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Graphical Abstract

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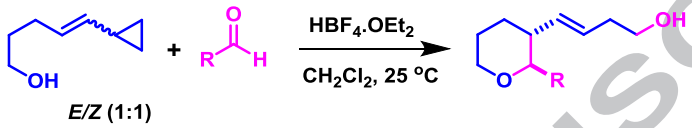

E/*Z* (1:1)

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Tandem vinylcyclopropane ring opening/Prins cyclization for the synthesis of 2,3-disubstituted tetrahydropyrans

B. V. Subba Reddy,*[a] V. Swathi,[a,b] Manika Pal Bhadra,[b] M. Kanaka Raju,[c] A. C. Kunwar[c]

[a]*Centre for Semiochemicals*, [b]*Centre for Chemical Biology*, [c]*Centre for Nuclear Magnetic Resonance and Structural Chemistry*, *CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India. E-mail:basireddy@iict.res.in, Fax: 91-40-27160512.*

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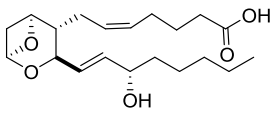
ABSTRACT

An efficient synthesis of 2,3-disubstituted tetrahydropyrans from aldehyde and cyclopropyl alkenol has been accomplished using $HBF_4.OEt_2$ as a promoter through a tandem vinylcyclopropane ring-opening/Prins cyclization. It is a convenient process to generate a structurally diverse and biologically relevant 2,3-disubstituted tetrahydropyrans in good yields with high selectivity.

Thromboxane A2 (TXA2) is a hormone, which is produced by blood platelets. It is a potent vasoconstrictor and initiates activation of new platelets and platelet aggregation (Figure 1).[1]

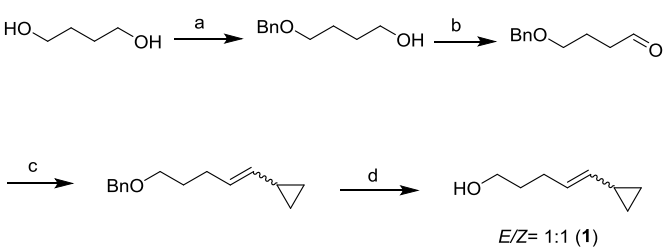


Thromboxane (TXA_2)

Figure 1. Biologically active 2,3-substituted tetrahydropyran

The Prins-type cyclization is one of the most efficient approaches for the construction of tetrahydropyran ring (THP), which is a backbone of several natural products.[2] In particular, Prins induced cascade reactions are very useful for the stereoselective synthesis of fused, bridged, and spirotetrahydropyran scaffolds.[3,4] It has been successfully employed to the synthesis of tetrahydropyran containing molecules.[5] However, a few methods are known in literature for the synthesis of 2,3-disubstituted tetrahydropyrans through a Prins cyclization.[6]

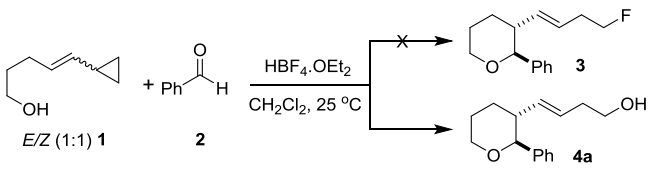
Following our interests on Prins-type cyclizations,[7] we herein report an efficient strategy for the stereoselective synthesis of (*E*)-4-(tetrahydro-2*H*-pyran-3-yl)but-3-en-1-ol derivatives. The requisite starting material, 5-cyclopropylpent-4-en-1-ol (**1**) was prepared by a known procedure (Scheme 1).[8] However, the precursor **1** was obtained as a 1:1 mixture of *E*/*Z* isomers. They could not be separated by column chromatography. Therefore, the Prins cyclization was performed using 1:1 mixture of *E*/*Z* isomers of **1**.



E/*Z*= 1:1 (**1**)

Scheme 1. Reaction conditions: a) BnBr, NaH, THF, r.t., 12h; b) PCC, celite, DCM, r.t., 4h; c) (cyclopropylmethyl)triphenylphosphonium bromide, *n*-BuLi, THF, -78 °C, 3h; d) Li, naphthalene, THF, -40 °C, 1h.

In a preliminary experiment, (*E*/*Z*)-5-cyclopropylpent-4-en-1-ol (**1**) (1.0 equiv) was treated with benzaldehyde (1.2 equiv) using $HBF_4.OEt_2$ (1 equiv) in dichloromethane. The reaction proceeded smoothly at 25 °C and the product **4a** was obtained in 85% yield with high stereocontrol (entry a, Table 1). Under the above conditions, we expected the formation of fluoro derivative **3** through a sequential Prins/fluorination process involving a tandem vinylcyclopropane ring opening by $HBF_4.OEt_2$. But unexpectedly, the compound **4a** was formed under present conditions (Scheme 2).



Scheme 2. Selective formation of 2,3-disubstituted tetrahydropyran (**4a**)

The effect of other acid catalysts such as $BF_3.OEt_2$ and TMSOTf was studied for this conversion (entries b, c, Table 1). Though, the reaction proceeded at 0 °C in the presence of 1 equiv of $BF_3.OEt_2$, the product **4a** was obtained relatively in lower yield than $HBF_4.OEt_2$ (entry b, Table 1). To our surprise, TMSOTf also afforded the product **4a** comparatively in lower yield than $HBF_4.OEt_2$ (entry c, Table 1). The reaction was also carried out using different amounts of the reagent ranging from a catalytic (10 mol%) to stoichiometric. However, the best conversions were achieved using a stoichiometric amount of Lewis acid. We further examined the effect of solvent for this reaction (entries d-g, Table 1). However, the reaction was sluggish either in THF or CH_3CN affording the desired product **4a** in trace amount. To our delight, DCM gave the best results (entries a-c, Table 1).

Table 1. Optimization of reaction conditions

Entry	Catalyst (1 equiv)[a]	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
a	$HBF_4.OEt_2$	DCM	25 °C	0.5	85
b	$BF_3.OEt_2$	DCM	0 °C	0.5	78
c	TMSOTf	DCM	0 °C	0.5	70
d	$HBF_4.OEt_2$	THF	25 °C	0.5	Trace
e	$HBF_4.OEt_2$	CH_3CN	25 °C	0.5	Trace
f	$BF_3.OEt_2$	THF	0 °C	0.5	Trace
g	$BF_3.OEt_2$	CH_3CN	0 °C	0.5	Trace

[a]The reaction was performed in 1 mmol scale using a stoichiometric amount of catalyst. [b]Isolated yield after chromatography.

To confirm the terminal hydroxyl group, **4a** was converted into its acetate derivative **4a'** using acetic anhydride and DMAP in dichloromethane. The structure and relative stereochemistry of **4a'** were established by 1D and 2D NMR experiments (Supporting information). The structures of **4a'** were derived by extensive NMR experiments including 2-D Nuclear Overhauser Effect Spectroscopy (NOESY) and Double Quantum Filtered Correlation Spectroscopy (DQFCOSY), Hetero-nuclear Single Quantum Correlations (HSQC) and Hetero-nuclear Multiple Bond Correlation (HMBC) experiments. The distinctive doublet at 3.94 ppm in **4a'** due to 1-H was used to initiate the assignments with the help of DQF-COSY and NOESY experiments. From the one dimensional ^1H NMR experiments, large coupling constants like : $^3J_{1\text{-H}/5\text{-H}}$ = 10.0, $^3J_{2\text{-H}'/3\text{-H}'}$ = 13.5, $^3J_{3\text{-H}'/4\text{-H}'}$ = 12.0, $^3J_{4\text{-H}'/5\text{-H}}$ = 13.0 Hz imply the di-axial disposition of the participating protons, which are consistent with the structure having six-membered ring in chair conformation as shown in the Figure **1**. Further support for the proposed structure was derived from small equatorial – equatorial and axial - equatorial couplings like: $^3J_{2\text{-H}/3\text{-H}}$ = 4.7, $^3J_{2\text{-H}/3\text{-H}'}$ = 2.5, $^3J_{2\text{-H}'/3\text{-H}}$ = 2.5, $^3J_{3\text{-H}/4\text{-H}}$ = 2.5, $^3J_{3\text{-H}/4\text{-H}'}$ = 4.0, $^3J_{3\text{-H}'/4\text{-H}}$ = 4.0 and $^3J_{4\text{-H}/5\text{-H}}$ = 4.0 Hz. Finally the characteristic NOE correlations, 1-H/2-H′, 1-H/4-H′, 2-H′/4-H′, 3-H′/5-H, provide emphatic support for the structure, with the six-membered ring taking $^5C_{2C}$ chair conformations. The coupling constant $^3J_{6\text{-H}/7\text{-H}}$ = 15.6 Hz and NOE correlations, 4-H′/6-H and 5-H/7-H, imply *trans* double bond between 6-H and 7-H protons. The energy minimized structure adequately supports the proposed structure of **4a'** (Figure 2).

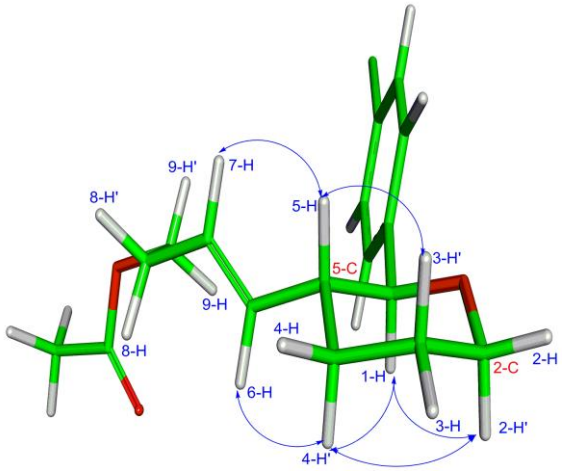
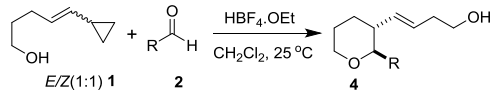
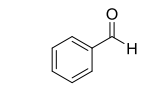
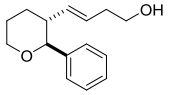
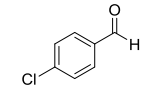
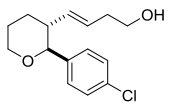
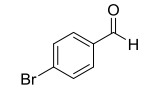
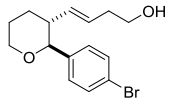
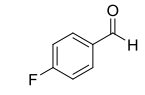
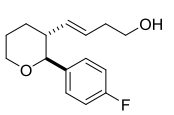
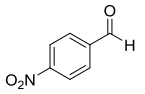
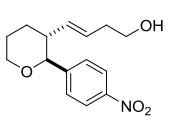
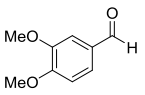
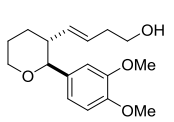
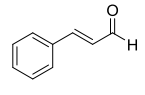
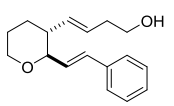
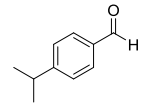
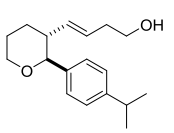
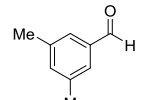
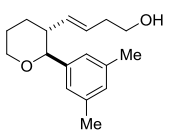
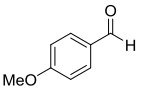
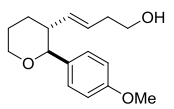
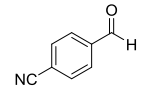
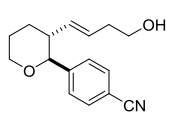
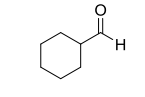
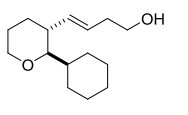
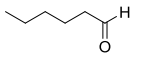
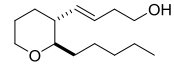
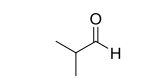
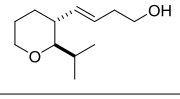


Figure 2. Energy minimized structure and characteristic NOEs of **4a'**

Encouraged by these initial findings, we extended this method to a diverse range of aldehydes and the results are summarized in Table 2. Interestingly, aryl aldehydes such as 4-chloro-, 4-bromo-, 4-fluoro-, 4-nitro-, 3,4-dimethoxy-, 4-isopropyl-, 3,5-dimethyl-, 4-methoxy-, 4-cyano-benzaldehydes participated well in this transformation (Table 2). This method was also successful with aliphatic aldehydes such as cyclohexanecarboxaldehyde, *n*-hexanal, and isobutyraldehyde under similar conditions. Acid sensitive α,β-unsaturated aldehyde (cinnamaldehyde) was also compatible under the reaction conditions. In all cases, the reactions proceeded well at ambient temperature with high selectivity. Only a single diastereomer was obtained in each reaction, the structure of which was established by ^1H and ^{13}C NMR and mass spectrometry. This method is highly diastereoselective affording high yields of products in a short reaction time (Table 2).

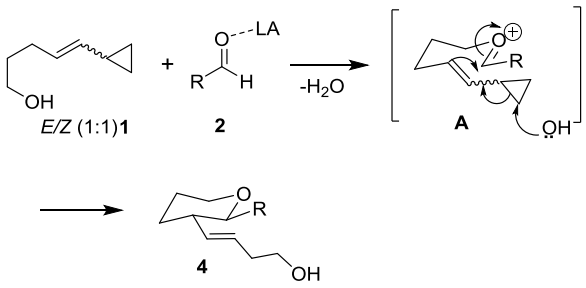
Table 2. Synthesis of 2,3-disubstituted THPs



Entry	Aldehyde (**2**)	Product (**3**)[a]	Time (h)	Yield(%)[b]
a		 **4a**	0.5	85
b		 **4b**	1.0	88
c		 **4c**	1.0	86
d		 **4d**	1.5	72
e		 **4e**	0.5	80
f		 **4f**	1.5	78
g		 **4g**	1.0	75
h		 **4h**	1.0	79
i		 **4i**	1.0	80
j		 **4j**	1.5	70
k		 **4k**	0.5	82
l		 **4l**	1.0	85
m		 **4m**	1.0	80
n		 **4n**	1.0	82

[a]All products were characterised by NMR and mass spectroscopy
[b]Yield refers to products after chromatography

Based on our previous observations, we proposed a possible reaction mechanism as shown in Scheme 3. The condensation of cyclopropyl alkenol with aldehyde in the presence of an acid catalyst generates an oxo-carbenium ion (**A**). A subsequent attack of an internal olefin on **A** followed by the ring opening of vinylcyclopropane would give the desired product (**4**).



Scheme 3. A plausible reaction mechanism

Though, the stereochemistry of product is totally dependent on the geometry of olefin in Prins cyclization using a homoallylic alcohol, there is no such effect was observed in the present case. Because the olefin used in the present work behaves differently than homoallylic alcohol. Furthermore, *Z*-isomer might be converted rapidly into *E*-isomer under acidic conditions.

In summary, we have developed an efficient method for the synthesis of a novel class of 2,3-disubstituted tetrahydropyrans in good yields. This approach provides a direct access to biologically relevant tetrahydropyrans with diverse substitution pattern. The notable features of this procedure are operationally simple, mild reaction conditions, short reaction times and high yields, which make it very useful and attractive.

Acknowledgments

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Supplementary data

Experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectrum of products can be found, in the online version, at http:// dx.doi.org/

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9. *General experimental procedure*: To a stirred solution of 5-cyclopropylpent-4-en-1-ol (1 mmol) and aldehyde (1.2 mmol) in dichloromethane (5 mL) was added $HBF_4.OEt_2$ (1 mmol). The resulting mixture was allowed to stir at 25 ^oC for the appropriate time (Table 2). After completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography.

- Tetrahydropyrans are obtained from aldehyde and (*E*)-cyclopropyl alkenol.
- It provides the products in good yields with high selectivity.
- It is a first example on a tandem vinylcyclopropane ring opening/Prins cyclization.
- It proceeds under extremely mild conditions in short reaction times.