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Hydrogenation of Vinylogous Esters

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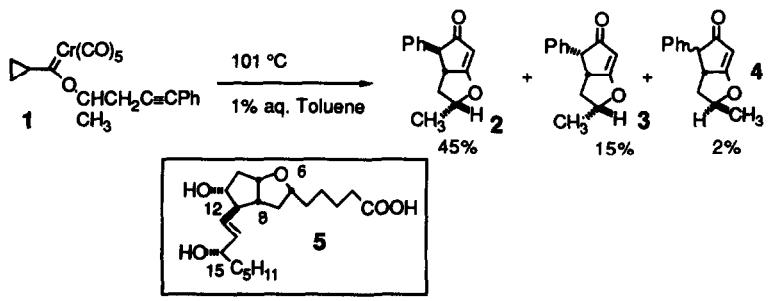
Summary: Methods for hydrogenation of the vinylogous ester linkage have been investigated. The ideal method appears to be hydrogenation over a palladium on charcoal catalyst, using THF as the solvent. Classical methods such as hydrogenation in hydroxylic solvents and Birch reduction were not successful with fused-ring vinylogous esters.

As part of a proposed synthesis of prostacyclin derivatives (e.g. **5**, Scheme 1), we required a method to convert vinylogous esters to saturated β–alkoxy alcohols. The intramolecular reaction between cyclopropylcarbene-chromium complexes and alkynes, as is set up in complex **1**,[1] produces vinylogous esters (e.g. **2-4**) with a very high degree of stereoselectivity in formation of the heterocyclic ring. Critical to the success of our prostacyclin synthesis is a method for complete reduction of a vinylogous ester. Development of methodology to effect this transformation is the subject of this communication.

SCHEME 1

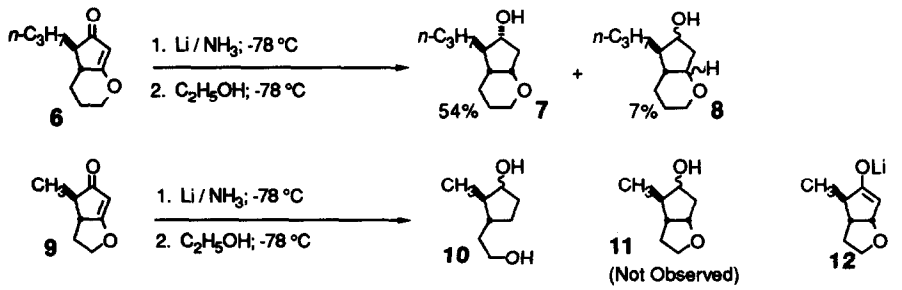


Reduction of vinylogous esters is precedented. Treatment of 3-methoxy-2-cyclohexenone with lithium/ ammonia and ethanol leads to 3-methoxycyclohexanol,[2a] however the product distribution is dependent upon reaction conditions. Exposure of fused ring vinylogous ester **6** to lithium/ammonia, followed by ethanol produced the expected compounds **7** and **8** (Scheme 2), while treatment of compound **9** under similar conditions led only to open-chain alcohol **10**. None of the desired product **11** was obtained, probably because the added strain of a 5,5-fused ring system accelerates β–elimination from enolate intermediate **12**. Under a variety of different conditions, compound **11** was never observed. Another possible solution is to effect a conjugate addition of hydride, however while reagents exist which effect 1,2-addition of hydride to 3-alkoxycyclopentenones,[3] we are not aware of a reagent which leads to 1,4 addition in the absence of 1,2-addition.

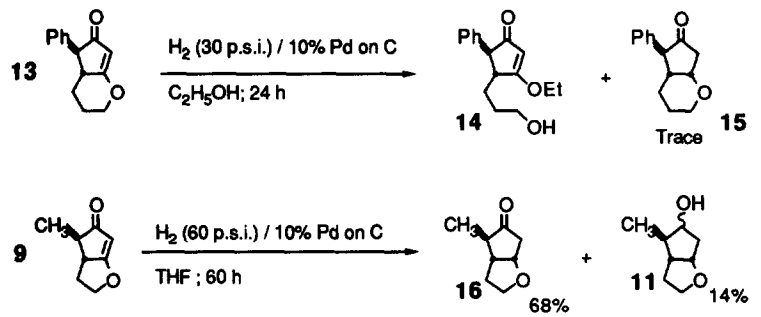
A possible method to effect the desired transformation is catalytic hydrogenation. Subsequent reduction of the ketone would afford the desired β–alkoxy alcohol derivatives. Only a few documented cases of vinylogous ester hydrogenation have

been reported.[4] From studies directed toward hydrogenation of dehydrogriseofulvin, it has been established that vinylogous esters are more difficult to hydrogenate than simple enones.[5] Other examples of vinylogous ester hydrogenation exist in which polarization of the alkene is diminished by further conjugation of the oxygen or alkene functionalities.[6] Hydrogenation according to a standard recipe for alkene reduction, with a palladium on carbon catalyst (10 mol %) and ethanol solvent, led to only the vinylogous transesterification product **14** in 60% yield (Scheme 3). This presumably arises via formation of a mixed ketal,[7] followed by elimination of the alcohol to give **14**. The hydrogenation reaction did not proceed in ethyl acetate using the same catalyst system at 35 psi H_2. Wilkinson's catalyst was ineffective for hydrogenation of this system, probably because the alkene is too sterically hindered. Diimide reduction, which is reported to work best with non-polarized alkenes,[8] also failed to give any hydrogenation product.

SCHEME 2



SCHEME 3

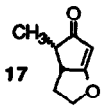
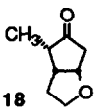
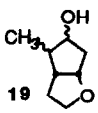
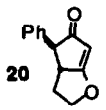
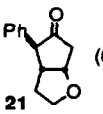
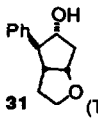
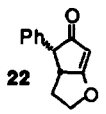
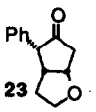
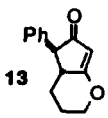
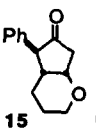
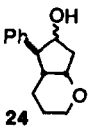
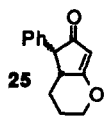
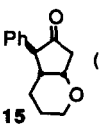
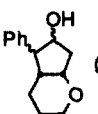
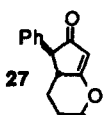
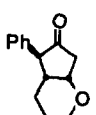
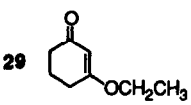
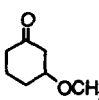


When the solvent for the hydrogenation reaction was THF, the desired reaction occurred. Both the β–alkoxy ketone and the β–alkoxy alcohol derivatives were obtained (Scheme 3). The hydrogenation requires H_2 pressures of 50-60 psi, and will not proceed to completion at lower pressures. This process was general for a variety of differently-substituted cyclopentapyran and cyclopentafuran derivatives as can be seen in the Table. In both ring systems, the only product obtained was that having the cis ring junction. In most cases, the minor amounts of alcohol products were formed as a mixture of alcohol stereoisomers. Complete saturation of the vinylogous ester linkage was achieved by subsequent reduction of the carbonyl group; a single stereoisomer identified as compound **31**[9] was obtained by treatment of ketone **21** with lithium aluminum hydride (see Table). In two cases, reduction of **17** and **25**, partial or complete cis-trans isomerization occurred, probably due to instability of this ring system.

The following is a typical procedure. A solution of compound **13** (0.100 g, 0.500 mmol) in THF (100 mL) was placed in a pressure bottle. To the solution was added 10% palladium on charcoal (0.050 g, 0.047 mmol, 10 mol %), and the bottle was placed upon a Parr hydrogenation apparatus. The solution was pressurized to 60 psi hydrogen and shaken for 24

h. The solution was then filtered, the solvent was removed on a rotary evaporator, and the residue after evaporation was purified by column chromatography on silica gel using 4:1 hexane-ethyl acetate as the eluent. Two fractions were isolated, the first identified as ketone **15** (0.072 g, 71%),[10] and the second identified as alcohol **24** (0.015 g, 14%).

TABLE. Scope and Limitations of the Vinylogous Ester Hydrogenation Procedure.

Reduction Substrate[a]	Reaction Time (25 °C, 60 psi H_2)	Product(s) and Yield
9	60 h	**16** (68%) (see ref. 10 for spectral data) **11** (14%)
 **17**	60 h	 **18** (25%) **16** (25%)  **19** (26%)
 **20**	48 h	 **21** (65%)  **31** (0%) (Treatment of **21** with $LiAlH_4$ produces **31** in 83% yield)
 **22**	48 h	 **23** (61%)
 **13**	72 h	 **15** (71%) (see ref. 10 for spectral data)  **24** (14%)
 **25**	72 h	 **15** (37%)  **26** (36%)
 **27** (Contains 10% minor stereoisomers)	72 h	 **28** (44%)
 **29**	72 h	 **30** (94%)

In summary, we have developed conditions which allow for complete saturation of a vinylogous ester linkage. Even in relatively strained vinylogous lactone derivatives hydrogenation proceeds without opening of the heterocyclic ring.

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9. a. This compound was assigned as the stereoisomer indicated due based on the similarity of the proton next to the alcohol (δ 3.99, ddd, J = 8.6, 8.6, 6.6 Hz) to the analogous proton in prostacyclin (δ 3.97, q, J = 8.7 Hz)[9b] and dihydroprostacyclin (**5**) (δ 3.91, q, J = 6.2 Hz).[9c] b. Kotovych, G.; Aarts, G.H.M.; Nakashima, T.T.; Bigam, G. *Can. J. Chem.* **1980**, *58*, 974-983. c. Kotovych, G.; Aarts, G.H.M. *Can. J. Chem.* **1980**, *58*, 2649-2659.

10. Compound **16**: ^{1}H NMR ($CDCl_3$): δ 4.62 (td, 1 H, J = 7.5, 2.7 Hz), 3.89 (td, 1 H, J = 8.4, 3.4 Hz), 3.71 (td, 1 H, J = 8.4, 6.3 Hz), 3.01 (quintet, 1 H, J = 7.2 Hz), 2.60 (dd, 1 H, J = 19.1, 7.5 Hz), 2.49 (m, 1 H), 2.22 (dd, 1 H, J = 19.1, 2.7 Hz), 1.95 (m, 1 H), 1.58 (m, 1 H), 1.05 (d, 3 H, J = 7.2 Hz);[11a] ^{13}C NMR ($CDCl_3$): δ 217.3, 78.7, 68.4, 48.3, 45.3, 44.3, 31.5, 13.4; IR (CH_2Cl_2): 1741 cm^{-1}. Compound **15**: ^{1}H NMR ($CDCl_3$): δ 7.30-7.10 (m, 3 H), 7.05 (d, 2 H, J = 9.1 Hz), 4.14 (q, 1 H, J = 2.8 Hz), 3.94 (br d, 1 H, J = 11.9 Hz), 3.61 (d, 1 H, J = 12.7 Hz), 3.44 (td, 1 H, J = 11.9, 2.1 Hz), 2.47 (d, 2 H, J = 2.8 Hz), 2.30 (dq, 1 H, J = 12.7, 2.8 Hz), 2.00-1.70 (m, 3 H), 1.47 (br d, 1 H, J = 9.5 Hz);[11b] ^{13}C NMR ($CDCl_3$): δ 215.8, 137.4, 128.7, 127.0, 74.2, 67.6, 54.0, 46.7, 43.1, 22.4, 19.6; IR (CH_2Cl_2): 1743 cm^{-1}.

11. a. The cis ring junction was assigned based on the pattern for the proton adjacent to oxygen at the ring junction (δ 4.62), which is similar to that reported in a similar system, prostacyclin (δ 4.66, ddd, J = 7.2, 6.5, 3.0 Hz).[9b] b. The cis ring junction was assigned based on a coupling constant between the protons at the ring junction (δ 4.14 and 2.30) of 2.8 Hz, which is more consistent with an axial-equatorial orientation of hydrogens and not the axial-axial orientation expected for the trans isomer.

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