ACS ORGANIC & INORGANIC Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/orginorgau

Article

Stereoselective Synthesis of Biologically Relevant Tetrahydropyridines and Dihydro-2*H*-pyrans via Ring-Expansion of Monocyclopropanated Heterocycles

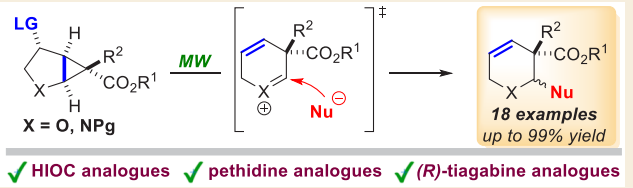
Robert Eckl, Sebastian Fischer, Carina M. Sonnleitner, Daniel Schmidhuber, Julia Rehbein, and Oliver Reiser*

Cite This: *ACS Org. Inorg. Au* 2022, 2, 169–174

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A stereoselective, scalable, and metal-free ring-expansion of monocyclopropanated pyrroles and furans has been developed, leading to value-added highly functionalized tetrahydropyridine and dihydro-2*H*-pyran derivatives. Featuring a cyclopropylcarbinyl cation rearrangement as the key step, the selective cleavage of the unactivated endocyclic cyclopropane C−C bond is achieved. Targeted transformations of the thus obtained six-membered heterocycles give access to versatile building blocks with relevance for drug synthesis.



KEYWORDS: *Tetrahydropyridines, Dihydro-2H-pyrans, Cyclopropanes, Furans, Pyrroles, Microwave-Assisted Synthesis, Ring-Expansion*

INTRODUCTION

Six-membered heterocycles are a key structural motif in a vast number of different physiologically active compounds.[1] The piperidine ring system in particular is one of the most common structural subunits in many drug targets.[2−4] HIOC (**1**),[5,6] (*R*)-tiagabine (**2**),[7] and pethidine (**3**)[8,9] are prominent representatives (Figure 1). HIOC (**1**) is a lead compound for the development of neuroprotectants[6] used in the therapy of neuro-degenerative diseases, (*R*)-tiagabine (**2**) is known as a GABA uptake inhibitor[7] and is involved in the treatment of epilepsy, and pethidine (**3**) is one of the most widely utilized opioids.[8]

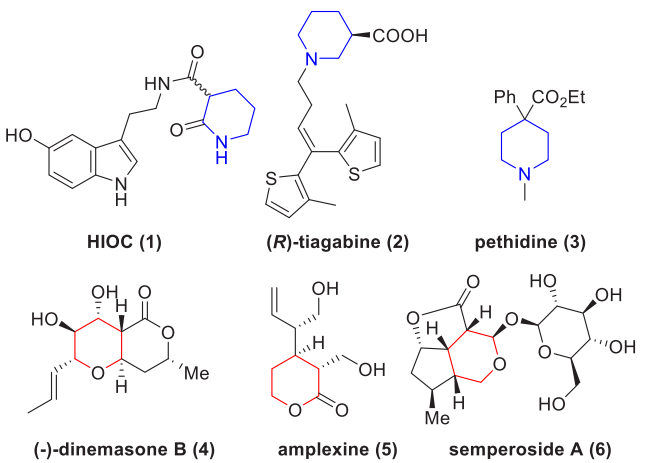


Figure 1. Important representatives of piperidine- or pyran-containing drug targets and natural products.

Likewise, pyrans[10,11] are key constituents in natural products such as (−)-dinemasone B (**4**), amplexine (**5**), and semperoside A (**6**), displaying various biological activities.[12−14] Despite much success,[15] the piperidine and pyran structure motifs remain a demanding challenge for organic synthesis, especially since ex-chiral pool precursors are not broadly available. Monocyclopropanated furans and pyrroles **7** (Figure 2) can be readily synthesized in diastereo- and enantiomerically pure forms from the parent heterocycles, the latter representing renewable resources that are inexpensive and available in bulk.[16−23] Therefore, the ring-expansion of such adducts could offer an attractive entry toward the piperidine or pyrane core.

Indeed, monocyclopropanated heterocycles **7**, representing donor−acceptor substituted cyclopropanes,[23−25] have been proven to undergo the chemo-, regio-, and stereoselective cleavage of the exocyclic cyclopropane bond, enabling various synthetic transformations such as rearrangements or ring-opening with nucleophiles and electrophiles.[24−29] In contrast, the selective cleavage of the endocyclic cyclopropane bond in **7**, which would result in the ring-expansion to piperidines or

Received: October 31, 2021
Revised: November 27, 2021
Accepted: November 29, 2021
Published: December 7, 2021

https://doi.org/10.1021/acsorginorgau.1c00042
ACS Org. Inorg. Au 2022, 2, 169–174

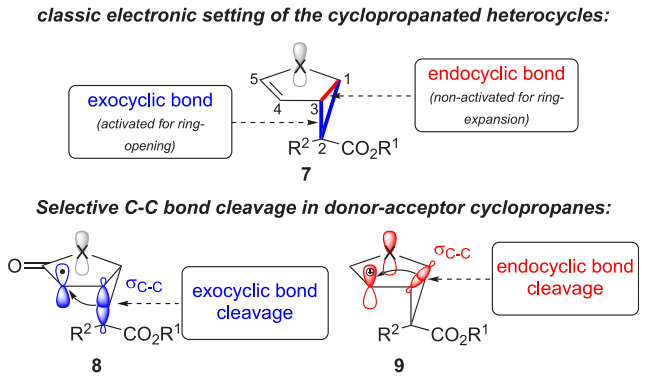
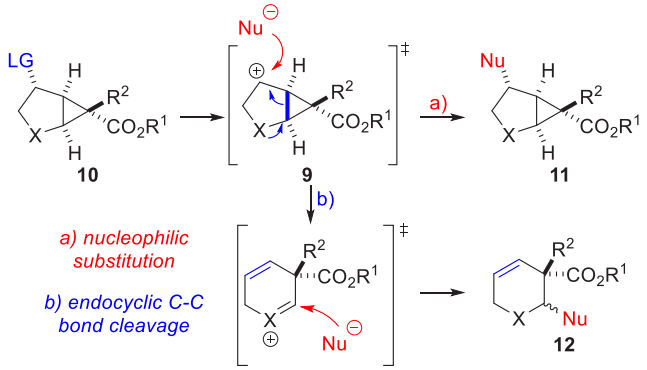


Figure 2. Analysis of the electronic properties in donor−acceptor cyclopropanes **7** and the selective C−C bond cleavage in **8** and **9**.

pyrans, remains a highly underexplored topic with only few examples reported.[21,27,30−34] By extension, a carbocyclic analogue would provide stereoselective access to substituted cyclohexenes.[35−37] We questioned if the inherent donor−acceptor electron flow in **7** can be reversed by generating an electron-deficient center at its C4 postion. In earlier work, we found that the radical intermediate **8** (X = NBoc) still results exclusively in the ring-opening of the exocyclic cyclopropane bond (Figure 2).[29] Here we report that generating a cyclopropylmethyl cation, i.e., **9** (X = NPg, O), as the key intermediate indeed results in the desired endocyclic ring-opening, giving access to highly functionalized tetrahydropyridine and dihydro-2*H*-pyran derivatives **12** (Scheme 1).

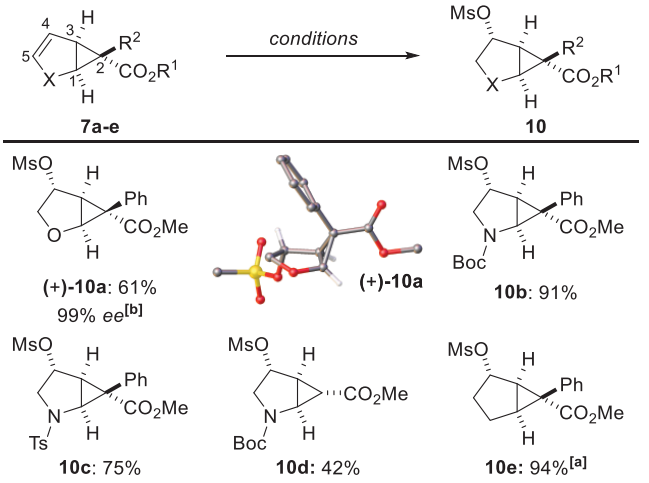
Scheme 1. Possible Reaction Pathways of Carbocation 9 with Nucleophiles (X = O, NPg, CH_2)



RESULTS AND DISCUSSION

Monocyclopropanated hetero- and carbocycles **7** were readily prepared by Cu(I)- or Rh(II)-catalyzed cyclopropanation[16,18−20] or by a light-mediated[17] cyclopropanation in racemic or enantiopure forms (see the SI for details). Aimed at introducing a leaving group at C4 to generate a cyclopropylmethyl cation of type **9**, we were pleased to see that hydroboration, followed by mesylation, gave rise to **10a−d**, while **10e** was accessible from **7e** by allylic oxidation, followed by hydrogenation and mesylation (Scheme 2). The perfect diastereoselectivity observed can be explained by the exclusive functionalization of the bicycle **7** from the convex side, which was confirmed by NMR analysis. Furthermore, the structure of (+)-**10a** was proven by single-crystal X-ray crystallography. Heating **10a** to 80 °C under microwave

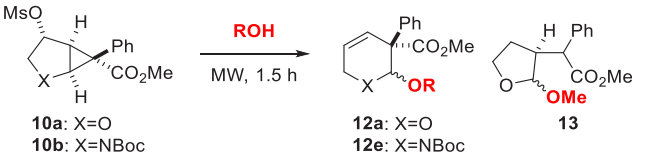
Scheme 2. Synthesis of Precursors 10[c]



[a]Conditions are as follows: (a) SeO_2 (1.1 equiv), 1,4-dioxane, 130 °C, MW, 1 h; (b) Pd/C (10 w/w %, 10 mol %), H_2 (60 bar), ethyl acetate, 25 °C, 2 h; (c) MsCl (1.1 equiv), NEt_3 (2.0 equiv), DCM, 0 °C, 1 h. [b]Determined by chiral HPLC by analyzing the corresponding alcohol (+)-**13a**. [c]Reaction conditions are as follows: (a) (i) 1 M BH_3·THF (1.1 equiv), THF, 0 to 25 °C, 3−18 h, (ii) H_2O_2, phosphate buffer (pH 7), 0 to 25 °C, 24 h; (b) MsCl (1.1 equiv), NEt_3 (2.0 equiv), DCM, 0 °C, 1 h.

irradiation (Table 1, entry 1) indeed gave rise to the desired pyran **12a** (55% yield). Additionally, however, the exocyclic

Table 1. Optimization of the Reaction Conditions



entry	X	ROH	base[a]	*T* (°C)	yield (of **12**)
1	O	MeOH		80	55% (+ 45% **13**)
2	O	MeOH	K_2CO_3	80	95%
3[b]	O	MeOH	K_2CO_3	80	76%
4	NBoc	MeOH	K_2CO_3	100	64%
5	O	MeOH	DBU	80	99%
6	NBoc	MeOH	DBU	100	99%

[a]Reaction conditions are as follows: 0.8 equiv of K_2CO_3 or 1.2 equiv of DBU. [b]The reaction was conducted under conventional heating with a reaction time 6 h.

ring-opening to **13** had occurred to an almost equal extent (45% yield). We suspected that the formation of methyl sulfonic acid in the course of the reaction would be sufficient to activate the ester group to cause the undesired exocyclic ring-opening.[38]

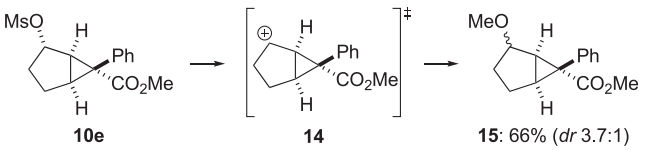
Indeed, adding K_2CO_3 as a non-nucleophilic base completely suppressed the formation of **13**, and the desired pyran derivative **12a** was obtained in a 95% yield (Table 1, entry 2). The benefit of microwave irradiation became apparent by comparison to conventional heating, when only 76% of **12a** was isolated even at an extended reaction time of 6 h (Table 1, entry 3). Moving to NBoc-pyrrole derivative **10b**, the combination of K_2CO_3 and microwave irradiation was also successful; however, increasing the reaction temperature to 100 °C was necessary for full conversion to obtain

https://doi.org/10.1021/acsorginorgau.1c00042
ACS Org. Inorg. Au 2022, 2, 169−174

12e (64%, Table 1, entry 4). An improvement was found by switching to DBU because it is soluble in most organic solvents, which allowed the synthesis of both 12a and 12e in almost quantitative yields (95−99%, Table 1, entries 5 and 6, respectively). Furthermore, computational studies with 10a as model substrate support the mechanistic assumptions and experimental results (see SI for details).

Subjecting the carbocyclic derivative 10e to the optimized reaction conditions, no ring-opening was observed but rather direct substitution to 15 (Scheme 3). The major diastereomer

Scheme 3. S_N1-Type Reaction of Carbocyclic Cyclopropane 10e[a]



[a]Reaction conditions are as follows: DBU (2.5 equiv), MeOH, 100 °C, 0.5 h. The combined isolated yield of two diastereomers is shown.

formed in 15 with the retention of the stereochemistry indicates that the reaction proceeds via an S_N1 pathway and thus through a cationic intermediate 14. Apparently, the ring-opening of the cyclopropylcarbinyl to the homoallyl cation is slow[39,40] in the absence of a donor, as present in precursors 10a−d.

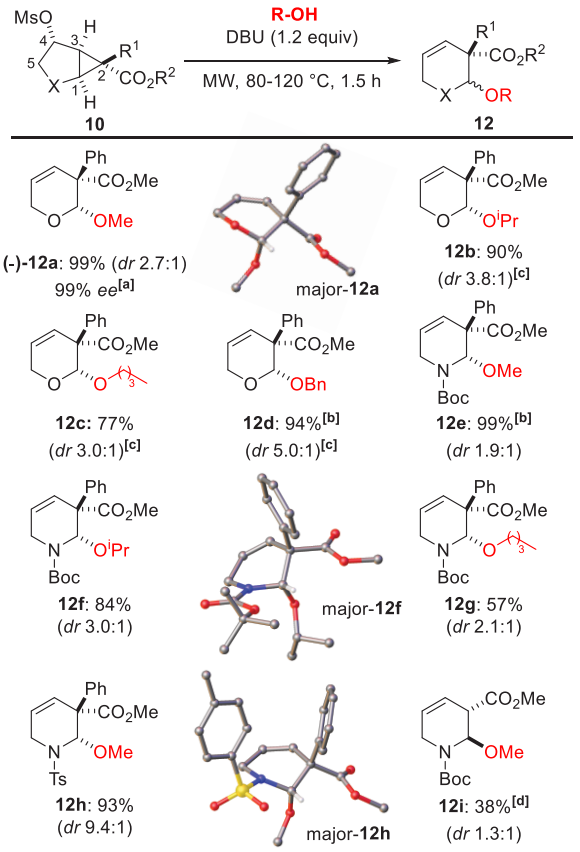
Besides methanol, other alcohols such as *i*PrOH, *n*-BuOH, and BnOH could be used as solvents in the ring-opening of 10a−10d, giving rise to the corresponding pyrans or dihydropyridines 12 (Scheme 4).

The transformations generally proceeded in high yields with exception of 12i, which was found to be unstable and suffered from elimination and oxidation that ultimately led to a pyridine derivative. Aiming to extend the scope of the process to nucleophiles that cannot be employed as solvents, we found that the reaction proceeds effectively in acetonitrile (for optimization studies, see the SI), thus allowing the introduction of more complex alcohols (16b, 16h, and 16i), carboxylic acids (16c), hydride (16d), or various C-nucleophiles (16e−g). Typically, epimers at the anomeric center were obtained, which could be readily separated in most cases (Scheme 5).

Few examples in the literature exist that show vinylcyclopropane epoxides are also suitable precursors to trigger the cyclopropane ring-opening.[41−43] Aiming at an alternative to mesylates 10, we explored vinylcyclopropane epoxides 18, which were readily obtained via a Corey−Chaykovsky epoxidation of 17 that again proceeded exclusively from the convex side (Scheme 6).

Treating furan-derived epoxide 18a with amberlyst 15 in methanol enabled the expected ring-expansion, which featured the cyclopropylmethyl cation as key intermediate, and pyran 19a was obtained in a 62% yield. To achieve the ring-expansion of pyrrole-derived epoxide 18b, harsher reaction conditions were required. A TFA/H_2O (9:1) mixture gave access to the dihydropyridine 19b in a 79% yield, and additional Boc-deprotection of the product was observed (Scheme 6). Notably and contrasting the formation of 13 under acidic conditions (Table 1, entry 1), no exocyclic cyclopropane ring-opening was observed, suggesting the

Scheme 4. Microwave-Assisted Ring-Expansion of 10a−d[e]



[a]Determined by chiral HPLC by analyzing the epimeric mixture. [b]The scale-up procedure is as follows:: 4.02 mmol 10a and 4.86 mmol 10b were employed to yield 1.22 g of 12d and 1.68 g of 12e. [c]Diastereomers were isolated in their pure form (see the SI for details). [d]Reaction conditions are as follows: 2,6-Lutidine (1.2 equiv), MeOH, MW, 60 °C, 16 h. [e]Reactions were conducted on a 0.3−2.8 mmol scale. The combined isolated yield of two diastereomers is given (the major diastereomer is shown).

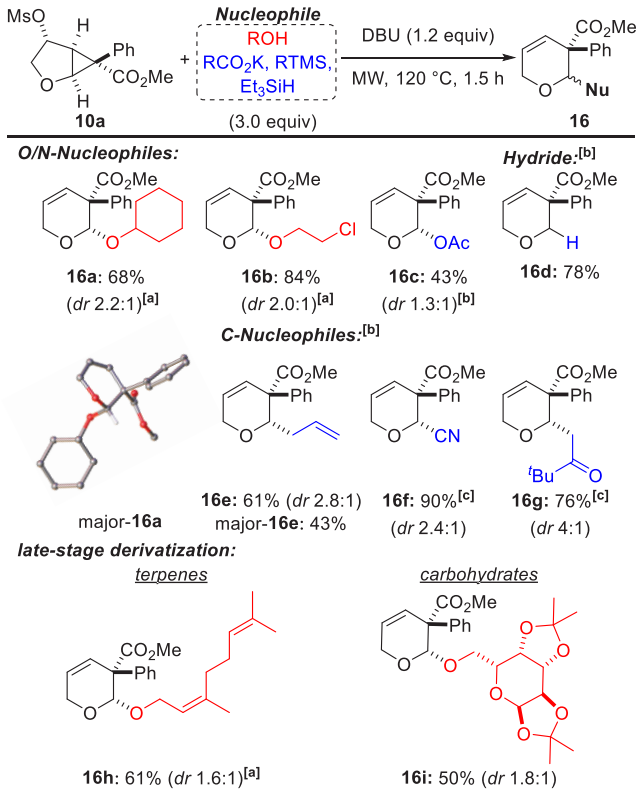
epoxide functionality is superior to a mesylate or ester for activation by protonation.

With a view to HIOC (1), (*R*)-tiagabine (2), and pethidine (3), dihydropyridine 12e and pyran 16d were converted to analogues of these drug targets (Scheme 7). The hydrolysis of the *N*/*O*-acetal 12e under acidic conditions gave access to cyclic imine 20 in a high yield (94%), which could be chemoselectively oxidized to the corresponding *δ*-lactam 21.

On the other hand, the chemoselective reduction of 20 was possible, giving rise to 22 or, following methylation and transesterification, to pethidine analogue 23. Coupling 22 to a lipophilic anchor, followed by saponification, provided the tiagabine derivative 24. Finally, substrates 12 and 16 are potent precursors for the synthesis of HIOC derivatives. If HIOC is once bound to the receptor, the resistance of the six-membered heterocycle against hydrolysis is known to be decisive for its biological activity. Thus, it was demonstrated that the sterically bulky and hydrolysis-resistant model substrate 16d could indeed be coupled to the serotonin-related tryptamine after the initial saponification within two high-yielding steps to afford HIOC analogue 26.

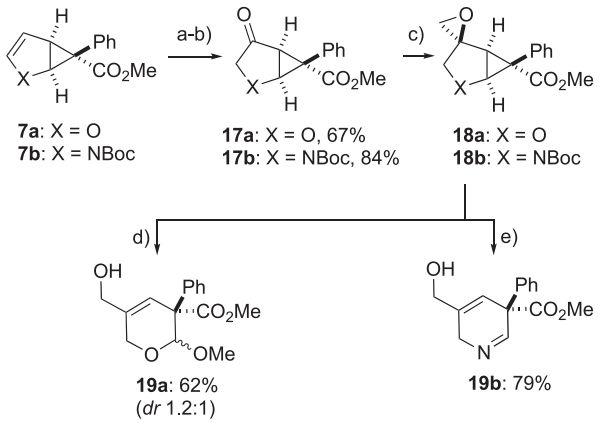
https://doi.org/10.1021/acsorginorgau.1c00042
ACS Org. Inorg. Au 2022, 2, 169−174

Scheme 5. Microwave-Assisted Ring-Expansion of 10a[d]



[a]Diastereomers were isolated in their pure form (see the SI for details). [b]No base was necessary. [c]Reaction time of 4 h. [d]Reactions were conducted on a 0.3 mmol scale. The combined isolated yield of two diastereomers is given (the major diastereomer is shown).

Scheme 6. Acid-Mediated Ring-Expansion of Vinylcyclopropane Epoxides 18 Starting from Monocyclopropanated Furan 7a and Pyrrole 7b[a]

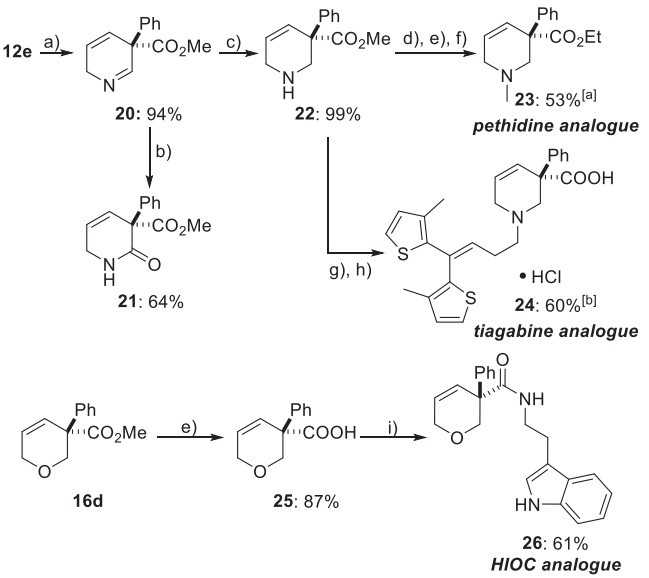


[a]Reaction conditions are as follows: (a) (i) 1 M BH_3·THF (1.1 equiv), THF, 0 to 25 °C, 3−18 h, (ii) H_2O_2, phosphate buffer (pH 7), 0 to 25 °C, 24 h; (b) oxalyl chloride (2.0 equiv), DMSO (3.0 equiv), NEt_3 (3.0 equiv), DCM, −65 to −45 °C, 3.5 h; (c) Me_3SOI (1.3 equiv), NaH (1.3 equiv), DMSO, 0 to 25 °C, 18 h; (d) amberlyst 15 (20 w/w%), MeOH (5.0 equiv), MeCN, 25 °C, 0.5 h; (e) TFA/H_2O (9:1), 25 °C, 1 h.

CONCLUSION

In summary, we developed a stereoselective microwave-assisted and Brønsted-acid-mediated ring-expansion of monocyclopropanated furans and pyrroles that gives access to various pyran and dihydropyridine derivatives in excellent yields. The established protocols benefit from versatility, scalability, and short reaction times under environmentally benign conditions. Furthermore, the variability of the obtained pyran and dihydropyridine derivatives was demonstrated by targeted transformations, which provided new derivatives of potent drug targets.

Scheme 7. Targeted Derivatization of 12e and 16d



[a]yield is given over three steps; [b]yield is given over two steps. [c]Reaction conditions are as follows: (a) TFA/H_2O (9:1), 25 °C, 45 min; (b) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (1.5 equiv), 2,3-dimethyl-2-butene (10 equiv), THF/H_2O, 25 °C, 24 h; c) $NaBH_3CN$ (10 equiv), CH_3COOH (10.0 equiv), MeOH, 25 °C, 45 min; (d) 37% aq. CH_2O (6.2 equiv), $Na(OAc)_3BH$ (3.0 equiv), MeCN, 25 °C, 1.5 h; (e) LiOH (5.0 equiv), MeOH/H_2O (9:1), 100 °C, 2.5 h; (f) 2 M $SOCl_2$, EtOH, 100 °C, 4.5 h; (g) 4,4-bis(3-methylthiophen-2-yl)but-3-en-1-yl methanesulfonate (1.2 equiv), K_2CO_3 (1.5 equiv), KI (10 mol %), 80 °C, 48 h; h) LiOH (5.0 equiv), MeOH/H_2O (9:1), 100 °C, 24 h; (i) (i) CDI (1.5 equiv), DCM, 25 to 50 °C, 27 h, (ii) tryptamine (1.02 equiv), pyridine (46 equiv), 25 °C, 24 h.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00042.

Experimental details, optimization studies, X-ray structure details, computations studies, and copies of NMR spectra (PDF)

Accession Codes

CCDC 2119362−2119366 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://doi.org/10.1021/acsorginorgau.1c00042
ACS Org. Inorg. Au 2022, 2, 169−174

AUTHOR INFORMATION

Corresponding Author

Oliver Reiser − *Institute of Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany;* orcid.org/0000-0003-1430-573X; Email: oliver.reiser@chemie.uniregensburg.de

Authors

Robert Eckl − *Institute of Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany*

Sebastian Fischer − *Institute of Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany*

Carina M. Sonnleitner − *Institute of Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany*

Daniel Schmidhuber − *Institute of Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany*

Julia Rehbein − *Institute of Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany;* orcid.org/0000-0001-9241-0637

Complete contact information is available at: https://pubs.acs.org/10.1021/acsorginorgau.1c00042

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the German Science Foundation (DFG; GRK 2620 Ion Pair Effects). We are grateful to Dr. Peter Kreitmeier for helpful discussions. We also acknowledge Brigitte Eichenseher, Johannes Floß, Birgit Hischa, and central analytics (all University of Regensburg) for technical and analytical support.

REFERENCES

(1) Baumann, M.; Baxendale, I. R. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. *Beilstein J. Org. Chem.* **2013**, *9*, 2265−2319.

(2) Babaee, S.; Zolfigol, M. A.; Zarei, M.; Abbasi, M.; Najafi, Z. Synthesis of pyridinium-based salts: Catalytic application at the synthesis of six membered O-heterocycles. *Mol. Catal.* **2019**, *475*, 110403.

(3) Goel, P.; Alam, O.; Naim, M. J.; Nawaz, F.; Iqbal, M.; Alam, M. I. Recent advancement of piperidine moiety in treatment of cancer- A review. *Eur. J. Med. Chem.* **2018**, *157*, 480−502.

(4) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. Recent advances in the synthesis of piperidones and piperidines. *Tetrahedron* **2003**, *59*, 2953−2989.

(5) Setterholm, N. A.; McDonald, F. E.; Boatright, J. H.; Iuvone, P. M. Gram-scale, chemoselective synthesis of N-2-(5-hydroxy-1H-indol-3-yl)ethyl-2-oxopiperidine-3-carboxamide (HIOC). *Tetrahedron Lett.* **2015**, *56*, 3413−3415.

(6) Shen, J.; Ghai, K.; Sompol, P.; Liu, X.; Cao, X.; Iuvone, P. M.; Ye, K. N-acetyl serotonin derivatives as potent neuroprotectants for retinas. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 3540−3545.

(7) Adkins, J. C.; Noble, S. Tiagabine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* **1998**, *55*, 437−460.

(8) Jones, L.; Othman, M.; Dowswell, T.; Alfirevic, Z.; Gates, S.; Newburn, M.; Jordan, S.; Lavender, T.; Neilson, J. P. Pain management for women in labour: An overview of systematic reviews. *Cochrane Database Syst. Rev.* **2012**, CD009234.

(9) Lomenzo, S. A.; Rhoden, J. B.; Izenwasser, S.; Wade, D.; Kopajtic, T.; Katz, J. L.; Trudell, M. L. Synthesis and biological evaluation of meperidine analogues at monoamine transporters. *J. Med. Chem.* **2005**, *48*, 1336−1343.

(10) Jacques, R.; Pal, R.; Parker, N. A.; Sear, C. E.; Smith, P. W.; Ribaucourt, A.; Hodgson, D. M. Recent applications in natural product synthesis of dihydrofuran and -pyran formation by ring-closing alkene metathesis. *Org. Biomol. Chem.* **2016**, *14*, 5875−5893.

(11) Larrosa, I.; Romea, P.; Urpí, F. Synthesis of six-membered oxygenated heterocycles through carbon-oxygen bond-forming reactions. *Tetrahedron* **2008**, *64*, 2683−2723.

(12) Silva, L. F. R. e; Lima, E. S.; Vasconcellos, M. C. d.; Aranha, E. S. P.; Costa, D. S.; Mustafa, E. V.; Morais, S. K. R. d.; Alecrim, M. d. G. C.; Nunomura, S. M.; Struwe, L.; Andrade-Neto, V. F. d.; Pohlit, A. M. In vitro and in vivo antimalarial activity and cytotoxicity of extracts, fractions and a substance isolated from the Amazonian plant Tachia grandiflora (Gentianaceae). *Mem. Inst. Oswaldo Cruz.* **2013**, *108*, 501−507.

(13) Xue, X.; Yin, Z.; Meng, X.; Li, Z. A carbohydrate-based approach for the total synthesis of (−)-dinemasone B, (+)-4a-epi-dinemasone B, (−)-7-epi-dinemasone B, and (+)-4a,7-Di-epi-dinemasone B. *J. Org. Chem.* **2013**, *78*, 9354−9365.

(14) Piccinini, P.; Vidari, G.; Zanoni, G. Enantioselective total synthesis of semperoside a. *J. Am. Chem. Soc.* **2004**, *126*, 5088−5089.

(15) Bailey, P. D.; Millwood, P. A.; Smith, P. D. Asymmetric routes to substituted piperidines. *Chem. Commun.* **1998**, 633−640.

(16) Fu, J.; Wurzer, N.; Lehner, V.; Reiser, O.; Davies, H. M. L. Rh(II)-Catalyzed Monocyclopropanation of Pyrroles and Its Application to the Synthesis Pharmaceutically Relevant Compounds. *Org. Lett.* **2019**, *21*, 6102−6106.

(17) Jurberg, I. D.; Davies, H. M. L. Blue light-promoted photolysis of aryldiazoacetates. *Chem. Sci.* **2018**, *9*, 5112−5118.

(18) Lehner, V.; Davies, H. M. L.; Reiser, O. Rh(II)-Catalyzed Cyclopropanation of Furans and Its Application to the Total Synthesis of Natural Product Derivatives. *Org. Lett.* **2017**, *19*, 4722−4725.

(19) Pilsl, L. K. A.; Ertl, T.; Reiser, O. Enantioselective Three-Step Synthesis of Homo-β-proline: A Donor-Acceptor Cyclopropane as Key Intermediate. *Org. Lett.* **2017**, *19*, 2754−2757.

(20) Gratia, S.; Mosesohn, K.; Diver, S. T. Highly Selective Ring Expansion of Bicyclo3.1.0hexenes. *Org. Lett.* **2016**, *18*, 5320−5323.

(21) Gharpure, S. J.; Shukla, M. K.; Vijayasree, U. Stereoselective synthesis of donor-acceptor substituted cyclopropafuranones by intramolecular cyclopropanation of vinylogous carbonates: divergent synthesis of tetrahydrofuran-3-one, tetrahydropyran-3-one, and lactones. *Org. Lett.* **2009**, *11*, 5466−5469.

(22) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. anti-Oligoannelated THF moieties: synthesis via push-pull-substituted cyclopropanes. *Org. Lett.* **2009**, *11*, 2317−2320.

(23) Reissig, H.-U.; Zimmer, R. Donor-acceptor-substituted cyclopropane derivatives and their application in organic synthesis. *Chem. Rev.* **2003**, *103*, 1151−1196.

(24) Schneider, T. F.; Kaschel, J.; Werz, D. B. A new golden age for donor-acceptor cyclopropanes. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504−5523.

(25) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular donor-acceptor cyclopropane ring-opening cyclizations. *Chem. Soc. Rev.* **2014**, *43*, 804−818.

(26) Budde, S.; Goerdeler, F.; Floß, J.; Kreitmeier, P.; Hicks, E. F.; Moscovitz, O.; Seeberger, P. H.; Davies, H. M. L.; Reiser, O. Visible-light mediated oxidative ring expansion of anellated cyclopropanes to fused endoperoxides with antimalarial activity. *Org. Chem. Front.* **2020**, *7*, 1789−1795.

(27) Ganesh, V.; Kundu, T.; Chandrasekaran, S. σ-Ferrier rearrangement of carbohydrate derived vinylcyclopropanes: a facile approach to oxepane analogs. *Tetrahedron* **2014**, *70*, 7268−7282.

(28) Kaschel, J.; Schneider, T. F.; Schirmer, P.; Maaß, C.; Stalke, D.; Werz, D. B. Rearrangements of Furan-, Thiophene- and N -Boc-Pyrrole-Derived Donor-Acceptor Cyclopropanes: Scope and Limitations. *Eur. J. Org. Chem.* **2013**, *2013*, 4539−4551.

(29) Gheorghe, A.; Schulte, M.; Reiser, O. Synthesis of functionalized pyrrolidin-2-ones and (S)-Vigabatrin from pyrrole. *J. Org. Chem.* **2006**, *71*, 2173−2176.
(30) Wurzer, N.; Klimczak, U.; Babl, T.; Fischer, S.; Angnes, R. A.; Kreutzer, D.; Pattanaik, A.; Rehbein, J.; Reiser, O. Heck-Type Coupling of Fused Bicyclic Vinylcyclopropanes: Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-1 H -azepines, 1,4-Cyclohexadienes, and 2 H -Pyrans. *ACS Catal.* **2021**, *11*, 12019−12028.
(31) Sonnleitner, C. M.; Park, S.; Eckl, R.; Ertl, T.; Reiser, O. Stereoselective Synthesis of Tropanes via a 6π-Electrocyclic Ring-Opening/ Huisgen 3 + 2-Cycloaddition Cascade of Monocyclopropanated Heterocycles. *Angew. Chem., Int. Ed.* **2020**, *59*, 18110−18115.
(32) Yedoyan, J.; Wurzer, N.; Klimczak, U.; Ertl, T.; Reiser, O. Regio- and Stereoselective Synthesis of Functionalized Dihydropyridines, Pyridines, and 2H-Pyrans: Heck Coupling of Monocyclopropanated Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 3594−3598.
(33) Sridhar, P. R.; Venukumar, P. A ring expansion-glycosylation strategy toward the synthesis of septano-oligosaccharides. *Org. Lett.* **2012**, *14*, 5558−5561.
(34) Cousins, G. S.; Hoberg, J. O. Synthesis and chemistry of cyclopropanated carbohydrates. *Chem. Soc. Rev.* **2000**, *29*, 165−174.
(35) Li, P.-F.; Yi, C.-B.; Qu, J. Hot water-promoted cyclopropylcarbinyl rearrangement facilitates construction of homoallylic alcohols. *Org. Biomol. Chem.* **2015**, *13*, 5012−5021.
(36) Banwell, M. G.; Ma, X.; Taylor, R. M.; Willis, A. C. Concise assembly of the polycyclic frameworks associated with the hapalindole and fischerindole alkaloids. *Org. Lett.* **2006**, *8*, 4959−4961.
(37) Wessjohann, L. A.; Mühlbauer, A.; Sinks, U.; Rise, F.; Hartshorn, M. P.; Merchán, M.; Robinson, W. T.; Roos, B. O.; Vallance, C.; Wood, B. R. 2-Halo-2-cyclohexenols from 6,6-Dihalobicyclo-[3.1.0]hexanes and Dimethyl Sulfoxide. Studies towards a Non-basic Hydroxide Equivalent. *Acta Chem. Scand.* **1997**, *51*, 1112−1115.
(38) Kim, C.; Hoang, R.; Theodorakis, E. A. Synthetic Studies on Norrisolide: Enantioselective Synthesis of the Norrisane Side Chain. *Org. Lett.* **1999**, *1*, 1295−1297.
(39) Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. Cyclopropylcarbinyl-type ring openings. Reconciling the chemistry of neutral radicals and radical anions. *J. Am. Chem. Soc.* **2002**, *124*, 4271−4281.
(40) Thielemann, W.; Schäfer, H. J.; Kotila, S. A facile entry to the taxane AB ring system by cyclopropyl-carbinyl-rearrangement of tricyclo[5.3.1.01,7]undecanols. *Tetrahedron* **1995**, *51*, 12027−12034.
(41) Shi, H.; De, S.; Wang, Q.; Gao, S.; Wang, X.; Chen, C. Construction of the 5,6,7-tricyclic skeleton of lancifodilactone F. *Tetrahedron Lett.* **2015**, *56*, 3225−3227.
(42) Penkett, C. S.; Byrne, P. W.; Teobald, B. J.; Rola, B.; Ozanne, A.; Hitchcock, P. B. The use of temporary tethers in the meta photocycloaddition reaction. *Tetrahedron* **2004**, *60*, 2771−2784.
(43) Corey, E. J.; Hong, B. Chemical Emulation of the Biosynthetic Route to Glycinoeclepin from a Cycloartenol Derivative. *J. Am. Chem. Soc.* **1994**, *116*, 3149−3150.

https://doi.org/10.1021/acsorginorgau.1c00042
ACS Org. Inorg. Au 2022, 2, 169−174