ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 2657

Received 26th November 2020,
Accepted 3rd February 2021

DOI: 10.1039/d0cc07745c

rsc.li/chemcomm

The reaction of prop-2-ynylsulfonium salts and sulfonyl-protected β-amino ketones to epoxide-fused 2-methylenepyrrolidines and S-containing pyrroles†

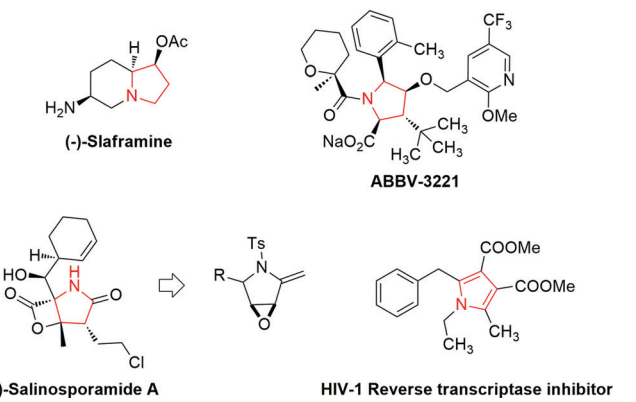
Tingting Jia,[ab] Gongruixue Zeng,[a] Chong Zhang,[a] Linghui Zeng,[a] Wenya Zheng,[a] Siyao Li,[a] Keyi Wu,[a] Jiaan Shao,*[ab] Jiankang Zhang*[ab] and Huajian Zhu *[ab]

A novel divergent domino annulation reaction of prop-2-ynylsulfonium salts with sulfonyl-protected β-amino ketones has been developed, affording various epoxide-fused 2-methylenepyrrolidines and S-containing pyrroles in moderate to excellent yields. Prop-2-ynylsulfonium salts act as C_2 synthons in the reactions providing a promising epoxide-fused skeleton in a single operation with readily accessible starting materials.

Five-membered nitrogenated heterocycles, pyrrolidines and pyrroles, are privileged structures for a large number of natural products and biologically active molecules (Scheme 1).[1,2] Epoxide-fused 2-methylenepyrrolidine, in particular, is a promising skeletal structure which is potentially useful for the rapid construction of densely substituted pyrrolidines and pyrrolidinones for use in natural product synthesis.[3] To the best of our knowledge, only Borhan's group have reported a strategy enabling construction of an epoxide-fused 2-methylenepyrrolidine unit *via* a one-pot tandem aza-Payne/hydroamination reaction.[4] Thus, development of a novel strategy for the construction of these epoxide-fused 2-methylenepyrrolidines would enable facile access to a relatively underexplored chemical space.

Propargyl sulfur ylide, which can be easily obtained by the reaction of propargyl bromide and dimethyl sulfide, that can be readily transformed into an allenic sulfonium salt.[5] According to previous reports, it can be viewed as a C_1 synthon and reacts with 2-(1*H*-indol-2-yl)phenols[6] and sulfonyl-protected *o*-amino aromatic aldimines[7] to afford indole-fused 4*H*-benzo[*e*][1,3]oxazines and hexahydropyrrolo[3,2-*b*]indoles, respectively (Scheme 2a). Beyond the application of C_1 synthons, Huang's group has also made great advances using propargyl sulfur ylides as C_2 synthons.[8] According to their research, propargyl sulfur ylides can transform into allenic sulfonium salts and be attacked by a nucleophile at the β-carbon atom, providing a zwitterionic intermediate, which can further go through intramolecular annulation to obtain complex heterocyclic products (Scheme 2b). On the basis of the proposed working model of prop-2-ynylsulfonium salts as C_2 synthons, we are eager to find a versatile synthon that can react with propargyl sulfur ylides to provide valuable chemical entities. Here we report a novel divergent domino annulation reaction of prop-2-ynylsulfonium salts with sulfonyl-protected β-amino ketones,[9] providing facile access to epoxide-fused 2-methylenepyrrolidines and S-containing pyrroles.

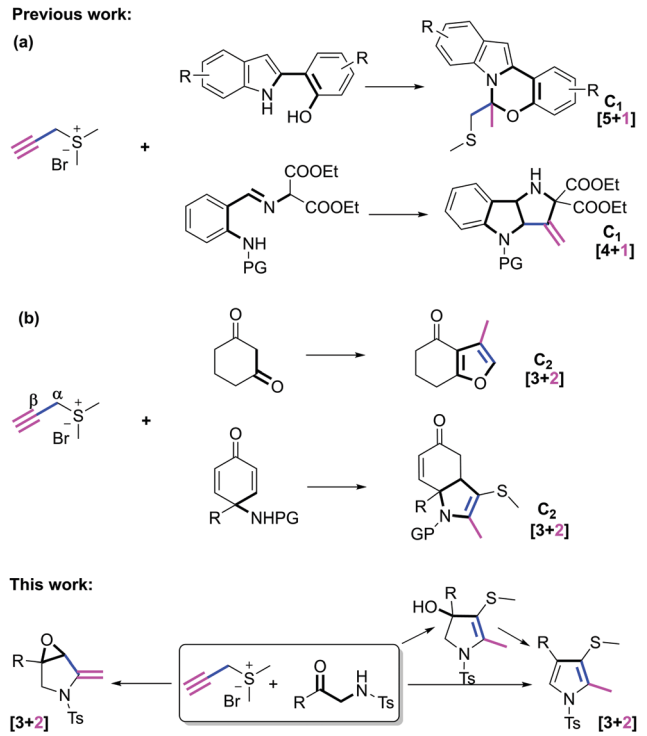
Our investigation commenced with prop-2-ynylsulfonium salt **1a** and *N*-sulfonyl-β-amino-1-phenylethanone **2a** as model substrates. As shown in Table 1, prop-2-ynylsulfonium salt **1a** was allowed to react with *N*-sulfonyl-β-amino-1-phenylethanone **2a** in the presence of Cs_2CO_3 (1.5 equiv.) in CH_3CN at 20 °C (Table 1, entry 1). The reaction gave the sequential [3+2]- and [2+1]-annulation product **3a** in 45% yield as well as S-containing pyrrole in 3% yield. A range of bases and solvents were screened



Scheme 1 Representative biologically active molecules containing pyrrolidine and pyrrole scaffolds.

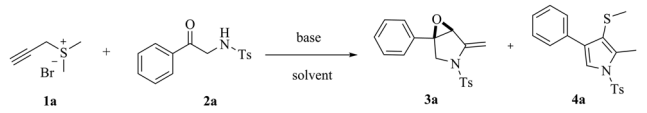
[a] *School of Medicine, Zhejiang University City College, Hangzhou, 310015, P. R. China. E-mail: zhuhj@zucc.edu.cn, zjk0125@yeah.net, shaoja@zucc.edu.cn*
[b] *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, 310058, P. R. China*

† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, NMR spectra, and X-ray crystal structure of **3f** and **4g**. CCDC 2040979 and 2040984. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc07745c



Scheme 2 Applications of prop-2-ynylsulfonium salt and this work.

Table 1 Screening of the reaction conditions[a]

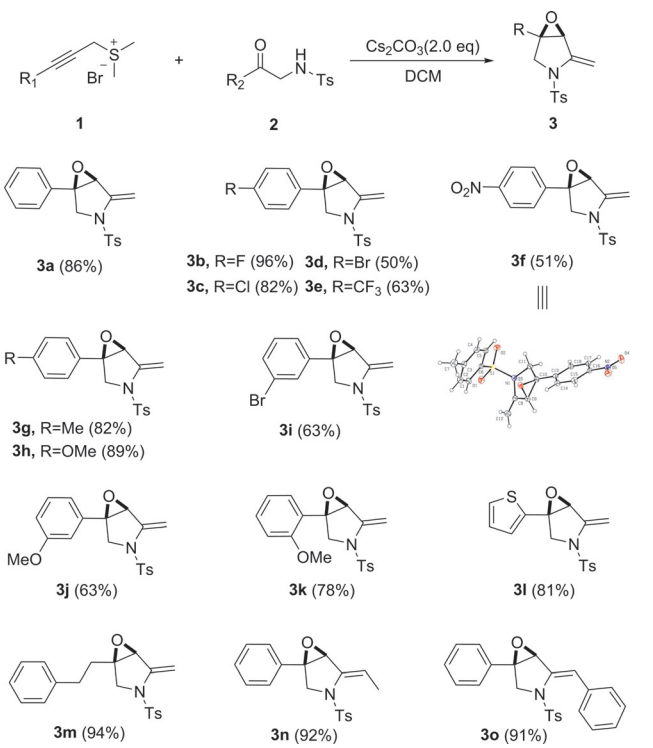


Entry	Solvent	Base	T (°C)	**1a**/**2a**/base	Yield[b] [%] **3a**	**4a**
1	CH_3CN	Cs_2CO_3	20	1.5 : 1 : 1.5	45	3
2	DMSO	Cs_2CO_3	20	1.5 : 1 : 1.5	42	4
3	THF	Cs_2CO_3	20	1.5 : 1 : 1.5	12	37
4	Acetone	Cs_2CO_3	20	1.5 : 1 : 1.5	20	33
5	DCM	Cs_2CO_3	20	1.5 : 1 : 1.5	56	8
6	DCM	K_2CO_3	20	1.5 : 1 : 1.5	52	27
7	DCM	DBU	20	1.5 : 1 : 1.5	47	4
8	DCM	DIPEA	20	1.5 : 1 : 1.5	32	30
9	DCM	TEA	20	1.5 : 1 : 1.5	38	36
10	THF	TEA	20	1.5 : 1 : 1.5	6	40
11	DCM	Cs_2CO_3	20	2 : 1 : 2	62	4
12	DCM	Cs_2CO_3	20	3 : 1 : 3	57	2
13	DCM	Cs_2CO_3	0	2 : 1 : 2	59	3
14	**DCM**	**Cs_2CO_3**	**0–10**	**2 : 1 : 2**	**86**	**2**
15	DCM	Cs_2CO_3	30	2 : 1 : 2	65	5
16[c]	THF	TEA	20	5 : 1 : 1.5	11	44
17[c]	THF	TEA	20	9 : 1 : 1.5	9	54
18[c]	THF	TEA	20	15 : 1 : 1.5	10	53
19[c]	THF	TEA	20	9 : 1 : 3	9	62
20[c]	THF	TEA	20	9 : 1 : 4	11	61
21[c]	**THF**	**TEA**	**30**	**9 : 1 : 3**	**8**	**66**
22[c]	THF	TEA	50	9 : 1 : 3	10	42

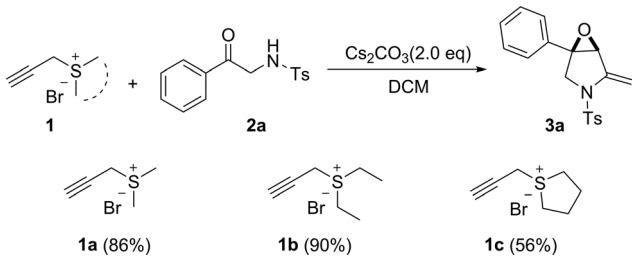
[a] The reaction was carried out with **1a**, **2a** (0.1 mmol), base and solvent (1 mL). [b] HPLC yields. [c] THF (2 mL).

to optimize the yield of **3a** (Table 1, entries 1–9). The reaction conducted in DCM gave a better yield of 56% when Cs_2CO_3 was used as a base (Table 1, entry 5). Screening of the loading of Cs_2CO_3 and synthon **1a** revealed that 2.0 equivalents of Cs_2CO_3 and **1a** gave a small improvement in the yield (Table 1, entries 11 and 12). Temperature also affected the reaction significantly: the yield increased from 62% to 86% as the temperature decreased from 20 °C to 0–10 °C (Table 1, entry 14). Interestingly, unexpected product **4a** was obtained in 66% yield when 9.0 equivalents of prop-2-ynylsulfonium salt **1a** reacted with **2a** in the presence of 3.0 equivalents of triethylamine (TEA) in THF at 30 °C (Table 1, entry 21). It is worth mentioning that the reaction feeding order has an effect on the yield of product **4a**.

Having established the optimal reaction conditions, we explored the substrate scope of these sequential [3+2]- and [2+1]-annulation reactions in the presence of Cs_2CO_3. As illustrated in Scheme 3, the reactions of *N*-sulfonyl-β-amino-1-phenylethanone **3** bearing either electron-rich or weakly electron-deficient substituents at the *para*-position on the benzene ring of R_2 produced the desired products (**3a–3c**, **3g–3h**) in good to high yields (82–96%), but bromine is the exception (**3d**), which had a reduced yield (50%). In the case of strong electron-withdrawing groups at the *para*-position of the benzene ring of R_2, reduced yields were obtained in 63% and 51%, respectively (**3e** and **3f**). Furthermore, substrates **2** with bromo- and methoxy-substituted phenyl rings at the *meta*-position were transformed into the desired products (**3i**, **3g**) in moderate yields (63%), while substrate **2** with a strong electron donating group at the *ortho*-position of the benzene ring could afford the product **3k** in 78% yield. Further investigation demonstrated that *N*-sulfonyl-β-amino-1-phenylethanones bearing



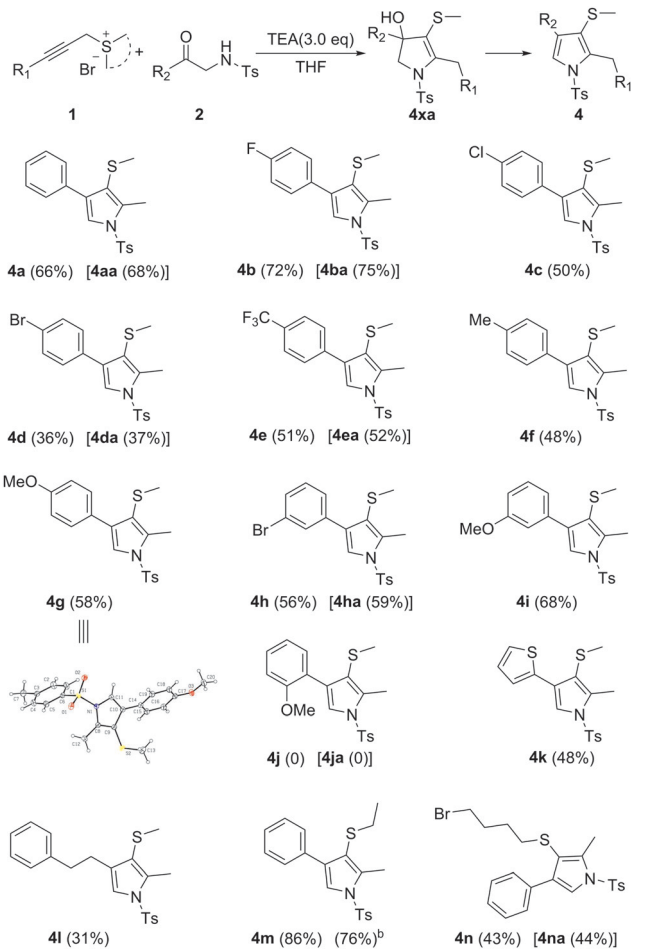
Scheme 3 Substrate scope of epoxide-fused 2-methylenepyrrolidines. Reactions were carried out with **1** (1.0 mmol), Cs_2CO_3 (1.0 mmol) and **2** (0.5 mmol) in DCM (5 mL) at 0–10 °C. Isolated yields are given.



Scheme 4 The influence of sulfonium salts for the yields of **3a**. Reactions were carried out at **1** (1.0 mmol), Cs_2CO_3 (1.0 mmol) and **2a** (0.5 mmol) in DCM (5 mL) at 0–10 °C. Isolated yields are given.

a thiophene ring and phenethyl were also efficient for the transformation, generating the annulation products (**3l** and **3m**) in high yields (81% and 94%). To our delight, 3-methylprop-2-yn-1-yldimethylsulfonium bromide and 3-phenylprop-2-yn-1-yldimethylsulfonium bromide[10] also reacted with **2a** smoothly, giving the corresponding products **3n** and **3o** in excellent yields (92% and 91%). Lastly, sulfonium salts **1a–1c** (Scheme 4) were tested under optimal conditions, which indicated that the yield of **3a** dropped sharply when tetrahydrothiophene sulfonium salt **1c** was employed in the reaction, but diethyl prop-2-ynylsulfonium bromide **1b** made no difference to the yield of **3a**. The structure of **3f** was characterized by single-crystal X-ray analysis (CCDC 2040979†).

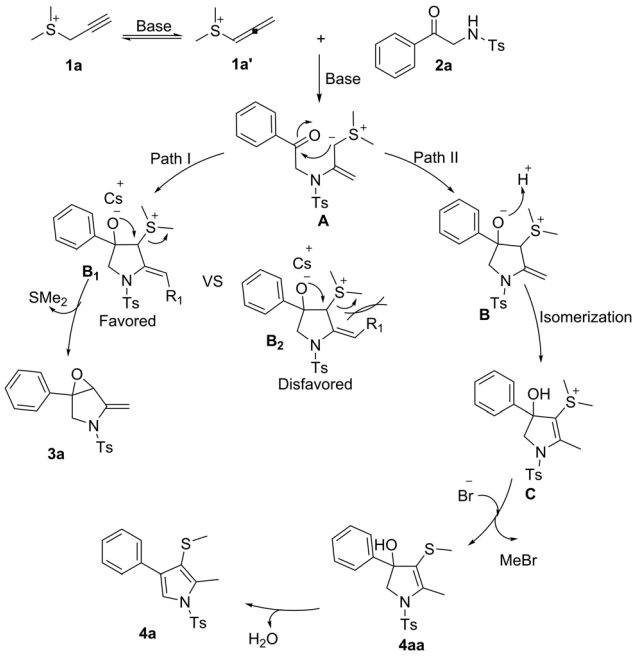
We then examined the scope of the reaction for S-containing pyrrole derivatives in the presence of TEA. As shown in Scheme 5, 2,3-dihydro-1*H*-pyrrol-3-ol (**4aa**) was observed in the reaction of model substrates in 68% yield and could be further transformed into **4a** (66% yield). It is noteworthy to point out that the hydroxyl group of the 2,3-dihydro-1*H*-pyrrol-3-ol derivatives tended to be eliminated spontaneously when electron-donating substituents were on the benzene ring of R_2, and the desired products (**4f**, **4g**, **4i**) could be obtained in moderate yields (48–68%). By contrast, relatively stable 2,3-dihydro-1*H*-pyrrol-3-ol derivatives (**4ba**, **4da**, **4ea**, **4ha**) were successfully isolated in 37–75% yields with an electron-withdrawing group (except for Cl atom) on the benzene ring of R_2, but the elimination reaction could also be conducted in the presence of MsCl and TEA in over 90% conversion. However, the *ortho*-substituents of R_2 bearing a methoxy group failed to furnish the desired products **4j** and **4ja**, presumably because the methoxy group sterically hindered the formation of stable intermediate **B** under standard conditions (Scheme 6). Surprisingly, the generality of this methodology was also demonstrated by using electron-rich groups of R_2, such as thiophene and phenethyl, and the corresponding eliminated products **4k** and **4l** can be obtained in 48% and 31% yields, respectively. Furthermore, different sulfonium salts were employed in the reaction. When ethyl methyl prop-2-ynylsulfonium bromide and diethyl prop-2-ynylsulfonium bromide were chosen as substrates, the same product **4m** was obtained in 76% and 86% yields, respectively. Meanwhile, tetrahydrothiophene sulfonium salt was also compatible with the transformation (**4n** and **4na**). However, when a H atom of R_1 was substituted by phenyl and alkyl, no desired products were



Scheme 5 Substrate scope of S-containing pyrroles. [a] Reaction conditions: **1** (4.5 mmol) was added to a stirred solution of **2** (0.5 mmol) in THF (10 mL) slowly. Subsequently, TEA was added to the reaction mixture and stirred at 30 °C. Isolated yields are given. [b] Substrate **1** was ethyl methyl prop-2-ynylsulfonium bromide.

observed. The structure of **4g** was unambiguously confirmed by X-ray crystallography (CCDC 2040984†).

According to our experimental results, we proposed a plausible mechanism for the domino annulation reactions (Scheme 6). Under the treatment of base, prop-2-ynylsulfonium salt **1a** isomerizes into allenic sulfonium salt **1a′** which is attacked by the N anion of **2a**, generating intermediate **A**. For path I, intermediate **A** then undergoes an intramolecular nucleophilic addition to form intermediate **B** in which the O anion conjugated with cesium to constitute "naked anions".[11] Finally, the desired product **3a** is obtained by an intramolecular nucleophilic addition. In the reaction process of **3n** and **3o**, favored intermediate $\mathbf{B_1}$ tended to be formed because of the steric- hindrance (Scheme 6). For path II, the O anion of intermediate B would capture a proton immediately, followed by a double-bond isomerization affording the intermediate **C**. Then, the Br anion attacked the Me_2S sulfonium to yield the product **4aa**. Finally, the hydroxyl group of **4aa** is eliminated to obtain product **4a**. It is worth noting that MsCl and TEA can speed up the departure of a hydroxyl when the benzene ring of substrate **2** has electron-withdrawing substituents.



Scheme 6 Plausible reaction mechanism.

In conclusion, we have developed a novel divergent domino annulation reaction of prop-2-ynylsulfonium salts and sulfonyl-protected β-amino ketones, generating epoxide-fused 2-methylenepyrrolidines and S-containing pyrroles in moderate to excellent yields under mild conditions. In this [3+2] annulation reaction, prop-2-ynylsulfonium salts were utilized as C_2 synthons. We believe that the novel annulation reaction will be promising to be used in the synthesis of natural products and pharmaceuticals.

We are grateful for the financial support from the National Natural Science Foundation of China (21702183 and 81803432), Agricultural and Social Development Fund of Hangzhou Science and Technology Committee (20191203B50) and The Second Round of Excellent Innovation Team of Hangzhou Municipal University in 2019 for L.-H. Zeng.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) E. Fattorusso and O. Taglialatela-Scafati, *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2007; (*b*) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139; (*c*) M. Cooper, A. Llinas, P. Hansen, M. Caffrey, A. Ray, S. Sjodin, I. Shamovsky, H. Wada, T. J. Jensen, U. Sivars, L. Hultin, U. Andersson, S. Lundqvist, K. Gedda, L. Jinton, N. Krutrok, R. Lewis, P. Jansson and C. Gardelli, *J. Med. Chem.*, 2020, **63**, 9705; (*d*) D. Habel, D. S. Nair, Z. Kallingathodi, C. Mohan, S. M. Pillai, R. R. Nair, G. Thomas, S. Haleema, C. Gopinath, R. V. Abdul, M. Fritz, A. R. Puente, J. L. Johnson, P. L. Polavarapu and I. Ibnusaud, *J. Nat. Prod.*, 2020, **83**, 2178; (*e*) T. W. Lyons, T. A. Martinot, C. Q. He, J. Qi and G. X. Shao, *Org. Process Res. Dev.*, 2020, **24**, 1457; (*f*) Z. H. Pei, X. F. Li, K. Longenecker, T. W. von Geldern, P. E. Wiedeman, T. H. Lubben, B. A. Zinker, K. Stewart, S. J. Ballaron, M. A. Stashko, A. K. Mika, D. W. A. Beno, M. Long, H. Wells, A. J. Kempf-Grote, D. J. Madar, T. S. McDermott, L. Bhagavatula, M. G. Fickes, D. Pireh, L. R. Solomon, M. R. Lake, R. Edalji, E. H. Fry, H. L. Sham and J. M. Trevillyan, *J. Med. Chem.*, 2006, **49**, 3520; (*g*) R. A. Pilli and M. de Oliveira, *Nat. Prod. Rep.*, 2000, **17**, 117; (*h*) D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151.

2 (*a*) D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon and Q. Jin, *J. Am. Chem. Soc.*, 1999, **121**, 54; (*b*) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435; (*c*) A. Furstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (*d*) H. Fan, J. N. Peng, M. T. Hamann and J. F. Hu, *Chem. Rev.*, 2008, **108**, 264; (*e*) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233; (*f*) M. Z. Wang, H. Xu, T. W. Liu, Q. Feng, S. J. Yu, S. H. Wang and Z. M. Li, *Eur. J. Med. Chem.*, 2011, **46**, 1463; (*g*) K. H. van Pee and J. M. Ligon, *Nat. Prod. Rep.*, 2000, **17**, 157; (*h*) T. Antonucci, J. S. Warmus, J. C. Hodges and D. G. Nickell, *Antiviral Chem. Chemother.*, 1995, **6**, 98; (*i*) K. Muralirajan, R. Kancherla and M. Rueping, *Angew. Chem., Int. Ed.*, 2018, **57**, 14787.

3 (*a*) L. W. Wang, H. J. Su, S. Z. Yang, S. J. Won and C. N. Lin, *J. Nat. Prod.*, 2004, **67**, 1182; (*b*) Y. K. T. Lam, O. D. Hensens, R. Ransom, R. A. Giacobbe, J. Polishook and D. Zink, *Tetrahedron*, 1996, **52**, 1481; (*c*) A. J. Humphrey and D. O'Hagan, *Nat. Prod. Rep.*, 2001, **18**, 494; (*d*) H. Gholami, A. Kulshrestha, O. K. Favor, R. J. Staples and B. Borhan, *Angew. Chem., Int. Ed.*, 2019, **58**, 10110; (*e*) S. Mizutani, K. Komori, T. Taniguchi, K. Monde, K. Kuramochi and K. Tsubaki, *Angew. Chem., Int. Ed.*, 2016, **55**, 9553.

4 (*a*) A. Kulshrestha, J. M. Schomaker, D. Holmes, R. J. Staples, J. E. Jackson and B. Borhan, *Chem. – Eur. J.*, 2011, **17**, 12326; (*b*) J. M. Schomaker, A. R. Geiser, R. Huang and B. Borhan, *J. Am. Chem. Soc.*, 2007, **129**, 3794; (*c*) A. Kulshrestha, N. S. Marzijarani, K. D. Ashtekar, R. Staples and B. Borhan, *Org. Lett.*, 2012, **14**, 3592.

5 M. Aso, M. Sakamoto, N. Urakawa and K. Kanematsu, *Heterocycles*, 1990, **31**, 1003.

6 P. H. Jia and Y. Huang, *Adv. Synth. Catal.*, 2018, **360**, 3044.

7 P. H. Jia, Q. L. Zhang, Q. M. Ou and Y. Huang, *Org. Lett.*, 2017, **19**, 4664.

8 (*a*) M. Aso, A. Ojida, G. Yang, O. J. Cha, E. Osawa and K. Kanematsu, *J. Org. Chem.*, 1993, **58**, 3960; (*b*) A. Ojida, F. Tanoue and K. Kanematsu, *J. Org. Chem.*, 1994, **59**, 5970; (*c*) P. H. Jia, Q. L. Zhang, H. X. Jin and Y. Huang, *Org. Lett.*, 2017, **19**, 412; (*d*) S. J. Shen, Y. L. Yang, J. Y. Duan, Z. H. Jia and J. Y. Liang, *Org. Biomol. Chem.*, 2018, **16**, 1068.

9 (*a*) M. Gunther, J. Lategahn, M. Juchum, E. Doring, M. Keul, J. Engel, H. L. Tumbrink, D. Rauh and S. Laufer, *J. Med. Chem.*, 2017, **60**, 5613; (*b*) I. V. Magedov, G. Luchetti, N. M. Evdokimov, M. Manpadi, W. F. A. Steelant, S. Van Slambrouck, P. Tongwa, M. Y. Antipin and A. Kornienko, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1392; (*c*) X. D. Li, M. Chen, X. Xie, N. Sun, S. Li and Y. H. Liu, *Org. Lett.*, 2015, **17**, 2984; (*d*) P. J. Wang, Y. Xiong, Y. Q. Qin, J. J. Zhang, N. N. Yi, J. N. Xiang and W. Deng, *Catal. Commun.*, 2019, **131**, 7.

10 P. W. Davies, N. Martin and N. Spencer, *Beilstein J. Org. Chem.*, 2011, **7**, 839.

11 S. I. Kim, F. X. Chu, E. E. Dueno and K. W. Jung, *J. Org. Chem.*, 1999, **64**, 4578.

