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Towards an efficient methodology for the synthesis of functionalized dihydropyrans by silyl-Prins cyclization: access to truncated natural products†

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We herein present a selective methodology for the synthesis of disubstituted dihydropyrans by silyl-Prins cyclization of *Z*-vinylsilyl alcohols mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf). The reaction features broad substrate scope, short reaction times and ease of process scale-up. Moreover, to showcase the applicability of the proposed method, we also report a facile and linear synthesis of analogues of rhopaloic acid and natural doremox fragrance.

Introduction

Marine metabolites are well recognized to be a prolific reservoir for drug development. Within them, the relevance of heterocyclic marine structures is of particular note due to the plethora of pharmacological properties associated with them (such as anticancer, anti-inflammatory, antibacterial or antiviral). Special interest has been focused on marine compounds with 2H or 4*H*-pyranyl moieties in their structure, due to their relatively large abundance and promising biological properties.[1] For instance, rhopaloic acid C,[2] isolated from the marine sponge *Rhopaloeides* sp., exhibits potent inhibitory action on the gastrulation of the starfish (*Asterina pectinifera*) embryo and induces apoptosis and autophagy in human bladder cancer (Fig. 1), whereas aspergillide, which is a 14-membered macrolide isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313, shows cytotoxic activity against mouse lymphocytic leukemia cells.[3]

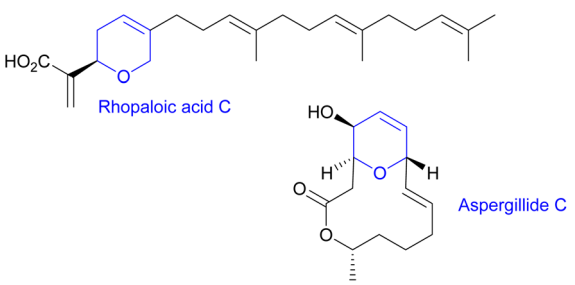
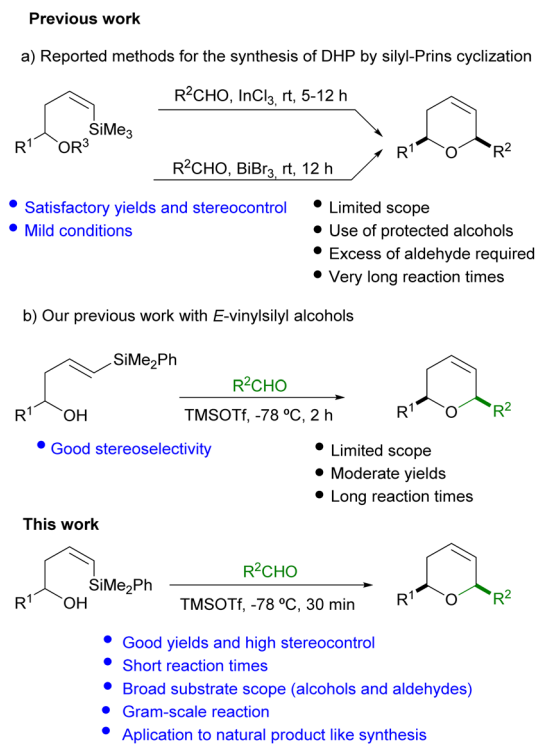


Fig. 1 Marine drugs bearing a dihydropyran unit.

As is known, the search for bioactive compounds has been a source of inspiration for the scientific community for decades. Two main strategies have attracted the interest of synthetic chemist: the first one is natural product synthesis which aims at the preparation of an identical structure to the naturally occurring product and usually implies a large number of steps, and low overall yield, to reach the desired target. A more recently developed approach is the diversity-oriented synthesis,



Scheme 1 Towards the synthesis of dihydropyrans by silyl-Prins cyclization.

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which focuses on the preparation of natural product analogues in which structural variation is aimed at as a means to achieve higher diversity in the final target. Moreover, natural product-like compounds have shown great potential for pharmaceutical drug discovery programs.

Over the years, a great number of synthetic methodologies have been described for the synthesis of dihydropyrans. Among others, Prins cyclization has emerged as a powerful tool for the preparation of saturated six membered oxacycles.[4,5] A convenient modification of this methodology, which employs electron-rich alkenyl silanes as nucleophiles, has allowed the synthesis of oxacycles bearing a double bond in their structure.[6] An important advantage of these Prins-type cyclizations is that they proceed with high reaction rates and selectivity.

Typically, allylsilyl alcohols have shown great potential for the synthesis of tetrahydropyrans bearing an exocyclic double bond (methylene tetrahydropyrans). On the other hand, the still underdeveloped silyl-Prins cyclization which employs vinylsilyl alcohols permits the preparation of 6-membered oxacycles bearing an endocyclic double bond (dihydropyrans).[7] The pioneering work of Dobbs in this area has opened the access to *cis*-2,6-disusbstituted dihydropyrans in good yields, by reaction of *Z*-(trimethyl)silyl homoallylic alcohols with aliphatic aldehydes under the mediation of $InCl_3$. However, only a limited number of aromatic aldehydes (with *p*-NO_2 or *p*-CF_3 electron withdrawing groups) provide the desired oxacycle (Scheme 1a).[8,9]

In another approach, Hinkle[10] has reported the reaction of TES protected *Z*-(trimethyl)silyl alcohols with aldehydes, in the presence of $BiBr_3$. The corresponding 2,6-*cis*-dihydropyrans are produced in good yield and selectivity when alkylic aldehydes or *p*-$CF_3C_6H_5CHO$ are used. However, lower yields and selectivities are observed for other aromatic aldehydes. Moreover, the need of a significant excess of aldehyde (2 equiv.) and the additional alcohol protection step also imply a relevant drawback (Scheme 1a).

Despite the mild conditions employed in the precedent publications, a common drawback is the rather long reaction time (up to 12 hours) required for completion. Moreover, the discrete number of examples reported, together with the scarce variety of substituents (R^1 and R^2) on the alcohol and aldehyde compatible with this cyclization, prompted us to explore and expand the scope of this methodology (Scheme 1).

Results and discussion

Following our interest in the synthesis of polisubstituted heterocycles using the silyl-Prins cyclization,[11,12] we now present a general, selective and short time protocol for the synthesis of a variety of *cis*-2,6-dihydropyrans, by siyl-Prins cyclization (mediated by trimethylsilyl trifluoromethanesulfonate) (TMSOTf) of *Z*-vinylsilyl alcohols which bear the phenyldimethylsilyl group.

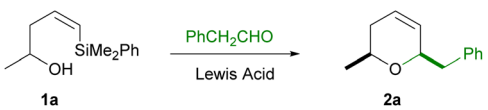
To find the optimal conditions for this cyclization, we choose the reaction of racemic *Z*-vinylsilyl alcohol **1a** with phenylacetaldehyde. The results are shown in Table 1.

As shown in Table 1, neither trimethylsilyl halides (TMSCl, TMSBr or TMSI) nor $BiCl_3$ were efficient Lewis acids for this cyclization, providing either low yields, low stereoselectivities or no reaction (entries 1–5). Pleasingly, both $BF_3{\cdot}OEt_2$ at 0 °C (entry 6) and TMSOTf at −78 °C (entries 9 and 10) showed to be efficient initiators for this process. From both acids, we choose TMSOTf for additional studies, due to the shorter reaction times and the slightly better yields (entry 9 *vs.* 6). Interestingly, the reaction was also effective and highly diastereoselective when 0.5 equiv. of the activator was used (entry 10). However, slightly lower yields of the dihydropyran were obtained, which prompted us to use stoichiometric amounts of the acid in further reactions.

Encouraged by these results, we decided to explore the generality of this reaction using different types of aldehydes and various R^1 substituents on the alcohol. The results are shown in Table 2.

As can be seen in the Table 2, the reaction of *Z*-phenyldimethylsilyl alkenols **1a–b** (being R^1 an alkylic substituent)

Table 1 Optimization of the silyl-Prins cyclization of *Z*-vinylsilyl alcohols bearing the phenyldimethylsilyl group

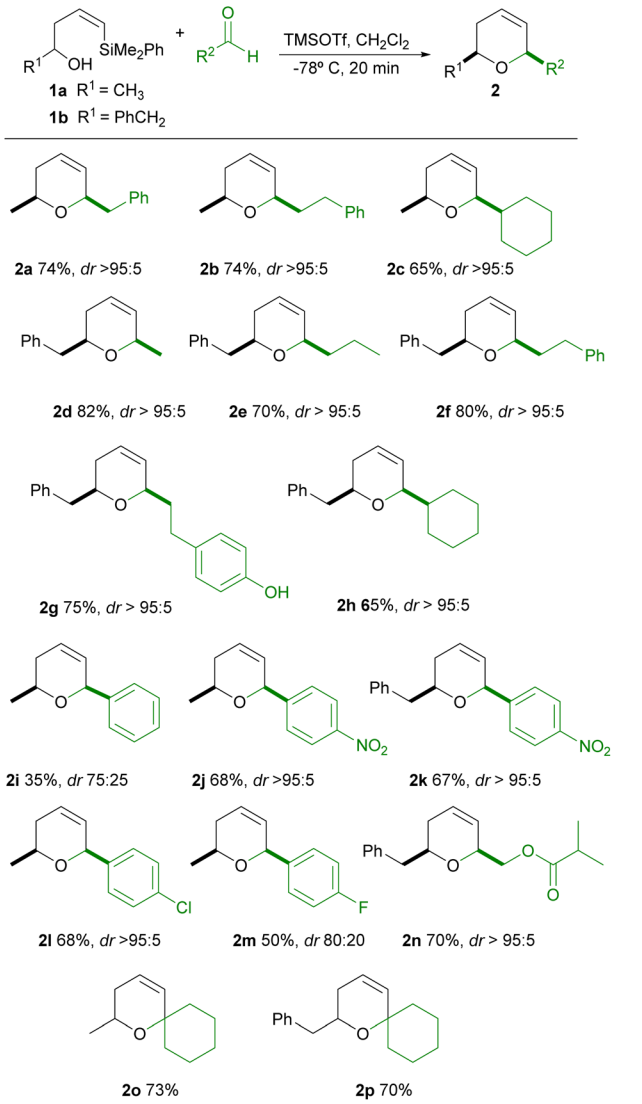


1a **2a**

Entry	Lewis acid (equiv.)	Reaction conditions[a]	dr[b]	Yield[c] (%)
1	TMSCl (1.2)/$BiCl_3$ (0.05)	0 °C, 40 min	>95 : 5	51
2	TMSCl (1.2)	0 °C, 60 min	—	n.r.[d]
3	$BiCl_3$ (0.5)	0 °C, 110 min	90 : 10	39
4	TMSBr (1.2)	−78 °C, 60 min	—	n.r.[d]
5	TMSI (1.0)	−78 °C, 100 min	70 : 30	53
6	$BF_3{\cdot}OEt_2$ (1.0)	0 °C, 60 min	>95 : 5	56
7	$BF_3{\cdot}OEt_2$ (1.0)	−78 °C, 60 min	—	n.r.[d]
8	$BF_3{\cdot}OEt_2$ (0.5)	−78 °C, 60 min	—	n.r.[d]
9	TMSOTf (1.0)	−78 °C, 20 min	>95 : 5	74
10	TMSOTf (0.5)	−78 °C, 25 min	>95 : 5	66

[a] Conditions: **1a** (0.36 mmol), phenylacetaldehyde (0.43 mmol), under N_2. [b] Diastereomeric ratio (dr) of 2,6-*cis*-tetrahydropyran : 2,6-*trans*-tetrahydropyran was determined by ^{1}H NMR analysis. [c] Isolated yields. [d] n.r. stands for no reaction.

Table 2 Scope of the silyl-Prins cyclization of *Z*-vinylsilyl alcohols bearing the phenyldimethylsilyl group[a,b,c]



[a] Conditions: **1** (1 equiv.), aldehyde (1.2 equiv.), TMSOTf (1 equiv.), −78 °C, 30 min, under N_2. [b] Isolated yields. [c] The ratio of stereoisomers was determined by ^{1}H NMR analysis.

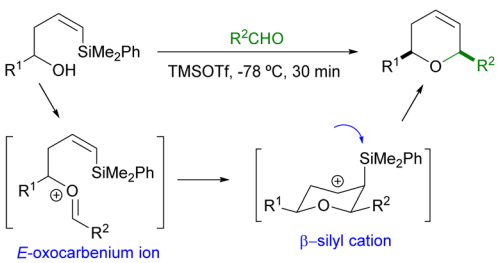
with alkylic aldehydes provide good yields of the corresponding dihydropyrans (**2a–h**). Moreover, excellent diastereoselectivity towards the *cis*-2,6-disubstituted dihydropyran is observed, since a single stereoisomer is always obtained. Interestingly, the appropriate election of R^1 and R^2 substituents on the starting alcohol and aldehyde permits the selective formation of regioisomers, such as **2a** and **2d**, both in excellent stereoselectivity and yield. We then attempted the synthesis of **2b** in larger scale (starting from 1.08 g of **1a**) and to our delight the desired dihydropyran was obtained in reproducible yield and selectivity (690 mg, 74%). Aiming to expand the possibilities of this methodology, we then decided to use aromatic aldehydes in the cyclization. Satisfactorily, we could observe the formation of the corresponding dihydropyran (**2j–l**), in good yield and excellent stereoselectivity, when deficient aromatic aldehydes are used. However, yields and stereoselectivities decrease for other aromatic aldehydes (**2i**, **2m**).[13] In addition, the reaction seems to be compatible with functional groups, such as esters (**2n**), maintaining good yield and excellent diasteroselectivity, which opens a convenient tool for further synthetic elaborations. Worthy of note is the reaction of **1a–b** with ketones, which gives in good yield spiro-dihydropyran structures **2o–p**, despite the poor ability of ketones to condense with alcohols during the rate-limiting step of Prins cyclization.[14] However, other cyclic ketones (such as cyclopentanone and cycloheptanone) were unreactive under these cyclization conditions. It has to be noted, as we have recently reported,[15] that this cyclization is readily influenced by the geometry of the vinylsilane, since the corresponding silyl-Prins cyclization with *E*-vinylsilyl alcohols is limited to alkylic aldehydes, requires longer reaction times (1–2 hours), and proceeds in lower yields.

The high stereoselectivity observed for the formation of 2,6-*cis*-dihydropyrans can be explained by the initial formation of an *E*-oxocarbenium ion, which will readily undergo 6-*endo* cyclization through a chair like transition state in which the substituents attached to C2 and C6 will adopt the most stable equatorial conformation. The corresponding β-silyl carbocation thus obtained will then undergo elimination of the silyl group to provide the final dihydropyran (Scheme 2).

Having stablished a wide scope of tolerable aldehydes in this process, we next explored the starting alcohol scope. For this purpose, we choose an alcohol bearing an R^1 aromatic ring substituent, in order to study the influence of such substituent in the outcome of the reaction. It's known that the oxonia-Cope rearrangement is a secondary process which is usually observed in Prins cyclizations when the starting alkenyl alcohol bears a substituent (such as phenyl) which is able to stabilize the corresponding oxocarbenium ion.[16] We envisaged the possibility of suppressing this competing oxonia-Cope rearrangement process under our conditions, since the fast reaction rates of this process could help to minimize the chance of occurrence of this side reaction. The results are shown in Table 3.

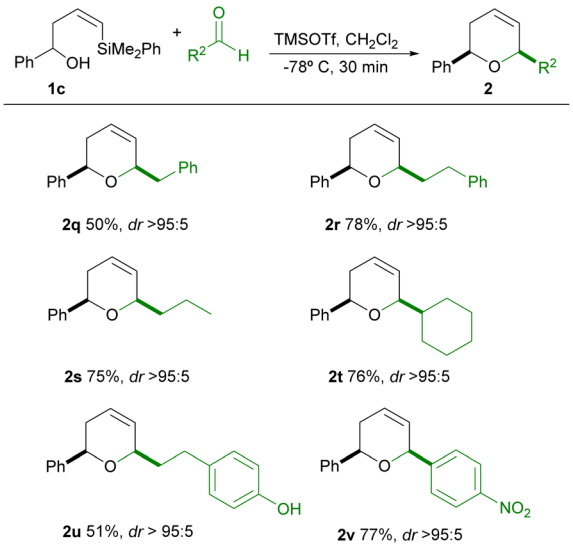
As can be seen in Table 3, the reaction of **1c** with either alkylic aldehydes or electron-deficient aromatic aldehydes in general proceeds in good yield and excellent stereoselectivity (**2q–2v**). In no case the symmetrical product of oxonia-Cope rearrangement could be observed in the reaction mixture.

We then decided to apply this efficient methodology to the synthesis of analogues of natural rhopaloic acid C.[2] For this

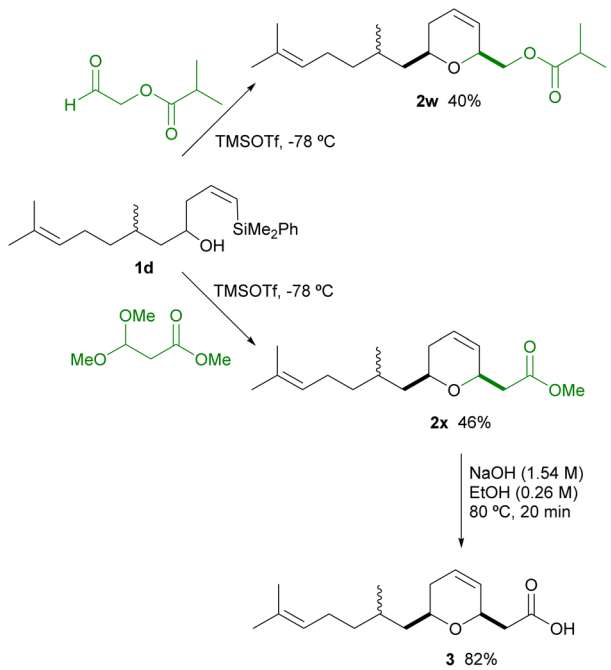


Scheme 2 Mechanistic proposal.

Table 3 Scope of the silyl-Prins cyclization of *Z*-vinylsilyl benzylic alcohol **1c** [a,b,c]

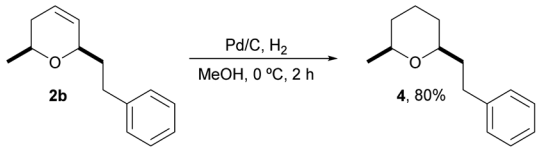


[a] Conditions: **1c** (1 equiv.), aldehyde (1.2 equiv.), TMSOTf (1 equiv.), −78 °C, 30 min, under N_2. [b] Isolated yields. [c] The ratio of 2,6-*cis* : 2,6-*trans*-diastereoisomers was determined by ^{1}H NMR analysis.



Scheme 3 Access to truncated natural rhopaloic acid.

purpose, we prepared vinylsilyl alcohol **1d** (from Citronellal), which was obtained as an inseparable mixture of diastereoisomers. Under the optimized conditions for this silyl-Prins cyclization, the reaction of **1d** with two different functionalyzed aldehydes, such as 2-(isobutyryloxy)acetaldehyde and methyl 3,3-dimethoxypropionate, were performed. As shown the



Scheme 4 Access to truncated natural doremox.

corresponding dihydropyrans **2w** and **2x**, bearing an ester functionality appended to C2, were obtained in moderate yields and excellent diastereoselectivity towards the 2,6-*cis*-dihydropyran. Both substrates bear a convenient functionalised group at C2, which could allow the preparation of more complex structures. For instance, further saponification of **2x**, under standard conditions, provided in high yield truncated rhopaloic acid **3** in high yield (Scheme 3).

Finally, we also prepared a tetrahydropyranyl analog **4** of natural doremox,[17] a rose oxide replacement fragrance, by standard hydrogenation of the corresponding dihydropyran **2b**, as shown in Scheme 4. Interestingly, **4** is also a regiosomeric analog of 2,2,5-trimethyl-5-phenyltetrahydropyran, which has been described as a synthetic odorant with a fragrance profile of fresh methyl pamplemousse odor and woody and camphoraceous notes.[18]

Conclusions

In conclusion, a general, effective and selective methodology for the synthesis of a variety of disubstituted dihydropyrans is described. The process is compatible with different substituents and functional groups both in the alcohol and the aldehyde. Moreover, excellent stereoselectivity towards the *cis*-2,6-disubstituted dihydropyrans are obtained in most cases. The applicability of this methodology has been shown by the synthesis of analogs of natural rhopaloic acid and natural doremox fragrance.

Author contributions

L. F. P. for project administration, investigation and methodology development, P. G.-A. for investigation and A. B. for conceptualization, supervision and writing and editing.

Conflicts of interest

There are no conflicts to declare.

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