Stereocontrolled Synthesis of Trisubstituted Tetrahydropyrans

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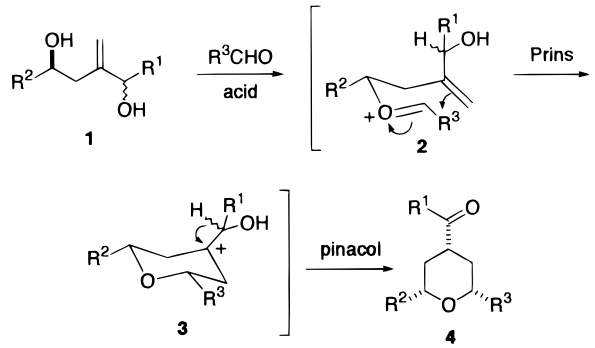
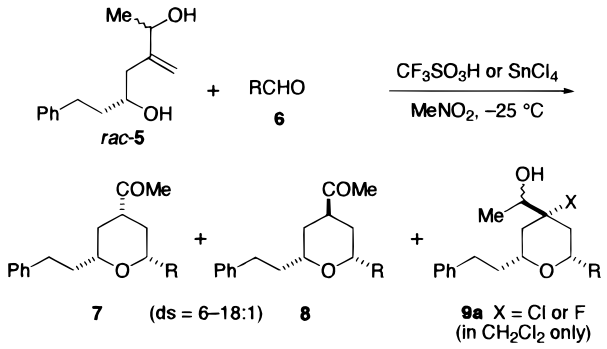
Tetrahydropyrans are structural features of a variety of biologically active natural products such as polyether antibiotics, marine toxins, and pheromones.[1] Although structurally complex tetrahydropyrans are most often assembled by cyclizations that form a C−O bond, the preparation of these heterocycles through C−C bond-forming Prins cyclizations is becoming increasingly important.[2−4] Recent studies in our laboratories have highlighted the opportunities in ring construction provided by employing a pinacol rearrangement to terminate a Prins cyclization.[4b,5] In this paper, we report a new Prins−pinacol reaction sequence that allows tetrahydropyrans having carbon side chains at C2, C4, and C6 to be conveniently synthesized by acid-promoted condensation of 2-methylene-1,4-diols with aldehydes (Scheme 1).

Reaction conditions for this new tetrahydropyran synthesis were initially optimized for the condensation of racemic diol **5** with 3-phenylpropanal (**6a**, R = $PhCH_2CH_2$, Scheme 2). In the presence of 0.5 equiv of $SnCl_4$, *rac*-**5** reacted with 2 equiv of **6a** within 2 h at −25 °C in nitromethane (0.25 M) to yield tetrahydropyrans **7a** and **8a** in a 10:1 ratio and 75% combined yield (Scheme 2). Of the other Lewis acids screened, $BF_3{\cdot}OEt_2$ (1 equiv) was the most effective and provided **7a** and **8a** in a similar ratio and 65% yield. Nitromethane was found to be the optimal solvent for the transformation; in the less cation-stabilizing solvent CH_2Cl_2, trapping of the tetrahydropyranyl carbenium ion generated in the Prins cyclization step by a halide nucleophile became competitive, and 4-chlorotetrahydropyrans **9a** (X = Cl, 25%) and 4-fluoro analogues **9a** (X = F, 15%) were isolated as significant side products.[6] When the $SnCl_4$-promoted condensation of *rac*-**5** and **6a** was carried out in the presence of 0.5 equiv of the proton-selective base 2,6-di-*tert*-butyl-4-methylpyridine,[7] the starting materials were recovered unchanged.[8] This experiment

Scheme 1



Scheme 2



suggests that a complex protic acid formed by the reaction of $SnCl_4$ with water,[9] which is a byproduct of the reaction, is the active catalyst for the reaction. Following up on this suggestion, the condensation of *rac*-**5** and **6a** was found to be efficiently realized with 0.5 equiv of trifluoromethanesulfonic acid (TfOH, −25 °C in $MeNO_2$) to furnish acetyltetrahydropyrans **7a** and **8a** in an 18:1 ratio and 81% combined yield.

Tetrahydropyrans **7a** and **8a** could be separated by silica gel chromatography and were shown to be acetyl epimers by their interconversion upon exposure to KOH in MeOH (thermodynamic ratio of **7a**:**8a** = 18:1). The observation of 11 signals in the ^{13}C NMR spectrum of both epimers established the *cis* stereochemistry of the side chains at C2 and C6, while the *cis* orientation of the C4 acetyl substituent in the major epimer **7a** was signaled by ^1H NMR nOe enhancements observed between the C2(C6) and C4 methine hydrogens.

Results of our initial survey of the preparation of all-*cis*-4-acetyl-2,6-disubstituted tetrahydropyrans **7** by this Prins−pinacol sequence are summarized in Table 1.[10] The synthesis was successful with the full range of aldehydes: aliphatic aldehydes having *prim*-, *sec*- *tert*-, or hydrogen α-substituents, α,β-unsaturated aldehydes, and benzaldehyde. Good yields and high stereoselectivities (ranging from 6 to 18:1) were obtained with both TfOH and $SnCl_4$.[11] No tetrahydropyran products having a *trans*

(1) (a) Westley, J. W., Ed. *Polyether Antibiotics*; Marcel Dekker: New York, 1983; Vol. I and II. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113 and earlier reviews in this series.(c) Elliott, M. C. *Contemp. Org. Synth.* **1997**, *4*, 238 and earlier reviews in this series.

(2) For reviews of the Prins reaction, see: (a) Adams, D. R.; Bhaynagar, S. D. *Synthesis* **1977**, 661. (b) Snider, B. B. The Prins and Carbonyl Ene Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 527−561.

(3) For representative recent examples, see: (a) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (b) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899. (c) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. (d) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141. (e) Masuyama, Y.; Gotoh, S.-y.; Kurusu, Y. *Synth. Commun.* **1995**, *25*, 1989. (f) Lolkema, L.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115. (g) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911.

(4) For brief reviews of our early work in this area, see: (a) Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

(5) For representative recent examples, see: (a) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379. (b) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927. (c) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

(6) The stereochemistry of the halide is assigned on the basis of precedent.[2b,3d] Chlorotetrahydropyran **9a** (X = Cl) was unchanged when exposed to $SnCl_4$ in $MeNO_2$ at −25 °C under the original reaction conditions, establishing that this compound is not an intermediate on the pathway to **7**.

(7) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966**, *88*, 986.

(8) This reaction was conducted in d_3-$MeNO_2$ at −25 °C for 1 h, or at room temperature for 24 h; in both reactions the ^1H NMR spectrum showed only **5** and **6**.

(9) (a) Farcasiu, D.; Marino, G.; Miller, G.; Kastrup, R. V. *J. Am. Chem. Soc.* **1989**, *111*, 7210. (b) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley: New York, 1985.

(10) General procedure: A solution of diol **5** (75 mg, 0.34 mmol), aldehyde (2.0 equiv), and dry $MeNO_2$ (1.4 mL) was cooled to −27 °C. Neat TfOH (12−25 mg, 0.08−0.17 mmol, 0.25−0.5 equiv) or $SnCl_4$ (44 mg, 0.17 mmol, 0.5 equiv) was added slowly while the internal reaction temperature was maintained below −25 °C. After 2 h at −25 °C, brine (1.5 mL) was added, and the reaction was diluted with $CHCl_3$ (20 mL) and washed with brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the resulting oil was purified on silica gel to give acetyltetrahydropyran **7**.

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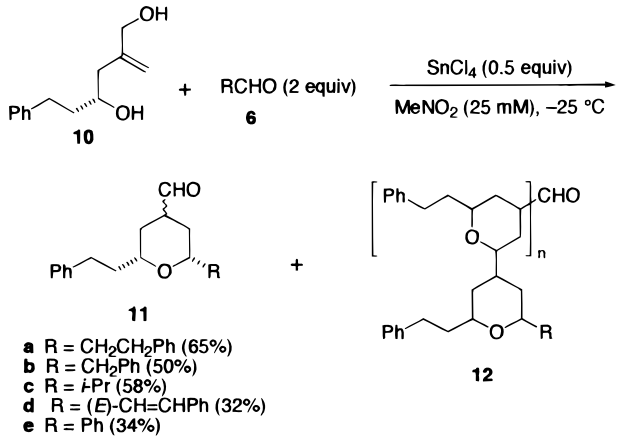
Table 1. Synthesis of all-*cis*-4-Acetyl-2,6-disubstituted Tetrahydropyrans **7**[a]

cmpd	RCHO	acid	stereosel[b]	Yield of **7**[c] (%)
7a	$PhCH_2CH_2CHO$	TfOH	18:1	81[d]
		$SnCl_4$	10:1	65
7b	MeCHO	TfOH	11:1	73[d]
		$SnCl_4$	10:1	66[d]
7c	$PhCH_2CHO$	TfOH[e]	6:1	61
		$SnCl_4$	8:1	56
7d	*i*-PrCHO	TfOH[e]	14:1	65
		$SnCl_4$	12:1	68
7e	*t*-BuCHO	TfOH	9:1	76[f]
		$SnCl_4$	10:1	50
7f	(*E*)-PhCH=CHCHO	TfOH	6:1	68[g]
		$SnCl_4$	8:1	59[g]
7g	PhCHO	TfOH[e]	8:1	61
		$SnCl_4$	6:1	76[f]

[a] Reactions were conducted in $MeNO_2$ and employed 75 or 150 mg of *rac*-**5** (0.25 M), and unless otherwise noted, 0.50 equiv of acid. All products are racemic. [b] Ratio of **7**:**8** in the crude reaction product by capillary GLC analysis. [c] Yield of stereoisomerically pure **7** after silica gel chromatography. [d] Stereoisomers **7** and **8** were not separated, and the yield refers to this mixture. [e] 0.25 equiv of TfOH was employed. [f] This product contained a trace of the minor diastereomer **8**. [g] This product contained a small amount of an acetal impurity.

Scheme 3

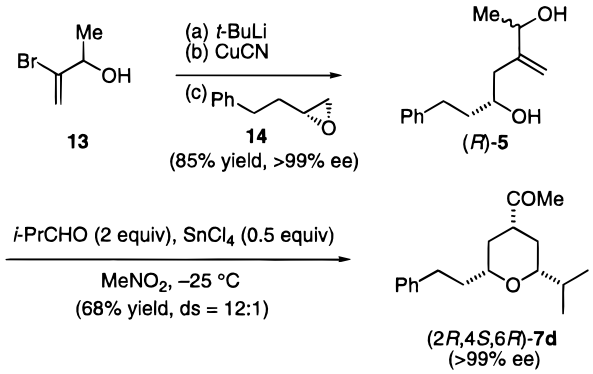


orientation of the C2 and C6 side chains were detected, and in all cases, the axial C4 acetyl epimer was the minor product. Epimers **7a** and **8a** were unchanged when resubmitted to both the TfOH and $SnCl_4$ reaction conditions, demonstrating that the stereochemistry at C4 derives from kinetic stereoselection.

Extension of this Prins−pinacol reaction to the preparation of substituted 4-formyltetrahydropyrans **11** was successful, but yields were considerably lower due to competitive formation of oligomers **12**[12] resulting from condensation of the formyl product **11** with the starting unsaturated diol **10** (Scheme 3). To minimize oligomerization, these reactions were carried out under dilute conditions (0.025 M **10**), and the monomeric products **11** were purified by vacuum distillation. Stereoselectivity was also lower in this series; formyltetrahydropyrans **11** were generated as 7:3 mixtures of formyl epimers with the α (equatorial) epimer being major.

Although our exploratory investigations were conducted with racemic unsaturated diol substrates, this Prins−pinacol reaction will provide ready access to enantiopure tetrahydropyrans. An

Scheme 4



illustrative example is provided in Scheme 4. Condensation of a "higher order" cuprate[13] derived from 3-bromo-3-buten-2-ol[14] with (*R*)-4-phenylbutylene oxide (>99% ee)[15] provided (*R*)-**5** in 85% yield. Subsequent condensation of this intermediate with isobutyraldehyde in the presence of $SnCl_4$ at −25 °C provided enantiopure (2*R*,4*S*,6*R*)-**7d**.[16,17]

The tetrahydropyran synthesis reported here is believed to occur by the sequence outlined in Scheme 1. Although two α-alkoxycarbenium ions can be generated from condensation of an aldehyde with unsaturated diol **1**, only the one derived from the homoallylic alcohol has proper stereoelectronics for an intramolecular Prins reaction.[18] Preferential cyclization of the more stable *E* oxonium ion stereoisomer generated form the homoallylic alcohol as depicted in **2** would generate **3**. A pinacol shift, occurring with preferential axial hydride delivery, would complete the reaction.[19,20]

In conclusion, all-*cis*-2,4,6-trisubstituted tetrahydropyrans can be synthesized in useful yields and high stereoselectivity from simple unsaturated diol and aldehyde precursors. Since the stereochemistry of the three side chains evolves from a single stereocenter of the unsaturated diol precursor, this reaction should be of particular utility for enantioselective construction of substituted tetrahydropyrans.

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Supporting Information Available: Experimental procedures for preparing (*R*)-**5** and **10** and analytical and spectroscopic data including tabulated ^{1}H NMR nOe data for tetrahydropyrans **7**, **8a**, and **11** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Although the transformation could be carried out with 0.25 equiv of TfOH (Table 1, preparation of **7c**,**d**,**g**), reactions using 0.5 equiv TfOH were generally higher yielding (Table 1, preparation of **7a**,**b**,**e**,**f**).

(12) Diagnostic LRMS (FAB) data for **12a**: *m*/*z* 323 (323 calcd for $C_{22}H_{27}O_2$, $n = 0$); 511 (511 calcd for $C_{35}H_{43}O_3$, $n = 1$), 699 (699 calcd for $C_{48}H_{59}O_4$, $n = 2$), 888 (888 calcd for $C_{61}H_{75}O_5$, $n = 3$), 1076 (1076 calcd for $C_{74}H_{91}O_6$, $n = 4$), 1264 (1264 calcd for $C_{87}H_{107}O_7$, $n = 5$), 1452 (1452 calcd for $C_{100}H_{123}O_8$, $n = 6$).

(13) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3928.

(14) Cousseau, J. *Synthesis* **1980**, 805.

(15) Racemic 4-phenylbutylene oxide was resolved using Jacobsen's *R*,*R*-(salen)Co catalyst: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(16) The other enantiomer was not detected by HPLC analysis using a 5μ Chiracel OD column. In a mixture containing 1% of the racemate, the other enantiomer was detectable (96:4 hexane-2-propanol, 7.0 and 8.1 min). Thus, (2*R*,4*S*,6*R*)-**7d** is formed in >99% ee: 8.1 min, $[\alpha]^{24}_D$ −15.4, $[\alpha]^{24}_{577}$ −20.6, $[\alpha]^{24}_{546}$ −24.3, $[\alpha]^{24}_{435}$ −36.0, $[\alpha]^{24}_{405}$ −37.7 ($c = 0.35$, $CHCl_3$).

(17) The diastereoselectivity of this reaction, and the enantiomeric purity of **7d**, were identical whether (*R*)-**5** was a 1.7:1, or 1:1.2, mixture of diastereomers. Thus, the configuration of the allylic alcohol does not affect in a detectable way the outcome of this reaction.

(18) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(19) We surmise that the factors favoring preferential axial shift of hydride in the pinacol step are related to those that favor axial attack of small external nucleophiles on cyclohexanones.[21]

(20) This is the first demonstration that a hydride migration, as well as an alkyl shift,[5] can be employed to terminate a Prins−pinacol reaction.

(21) Reviews: (a) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521. (b) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263.