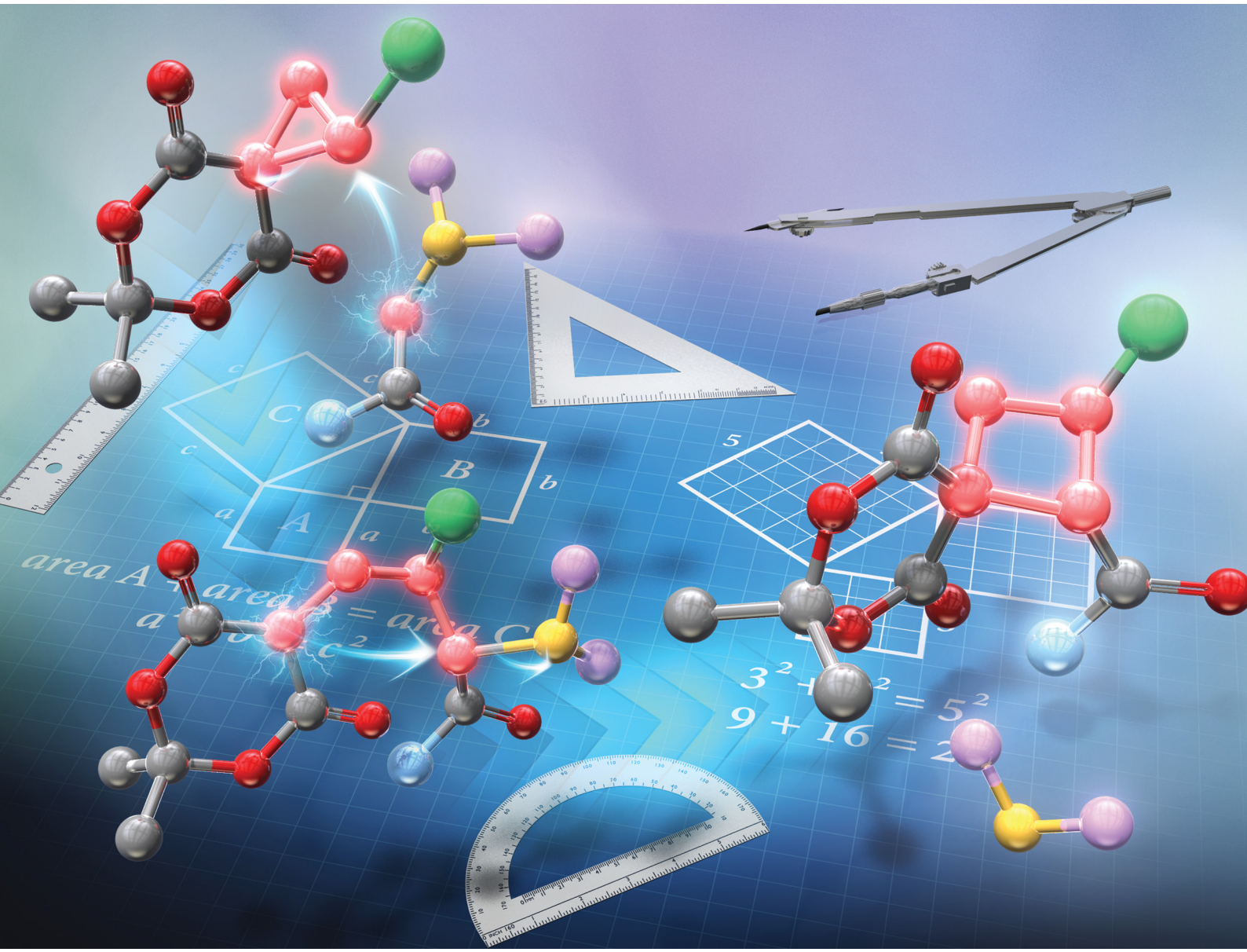
Volume 60
Number 34
30 April 2024
Pages 4501–4622

ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

Hisanori Nambu, Takayuki Yakura *et al.*

Ring expansion of spirocyclopropanes with stabilized sulfonium ylides: highly diastereoselective synthesis of cyclobutanes

60 YEARS ANNIVERSARY

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 4537

Received 11th December 2023,
Accepted 7th March 2024

DOI: 10.1039/d3cc06033k

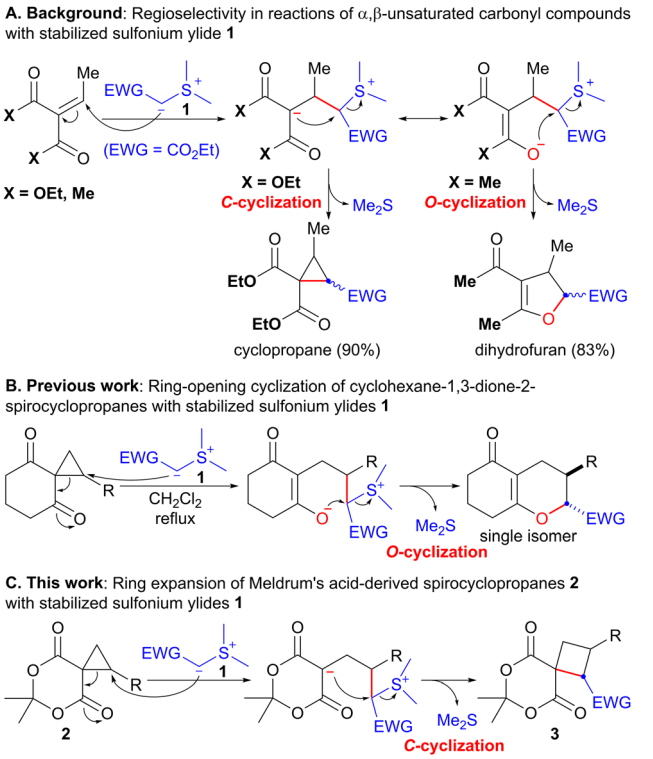
rsc.li/chemcomm

Ring expansion of spirocyclopropanes with stabilized sulfonium ylides: highly diastereoselective synthesis of cyclobutanes†

Hisanori Nambu, *[ab] Yuta Onuki,[a] Kana Aso,[a] Momoka Kanamori,[a] Keisuke Tomohara,[b] Kiyoshi Tsuge[c] and Takayuki Yakura*[a]

A novel method was devised for regioselective ring expansion of Meldrum's acid-derived spirocyclopropanes to spirocyclobutanes with stabilized sulfonium ylides, affording 1,2-*trans*-disubstituted 6,8-dioxaspiro[3.5]nonane-5,9-diones in up to 87% yields without the formation of any isomers. The aforementioned reaction was also applied to the barbituric acid-derived spirocyclopropane, resulting in the formation of the corresponding cyclobutanes.

Sulfonium ylides stabilized by electron-withdrawing groups (EWG) have been used as a versatile methylene synthon in the synthesis of a variety of carbo- and heterocyclic compounds.[1,2] As a pioneering work, Payne reported that the reaction of α,β-unsaturated diethylmalonate with EWG-stabilized sulfonium ylide **1** (EWG = CO_2Et) afforded cyclopropane in 90% yield (Scheme 1A).[3] In this reaction, the Michael addition of **1** followed by S_N2-type cyclization of the carbanion (*C*-cyclization) proceeded with the concomitant release of the sulfide. In contrast, the reaction of the corresponding 1,3-diketone with stabilized sulfonium ylide **1** unexpectedly produced dihydrofuran in 83% yield through enolate cyclization (*O*-cyclization, Scheme 1A).[3] The regioselectivity of these reactions may be attributed to the inherent difference between esters and ketones. Recently, we reported the ring-opening cyclization of spirocyclopropanes[4] with EWG-stabilized sulfonium ylides **1** to afford hexahydrobenzopyranone as a single isomer *via* the regioselective ring-opening of cyclopropane with sulfonium ylide **1** and subsequent S_N2-type *O*-cyclization (Scheme 1B, eqn (1)).[4f] Considering the similar reactivity of cyclopropane and carbon–carbon double bonds, we expected that the reaction of ester-derived spirocyclopropane **2** with stabilized sulfonium ylide **1** would provide spirocyclobutane **3** through *C*-cyclization (Scheme 1C). Because cyclobutane is a useful scaffold found in several biologically active natural products and pharmaceutically active compounds,[5] the development of a synthetic method for cyclobutane is currently the subject of intense research.[6] Although several instances of



Scheme 1 Reactions of various carbonyl compounds with stabilized sulfonium ylides **1** as nucleophiles.

[a] *Faculty of Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan. E-mail: yakura@pha.u-toyama.ac.jp*
[b] *Laboratory of Pharmaceutical Manufacturing Chemistry, Kyoto Pharmaceutical University, Kyoto 607-8412, Japan. E-mail: hnambu@mb.kyoto-phu.ac.jp*
[c] *Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan*

† Electronic supplementary information (ESI) available: General procedures, analytical data, and NMR spectra (PDF). CCDC 2312076 (**3a**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc06033k

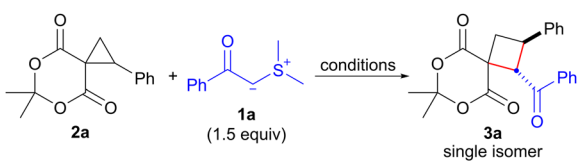
cyclopropane to cyclobutane ring expansion have been documented thus far,[7,8] to the best of our knowledge, there have been no examples of sulfonium ylide-mediated ring expansion (*C*-cyclization).[9] Herein, we describe the ring expansion of Meldrum's acid-derived spirocyclopropanes **2** to spirocyclobutanes **3** using EWG-stabilized sulfonium ylides **1** (Scheme 1C).

Initially, we examined the reaction of 6,6-dimethyl-1-phenyl-5,7-dioxaspiro[2.5]octane-4,8-dione (**2a**)[10] with dimethylsulfonium benzoylmethylide (**1a**) as an EWG-stabilized sulfonium ylide (Table 1). The ring expansion of **1a** proceeded under the reaction conditions previously reported by our group (1.5 equiv. of **1a** in refluxing CH_2Cl_2),[4f] affording 1-benzoyl-7,7-dimethyl-2-phenyl-6,8-dioxaspiro[3.5]nonane-5,9-dione (**3a**) after 24 h in 75% yield (entry 1). Notably, no isomer formation was observed during this process. The structure of **3a** including its stereochemistry was confirmed by a single-crystal X-ray diffraction analysis. This analysis revealed that the structure corresponds to that of cyclobutane with a 1,2-*trans* configuration (see ESI† for details). Screening of the solvents at reflux revealed that benzene and halogenated solvents, such as dichloromethane and 1,2-dichloroethane, were suitable for this reaction (entry 1 *vs.* entries 2–5). Finally, we found that chlorobenzene at 80 °C was the most effective and afforded **3a** in 86% yield after 6 h (entry 6).

After determining the optimal conditions, we investigated the reaction of spirocyclopropane **2a** using a range of sulfonium ylides **1** that are stabilized by carbonyl functional groups (Table 2). The reaction with 1.5 equiv. of *p*-methoxybenzoyl sulfonium ylide **1b** in chlorobenzene at 80 °C afforded the corresponding spirocyclobutane **3b** as the sole product after 6 h in 74% yield (entry 2). The use of *m*- and *o*-methoxybenzoyl sulfonium ylides **1c**[11] and **1d**[12] provided the corresponding products **3c** and **3d** in 86% and 87% yields, respectively (entries 3 and 4). The reaction with sulfonium ylide **1e** bearing a *p*-nitro group as a strong EWG decreased the product yield, and a significantly longer reaction time was required to achieve full conversion (61% yield, 24 h, entry 5 *vs.* entry 1). In contrast, the reaction with *p*-chlorobenzoyl sulfonium ylide **1f** under the optimized conditions proceeded smoothly to completion within 5 h, furnishing **3f** in 83% yield (entry 6). We also investigated the suitability of an acetyl sulfonium ylide for this reaction. To this end, we used tetrahydrothiophenium acetylmethylide (**1g**) because of the difficulty in preparing dimethylsulfonium acetylmethylide. The reaction of **2a** with **1g** afforded the desired product **3g** as a single isomer, albeit with a prolonged reaction time and lower yield (24 h, 36% yield, entry 7 *vs.* entry 1). Moreover, ethoxycarbonyl group-substituted sulfonium ylide **1h** was used in the present protocol, and the corresponding cyclobutane **3h** was obtained in 53% yield after 23 h (entry 8).

Next, we examined the scope of the reaction with the spirocyclopropane substrates **2** using benzoyl-substituted sulfonium ylide **1a** (Table 3). Treatment of spirocyclopropanes **2b**, **2c** and **2d**, which possess *p*-acetoxy-, *p*-methyl-, and *p*-bromophenyl groups on the cyclopropane, respectively, with **1a** under the optimized conditions (chlorobenzene at 80 °C), afforded the corresponding products **3i**, **3j**, and **3k** in 64%–80% yields with perfect diastereoselectivities (entries 1–3). The

Table 1 Ring expansion of spirocyclopropane **2a** with sulfonium ylide **1a**

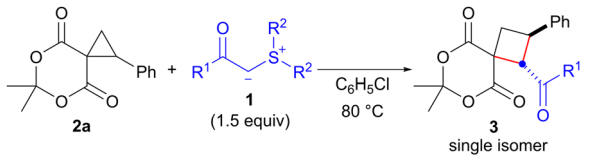


2a **1a** (1.5 equiv) **3a** single isomer

Entry	Solvent	Temp.	Time (h)	Yield[a] (%)
1	CH_2Cl_2	Reflux	24	75
2	EtOAc	Reflux	4.5	60
3	Benzene	Reflux	5	74
4	CH_3CN	Reflux	24	59
5	$ClCH_2CH_2Cl$	Reflux	7	75
6	C_6H_5Cl	80 °C	6	86

[a] Isolated yield.

Table 2 Ring expansion of spirocyclopropane **2a** with sulfonium ylides **1a–h**

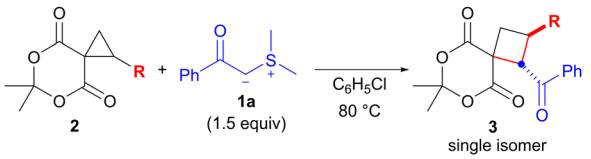


2a **1** (1.5 equiv) **3** single isomer

	Sulfonium ylide			Product	
Entry		R^1	R^2	Time (h)	Yield[a] (%)
1	**1a**	C_6H_5	Me	6	**3a** 86
2	**1b**	*p*-$MeOC_6H_4$	Me	6	**3b** 74
3	**1c**	*m*-$MeOC_6H_4$	Me	6	**3c** 86
4	**1d**	*o*-$MeOC_6H_4$	Me	6	**3d** 87
5	**1e**	*p*-$NO_2C_6H_4$	Me	24	**3e** 61
6	**1f**	*p*-ClC_6H_4	Me	5	**3f** 83
7	**1g**	Me	$-(CH_2)_4-$	24	**3g** 36
8	**1h**	EtO	Me	23	**3h** 53

[a] Isolated yield.

Table 3 Ring expansion of spirocyclopropanes **2b–h** with sulfonium ylides **1a**



2 **1a** (1.5 equiv) **3** single isomer

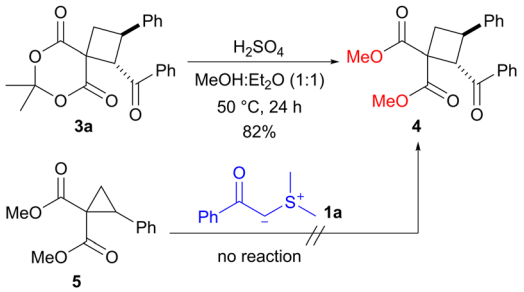
	Spirocyclopropane			Product	
Entry		R	Time (h)		Yield[a] (%)
1	**2b**	*p*-$AcOC_6H_4$	3	**3i**	64
2	**2c**	*p*-MeC_6H_4	6	**3j**	74
3	**2d**	*p*-BrC_6H_4	6	**3k**	80
4	**2e**	*m*-$MeOC_6H_4$	12	**3l**	69
5	**2f**	2-naphthyl	48	**3m**	80
6	**2g**	Vinyl	24	**3n**	68
7	**2h**	H	24	**3o**	26

[a] Isolated yield.

reaction of *m*-methoxyphenyl-substituted spirocyclopropane **2e** for 12 h provided cyclobutane **3l** in 69% yield (entry 4). Although spirocyclopropane **2f**, which possesses a 2-naphthyl group, required a relatively long reaction time (48 h), **3m** was obtained in a good yield (80%, entry 5). There was a concern that the use of vinyl-substituted spirocyclopropane **2g** would compete with the conjugate addition, but the reaction of **2g** proceeded uneventfully and afforded the desired product **3n** in 68% yield (entry 6). Finally, the reaction of the simple spirocyclopropane **2h** (R = H)[13] was investigated (entry 7). A 2′,3′-nonsubstituted spirocyclopropane was found to be less reactive than an aryl-substituted one,[4e] which resulted in a lower yield of product **3o** (26% yield).

A plausible mechanism for the ring expansion of spirocyclopropane **2** with sulfonium ylide **1**, stabilized by an acyl group, is shown in Scheme 2. The ring opening of spirocyclopropane **2** would proceed through the nucleophilic attack of the carbanion in **1** on the electrophilic cyclopropane carbon possessing an R^1 substituent in **A**. This reaction would lead to the formation of betaine intermediates **B** and **C**. S_N2-type *C*-cyclization of the carbanion in **B** would occur smoothly to afford *trans*-product **3** with the concomitant release of dimethyl sulfide. In contrast, the *C*-cyclization of **C** would hardly proceed owing to the severe steric repulsion between the acyl group (R^2CO) and substituent R^1 in **C**. Consequently, intermediate **C** could be converted into cyclization precursor **B** through reversible intramolecular proton transfer *via* the stabilized sulfonium ylide **D**,[14,15] finally providing *trans*-isomer **3**.

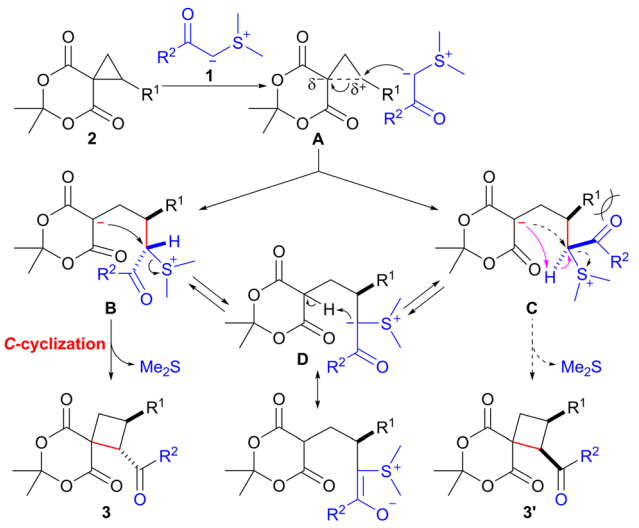
To demonstrate the utility of the present protocol, we examined the conversion of spirocyclobutane **3a** into highly substituted non-spiro cyclobutane **4** (Scheme 3). The treatment of **3a** with sulfuric acid in methanol/diethyl ether (1 : 1) at 50 °C led to a transesterification process, resulting in the formation of dimethyl ester. The reaction yielded the corresponding cyclobutane **4** in 82% yield. Since the reaction of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**5**) with sulfonium ylide **1a** did not proceed,[4f,16] spiro form **3a** was required for the synthesis of diester **4**. This ring-expansion reaction of spirocyclopropanes could be a useful method for the preparation of substituted cyclobutanes.



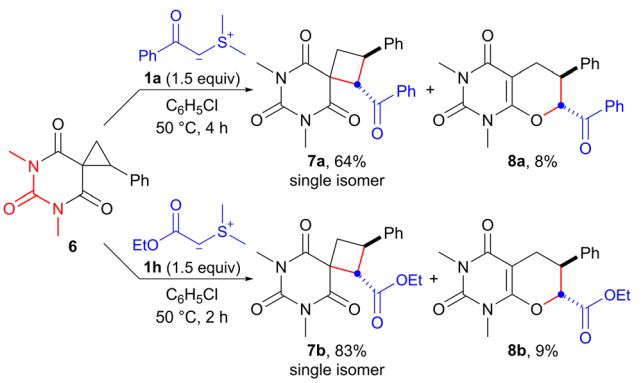
Scheme 3 Conversion of spirocyclobutane **3a** into cyclobutane **4**.

Having achieved ring expansion of ester-derived spirocyclopropanes, we further investigated the reaction of an amide-derived spirocyclopropane with an EWG-stabilized sulfonium ylide. The reaction of spirocyclopropane **6**,[17] derived from barbituric acid, with sulfonium ylides **1a** and **1h** in chlorobenzene proceeded smoothly at 50 °C to provide the corresponding spirocyclobutanes **7a** and **7b** in 64% and 83% yields, respectively (Scheme 4). Interestingly, unexpected products **8a** and **8b**, which indicated that S_N2-type *O*-cyclization of the enolate ion instead of the carbanion would occur, were also obtained in 8% and 9% yields, respectively. Although the results are still preliminary, the reaction of barbituric acid-derived spirocyclopropane with sulfonium ylide exhibits promise as a synthetic method of spirobarbiturate cyclobutane analogs. These compounds have potential as pharmaceutical agents.[18]

In conclusion, we devised a novel method for regioselective ring expansion of cyclopropanes to cyclobutanes using stabilized sulfonium ylides. Meldrum's acid-derived spirocyclobutanes with EWG-stabilized sulfonium ylides afforded the corresponding spirocyclobutanes as single diastereomers in yields of up to 87%. The present reaction provides an efficient route to highly substituted cyclobutanes. To the best of our knowledge, this is the first example of a ring expansion of cyclopropanes with sulfonium ylides. This reaction may be envisaged as a



Scheme 2 Plausible reaction mechanism.



Scheme 4 Ring expansion of barbituric acid-derived spirocyclopropane **6** with sulfonium ylides **1a** and **1h**.

formal [3+1] cycloaddition, facilitating the construction of the four-membered ring system.[19] The expansion reaction could be applied to the transformation of barbituric acid-derived spirocyclopropane into the corresponding spirocyclobutane. Ongoing efforts are being made to apply the present method to the synthesis of a variety of cyclobutane derivatives.

This research was supported, in part, by a Grant-in-Aid for Scientific Research (C) (Grant No. 21K05048) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and by a Grant from Hoansha Foundation (Osaka, Japan).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For recent reviews, see: (*a*) D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, 2019, **119**, 8701–8780; (*b*) G. D. Bisag, S. Ruggieri, M. Fochi and L. Bernardi, *Org. Biomol. Chem.*, 2020, **18**, 8793–8809; (*c*) P. Y. Ushakov, S. L. Ioffe and A. Y. Sukhorukov, *Org. Chem. Front.*, 2022, **9**, 5358–5382.

2 For recent examples, see: (*a*) C. Wang, L. Fang, L. Zhang, Y. Wang, F. Gao and Z. Wang, *Org. Chem. Front.*, 2022, **9**, 2204–2208; (*b*) X. Wang, J. Yu, M. Xu, H. Mao, Y. Shan, X. Lv and L. Zhou, *Org. Lett.*, 2022, **24**, 5896–5901; (*c*) W. Yu, C.-H. Tung and Z. Xu, *Adv. Synth. Catal.*, 2022, **364**, 3749–3753; (*d*) J. Yu, X. Wang, M. Xu, B. Zhang, Z. Xiong, H. Mao, X. Lv and L. Zhou, *Org. Chem. Front.*, 2023, **10**, 916–922; (*e*) M. Xu, M. You, Y. Su, B. R. Lu, L. Liu, X. Lv, S. Wang, H. Mao and L. Zhou, *Org. Chem. Front.*, 2023, **10**, 1521–1526.

3 G. B. Payne, *J. Org. Chem.*, 1967, **32**, 3351–3355.

4 (*a*) H. Nambu, M. Fukumoto, W. Hirota and T. Yakura, *Org. Lett.*, 2014, **16**, 4012–4015; (*b*) H. Nambu, M. Fukumoto, W. Hirota, N. Ono and T. Yakura, *Tetrahedron Lett.*, 2015, **56**, 4312–4315; (*c*) H. Nambu, N. Ono and T. Yakura, *Synthesis*, 2016, 1892–1901; (*d*) H. Nambu, W. Hirota, M. Fukumoto, T. Tamura and T. Yakura, *Chem. – Eur. J.*, 2017, **23**, 16799–16805; (*e*) H. Nambu, Y. Onuki, N. Ono and T. Yakura, *Adv. Synth. Catal.*, 2018, **360**, 2938–2944; (*f*) H. Nambu, Y. Onuki, N. Ono, K. Tsuge and T. Yakura, *Chem. Commun.*, 2019, **55**, 6539–6542; (*g*) H. Nambu, T. Tamura and T. Yakura, *J. Org. Chem.*, 2019, **84**, 15990–15996; (*h*) Y. Onuki, H. Nambu and T. Yakura, *Chem. Pharm. Bull.*, 2020, **68**, 479–486; (*i*) H. Nambu, Y. Onuki, K. Yamazaki and T. Yakura, *Heterocycles*, 2021, **103**, 1099–1107; (*j*) Y. Onuki, K. Yamazaki, N. Ono, Y. Masuda, T. Yakura and H. Nambu, *Adv. Synth. Catal.*, 2023, **365**, 2536–2544.

5 (*a*) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559–1581; (*b*) M. R. Bauer, P. D. Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer and B. C. Whitehurst, *RSC Med. Chem.*, 2021, **12**, 448–471; (*c*) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and S. Blanco-Ania, *ChemMedChem*, 2022, **17**, e202200020; (*d*) P. Yang, Q. Jia, S. Song and X. Huang, *Nat. Prod. Rep.*, 2023, **40**, 1094–1129.

6 For selected reviews, see: (*a*) E. M. Carreira and T. C. Fessard, *Chem. Rev.*, 2014, **114**, 8257–8322; (*b*) S. Poplata, A. Tröster, Y.-Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**, 9748–9815; (*c*) J. Li, K. Gao, M. Bian and H. Ding, *Org. Chem. Front.*, 2020, **7**, 136–154; (*d*) D. Sarkar, N. Bera and S. Ghosh, *Eur. J. Org. Chem.*, 2020, 1310–1326; (*e*) J. Großkopf, T. Kratz, T. Rigotti and T. Bach, *Chem. Rev.*, 2022, **122**, 1626–1653; (*f*) R. Guo and M. K. Brown, *Acc. Chem. Res.*, 2023, **56**, 2253–2264.

7 For selected reviews, see: (*a*) D. J. Mack and J. T. Njardarson, *ACS Catal.*, 2013, **3**, 272–286; (*b*) V. Pirenne, B. Muriel and J. Waser, *Chem. Rev.*, 2021, **121**, 227–263; (*c*) B. Biletskyi, P. Colonna, K. Masson, J.-L. Parrain, L. Commeiras and G. Chouraqui, *Chem. Soc. Rev.*, 2021, **50**, 7513–7538.

8 For selected examples, see: (*a*) H. Nemoto, H. Ishibashi, M. Nagamochi and K. Fukumoto, *J. Org. Chem.*, 1992, **57**, 1707–1712; (*b*) B. M. Trost and T. Yasukata, *J. Am. Chem. Soc.*, 2001, **123**, 7162–7163; (*c*) F. Kleinbeck and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 9178–9179; (*d*) Z. Wu, D. Leboeuf, P. Retailleau, V. Gandon, A. Marinetti and A. Voituriez, *Chem. Commun.*, 2017, **53**, 7026–7029; (*e*) C.-G. Zhao, Z.-T. Feng, G.-Q. Xu, A. Gao, J.-W. Chen, Z.-Y. Wang and P.-F. Xu, *Angew. Chem., Int. Ed.*, 2020, **59**, 3058–3062; (*f*) D. P. Hari, J. C. Abell, V. Fasano and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2020, **142**, 5515–5520; (*g*) W. Ouyang, J. Huo and J. Wang, *Synlett*, 2023, 1507–1511; (*h*) M. Takatsuki, H. Aoyama, K. Murai, M. Arisawa and M. Sako, *Chem. Commun.*, 2023, **59**, 7467–7470.

9 Chen and co-workers reported the ring expansion reaction of electron-deficient cyclopropanes with arsonium ylides. Y.-L. Chen, W.-G. Cao, W.-Y. Ding and X.-H. Sun, *Chin. J. Chem.*, 2005, **23**, 81–84.

10 Y. R. Lee and J. H. Choi, *Bull. Korean Chem. Soc.*, 2006, **27**, 503–507.

11 S. J. Sabounchei, A. Yousefi, M. Ahmadianpoor, A. Hashemi, M. Bayat, A. Sedghi, F. A. Bagherjeri and R. W. Gable, *Polyhedron*, 2016, **117**, 273–282.

12 S. K. Pagire, N. Kumagai and M. Shibasaki, *ACS Catal.*, 2021, **11**, 11597–11606.

13 H. Nambu, N. Ono, W. Hirota, M. Fukumoto and T. Yakura, *Chem. Pharm. Bull.*, 2016, **64**, 1763–1768.

14 Aggarwal and co-workers reported that a similar proton transfer event could intervene in sulfonium ylide-mediated cyclopropanations under certain conditions. S. L. Riches, C. Saha, N. F. Filgueira, E. Grange, E. M. McGarrigle and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 7626–7630.

15 Crudden and co-workers also reported the deprotonation and reprotonation on the carbon atom of an α-hydroxy sulfonium ylide in the Corey–Chaykovsky epoxidation. D. R. Edwards, J. Du and C. M. Crudden, *Org. Lett.*, 2007, **9**, 2397–2400.

16 The spiro structure is crucial for the success of this ring expansion. (*a*) S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, 1975, **97**, 3239–3241; (*b*) P. M. Jüstel, A. Stan, C. D. Pignot and A. R. Ofial, *Chem. – Eur. J.*, 2021, **27**, 15928–15935.

17 (*a*) X. Wang and Y. R. Lee, *Bull. Korean Chem. Soc.*, 2013, **34**, 1735–1740; (*b*) P. Qian, B. Du, R. Song, X. Wu, H. Mei, J. Han and Y. Pan, *J. Org. Chem.*, 2016, **81**, 6546–6553.

18 For a review, see: A. Bagherinejad and A. Alizadeh, *Org. Biomol. Chem.*, 2022, **20**, 7188–7215.

19 Doyle and co-workers reported catalytic asymmetric [3+1]-cycloaddition with sulfonium ylides. Y. Deng, L. A. Massey, P. Y. Zavalij and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2019, **58**, 1955–1959.

