SUBSTITUENT EFFECTS ON THE REGIOCHEMICAL AND STEREOCHEMICAL COURSE OF THE NUSSBAUMER-FRATER VARIATION OF THE PRINS CYCLIZATION

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Abstract – Eleven vinylogous carbonates were examined in the Nussbaumer-Frater variation of the Prins cyclization to provide 2,3,4,6-tetrasubstituted tetrahydropyrans. Results indicate that substrate olefin geometry is a more reliable control element than preset substrate vicinal stereochemistry for establishing C2-C3 vicinal stereochemistry in tetrahydropyran products.

The Prins cyclization has been developed into an effective route for the preparation of complex tetrahydropyrans.1 Refinements of this methodology are plentiful in the recent literature.2 Consequently, subtle aspects of reactions have been revealed and numerous applications in the field of natural products synthesis have been reported.3,4 Not surprisingly, the Nussbaumer-Frater variant of the Prins cyclization has become increasingly popular.5,6 We recently reported a study of this reaction that revealed a variety of reaction pathways that compete with the usual cyclization to provide tetrahydropyrans.6 For example, when vinylogous carbonates (1a and 1b) were subjected to the Nussbaumer-Frater conditions, the major products were 3a (50%) and 4 (41%), respectively, rather than the expected tetrahydropyrans (2a and 2b) (both formed in lesser amounts) (Scheme 1). In addition, both cyclization substrates (1a and 1b) gave both dioxabicyclo[3.2.1]octanes (3a and 3b), indicating that stereochemistry across the initial C2-C3 bond had been compromised.

Scheme 1
In this paper we present studies designed to: (1) shed light on how C\textsubscript{2} substituents effect partitioning between products of type 2, 3 and 4 (2) determine when C\textsubscript{2}-C\textsubscript{3} vicinal stereochemical relationships can be transferred reliably from starting substrate into products and (3) examine the effect of moving the C\textsubscript{3} substituent to C\textsubscript{5} on control of vicinal stereochemistry in cyclization products.

The cyclization substrates selected for study (6, 8 and 10) and their preparation from the corresponding homoallylic alcohols (5, 7 and 9) are shown in Scheme 2. The reasons for selecting these substrates have been delineated in the introduction and will be further enumerated below. The alcohols used to prepare the cyclization substrates were either known or were prepared by standard procedures.\textsuperscript{7-14} Several of the substrates were prepared as mixtures of stereoisomers, as will be explained below. Conversion of the alcohols to the vinylogous carbonate cyclization substrates was accomplished using a known procedure.\textsuperscript{15} The yields are shown in parentheses. The reactions were straightforward with one exception. The reaction of 7c with ethyl propiolate gave a 75% yield of a 2:3 mixture of 8c and the product derived from migration of the TBDPS group to the 2\textsuperscript{o} hydroxyl group followed by reaction of the 1\textsuperscript{o} hydroxyl group with ethyl propiolate. These isomers were separable (with difficulty) and were distinguishable by NMR spectroscopy.

Cyclizations were conducted by treating the vinylogous carbonate substrates with trifluoroacetic acid (10 equivalents) in dichloromethane at room temperature for minutes to hours depending upon the substrate. Crude product mixtures were treated with potassium carbonate in ethanol to hydrolyze intermediate
trifluoroacetates. The product mixtures were then separated by chromatography over silica gel. Products were characterized (1H and 13C NMR, IR, MS) and structures were assigned based on spectral data, including COSY and difference NOE experiments.

Results with diastereomeric substrates (6a and 6b) are summarized in Scheme 3. These substrates differ from 1a and 1b only by substitution of a methyl group for the C2-benzyloxymethyl group. It had been anticipated that this change would eliminate formation of products of type 3 and 4, and this was the case. The major products were tetrahydropyrans typically formed in Prins cyclization reactions. Erosion of stereochemistry across the C2-C3 bond, however, persisted in the syn-C2-C3 substrate (6a).16 For example substrate (6a), with 19:1 stereochemical homogeneity across C2-C3, rearranged to a 6:1 mixture of 11 and 12. Thus the stereochemical homogeneity of the starting substrate was slightly eroded in the products (19:1 to 6:1). On the other hand, cyclization of anti-C2-C3 substrate (6b), with 10:1 stereochemical homogeneity across the C2-C3 bond, gave a 10:1 mixture of 12 and 11, respectively. This suggests that 6b does not undergo stereochemical erosion. Both 6a and 6b gave alcohols (13) as minor products. These products most likely result from protonation of the starting vinylogous carbonate, [3,3]-sigmatropic rearrangement of the intermediate oxocarbenium ions, and “hydrolysis” of the newly formed oxocarbenium ion. This process has been previously observed by us and others.6 The fact that 6a and 6b give (largely) Z-13 and E-13, respectively, suggests that these rearrangements occur (largely) via a chair-like transition state. Finally, we note that “other products” from this reaction consisted of at least five tetrahydropyrans and tetrahydrofurans with no single compound dominating the mixture.

Scheme 3

Results with diastereomeric substrates (6c and 6d) are summarized in Scheme 4. These substrates behave qualitatively like 6a and 6b. Stereochemical erosion across C2-C3 is pronounced for the syn-diastereomer (6c) and minimal for the anti-diastereomer (6d). Stereochemical homogeneity of rearrangement-hydrolysis products (Z-13 and E-13) is also lower from 6c than 6d. The appearance of 15c (11%) and 15d (10%) as products is consistent with the previously reported behavior of 6e.6 Once again stereochemical homogeneity is lower in such products derived from the syn-diastereomer (6c). For
example, two stereoisomers of $15c$ were also observed in 9% combined yield, but stereoisomers of $15d$ were not observed in the reaction of the anti-diastereomer ($6d$).

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\text{Scheme 4}
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The results with substrates ($6a$-$6d$) indicate that substrates with an anti-$C_2$-$C_3$ relationship ($6b$ and $6d$) behave well in the Nussbaumer-Frater version of the Prins cyclization, whereas substrates with a syn-$C_2$-$C_3$ relationship ($6a$ and $6c$) are problematic. We suggest that this observation results from the need for the $C_3$ substituent to occupy an axial site in chair-like processes emanating from the syn-$C_2$-$C_3$ substrates (see $C^1$), whereas all chair-like processes (cyclizations and sigmatropic rearrangements) can take place with all substituents equatorially disposed when starting with anti-$C_2$-$C_3$ substrates (see $C^2$). Thus, boat-like processes that result in erosion of the $C_2$-$C_3$ stereochemical relationship ($C^1$ to $B^1$ to $B^2$) may begin to intervene with syn-$C_2$-$C_3$ substrates (Scheme 5), and are less likely to intervene with anti-$C_2$-$C_3$ substrates ($C^2$ to $C^3$). The take-home message is that cyclizations of anti-$C_2$-$C_3$ substrates are likely to be more stereoselective than cyclizations of syn-$C_2$-$C_3$ substrates.

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\text{Scheme 5}
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Vinylogous carbonates ($8a$ and $10$) are isomeric with $6a$ and $6b$, the difference being that the $C_3$ methyl group (in $6a$ and $6b$) resides at $C_5$ (in $8a$ and $10$). These substrates were selected because it was felt that
they might provide 2,3,4,6-tetrasubstituted tetrahydropyrans with more reliable control of relative stereochemistry than substrates of type 6a-6d, in which considerable erosion of stereochemistry was observed in substrates expected to give all-cis tetrahydropyrans (6a and 6c). Cyclization of 8a was expected to provide all-cis tetrahydropyran (16), whereas cyclization of 10 was expected to provide the isomeric tetrahydropyran (17), both via chair-like transition states. These expectations were realized. Prins cyclization of a 5:1 mixture of 8a and 10 gave a 5:1 mixture of tetrahydropyrans (16 and 17), respectively (Scheme 6). On the other hand, pure 10 provided only tetrahydropyran (17) in 69% yield. Thus it appears that olefin geometry can be reliably used to control vicinal stereochemistry.

Any doubts that the cyclizations of 8a and 10 represent a stereospecific process were alleviated by the reactions shown below. Substrates (8b-8f) all cyclized under standard conditions to provide all-cis 2,3,4,6-tetrasubstituted tetrahydropyrans of type 18 in yields ranging from 30-71% (Scheme 7). Whereas it is possible that tetrahydropyrans diastereomeric at C₃ (or other positions) were formed in low yield, they escaped our detection.

Several of the cyclizations merit further discussion. Substrate (8b) provided dioxabicyclo[3.2.1]octane (19) (34%), dioxabicyclo[4.3.0]nonane (20) (5%) and alcohol (7b) (15%) in addition to the aforementioned tetrahydropyran (18b) (34%). Thus, just as with substrates (1a and 1b) (Scheme 1), a
benzyloxymethyl substituent at the original carbinol center trapped a presumed intermediate carbenium ion to give a bicyclization product (19). Unlike substrates \(1a\) and \(1b\), this product was stereochemically homogenous across the \(C_2-C_3\) bond. This suggests that if a \([3,3]\)-sigmatropic rearrangement is underlying this reaction, it takes place via chair-like transition state and is irreversible, thus establishing clean \(C_2-C_3\) stereochemistry. The formation of bicyclization product (20) could involve cyclization of \(8b\) to a tetrahydrofuran followed by trapping of the intermediate carbenium ion by the acetic acid sidechain and subsequent loss of an ethyl group, or an acid-promoted intramolecular Diels-Alder reaction followed by hydrolysis of the initial cycloadduct. Regardless of the mechanism, the formation of 20 represents a minor pathway that resembles the formation of compound (4) in reactions of \(1a\) (also a minor pathway) and \(1b\) (where it is the major pathway). Homoallylic alcohol (7b) is merely the result of “hydrolysis” of the starting substrate (8b).

Substrate \((8c)\) behaved similarly to \(8b\), only the yield of the “neighboring group participation product” \((19c)\) was reduced to 12% and the yield of tetrahydropyran \((18c)\) increased to 49%. Substrate \((8d)\) was examined because it is analogous to \(8b\) only the –OBn group was replaced by an –SBn group. It is notable that this substrate did not give a product derived from neighboring group participation. Tetrahydropyran \((18d)\) was obtained in 21% yield. Starting material (30%) and hydrolysis product \((7d)\) (26%) were also isolated. Substrate \((8e)\) provided only tetrahydropyran \((18e)\) in good yield (71%). Substrate \((8f)\) gave only tetrahydropyran \((18f)\) (70%), illustrating that homolagation of the benzyloxymethyl sidechain eliminates complications resulting from neighboring group participation.\(^\text{18}\) We note that Prins cyclization of the \(\Delta^{4,5}\)-trans isomer of \(8f\) has recently been reported by the Willis group to provide the \(C_3\) diastereomer of \(18f\), another indication that this cyclization represents a stereospecific process.\(^\text{5}\)

The studies delineated above suggest that when selecting a Prins cyclization precursor for the synthesis of a 2,3,6-trisubstituted tetrahydropyran-4-ol, substrates in which \(C_2-C_3\) vicinal stereochemistry is constructed during the cyclization (substrates of type \(8\) or \(10\)) are more reliable, from the standpoint of stereocontrol, than substrates of with preset \(C_2-C_3\) vicinal stereochemistry (substrates of type \(1\) or \(6\)). Although this is the first direct comparison of these two approaches, the results with substrates of type \(8\) and \(10\) are consistent with studies where the oxocarbenium ion cyclization precursor was generated by reaction of a homoallylic alcohol with an aldehyde in the presence of trifluoroacetic acid (Willis).\(^\text{1}\) We note that others (Willis and Nokami)\(^\text{1}\) have observed crossover products in related Prins cyclizations, whereas we do not observe such products using vinylogous carbonates as the entry point to Prins cyclization intermediates (the Nussbaumer-Frater variation). Finally, we note that lower transmission of stereochemical information from starting olefin to product has been reported in other variations of the
Prins cyclization route to tetrahydropyran-4-ols (Metzger). In summary, the Nussbaumer-Frater variation of the Prins cyclization should now be usable in a stereochemically predictable manner for the preparation of a variety of 2,3,6-trisubstituted tetrahydropyran-4-ols. Of course the best Prins cyclization method for preparing a given tetrahydropyran-4-ol will depend on the target itself.

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REFERENCES AND NOTES


7. For **5a** and **5b** see: R. W. Hoffmann and H.-J. Zeiss, *J. Org. Chem.*, 1981, **46**, 1309. Alcohol (**5a**) was prepared as a 19:1 mixture with **5b** using the crotyl boronate methodology of Hoffmann. Alcohol (**5b**) was prepared as a 10:1 mixture with **5a** using CrCl2-NiCl2 crotylation methodology: T. Hiyama, K. Kimura, and H. Nozaki, *Tetrahedron Lett.*, 1981, **22**, 1037. These ratios carried over to cyclization substrates (**6a** and **6b**).

8. For **5c** and **5d** see: K. Mikami, N. Kishi, T. Nakai, and Y. Fujita, *Tetrahedron*, 1986, **42**, 2911. Alcohol (**5c**) was prepared as a 20:1 mixture with **5d**. Alcohol (**5d**) was prepared as a 20:1 mixture with **5c**. These ratios carried over to cyclization substrates (**6c** and **6d**). Alcohols (**5c** and **5d**) were prepared from acrolein using the methods using the methods of Hoffmann and Nozaki (reference 7), respectively.

9. For **7a** and **9** see: W. Adam, C. R. Saha-Moller, and K. S. Schmid, *Tetrahedron: Asymmetry*, 1999, **10**, 315 and J. C. Esing, G. S. Ferguson, D. W. Moore, R. W. Schultz, and D. W. Thompson *J. Org. Chem.*, 1985, **50**, 2124, respectively. We prepared alcohol (**7a**) by reduction of 4-hexyn-2-ol with Pd/BaSO4/pyridine (to give **7a**) or Li/NH3 (to give **9**). Alcohol (**7a**) prepared in this manner was a 5:1 mixture with **9**. It was later discovered that the low selectivity was most likely due to use of greater than 1 atmosphere of hydrogen in the alkyne reduction. Alcohol (**9**) was stereochemically homogenous. These ratios carried over to cyclization substrates (**8a** and **10**).

10. Alcohol (**7b**) [B. H. Lipshutz and J. C. Barton, *J. Org. Chem.*, 1988, **53**, 4495] was prepared by opening the benzyl ether of glycidol with 1-lithiopropylene in the presence of BF3-etherate (89%), followed by semi-hydrogenation of the alkyne using Pd/BaSO4 in pyridine at one atmosphere (60%).

11. Alcohol (**7c**) was prepared from the TBDPS ether of glycidol [J.-F. Hoeffler, D. Tritsch, C. Grosdemange-Billiard, and M. Rohmer, *Eur. J. Biochem.*, 2002, **269**, 4446; L. D. Juliawaty, Y. Watanabe, M. Kitajima, S. A. Achmad, H. Takayama, and N. Aimi, *Tetrahedron Lett.*, 2002, **43**, 8657] as follows: (1) 1-lithiopropylene (2 eq), BF3-Et2O (2 eq), THF, -78 °C, 3 h, 88%; (2) H2 (1 atm), Pd/BaSO4, pyridine (solvent), rt, 78%. We note that it was important to conduct alkyne hydrogenations at no greater than one atmosphere of hydrogen, otherwise the amount of contamination by E-geometrical isomers increased.

12. Alcohol (**7d**) was prepared as follows: (1) epichlorohydrin (3 eq), PhSH (1 eq), NaOH (3 eq), CH2Cl2, rt, 10 min, 83%; (2) 1-lithiopropylene (2 eq), BF3-Et2O (2 eq), THF, -70 °C, 3 h, 75%; (3) H2 (1 atm), Pd/BaSO4, methanol (solvent), rt, 99%. For reduction of alkynes to alkenes in the

13. Alcohol (7e) was prepared as follows: (1) epichlorohydrin (3 eq), PhSH (1 eq), NaOH (3 eq), CH2Cl2, rt, 10 min, 70%; (2) 1-lithiopropyne (2 eq), BF3-Et2O (2 eq), THF, -70 °C, 3 h, 75%; (3) H2 (1 atm), Pd/BaSO4, methanol (solvent), rt, 75%.

14. (S)-7f was prepared from (R)-4-benzyloxy-1,2-butanediol [H. F. Sneddon, M. J. Gaunt, S. V. Ley, *Org. Lett.*, 2003, **5**, 1147; D. Misiti, G. Zappia, and G. D. Monache, *Gazz. Chim. Ital.*, 1995, **125**, 219] as follows: (1) SOCl2 (1.2 eq), CCl4, 95 °C (oil bath), 1 h; then RuCl3-3H2O (0.01 eq), NaIO4 (1.5 eq), H2O, rt, 1 h, 81% of cyclic sulfate; (2) 1-lithiopropyne (2 eq), BF3-Et2O, THF, -78 °C to rt, 14 h, 52%; (3) H2 (1 atm), Pd/BaSO4, pyridine (solvent), rt, 100%. For the cyclic sulfate preparation see Y. Gao, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538. In our hands, this route to (S)-7f was operationally easier than going from the diol to the corresponding epoxide with subsequent opening of the epoxide [Y. J. Liu, B. E. Tropp, and R. Engel, *Can. J. Chem.*, 1993, **71**, 206]. Racemic 7f was also prepared from benzyl 3-butenyl ether by sequential epoxidation with MCPBA (57%), epoxide opening with 1-lithiopropyne and BF3-Et2O in THF (86%), and semi-hydrogenation using Pd/BaSO4 in pyridine (99%).


17. We have previously suggested that oxocarbenium ion E/Z isomerization may play a role in the formation of products such as 19 (and 3 in the reactions of 1a and 1b). Rychnovsky and Jasti (see reference 3) have suggested that the presence of Z-oxocarbenium ions may also be partially responsible for racemization that accompanies some Prins cyclization reactions.

18. Procedures for the preparation 8f and 18f: A 1-L three-necked round bottom flask under argon was charged with 18 mL (17.4 g, 177 mmol) of ethyl propiolate, 177 mL of dry diethyl ether and 25 mL (17.9 g, 177 mmol) of triethylamine. To the resulting yellow mixture was added a solution of 26 g (118 mmol) of alcohol (7f) in 170 mL of dry diethyl ether via cannula. The brown solution was stirred for 72 h. The mixture was diluted with 300 mL of diethyl ether and washed with two 200-mL portions of 1M aqueous KH2SO4, two 200-mL portions of saturated aqueous NaHCO3 and 200 mL of brine. The organic phase was separated, dried (MgSO4) and concentrated in vacuo to afford 42 g of a brown oil. The oil was chromatographed over 800 g of silica gel (230-400 mesh, eluted with 10% diethyl ether/90% hexanes) to give 24.2 g (64%) of vinylogous carbonate (8f) as a pale yellow oil: IR (neat) 1708, 1639, 1622 cm⁻¹; 1H-NMR (400 MHz, CDCl3) δ 1.29 (t, J = 7.1, 3H, OCH2CH3), 1.62 (ddd, J = 6.8, 0.8, 0.8, 3H, CH3), 1.80-2.00 (m, 2H, CH2CH2OBn), 2.3-2.45 (m,
2H, CH2=CH), 3.50-3.60 (m, 2H, CH2OBn), 4.18 (q, J = 7.1, 2H, OCH2CH3), 4.16-4.22 (m, 1H, CHO), 4.50 (ABq, J = 11.9, 2H, OCH2Ph), 5.29 (d, J = 12.4, 1H, CH=CHCO2Et), 5.40 (m, 1H, CH=CHCH3), 5.62 (m, 1H, CH=CHCH3), 7.27-7.39 (m, 5H, ArH), 7.56 (d, J = 12.4, 1H, CH=CHCO2Et); 13C-NMR (100 MHz, CDCl 3) δ 12.9 (CH3), 14.3 (CH3), 32.0 (CH2), 34.4 (CH2), 39.6 (CH2), 65.8 (CH2), 73.1 (CH2), 80.7 (CH), 97.0 (CH), 124.2 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 138.8 (C), 162.7 (CH), 168.1 (C); exact mass (ESI) calcd for C19H26O4Na m/z 341.1723, found m/z 341.1728. A 2-L three-necked round-bottom flask under argon was charged with 24.2 g (76 mmol) of 7f and 700 mL of dry dichloromethane. The solution was cooled in an ice-water bath and 59 mL (86.7 g, 760 mmol) of trifluoroacetic acid was added slowly via syringe. The ice bath was removed and the mixture was stirred for 2 h. The solution was cooled in an ice-water bath and 300 mL of saturated aqueous NaHCO3 was added slowly. The organic phase was separated and the aqueous phase was extracted with three 200-mL portions of dichloromethane. The combined organic phases were dried (Na2SO4) and concentrated in vacuo to afford 26 g of a yellow oil. The oil was dissolved in 700 mL of absolute ethanol and 5.25 g (38 mmol) of anhydrous potassium carbonate was added. The mixture was stirred for 16 h at room temperature. The resulting solution was concentrated in vacuo and diluted with 500 mL of ethyl acetate. The solution was washed with 200 mL of water. The aqueous layer was separated and extracted with two 200-mL portions of ethyl acetate. The combined organic layers were dried (MgSO4) and concentrated in vacuo to afford 26 g of a yellow oil which was purified by chromatography over 800 g of silica gel (230-400 mesh, eluted with 40% ethyl acetate/60% hexanes) to give 17.9 g (70%) of tetrahydropyran (18f) as a colorless oil: IR (neat) 3450, 1735 cm−1; 1H-NMR (400 MHz, CDCl3) δ 0.90 (d, J = 7.1, 3H, CH3), 1.27 (t, J = 7.1, 3H, OCH2CH3), 1.39 (q, J = 12.1, 1H, CH2CHOH), 1.59 (broad s, 1H, OH), 1.65 (ddd, J = 12.4, 4.6, 2.5, 1H, CH2CHOH), 1.70-1.88 (m, 2H, CH2CH2OBn), 1.89-1.96 (m, 1H, CHCH3), 2.37 (dd, J = 15.2, 5.1, 1H, CH2CO2Et), 2.59 (dd, J = 15.2, 8.6, 1H, CH2CO2Et), 2.63 (m, 3H, CH2CH2OBn), 3.50-3.60 (m, 3H, CHCH2CH2OBn), 3.85 (ddd, J = 7.9, 5.0, 2.0, 1H, CHCH2CO2Et), 3.96 (ddd, J = 11.6, 4.6, 1H CHOH), 4.15 (q, J = 7.1, 2H, OCH2CH3), 4.67 (s, 2H, OCH2Ph), 7.27-7.41 (m, 5H, ArH); 13C-NMR (100 MHz, CDCl3) δ 4.9 (CH3), 14.2 (CH3), 34.9 (CH2), 35.9 (CH2), 37.7 (CH), 38.2 (CH2), 60.4 (CH2), 66.7 (CH2), 70.6 (CH), 73.0 (CH2), 73.2 (CH), 75.0 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 138.4 (C), 171.4 (C); exact mass (ESI) calcd for C19H28O5Na m/z 359.1829, found m/z 359.1807. Coupling patterns of THP ring protons agree with the assigned stereochemistry (and disagree with other possible stereochemistry). The cis-relationship of protons on C2, C3, C4 and C6 was established by difference NOE experiments.