ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2025, **61**, 17637

Received 15th September 2025,
Accepted 7th October 2025

DOI: 10.1039/d5cc05319f

rsc.li/chemcomm

Total synthesis of brevianamides X, Y and Z†

Monosij Nandy, Apurba Das, Debgopal Jana, Satadru Dutta and Alakesh Bisai *

Brevianamides X (1) and Y (2) are relatively new members of the bicyclo[2.2.2]diazaoctane alkaloid family, whose biosynthetic origins remain unresolved. We report the asymmetric total synthesis of (+)-brevianamides Y (2), Z (16) and (±) brevianamide X (1) through a hydroxyproline-guided cascade. Oxidation timing governs divergence, affording concise routes and underscoring hydroxyproline as a privileged scaffold.

The brevianamides, a subclass of the bicyclo[2.2.2]diazaoctane alkaloids, are structurally complex fungal metabolites that have long challenged the synthetic community.[1] More recently, the isolation of brevianamides X (**1**) and Y (**2**) by Qi and co-workers from the deep-sea-derived *P. brevicompactum* DFFSCS0252, expanded the structural diversity of this class, introducing natural products bearing spiro-oxindole functionalities.[2] Within this family, (+)-brevianamides A (**4**) and B (**6**) were the first isolated in 1969,[3] and feature an unusual indoxyl motif and an anti-configured bicyclo[2.2.2]diazaoctane core. In contrast to (+)-brevianamides A (**4**) and B (**6**), (+)-brevianamide X (**1**) adopts a *syn*-configured core, while (+)-brevianamide Y (**2**) retains the *anti*-configuration. This clear division between indoxyl-containing (+)-brevianamides A (**4**) and B (**6**) and oxindole-containing (+)-brevianamides X (**1**) and Y (**2**), as well as their contrasting stereochemistry, points to diverging biosynthetic logic (Fig. 1). Beyond the brevianamides, related alkaloids such as stephacidin A (**3**) and paraherquamide (**5a**) underscore the structural versatility of this framework, with members of the family exhibiting diverse biological activities including insecticidal, anticancer, and anthelmintic properties.[4] Since their isolation in 1969, for more than five decades, the total synthesis of (+)-brevianamide A (**4**) has remained an unsolved challenge. Pioneering efforts were led by Williams and co-workers, who over several decades developed multiple synthetic approaches to brevianamide B (**6**) and its enantiomer, yet these efforts consistently did not provide (+)-brevianamide A (**4**).[5]

A landmark breakthrough came in 2020, when the Lawrence group disclosed the first successful total synthesis of (+)-brevianamide A (**4**), elegantly combining biomimetic reasoning with experimental validation. This synthesis rapidly inspired further activity in the field.[6]

In 2021, Smith and co-workers reported the total synthesis of brevianamide A (**4**), albeit in racemic form, and afterwards the Gagosz group also reported an expedited total synthesis of (±)-brevianamide A (**4**), strategically exploiting gold(I)-catalysis.[7] Building on these landmark contributions, our group subsequently developed an asymmetric total synthesis, demonstrating that hydroxyproline-derived diketopiperazines could serve as privileged intermediates to access (+)-brevianamides A (**4**) and

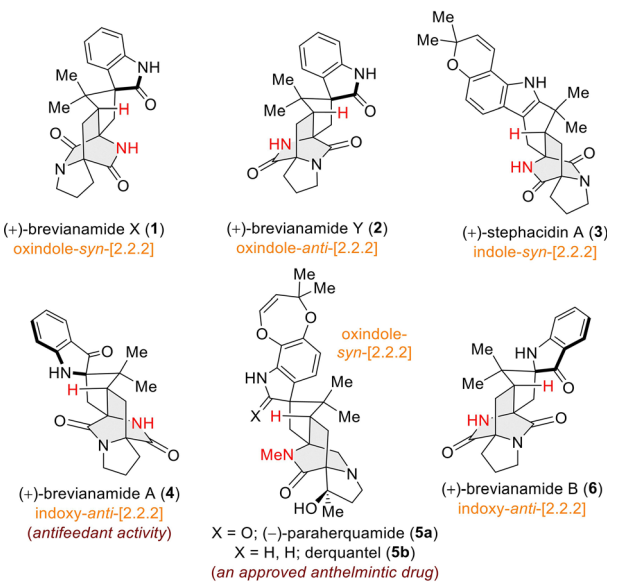


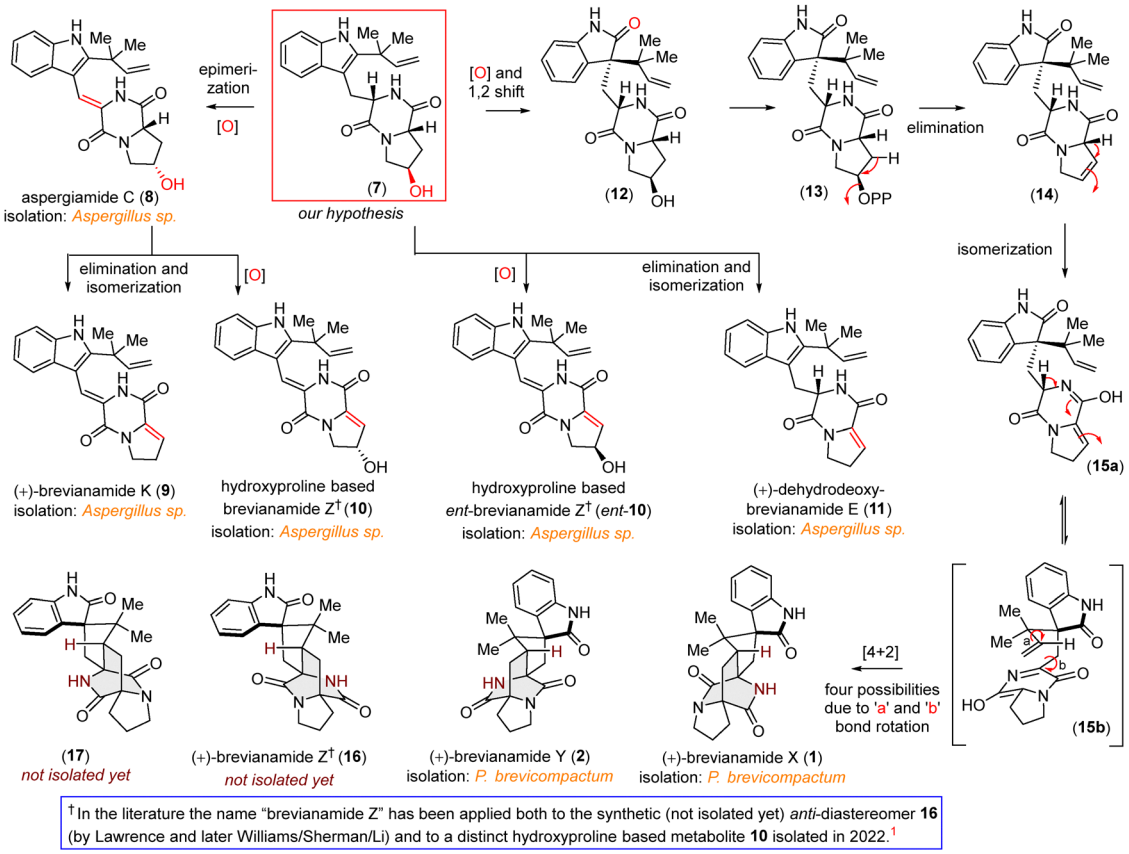
Fig. 1 Structural diversity within bicyclo[2.2.2]diazaoctane alkaloids.

Department of Chemical Sciences, Indian Institute of Science Education and Research Kolkata, Mohanpur Campus, Nadia, Kalyani, 741 246, West Bengal, India. E-mail: alakesh@iiserkol.ac.in

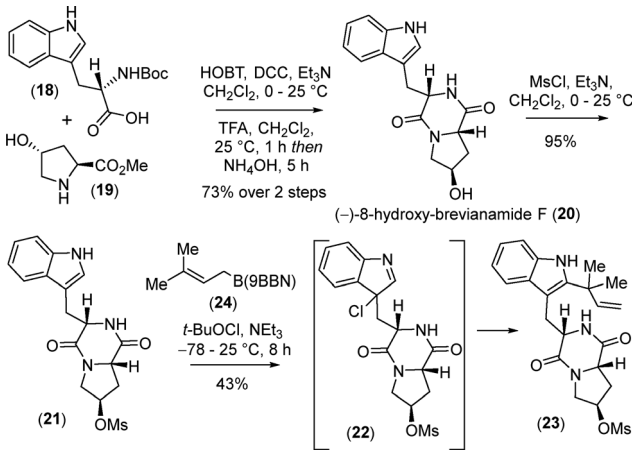
† This work is dedicated respectfully to Prof. Srinivasan Chandrasekaran, Department of Organic Chemistry, IISc Bangalore, on the occassion of his 80th Birthday.

B (**6**).[8] In parallel, Sherman and co-workers reported a bioengineered pathway that enabled the production of (+)-brevianamides A (**4**) and B (**6**).[9] The resulting synthetic and biosynthetic framework subsequently paved the way for the unified synthesis of brevianamides X (**1**) and Y (**2**), further expanding our understanding of structural divergence in this class. In 2015, Qin and co-workers reported a 20-step synthesis of the unnatural enantiomer of brevianamide Y (*ent*-**2**).[10] In 2020, during their biosynthetic investigations, Williams, Sherman, and Li accomplished a 12-step synthesis of natural (+)-brevianamide Y (**2**).[11] Subsequently, the Lawrence group demonstrated that (+)-dehydrodeoxybrevianamide E (**11**) could also be converted to (+)-brevianamide Y (**2**).[6] Despite their structural kinship to (+)-brevianamides A (**4**) and B (**6**), the biosynthetic origins of brevianamides X (**1**) and Y (**2**) are under investigation, as no dedicated biosynthetic gene cluster has yet been identified.[11] We were inspired by the structural features of hydroxyproline-derived natural products, which are frequently encountered in fungal secondary metabolism. At the core of our proposal lies the hydroxyproline-derived diketopiperazine (**7**), which we regard as a plausible biosynthetic progenitor of the brevianamide family (Scheme 1). This scaffold possesses both the oxidation handles and conformational bias needed to channel biosynthetic flux toward multiple divergent products. From **7**, epimerization and oxidation rationalize the known natural product aspergiamide C (**8**) and elimination and isomerisation of **8** would lead to brevianamide K (**9**). Meanwhile, selective oxidation of **7** and **8** would furnish the recently reported hydroxyproline-derived brevianamide Z (**10** and *ent*-**10**). Moreover, plausible biosynthetic conversion of **7** to (+)-dehydrodeoxybrevianamide E (**11**) provides a direct bridge to the well-established pathway of (+)-brevianamides A (**4**) and B (**6**), further supporting the centrality of this intermediate.[12,13] Crucially, oxidation of **7** followed by a [1,2]-shift generates oxindole **12**, which *via* elimination yields the intermediate **14**, which could undergo elimination–isomerisation directly coupled with an intramolecular [4+2] cycloaddition, thereby forging the bicyclo[2.2.2]diazaoctane skeleton in a single cascade. Conformational freedom around bonds *a* and *b* in the cycloaddition transition state would, in principle, give rise to four possible stereochemical outcomes, thereby unifying the origin of both brevianamide Y (**2**) and brevianamide X (**1**). Additional putative molecules such as **16** and **17**, although not yet isolated, can also be rationalized as shunt or alternative products within this framework. Notably, **16** was designated as (+)-brevianamide Z by Lawrence and has been proposed as a potential future natural product.[6]

Overall, this hypothesis considers **7** as a biosynthetic linchpin, offering a possible unifying rationale for the origin of (+)-brevianamides X (**1**) and Y (**2**), while simultaneously connecting them to related congeners of the brevianamide family. In order to experimentally probe our hypothesis, we required synthetic access to the activated oxindole intermediate (**13**),



Scheme 1 Plausible biosynthetic network from hydroxyproline-derived intermediates leading to brevianamides X and Y.



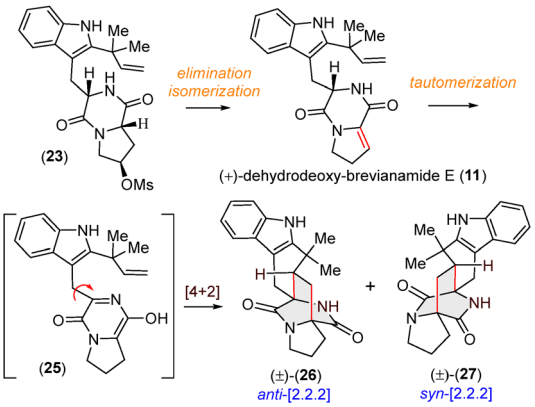
Scheme 2 Synthesis of hydroxyproline-derived diketopiperazine **23**.

which we had postulated to undergo elimination–isomerization followed by a [4+2]-cycloaddition *en route* to brevianamides X (**1**) and Y (**2**) (Scheme 1). To this end, we designed a hydroxyproline-derived diketopiperazine **23** as a much simpler synthetic surrogate of **13**. The synthesis commenced with amide coupling between Boc-protected L-tryptophan (**18**) and L-hydroxyproline methyl ester (**19**), followed by deprotection and cyclization, which furnished (−)-8-hydroxybrevianamide F (**20**) in 73% yield over two steps. Mesylation of the secondary alcohol gave **21** in excellent yield, which was subjected to reverse prenylation under the Danishefsky protocol.[14] This transformation provided the desired compound **23** in 43% yield (Scheme 2).

With **23**, we next investigated the proposed elimination–isomerisation-[4+2] cascade (Scheme 3). Treatment of **23** with Et_3N/DIPEA in THF was not successful. Employing stronger non-nucleophilic bases improved reactivity, DBN or DBU promoted smooth elimination isomerisation, delivering (+)-dehydrodeoxybrevianamide E (**11**) alongside the cycloadducts (±)-**26** and (±)-**27** in modest yields. Upon heating, however, **11** was no longer observed. Specifically, under conditions with DBU at 80 °C, the [4+2] cycloaddition proceeded cleanly, affording the *anti*-diastereomer (**26**) and *syn*-diastereomer (**27**) in 25% and 48% yields, respectively. Heating isolated **11** at 80 °C with DBU resulted in the formation of **26** and **27** in a comparable diastereomeric ratio. These results provide direct chemical evidence that the cascade proceeds stepwise: initial elimination–isomerisation generates **11**, which then tautomerizes to the conjugated diene **25**, enabling an intramolecular [4+2] cycloaddition.

With the cascade conditions in hand, our attention turned to the synthesis of brevianamides X (**1**) and Y (**2**). Diketopiperazine **23** was converted to oxindole **29** as a single diastereomer upon treatment with NCS/H_2O to give 61% yield. The exclusive formation of **29** likely reflects the inherent structural bias of the diketopiperazine **23**. Guided by our hypothesis, we anticipated that base-mediated activation of the compound **29** (synthetic surrogate of **13**) would trigger an elimination–isomerisation sequence followed by a [4+2] cycloaddition.

In principle, this cycloaddition could proceed with both the *syn*- and *anti*-configured adducts. Experimentally, however,



entry[a]	base[b]	solvent	temp.	time	yield[c] (11)	(26)	(27)
1.	Et_3N	THF	25 °C	24 h	-	-	-
2.	DIPEA	THF	100 °C	24 h	-	-	-
3.	DBN	THF	60 °C	4 h	31%	11%	18%
4.	DBU	THF	60 °C	4 h	34%	10%	12%
5.	DBU	THF	80 °C	10 h	-	25%	48%

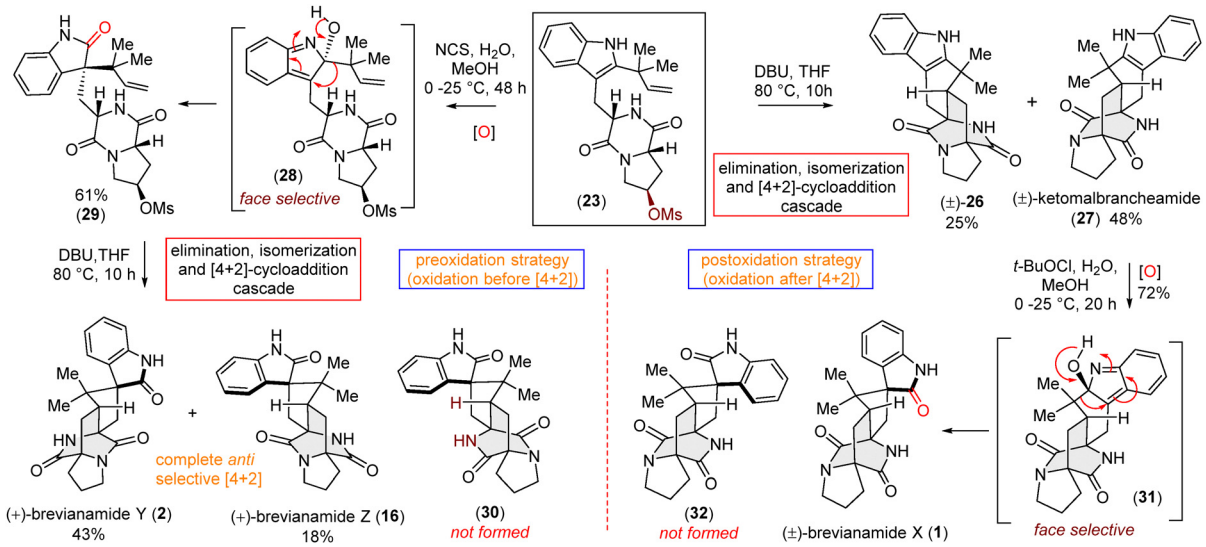
[a]all reactions were carried out at 0.15 mmol scale. [b]2.5 equiv. [c]isolated yield.

Scheme 3 'L-(4*R*)-hydroxyproline-guided cascade' optimization.

under DBU-mediated conditions, the [4+2] cycloaddition proved to be highly anti-selective, providing (+)-brevianamide Y (**2**) in 43% yield, accompanied by (+)-brevianamide Z (**16**) in 18% yield, while no trace of brevianamide X (**1**) or other *syn*-diastereomer **30** was detected. The anti-selectivity can be attributed to the inherent diastereocontrol of the azadiene intermediate **15b**. Notably, when the cycloaddition involves an indole (*e.g.*, **25**), partial syn-selectivity is observed, whereas with an oxindole such as **15b**, the reaction proceeds with complete anti-selectivity.

Thus, the pre-oxidation strategy delivers (+)-brevianamide Y (**2**) but not brevianamide X (**1**). This selectivity prompted us to consider an alternative sequence, wherein oxidation occurs after the [4+2] cycloaddition. In this post-oxidation strategy, the cycloaddition first generates the *syn*-configured framework **27**, which then undergoes a face-selective oxidation under *t*-BuOCl/H_2O conditions affording (±)-brevianamide X (**1**) as a single product. The stereochemical outcome can be rationalized by initial chlorination of the indole, followed by face-selective water addition to give **31**, and a subsequent ring contraction that furnishes brevianamide X (**1**) as a single diastereomer. Overall, these results establish an elegant chemical logic: oxidation before the [4+2] event directs the pathway toward the *anti*-configured brevianamide Y (**2**), whereas oxidation after the cycloaddition enables access to the *syn*-configured brevianamide X (**1**). Together, the results identify oxidation timing as the central control element in the structural diversification of the brevianamides (Scheme 4).

In summary, a hydroxyproline-derived diketopiperazine strategy has provided concise access to three brevianamides: (±)-X (**1**), (+)-Y (**2**), and (+)-Z (**16**). L-(4*R*)-hydroxyproline has emerged as a privileged scaffold, preorganising the system for a base-promoted elimination–isomerisation–[4+2] cascade that



Scheme 4 Total synthesis of brevianamides X, Y and Z controlled by oxidation timing.

efficiently built the bicyclo[2.2.2]diazaoctane framework. Crucially, oxidation timing dictated divergence, with pre-oxidation delivering brevianamide Y (**2**) and post-oxidation channeling to brevianamide X (**1**). In total, brevianamides Y (**2**) (7.8% overall yield), Z (**16**) (3.2% overall yield), and X (**1**) (10.3% overall yield) were completed in six steps, highlighting L-(4*R*)-hydroxy proline as a unifying synthetic and biosynthetic scaffold for brevianamide alkaloids and offering broader implications for the design of cascade-based strategies in alkaloid assembly.

This work is supported by grants from the STARS, MoE [2023, 0753], SERB [CRG/2023/000782], and [SCP/2022/000486]. M. N. gratefully thanks the PMRF for the research fellowships. A. D., S. D. and D. J. thank the UGC for the predoctoral fellowships.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental details and spectral analysis. See DOI: **https://doi.org/10.1039/d5cc05319f**.

Notes and references

1 (*a*) J. M. Finefeld, J. C. Frisvad, D. H. Sherman and R. M. Williams, *J. Nat. Prod.*, 2012, **75**, 812; (*b*) L. Du, L. Dian, S. A. Newmister, Y. Xia, G. Luo, D. H. Sherman and S. Li, *Chem. Rev.*, 2025, **125**, 1718.
2 X. Xu, X. Zhang, X. Nong, J. Wang and S. Qi, *Mar. Drugs*, 2017, **15**, 43.
3 (*a*) A. J. Birch and J. J. Wright, *J. Chem. Soc. D*, 1969, 644–645; (*b*) A. J. Birch and J. J. Wright, *Tetrahedron*, 1970, **26**, 2329; (*c*) A. E. A. Porter and P. G. Sammes, *J. Chem. Soc. D*, 1970, 1103a.
4 (*a*) A. P. Robertson, C. L. Clark, T. A. Burns, D. P. Thompson, T. G. Geary, S. M. Trailovic and R. J. Martin, *J. Pharmacol. Exp. Ther.*, 2002, **303**, 853; (*b*) P. R. Little, A. Hodge, S. J. Maeder, N. C. Wirtherle, D. R. Nicholas, G. C. Cox and G. A. Conder, *Vet. Parasitol*, 2011, **181**, 180.
5 (*a*) R. M. Williams, J. Cao and J. E. Verdier, *J. Am. Chem. Soc.*, 1988, **110**, 5927; (*b*) R. M. Williams, C. H. Allen and J. Cao, *J. Am. Chem. Soc.*, 1998, **120**, 1090; (*c*) L. A. Adams, M. W. N. Valente and R. M. Williams, *Tetrahedron*, 2006, **62**, 5195; (*d*) R. M. Williams, C. H. Allen and D. Fu, *Org. Lett.*, 2007, **9**, 4255; (*e*) R. J. K. Taylor and H. A. Simpkins, *J. Am. Chem. Soc.*, 2009, **131**, 4214; (*f*) J. R. Scheerer, M. P. Paquette and D. S. Tan, *J. Org. Chem*, 2016, **81**, 2293; (*g*) J. C. Perkins, X. Wang, R. D. Pike and J. R. Scheerer, *J. Org. Chem.*, 2017, **82**, 13656.
6 (*a*) R. C. Godfrey, N. J. Green, G. S. Nichol and A. L. Lawrence, *Nat. Chem.*, 2020, **12**, 615; (*b*) R. C. Godfrey, H. E. Jones, N. J. Green and A. L. Lawrence, *Chem. Sci.*, 2022, **13**, 1313.
7 (*a*) F. Xu and M. W. Smith, *Chem. Sci.*, 2021, **12**, 13756; (*b*) A. Mansour, N. J. Green and F. Gagosz, *Org. Lett.*, 2022, **24**, 7200.
8 M. Nandy, A. Das, S. Niyogi, A. Khatua, D. Jana and A. Bisai, *Org. Lett.*, 2024, **26**, 10424.
9 C. P. Sandoval Hurtado, S. P. Kelly, V. V. Shende, M. Perez, B. J. Curtis, S. A. Newmister, K. Ott, F. Pereira and D. H. Sherman, *ACS Catal.*, 2025, **15**, 6711.
10 W.-F. Qin, T. Xiao, L.-F. Deng, Y. Wang and Y. Qin, *Chem. Commun.*, 2015, **51**, 16143.
11 Y. Ye, L. Du, X. Zhang, S. A. Newmister, M. McCauley, J. V. Alegre-Requena, W. Zhang, S. Mu, A. Minami, A. E. Fraley, M. L. Adrover-Castellano, N. A. Carney, V. V. Shende, F. Qi, H. Oikawa, H. Kato, S. Tsukamoto, R. S. Paton, R. M. Williams, D. H. Sherman and S. Li, *Nat. Catal.*, 2020, **3**, 497.
12 (*a*) E. Ge, C. Huang, J. Li, T. Chen, J. Tang, W. Liu and Y. Long, *Mar. Drugs*, 2021, **19**, 402; (*b*) P. S. Steyn, *Tetrahedron*, 1973, **29**, 107.
13 L. Li, Q.-H. Chang, S.-S. Zhang, K. Yang, F.-L. Chen, H.-J. Zhu, F. Cao and Y.-F. Liu, *J. Mol. Struct.*, 2022, **1261**, 132904.
14 J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 11964.

