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Asymmetric total syntheses of immunosuppressive diterpenoids triptobenzenes N and R *via* a remote Csp^3–H functionalization†‡

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The total syntheses of the naturally occurring diterpenoids triptobenzenes N (1c) and R (1d) have been accomplished *via* a late-stage δ-Csp^3–H functionalization of an enone intermediate. The highly functionalized dienone intermediate 2 was utilized as a common scaffold for this study. An XRD analysis of compounds 8 and 4 confirmed the stereochemistry of the quaternary centers of the abietane core. Finally, a chemoselective ketal protection and reduction completed the first total syntheses of the immunosuppressive diterpenoids triptobenzenes N (1c) and R (1d).

The abietane diterpenoids (**1a–d**; Fig. 1) are architecturally complex secondary metabolites sharing a carbotricyclic core having a *trans*-decalin motif and are useful targets for drug discovery.[1] In the modern era, scientists have been interested in synthesizing such diterpenoids not only because of their interesting structural scaffolds but also for their important bioprofiles.[1] In 1999, Li *et al.* isolated diterpenoids named triptobenzenes L (**1a**) and N (**1c**) as well as 15 other diterpenoids from the T_{II} extract of *T. wilfordii*.[2] Later, in 2013, Song *et al.* isolated triptobenzene R (**1d**) from the roots of *T. wilfordii*, along with four more abietane diterpenoids.[3] Structurally, both triptobenzenes N (**1c**) and R (**1d**) contain two quaternary stereogenic centers and a primary alcohol group in the 'A' ring. Triptobenzene N (**1c**) also contains an additional benzylic ketone functionality. Recent studies revealed significant pharmacological activities of the isolate of *T. wilfordii*, including antifertility,[4] *anti*-rheumatoid-arthritis[5] and immunosuppressive[6] activities.

Structurally, abietane diterpenoids **1a–d** share a common 6/6/6 carbotricyclic framework with three contiguous stereogenic centers [four for each of **1a** and **1b**] where a *trans*-decalin scaffold is embedded with an aromatic ring (Fig. 1). Importantly, two stereogenic centers feature challenging all-carbon quaternary centers situated at the 1 and 3 positions of the cyclohexane **A** ring.[7]

Despite important bioprofiles reported for selected congeners, there are only a few reports on asymmetric total syntheses of diterpenoids **1a–d**. In 2018, Carter *et al.* reported on an L-proline–sulfonamide-catalyzed Yamada–Otani reaction and a Pummerer reaction as key strategies for synthesizing aromatic abietane diterpenoids.[8] In 2023, Chou *et al.* reported a semi-synthetic route to aromatic abietanes starting from commercially available dehydroabietic acid.[9] Recently, our group[10] reported a catalytic asymmetric approach to diterpenoids **1a–b**. However, no synthesis of immunosuppressive diterpenoids triptobenzenes N (**1c**) and R (**1d**) has yet been reported.

Metal-free activation of typically inert Csp^3–H bonds is one of the most important research topics of modern organic synthesis. In this regard, in 2022, our group reported on functionalization of an aliphatic Csp^3–H bond of an indolosesuquiterpene moiety for the total syntheses of naturally xiamycins C–F achieved by utilizing the pioneering work of Tahara *et al.*[11a,b] Herein, we report a highly regioselective remote Csp^3–H activation for the first total

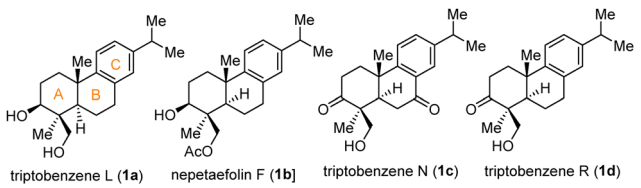

Fig. 1 Naturally occurring abietane diterpenoids **1a–d**.

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‡ Electronic supplementary information (ESI) available. CCDC 2411032 (**8**) and 2417922 (**4**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5cc02354h

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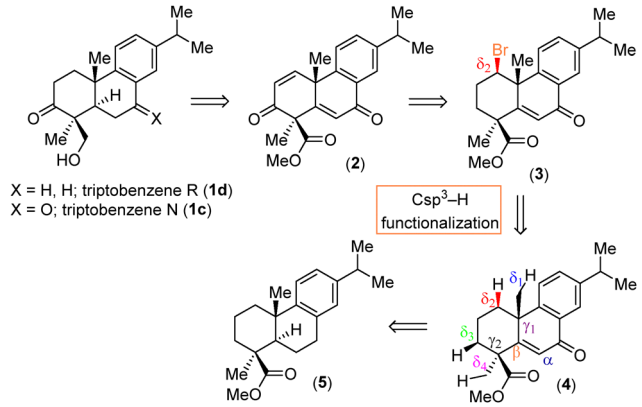


Scheme 1 Our retrosynthetic analysis.

syntheses of the abietane diterpenoids triptobenzenes N (**1c**) and R (**1d**). Our retrosynthetic approach is outlined in Scheme 1. It was envisioned that a collective total synthesis of naturally occurring abietane diterpenoids **1c–d** could be accomplished from an advanced highly functionalized enone **2** (Scheme 1). Enone **2** could be made by carrying out a β-elimination of tricyclic bromo compound **3** followed by allylic oxidation. The secondary bromide **3** could be derived from the enone **4** *via* a key formal Csp^3–H functionalization,[11a,b] which in turn could be accessed from the methyl calistrisate **5** in two steps (Scheme 1).

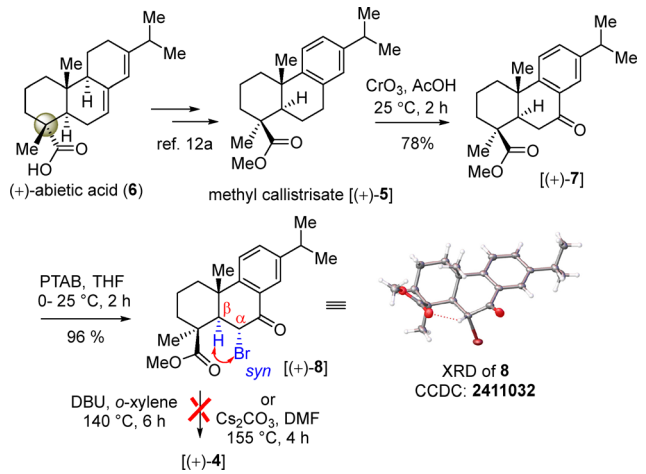
Based on above hypothesis, we started our synthesis from abietic acid **6**, a naturally occurring diterpenoid (Scheme 2). Compound **6** was converted to methyl calistrisate **5** following our reported procedure (Scheme 2).[12a]

Then, benzylic oxidation of **5** afforded product **7** in 78% yield. Next, we thought of accessing enone **4** following a two-step protocol, namely α-bromination of **7** with phenyl trimethyl ammonium tribromide (PTAB) followed by β-elimination. Although, a reaction of **7** with PTAB afforded, in 96% yield, α-bromo ketone **8**, whose identity was unequivocally proved from an X-ray analysis [CCDC 2411032‡], we were unfortunately unable to access enone **4** from **8** under base-promoted β-elimination. In fact, the XRD analysis of **8** (as reported earlier by Clark *et al.*,[12b] CCDC 2411032‡) showed a *syn* orientation of β-H with the α-Br atom. Additionally, epimerization of α-Br was considered probably not possible due to the 'α-H' of keto **8** being stabilized through an H-bonding interaction with 'O' of the ester (Scheme 2). Gratifyingly, a one-step procedure using SeO_2 under an elevated temperature afforded **4** in 82% yield.[13] The structure of **4** was also confirmed from an XRD analysis (CCDC 2417922‡). A plausible mechanism for enone formation through intermediate **7a** is shown in Scheme 3.

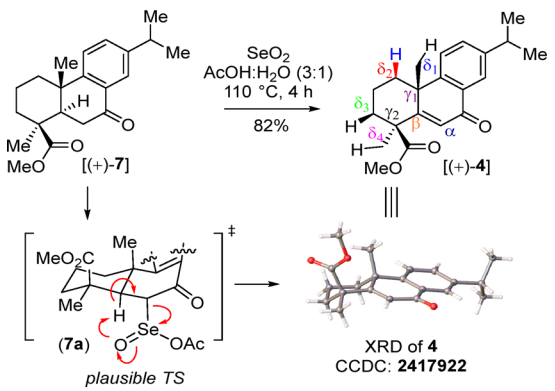
Having secured enone **4**, we next looked into the key Csp^3–H functionalization (Table 1). Towards this goal, we screened various conditions under metal-free formal C–H activation pathway affording Csp^3–H halogenation. Initially, we tried several reactions using iodine with $PhI(OAc)_2$ in the presence of light or under an elevated temperature. However, to our displeasure, these reactions led to a multitude of spots or decomposition of the mass balance. Initially, it was believed that the presence of angular methyl and axial ester at the 1,3-position of the A ring (Fig. 1) would create difficulties for the Csp^3–H bond activation.

Thus, we thought of investigating our previously reported conditions on the formal Csp^3–H functionalization (Table 1).[11a,b] We hence carried out a thorough screening of acids, solvents, electrophiles, and the best result was obtained using NBS as an electrophile in the presence of catalytic sulfuric acid in acetic anhydride solvent (Table 1). Following an exhaustive optimization, it was found that product **3** could be obtained in an isolated yield of 68% (entry 8, Table 1). Delightfully, secondary bromide **3** was obtained as a single diastereomer (dr > 20 : 1), suggesting a highly face-selective nature of this δ-Csp^3–H functionalization.

A proposed mechanism for the Csp^3–H functionalization of **4** with NBS in the presence of catalytic sulfuric acid is illustrated in Scheme 3. According to this proposal, activation of the enone **4** with acetic anhydride leads to enol acetate carbocation intermediate **4b** *via* protonated species **4a** (Scheme 3). Next, a *syn*-selective 1,2-migration of the angular methyl group occurs, forming olefin intermediate **4d** *via* a relatively stable benzylic carbocation **4c** (Scheme 3). Subsequently, the formation of a bromonium ion intermediate **4e** from the convex face is followed by another *syn*-selective 1,2-migration of the methyl group (see, intermediates **4f–g**) ultimately resulting in compound **3** as a single diastereomer (Scheme 4).[11b]

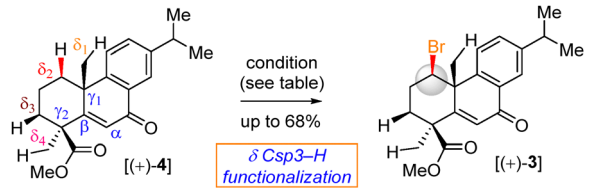


Scheme 2 Synthesis of α-bromo ketone **8**.



Scheme 3 Synthesis of enone [(+)-**4**].

Table 1 Optimization of δ-Csp^3–H functionalization of [(+)-**4**]

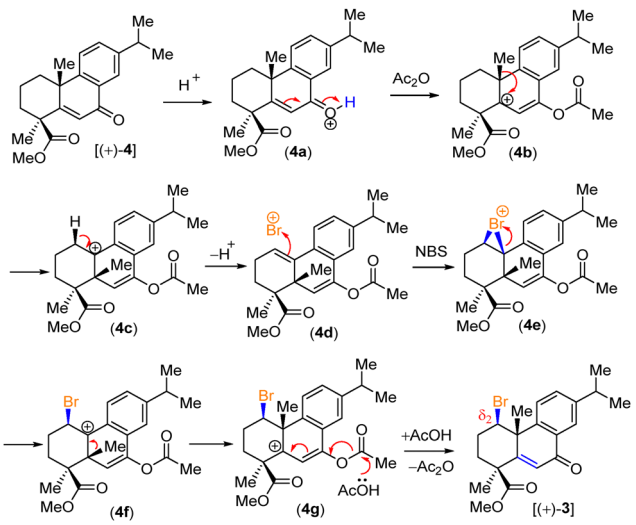


Entry	Solvent	Br$^+$ source	H$^+$ source (cata.)	Temp (°C)	Time (h)	Yield[a,b] (%)
1.	CH_2Cl_2	Br_2 (1.1 eq.)	HCl	20	8	—[c]
2.	Ac_2O	Br_2 (1.2 eq.)	AcOH	25	8	—[c]
3.	AcOH	NBS (1.2 eq.)	H_2SO_4	20	6	—[d]
4.	CH_2Cl_2	NBS (1.1 eq.)	H_2SO_4	20	4	13
5.	CH_2Cl_2	NBS (1.1 eq.)	H_2SO_4	25	8	17
6.	DCE[e]	NBS (1.1 eq.)	H_2SO_4	25	8	38
7.	Ac_2O	NBS (1.1 eq.)	H_2SO_4	25	2	57
8.	Ac_2O	NBS (1.1 eq.)	H_2SO_4	25	4	68
9.	Ac_2O	NBS (1.1 eq.)	H_2SO_4	30	4	63
10.	Ac_2O	NBS (1.1 eq.)	H_2SO_4	40	6	62

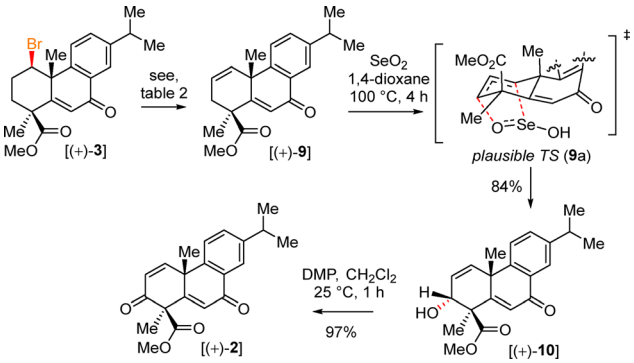
[a] Optimization reactions were carried out on 0.10 mmol of substrate. [b] Yields are reported for products obtained after column chromatography. [c] Starting materials at levels of 48–56% were recovered in addition to decomposition products. [d] Complex mixture of products. [e] DCE = 1,2-dichloroethane.

After successful δ-Csp^3-bromination, an E2-elimination of secondary bromide **3** was performed to achieve olefin **9** in 96% yield (Scheme 5 and Table 2).[14]

Next, allylic oxidation of olefin **9** with SeO_2 under an elevated temperature afforded allylic alcohol **10** in 84% yield as a single diastereomer (dr > 20 : 1). A plausible transition state for the allylic oxidation is depicted in Scheme 5. Due to steric hindrance created by the angular methyl group, SeO_2 was believed to approach from the α-face of **9**, forming a single diastereomer of **10**. Next, DMP oxidation of **10** afforded diketo intermediate **2** in 97% yield (Scheme 5). Furthermore, hydrogenation of bis-enone derivative **2** in the presence of 10% (w/w)



Scheme 4 Plausible mechanism of Csp^3–H bromination of [(+)-**4**].



Scheme 5 Synthesis of di-enone [(+)-**2**].

Table 2 Optimization of E2-elimination of secondary bromide **3**

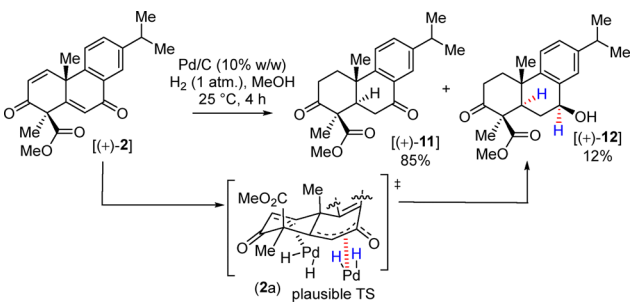
Entry[a]	Solvent	Base	Temp (°C)	Time (h)	Yield[b] (%)
1.	*o*-Xylene	DBU	140	6	45
2.	DMF	Na_2CO_3	155	6	52
3.	DMF	K_2CO_3	155	4	77
4.	DMF	Cs_2CO_3	155	1	96

[a] Optimization was carried out on 0.10 mmol of substrate. [b] Yields are reported for products obtained after column chromatography.

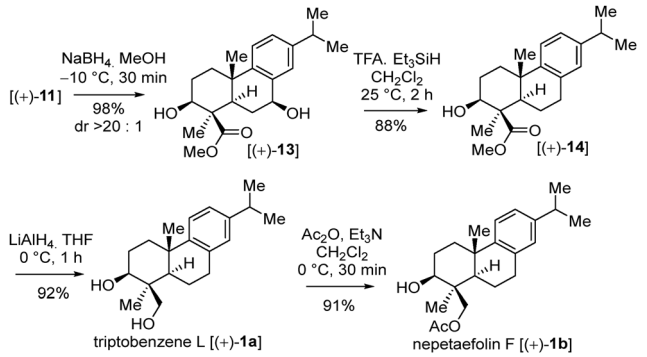
Pd/C and H_2 (1 atm.) furnished **11** in 85% yield along with **12** as an over-reduced product (Scheme 6). During a longer period of hydrogenation, the benzylic enone could also co-ordinate with the Pd surface and stereoselectively transfer H_2 onto the more exposed α-face of enone **2** (Scheme 6).

Next, a highly diastereoselective reduction of diketone **11** with $NaBH_4$ at −10 °C for 30 min furnished diol **13** in 98% yield with a dr > 20 : 1 (Scheme 7). With diol **13** secured, we then moved ahead with the synthesis of triptobenzene L (**1a**). Accordingly, chemoselective reduction of **13** using TFA/Et_3SiH furnished the β-hydroxy ester **14** in 88% yield, which was followed by $LiAlH_4$ reduction to complete the synthesis of triptobenzene L (**1a**) (Scheme 7). Along a similar line, a site-selective monoacetylation of triptobenzene L (**1a**) completed the total synthesis of nepetaefolin F (**1b**) (Scheme 7).

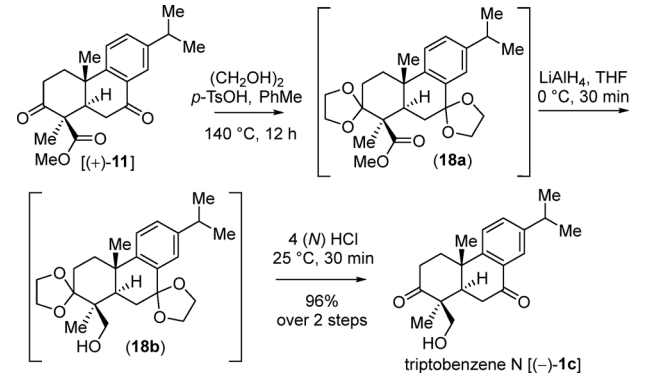
Next, total syntheses of triptobenzene N (**1c**) and triptobenzene R (**1d**) were undertaken (Schemes 8 and 9). In this regard, bis-ketal protection of **11** using excess equivalents of ethylene glycol in the presence of catalytic *p*-TSA under refluxing toluene



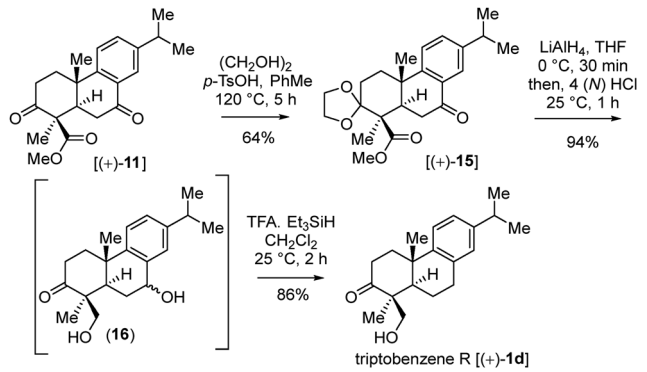
Scheme 6 Synthesis of di-ketone [(+)-**11**].



Scheme 7 Total syntheses of triptobenzene L [(+)-**1a**] and nepetaefolin F [(+)-**1b**].



Scheme 8 Total synthesis of triptobenzene N [(−)-**1c**].



Scheme 9 Total synthesis of triptobenzene R [(+)-**1d**].

furnished bis-ketal **18a** (Scheme 8).[15] Next, $LiAlH_4$ reduction of **18a** in the same pot (see **18b**) followed by deprotection of bis-ketal completed the first total synthesis of triptobenzene N (**1c**) (Scheme 8).

Conversely, the chemoselective ketal protection in refluxing toluene afforded **15** in 64% yield (Scheme 9).[16] Finally, $LiAlH_4$ reduction of ester **15** followed by the ketal deprotection (see diol **16**), and subsequent treatment with TFA/Et_3SiH completed the first total synthesis of triptobenzene R (**1d**) (Scheme 9).

In conclusion, the first total syntheses of the immunosuppressive diterpenoids triptobenzenes N (**1c**) and R (**1d**) have been accomplished *via* a key Csp^3–H functionalization. XRD analyses of enone **4** and α-bromoketone **8** indirectly confirmed the stereochemistry of the quaternary centers of these diterpenoids. Further application of this Csp^3–H functionalization strategy in the context of total syntheses of other complex natural products is ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included in the ESI.‡ CCDC 2411032 and 2417922 contain the crystallographic data for compounds **8** and **4** reported in this article.‡

Notes and references

1 H. Duan, Y. Takaishi, H. Momota, Y. Ohmoto, T. Taki, Y. Jia and D. Li, *J. Nat. Prod.*, 1999, **62**, 1522–1525.
2 C. G. Zhang, G. X. Chou, X. D. Mao, Q. S. Yang and J. L. Zhou, *J. Nat. Prod.*, 2017, **80**, 1742–1749.
3 J.-Y. Lia, Y. Peng, L.-Z. Lia, P.-Y. Gao, C. Gao, S.-X. Xia and S.-J. Song, *Helv. Chim. Acta*, 2013, **96**, 313–319.
4 J.-P. Bai and Y.-L. Shi, *Contraception*, 2002, **65**, 441–445.
5 J. Cibere, Z. Deng, Y. Lin, R. Ou, Y. He, Z. Wang, A. Thorne, A. J. Lehman, I. K. Tsang and J. M. Esdaile, *J. Rheumatol.*, 2003, **30**, 465–467.
6 J. M. Fidler, G. Y. Ku, D. Piazza, R. Xu, R. Jin and Z. Chen, *Transplantation*, 2002, **74**, 445–457.
7 J.-W. Yang and Y. Orihara, *Tetrahedron*, 2002, **58**, 1265–1270.
8 X. Li and R. G. Carter, *Org. Lett.*, 2018, **20**, 5546–5549.
9 X.-D. Mao, T.-T. Du, Q. Gu Li. Yang, H.-L. Shi, R. Hong and G.-X. Chou, *ACS Omega*, 2023, **8**, 14830–14840.
10 (*a*) R. Murmu, D. Jana, S. Noskar, M. Majhi and A. Bisai, *J. Org. Chem.*, 2025, **90**, 4973–4992; (*b*) R. Murmu, S. Kundu, M. Maji, S. Pal, A. Mondal and A. Bisai, *Chem. Commun.*, 2024, **60**, 9737–9740.
11 (*a*) H. Mizuno, T. Ohsawa and A. Tahara, *Chem. Pharm. Bull.*, 1976, **24**, 1527–1531; (*b*) M. Munda, R. Nandi, V. R. Gavit, S. Kundu, S. Niyogi and A. Bisai, *Chem. Sci.*, 2022, **13**, 11666–11671.
12 (*a*) M. Munda, D. Chatterjee, M. Majhi, S. Biswas, D. Pal and A. Bisai, *RSC Adv.*, 2024, **14**, 20420–20424; (*b*) J. F. Cutfield, T. N. Waters and G. R. Clark, *J. Chem. Soc., Perkin Trans. 2*, 1974, 150–157.
13 M. A. El Had, J. J. Guardia, J. M. Ramos, M. Taourirte, R. Chahboun and E. Alvarez-Manzaneda, *Org. Lett.*, 2018, **20**, 5666–5670.
14 R. P. Robinson, L. Buckbinder, A. I. Haugeto, P. A. McNiff, M. L. Millham, M. R. Reese, J. F. Schaefer, Y. A. Abramov, J. Bordner, Y. A. Chantigny, E. F. Kleinman, E. R. Laird, B. P. Morgan, J. C. Murray, E. D. Salter, M. D. Wessel and S. A. Yocum, *J. Med. Chem.*, 2009, **52**, 1731–1743.
15 J.-L. Dong, L.-S.-H. Yu and J.-W. Xie, *ACS Omega*, 2018, **3**, 4974–4985.
16 (*a*) F. Ono, H. Takenaka, T. Fujikawa, M. Mori and T. Sato, *Synthesis*, 2009, 1318–1322; (*b*) S. Kundu, D. Jana, N. Mandal, A. Mondal, R. Murmu, N. K. Roy, A. Datta and A. Bisai, *Chem. Sci.*, 2024, **15**, 14946–14953.

