ACES Asian Chemical Editorial Society

doi.org/10.1002/ajoc.202400096

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

www.asianjoc.org

Stereoselective Synthesis of Polysubstituted Tetrahydropyrans by Brønsted Acid-Mediated Hydroxyalkoxylation of Silylated Alkenols

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A convenient route for the preparation of tetrahydropyran (THP) derivatives with a quaternary and tertiary vicinal stereocenters is reported. The atom economy acid-catalyzed cyclization of allylsilyl alcohols provided polysubstituted tetrahydropyrans in good yields and excellent diastereoselectivities (> 95:5). In comparison with the traditional oxymercuration procedure, this approach resulted to be more efficient in both yield and stereocontrol.

Tetrahydropyran derivatives (THPs) are privileged scaffolds that represent one of the most common motifs in oxygen-containing natural products. A great number of drugs containing this moiety have shown interesting biological activities in a plethora of applications. However, most of these natural products cannot be isolated in high amounts from nature and their synthesis in the lab is often faced as a desirable alternative. Total synthesis approaches are usually attempted once the corresponding methodology to prepare the key substrates has been developed. In this sense, the abundant presence of certain substitution patterns in tetrahydropyran rings found in natural products has permitted the development of a wide variety of synthetic methodologies towards these frameworks. However, other substitution patterns of scarcer occurrence in natural products still need further methodologic research. In this context, while there are a great variety of methodologies for the synthesis of 2,6-disubstituted tetrahydropyrans, limited number of approaches have been described for the stereocontrolled synthesis of polysubstituted tetrahydropyrans with a quaternary stereocenter at C2. Important examples of natural products containing this type of polysubstituted tetrahydropyranyl moiety include plant-derived bioactive terpenes such as the known fragrance linaloyl oxide,[1] the diterpernoic diol (**A**) isolated from an African plant of the genus *Anisopappus pinnatifidus*[2] or (+)-cinenic acid, which is a degradation product of certain saponins of *Ginseng* root.[3] Other structures of this type found in marine living organisms are (+)-tanikolide,[4] which was isolated from the marine algae cyanobacterium *Lyngbya majuscule* and exhibits antifungal activity against *C. albicans*, *(−)*-malyngolide,[5] which shows antimicrobial activity against *Streptococcus pyogenes, smegmatis*, *Staphylococcus* and *Mycobacterium Pseudomonas* or 2,2,5,6-tetrasubstituted tetrahydropyran (**B**), isolated from the extract of marine sponge of the genus *Haliclon*a sp[6] (Figure 1). All these natural products bear a quaternary C2 carbon, whose construction often implies a synthetic challenge.

There is a great variety of protocols aiming the stereoselective synthesis of polysubstituted tetrahydropyrans. Very reliable approaches, within the one-component methods, are cyclizations leading to the formation of the O–C2 bond, such as 6-*exo-tet* cyclizations of epoxyalcohols or 6-*exo-trig* cyclizations of unsaturated alcohols.[7,8] Regarding the 6-*exo-trig* cyclizations of alkenols, either the stoichiometric metal-mediated alkene addition (with the use of mercury or seleno salts)[9] or the catalytic version (with Pd or other transition metal complexes)[10] are well-established strategies. However, the metal-free acid-catalyzed cyclization of alkenols,[11,12] despite its simplicity and high atom economy, hasn't been widely employed due to several drawbacks, such as frequent side reactions, lack of general processes and absence of methodologies for the

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202400096

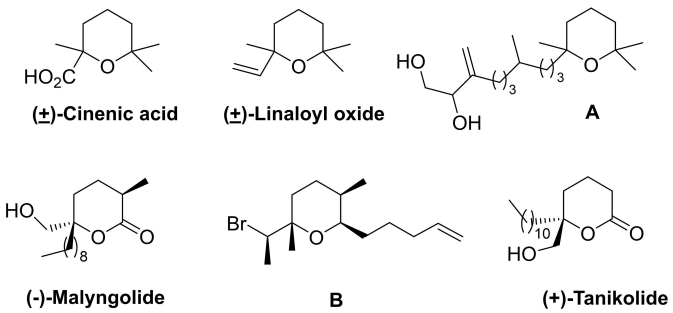
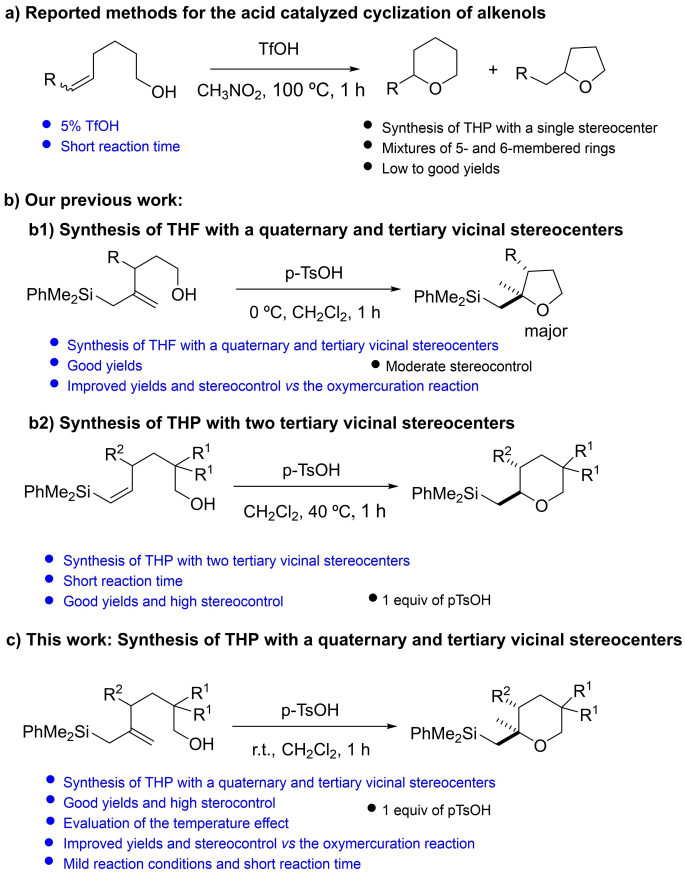


Figure 1. Selected examples of bioactive natural products containing 2,2'-substituted tetrahydropyranyl moieties

stereoselective construction of oxacycles with various stereogenic centers.

We[13] and others[14] have reported a general and high yielding acid-catalyzed cyclization of alkenols activated by the presence of a neighboring silyl group, in which the efficient synthesis of polysubstituted tetrahydrofurans has been achieved. Lately, we have also described the use of vinylsilyl alcohols for the selective preparation of tetrahydropyrans with two contiguous tertiary stereocenters (at C2 and C3) (Scheme 1).[15]

Following our interest for the synthesis of different types of heterocycles using the chemistry of organosilanes,[16] in this work we want to go a step forward in order to increase the synthetic toolbox for the preparation of THP derivatives. Thus, we now present an expansion of the synthetic opportunities of the acid-catalyzed cyclization of silylated alkenols towards the stereoselective preparation of polysubstituted tetrahydropyrans containing a quaternary and a vicinal tertiary stereogenic centers. For this purpose, we will use allylsilyl alcohols as starting materials, which acid-catalyzed cyclization under mild conditions would permit the very stereocontrolled creation of a quaternary stereogenic center at C2 (Scheme 1).



Scheme 1. Previous and current work

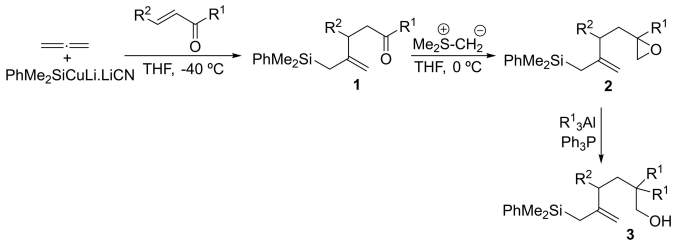
Results and Discussion

The starting silylated alkenols needed for this study were prepared using our well-stablished methodology of silylcupration of allenes followed by capture of the intermediate vinylcuprate with α,β-unsaturated ketones.[17] Two further conventional steps, such as sulfur ylide epoxidation and alkylation of the corresponding epoxide with trialkylaluminum reagents, provided the desired primary alcohols **3** (Scheme 2).[18]

Once we got a convenient methodology for the synthesis of the starting materials, we carried out the optimization of the acid-mediated cyclization reaction under different acid mediators (either Brønsted or Lewis acids), choosing a model substrate (**3a**) which provided a tetrahydropyranyl derivative with a single stereocenter. As shown in Table 1, the reaction promoted by TMSOTf gave rise to an unresolved complex mixture (Table 1, entry 1). Interestingly, a solution of the allylsilyl alcohol in $CHCl_3$ favored the formation of the desired cyclic tetrahydropyran **4a**, although in modest yield and requiring a long reaction time (Table 1, entry 2). On the other hand, in the presence of either $BF_3{\cdot}OEt_2$ or triflic acid alcohol **3a** underwent both acid-catalyzed cyclization and desilylation, generating tetrahydropyran **6a** (Table 1, entry 3 and 4). Next attempt, with the use of the Brønsted acid *p*-TsOH, provided the best result for the cyclization (either at room temperature or 40 °C), furnishing the desired silylated tetrahydropyran derivative **4a** in good yield (Table 1, entry 5 and 6). From both, we chose entry 6 for further experiments due to the shorter reaction time (only 30 min).

We next studied the stereoselectivity in the formation of tetrahydropyrans with contiguous stereogenic centers at C2 and C3, under the optimized conditions found for alcohol **3a** (Table 1, entry 6). The results are shown in table 2.

As shown, the application to alcohols **3d,g,h,i** of the optimal cyclization conditions obtained for tetrahydropyran **4a** (40 °C, 30 min) provided good yields but low stereocontrol (Table 2, entries 1, 3, 5 and 7) in the creation of the new quaternary stereocenter at C2. It has to be noted that the best stereoselectivity, under these conditions, was obtained when a bulky group is present at C3 (Table 2, entry 3). We then reasoned that a decrease in the reaction temperature (provided that allylsilyl alcohols should be reactive enough under these conditions) could lead to improved levels of stereoselectivity. Fortunately, the use of lower temperatures (room temperature) for the cyclization afforded the desired tetrahydropyrans in good yields



Scheme 2. Preparation of the starting allylsilyl alcohols **3**

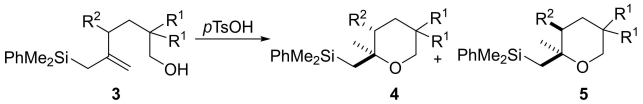
Table 1. Screening of the cyclization conditions.[a]

3a 4a 6a

Entry	Acid	Temperature (°C)	Time	Product (yield)[d]
1	TMS·OTf	r.t.[b]	24 h	Complex mixture
2	$CHCl_3$	r.t.[b]	48 h	**4a** (39%)
3	$BF_3 \cdot OEt_2$	-78[c]	2 h	**6a** (58%)
4	TfOH	r.t.[b]	1 h	**6a** (50%)
5	*p*-TsOH	r.t.[b]	1 h	**4a** (64%)
6	*p*-TsOH	40	30 min	**4a** (66%)

[a] Reaction conditions: **3a** (1 mmol), acid (1 mmol). [b] An average room temperature of 20 °C has been estimated [c] Similar result was obtained when the reaction was done at r.t., although other unidentified subproducts were observed in the reaction mixture. [c] Isolated yield.

Table 2. Influence of the temperature in the stereoselectivity of the cyclization.[a]



3 4 5

Entry	R^1	R^2	Temperature (°C)	Time	*dr* (**4**:**5**)[c]	Product (yield %)[d]
1	Me	Bu	40	30 min	60:40	**4d**+**5d** (68)
2	Me	Bu	r.t.[b]	1 h	>95:5	**4d** (65)
3	Me	^{i}Pr	40	30 min	80:20	**4g**+**5g** (70)
4	Me	^{i}Pr	r.t.[b]	1 h	>95:5	**4g** (65)
5	Me	Ph	40	30 min	50:50	**4h**+**5h** (71)
6	Me	Ph	r.t.[b]	1 h	>95:5	**4h** (70)
7	Et	Me	40	30 min	65:35	**4i**+**5i** (69)
8	Et	Me	r.t.[b]	1 h	>95:5	**4i** (72)

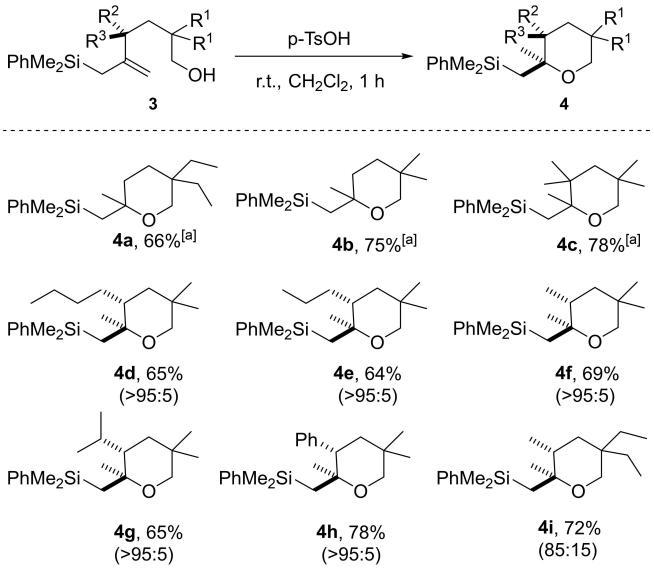
[a] Reaction conditions: **3** (1 mmol), pTsOH (1 mmol) in CH_2Cl_2. [b] An average room temperature of 20 °C has been estimated. [c] Determined by ^{1}H-NMR. [d] Isolated yield.

and with excellent diastereoselectivities (Table 2, entries 2, 4, 6 and 8).

With the optimal conditions in hand for both yield and selectivity, we focused our attention on the study of a variety of substituted allylsilyl alcohols. As shown in Scheme 3, a set of tetrahydropyranyl derivatives with either alkyl or aryl substituents at C3 were obtained in good to very good yields and with excellent diastereoselectivities (>95:5) for most cases.

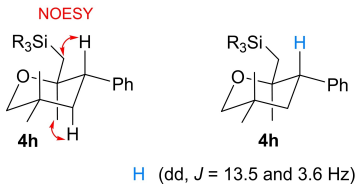
The relative stereochemistry of tetrahydropyrans **4** was assigned on the basis of NOESY experiments. Thus, for compounds **4d**–**i** a NOESY correlation was found between R_3Si-CH_2 and the hydrogen at C3, and between Hax at C4 and Me at C2. The axial conformation of hydrogen at C3 was confirmed by the corresponding coupling constants (Scheme 4).

Regarding the stereochemical outcome of the process, the cyclization of allylsilyl alcohols, mediated by *p*-TsOH at room temperature, provides a single diastereoisomer, which corresponds to the one that has an *anti* relationship between the R^2 and the silyl group. A plausible mechanism for this cyclization involves the initial addition of a proton to the allylsilane moiety



[a] Reaction at 40 °C during 30 minutes

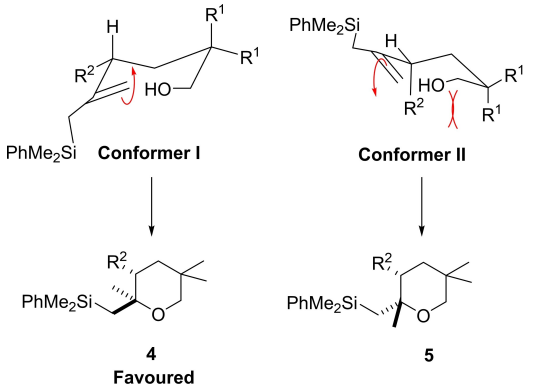
Scheme 3. Scope of the acid-promoted cyclization



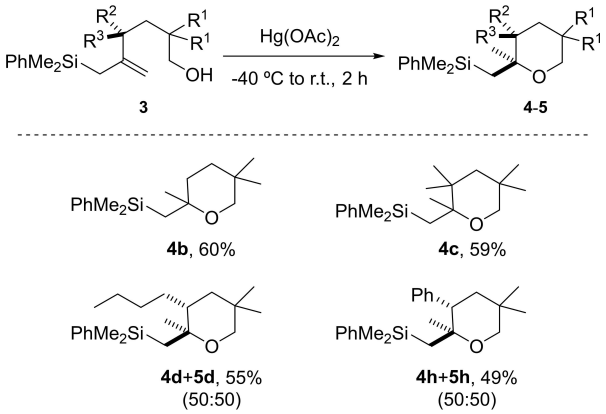
Scheme 4. Stereochemistry assignment

to give a β to silicon stabilized carbocation, which in turn will be intramolecularly trapped by the hydroxyl group. In this process, we could draw two possible reactive chair-like conformations (both with a perpendicular arrangement between the silyl group and the double bond) such as **I** and **II**. From both, the unfavourable 1,3-diaxial interaction between R^2 and R^1 shown in conformer **II** would account for the preferred conformer **I**, which is in accordance with our results (Scheme 5).

To evaluate the benefits of this methodology towards the classical mercury-catalyzed cyclization, we carried out the cyclization of some of our substrates in presence of $Hg(OAc)_2$. As shown in Scheme 6, significant longer reaction time and erosion of both yields and diastereoselectivities are observed using this methodology, which makes our *p*-TsOH promoted methodology more efficient and sustainable than the traditional reported alternative.



Scheme 5. Plausible chair-like reactive conformations for alcohols **3**



Scheme 6. Mercury-catalyzed alternative methodology for the synthesis of **4**–**5** derivatives

Conclusions

In conclusion, we have described an efficient and general methodology for the stereoselective preparation of tetrahydropyran derivatives with vicinal quaternary and tertiary centers at C2 and C3, through an acid-mediated cyclization of allylsilyl alcohols. The reaction is compatible with alkyl and aryl groups at 3-position of the THP ring and this protocol forms selectively the *anti* product between silyl group and C3 substituent. The influence of the temperature in the diastereoselectivity of the cyclization has been studied. In comparison with the traditional methodology for the synthesis of these analogues involving oxymercuration procedures, our methodology shows to be more efficient in both yield and stereoselectivity. The presence of a silicon group attached to the final products would provide new opportunities for further functionalization.

Experimental section

Synthesis of tetrahydropyranyl derivatives 4 by acid-catalyzed cyclization of allylsilyl alcohols 3. To a solution of *p*-TsOH (1 mmol) in dry CH_2Cl_2 (10 mL) is added a solution of the alcohol (1 mmol) in CH_2Cl_2. The mixture is stirred under N_2 in the shown conditions and quenched with saturated solution of $NaHCO_3$ (5 mL). The organic layer was washed 3 times with $NaHCO_3$, dried over $MgSO_4$, evaporated in vacuo and purified by flash chromatography (EtOAc/hexane).

Supporting Information

The characterization of products can be found in the Supporting Information.

Acknowledgements

We gratefully acknowledge the Ministry of Science and Innovation, Spain for financial support by grant PID2021-125909OB-I00 and the Ministry of Science and Innovation, Spain and the European Union NextGenerationEU/PRTR for finantial support by grant TED2021-131705B-C21

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: polysubstituted tetrahydropyrans · acid promoted cyclization · stereoselectivy in the creation of quaternary center

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[18] The unstability under chromatography conditions shown by **3** made necessary to proceed to the next step without previous purification.

Manuscript received: March 5, 2024
Revised manuscript received: March 26, 2024
Accepted manuscript online: April 3, 2024
Version of record online: May 3, 2024