deactivates the system to the extent that the alkoxyaluminate does not react, and merely serves to sterically block attack on that side of the epoxide. This observation is consistent with Fried's results,[5a] where he found that blocking the primary alcohol of **4** with a bulky ether group led to a ratio of about 1:3 also favoring the wrong isomer **6**.

In summary, we have found that superficially innocuous changes in the amount of "excess"[11] reagent used to prepare alkynylalanes for epoxide-opening reactions can lead to great changes in the resulting regioselectivity, even to the extent of reversing the isomer ratios. As a consequence, the substitution of an alanate for the usual alane reagent can sometimes be useful in achieving desired regioselectivity. Our data on the opening of epoxides **4** and **7** are tabulated in Table I. It has been our experience in general that the regioselectivity of these reactions is often governed by effects more subtle than one might anticipate from the literature; this should be considered by those who want to use these reactions synthetically.[14]

Experimental Section

The Alanate Opening of Epoxide 4. To a solution of 2.275 g (12.5 mmol, 8 equiv) of octyne ether **1a** in 10 mL of dry toluene, stirred under argon at 0 °C, was added 8.06 mL of 1.55 M *n*-butyllithium (12.5 mmol, 8 equiv) dropwise via syringe. After 15 min, 6.25 mL of 1.0 M DMCA (6.25 mmol, 4 equiv) was added dropwise via syringe, and the stirring was continued at 0 °C for 50 min more. Epoxide **4** (225 mg, 1.56 mmol) was then added as a solution in 2–3 mL of toluene, dropwise via syringe. The reaction was allowed to warm to room temperature overnight and was then heated in a 60 °C oil bath for 4 h. After careful quenching (saturated sodium sulfate at 0 °C), the mixture was added to 100 mL of water and 100 mL of ether and was filtered through a Celite pad to clarify. The water layer was separated and extracted with two 50-mL portions of ether. The combined ether layers were dried over molecular sieves and concentrated in vacuo. The ratio of the two isomers **5**/**6** was determined to be 1:4.4 by HPLC (1:1 acetone/hexane as solvent). The structures were verified by NMR as in ref 12. The two isomers were very difficult to separate chromatographically and were normally carried on as a mixture for synthetic purposes.

The Alanate Opening of Epoxide 7. To a solution of 2.609 g (14.3 mmol, 3 equiv) of octyne ether **1a** in 10 mL of dry toluene, stirred under argon at 0 °C, was added 9.21 mL of 1.55 M *n*-butyllithium (14.3 mmol, 3 equiv), dropwise via syringe. After the mixture was stirred 15 min, 7.13 mL of 1.0 M DMCA (7.13 mmol, 1.5 equiv) was added dropwise via syringe. After the mixture was stirred 50 min more, a solution of epoxide **7** (0.8 g, 4.76 mmol) in 10 mL of dry toluene was added dropwise via syringe. The ice bath was removed, and the mixture was warmed to 80 °C and stirred for 8 h. After cooling to room temperature, the mixture was worked up as described in the example above. By HPLC (7:3 hexane/ethyl acetate solvent), the ratio of isomers **8**/**9** was 3.35:1. To further verify the structural assignments and ratio, the crude product was hydrolyzed to a mixture of the corresponding ketones with acetonitrile/sulfuric acid/water (12 h at 25 °C), as described in ref 6b. The isomers were then separated by flash chromatography to afford the ketones corresponding to **8** and **9**, 809 and 258 mg, respectively. The total, chromatographed yield of the two isomers, overall for the two steps, was 74%.

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4-Chlorooctahydro-2*H*-1-benzopyrans and 4-Chloro-4a,5,6,7,8,8a-hexahydro-2*H*-1-benzopyrans via the Lewis Acid Promoted Cyclization of Acetals Derived from *trans*-2-Vinylcyclohexanol and *trans*-2-Ethynylcyclohexanol: Synthesis, Structure, and Mechanism[1]

Michelle L. Melany, George A. Lock,[†] and David W. Thomspon*

Department of Chemistry, College of William and Mary, Williamsburg, Virginia 23185

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There is current interest in the tetrahydropyran and dihydropyran nuclei as they occur in a number of natural products which have received recent attention.[2] The major route to hydropyrans has been the *carbon–oxygen* bond-forming cyclization of 1,5-diols and closely related structures or difunctional compounds prepared from 1,5-diols.[3] We wish to report a facile and selective synthetic route to substituted octahydro-2*H*-1-benzopyrans and 4a,5,6,7,8,8a-hexahydro-2*H*-1-benzopyrans via a Lewis acid promoted *carbon–carbon* bond-forming cyclization of acetals derived from 2-vinyl- and 2-ethynylcyclohexanol and the acetal-forming reagents ethyl vinyl ether and MEM chloride. The syntheses described herein with our earlier work[4] should have general applicability for entry into the tetrhydropyran and 5,6-dihydro-2*H*-pyran subunits. Additionally, the product distributions and structures for the ethyl vinyl ether based acetals of the two trans cyclohexanols give substantial insight into the cyclization pathway.

Results and Discussion

The ethyl vinyl ether and MEM acetals of *trans*-2-vinyl- and *trans*-2-ethynylcyclohexanol are formed readily by well-known methods.[5] The acetals derived from ethyl vinyl ether are isolated as an approximately equal (50:50 ± 5) mixture of diastereomers. Cyclization of the unsaturated acetals is effected in a straightforward fashion by adding the substrate to a methylene chloride solution of titanium tetrachloride. The ethynyl–acetal cyclizations are optimal at −63 °C; the vinyl–acetals give excellent yields at −45 °C. Products and yields are listed in Chart I.

A noteworthy feature of the cyclizations is that the diastereomeric mixture of the ethyl vinyl ether–acetal of *trans*-2-vinylcyclohexanol leads essentially (97%) to only one of four possible stereoisomeric products. Likewise, the diastereomeric mixture of the *trans*-2-ethynylcyclohexanol ethyl vinyl ether acetal leads to only one (98%) of two possible diastereomeric products. The structures of these products as determined by NMR are shown in Chart I. For both stereoisomeric products the 2-methyl groups in the ^{13}C NMR spectra are at ca. 22 ppm (relative to Me_4Si). From the work of Eliel et al.[6] and Kleinpeter et al.,[7] this establishes the positions of the methyl groups as equatorial, consistent with the large conformational energy for a 2-methyl substituent of ca. 2.9 kcal/mol.[6] The chloride substituent in the saturated product is also equatorial as indicated by the splitting pattern of the axial 4-hydrogen (3.0 ppm, $J_{a-a} \sim 10$ Hz, $J_{a-e} \sim 3.5$ Hz). This equatorial preference for chloride is surprising given its conformational energy in tetrahydropyrans of ca. 0.3 kcal/mol[6] and when compared with observations of mixed axial–equatorial attachments in cyclohexane chemistry.[8,9] This

[†] Hercules, Inc.

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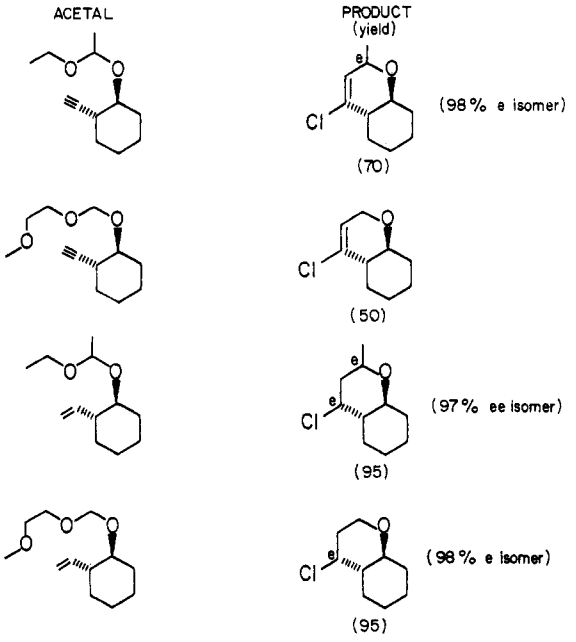
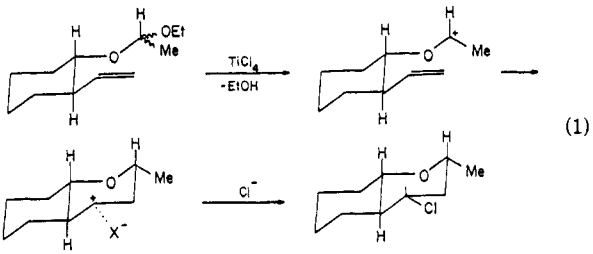
Chart I. Summary of Acetal Cyclization Reactions



strong equatorial preference suggests that a free 4-carbocation is not involved in product formation and that the Lewis acid may play a significant role in delivering the halogen to the developing 4-carbocationic center.[8,10] The chloride in 4-chlorooctahydro-2*H*-1-benzopyran is also equatorial (98%).

The observation that the mixture of the ethyl vinyl ether–acetal diastereomers for each cyclohexanol leads to a single product strongly supports the anticipated cyclization pathway which involves a common, relatively free trigonal oxocarbocationic intermediate as illustrated in eq 1. The equatorial preference of the methyl substituent is explicable in terms of minimizing 1,3-diaxial interactions in the cationic intermediate.



(1)

The synthetic facility and selectivity of these acetal cyclizations to products with halogen and olefin functionalities for further structural elaboration should have a generality that will be useful in achieving more elaborate synthetic goals.

Experimental Section

General Methods and Materials. ^1H NMR spectra were measured at 360 and 80 MHz on Nicolet NTC 360 and Varian FT-80A spectrometers; ^{13}C NMR spectra were run with the FT-80A spectrometer.

Ethyl vinyl ether, MEM chloride, and $TiCl_4$ (99.9%) were purchased from Aldrich and used without further purification. Measured quantities of $TiCl_4$ were transferred into smaller ampules in a drybox. For each reaction the ampules were opened in the atmosphere, and the $TiCl_4$ was rapidly added into CH_2Cl_2 in the reaction flask. Thus, atmospheric moisture was not vigorously excluded from the cyclizationed reactions. Methylene chloride was distilled from P_2O_5 prior to use. *trans*-2-Ethynylcyclohexanol was prepared by the method of Hanack, Kungmann, and Schumaher;[11] *trans*-2-vinylcyclohexanol was prepared by the method of Crandall, Arrington, and Hen.[12]

Analytical GLC analysis was done with Hewlett-Packard Models 5710A and 5790A FID chromatographs. The columns used were a 10 ft × $^1/_8$ in. 10% Carbowax 20M and a 30-m methyl silicone capillary. Preparative separations were done on a Hewlett-Packard 5750 instrument equipped with a 10 ft × $^1/_4$ in. 20% Carbowax column. Yields were determined by the internal standard technique and corrected for response factors.[4]

Typical Synthetic Procedure. A 250-mL three-necked round-bottomed flask was charged with CH_2Cl_2 (100 mL) and $TiCl_4$ (ca. 15 mmol). The acetals (neat) (10 mmol) were added dropwise via syringe in a solution of Lewis acid cooled to the appropriate temperature (−63 °C for the ethynyl–acetals, −45 °C for the vinyl–acetals). The reactions were allowed to proceed for 15 min, after which they were quenched with methanol (5 mL) followed by 3 N hydrochloric acid. Products were isolated into an organic phase by extraction with ether. Samples for spectra studies were isolated by preparative GLC.

4-Chloro-2-methyloctahydro-2*H*-1-benzopyran: ^{13}C NMR ($CDCl_3/Me_4Si$) δ 22.0 (CH_3), 25.6, 25.8, 28.8, and 32.9 (CH_2), 45.6 (C_3), 50.6 (C_{10}), 62.7 (C_4), 72.8 (C_2), 80.8 (C_9).

4-Chlorooctahydro-2*H*-1-benzopyran: ^{13}C NMR ($CDCl_3/Me_4Si$) δ 25.4, 25.9, 29.0, 33.1, and 38.5 (CH_2), 51.4 (C_{10}), 62.9 (C_4), 67.5 (C_2), 82.0 (C_9).

4-Chloro-2-methyl-4a,5,6,7,8,8a-hexahydro-2*H*-1-benzopyran: ^{13}C NMR ($CDCl_3/Me_4Si$) δ 21.5 (CH_3) 25.5, 26.3, 28.3, and 32.5 (CH_2), 46.5 (C_{10}), 71.9 (C_2), 80.4 (C_9), 129.2 (C_3), 134.6 (C_4).

4-Chloro-4a,5,6,7,8,8a-hexahydro-2*H*-1-benzopyran: ^{13}C NMR ($CDCl_3/Me_4Si$) δ 25.2, 26.9, 28.1, and 32.2 (CH_2), 46.2 (C_{10}), 66.6 (C_2), 80.1 (C_9), 124.0 (C_3), 134.0 (C_4).

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Registry No. 2-Ethynylcyclohexanol ethyl vinyl ether acetal (isomer 1), 97690-73-8; 2-ethynylcyclohexanol ethyl vinyl ether acetal (isomer 2), 97747-34-7; 2-ethynylcyclohexanol (methoxyethoxy)methyl ether, 97690-74-9; 2-ethenylcyclohexanol ethyl vinyl ether acetal (isomer 1), 97690-75-0; 2-ethenylcyclohexanol ethyl vinyl ether acetal (isomer 2), 97747-35-8; 2-ethenylcyclohexanol (methoxyethoxy)methyl ether, 97690-76-1; (2A,4AA,8AB)-4-chloro-2-methyl-4a,5,6,7,8,8a-hexahydro-2*H*-benzopyran, 97690-77-2; *trans*-4-chloro-4a,5,6,7,8,8a-hexahydro-2*H*-benzopyran, 97690-78-3; (2A,4A,4AA,6AB)-4-chloro-2-methyloctahydro-2-*H*-benzopyran, 97690-79-4; (4A,4AA,8AB)-4-chlorooctahydro-2*H*-benzopyran, 97690-80-7; $TiCl_4$, 7550-45-0.

Comparison of Phenolic Couplings on $KMnO_4$ and K_2MnO_4 Surfaces

Fredric M. Menger* and David W. Carnahan

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received December 11, 1984

Several synthetically exploitable oxidations using solid permanganate systems have been recently reported. Examples include zinc permanganate on silica gel (tetrahydropyran to valerolactone, 69%),[1] potassium permanganate on molecular sieves (benzyl alcohol to benzaldehyde, 80%),[2] solid potassium permanganate with ultrasonication (1-octanol to octanoic acid, 81%),[3] potassium permanganate on bentonite (1-octen-3-ol to 1-octen-3-one, 92%),[4] and crystalline sodium permanganate (5α-androstan-17β-ol to 5α-androstan-17-one, 84%).[5] Easy workup ranks as the most valuable feature of such oxidations; a satisfactory state of purity is often achieved by mere filtration of solids and removal of solvent. The heterogeneous oxidations also manifest a selectivity not present with corresponding solution systems. Whereas olefins, for example, are inert toward solid permanganate,[6] carbon–carbon double bonds oxidize almost instantly in aqueous permanganate.[7]

We report here an interesting reactivity difference between solid potassium permanganate ($KMnO_4$) and solid potassium manganate (K_2MnO_4) in the oxidative coupling of phenols.[8] Thus, $KMnO_4$ oxidation of 2,6-dimethylphenol, 2,6-diisopropylphenol, and 2,6-di-*tert*-butylphenol (12 mmol phenol, 48 mmol $KMnO_4$, 25 mL $CHCl_3$, 51 °C, 1.5 h) gave the corresponding diphenoquinone in >90% yield. This far exceeds the yields listed for other transition-metal compounds (e.g., Ag^{II}, 32%; $Cu^{II} + S_2O_8^{2-}$, 47%; MnO_2, 53%).[9] When K_2MnO_4 was used instead of $KMnO_4$, but with the reaction conditions kept otherwise constant, the product is exclusively poly(2,6-dialkyl-1,4-phenylene oxide).[10] Addition of pulverized KOH (12 mmol) to the $KMnO_4$ system also gave the polyphenylene oxide (85%) along with the diphenoquinone (15%). This behavior resembles that found by Tsuruya et al.[11] in the oxidation of 2,6-dimethylphenol by $KOH/CuCl_2$; C–O coupling increases at the expense of C–C coupling as the $KOH/CuCl_2$ ratio is elevated.

The high efficiency of diphenoquinone formation with solid $KMnO_4$ suggested a possible application in the intramolecular oxidative coupling of diphenolic substrates. Although this is an important process in the biosynthesis of natural products, attempts to emulate the biological reaction in the laboratory have been often troubled by low yields.[12] To test the efficacy of the solid $KMnO_4$ method in intramolecular systems, we synthesized (2-hydroxyphenyl)(4-hydroxyphenyl)methane and 1-(3-hydroxyphenyl)-3-(4-hydroxyphenyl)propane by known procedures.[12,13] Unfortunately, both substrates displayed absolutely no reaction even after 24 h of refluxing in $CHCl_3$ over solid $KMnO_4$. The only observable change was a decrease in the original NMR peak amplitudes, suggesting that substrate was being partially adsorbed onto the solid. Proof that adsorption blocks the reactive sites on the permanganate crystals comes from the following experiment: 2-Octanol (1.0 mmol) in heptane was treated with solid $KMnO_4$ (4.0 mmol) in the usual manner.[5] When about half of the 2-octanol had been oxidized to 2-octanone, a bisphenol (0.45 mmol) was added to the reaction mixture. Oxidation of the 2-octanol ceased immediately. The unhindered phenols must bind competitively, via their hydroxyls, to the permanganate surface where further reaction does not take place.[14]

$KMnO_4$ and K_2MnO_4 also behaved differently in the oxidation of aliphatic alcohols. Thus, refluxing 2-octanol in heptane over powdered $KMnO_4$ (<210 mesh) for 4 h gave ketone in 80% yield. On the other hand, reaction of 2-octanol with K_2MnO_4 under identical conditions gave <2% ketone. Solid $K_3(MnO_4)_2$, a mixed-valence salt comprised of alternating MnO_4^- and MnO_4^{2-} centers sufficiently close to allow site-transfer electronic conductivity,[15] likewise failed to oxidize alcohols.

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