Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8679-8682, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02008-4

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

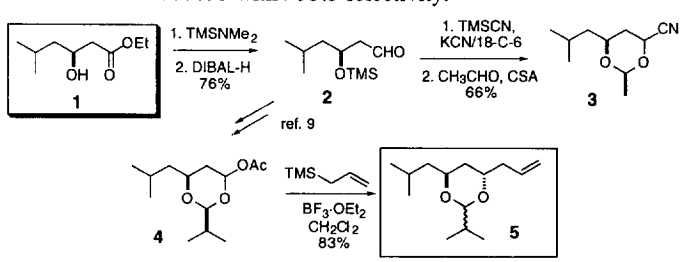
Yueqing Hu, Donald J. Skalitzky, and Scott D. Rychnovsky*
Department of Chemistry, University of California,
Irvine, CA 92697-2025
Key Words: Prins cyclization, 1,3-diols, tetrahydropyrans .

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.

Prins cyclizations have been used to prepare a variety of monooxygenated rings.[1] Cyclizations of mixed acetals to tetrahydrofurans were among the early examples of this reaction,[2,3] which has since been extended to the preparations of oxepanes[4] and oxocanes.[5] Mixed acetals derived from unsaturated alcohols are the most common precursors, although there are isolated examples using acetals of unsaturated diols.[6] We became interested in Prins cyclizations as an approach to oxygenated tetrahydropyran rings found in natural products such as altohyrtin (spongistatin).[7] The cyclization substrates were envisioned to arise from straightforward extensions of our 1,3-diol synthon chemistry.[8,9] 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.[10] 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.[8] 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.[9] The coupling of acetate **4** with allyltrimethylsilane was promoted by $BF_3{\cdot}OEt_2$, and produced the trans adduct **5** with >95:5 selectivity.[9]

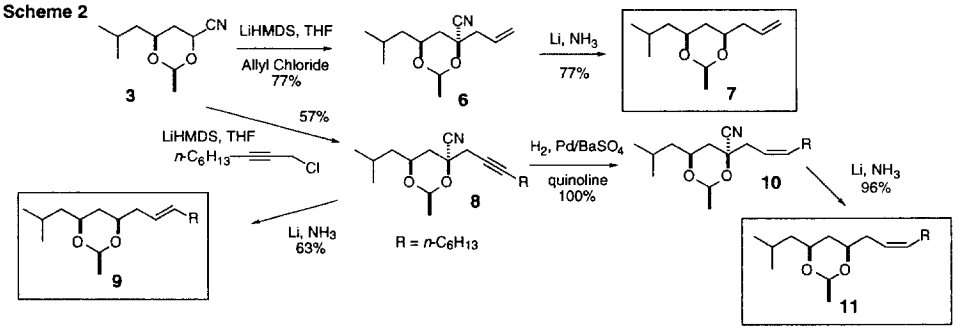
Scheme 1



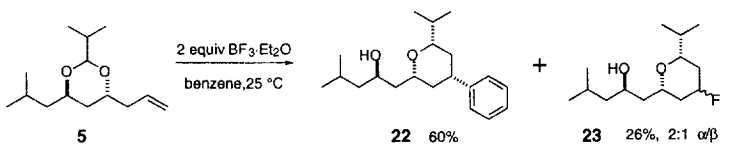
The cis adducts **7**, **9**, and **11** were prepared by alkylation and reductive decyanation of 4-cyano-1,3-dioxane **3** as shown in Scheme 2. Deprotonation of **3** with LiHMDS and alkylation with allyl

chloride gave **6** as a single stereoisomer, and reductive decyanation with Li/NH_3 produced the all-equatorial adduct **7** with >99:1 selectivity. The stereoselectivity of the reductive decyanation route complements that of the $BF_3{\cdot}OEt_2$-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**.

Scheme 2

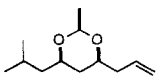
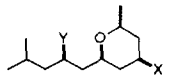
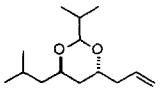
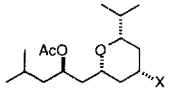
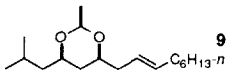
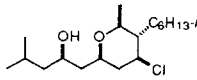
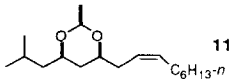
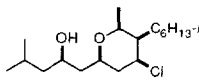
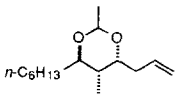
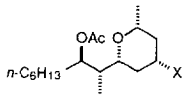
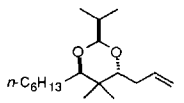
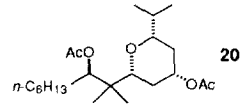
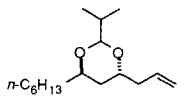
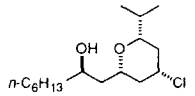


Prins cyclizations were initially investigated using $TiCl_4$.[3] Entries 1,5,6, and 9 in Table 1 show that each of these cyclizations proceed in high yield, and with the exception of the *Z*-alkene **11**, the stereoselectivity is better than 93:7 in each case. Alkene **11** leads to a 2:1 mixture of 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.[11] 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.[6] The best general conditions are **C** in Table 1 and involve cyclization with 4 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. HOAc, and 2 equiv. TMSOAc in cyclohexane at 25 °C.[12] 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[13] (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**.[9] 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**



(1)

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

Entry #	SM		Conditions[a]	Yield	Product		Selectivity[b]
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. $TiCl_4$, CH_2Cl_2, -78 °C, 2 h. **B**: i. 4 equiv. $BF_3{\cdot}OEt_2$, 10equiv. HOAc, cyclohexane, 25 °C; ii. Ac_2O, Et_3N, DMAP. **C**: i. 4 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. HOAc, 2 equiv. TMSOAc, cyclohexane, 25 °C; ii. Ac_2O, Et_3N, DMAP. **D**: i. 2 equiv. $BF_3{\cdot}2AcOH$, CH_2Cl_2, -10–0° C; ii. Ac_2O, Et_3N,DMAP. **E**: i. 10 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. HOAc, cyclohexane, 25°C; ii. Ac_2O,Et_3N, DMAP. **F**: 2 equiv. $TiCl_4$, CH_2Cl_2, -98 °C, 2 h.
(b) The major isomer is shown andthe second isomer results from axialtrapping 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.[14]

References and Footnotes

[1] Snider, B. B. in *Comprehensive Organic Synthesis*, ; Trost, B. M., Fleming, I. and Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, pp 527-561.

[2] (a) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479-485. (b) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053-1061.

[3] (a) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275-277. (b) Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653-2654. (c) Nikolic, N. A.; Gonda, E.; Longford, C. P. D.; Lane, N. T.; Thompson, D. W. *J. Org. Chem.* **1989**, *54*, 2748-2751. (d) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925-3927.

[4] Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695-5707.

[5] Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386-4399.

[6] (a) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915-5918. (b) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035-2038.

[7] Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243-1246.

[8] Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550-5551.

[9] (a) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, *57*, 4336-4339. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555-556. (c) Boons, G.-J.; Everson, R.; Smith, S.; Stauch, T. *Synlett* **1996**, 536-538.

[10] Racemic 3-hydroxy esters were used in these studies.

[11] Bartlett, P. A. in *Asymmetric Synthesis* ; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341-409.

[12] Sample experimental: cyclization of **5** to **16** (X = OAc). 4-Allyl-1,3-dioxane **5** (200 mg, 0.88 mmol), AcOTMS (265 μL, 1.76 mmol, 2 equiv) and AcOH (506 μL, 8.80 mmol, 10 equiv) were dissolved in 13 mL cyclohexane under N_2 at room temperature. $BF_3{\cdot}Et_2O$ (435 μL, 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_2Cl_2 (× 3). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was treated with excess Ac_2O, Et_3N and a catalytic amount of DMAP in CH_2Cl_2. Aqueous workup and purification by flash chromatography (SiO_2, 10% EtOAc/hexanes) gave 245 mg (0.75 mmol, 84 %) product of 94:6 mixture of diastereomers as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 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). ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 169.8, 169.8; CH, 79.9, 71.2, 70.3, 69.3, 32.4, 24.1; CH_2, 43.5, 40.7, 37.1, 33.7; CH_3, 22.3, 21.7, 20.6, 20.6, 18.0, 17.9. IR (neat, cm^{-1}) 2959, 2873, 1739, 1468, 1369, 1241, 1162, 1027. Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.86, H, 9.69.

[13] Tetrahydropyran **16** (X = F, entry 4) was produced as a 2:1 mixture of equatorial and axial fluorides.

[14] This work was supported by the NIH, the NSF, and Pfizer, Inc.

(*Received in USA* 23 *August* 1996; *accepted* 7 *October* 1996)