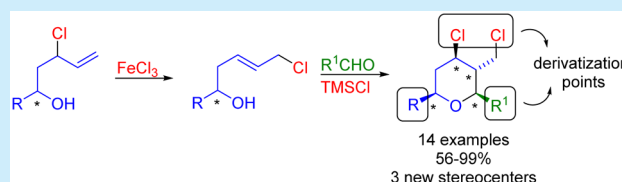


Direct Access to 2,3,4,6-Tetrasubstituted Tetrahydro-2H-pyrans via Tandem  $S_N2'$ –Prins CyclizationJimena Scoccia,<sup>||,⊥</sup> Sixto J. Pérez,<sup>‡</sup> Victoria Sinka,<sup>†</sup> Daniel A. Cruz,<sup>‡</sup> Juan M. López-Soria,<sup>†</sup> Israel Fernández,<sup>§</sup> Víctor S. Martín,<sup>‡</sup> Pedro O. Miranda,<sup>\*,†</sup> and Juan I. Padrón<sup>\*,†,‡</sup><sup>†</sup>Instituto de Productos Naturales y Agrobiología, CSIC, Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain<sup>‡</sup>Instituto Universitario de Bio-Organica “Antonio González” (CIBICAN), “Síntesis Orgánica Sostenible, Unidad Asociada al CSIC”, Departamento de Química Orgánica, Universidad de La Laguna, Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain<sup>§</sup>Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Centro de Innovación en Química Avanzada (ORFEO–CINQA), Universidad Complutense de Madrid, 28040 Madrid, Spain<sup>||</sup>Departamento de Química, Universidad Nacional del Sur, Av Alem 1253, 800 Bahía Blanca, Argentina<sup>⊥</sup>INQUISUR, CONICET, Av Alem 1253, 800 Bahía Blanca, Argentina

## Supporting Information

**ABSTRACT:** A new, direct, and diastereoselective synthesis of activated 2,3,4,6-tetrasubstituted tetrahydro-2H-pyrans is described. In this reaction, iron(III) catalyzed an  $S_N2'$ –Prins cyclization tandem process leading to the creation of three new stereocenters in one single step. These activated tetrahydro-2H-pyran units are easily derivatizable through CuAAC conjugations in order to generate multifunctionalized complex molecules. DFT calculations support the in situ  $S_N2'$  reaction as a preliminary step in the Prins cyclization.



Functionalized tetrahydropyrans are structural motifs ubiquitous in a myriad of biologically active natural products.<sup>1,2</sup> Several approaches to the synthesis of such moieties have been developed throughout the years with special emphasis on Prins cyclization recently.<sup>3–11</sup> Among the plethora of substituted oxanes, 2,3,4,6-tetrasubstituted tetrahydro-2H-pyrans (2,3,4,6-THPs) constitute attractive targets since they are present in natural products,<sup>12,13</sup> have great potential as bioisosteres of amino acids,<sup>14</sup> and are precursors of vinylcyclopropanes<sup>15</sup> and other species of high interest in medicinal chemistry.<sup>16</sup> Moreover, the introduction of four different substituents in the tetrahydro pyran ring may indeed affect its three-dimensional molecular structure and, therefore, its biological activity.<sup>17,18</sup> Also, it provides excellent opportunities toward the introduction of molecular complexity. However, despite their attractiveness as synthetic targets, there have been few reports on the synthesis of 2,3,4,6-THPs using Prins cyclization conditions,<sup>19–22</sup> most notably due to the existence of competitive pathways that result in racemization problems and/or mixtures of undesired products.<sup>8,23–26</sup> Additionally, the creation of new stereogenic centers, controlled by pre-existing stereochemical features, is often a challenge in acyclic molecules since it is not always easy to reduce the number of degrees of rotational freedom in a molecule.<sup>27</sup> In the present work, we report our findings on the stereocontrolled one-pot synthesis of 2,3,4,6-THPs.

Initially, alcohol **1** was prepared in order to achieve the iron-catalyzed synthesis of disubstituted seven-membered oxacycles **2** as precursors for  $\Delta^4$ -2,7-disubstituted oxepenes **3**. However,

instead of the expected seven-membered ring, the observed cyclic product turned out to be the six-membered oxacycle **4** (2,3,4,6-THP) adorned with four stereogenic centers, three of them generated in one single step (Figure 1). The reaction

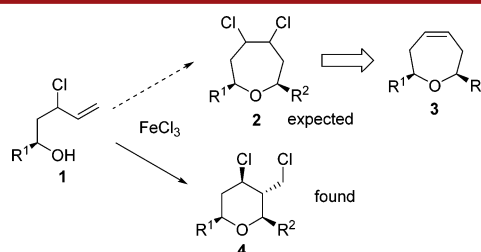


Figure 1. Initial approach for the synthesis of oxacycles.

proceeded with excellent stereocontrol and with all substituents being in the equatorial position (see below, Figure 2). The presence of a primary alkyl chloride at the 3-position is of further interest since, by judicious choice of reaction conditions, it can be converted into a wide variety of functional groups, allowing us the preparation of more complicated derivatives.

First, we carefully explored the reaction conditions in order to improve the reaction yield of the 2,3,4,6-THP **4a** (Table 1). Taking into account that in previous works DCM and TMSCl have both proven to be suitable solvents and co-catalysts to

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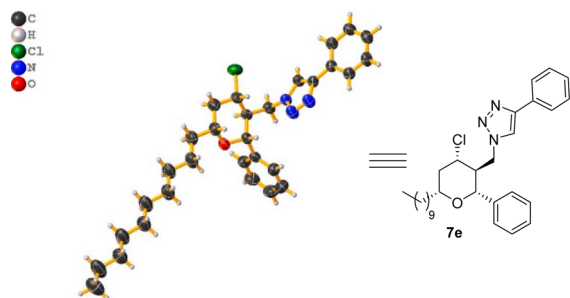


Figure 2. ORTEP plot and structure of triazole 7e.

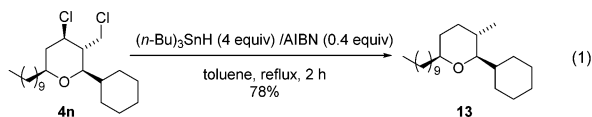
Table 1. Optimization of the Reaction Conditions for the Tandem  $S_N2'$ –Prins Cyclization of 1 with Isovaleraldehyde<sup>a</sup>

entry	cat. (equiv)	TMSCl (equiv)	time (h)	yield <sup>b</sup> (%)
1	FeCl <sub>3</sub> (1)		0.5	80
2	InCl <sub>3</sub> (1)		0.5	35
3	FeCl <sub>3</sub> (0.1)	1.1	20	71
4	FeCl <sub>3</sub> (0.2)	1.1	20	73
5	Fe(acac) <sub>3</sub> (0.1)	1.1	20	48
6	Fe(acac) <sub>3</sub> (0.2)	1.1	20	50
7	InCl <sub>3</sub> (0.1)	1.1	20	49
8	InCl <sub>3</sub> (0.2)	1.1	20	57
9	Fe(OTf) <sub>3</sub> (0.1)	1.1	20	60

<sup>a</sup>Reaction conditions: 1 (1.0 mmol), isovaleraldehyde (1.1 mmol), [Fe], dry CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), rt, 0.5–20 h. The stereochemistry of the THPs was assigned by GOESY experiments (see the Supporting Information). <sup>b</sup>Yields of products after purification by silica gel column chromatography.

carry out Prins cyclizations, respectively,<sup>28</sup> we focused on the nature of the metal source. Although stoichiometric amounts of FeCl<sub>3</sub> were effective, the corresponding workup and purification turned out to be inconvenient. Replacement of the iron halide source with organoiron or indium catalysts did not improve reaction yields. Thus, we settled on the use of 20 mol % of FeCl<sub>3</sub> and 1.1 equiv of TMSCl as the best reaction conditions (Table 1).

Next, we explored the scope of the reaction by using a variety of aldehydes alongside alcohols bearing different substituents at the R<sup>1</sup> position (Table 2). The use of either alkyl and branched aldehydes or unsaturated aldehydes gave excellent yields (Table 2, entries 1–4). Similarly, the use of aromatic aldehydes having either electron-withdrawing or electron-donating groups gave rise to the corresponding THP structures 4 in good yields (Table 2, entries 5–8). On the other hand, long alkyl chain R<sup>1</sup> substituents also led to THPs 4 with moderate to good yields (Table 2, entries 9–13). The use of unsaturated aldehydes is important from a synthetic point of view since the alkene component allows the further functionalization of the molecule in a straightforward manner. Thus, successful dehalogenation with AIBN/(*n*-Bu)<sub>3</sub>SnH led to the corresponding 2,6-dialkyl-3-methyl tetrahydro-2*H*-pyran (eq 1).

Table 2. Scope of the Tandem  $S_N2'$ –Prins Cyclization<sup>a</sup>

Reaction scheme showing the synthesis of 4a-m from alcohol 1 and aldehyde 5. Reagents: FeCl<sub>3</sub> (20 mol %), TMSCl (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt.

entry	R <sup>1</sup>	R <sup>2</sup>	time (h)	yield <b>4</b> <sup>b</sup> (%)	
1	Et	<i>n</i> -Bu	<b>4b</b>	0.5	89
2	Et	Cy	<b>4c</b>	1	99
3	Et	3-butenyl	<b>4d</b>	6	72
4	Et	ethenyl	<b>4e</b>	8	61
5	Et	Ph	<b>4f</b>	18	77
6	Et	<i>p</i> -OMe-Ph	<b>4g</b>	20	69
7	Et	<i>p</i> -NO <sub>2</sub> -Ph	<b>4h</b>	20	88
8	Et	<i>p</i> -F-Ph	<b>4i</b>	20	93
9	7-octenyl	<i>i</i> -Bu	<b>4j</b>	18	60
10	7-octenyl	Ph	<b>4k</b>	20	63
11	<i>n</i> -decyl	<i>i</i> -Bu	<b>4l</b>	19	56
12	<i>n</i> -decyl	Ph	<b>4m</b>	20	71
13	<i>n</i> -decyl	Cy	<b>4n</b>	20	62

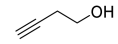
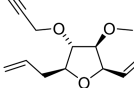
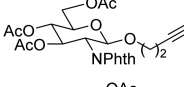
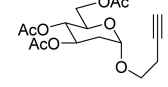

<sup>a</sup>Reaction conditions: 1 (1.0 mmol), 5 (1.1 mmol), FeCl<sub>3</sub> (20 mol %), TMSCl (1.1 mmol) dry CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), rt. The stereochemistry of the THPs was assigned by GOESY experiments (see the SI). <sup>b</sup>Yields of products determined by <sup>1</sup>H NMR analysis with hexamethyldisilane as the internal standard.

Our next goal was to increase the molecular complexity by taking advantage of the presence of the primary alkyl chloride in THPs of structure 4. In this sense, the copper(I)-catalyzed alkyne azide cycloaddition (CuAAC) is a convenient, versatile, and reliable two-step coupling procedure of two molecules that allows the generation of complexity in a quick, simple, and modular fashion.<sup>29–31</sup> Moreover, the triazole moiety is a well-known bioisoster of the peptidic bond which enhances its biological interest.<sup>32</sup> By way of a chemoselective  $S_N2'$  displacement of the primary chloride by azide ion in quantitative yield, the subsequent CuAAC was achieved under microwave conditions and with no need for azide purification.

The results gathered in Table 3 clearly highlight the utility of these THP units as building blocks for the assembly of large molecules by quickly “clicking” them with small building blocks 6. Thus, the use of homopropargylic alcohol (Table 3, entry a) and phenylacetylene (Table 3, entry e) gave good yields as well as the use of carbohydrate derivatives of glucosamine and furanose (Table 3, entries b and c). On the contrary, the use of glacial derivatives gave only moderate yields (Table 3, entry d). The ability of carbohydrate moieties to form hydrogen bonds and to provoke conformational changes in molecules makes this combination very attractive from a pharmacological point of view. Moreover, the relative configuration of the four stereocenters in the final THP as well as its chairlike conformation with the attached triazolyl moiety were confirmed by X-ray diffraction analysis of 7e (Table 3, entry e) (Figure 2).<sup>33</sup>

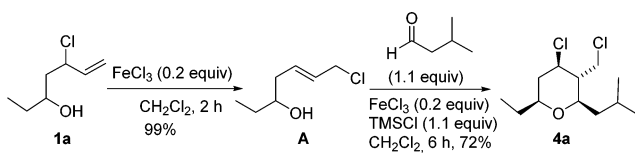
In order to gain more insight into the reaction mechanism involved in the formation of THP 4a, alcohol 1a was treated with substoichiometric amounts of FeCl<sub>3</sub> (0.2 equiv, Scheme 1). This reaction leads to the chloro intermediate A, very likely via an  $S_N2'$ -type reaction. When this intermediate was reacted with isovaleraldehyde under stoichiometric amounts of FeCl<sub>3</sub>, THP 4a was obtained as the final product. Consequently, the relative *syn/anti* stereochemistry at the chlorine atom in the

Table 3. CuAAC Reaction of Activated THPs

1) NaN <sub>3</sub> (10 equiv) DMF (0.1 M), 75 °C, 24 h 2) alkyne <b>6a-e</b> (1 equiv) CuSO <sub>4</sub> ·5H <sub>2</sub> O (0.05 equiv) L-(+)-NaAsc (0.2 equiv) t-BuOH/H <sub>2</sub> O (1:1) MW 200 W, 80 °C, 1.5 h				
entry	R <sup>1</sup>	R <sup>2</sup>	<b>6</b>	yield <b>7</b> (%) <sup>a</sup>
a	Et	<i>i</i> -Bu		<b>7a</b> 75
b	Et	<i>i</i> -Bu		<b>7b</b> 68
c	Et	<i>i</i> -Bu		<b>7c</b> 68
d	<i>n</i> -decyl	<i>i</i> -Bu		<b>7d</b> 40
e	<i>n</i> -decyl	Ph		<b>7e</b> 80

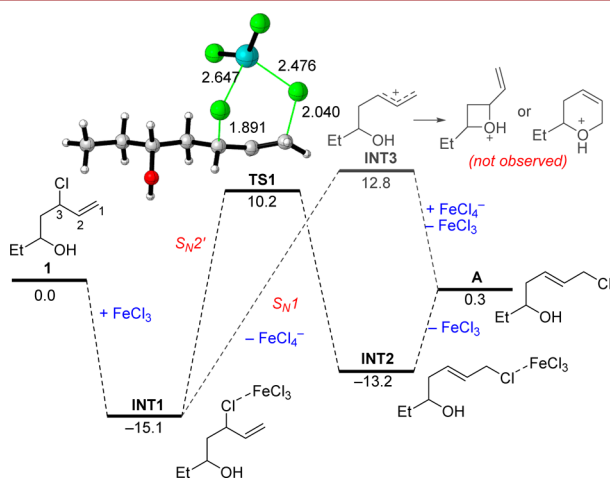
<sup>a</sup>Yield of isolated product.

## Scheme 1. Mechanistic Experiments



starting material is irrelevant for the outcome of the subsequent Prins-cyclization reaction.

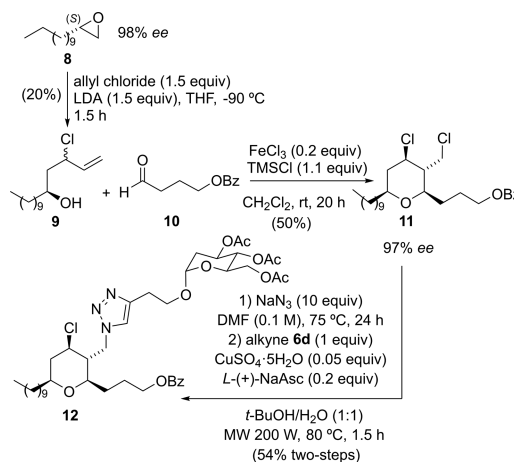
Density functional theory calculations at the dispersion-corrected PCM(CH<sub>2</sub>Cl<sub>2</sub>)-B3LYP-D3/def2-SVP level support the proposed S<sub>N</sub>2' mechanism for the initial iron-mediated transformation. As depicted in Figure 3, alcohol **1** is



**Figure 3.** Computed reaction profile (PCM(CH<sub>2</sub>Cl<sub>2</sub>)-B3LYP-D3/def2-SVP level) for the reaction between alcohol **1** and FeCl<sub>3</sub>. Relative energies (ZPVE included) and bond distances are given in kcal/mol and angstroms, respectively.

transformed, in the presence of FeCl<sub>3</sub>, into INT1 in an exothermic transformation; a strong interaction between the chloride atom of **1** and the iron(III) center (the associated computed Wiberg bond index for this Fe–Cl bond is 0.35) evolves into INT2 in a slightly endothermic process ( $\Delta E_R = +1.9$  kcal/mol) via transition state TS1 with an activation barrier of +25.3 kcal/mol. This saddle point is associated with the concomitant C3–Cl bond rupture/Cl–C1 bond formation mediated by transition-metal fragment in an S<sub>N</sub>2'-type reaction. INT2 is finally transformed into the observed intermediate **A** via the release of FeCl<sub>3</sub> which acts, therefore, as a catalyst for the process. Alternatively, it can be suggested that INT1 can be transformed into the allylic cation INT3 via a S<sub>N</sub>1 reaction. However, the computed high endothermicity associated with the FeCl<sub>4</sub><sup>−</sup> release ( $\Delta E_R = +27.9$  kcal/mol) together with the experimentally observed lack of formation of oxetane or dihydropyran derivatives makes this alternative pathway highly unlikely. The subsequent exothermic Prins cyclization from the highly reactive intermediate **A** drives the complete transformation forward and leads to the observed THP **4a**.<sup>8</sup>

The transformation, therefore, involves a first step consisting of an S<sub>N</sub>2' reaction followed by a Prins cyclization in which no competitive [3,3]-sigmatropic rearrangement is detected. Hence, a stereoselective process should take place without any further racemization. To check this hypothesis, an enantioselective synthesis of conjugated THP **12** was carried out (Scheme 2). Starting from the commercially available

Scheme 2. Synthesis of Enantioenriched Triazole **12**

racemic 1-epoxydodecane, a kinetic resolution was effected using Jacobsen's catalyst to obtain the epoxide **8**.<sup>34,35</sup> The opening of this epoxide using the conditions described by Miginiac and co-workers<sup>36</sup> led us to enantioenriched alcohol **9**, with a completely defined stereocenter at the  $\alpha$ -position of the hydroxyl group. Since this stereocenter will be critical to the successful generation of the three new stereocenters, enantiomeric excess in the cyclization process was analyzed using 4-oxobutyl benzoate as the aldehyde **10**. As expected, the overall outcome of the reaction was not affected by the possible oxonium-Cope rearrangement, and consequently, no loss of the stereochemical integrity was observed in the Prins cyclization process leading to THP **11**. CuAAC reaction was then fruitfully performed with the  $\alpha$ -glucal derivative **6d** to afford the enantiomerically pure triazole **12** with an overall yield of 54%.

In conclusion, we have developed a new method to obtain 2,3,4,6-tetrasubstituted tetrahydro-2H-pyrans with the creation

of three new stereocenters in one reaction step and in a stereoselective manner. These activated THPs are generated through a tandem  $S_N2'$ –Prins cyclization catalyzed by iron(III) salts. DFT calculations support the in situ  $S_N2'$  reaction as a preliminary step of the Prins cyclization. The chlorine unit is easily derivatizable chemoselectively, via  $S_N2$  and click chemistry, which generates multifunctionalized complex molecules of interest from a biological point of view. We expect this method will be useful to the synthetic community and will change the approach to the synthesis of highly functionalized 2,3,4,6-THPs.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b02270](https://doi.org/10.1021/acs.orglett.7b02270).

Complete experimental procedures, characterization data,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds, crystallographic data for **7e**, and computational details (PDF)

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### Notes

The authors declare no competing financial interest.

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