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Synthesis of *cis* and *trans* 2,4,6-Tetrahydropyranols *via* Prins-Type Cyclization and Mitsunob Inversion

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Prins cyclization of substituted homoallylic alcohol with aryl/aliphatic aldehyde in the presence of a boron trifluoride etherate and trifluoro acetic acid followed by hydrolysis of the resulting trifluoroacetate give substituted *cis* 2,4,6- tetrahydropyranol products **1-5(c)**, then Mitsunobu inversion subsequent methanolysis furnished *trans* 2,4,6-tetrahydropyranol products **1-5(d)** stereoselectively in good yield. Our present work reports the synthesis and characterization of these **1-5(c,d)** products.

Keywords: Prins cyclization, Mitsunobu reaction, Tetrahydropyranols, Lewis acid, Homoallylic alcohols.

INTRODUCTION

Saturated oxygen heterocyclic six membered rings are an integral part of so many biologically active products [1]. The Prins cyclization of the substituted homoallylic alcohols and aryl/aliphatic aldehydes are generally promoted by strong Brønsted or Lewis or protic acidic conditions is an old reaction [2,3] that is now emerging as an efficient method for the substituted tetrahydropyrans synthesis [4,5]. Oxygen hetero atoms can be captured at the 4-position of the tetrahydropyranols ring, although most acids lead to esters that must be hydrolyzed to form 4-hydroxy tetrahydropyranols products [6,7]. The majority Prins cyclizations use super stoichiometric acid to promote the reaction due to the acid counterion is trapped in the product, thus consuming the acid [3]. In general, 2,4,6-*cis* tetrahydropyranols all equatorial substituted are obtained in high diastereoselectivity [5]. Rychnovsky *et al*. [8] developed the first axial-selective Prins cyclization method to the hetero atom at the 4-position, escalating the synthetic scope of this reaction. In fact, selective methodology for the axial/equatorial 4-position synthesis substituent *via* Prins cyclization are dependent on the reactants, experimental conditions and Lewis acids [2].

Tetrahydropyran analogues of the alcohol 3,6-dimethyl-2-phenyltetrahydro-2*H*-pyran-4-ol (**1c**, Table-1) are part of a products isolated series from *Plectranthus sylvestris* (labiatae) extracts which present potent antioxidant and anti-inflammatory properties [9]. In addition, protein database (PDB) [10] revealed that the compound **1c** presents 100 % of structural similarity with a drug crystallized in estrogen receptor. Estrogen receptors a (ERa) and b (ERb) are ligand-inducible transcription factors that are involved in regulating cell growth, propagation and separation in various normal and cancerous tissues [11].

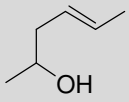
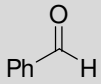
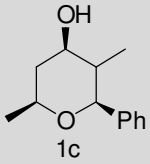
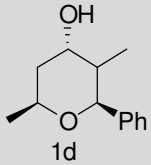
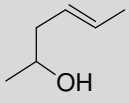
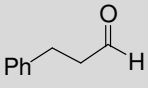
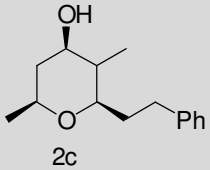
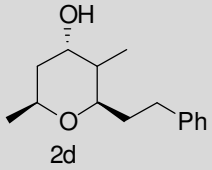
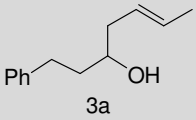
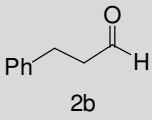
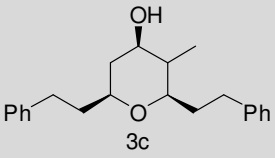
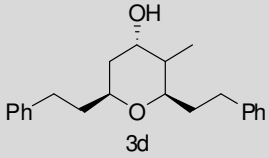
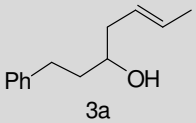
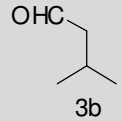
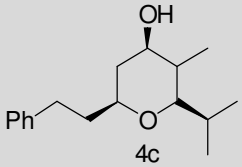
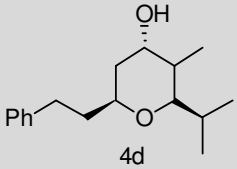
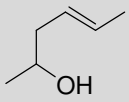
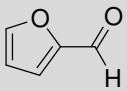
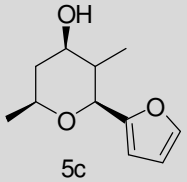
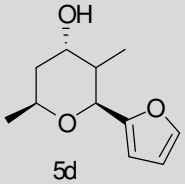
Vasconcellos *et al.* [12,13] reported the biological activities compounds *via* Prins cyclization reaction synthesis. Herein, the diastereoselective syntheses of tetrahydropyran derivatives compounds **1-5(c,d)** (Table-1) and their configurational determinations by NMR spectroscopy.

One surprising aspect of the boron trifluoride etherate and trifluoro acetic acids reaction is the isolation equatorial of tetrahydropyranols product (**1c**) as a significant component. Prins reactions generally give predominantly equatorial 4-heteroatom products and all previously reported 4-oxygen tetrahydropyranols showed high equatorial selectivity [6,7]. Rychnovsky *et al*. [14] mentioned that the axial selectivity was a function of lifetime and reactivity of the ion pair, with reactive nucleophiles, such as bromide anion, leading to high axial selectivity. Typical oxygen nucleophiles, such as $CF_3CO_2^-$ or $AcO{\cdot}BF_3^-$, have low nucleophilicity and lead to about 20:1 selectivity for the equatorial product [15]. The boron trifluoride etherate and trifluoro acetic acids reaction, still favouring the equatorial product shows a much lower level of selectivity.

EXPERIMENTAL

All dry reactions were performed under a positive pressure of nitrogen in an oven-dried glassware. Dichloromethane was degassed and dried by filtration through alumina. Ethyl acetate, toluene and hexanes were distilled over CaH_2 under nitrogen

TABLE-1
BF_3·OEt_2/TFA MEDIATED PRINS CYCLIZATION OF ALDEHYDES WITH HOMOALLYLIC ALCOHOLS AND MITSUNOBU REACTION

Entry	Alcohol (a)	Aldehyde (b)	Products[a]		Time (c/d)(h)	Yield (c/d)(%)[b]
			cis-2,4,6-Tetrahydropyranol (c)	*trans*-2,4,6- Tetrahydropyranol (d)		
1	 1a	 1b	 1c	 1d	0.5/10	54/48
2	 1a	 2b	 2c	 2d	0.3/12	62/45
3	 3a	 2b	 3c	 3d	0.6/10	58/46
4	 3a	 3b	 4c	 4d	0.4/14	47/53
5	 1a	 4b	 5c	 5d	0.5/10	58/51

[a]All products were characterized by ^1H & ^{13}C NMR and EIMS; [b]Products yields are after isolation by column chromatography.

at atmospheric pressure prior to use. All available commercially reagents were used as received, unless otherwise stated. Thin layer chromatography was performed on Whatman K6F (250 µm) silica gel plates and visualized using *p*-anisaldehyde stain. ^1H NMR and ^{13}C NMR spectra were recorded at room temperature at 500 and 125 MHz, respectively. ^1H NMR reported spectra are in ppm on δ scale and referenced with internal tetramethylsilane. ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$.

General procedure for the *cis*-2,4,6-tetrahydropyranols derivative (1c): To a solution of 4-hexen-2-ol (1.0 g, 10 mmol) in 10 mL of dichloromethane, benzaldehyde (1.38 g, 13 mmol) was added. The reaction mixture was cooled to 0-5 °C and slow addition of trifluoro acetic acid (3.42 g, 30 mmol) at the same temperature. Then boron trifluoride etherate (2.83 g, 20 mmol) was added drop-wise at 0-5 °C. Reaction mixture was stirred for 3 h at 0-5 °C. After completion of reaction 5 % sodium bicarbonate solution (10 mL) was added, followed by extraction with dichloromethane (3 × 10 mL). The combined organic layer dried over sodium sulfate and solvent evaporated under reducing pressure. The crude was dissolved in methanol (10 mL) and added potassium carbonate (1.38 g, 10 mmol). Reaction mixture was stirred for 1 h at room temperature. Then methanol was removed under reduced pressure and water (10 mL) was added. The reaction mixture was extracted with dichloromethane (2 × 10 mL) and combined organic layer was dried over sodium sulfate. Solvent was removed under reduced pressure. The crude was purified by column chromatography on silica gel (30-60 % ethyl acetate/hexanes) to get *cis*-2,4,6 tetrahydropyranol derivative (**1c**).

General procedure for *trans*-2,4,6-tetrahydropyranols derivative (1d): To a solution of (2S,4R,6S)-3,6-dimethyl-2-phenyltetrahydro-2*H*-pyran-4-ol (**1c**) (0.75 g, 3.63 mmol) in 7.5 mL of toluene, 4-nitrobenzoic acid (0.66 g, 4.0 mmol) and triphenylphosphine (1.43 g, 5.45 mmol) were added under dry nitrogen. The reaction mixture was cooled to 0-5 ºC and slow addition of diethylazodicarboxylate (0.82 g, 4.72 mmol) at the same temperature. Then reaction mixture was heated to 80-90 ºC. Reaction mixture was stirred for 10 h at the same temperature. Solvents distilled under reduced pressure. 5 % sodium bicarbonate solution (10 mL) was added, followed by extraction with dichloromethane (3 × 10 mL). The combined organic layer dried over sodium sulfate and solvent evaporated under reduced pressure. The crude was dissolved in methanol (10 mL) and added potassium carbonate (1 g, 7.27 mmol). Reaction mixture was stirred for 1 h at room temperature. Filtered the solids and then methanol was removed under reduced pressure and water (10 mL) was added. The reaction mixture was extracted with dichloromethane (2 × 10 mL) and combined

organic layer was dried over sodium sulfate. Solvent was removed under reduced pressure. The crude was purified by column chromatography on silica gel (30-60 % ethyl acetate/ hexanes) to get *trans*-2,4,6 tetrahydropyranol derivative (**1d**).

(2S,4R,6S)-3,6-dimethyl-2-phenyltetrahydro-2*H*-pyran-4-ol (1c): R_f = 0.35 (1:4 ethyl acetate-hexanes); IR (KBr) 3464, 2971, 1643, 1136; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (d, *J* = 7.0 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.50 (m, 2H), 1.76 (m, 1H), 2.11-2.19 (m, 1H), 3.64 (qdd, *J* = 16.3, 12.2, 2.5, 1H), 4.14 (ddd, *J* = 10.1, 7.2, 4.3 Hz, 1H), 4.52 (d, *J* = 2.5 Hz, 1H), 7.21-7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.0, 21.6, 36.7, 40.2, 71.3, 72.3, 79.8, 125.5, 126.6, 127.9, 141.0; Mass: (*m/z*) 206.28 found 207 (M^{+1}).

(2S,4S,6S)-3,6-dimethyl-2-phenyltetrahydro-2*H*-pyran-4-ol (1d): R_f = 0.40 (1:4 ethyl acetate-hexanes); white solid; m.p.: 110-115 °C; IR (KBr) 3464, 2971, 1643, 1136; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.57-1.62 (m, 1H), 1.75 (m, 3.0 Hz, 1H), 1.84-1.94 (m, 1H), 4.06 (dd, *J* = 4.1, 2.4 Hz, 1H), 4.08 (qdd, *J* = 15.3, 14.2, 2.5 Hz, 1H), 5.07 (dd, *J* = 2.8 Hz, 1H), 7.19 (m, 1H), 7.28-7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 21.9, 35.7, 40.6, 68.7, 70.8, 75.2, 125.5, 126.4, 127.9, 141.8; Mass: (*m/z*) 206.28 found 207 (M^{+1}).

(2R,4R,6S)-3,6-dimethyl-2-phenethyltetrahydro-2*H*-pyran-4-ol (2c): R_f = 0.3 (1:4 ethyl acetate-hexanes); IR (KBr) 3410, 2973, 1451, 1102; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.5 Hz, 3H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.36 (m, 1H), 1.6-1.71 (m, 3H), 1.80-1.85 (m, 1H), 1.94 (m, 1H), 2.63 (m, 1H), 2.8 (m, 1H), 3.29 (ddd, *J* = 8.6, 4.5, 2.2 Hz, 1H), 3.46 (dqd, *J* = 11.2, 6.5, 2.1 Hz, 1H), 3.82 (m, 1H), 7.19-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9, 21.6, 32.2, 34.3, 37.1, 37.9, 71.1, 72.1, 125.7, 128.3, 128.4, 142.1; Mass: (*m/z*) 234.33 found 235 (M^{+1}).

(2R,4S,6S)-3,6-dimethyl-2-phenethyltetrahydro-2*H*-pyran-4-ol (2d): R_f = 0.35 (1:4 ethyl acetate-hexanes); IR (KBr) 3452, 3090, 3024, 2970, 2924, 1540, 1480; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 7.8 Hz, 3H), 1.46-1.64 (m, 5H), 1.89 (m, 1H), 2.62 (m, 1H), 2.80 (m, 1H), 3.85 (qdd, *J* = 16.2, 15.2, 2.8 Hz, 1H), 3.87 (dd, *J* = 5.2, 2.4 Hz, 1H), 4.52 (d, *J* = 9.4 Hz, 1H), 7.13- 7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 21.8, 32.3, 34.5, 36.0, 38.3, 68.4, 70.9, 73.3, 125.6, 128.3, 128.4, 142.3; Mass: (*m/z*) 234.33 found 235 (M^{+1}).

(2R,4R,6S)-3-methyl-2,6-diphenethyltetrahydro-2*H*-pyran-4-ol (3c): R_f = 0.6 (1:4 ethyl acetate-hexanes); m.p.: 94–96 °C; IR (KBr) 3392, 3026, 2941, 2920, 1059, 700; White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (q, *J* = 11.6 Hz, 2H), 1.41 (s, 1H), 1.75 (dddd, *J* = 13.4, 9.8, 7.0, 4.5 Hz, 2H), 1.98–1.91 (m, 4H), 2.73 (ddd, *J* = 13.5, 8.6, 7.5 Hz, 2H), 2.87 (ddd, *J* = 14.2, 9.2, 5.4 Hz, 2H), 3.27–3.23 (m, 2H), 3.75 (tt, *J* = 10.5, 4.4 Hz, 1H), 7.30–7.19 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 128.6, 128.4, 125.8, 74.4, 68.3, 41.5, 37.8, 32.0; Mass: (*m/z*) 324.4 found 325 (M^{+1}).

(2R,4S,6S)-3-methyl-2,6-diphenethyltetrahydro-2*H*-pyran-4-ol (3d): R_f = 0.5 (1:4 ethyl acetate-hexanes); White solid: m.p.: 69-72 °C; IR (KBr) 3392, 3026, 2918, 1093, 750, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, *J* = 2.8 Hz, 1H), 1.54–1.49 (m, 2H), 1.64 (dd, *J* = 14.5, 2.6 Hz, 2H), 1.70 (dddd, *J* = 13.5, 10.3, 7.0, 3.5 Hz, 2H), 1.86 (dtd, *J* = 14.4, 9.5, 5.4 Hz, 2H), 2.72 (ddd, *J* = 13.5, 9.1, 7.4 Hz, 2H), 2.89 (ddd, *J* = 14.2, 9.1, 5.4 Hz, 2H), 4.25 (q, *J* = 2.5 Hz, 1H), 3.76–3.71 (m, 2H), 7.30–7.17 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 128.60, 128.4, 125.8, 70.7, 65.0, 39.0, 38.1, 32.0; Mass: (*m/z*) 324.4 found 325 (M^{+1}).

(2S,4R,6S)-2-isopropyl-3-methyl-6-phenethyltetrahydro-2*H*-pyran-4-ol (4c): R_f = 0.5 (1:4 ethyl acetate-hexanes); Colourless oil; IR (KBr) 3367, 3028, 2951, 2871, 1050, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.5 Hz, 3H), 1.0 (d, *J* = 6.8 Hz, 3H), 1.2–1.12 (m, 2H), 1.75–1.65 (m, 2H), 1.93–1.85 (m, 2H), 2.00–1.97 (m, 1H), 2.75 (m, 1H), 2.82 (m, 1H), 2.90 (ddd, *J* = 11.5, 7.3, 1.7 Hz, 1H), 3.22–3.17 (m, 1H), 3.74 (tt, *J* = 10.5, 4.4 Hz, 1H), 7.19–7.16 (m, 3H), 7.29–7.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 128.6, 128.4, 125.8, 80.7, 74.0, 68.8, 41.5, 38.4, 37.8, 33.2, 31.8, 19.0, 18.8; Mass: (*m/z*) 262.39 found 263 (M^{+1}).

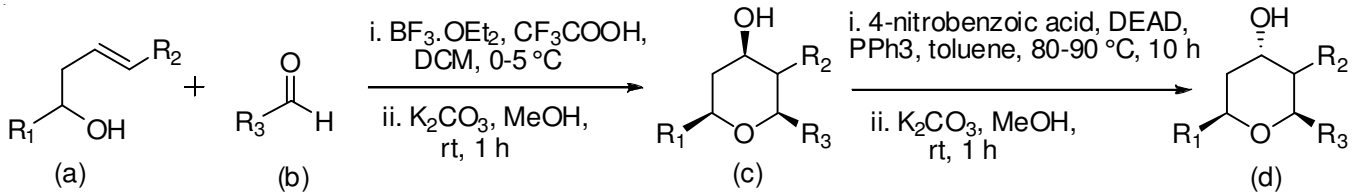
(2S,4S,6S)-2-isopropyl-3-methyl-6-phenethyltetrahydro-2*H*-pyran-4-ol (4d): R_f = 0.4 (1:4 ethyl acetate-hexanes); Colourless oil; IR (KBr) 3390, 3028, 2947, 1057, 737, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.5 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.33 (s, 1H), 1.51–1.43 (m, 2H), 1.60–1.55 (m, 2H), 1.67–1.63 (m, 2H), 1.80 (m, 1H), 2.73–2.65 (m, 1H), 2.83 (m, 1H), 3.36 (ddd, *J* = 11.5, 7.2, 1.9 Hz, 1H), 3.70–3.65 (m, 1H), 4.26 (q, *J* = 2.5 Hz, 1H), 7.22–7.15 (m, 3H), 7.29–7.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 128.6, 128.3, 125.7, 76.7, 70.5, 65.2, 39.1, 38.1, 36.0, 33.4, 31.9, 19.0, 18.7; Mass: (*m/z*) 262.39 found 263 (M^{+1}).

(2S,4R,6S)-2-(furan-2-yl)-3,6-dimethyltetrahydro-2*H*-pyran-4-ol (5c): R_f = 0.35 (1:4 ethyl acetate-hexanes); IR (KBr) 3412, 2916, 1454, 1102; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.44 (m, 1H), 1.70-1.76 (m, 1H), 2.26-2.29 (m, 1H), 3.64 (m, 1H), 4.0 (ddd, *J* = 10.2, 7.0, 4.5 Hz, 1H), 4.52 (d, *J* = 2.6 Hz, 1H), 6.24 (m, 1H), 6.34 (m, 1H), 7.36 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ 5.7, 21.6, 36.8, 38.1, 70.6, 72.8, 75.7, 106.1, 110.1, 141.3, 153.6; Mass: (*m/z*) 196.24 found 197 (M^{+1}).

(2S,4S,6S)-2-(furan-2-yl)-3,6-dimethyltetrahydro-2*H*-pyran-4-ol (5d): R_f = 0.40 (1:4 ethyl acetate-hexanes); IR (KBr) 3435, 2973, 1724, 1147; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.50-1.56 (m, 1H), 1.70 (m, 1H), 1.94-2.0 (m, 2H), 3.98 (m, 1H), 4.06 (qdd, *J* = 15.2, 14.8, 2.2 Hz, 1H), 5.06 (d, *J* =2.6 Hz, 1H), 6.24 (m, 1H), 6.34 (m, 1H), 7.37 (m,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 21.8, 35.5, 38.7, 69.1, 70.2, 71.3, 106.0, 109.9, 141.2, 153.4; Mass: (*m/z*) 196.24 found 197 (M^{+1}).

RESULTS AND DISCUSSION

The synthetic route for the diastereoselective preparation of **1-5(c)** compounds is shown in **Scheme-I**. Initially, 4-hexen-2-ol (**1a**) and 1-phenylhept-5-en-3-ol (**3a**) were prepared in high yields in an aqueous medium from the Barbier reaction between acetaldehyde and 1-bromobut-2-ene and 3-phenyl-propanal and 1-bromobut-2-ene, respectively promoted by tin(II) chloride. Compounds **1c**, **2c** and **5c** were prepared on total 2,4,6-equatorial diastereoselectivity from Prins cyclization reaction between 4-hexen-2-ol (**1a**) and benzaldehyde (**1b**), 3-phenylpropanal (**2b**) and furnaldehyde (**4b**), respectively.



Scheme-I: Prins cyclization with $BF_3.OEt_2$, TFA and Mitsunobu inversion

Compounds **3c** and **4c** were prepared between 1-phenylhept-5-en-3-ol (**3a**) and 3-phenylpropanal (**2b**), 3-methylbutanal (**3b**) respectively, only by $BF_3{\cdot}OEt_2$ (Lewis acid) and trifluoro acetic acid (TFA), in moderate to good yields and on mild conditions. Then compounds **1-5(c)** undergo Mitsunobu inversion and subsequent methanolysis efficiently furnished the *trans*-2,4,6 tetrahydropyranols **1-5(d)** [16].

Some general mechanistic proposals have been described to explain the high selectivity of 2,4,6-*cis* in the Prins reaction. Based on some most accepted reaction mechanisms explaining the 2,4,6-*cis* preferential geometry for this cyclization, proposed by Farrugia [17], we proposed a general mechanism **Scheme-II**. The mechanism starts with the nucleophilic attack of alcohol 'A' on the complexed aldehyde-Lewis acid (stage-i) leading to intermediate 'B' formation. Stage-ii is a proton exchange followed by elimination (stage-iii) with intermediate 'D' formation. The stage-iv subsequently occurs by synchronously nucleophilic attack through the transition state 'E', which produce 'F'. It should be noted that the nucleophilic attack on step 'E' occurs preferentially on equatorial position which is a more stable transition state and axial position which is a lower stable transition state. Another proposal explaining the equatorial stereoselectivity on C4 of tetrahydropyran derivatives was based on the theoretical studies by Farrugia *et al.* [18].

The 2,4,6-*cis* geometry determination in the compounds **1-5(c)** were made based on the NMR spectroscopy. In these *cis*-2,4,6-tetrahydropyranols compounds spectra there is a strong spatial coupling between the hydrogens H_a, H_b and H_c in 1c. Such coupling would not be observed in the *trans*-2,4,6-tetrahydropyranols (**1d**) (Fig. 1).

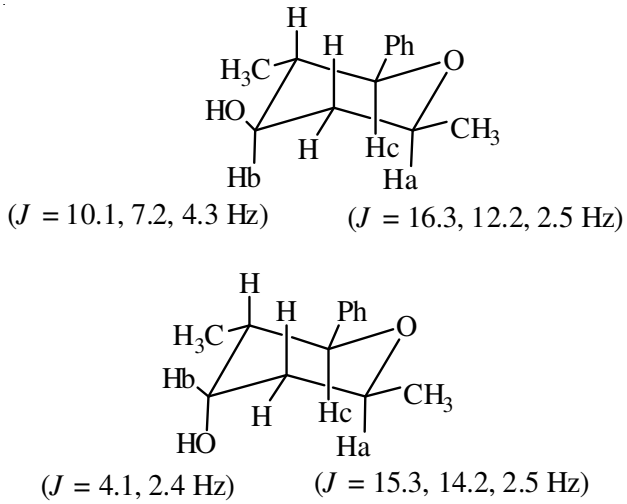
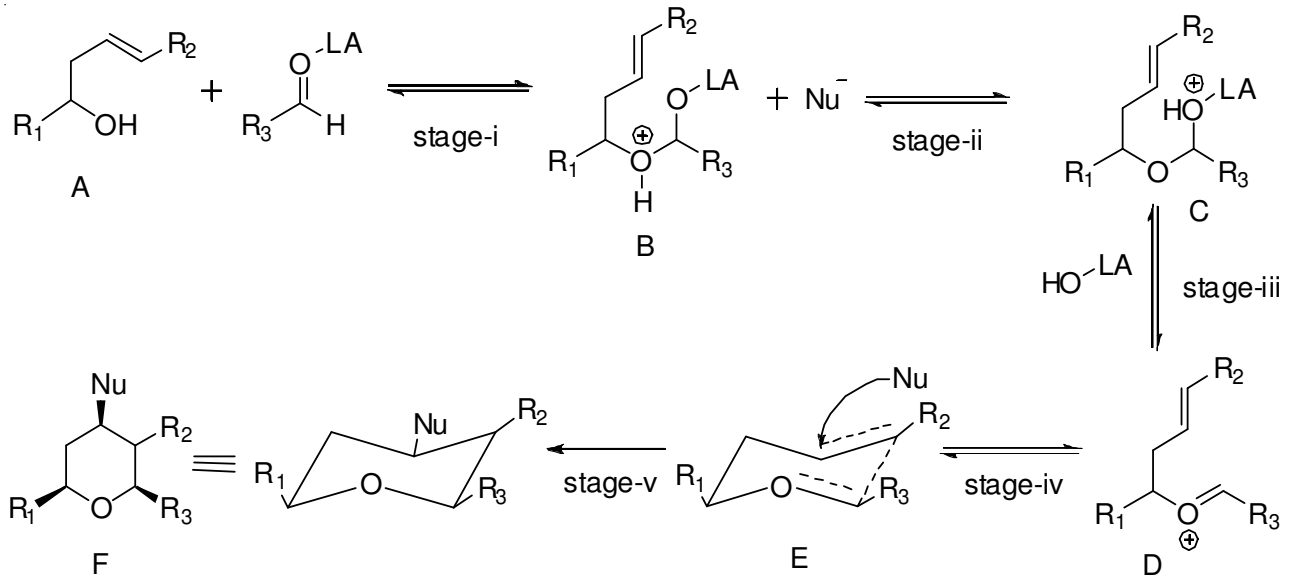


Fig. 1. Coupling constants of the products **1c** and **1d**

Conclusion

In this work, the Lewis acids such as $BF_3.OEt_2$ and trifluoro acetic acid (TFA) are proved to be a useful and novel reaction catalytic system for Prins-cyclization, avoiding the expensive catalysts. The substrates shows significant increasing in reactivity, reducing the reaction time and improving the yields. Finally, we are able to prepare in good yields *cis*-2,4,6-tetrahydropyranols and *trans*-2,4,6- tetrahydropyranols derivatives **1-5(c-d)** in the presence of $BF_3.OEt_2$ and TFA followed by Mitsunobu inversion. We determinate its *cis*/*trans* configurations by spectroscopy studies.



Scheme-II: General mechanisms to obtained the **1-5(c,d)** *cis*/*trans* compounds from the Prins cyclization reactions

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