Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2023, **14**, 8070

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 27th May 2023
Accepted 6th July 2023

DOI: 10.1039/d3sc02695g

rsc.li/chemical-science

Open Access Article. Published on 12 July 2023. Downloaded on 4/27/2024 3:58:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

2,5-disubstituted bicyclo[2.1.1]hexanes as rigidified cyclopentane variants†

Shashwati Paul,[a] Daniel Adelfinsky,[a] Christophe Salome,[b] Thomas Fessard*[b] and M. Kevin Brown*[a]

Identification of rigid counterparts for common flexible scaffolds is crucial to the advancement of medicinal chemistry. Here we showcase a new class of building blocks, 2,5-disubstituted bicyclo[2.1.1]hexanes that can act as rigidified *cis*-, or *trans*-1,3-disubstituted cyclopentanes, common motifs in drugs. The scalable synthesis of these structures was enabled through the use of C–H functionalization logic and cycloaddition reactions.

Introduction

Conformational rigidification is an established strategy in medicinal chemistry to improve affinity, selectivity, and metabolic stability of a parent drug molecule by presenting defined exit vectors.[1] As such, many bicyclic and polycyclic scaffolds have been designed that fulfill these features. Small rings such as, cyclobutane and cyclopropane moieties have also been extensively employed in medicinal chemistry due to their rigid structure.[2]

A recent analysis of the most common rings found in drugs ranked cyclopentane as the 18th most common.[3] However, cyclopentane is flexible due to facile interconversion between the half-chair and envelope conformations. Despite considerable progress in the conformational restriction strategy,[1] rigidification of cyclopentane rings has not seen significant development.

Among substituted cyclopentane rings, 1,3-disubstitution is particularly common. These structures have appeared in numerous patents and journals (Fig. 1A). Furthermore, 3-oxocyclopentanecarboxylic acid is a popular building block for the synthesis of various 1,3-disubstituted cyclopentanes (Fig. 1A and B).[4] Cognizant of the commonality of these structures, we sought to develop a rigidified 1,3-disubstituted cyclopentane variant in the form of a 2,5-disubtituted-bicyclo[2.1.1]hexane (Fig. 1C). In the case of *syn*-1,3-disubstituted cyclopentanes, rigidification can allow for disfavored conformations to be adopted (Fig. 1C). For *anti*-1,3-disubstituted cyclopentanes, which are conformationally flexible, the bicyclo[2.1.1]hexane analog can lock the conformation (Fig. 1C). In each case the exit vectors between the cyclopentane and bicyclo[2.1.1]hexane are similar (Fig. 1C).

Recent studies involving bicyclo[2.1.1]hexanes have focused on 1,2/1,5-disubstituted variants, which are not appropriate for rigidification of 1,3-disubstituted cyclopentanes.[5,6] The required 2,5-substitution pattern has only been prepared in low yields (Fig. 1D).[7] In addition, synthesis of this substitution pattern is challenging as four stereoisomers is possible. In this manuscript, we address these challenges though development of efficient routes for 2,5-disubstituted bicyclo[2.1.1]hexanes synthesis and diastereoselective further functionalization (Fig. 1D).

The most common method for synthesizing bicyclo[2.1.1]hexanes is a crossed [2 + 2]-cycloaddition reaction.[5a] However, the synthesis of bicyclo[2.1.1]hexanes *via* crossed [2 + 2] cycloaddition is limited to preparing structures with a bridgehead substituents.[7] Our interest is to establish a route that can incorporate two functional handles so that the target can be easily manipulated for rapid incorporation into drug molecules. In an orthogonal approach, we also envisioned that C–H functionalization logic could be applied to substitute the bridging positions of a mono substituted bicyclo[2.1.1]hexane.[8] Thus, two distinct strategies are presented to allow for the synthesis of diverse *syn*- and *anti*-2,5-disubstituted bicyclo[2.1.1]hexanes by either [2 + 2] cycloaddition or C–H functionalization (Fig. 1E).

Results and discussion

To gain access to a wide array of bicyclo[2.1.1]hexane molecular diversity, a crossed [2 + 2]-cycloaddition strategy was pursued (Scheme 1A). Several substrate classes (**3–6**) were examined under both direct excitation as well as sensitized with ITX (*i*-prthioxanthone) as shown in Scheme 1B. It was found that judicious positioning of the substituents and oxidation state was necessary as only substrate **6** under direct irradiation

[a]*Department of Chemistry, Indiana University, 800 E. Kirkwood Ave, Bloomington, IN 47405, USA. E-mail: brownmkb@indiana.edu*

[b]*SpiroChem AG, Rosental Area, WRO-1047-3, Mattenstrasse 22, 4058 Basel, Switzerland*

† Electronic supplementary information (ESI) available. CCDC 2084268. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc02695g

© 2023 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 12 July 2023. Downloaded on 4/27/2024 3:58:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

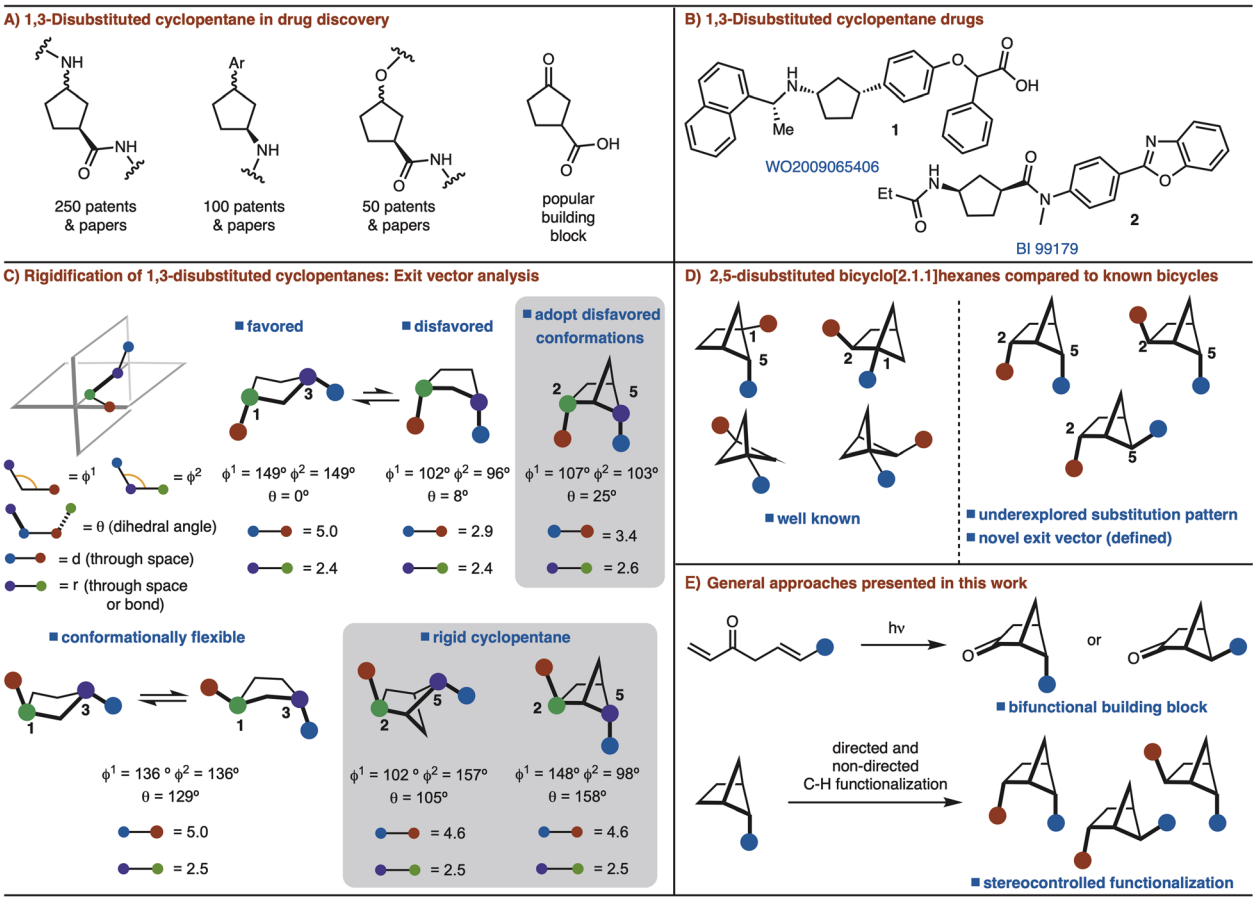
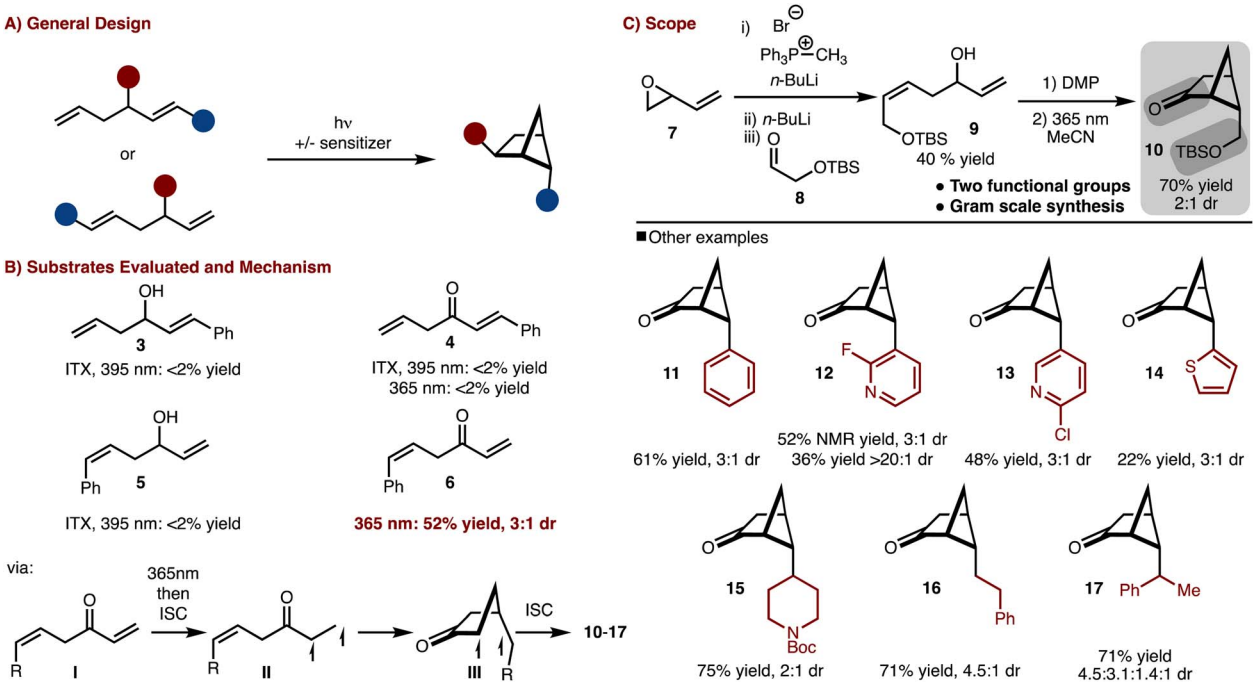


Fig. 1 Bicyclo[2.1.1]hexanes.



Scheme 1 Crossed [2 + 2]-cycloaddition.

Open Access Article. Published on 12 July 2023. Downloaded on 4/27/2024 3:58:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

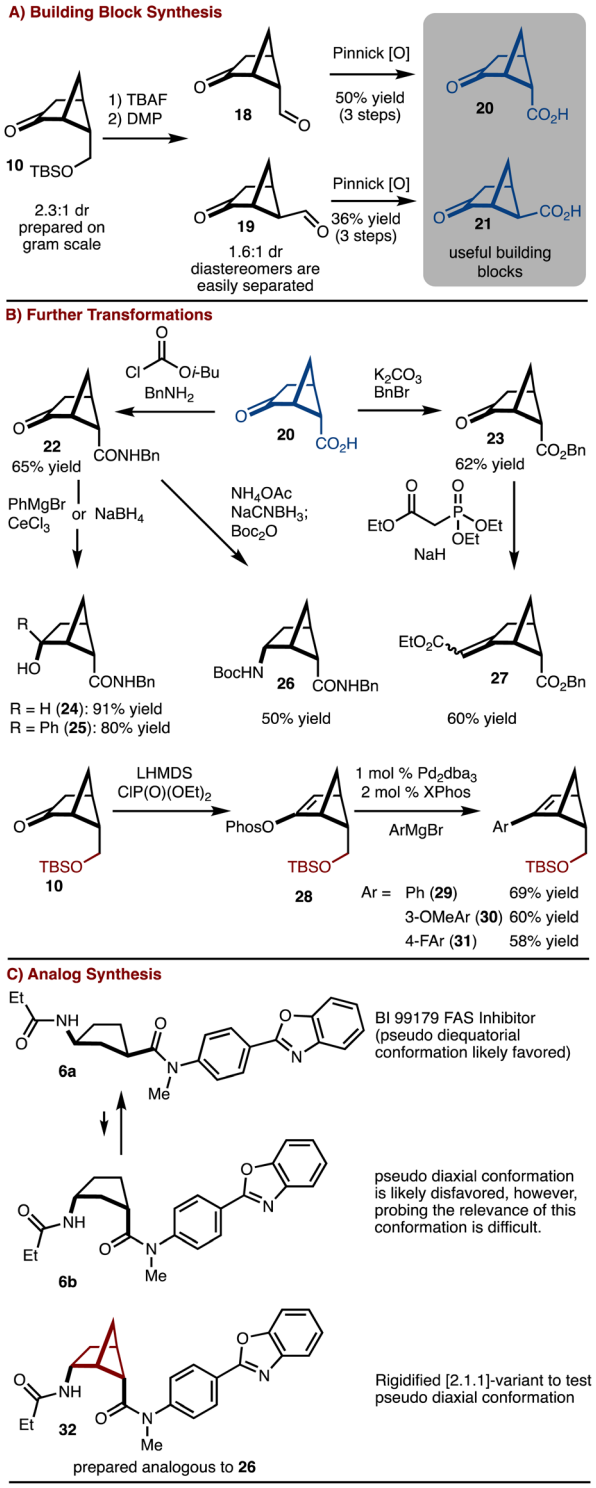
underwent cycloaddition (see the SI† for more details).[9] The reaction likely proceeds *via* excitation of the ketone (**I**) to the S_1 (n–π^*) followed by rapid intersystem crossing (ISC) to the T_1 (π–π^*) (**II**). 1,5-radical addition to the alkene results in the formation of **III**, which upon ISC and radical recombination results in the formation of the products. The observed diastereoselectivity is likely the result of positioning of the R-group away from the bridging methylene hydrogen that projects over the four-membered ring.

With this knowledge in hand the synthesis of bifunctional bicyclo[2.1.1]hexane building block was pursued (Scheme 1C). Allylic/homoallylic alcohol **9** could be readily prepared from butadiene oxide *via* a three-step one pot procedure.[10] Subsequent oxidation with DMP and exposure to 365 nm LEDs allowed for a crossed [2 + 2]-cycloaddition to occur to generate **10** in 70% yield and 2 : 1 dr. Thus in only two steps, bicyclo[2.1.1]hexane **9**, with two functional group handles, could be easily prepared on multi gram scale.[11]

Furthermore, the scope could be expanded to allow for diverse product formation (products **11**–**17**, Scheme 1C). The products were generally formed in ~3 : 1 dr. The approach was tolerant of both aryl (product **11**), heteroaryl (products **12**–**14**) and alkyl substitution (products **15**–**17**). However, in some cases, the heteroaryl starting materials underwent polymerization under the photochemical conditions (*e.g.*, thiophene), which resulted in lower yield.

The silyl ether product **10** was found to be particularly useful as deprotection oxidation led to the formation of readily separable aldehydes **18** and **19** (Scheme 2). Oxidation to the corresponding acids allowed for synthesis of useful building blocks **20** and **21**, which are rigidified variants of the common building block **4**. These keto/acid building blocks could be easily elaborated to various compounds. For example, esterification and olefination results in the formation of **27**. Alternatively, amide bond formation followed by addition of $NaBH_4$ or PhMgBr results in **24** and **25**, respectively. In addition, reductive amination can be carried out to provide **26**. This intermediate can be useful in the construction of rigid peptidomimetics.[12] In all cases involving the ketone, the products were generated as single observable diastereomers by nucleophilic attack from the convex face of the bicyclo[2.1.1]hexane. In addition, bicyclo[2.1.1] hexenes **29**–**31** could be prepared by cross coupling of a generated enol phosphate **28**. It should be emphasized that synthesis of bicyclo[2.1.1]-hexenes is challenging and finds little precedent.[13]

To further underscore the significance of the rigidified building blocks, a case study was explored (Scheme 2C). FAS inhibitor BI 99179 (**6a**) is a *syn*-1,3-substituted cyclopentane.[14] The likely preferred conformation is that in which the two substituents are diequatorial. However, an important question to ask is if the diaxial conformation **6b** is biologically relevant either in an induced fit scenario,[15] or results in off target complications. Probing this hypothesis would be challenging with access to only the parent compound. Here, the bicyclo[2.1.1]hexane variant **32** can be prepared and used to address this question. Future studies will focus on comparative biological studies.

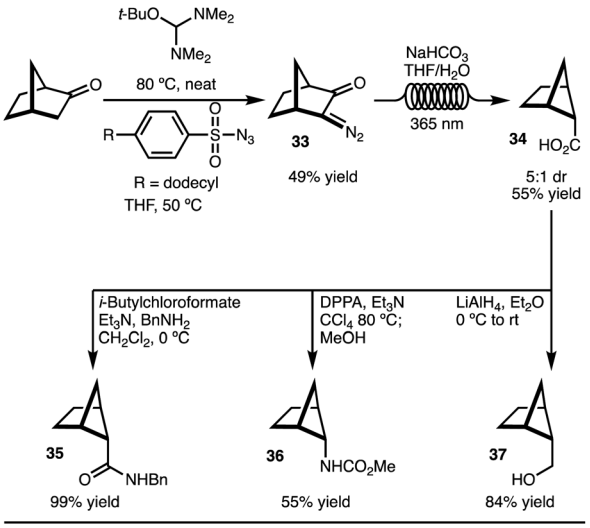


Scheme 2 Building block synthesis and reactions.

To explore the C–H functionalization approach towards 2,5-disubstituted bicyclo[2.1.1]-hexanes, a suitable precursor was needed (Scheme 3). It was envisioned that carboxylic acid **34** could serve as an appropriate starting material. This intermediate was easily prepared on gram scale in 5 : 1 dr from norbornanone by application of a photochemical Wolff rearrangement of diazoketone **33** (Scheme 3).[16] Two key factors were crucial to realize the

© 2023 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 12 July 2023. Downloaded on 4/27/2024 3:58:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

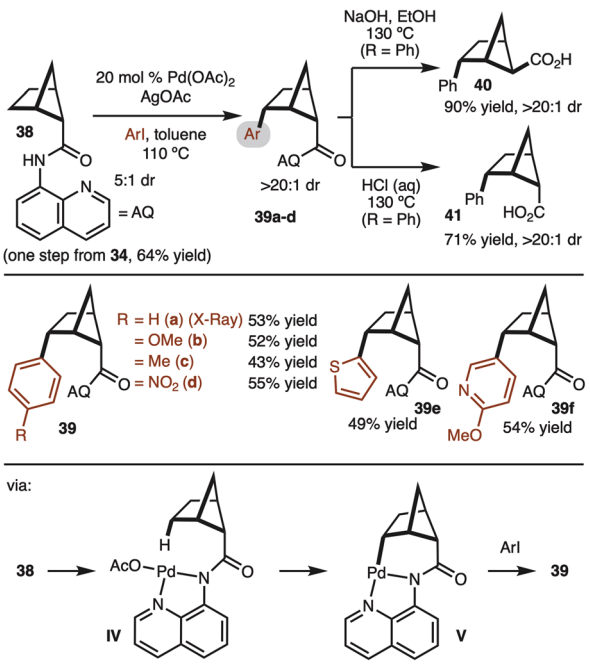


Scheme 3 Synthesis of bicyclo[2.1.1]hexane carboxylic acid.

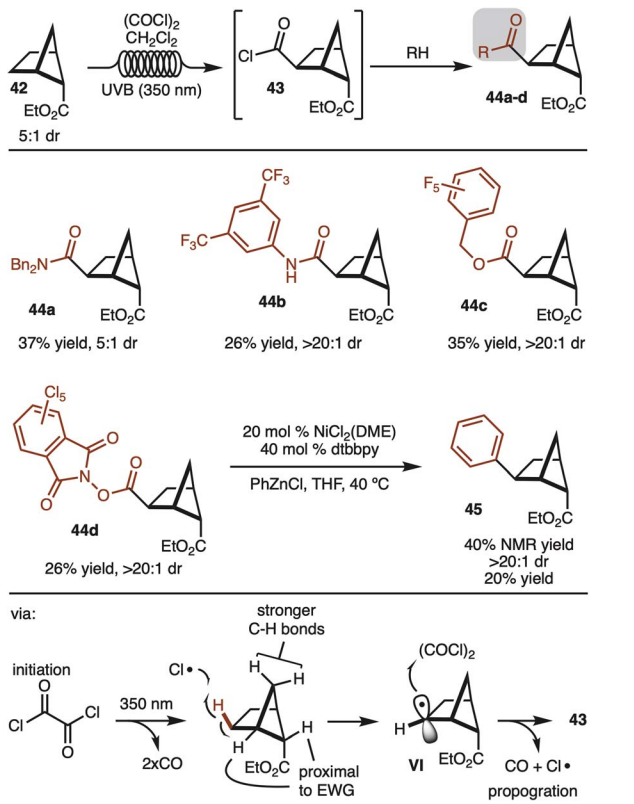
synthesis of gram quantities of product and make this approach a viable synthetic strategy accessible to most chemists: (1) use of commercially available, safe, and inexpensive dodecylbenzenesulfonylazide, and (2) the application of the photochemical Wolff rearrangement in flow. Finally, to demonstrate that the carboxylic acid **34** is a useful building block, the conversion to amide (**35**), carbamate (**36**), and alcohol (**37**) functional groups were easily accomplished. All of these substituents are of high relevance to medicinal chemists.

With access to gram quantities of **34**, C–H functionalization was explored. The first successful strategy is illustrated in Scheme 4. Pioneering work from Daugulis and Yu have demonstrated the utility of the 8-aminoisoquinoline (AQ) for directed Pd-catalyzed C–H functionalization.[17] This system could be used to convert **38** to aryl bicyclo[2.1.1]hexanes with good control of diastereoselectivity (structure **39** confirmed by X-ray). The γ-selectivity of the reaction is likely the result positioning of the Pd-complex in **IV** close the C–H bond. Reaction at the β-site does not occur since the C–H bond is tertiary and orthogonal to the amide. A brief survey of substrates demonstrated tolerance to electron-rich (product **39b**), electron-poor (product **39d**), and heterocyclic aryl iodides (products **39e,f**). Notably, while the starting material was a 5 : 1 mixture of diastereomers, the products were formed in >20 : 1 dr. At this stage it is not clear if the minor diastereomer decomposes or undergoes epimerization under the rection conditions. The relative stereochemistry was determined by X-ray crystallography analysis (Scheme 4). Next, the removal of 8-aminoquinoline was attempted. Under basic hydrolysis conditions, the carboxylic acid undergoes epimerization to deliver thermodynamically favored product **40**. Whereas when the hydrolysis was conducted under acidic conditions, the relative configuration of the acid moiety was retained **41**.[18]

Alternative strategies that do not use directing groups were also explored. It was discovered that irradiation of ester **42** (5 : 1 dr) with UVB (350 nm) in the presence of oxalyl chloride led to formation of acid chloride **43** with complete stereocontrol for the newly formed C–C bond (Scheme 5).[19] The generated acid chloride (**43**) could be intercepted with various alcohols or amines to provide products **44a–d**. While the starting ester was



Scheme 4 Directed C–H arylation.



Scheme 5 C–H carboxylation.

Open Access Article. Published on 12 July 2023. Downloaded on 4/27/2024 3:58:32 PM. This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

a 5 : 1 mixture of diastereomers, the products resulting from the minor diastereomer could generally be separated by simple column chromatography. In addition, redox active ester **44d** could also be generated and subjected to decarboxylative cross coupling to provide access to **45** as a single observable diastereomer.[20] Notably, this route offers a strategy to synthesize the other diastereomer than the one shown in Scheme 4.

The reaction likely proceeds by initial generation of chlorine radical by irradiation of oxalyl chloride by UV light.[19] Chlorine radical then abstracts the indicated hydrogen to generate **VI**. The selectivity in the reaction can be rationalized in that chlorine radical reacts with the weakest C–H bond. The bonds proximal to the ester are deactivated, whereas the methylene CH_2 are stronger by virtue of a strain induced rehybridization.[21] Finally, capture of the secondary radical by oxalyl chloride generates the product and chlorine radical to propagate the chain.

Conclusions

In summary, an approach towards the rigidification of medicinally relevant 1,3-disubstituted cyclopentanes with 2,5-disubstituted bicyclo[2.1.1]hexanes is presented. To prepare the desired structures, two distinct strategies were devised. One involving [2 + 2]-cycloaddition that allowed for the synthesis of keto-acid building blocks. Whereas a C–H functionalization strategy allowed for incorporation of aryl and carboxyl groups with control of stereochemistry. Overall, a diverse range of molecular architectures can be prepared that constitute an enrichment of the toolbox of drug designers and medicinal chemists.

Data availability

The ESI† contains method description, product characterization data, and NMR spectra.

Author contributions

S. P., C. S., T. F., and M. K. B. designed the project. Experiments were carried out by S. P. and D. A. S. P. and M. K. B. co-wrote the manuscript and all authors provided comments.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Indiana University and the NIH (R35GM131755) and SpiroChem AG for financial support. This project was partially funded by the Vice Provost for Research through the Research Equipment Fund and the NSF MRI program, CHE-1726633 and CHE-1920026. Support for the acquisition of the Bruker Venture D8 diffractometer through the Major Scientific Research Equipment Fund from the President of Indiana University and the Office of the Vice President for Research is gratefully acknowledged.

Notes and references

1 (*a*) Z. Fang, Y. Song, P. Zhan, Q. Zhang and X. Liu, *Future Med. Chem.*, 2014, **6**, 885–901; (*b*) C. Borsari, D. Rageot, A. Dall'Asen, T. Bohnacker, A. Melone and A. M. Sele, *J. Med. Chem.*, 2019, **62**, 8609–8630; (*c*) W. Wang, S. Wang, Y. Liu, G. Dong, Y. Cao and Z. Miao, *Eur. J. Med. Chem.*, 2010, **45**, 6020–6026; (*d*) D. Im, H. Moon, J. Kim, Y. Oh, M. Jang and J.-M. Hah, *J. Enzyme Inhib. Med. Chem.*, 2019, **34**, 1716–1721; (*e*) B. Springthorpe, *et al.*, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6013–6018; (*f*) K. Fominova, T. Diachuk, D. Granat, T. Savchuk, V. Vilchynskyi and O. Svitlychnyi, *Chem. Sci.*, 2021, **12**, 11294–11305; (*g*) O. O. Grygorenko, D. M. Volochnyuk and B. V. Vashchenko, *Eur. J. Org. Chem.*, 2021, **2021**, 6478–6510; (*h*) V. I. Savych, V. L. Mykhalchuk, P. V. Melnychuk, A. O. Isakov, T. Savchuk, V. M. Timoshenko, S. A. Siry, S. O. Pavlenko, D. V. Kovalenko, O. V. Hryshchuk, V. A. Reznik, B. A. Chalyk, V. S. Yarmolchuk, E. B. Rusanov and P. K. Mykhailiuk, *J. Org. Chem.*, 2021, **86**, 13289–13309; (*i*) J. Zhou, E. L. Campbell-Conroy, A. Silina, J. Uy, F. Pierre, D. J. Hurley, N. Hilgraf, B.-A. Frieman and M. P. DeNinno, *J. Org. Chem.*, 2015, **80**, 70–79; (*j*) D. Dibchak, V. Shcherbacova, A. V. Denisenko and P. K. Mykhailiuk, *Org. Lett.*, 2019, **22**, 8909–8914; (*k*) Exit vector analysisO. O. Grygorenko, P. Babenko, D. M. Volochnyuk, O. Raievskyi and I. V. Komarov, *RSC Adv.*, 2016, **6**, 17595–17605.

2 (*a*) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, *ChemMedChem*, 2022, **17**, e202200020; (*b*) T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712–8756.

3 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.

4 More than 100 patents uses this compound as reactant. For example(*a*) R. Jiao, S. D. Goble, S. G. Mills, G. Morriello, A. Pasternak, L. Yang, C. Zhou, G. Butora, S. Kothandaraman, D. Guiadeen and C. Moyes, WO2003093231, 2003; (*b*) S. G. Dann, M. Goodman, L. Nichol and T. L. Vanarsdale, WO2022018596, 2022; (*c*) P. Kocis, M. Tolar and J. Hey, WO2017027582, 2017; (*d*) D. Sun, Y. Yang, Y. Zheng, Y. Zhang and Y. Qu, CN104327076, 2015; (*e*) Y. Zhang, A. Kubota, N. M. Niyaz, T. Barton, T. K. Trullinger, C. T. Lowe, P. R. Leplae, A. M. Buysse, M. J. Walsh, N. Garizi, R. Hunter and D. Knueppel, *US Pat.*, 20150111734, 2015.

5 (*a*) A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **17**, 20515–22052; (*b*) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc and F. Glorius, *Nature*, 2022, **605**, 477–482; (*c*) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. E. M. Crisenza and D. J. Procter, *Nat. Chem.*, 2023, **15**, 535–541; (*d*) M. Shen, Y. Tu, G. Xie, Q. Niu, H. Mao, T. Xie, R. A. Flowers, X. Lv and X. Wang, *J. Org. Chem.*, 2015, **80**, 52–61; (*e*) L. Herter,

© 2023 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 12 July 2023. Downloaded on 4/27/2024 3:58:32 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

I. Koutsopetras, L. Turelli, T. Fessard and C. Salomé, *Org. Biomol. Chem.*, 2022, **20**, 9108–9111.

6 R. Guo, Y.-C. Chang, L. Herter, C. Salome, S. E. Braley, T. C. Fessard and M. K. Brown, *J. Am. Chem. Soc.*, 2022, **144**, 7988–7994.

7 (*a*) J. Meinwald and J. K. Crandall, *J. Am. Chem. Soc.*, 1966, **88**(6), 1292–1301; (*b*) T. W. Gibson and W. F. Erman, *J. Org. Chem.*, 1972, **37**, 1148–1154; (*c*) P. Conti and A. P. Kozikowski, *Tetrahedron Lett.*, 2000, **41**, 4053–4056.

8 W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976–1991.

9 For substrates **3** and **5**, sensitization of the alkeneyl arene unit was attemptedR. C. Epplin, S. Paul, L. Herter, C. Salome, E. N. Hancock, J. F. Larrow, E. W. Baum, D. R. Dunstan, C. Ginsburg-Moraff, T. C. Fessard and M. K. Brown, *Nat. Commun.*, 2022, **13**, 6056.

10 E. J. Enholm, H. Satici and G. Prasad, *J. Org. Chem.*, 1990, **55**, 324–329.

11 (*a*) Same as (7a).; (*b*) S. Wolff and W. C. Agosta, *J. Am. Chem. Soc.*, 1983, **105**, 1292–1299; (*c*) W. G. Dauben, J. M. Cogen, G. A. Ganzer and V. Behar, *J. Am. Chem. Soc.*, 1991, **113**, 5817–6582.

12 I. V. Komarov, A. O. Grigorenko, A. V. Turov and V. P. Khilya, *Russ. Chem. Rev.*, 2004, **8**, 785–810.

13 K. B. Wiberg and R. W. Ubersax, *J. Org. Chem.*, 1972, **37**, 3827–3834.

14 J. T. Kley, J. Mack, B. Hamilton, S. Scheuerer and N. Redemann, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5924–6592.

15 (*a*) E. Chiarparin, M. J. Packer and D. M. Wilson, *Future Med. Chem.*, 2019, **11**, 79–82; (*b*) H. Finch, *Drug Discov.*, 2014, **19**, 320–325; (*c*) D. D. Boehr, R. Nussinov and P. E. Wright, *Nat. Chem. Biol.*, 2009, **5**, 789–796.

16 K. B. Wiberg, B. R. Lowry and T. H. Colby, *J. Am. Chem. Soc.*, 1961, **83**, 3998–44007(a) (b) 7(b) (b).

17 (*a*) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169.

18 D. P. Affron and J. A. Bull, *Eur. J. Org. Chem.*, 2016, **2016**, 139–149.

19 (*a*) D. E. Collin, K. Kovacic, M. E. Light and B. Linclau, *Org. Lett.*, 2021, **23**, 5164–5169; (*b*) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, 1942, **64**, 329–333.

20 F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer and P. S. Baran, *Angew. Chem., Int. Ed.*, 2017, **56**, 3319–3323.

21 Z. Tian, A. Fattahi, L. Lis and S. R. Kass, *J. Am. Chem. Soc.*, 2006, **128**, 17087–17092.

© 2023 The Author(s). Published by the Royal Society of Chemistry