

# Synthesis of novel 2,6-disubstituted-3,4-dimethylidene tetrahydropyrans via Prins-type cyclization†

Yong Seo Cho,\* Kaliyan Karupaiyan, Hyun Jung Kang, Ae Nim Pae,\* Joo Hwan Cha, Hun Yeong Koh and Moon Ho Chang

Biochemicals Research Center, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea

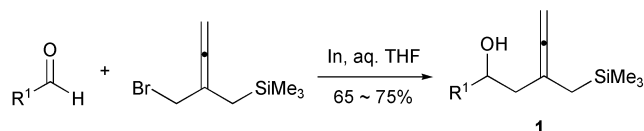
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Synthesis of novel substituted tetrahydropyrans with adjacent *exo*-methylene groups at the C3 and C4 positions via Prins-type cyclization has been described.

Tetrahydropyrans are structural features of a variety of biologically active natural products such as polyether antibiotics, marine toxins, and pheromones.<sup>1</sup> Prins cyclization is a powerful method of preparing tetrahydropyran rings. A number of groups have been investigating Prins cyclization reactions and applying these reactions to natural product syntheses.<sup>2</sup> In most cases, these cyclic compounds are either 2,6-disubstituted dihydropyran or 2,4,6-trisubstituted tetrahydropyran derivatives.

Herein, we report a novel synthesis of 2,6-disubstituted-3,4-dimethylidene tetrahydropyran derivatives via Prins-type cyclization. The required homoallenyl alcohol **1** was prepared in good yield by the reported procedure modifying the solvent to 25% aqueous THF instead of DMF for convenience, as shown in Scheme 1.<sup>3</sup>



Scheme 1 Preparation of homoallenyl alcohol.

An optimized reaction system of the Prins-type cyclization of homoallenyl alcohol was observed using TMSOTf as a Lewis acid in diethyl ether. The reaction of homoallenyl alcohol **1** with aldehyde **2** (2.0 equiv.) in the presence of TMSOTf (1.5 equiv.) at  $-78\text{ }^{\circ}\text{C}$  in diethyl ether proceeded smoothly to furnish 2,6-disubstituted tetrahydropyrans **3** with two adjacent *exo*-methylene groups at C3 and C4 positions in excellent yields. The results of the Prins-type cyclization reactions of homoallenyl alcohols are provided in Table 1.

NOE experiments of a cyclic product **3** showed that the R<sup>1</sup> and R<sup>2</sup> groups are in position with a *cis* relationship (Fig. 1). The R<sup>1</sup> and R<sup>2</sup> groups must have been equatorially disposed via a chair like transition state as shown in Fig. 2.

It was observed that most cases of the reaction of homoallenyl alcohols (entries 1–3) with R<sup>1</sup> = phenyl had longer reaction times (5–7 h) and the yield was little decreased compared with other homoallenyl alcohols where R<sup>1</sup> = benzyl or ethyl. In the case of R<sup>1</sup> = benzyl or ethyl, the reactions were completed in 2–5 h to afford products in very high yield. When we used a compound containing two aliphatic substituents (entry 8), a lower yield was obtained which could be attributed to the volatility of compound **3h** (entry 8).

To survey the scope of this method, we investigated a Prins-type reaction of various long chain aldehydes bearing an unsaturated carbon–carbon bond with a phenyl  $\beta$ -hydroxy allenylsilane under the same reaction conditions. The results are summarized in Table 2. The various substituted aldehydes

Table 1 Synthesis of 2,6-disubstituted-3,4-dimethylidene tetrahydropyrans<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	Time/h	Yield (%) <sup>b</sup>
1	Ph	Ph	5.0	<b>3a</b> (80)
2	Ph	Bn	7.5	<b>3b</b> (61)
3	Ph	Et	7.0	<b>3c</b> (98)
4	Bn	Bn	5.0	<b>3d</b> (91)
5	Bn	Et	4.0	<b>3e</b> (98)
6	Bn	Propyl	4.0	<b>3f</b> (92)
7	Bn	3-Furyl	4.0	<b>3g</b> (95)
8	Et	Et	4.5	<b>3h</b> (75)
9	Ph		4.0	<b>3i</b> (100)
10	Bn		4.5	<b>3j</b> (94)
11	Et	Bn	3.5	<b>3k</b> (100)
12	Bn		2.0	<b>3l</b> (86)
13	Ph		5.0	<b>3m</b> (86)

<sup>a</sup> All reactions were conducted in dry Et<sub>2</sub>O at  $-78\text{ }^{\circ}\text{C}$  in the presence of 1.5 eq. TMSOTf. <sup>b</sup> Isolated yield.

having alkynyl groups (entries 1–3) or alkenyl groups (entries 4–6) could afford the desired products **4** in good yields. However, these yields were somewhat lower compared to those of the simple aldehydes in Table 1.

These resulting dimethylidene tetrahydropyran derivatives could be conveniently used as good partners for dieneophiles in the Diels–Alder reaction to prepare various polycyclic pyrans.

In conclusion, we have developed a novel methodology for the synthesis of *cis*-2,6-disubstituted-3,4-dimethylidene tetra-

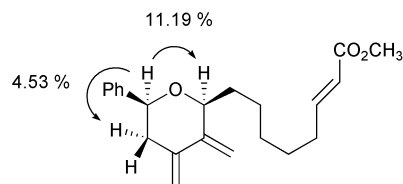


Fig. 1 NOE of compound **4f**.

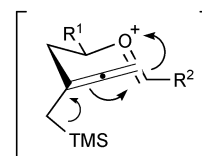
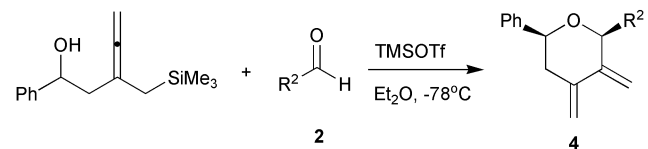


Fig. 2

† Electronic Supplementary Information (ESI) available: Experimental section. See <http://www.rsc.org/suppdata/cc/b3/b307320c/>

**Table 2** Synthesis of 2,6-disubstituted-3,4-dimethylidene tetrahydropyrans<sup>a</sup>



Entry	R <sup>2</sup>	Time/h	Yield (%) <sup>b</sup>
1		3.0	<b>4a</b> (86)
2		3.0	<b>4b</b> (81)
3		3.5	<b>4c</b> (70)
4		3.0	<b>4d</b> (71)
5		4.0	<b>4e</b> (78)
6		4.0	<b>4f</b> (60)

<sup>a</sup> All reactions were conducted in dry Et<sub>2</sub>O at -78 °C in the presence of 1.5 eq. TMSOTf. <sup>b</sup> Isolated yield.

hydropyan derivatives *via* a Prins-type cyclization reaction using TMSOTf as a Lewis acid in diethyl ether. Further studies

to apply these 3,4-dimethylidene tetrahydropyrans to synthesise various polycyclic pyrans are in progress.

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