and manganese acyl complexes, if formed, react differently with alkynes; i.e., hydroxy-substituted unsaturated lactones are obtained by using cobalt,[11] while saturated lactones lacking a hydroxyl substituent are formed with manganese carbonyl complexes.

The following general procedure was used: To 2.0 mmol of $Mn(CO)_5Br$ in CH_2Cl_2 (35 mL) was added 5 N NaOH (35 mL) containing benzyltriethylammonium chloride. The reaction mixture was stirred under nitrogen for 3 h at 35–40 °C. The gas was switched from nitrogen to carbon monoxide, a methylene chloride (2 mL) solution of methyl iodide (0.82 mL, 5.0 mmol) was added, and the mixture was stirred at room temperature for 15 min. The alkyne (2.0 mmol) in CH_2Cl_2 (2 mL) was added, and the solution was stirred at 35 °C for 36 h. The layers were separated, the aqueous phase was washed with ether (3 × 15 mL), neutralized to pH 7 with HCl, and then extracted with ether (3 × 20 mL), dried ($MgSO_4$), and concentrated. Pure lactone (confirmed by gas chromatography and analysis) was obtained by thin-layer chromatography (silica gel) using hexane–ether (3:1) as the developing solvent.

In conclusion, phase-transfer-catalyzed reaction of manganese carbonyl complexes with methyl iodide, carbon monoxide, and alkynes constitutes a simple and novel approach to the synthesis of γ-butyrolactones.

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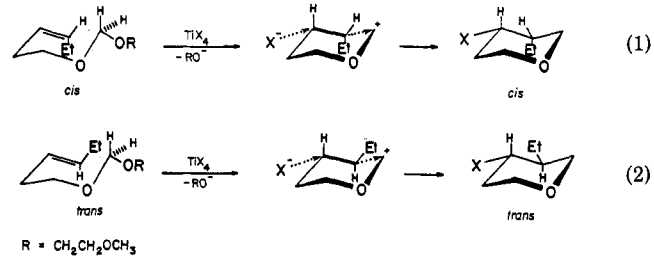
A Selective Synthesis of 3-Alkyl-4-halotetrahydropyrans via the Titanium Tetrahalide Promoted Cyclization of Unsaturated Acetals

Summary: A stereospecific, high-yield approach to the synthesis of *cis*- and *trans*-3-ethyl-4-chloro(bromo)tetrahydropyrans and *all-cis*- and *all-trans*-2-methyl-3-ethyl-4-chloro(bromo)tetrahydropyrans via the Lewis acid promoted carbon–carbon bond-forming cyclization of acetals derived from *cis*- and *trans*-3-hexen-1-ol is described.

Sir: In 1969 Stapp[1] reported the synthesis of six 4-halo-3-alkyltetrahydropyrans from the direct reaction of 1-alkenes, paraformaldehyde, and hydrogen halides. While the yields of the tetrahydropyrans were satisfactory, the stereoselectivity was limited with the author stating that "throughout this work 3-alkyl-4-halotetrahydropyrans are cis/trans isomer mixtures" (60–85% trans).[1] The isolation of 3-buten-1-ol from a reaction of propylene, paraformaldehyde, and hydrogen chloride suggested a pathway involving homoallylic alcohols. Indeed, earlier Hanschke[2a] and Colonge and Boisde[2b] had shown that the terminal homoallylic alcohols 3-buten-1-ol and 4-penten-2-ol react with simple aldehydes in the presence of hydrogen halide to give 4-halotetrahydropyrans in yields of 40–65%. No stereochemical characterization was reported.

With the increasing interest in tetrahydropyran nuclei within the natural products area, we wish to report a stereospecific, high-yield approach, related to the above-mentioned chemistry, to the synthesis of *cis*- and *trans*-3-alkyl-4-halotetrahydropyrans. Specifically, we describe the selective synthesis of *cis*- and *trans*-3-ethyl-4-chloro(bromo)tetrahydropyrans and *all-cis*- and *all-trans*-2-methyl-3-ethyl-4-chloro(bromo)tetrahydropyrans via the Lewis acid promoted carbon–carbon bond-forming cyclization of acetals derived from *cis*- and *trans*-3-hexen-1-ol.

The acetal cyclization reactions we examined are summarized in Table I. The MEM chloride and ethyl vinyl ether based acetals of *cis*- and *trans*-3-hexen-1-ol are readily prepared in high yield by well-established procedures.[3,4] These acetals are clearly similar to the α-halo ethers proposed by Stapp as intermediates in his hydropyran synthesis. The acetals are rapidly cyclized in the presence of titanium tetrachloride or tetrabromide under mild conditions, and the yields of tetrahydropyran products are excellent.[5] However, more striking is the excellent selectivity. The cis and trans MEM chloride acetals give predominately *cis*- and *trans*-3-ethyl-4-halotetrahydropyrans, respectively, with a ca. 9:1 selectivity ratio.[6] This cis to cis, trans to trans reaction pattern can be rationalized by a pathway involving trans addition of an oxocarbocation and X^- to the unsaturation as illustrated in eq 1 and 2.



(1)

(2)

R = $CH_2CH_2OCH_3$

Trans addition predominates in cationic polyene cyclizations reported by Johnson et al.[10] In view of stereochemical studies of product formation from conformationally locked 4-*tert*-butylcyclohexenyl cations, it does not appear that a free carbocation at the 4-carbon is involved since this should lead to substantial axial attack of the incoming halogen.[11]

The ethyl vinyl ether acetals cyclize with almost complete selectivity to one of four diastereomers. The *trans*-acetal gives *all-trans*-2-methyl-3-ethyl-4-halotetrahydropyrans while the *cis*-acetal gives *all-cis*-tetrahydropyran products.[12] The conformations of the all-trans products are clearly 2,3,4-equatorial. For the all-cis products, the predominant conformation must be equatorial methyl, axial ethyl, equatorial halogen since conformational energies are ca. 2.9 (2-Me), 1.4 (3-Et), and 0.3 kcal/mol (halogen). The all-trans and all-cis isomers are the products which one would expect on the basis of the observed preference for trans addition in tetrahydropyran formation seen above in the 3-ethyl-4-halo analogues and

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(5) For a typical cyclization reaction 15 mmol of an unsaturated acetal dissolved in ca. 100 mL of dry CH_2Cl_2 was treated with 20 mmol of $TiCl_4$ at −45 °C. The reaction mixture was stirred for 30 min after which 5 mL of CH_3OH followed by 35 mL of 3 N HCl saturated with NaCl was added. The products were extracted with diethyl ether and isolated for spectral analysis by preparative GLC.

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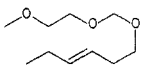
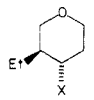
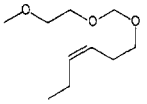
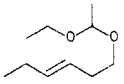
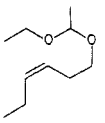
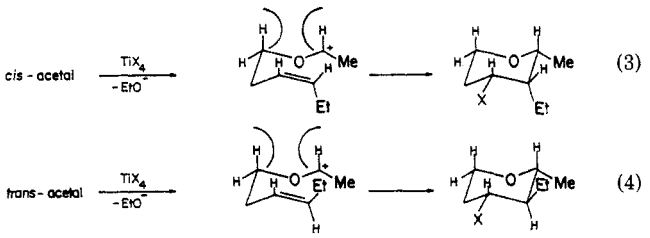
Table I

acetal	Lewis acid	major product (yield,[a] %)	^{13}C NMR, δ ($CDCl_3/Me_4Si$)
			
	$TiCl_4$	X = Cl (94; 92% trans)	11.0 (CH_3), 22.3, 36.4 (CH_2), 46.2 (EtCH), 61.5 (ClCH), 67.2, 70.8 (OCH_2)
	$TiBr_4$	X = Br (98; 89% trans)	11.1 (CH_3), 24.0, 37.7 (CH_2), 46.6 (EtCH), 54.7 (BrCH), 68.2, 71.4 (OCH_2)
			
	$TiCl_4$	X = Cl (92; 95% cis)	10.7 (CH_3), 21.5, 34.8 (CH_2), 42.8 (EtCH), 60.1 (ClCH), 62.6, 67.0 (OCH_2)
	$TiBr_4$	X = Br (74; 87% cis)	10.6 (CH_3), 23.6, 35.1 (CH_2), 42.7 (EtCH), 56.5 (BrCH), 63.3, 67.7 (OCH_2)
			
	$TiCl_4$	X = Cl (85; 96% all-trans)	9.2 (CH_3CH_2), 20.0 (2-CH_3), 21.1, 38.1 (CH_2), 51.8 (EtCH), 60.4 (ClCH), 67.1 (2-CH_2), 76.9 (CH_3CHO)
	$TiBr_4$	X = Br (>99; 98% all-trans)	9.1 (CH_3CH_2), 20.1 (2-CH_3), 22.6, 39.2 (CH_2), 52.0 (EtCH), 54.0 (BrCH), 68.1 (2-CH_2), 77.1 (CH_3CHO)
			
	$TiCl_4$	X = Cl (96; 97% all-cis)	16.0, 19.0 (CH_3), 16.7 (CH_3CH_2) 32.4 (4-CH_2), 48.3 (EtCH), 62.0 (ClCH) 66.1 (2-CH_2), 76.2 (CH_3CHO)
	$TiBr_4$	X = Br (>99; 98% all-cis)	15.9, 19.1 (CH_3), 18.0 (CH_3CH_2), 33.1 (4-CH_2), 48.8 (EtCH), 55.1 (BrCH), 67.2 (2-CH_3), 76.5 (CH_3CHO)

[a] Yields determined by GLC (corrected for response factors).

on the basis of the preference for the 2-methyl group to adopt the equatorial site so as to minimize the 1,3-diaxial methyl–hydrogen interaction in a carbocation intermediate (eq 3 and 4).



The lack of selectivity in Stapp's synthesis may arise from a nonselective proton elimination to give a cis–trans mixture of the homoallylic intermediates and/or the use of hydrogen halide acids which may not lead to selective equatorial additions at the 4-carbon. Preliminary cyclization studies with gaseous hydrogen chloride and hydrogen bromide and acetals of homoallylic alcohols has indicated a substantial lack of selectivity and several byproducts. The fact that $TiCl_4$ and $TiBr_4$ form strong Lewis acid–base adducts with oxygen-donating substrates may lead to a more concerted and thus selective trans (equatorial) delivery of halides to the 4-carbon.[11]

With the strong preference for trans addition of the oxocarbocation and halogen across the double bond and with enhanced 1,3-diaxial interactions across the oxygen, the unsaturated acetal cyclizations hold substantial promise for the selective synthesis of substituted tetrahydropyrans. We are continuing studies in this area with a variety of substituents and Lewis acids.

(6) The product from the cyclization of the *cis*-acetal has a longer GLC retention time than that for the *trans*-acetal; it is expected that the cis product have the longer retention time.[1,7] The *trans*-3-ethyl-4-halotetrahydropyrans will exist overwhelmingly in the equatorial–equatorial conformation since the conformational energies of the ethyl group and halogens are ca. 1.4 and 0.3 kcal/mol, respectively.[8] The conformation of the cis isomers will be predominately that with an equatorial ethyl group and axial halogens. This latter situation does exist for the products from the *cis*-acetal cyclization as indicated by the ^1H NMR pattern for the 4-protons. A pseudoquartet is observed which arises from coupling of an equatorial 4-hydrogen (axial X) to the three adjacent equatorial and axial protons with the three coupling constants approximately equal at 4 Hz. For the trans products the resonance of the axial 4-hydrogen is shifted upfield as expected;[9] the splitting pattern is obscured by overlap with the 2- and 6-hydrogens. The ^{13}C NMR shifts for the ethyl group carbons of the cis and trans products differ only slightly and verify that the ethyl group is essentially in the same (equatorial) disposition in both product isomers; the axial and equatorial methyl carbon shifts for a 3-ethyl group are expected to be significantly separated as seen in the data for *all-cis*- and *all-trans*-2-methyl-3-ethyl-4-halotetrahydropyrans (see Table I, 16.0 vs. 9.2 for halo = Cl and 15.9 vs. 9.1 for halo = Br).

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(12) The products from the cyclization of the *cis*-acetal have 2-methyl ^{13}C NMR chemical shifts in the range 19.0–20.1 ppm. In view of the work of Eliel et al.[8] and Gambaro et al.[7] coupled with substituent effects on chemical shifts,[13] these δ values confirm the 2-methyl groups as being equatorial. From the prior results with the cis MEM acetals we expect trans addition across the unsaturation such that the ethyl group is axial and the halogen is equatorial. In the *cis*-acetal cyclization products, the significant downfield shifts of the ethyl group methyl carbons (~16 ppm) relative to those in the *cis*- and *trans*-3-ethyl-4-halotetrahydropyrans (~11 ppm) are consistent with axial ethyl dispositions. Furthermore, the halogens are clearly equatorial as indicated by the ^1H NMR patterns for the 4-hydrogens. The width of the patterns are ~22 Hz which necessitates an axial–axial coupling; overall, the patterns are approximated with J_{aa} ~ 11 Hz and J_{ee} ~ 4.2 and 4.8 Hz. Thus, the *cis*-acetal cyclization products are all-cis. Finally, the *cis*-acetal products have longer GLC retention times than their *trans*-acetal congeners. From a similar line of argument all-trans products result from *trans*-acetal cyclizations.

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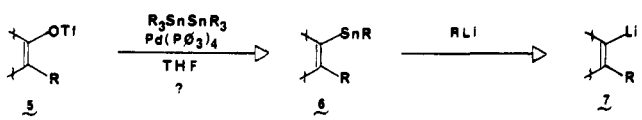
A Regioselective Entry to Vinyllithiums from Unsymmetrical Ketones via Enol Triflates†

Summary: The first method for the regioselective preparation of either the "kinetic" or "thermodynamic" vinyllithium from an unsymmetrical ketone is described.

Sir: The importance of organolithium compounds to the synthetic chemist can hardly be overestimated. Real utility has necessarily been contingent upon the development of facile and selective methods for the preparation of organolithium compounds. One device that can now be routinely employed to control the regioselectivity of aryl- and vinyllithium formation is the use of heteroatoms for directing metalations.[2] One of the more important methods for the regioselective preparation of vinyllithiums is from ketones via their hydrazones.[3,4] The trisylhydrazone **4**, derived from an unsymmetrical ketone can be fragmented to the less substituted vinyllithium **3** according to Bond's modification[3] of the Shapiro reaction;[5] however, the more highly substituted vinyllithium **2** is not accessible from hydrazones (Scheme I). We describe herein the first general method for regioselective entry to both the "kinetic" and "thermodynamic" vinyllithiums from unsymmetrical ketones.

It has been well established that vinylstannanes will undergo transmetalations with alkyl- or aryllithiums to generate vinyllithiums.[6,7] Alternatively, vinylstannanes can be converted to vinyllithiums via their corresponding halides. A new and general route to vinylstannanes is suggested by the recent and rather significant observations of Scott, Crisp, and Stille.[8] They observed that tetrakis(triphenylphosphine)palladium can catalyze the coupling of vinyl triflates with a variety of organostannanes (vinyl, alkynyl, alkyl). Extension of this chemistry to the



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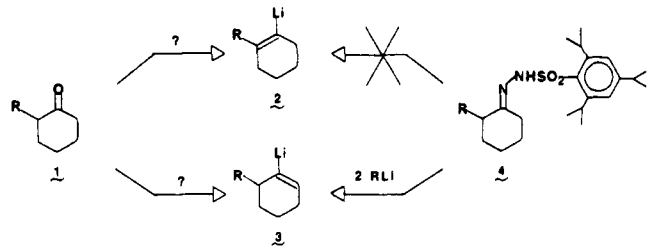
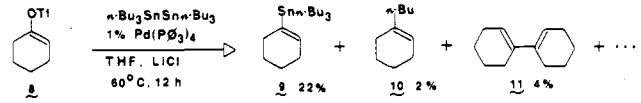
current problem raises the question of whether the coupling of a vinyl triflate and a distannane can be effected

Scheme I



to give vinylstannanes. A few examples have been recently reported concerning related coupling of vinyl triflates with stannylaluminiums and stannylmagnesiums, but these reactions do not appear to be synthetically useful.[9]

The palladium-catalyzed coupling of 1-cyclohexenyl triflate with hexabutyldistannane produced the desired vinylstannane **9** in a disappointingly low yield. This result would be understandable if, as is possible,[8] the product vinylstannane **9** were to compete with hexabutyldistannane in the coupling reaction with the vinyl triflate. However, only a small amount of 1,1'-bicyclohexenyl could be found. The only other low molecular weight compound (M_r < 500) that could be found was 1-*n*-butylcyclohexene (2%).



The coupling reactions of a variety of enol triflates were found to be highly successful with hexamethyldistannane, perhaps due to its more sterically accessible tin–tin bond.[10] Most of the vinyltrimethylstannanes indicated in Table I could be easily isolated from reaction mixtures that were exceptionally clean as indicated by capillary GC. The following procedure for the preparation of 6-methyl-1-trimethylstannylcyclohexene **25** is typical. A 50-mL round-bottom flask was charged in order with 5.0 mL of THF, 0.191 g (0.78 mmol) of the enol triflate **8**, 0.230 g (0.702 mmol) of hexamethyldistannane, 0.21 g (4.95 mmol) of lithium chloride, and 0.012 g (0.014 mmol) of tetrakis(triphenylphosphine)palladium(0). The mixture was deoxygenated by the freeze–thaw method (−196 → 25 °C, three cycles) and stirred at 60 °C for 10 h under argon. The initially yellow mixture became colorless and usually became dark at the end of the reaction. Upon verifying by GC that all of the distannane was consumed, the reaction mixture was partitioned between a pH 7 buffer and

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(10) The corresponding coupling reaction with hexamethyldisilane failed. The reaction of **8** with (trimethylstannyl)trimethylsilane gave a 19% yield of 1-cyclohexenyltrimethylsilane along with a 12% yield of **12**.

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