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

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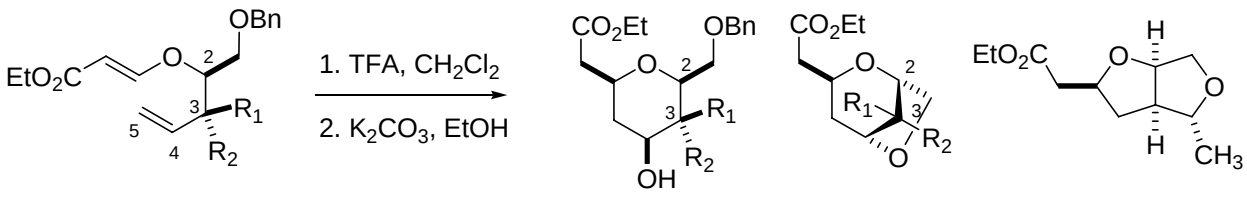
Abstract – Eleven vinylogous carbonates were examined in the Nussbaumer-Frater variation of the Prins cyclization to provide 2,3,4,6-tetrasubstituted tetrahydropyrans. Results indicate that substrate olefin geometry is a more reliable control element than preset substrate vicinal stereochemistry for establishing C_2-C_3 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 C_2-C_3 bond had been compromised.

Scheme 1

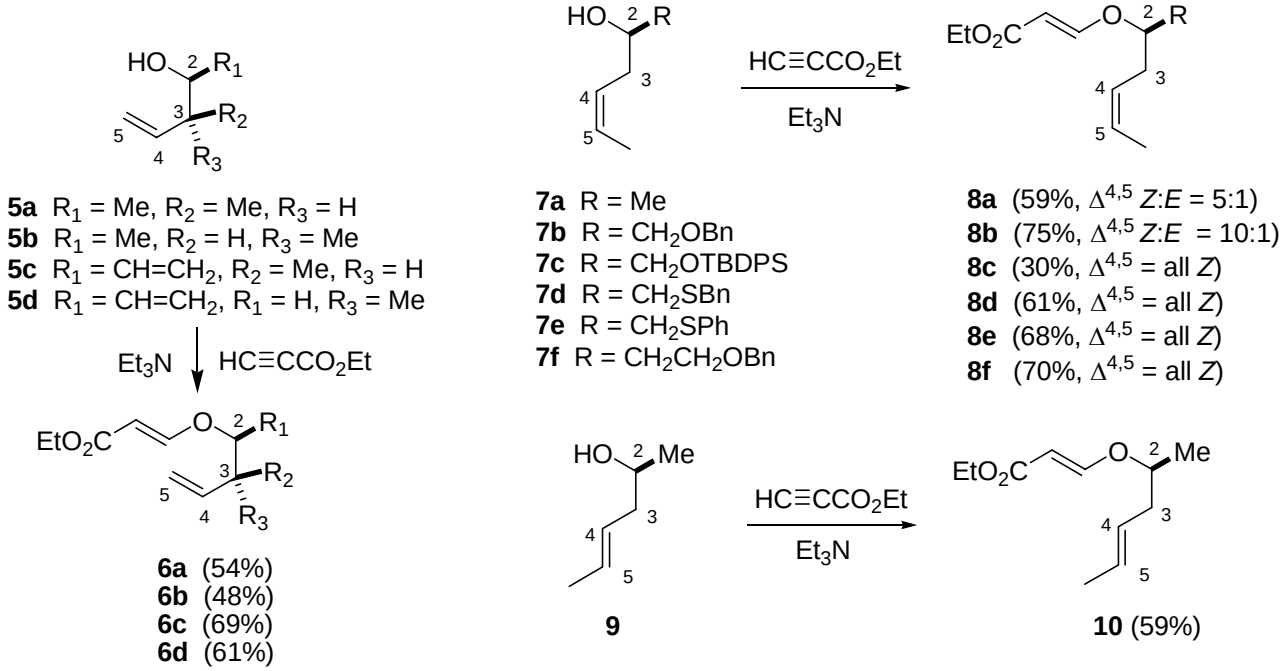


1 **a** R_1 = Me, R_2 = H; **b** R_1 = H, R_2 = Me **2** **3** **4**

In this paper we present studies designed to: (1) shed light on how C_2 substituents effect partitioning between products of type **2**, **3** and **4** (2) determine when C_2-C_3 vicinal stereochemical relationships can be transferred reliably from starting substrate into products and (3) examine the effect of moving the C_3 substituent to C_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.[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.[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° hydroxyl group followed by reaction of the 1° hydroxyl group with ethyl propiolate. These isomers were separable (with difficulty) and were distinguishable by NMR spectroscopy.

Scheme 2

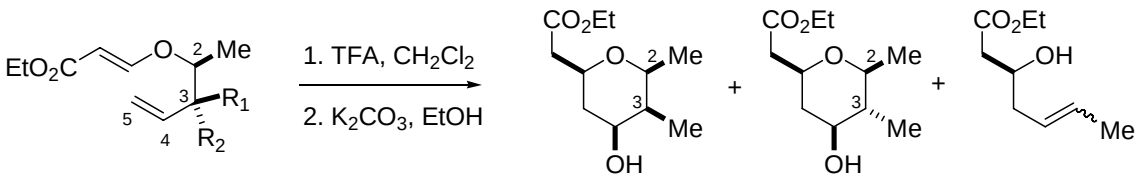


Cyclizations were conducted by treating the vinylogous carbonate substrates with trifluoroacetic acid (10 equivalents) in dichloromethane at room temperature for minutes to hours depending upon the substrate. Crude product mixtures were treated with potassium carbonate in ethanol to hydrolyze intermediate

trifluoroacetates. The product mixtures were then separated by chromatography over silica gel. Products were characterized (^{1}H and ^{13}C NMR, IR, MS) and structures were assigned based on spectral data, including COSY and difference NOE experiments.

Results with diasteromeric 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 C_2-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 C_2-C_3 bond, however, persisted in the *syn*-C_2-C_3 substrate (**6a**).[16] For example substrate (**6a**), with 19:1 stereochemical homogeneity across C_2-C_3, 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*-C_2-C_3 substrate (**6b**), with 10:1 stereochemical homogeneity across the C_2-C_3 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



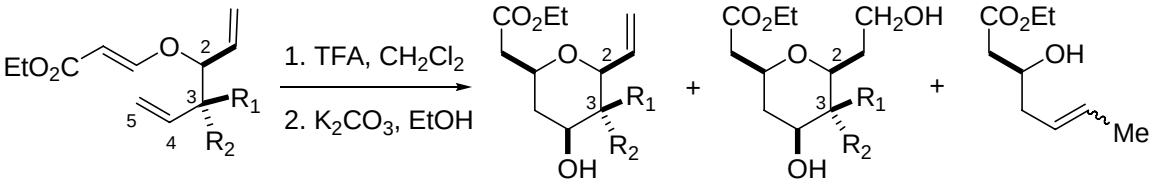
11 **12** **13**

6a R_1 = Me, R_2 = H (**6a**:**6b** = 19:1) 72-76% (**11**:**12** = 6:1) 4% (*E*:*Z* = 1:6)
6b R_1 = H, R_2 = Me (**6a**:**6b** = 1:10) 76-78% (**11**:**12** = 1:10) 4% (*E*:*Z* = 5:1)

Results with diastereomeric substrates (**6c** and **6d**) are summarized in Scheme 4. These substrates behave qualitatively like **6a** and **6b**. Stereochemical erosion across C_2-C_3 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**).

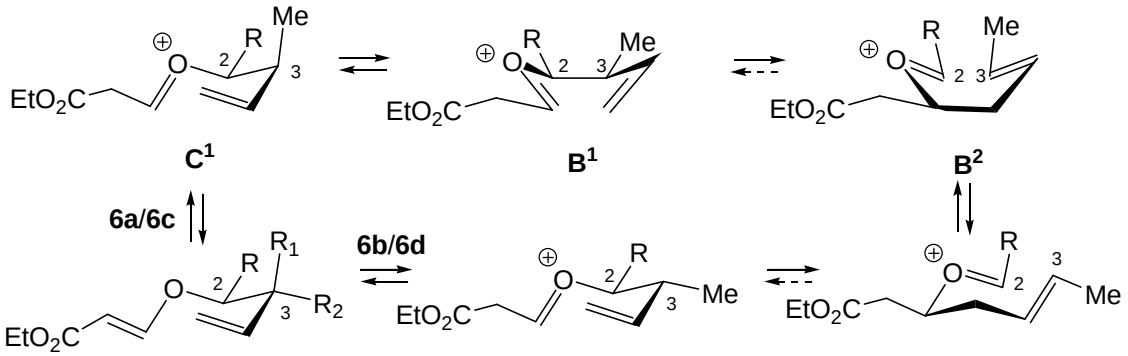
Scheme 4



6c R_1 = Me, R_2 = H (**6c**:**6d** = 20:1) 25% 20% 11% ---- 5-11% (*E*:*Z* = 1:2.5)
6d R_1 = H, R_2 = Me (**6d**:**6c** = 20:1) trace 47% ---- 10% 13-14% (*E*:Z = 8:1)
6e R_1 = R_2 = H

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 $\mathbf{C}^1$), 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 $\mathbf{C}^2$). Thus, boat-like processes that result in erosion of the C_2-C_3 stereochemical relationship ($\mathbf{C}^1$ to $\mathbf{B}^1$ to $\mathbf{B}^2$) 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 ($\mathbf{C}^2$ to $\mathbf{C}^3$). 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.

Scheme 5

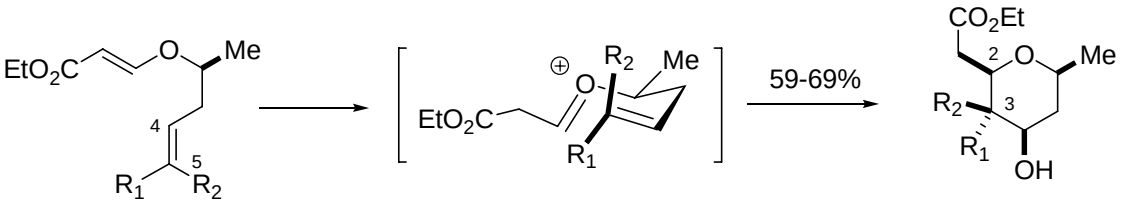


6a/6c R_1 = Me R_2 = H
6b/6d R_1 = H R_2 = Me

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.

Scheme 6

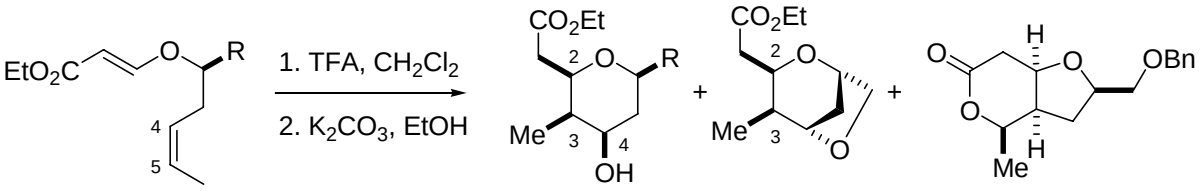


8a R_1 = H, R_2 = Me (**8a**:**10** = 5:1)
10 R_1 = Me, R_2 = H

16 R_1 = H, R_2 = Me
17 R_1 = Me, R_2 = H

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 C_3 (or other positions) were formed in low yield, they escaped our detection.

Scheme 7



	18	**19**	**20**	**7**
8b R = CH_2OBn	34%	34%	5%	15%
8c R = $CH_2OTBDPS$	49%	12%	----	----
8d R = CH_2SBn	21%	----	----	26%
8e R = CH_2SPh	71%	----	----	----
8f R = CH_2CH_2OBn	70%	----	----	----

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 substitutent at the original carbinol center trapped a presumed intermediate carbenium ion to give a bicyclization product (**19**).[17] 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 homolgation of the benzyloxymethyl sidechain eliminates complications resulting from neighboring group participation.[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.[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).[1] We note that others (Willis and Nokami)[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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6. C. E. Bennett and D. J. Hart, *Org. Lett.*, 2003, **5**, 1499.
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 $CrCl_2$-$NiCl_2$ 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 $Pd/BaSO_4$/pyridine (to give **7a**) or Li/NH_3 (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-lithiopropyne in the presence of BF_3-etherate (89%), followed by semi-hydrogenation of the alkyne using $Pd/BaSO_4$ 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-lithiopropyne (2 eq), BF_3-Et_2O (2 eq), THF, -78 ^oC, 3 h, 88%; (2) H_2 (1 atm), $Pd/BaSO_4$, 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.[9]
12. Alcohol (**7d**) was prepared as follows: (1) epichlorohydrin (3 eq), PhSH (1 eq), NaOH (3 eq), CH_2Cl_2, rt, 10 min, 83%; (2) 1-lithiopropyne (2 eq), BF_3-Et_2O (2 eq), THF, -70 ^oC, 3 h, 75%; (3) H_2 (1 atm), $Pd/BaSO_4$, methanol (solvent), rt, 99%. For reduction of alkynes to alkenes in the

presence of thioethers see E. Schaumann, A. Kirschning, and F. Narjes, *J. Org. Chem.*, 1991, **56**, 717.

13. Alcohol (**7e**) was prepared as follows: (1) epichlorohydrin (3 eq), PhSH (1 eq), NaOH (3 eq), CH_2Cl_2, rt, 10 min, 70%; (2) 1-lithiopropyne (2 eq), BF_3-Et_2O (2 eq), THF, -70 ^oC, 3 h, 75%; (3) H_2 (1 atm), Pd/$BaSO_4$, 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) $SOCl_2$ (1.2 eq), CCl_4, 95 ^oC (oil bath), 1 h; then $RuCl_3$-$3H_2O$ (0.01 eq), $NaIO_4$ (1.5 eq), H_2O, rt, 1 h, 81% of cyclic sulfate; (2) 1-lithiopropyne (2 eq), BF_3-Et_2O, THF, -78 ^oC to rt, 14 h, 52%; (3) H_2 (1 atm), Pd/$BaSO_4$, 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 BF_3-Et_2O in THF (86%), and semi-hydrogenation using Pd/$BaSO_4$ in pyridine (99%).
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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 $KHSO_4$, two 200-mL portions of saturated aqueous $NaHCO_3$ and 200 mL of brine. The organic phase was separated, dried ($MgSO_4$) 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1, 3H, $OCH_2C\underline{H}_3$), 1.62 (ddd, J = 6.8, 0.8, 0.8, 3H, $C\underline{H}_3$), 1.80-2.00 (m, 2H, $C\underline{H}_2CH_2OBn$), 2.3-2.45 (m,

2H, C$\underline{H}_2$CH=CH), 3.50-3.60 (m, 2H, C$\underline{H}_2$OBn), 4.18 (q, *J* = 7.1, 2H, OC$\underline{H}_2$CH$_3$), 4.16-4.22 (m, 1H, CHO), 4.50 (ABq, *J* = 11.9, 2H, OCH$_2$Ph), 5.29 (d, *J* = 12.4, 1H, CH=C$\underline{H}$CO$_2$Et), 5.40 (m, 1H, C$\underline{H}$=CHCH$_3$), 5.62 (m, 1H, CH=C$\underline{H}$CH$_3$), 7.27-7.39 (m, 5H, ArH), 7.56 (d, *J* = 12.4, 1H, C$\underline{H}$=CHCO$_2$Et); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 12.9 (CH$_3$), 14.3 (CH$_3$), 32.0 (CH$_2$), 34.4 (CH$_2$), 59.6 (CH$_2$), 65.8 (CH$_2$), 73.1 (CH$_2$), 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 $C_{19}H_{26}O_4Na$ *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 NaHCO$_3$ 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 (Na$_2$SO$_4$) 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 (MgSO$_4$) 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}; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.90 (d, *J* = 7.1, 3H, CH$_3$), 1.27 (t, *J* = 7.1, 3H, OCH$_2$C$\underline{H}_3$), 1.39 (q, *J* = 12.1, 1H, C$\underline{H}_2$CHOH), 1.59 (broad s, 1H, OH), 1.65 (ddd, *J* = 12.4, 4.6, 2.5, 1H, C$\underline{H}_2$CHOH), 1.70-1.88 (m, 2H, C$\underline{H}_2$CH$_2$OBn), 1.89-1.96 (m, 1H, C$\underline{H}$CH$_3$), 2.37 (dd, *J* = 15.2, 5.1, 1H, C$\underline{H}_2$CO$_2$Et), 2.59 (dd, *J* = 15.2, 8.6, 1H, C$\underline{H}_2$CO$_2$Et), 3.50-3.60 (m, 3H, C$\underline{H}$CH$_2$C$\underline{H}_2$OBn), 3.85 (ddd, *J* = 7.9, 5.0, 2.0, 1H, C$\underline{H}$CH$_2$CO$_2$Et), 3.96 (ddd, *J* = 11.6, 4.6, 4.6, 1H C$\underline{H}$OH), 4.15 (q, *J* = 7.1, 2H, OC$\underline{H}_2$CH$_3$), 4.67 (s, 2H, OCH$_2$Ph), 7.27-7.41 (m, 5H, ArH); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 4.9 (CH$_3$), 14.2 (CH$_3$), 34.9 (CH$_2$), 35.9 (CH$_2$), 37.7 (CH), 38.2 (CH$_2$), 60.4 (CH$_2$), 66.7 (CH$_2$), 70.6 (CH), 73.0 (CH$_2$), 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 $C_{19}H_{28}O_5Na$ *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 C$_2$, C$_3$, C$_4$ and C$_6$ was established by difference NOE experiments.