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RESEARCH ARTICLE

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Cite this: *Org. Chem. Front.*, 2025, **12**, 6513

Expanding the silyl-Prins toolbox: selective access to C4-quaternary stereocenters in tetrahydropyrans using internal cyclopropylsilyl alcohols

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Received 4th July 2025,
Accepted 6th August 2025

DOI: 10.1039/d5qo00984g

rsc.li/frontiers-organic

Our ongoing research into silyl-Prins cyclizations has now provided a promising solution for the stereoselective synthesis of tetrahydropyrans bearing quaternary centers at C4. Building on the previous success with terminal cyclopropylsilyl alcohols, we now demonstrate that internal cyclopropylsilyl alcohols can also be effectively employed to construct highly substituted tetrahydropyrans. This new approach delivers products featuring both a quaternary center at C4 and a tertiary center at C6 with excellent stereocontrol. These findings not only broaden the scope of silyl-Prins cyclization but also establish a general and efficient strategy for accessing complex oxacyclic architectures with precise stereochemical outcomes.

Introduction

The development of new synthetic methodologies for producing scaffolds of industrial importance is highly valuable.

Many commercially available drugs trace their origins to the discovery of natural products with important medicinal properties. Consequently, organic chemists have long focused on developing rapid and efficient processes to construct these essential scaffolds.[1]

Another key area that has contributed to the development of numerous drugs is the generation of libraries of analogues based on bioactive natural products.[2,3] Some of these derivatives have demonstrated significantly enhanced properties and have ultimately received FDA approval as new treatments for human diseases. In this context, a key factor to consider when selecting the optimal synthetic route to a target compound is its potential to enable the preparation of a series of analogues by incorporating different reagents in one of the final steps of the sequence.

Among the vast array of biologically active natural products, saturated cyclic ethers have played a crucial role in medicinal chemistry. Many of these molecules feature polysubstituted tetrahydropyrans with one or more quaternary carbons. Notably, those with quaternary stereocenters at C4 are present in various natural and synthetic antibiotics of significant relevance, such as spliceostatin K,[4] a polyketide isolated from *Pseudomonas* sp. bacteria with cytotoxic activity against MDA-MB-231 and A-549 cell lines; kidamycin,[5] a member of the pluramycin family isolated from *Streptomyces phaeoverticillatus* which displays potent cytotoxic activity against leukemia L-1210 as well as antibacterial activity, and oliceridine,[6] an opioid agonist approved in 2020 in the USA for the intravenous treatment of moderate-to-severe post-operative pain, highlighting their importance in drug discovery and development (Fig. 1).

To solve the synthetic challenges associated with the preparation of these structurally complex frameworks, different

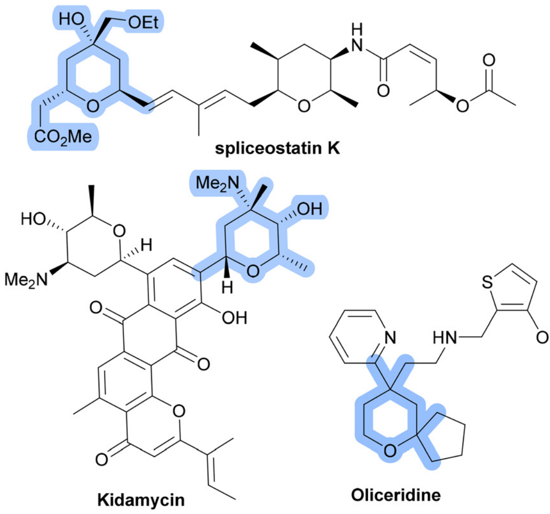

Fig. 1 Biologically active tetrahydropyranyl derivatives containing C4 quaternary stereocenters.

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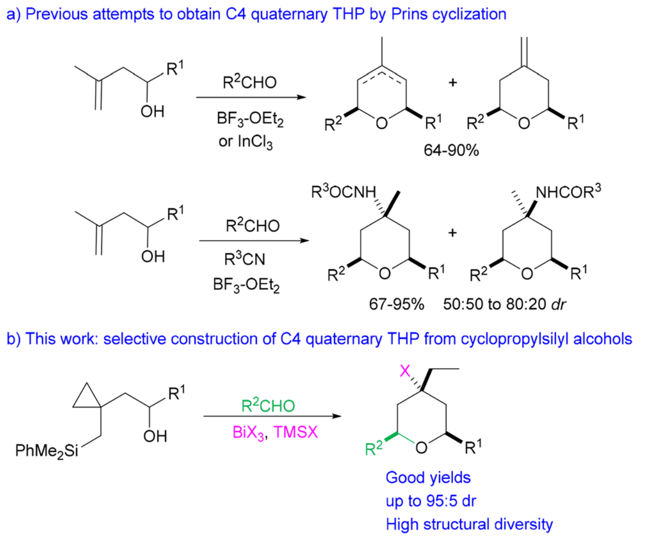
approaches have been devised. One such approach, the Prins cyclization, has proven highly effective in generating libraries of substituted oxacycles by simply varying the electrophilic reagent used in the process.[7] Furthermore, the versatility of this method allows for the selective preparation of different stereoisomers by choosing the appropriate starting materials, catalyst, or reaction conditions.[8] Despite these advancements, challenges remain in this field, particularly in the stereoselective synthesis of tetrahydropyrans containing quaternary centers, particularly at C4.[9,10] Most reported Prins-type methodologies produce either tertiary stereogenic carbons or sp^2 carbons at this position.[11,12] In contrast, strategies for constructing quaternary stereocenters at C4—beyond domino processes for spirobicycle[13] synthesis—are exceedingly rare. Even among these limited approaches, the majority (with rare exceptions)[14] yield random mixtures of the two possible epimers at C4,[15,16] significantly diminishing their practical value for medicinal chemistry applications (Scheme 1).

In recent years, our research has focused on developing procedures for the selective synthesis of various types of substituted oxacycles[17,18] through silyl-Prins cyclization of alkenylsilyl alcohols and aldehydes. This approach has allowed us to explore new methods for constructing oxacyclic frameworks with a high degree of control over substitution patterns and stereochemistry. We have recently introduced an interesting and nearly unprecedented variant of this approach that employs terminal cyclopropylsilyl alcohols as the π-nucleophilic component in the cyclization.[19] The results have been compelling, providing a very general methodology for constructing 2,3,4,6-tetrasubstituted tetrahydropyrans in which three new tertiary stereocenters have been created with complete selectivity. By strategically selecting substituents on the alcohol or aldehyde and optimizing the choice of Lewis acid, we have successfully synthesized a diverse array of compounds with high efficiency and selectivity.



Scheme 1 Prins-type strategies to access tetrahydropyrans with C4 quaternary stereocenters.

We here present another example of the silyl-Prins cyclization, where the use of internal cyclopropylsilyl alcohols facilitates the efficient construction of polysubstituted tetrahydropyrans featuring a newly created quaternary center at C4, along with a tertiary stereocenter at C6, with high levels of stereocontrol (Scheme 1).

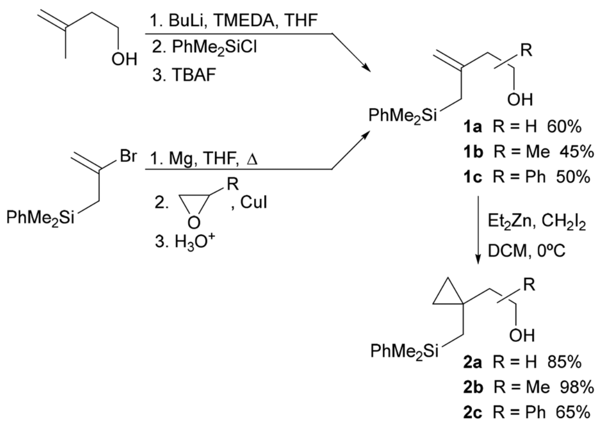
Results and discussion

The starting cyclopropylsilyl alcohols **2a–c** were synthesized following the procedures outlined in Scheme 2. Their precursors, allylsilyl alcohols **1a–c**, were obtained through two distinct approaches: (i) treatment of 3-methylbut-3-en-1-ol with BuLi, generating a dianion that reacts with $PhMe_2SiCl$ to form a disilylated intermediate, which undergoes selective desilylation with TBAF to afford **1a** or (ii) reaction of 2-bromo-3-phenyldimethylsilylpropene with magnesium, followed by addition of methyl- or phenyloxirane, yielding **1b** and **1c**. Subsequent cyclopropanation of **1a–c** efficiently furnishes the target cyclopropylsilyl alcohols **2a–c** in high yields (Scheme 2).

To establish the optimal conditions for the Prins cyclization, we chose the reaction of cyclopropylsilyl alcohol **2b** with *p*-chlorobenzaldehyde, using a variety of Lewis acids and conditions. The results are shown in Table 1.

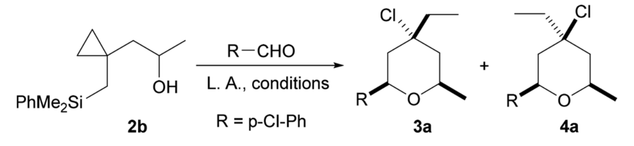
As shown, the reaction mediated by either $BF_3{\cdot}OEt_2$ or TMSOTf provided a complex mixture from which it was difficult to identify any product (Table 1, entries 1 and 2). The use of $BiCl_3$ or TMSCl afforded the products of Prins cyclization although in low yield (Table 1, entries 3 and 4). Finally, the best results were obtained using a mixture of catalytic $BiCl_3$ and stoichiometric TMSCl which, at 0 °C, furnished a 4 : 1 mixture of tetrahydropyrans **3a** and **4a** (Table 1, entry 5). By lowering the temperature to−78 °C, a single stereoisomer **3a** was obtained in very good yield (Table 1, entry 6).

With the optimal conditions in hand, we next decided to evaluate the generality of the process employing cyclopropylsilyl alcohols **2a** and **2b** and a wide variety of aldehydes. The results are shown in Scheme 3.



Scheme 2 Synthesis of starting cyclopropylsilyl alcohols.

Table 1 Optimization of the cyclization conditions[a]

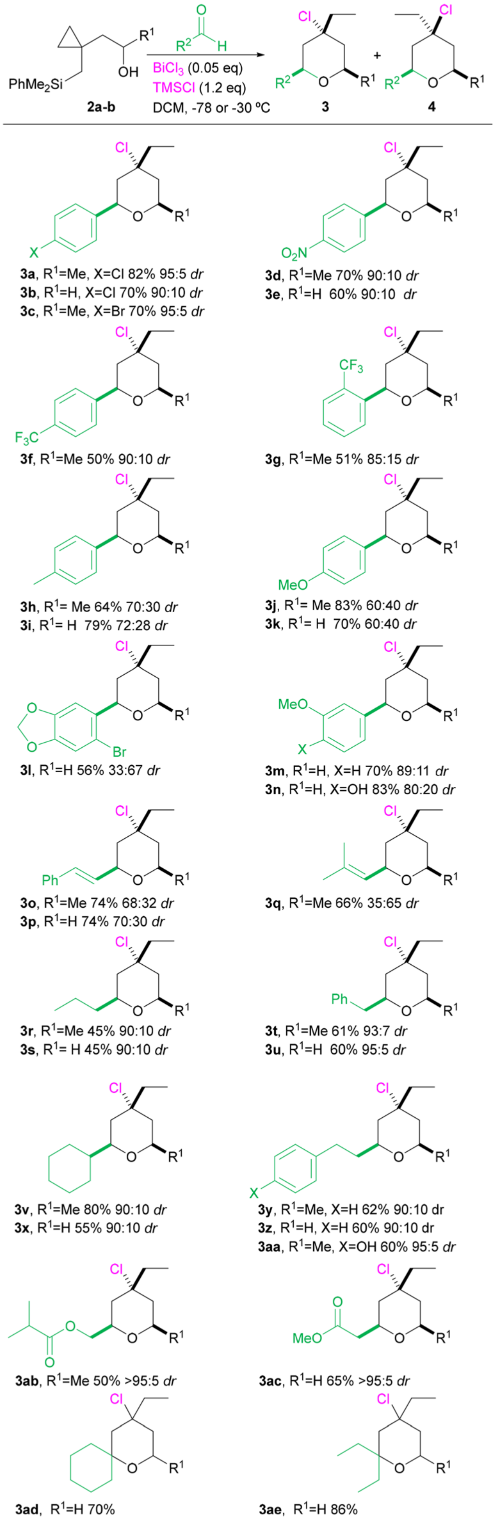


Entry	Lewis acid	T[a], time	dr[b] 3a : 4a	Yield (%)
1	$BF_3{\cdot}OEt_2$	−78 °C, 5 h		CM[c]
2	TMSOTf	−78 °C, 3 h		CM[c]
3	$BiCl_3$	0 °C, 7 h	73 : 27	40
4	TMSCl	0 °C, 24 h		15
5	$BiCl_3$ (0.05 eq.)/ TMSCl (1.2 eq.)	0 °C, 2 h	80 : 20	59
6	$BiCl_3$ (0.05 eq.)/ TMSCl (1.2 eq.)	−78 °C, 5 h	95 : 5	82

[a] General reaction conditions: cyclopropylsilyl alcohol **2b** (0.20 mmol, 1 equiv.), *p*-chlorobenzaldehyde (0.24 mmol, 1.2 equiv.), dry dichloromethane (5 mL). [b] Determined by NMR analysis of the crude mixture. [c] CM stands for complex mixture.

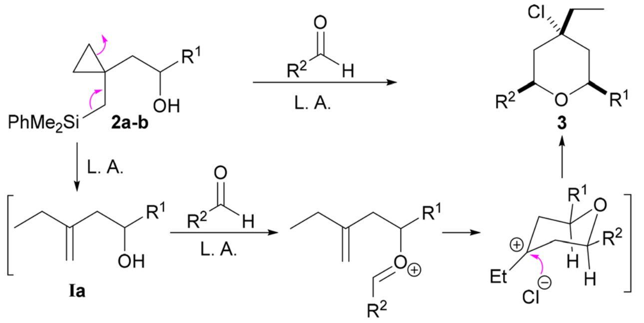
As illustrated in Scheme 3, the Prins cyclization of cyclopropylsilyl alcohols **2a** and **2b** with aldehydes proved to be a very general process, working for either arylic (both electron-rich and electron-poor), vinylic and alkylic aldehydes. The reaction is high yielding, providing polysubstituted tetrahydropyrans in which a quaternary and a tertiary stereogenic centers have been created in one pot. Moreover, high levels of stereoselectivity towards the formation of a single or very major diastereoisomer were observed in most cases, both for primary and secondary alcohols (**3a–3g**, **3m**, **3r–3z** and **3aa–3ac**). The only deviation from this general trend arises with less reactive aldehydes, such as aromatic aldehydes bearing electron-donating groups (**3h–3l**) and vinylic aldehydes (**3o–3q**), which yield mixtures of epimers at the quaternary center. Notably, the reaction remains compatible with aldehydes featuring ester groups (**3aa**, **3ab**) and even extends to certain ketones (**3ac**, **3ad**), demonstrating its broad applicability. The mechanism proposed for this interesting process is depicted in Scheme 4.

An initial acid-catalyzed opening of the cyclopropyl ring, facilitated by trace amounts of acid in the reaction medium, generates a stabilized β-silicon cation. This intermediate readily undergoes evolution *via* the loss of the silyl group,[20] forming a homoallylic alcohol **Ia.**[21] Subsequent Prins cyclization in the presence of an aldehyde produces a tertiary tetrahydropyranyl cation, which is ultimately trapped by the Lewis acid counterion to give the thermodynamically more stable isomer.[22] To assess the plausibility of the proposed mechanism, we examined the reaction of alcohol **Ib** (analogous to intermediate alcohol **Ia**) under the optimized conditions. As illustrated in Scheme 5, the Prins cyclization of alcohol **Ib** yielded the corresponding tetrahydropyranyl derivative **5**, maintaining good stereocontrol although in lower yield.[23]

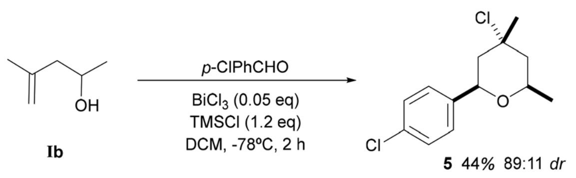


Scheme 3 Substrate scope in Prins cyclization of internal cyclopropylsilyl alcohols **2a** and **2b** mediated by $BiCl_3$/TMSCl.

With these promising results in hand, we decided to study the possibility of introducing other halogens at C4. The optimization process revealed that while the use of equimolar amounts of $BiBr_3$ facilitated the formation of Prins products, yields and stereocontrol remained low (Table 2, entry 1). As shown, the best results were achieved using catalytic amounts



Scheme 4 Proposed mechanism for the Prins cyclization of cyclopropylsilyl alcohols.



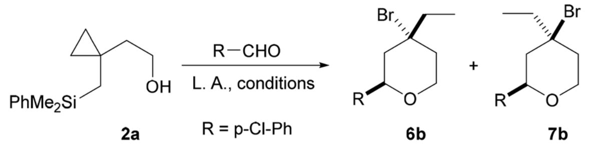
Scheme 5 Control experiment.

of $BiBr_3$ in combination with equimolar amounts of TMSBr (Table 2, entry 3).

We then studied the generality of the process by employing aldehydes with varying electronic properties. The results are summarized in Scheme 6.

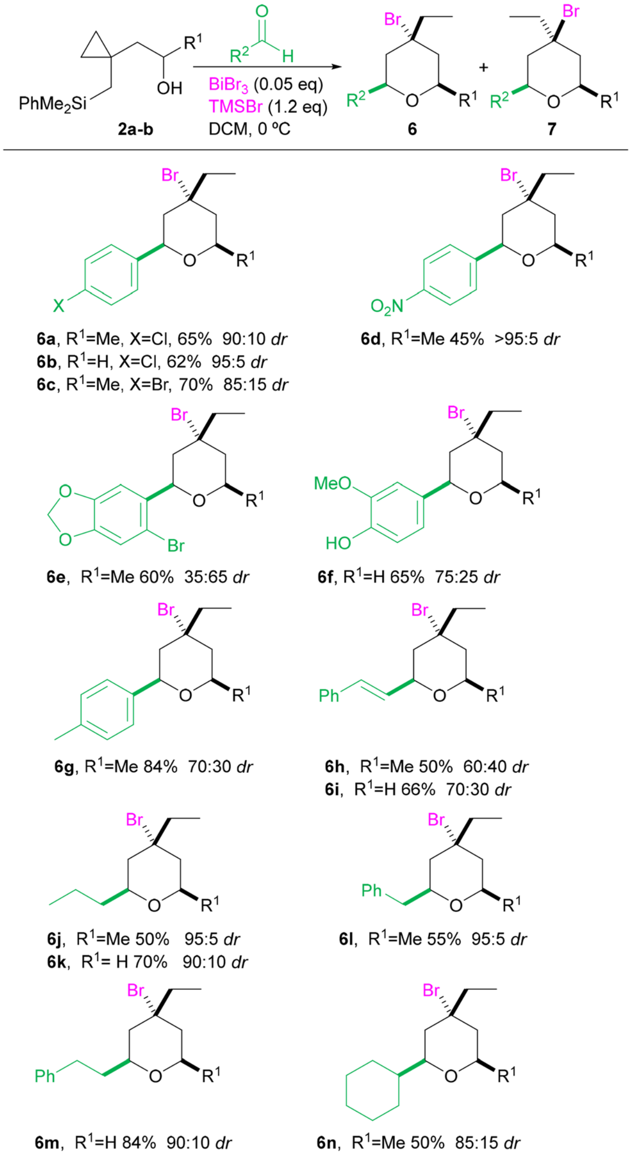
Scheme 6 illustrates the broad applicability of the process. Again, the reaction proved effective for a wide range of aldehydes, including aromatic, vinylic and aliphatic substrates. Furthermore, high yields and excellent stereoselectivity were observed in most cases (**6a–6d**, **6j–6n**), favoring the formation of a single or predominant diastereoisomer. As observed in the reactions with chlorinating agents (Table 2), a significant exception arose with less reactive aldehydes which led to epimeric mixtures at the quaternary center (**6e–6i**), deviating from the otherwise high stereoselectivity of the reaction.

Table 2 Optimization of the cyclization conditions to obtain C4 bromo derivatives[a]



Entry	Lewis acid	T^a, time	dr[b] **6b : 7b**	Yield (%)
1	$BiBr_3$ (1.2 eq.)	−78 °C, 5 h	45 : 55	30
2	Br_2	0 °C, 6 h		n.r.[c]
3	$BiBr_3$ (0.05 eq.)/ TMSBr (1.2 eq.)	0 °C, 1 h	90 : 10	62

[a] General reaction conditions: cyclopropylsilyl alcohol **2a** (0.20 mmol, 1 equiv.), *p*-chlorobenzaldehyde (0.24 mmol, 1.2 equiv.), dry dichloromethane (5 mL). [b] Determined by NMR analysis of the crude mixture. [c] n.r. stands for no reaction.



Scheme 6 Substrate scope in Prins cyclization of cyclopropylsilyl alcohols **2a** and **2b** mediated by $BiBr_3$/TMSBr.

Stereochemical assignments of tetrahydropyranyl derivatives were established using ^1H NMR and NOESY experiments, with definitive confirmation provided by the X-ray crystal structure of compound **7e** (Fig. 2).

We concluded by assessing how the arrangement of substituents on the precursor alcohol affects stereocontrol in the cyclization process. To this end, we selected a 2-substituted alcohol (**2c**) as a model substrate. Interestingly, cyclization using either chlorinating or brominating agents, in combination with aldehydes of varying electronic character, yielded nearly equimolar mixtures of the C5 epimeric tetrahydropyrans. This outcome suggests that, for this system, the relative energies of the chair-like transition states are nearly equi-

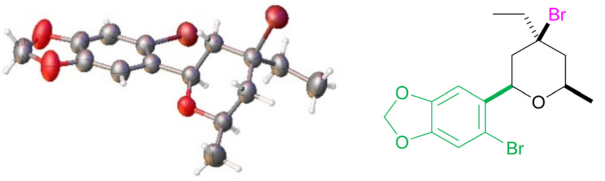
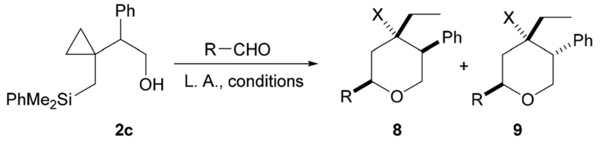


Fig. 2 X-ray crystal structure of compound **7e**; displacement ellipsoids at 50% probability. H atoms are omitted for clarity. Color key: C (grey), O (red), Br (orange). CCDC: 2448365.



Scheme 7 Substrate scope in Prins cyclization of 2-substituted cyclopropylsilyl alcohols.

valent, which accounts for the lack of strong stereocontrol in the cyclization step (Scheme 7).

Conclusions

In conclusion, the methodology presented herein significantly advances the field of stereoselective tetrahydropyran synthesis by addressing the longstanding challenge of constructing quaternary centers at C4. Building upon our earlier work with terminal cyclopropylsilyl alcohols, the use of internal cyclopropylsilyl alcohols in silyl-Prins cyclizations has proven to be a powerful extension of this strategy. This approach enables the efficient and highly stereoselective formation of complex tetrahydropyran frameworks bearing both quaternary and tertiary stereocenters. The high level of control over substitution and stereochemistry achieved in this work offers new opportunities for the synthesis of structurally diverse oxacycles with potential utility in medicinal chemistry and natural product synthesis.

Author contributions

Conceptualization, A. B.; methodology and investigation, P. G. A. and A. C.; validation, P. G. A. and A. B.; writing—original draft preparation, A. B.; and supervision, A. B. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

Supplementary information is available. Detailed experimental procedures, spectroscopic characterization, 1H and 13C NMR spectra for new products and X-ray crystal structure data for compound **7e** are provided. See DOI: https://doi.org/10.1039/d5qo00984g.

Crystallographic data for compound number **7e** has been deposited at the CCDC under CCDC: 2448365 and can be obtained from https://www.ccdc.cam.ac.uk/.[24]

Acknowledgements

We are grateful for financial support from grants TED2021-131705B-C21 and PID2021-125909OB-I00 funded by MICIU/AEI/10.13039/501100011033 and NextGenerationEU/PRTR. P. G.-A. acknowledges a predoctoral fellowship funded by the University of Valladolid.

References

1 D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, Organic synthesis provides opportunities to transform drug discovery, *Nat. Chem.*, 2018, **10**, 383–394.

2 M. Garcia-Castro, S. Zimmermann, M. G. Sankar and K. Kumar, Scaffold diversity synthesis and its application in probe and drug discovery, *Angew. Chem., Int. Ed.*, 2016, **55**, 7586–7605.

3 E. C. Barnes, R. Kumara and R. A. Davis, The use of isolated natural products as scaffolds for the generation of chemically diverse screening libraries for drug discovery, *Nat. Prod. Rep.*, 2016, **33**, 372–381.

4 H. Zhao, B. Zhang, L.-F. Ma, L.-M. Shi and Z.-J. Zhan, Cytotoxic spliceostatin analogs from *Pseudomonas sp.*, *Chem. Biodiversity*, 2019, **16**, e1900266.

5 Z. Fei and F. E. McDonald, Stereo- and regioselective glycosylations to the bis-C-arylglycoside of kidamycin, *Org. Lett.*, 2007, **9**, 3547–3550.

6 A. Markham, Oliceridine: first approval, *Drugs*, 2020, **80**, 1739–1744.

7 For selected reviews: (*a*) X. Han, G. Peh and P. E. Floreancig, Prins-type cyclization reactions in natural product synthesis, *Eur. J. Org. Chem.*, 2013, 1193–1208; (*b*) E. Reyes, L. Prieto, U. Uria, L. Carrillo and J. L. Vicario, Recent Advances in the Prins Reaction, *ACS Omega*, 2022, **7**, 31621–31627.

8 (*a*) A. Budakoti, P. K. Mondal, P. Verma and J. Khamrai, Prins cyclization-mediated stereoselective synthesis of tetrahydropyrans and dihydropyrans: an inspection of twenty years, *Beilstein J. Org. Chem.*, 2021, **17**, 932–963.

9 S. Bondalapati, U. C. Reddy, P. Saha and A. K. Saikia, An efficient synthesis of dihydro- and tetrahydropyrans via oxonium–ene cyclization reaction, *Org. Biomol. Chem.*, 2011, **9**, 3428–3438.

10 A. Y. Sidorenko, A. V. Kravtsova, A. Aho, I. Heinmaa, J. Wärnå, H. Pazniak, K. P. Volcho, N. F. Salakhutdinov, D. Y. Murzin and V. E. Agabekov, Highly selective Prins reaction over acid-modified halloysite nanotubes for synthesis of isopulegol-derived 2H-chromene compounds, *J. Catal.*, 2019, **374**, 360–377.

11 C. Olier, M. Kaafarani, S. Gastaldi and M. P. Bertrand, Synthesis of tetrahydropyrans and related heterocycles via prins cyclization; extension to aza-prins cyclization, *Tetrahedron*, 2010, **66**, 413–445.

12 C. Díez-Poza and A. Barbero, Synthesis of O- and N-heterocycles by silyl-Prins cyclization of allylsilanes, *Eur. J. Org. Chem.*, 2017, 4651–4665.

13 P. Padmaja, P. N. Reddy and B. V. Subba Reddy, Tandem Prins cyclizations for the construction of oxygen containing heterocycles, *Org. Biomol. Chem.*, 2020, **18**, 7514–7532.

14 K. Zheng, X. Liu, S. Qin, M. Xie, L. Lin, C. Hu and X. Feng, Completely OH-selective $FeCl_3$-catalyzed Prins cyclization: highly stereoselective synthesis of 4-OH-tetrahydropyrans, *J. Am. Chem. Soc.*, 2012, **134**, 17564–17573.

15 (*a*) A. Y. Sidorenko, Y. M. Kurban, A. F. Peixoto, N. S. Li-Zhulanov, J. E. Sánchez-Velandia, A. Aho, J. Wärnå, Y. Gu, K. P. Volcho, N. F. Salakhutdinov, D. Y. Murzin and V. E. Agabekov, *Appl. Catal., A*, 2023, **649**, 118967; (*b*) A. Scmmeat and U. Sequin, Concerning the products obtained from the condensation of 4-methyl-4-penten-2-ol with benzaldehyde, *Tetrahedron*, 1985, **41**, 949–953.

16 (*a*) B. Sarmah, G. Baishya and R. K. Baruah, First example of a Prins–Ritter reaction on terpenoids: a diastereoselective route to novel 4-amido-octahydro-2H-chromenes, *RSC Adv.*, 2014, **4**, 22387–22397; (*b*) M. Laluc, R. Barakov, P. Mäki-Arvela, N. Shcherban and D. Y. Murzin, Catalytic activity of hierarchical beta zeolites in the Prins cyclization of (-)-isopulegol with acetone, *Appl. Catal., A*, 2021, **618**, 118131.

17 (*a*) C. Díez-Poza and A. Barbero, Unexpected domino silyl-Prins/aryl migration process from geminal vinylsilyl alcohols synthesis approaches, *Org. Lett.*, 2021, **23**, 8385–8389; (*b*) C. Díez-Poza, L. Fernández-Peña, P. González-Andrés and A. Barbero, Changing the reaction pathway of silyl-Prins cyclization by switching the lewis acid: application to the synthesis of an antinociceptive compound, *J. Org. Chem.*, 2023, **88**, 6776–6783.

18 P. González-Andrés, C. Díez-Poza, L. F. Peña, D. Gónzalez-Pinardo, I. Fernández and A. Barbero, Insight into the Key Factors that Influence the Reaction Pathways in the Silyl-Prins Cyclization of gem-Vinylsilyl Alcohols, *Adv. Synth. Catal.*, 2025, **367**, e202401437.

19 L. F. Peña and A. Barbero, Terminal Cyclopropylsilyl Alcohols as Useful Key Units to Access 2,3,4,6-Tetrasubstituted Tetrahydropyran Scaffolds by Stereocontrolled Prins Cyclization, *Org. Lett.*, 2024, **26**, 5202–5207.

20 Further studies employing more electrofugal silyl groups will contribute to a deeper understanding of the reaction mechanism.

21 For selected examples of synthesis of homoallylic alcohols from organosilicon compounds: (*a*) X. Chen, X. Gong, Z. Li, G. Zhou, Z. Zhu, W. Zhang, S. Liu and X. Shen, Direct transfer of tri- and di-fluoroethanol units enabled by radical activation of organosilicon reagents, *Nat. Commun.*, 2020, **11**, 2756; (*b*) Y. Zhang, Y. Zhang and X. Shen, Alkoxyl-radical-mediated synthesis of functionalized allyl tert-(hetero)cyclobutanols and their ring-opening and ring-expansion functionalizations, *Chem. Catal.*, 2021, **1**, 423–436; (*c*) F. Chen and L. Chu, Photoredox-catalyst-controlled divergent alkylation of a-CF_3-olefins, *Chem. Catal.*, 2022, **2**, 1245–1256; (*d*) Z. Li, Y. Zhang, Y. Zhang, X. He and X. Shen, Diastereoselective Synthesis of Monofluorocyclohexenes through photocatalyzed Cascade Cyclization of gem-Difluoroalkenes and α,β-Unsaturated Carbonyl Compounds, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303218; (*e*) X. Chen, Z. Zhu, S. Liu, Y.-H. Chen and X. Shen, $MnBr_2$ catalyzed regiospecific oxidative Mizoroki-Heck type reaction, *Chin. Chem. Lett.*, 2022, **33**, 2391–2396.

22 O. L. Epstein and T. Rovis, A Sakurai-Prins-Ritter Sequence for the Three-Component Diastereoselective Synthesis of 4-Amino Tetrahydropyran, *J. Am. Chem. Soc.*, 2006, **128**, 16480–16481.

23 The low yield of compound **5** is attributed to the formation of unidentified by-products.

24 A. Barbero, CCDC 2448365 (**7e**): Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2n5qj3**.