more highly substituted systems cyclize less efficiently but still show useful levels of stereoselectivity. An unusual result was found when the cyclization of **5**

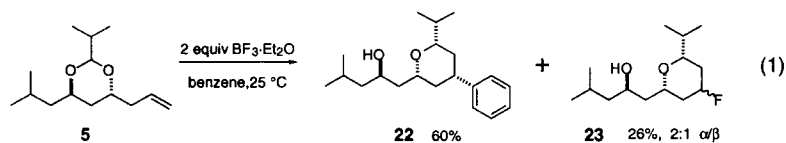


Table 1. Prins Cyclization of 4-Allyl-1,3-Dioxanes Promoted by Lewis Acids.

Entry #	SM	Conditions <sup>a</sup>	Yield	Product	Selectivity <sup>b</sup>	
1		7 A	81% (X = Cl, Y = OH)		15	93:7
2		B	86% (X, Y = OAc)			91:7:2
3		5 C	84% (X = OAc)		16	94:6
4		D	54% (X = OAc) 33% (X = F)			
5		9 A	71%		17	98:2
6		11 A	70%		18	67:33
7		12 E	65% (X = OAc) 14% (X = F)		19	88:7:5
8		13 C	41%		20	83:17
9		14 F	95%		21	95:5

(a) Conditions. **A**: 2 equiv.  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h. **B**: i. 4 equiv.  $\text{BF}_3\cdot\text{OEt}_2$ , 10 equiv. HOAc, cyclohexane,  $25^\circ\text{C}$ ; ii.  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP. **C**: i. 4 equiv.  $\text{BF}_3\cdot\text{OEt}_2$ , 10 equiv. HOAc, 2 equiv. TMSOAc, cyclohexane,  $25^\circ\text{C}$ ; ii.  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP. **D**: i. 2 equiv.  $\text{BF}_3\cdot 2\text{AcOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-10$ – $0^\circ\text{C}$ ; ii.  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP. **E**: i. 10 equiv.  $\text{BF}_3\cdot\text{OEt}_2$ , 10 equiv. HOAc, cyclohexane,  $25^\circ\text{C}$ ; ii.  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP. **F**: 2 equiv.  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-98^\circ\text{C}$ , 2 h. (b) The major isomer is shown and the second isomer results from axial trapping at the 4-position of the tetrahydropyran ring. The configurations of other minor isomers were not determined.

was attempted in benzene, eq. 1. The major product **22** arose from a stereoselective Friedel-Crafts alkylation of benzene by the intermediate secondary cation. Each of these cyclizations proceeds in reasonable to excellent yield with complete stereochemical induction at the 4- and 6-positions of the newly formed tetrahydropyran ring.

The single stereogenic center in 3-hydroxy ester **1** directs the introduction of three new stereogenic centers in tetrahydropyran products **15** and **16**. Thus in a few steps, readily available 3-hydroxy esters can be converted into single diastereomers of complex tetrahydropyrans. These transformations will be valuable in natural products synthesis.<sup>14</sup>

#### References and Footnotes

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- <sup>10</sup> Racemic 3-hydroxy esters were used in these studies.
- <sup>11</sup> Bartlett, P. A. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341-409.
- <sup>12</sup> Sample experimental: cyclization of **5** to **16** (X = OAc). 4-Allyl-1,3-dioxane **5** (200 mg, 0.88 mmol), AcOTMS (265  $\mu$ L, 1.76 mmol, 2 equiv) and AcOH (506  $\mu$ L, 8.80 mmol, 10 equiv) were dissolved in 13 mL cyclohexane under N<sub>2</sub> at room temperature. BF<sub>3</sub>·Et<sub>2</sub>O (435  $\mu$ L, 3.53 mmol, 4 equiv) was added dropwise. After stirring for 4 h, the reaction was quenched with saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> ( $\times$  3). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated. The resulting mixture was treated with excess Ac<sub>2</sub>O, Et<sub>3</sub>N and a catalytic amount of DMAP in CH<sub>2</sub>Cl<sub>2</sub>. Aqueous workup and purification by flash chromatography (SiO<sub>2</sub>, 10% EtOAc/hexanes) gave 245 mg (0.75 mmol, 84 %) product of 94:6 mixture of diastereomers as a pale yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.19 (dddd, *J* = 8.5, 8.5, 5.0, 3.5 Hz, 1 H); 4.85 (tt, *J* = 11.0, 5.0 Hz, 1 H); 3.30 (tt, *J* = 10.5, 1.5 Hz, 1 H); 2.94 (ddd, *J* = 11.0, 6.5, 2.0 Hz, 1 H); 2.02 (s, 3 H); 2.00 (s, 3 H); 1.98-1.86 (m, 1 H); 1.68-1.48 (m, 5 H); 1.35-1.17 (m, 4 H); 0.95-0.83 (m, 12 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  C, 169.8, 169.8; CH, 79.9, 71.2, 70.3, 69.3, 32.4, 24.1; CH<sub>2</sub>, 43.5, 40.7, 37.1, 33.7; CH<sub>3</sub>, 22.3, 21.7, 20.6, 20.6, 18.0, 17.9. IR (neat, cm<sup>-1</sup>) 2959, 2873, 1739, 1468, 1369, 1241, 1162, 1027. Anal. Calcd for C<sub>18</sub>H<sub>32</sub>O<sub>5</sub>: C, 65.82; H, 9.82. Found: C, 65.86, H, 9.69.
- <sup>13</sup> Tetrahydropyran **16** (X = F, entry 4) was produced as a 2:1 mixture of equatorial and axial fluorides.
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