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First total synthesis of type II abyssomicins: (\pm)-abyssomicin 2 and (\pm)-neoabyssomicin B \dagger

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The intramolecular Diels–Alder reaction (IMDA) of a butenolide derivative, as an entry to the type II abyssomicin scaffold, and the total synthesis of (\pm)-abyssomicin 2 and (\pm)-neoabyssomicin B are reported for the first time. A facile route to the IMDA precursor, the formation of a type I intermediate and two paths to (\pm)-neoabyssomicin B are also discussed.

The family of abyssomicins is a subclass of class I spirotetronate polyketides with fascinating architectures and engaging biological activities, comprising more than 40 members to date.^{1,2} According to their structure, abyssomicins are classified as type I, e.g. abyssomicin C (1), or their “enantiomeric” counterparts at C-15 type II, e.g. abyssomicin 2 (2) and neoabyssomicin B (3) (Fig. 1).^{1,3} Abyssomicin C (1) was the first member to captivate scientific interest due to its inhibitory activity against methicillin-resistant *Staphylococcus aureus* and other Gram-positive bacteria.⁴ Recently, type II abyssomicins have also garnered increasing attention. Thus, abyssomicin 2 (2) was discovered during screening to identify HIV-1 reactivators exhibiting latent HIV activation selectively and antimicrobial activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).⁵ Also, many studies have been performed on the biosynthetic pathways leading to both types of compounds,^{6–8} and many impressive syntheses have been reported for abyssomicin C (1) and type I analogues.^{9–11} However, no reported synthetic methods for type II abyssomicins exist.

A biomimetic strategy towards both types of compounds implies the construction of key-intermediates 4 (type I) or 6 (type II) from the corresponding substituted butenolides 5 or 7 via a stereoselective intramolecular Diels–Alder reaction

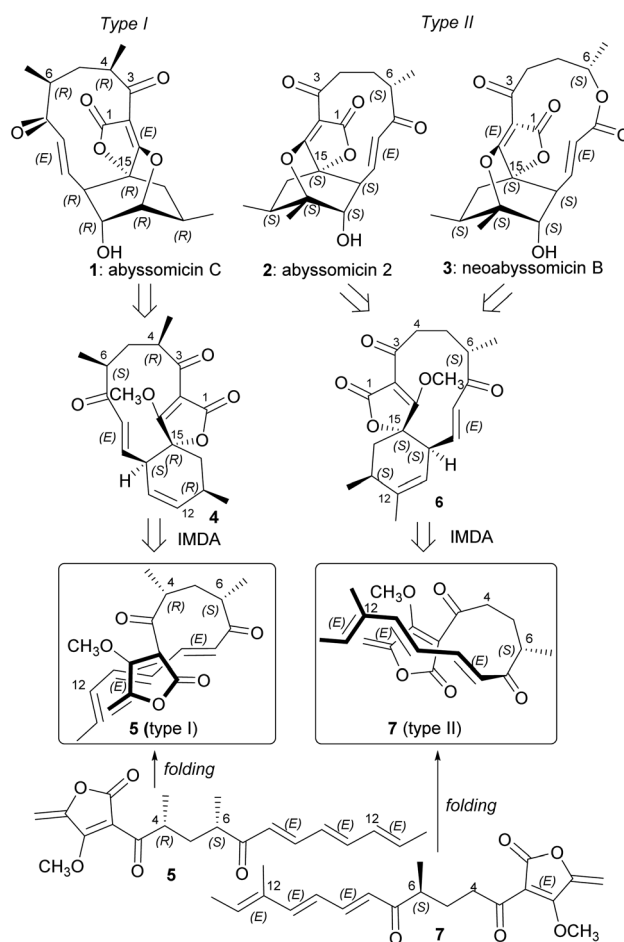


Fig. 1 Representative type I and type II abyssomicins and biomimetic approaches.

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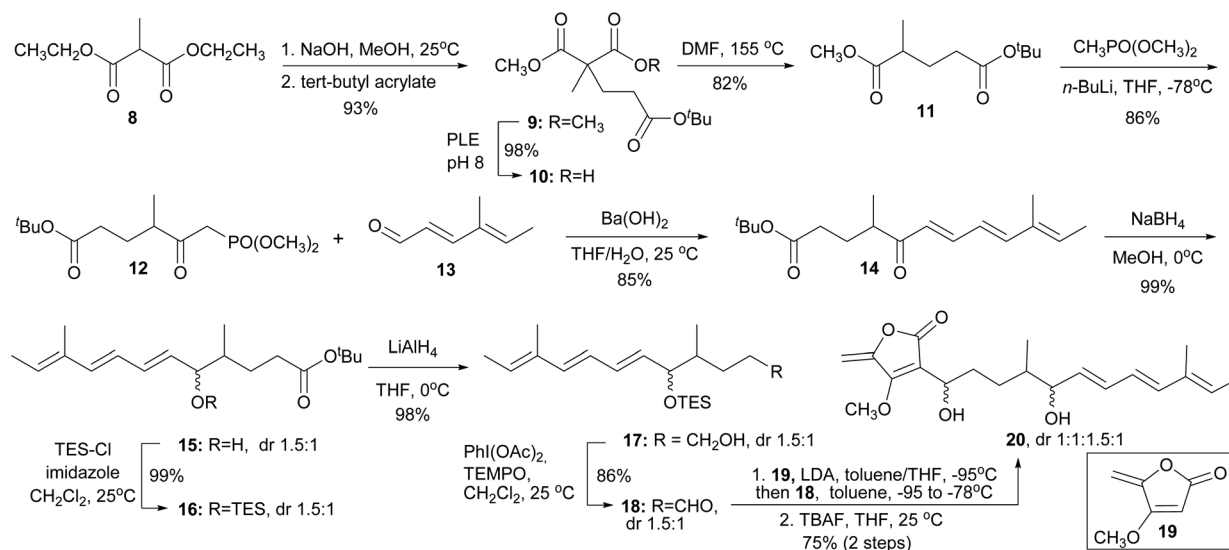
(IMDA) which establishes the carbon frameworks and their stereogenic centres in one step (Fig. 1).

This bioinspired approach has been applied successfully in the case of the type I abyssomicin scaffold by Sorensen, who first achieved the total synthesis of abyssomicin C (**1**) from **5** in 4 high-yielding steps.⁹ Other researchers also developed alternative biomimetic routes to intermediate **4**,^{10a,b} and we recently reported an improved formal synthesis of abyssomicin C (**1**) addressing synthetic issues of previous methods.^{10c} Notably, the two IMDA precursors, **5** and **7**, differ only in the position of one methyl group in the side chain (placed on C-4 at **5** and on C-12 at **7**), yet they must fold oppositely to lead to the desired systems. Although only the formation of type I isomer **4** from **5** has been reported, the stereochemical outcome of the cycloaddition of **7** and the chemical synthesis of type II carbon frameworks remain unexplored. Hence, we strove to explore the potential of this powerful transformation as an entry to type II abyssomicins and the chemistry of these fascinating systems.

Aiming to study the crucial IMDA of diketone **7**, we pursued a convenient racemic synthesis using readily available starting materials (Scheme 1). Consequently, starting from diethyl 2-methylmalonate (**8**), a Michael addition reaction of the sodium salt of dimethyl methylmalonate, prepared *in situ* after a deprotonation/transesterification reaction with NaOH in MeOH, on *tert*-butyl acrylate afforded triester **9**. This method proved superior to other procedures involving dimethyl methyl malonate as a starting material and NaH or tetrabutylammonium hydroxide as a base.¹² Selective hydrolysis of **9** to the desired mono acid **10** was first attempted using KOH in MeOH or EtOH.¹³ However, transesterification by-products were formed in this case. Moreover, the use of LiOH in THF led to **10** in poor yield (32%). Eventually, enzymatic hydrolysis of **9** with pig liver esterase (PLE) afforded **10** almost quantitatively, which after decarboxylation led to diester **11** in 82% yield.

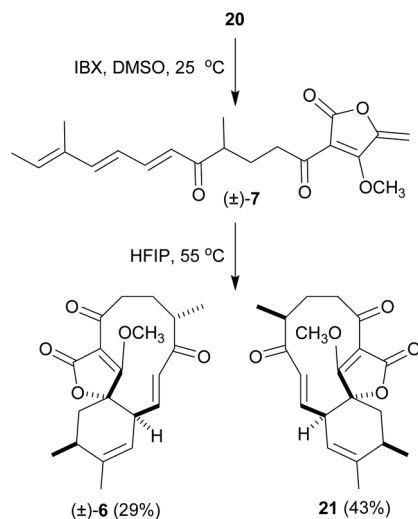
The latter was subjected to a selective nucleophilic substitution by the anion of dimethyl methyl phosphonate, completing the synthesis of ketophosphonate **12** in 86% yield. Subjection of the latter to a Wadsworth–Horner–Emmons reaction with the known aldehyde **13**, freshly prepared in three steps from tiglic aldehyde,¹⁵ using Ba(OH)₂ as a base¹⁶ established the required double bonds and the methyl substitution on the side chain and afforded the keto-ester **14** in high yield (85%) and geometrical purity (≥93% *all-trans*). Selective reduction and triethylsilylation of **14** generated *tert*-butyl ester **16** in 99% yield.^{11c} To our surprise, the direct reduction of **16** with DIBAL-H led to decomposition products and low yields of aldehyde **18**. In contrast, the use of LiAlH₄, furnished alcohol **17**, in 98% yield. Thus, oxidation of the latter with PhI(OAc)₂/TEMPO (86% yield) provided aldehyde **18**, which was subjected to an anionic coupling with tetronate **19**¹⁷ followed by desilylation of the corresponding alcohol to give rise to diol **20** in 75% yield over two steps. The above route allowed the convenient and scalable preparation of diol **20**, in 12 steps and 33.8% overall yield from **8**.

Subsequently, an oxidation-IMDA protocol that proved successful in the improved formal synthesis of abyssomicin C,^{10c} where the IMDA precursor **5** was sensitive, was applied on diol **20**. Thus, the [4 + 2]-cyclization was performed after oxidizing the latter to diketone (**±**)-**7**, omitting concentration after work-up or purification procedures (Scheme 2). 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was selected as an IMDA-solvent, as it has been shown to accelerate Diels–Alder reactions at low temperatures due to its hydrogen-bond donating ability and its low nucleophilicity.¹⁸ Although the oxidation step proceeded well, the direct addition of HFIP to the crude oxidation reaction mixture of **20** after its complete conversion to (**±**)-**7** led mainly to decomposition products. Thus, we turned to an alternative procedure, and HFIP was added to the ethereal extracts of diketone (**±**)-**7** from the oxidation reaction



Scheme 1 Preparation of diol **20**.





Scheme 2 Oxidation-IMDA reaction of 20.

mixture. The formation of two isomers was observed, the type I (\pm)-6 (29% yield) and the type II 21 (43% yield), respectively, indicating that precursor (\pm)-7 folds in two ways during cycloaddition. It should be noted that HFIP proved superior to other solvents, such as chloroform and toluene, resulting in lower yields and (\pm)-6/21 ratios. Although a systematic study and a thorough computational and experimental investigation are required to explore the reasons that affect the stereochemical results of this crucial reaction, it is noteworthy that divergent facial selectivities are observed in the IMDA reaction of the two precursors 5 and (\pm)-7, *i.e.*, by simply moving a methyl unit from C4 to C12. The mixture of the two isomers was inseparable by simple flash column chromatography, and preparative thin layer chromatography (prep TLC) was required for their complete separation.

The structure of 21 was further confirmed by X-ray analysis (Fig. 2).

Unfortunately, compound (\pm)-6 was sensitive to purification. It was isolated as a \sim 5:1 inseparable mixture with a cycloaddition product whose formation was observed after prep TLC.[‡] However, (\pm)-6 was successfully epoxidized with *m*-CPBA to afford 22, isolated as a single isomer, in 73% yield

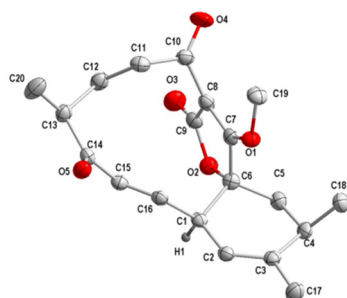
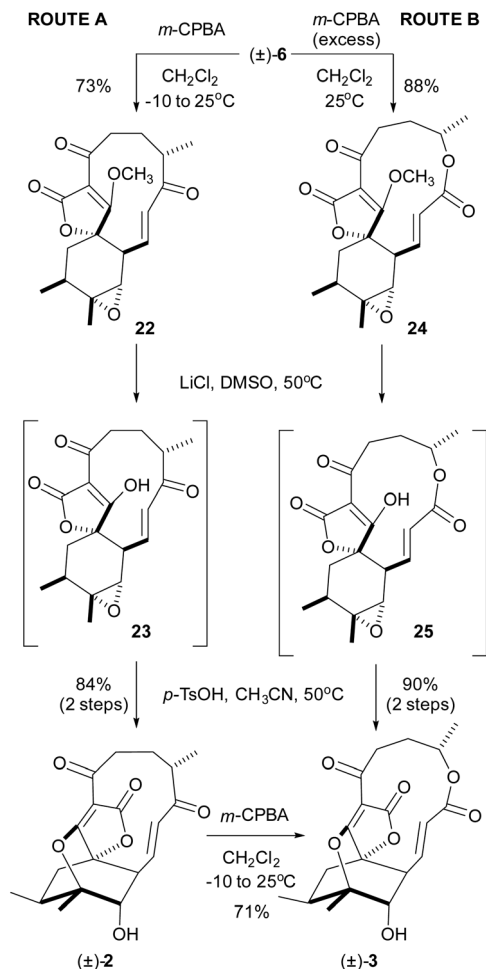


Fig. 2 Structure of 21 by X-ray analysis.

Scheme 3 Final transformations and completion of synthesis of (\pm)-abyssomicin 2 ((\pm)-2) and (\pm)-neoabyssomicin B ((\pm)-3).

(Scheme 3, route A). These conditions proved superior to the use of dimethyldioxirane,⁹ which led to a mixture of products and incomplete conversion of (\pm)-6 to 22. Moreover, a one-pot procedure, including demethylation of 22 with LiCl/DMSO and intramolecular epoxide opening, established the oxygen bridge and led to (\pm)-abyssomicin 2 ((\pm)-2) in 84% yield. Lastly, a Baeyer-Villiger oxidation of the latter with *m*-CPBA led to (\pm)-neoabyssomicin B ((\pm)-3) in 71% yield (43.5% from (\pm)-6). The above sequence of transformations agrees with those proposed biosynthetically.⁸ However, an alternative route to (\pm)-3 from (\pm)-6, where the Baeyer-Villiger oxidation of the 11-membered ring ketone precedes the formation of the oxygen bridge, was ensured by using an excess of *m*-CPBA, followed by demethylation and *in situ* intramolecular epoxide opening of the resulting epoxide lactone 24 (Scheme 3, route B). This sequence of transformations led to (\pm)-3 in substantially higher yield (79% from (\pm)-6) than route A. The pathway *via* route B introduces an alternative sequence of transformations to neoabyssomicin B, which is worth investigating biosynthetically.



Conclusions

In conclusion, the first total synthesis of type II abyssomicins was achieved *via* an efficient methodology based on a biomimetic approach involving the IMDA of a suitably substituted butenolide derivative. A facile racemic synthetic route was developed for a proof of concept. Thus, the synthesis of the IMDA precursor (\pm)-7 was based on an efficient coupling of tetronate derivative **19** with aldehyde **18**, prepared *via* a convenient high-yielding barium-assisted Wadsworth–Horner–Emmons reaction to establish the sensitive keto–triene side chain. In contrast to the IMDA of abyssomicin C precursor **5**, providing type I isomer **4** as a single isomer, the cycloaddition of (\pm)-7 gives rise to type II and type I isomers (\pm)-**6** and **21**, respectively, providing an entry to both types of abyssomicin systems. Thus, the key-intermediate (\pm)-**6** led to (\pm)-abyssomicin **2** ((\pm)-**2**), which was prepared in 16 steps from **8** and 6% overall yield. Also, two sequences of transformations from (\pm)-**6** led to (\pm)-neoabyssomicin B ((\pm)-**3**) manoeuvring a Baeyer–Villiger reaction after or before the formation of the oxygen bridge, with the second one being more efficient. Thus, (\pm)-**3** was prepared from **8** in 17 steps and 4.3% overall yield *via* (\pm)-abyssomicin **2** ((\pm)-**2**), as proposed biosynthetically, or in 16 steps and 7.8% overall yield *via* the epoxide–lactone **24**, introducing a possible different biosynthetic pathway. The stereoselectivity of the IMDA reaction and the subsequent transformations to the final products also allow application of this approach to the asymmetric synthesis of **2** and **3** starting from **7**. The information obtained from studying the above systems enriched our knowledge of the exciting world of abyssomicins. The factors that affect the stereochemical outcome of the IMDA reaction in order to control it in one direction and the development of an asymmetric route to these natural products and new abyssomicin systems are under investigation and will be reported in due course.

Author contributions

A. C. methodology, investigation, data curation, validation, writing part of original draft, review, editing, funding acquisition. G. D. A. investigation, validation; V. P., C. P. R. formal analysis and methodology; J. M. H. data curation; V. M. data curation, writing – original draft; A. S. F. investigation, data curation, review and editing; E. A. C. writing part of the original draft, review and editing; V. P. V. conceptualization, project administration, supervision, resources, data curation, visualization, writing – original draft, review and editing.

Conflicts of interest

There are no conflicts to declare.

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References

† The structure of this by-product could not be fully elucidated, but it was presumably attributed to the formation of a ring similar to the abyssomicin D system. See ESI† for details.

- For a review on abyssomicins, see: C. Sadaka, E. Ellsworth, P. R. Hansen, R. Ewin, P. Damborg and J. L. Watts, *Molecules*, 2018, **23**, 1371.
- For more recent discoveries, see: (a) N. Bunbamrung, S. Kittisrisopit, C. Intaraudom, A. Dramaee, C. Thawai, N. Niemhom, D. J. Harding, P. Auncharoen and P. Pittayakhajonwut, *Phytochemistry*, 2021, **185**, 11270; (b) J. Zhang, B. Li, Y. Qin, L. Karthik, G. Zhu, C. Hou, L. Jiang, M. Liu, X. Ye, M. Liu, T. Hsiang, H. Dai, L. Zhang and X. Liu, *Appl. Microbiol. Biotechnol.*, 2020, **104**, 1533–1543; (c) H. Huang, Y. Song, X. Li, X. Wang, C. Ling, X. Qin, Z. Zhou, Q. Li, X. Wei and J. Ju, *J. Nat. Prod.*, 2018, **81**(8), 1892–1898; (d) N. Bunbamrungr, C. Intaraudoma, A. Dramaee, C. Thawail, S. Tadtong, P. Auncharoen and P. Pittayakhajonwuta, *Phytochemistry*, 2020, **172**, 112275.
- (a) Y. Song, Q. Li, F. Qin, C. Sun, H. Liang, X. Wei, N. Wong, L. Ye, Y. Zhang, M. Shao and J. Ju, *Tetrahedron*, 2017, **73**, 5366–5372; (b) A. Alsultan, M. Aatif and G. Muteeb, *Pharmacogn. Mag.*, 2022, **18**, 80.
- For isolation and bioactivity of abyssomicin C and its atropisomer, see: (a) B. Bister, D. Bischoff, M. Strobele, J. Riedlinger, A. Reicke, F. Wolter, A. T. Bull, H. Zahner, H.-P. Fiedler and R. D. Sussmuth, *Angew. Chem., Int. Ed.*, 2004, **43**, 2574–2576, (*Angew. Chem.*, 2004, **116**, 2628–2630); (b) J. Riedlinger, A. Reicke, H. Zahner, B. Krismer, A. T. Bull, L. A. Maldonado, A. C. Ward, M. Goodfellow, B. Bister, D. Bischoff, R. D. Sussmuth and H.-P. Fiedler, *J. Antibiot.*, 2004, **57**, 271–279; (c) S. Keller, H. S. Schadt, I. Ortel and R. D. Sussmuth, *Angew. Chem., Int. Ed.*, 2007, **46**, 8284–8286, (*Angew. Chem.*, 2007, **119**, 8433–8435); (d) J. S. Freundlich, M. Lalgondar, J.-R. Wei, S. Swanson, E. J. Sorensen, E. J. Rubin and J. C. Sacchetini, *Tuberculosis*, 2010, **90**, 298–300; (e) H.-P. Fiedler, *Mar. Drugs*, 2021, **19**, 299.
- (a) Y. Igarashi, L. Yu, S. Miyana, T. Fukuda, N. Saitoh, H. Sakurai, I. Saiki, P. Alonso-Vega and M. E. Trujillo, *J. Nat. Prod.*, 2010, **73**, 1943–1946; (b) B. Leon, G. Navarro, B. J. Dickey, G. Stepan, A. Tsai, G. S. Jones, M. E. Morales, T. Barnes, S. Ahmadyar, M. Tsiang, R. Geleziunas, T. Cihlar, N. Pagratis, Y. Tian, H. Yu and R. G. Linington, *Org. Lett.*, 2015, **17**, 262–265.
- (a) M. H. Lacoske and E. A. Theodorakis, *J. Nat. Prod.*, 2015, **78**, 562–575; (b) A. Braddock and E. A. Theodorakis, *Mar. Drugs*, 2019, **17**, 232–247.



- 7 (a) E. M. Gottardi, J. M. Krawczyk, H. von Suchodoletz, S. Schadt, A. Mühlenweg, G. C. Uguru, S. Pelzer, H.-P. Fiedler, M. J. Bibb, J. E. M. Stach and R. D. Süßmuth, *ChemBioChem*, 2011, **12**, 1401–1410; (b) L. Vieweg, S. Reichau, R. Schobert, P. F. Leadlay and R. D. Süßmuth, *Nat. Prod. Rep.*, 2014, **31**, 1554–1584.
- 8 (a) J. Tu, S. Li, J. Chen, Y. Song, S. Fu, J. Ju and Q. Li, *Microb. Cell Fact.*, 2018, **17**, 28; (b) Q. Li, W. Ding, J. Tu, C. Chi, H. Huang, X. Ji, Z. Yao, M. Ma and J. Ju, *ACS Omega*, 2020, **32**(5), 20548–20557; (c) Q. Li, W. Ding, Z. Yao, J. Tu, L. Wang, H. Huang, S. Li and J. Ju, *Org. Lett.*, 2018, **20**, 4854–4857; (d) X. Ji, J. Tu, Y. Song, C. Zhang, L. Wang, Q. Li and J. Ju, *ACS Catal.*, 2020, **10**, 2591–2595; (e) W. Ding, C. Chi, X. Wei, C. Sun, J. Tu, M. Ma, Q. Li and J. Ju, *Chin. J. Chem.*, 2021, **39**(7), 1871–1877.
- 9 For a biomimetic total synthesis of abyssomicin C, see: C. W. Zapf, B. A. Harrison, C. Drahl and E. J. Sorensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 6533–6537, (*Angew. Chem.*, 2005, **117**, 6691–6695).
- 10 For improved formal biomimetic syntheses of abyssomicin C, see: (a) B. Snider and Y. Zou, *Org. Lett.*, 2005, **7**, 4939–4941; (b) E. A. Couladouros, E. A. Bouzas and A. D. Magos, *Tetrahedron*, 2006, **62**, 5272–5279; (c) V. P. Vidali, A. Canko, A. D. Peroulis, E. T. Georgas, E. Bouzas, J. M. Herniman and E. A. Couladouros, *Eur. J. Org. Chem.*, 2020, 4547–4557.
- 11 For other total syntheses, hemisynthesis and synthesis of abyssomicin C analogues and other type I systems, see: (a) K. C. Nicolaou and S. T. Harrison, *Angew. Chem., Int. Ed.*, 2006, **45**, 3256–3260, (*Angew. Chem.*, 2006, **118**, 3334–3338); (b) K. C. Nicolaou and S. T. Harrison, *J. Am. Chem. Soc.*, 2007, **129**, 429–440; (c) K. C. Nicolaou, S. T. Harrison and J. S. Chen, *Synthesis*, 2009, 33–42; (d) F. Bihelovic and R. N. Saicic, *Angew. Chem., Int. Ed.*, 2012, **51**, 5687–5691, (*Angew. Chem.*, 2012, **124**, 1–6); (e) F. Bihelovic, I. Karadzic, R. Matovic and R. N. Saicic, *Org. Biomol. Chem.*, 2013, **11**, 5413–5424; (f) Q. Wang, F. Song, X. Xiao, P. Huang, L. Li, A. Monte, W. M. Abdel-Mageed, J. Wang, H. Guo, W. He, F. Xie, H. Dai, M. Liu, C. Chen, H. Xu, M. Liu, A. M. Piggott, X. Liu, R. J. Capon and L. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1231–1234, (*Angew. Chem.*, 2013, **125**, 1269–1272); (g) R. Matovic, F. Bihelovic, M. Gruden-Pavlovic and R. N. Saicic, *Org. Biomol. Chem.*, 2014, **12**, 7682–7685; (h) L. Monjas, P. Fodran, J. Kollback, C. Cassani, T. Olsson, M. Genheden, D. G. J. Larsson and C.-J. Wallentin, *Beilstein J. Org. Chem.*, 2019, **15**, 1468–1474; (i) A. L. Zografos, A. Yiotakis and D. Georgiadis, *Org. Lett.*, 2005, **7**, 4515–4518.
- 12 (a) H. Quast and J. Christ, *Liebigs Ann.*, 1984, **6**, 1180–1192; (b) H. Quast, J. Christ, Y. Gorlach and W. von der Saal, *Tetrahedron Lett.*, 1982, **23**, 3653–3656; (c) Y. Odanaka, T. Kanemitsu, K. Iwasaki, Y. Mochizuki, M. Miyazaki, K. Nagata, M. Kato and T. Itoh, *Tetrahedron*, 2019, **75**, 209–219.
- 13 M. Newcomb, J. H. Horner, M. A. Filipkowski, C. Ha and S.-U. Park, *J. Am. Chem. Soc.*, 1995, **117**, 3674–3684.
- 14 S. Banerjee, W. J. Wiggins, J. L. Geoghegan, C. T. Anthony, E. A. Woltering and D. S. Masterson, *Org. Biomol. Chem.*, 2013, **11**, 6307–6319.
- 15 (a) J.-H. Zhou, B. Jiang, F.-F. Meng, Y.-H. Xu and T.-P. Loh, *Org. Lett.*, 2015, **17**, 4432–4435; (b) J. Wunderlich, T. Roß, M. Schröder and F. Hahn, *Org. Lett.*, 2020, **22**, 4955–4959.
- 16 (a) S. Jeanmart, *Synlett*, 2002, 1739–1740; (b) I. Paterson, K.-S. Yeung and J. B. Smaill, *Synlett*, 1993, 774–776; (c) S. K. Chattopadhyay and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2429; (d) K. C. Nicolaou, Y. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou and A. O'Brate, *J. Am. Chem. Soc.*, 2003, **125**, 15443–15454.
- 17 (a) K. Horo, N. Hikage, A. Inagaki, S. Mori, K. Nomura and E. Yoshii, *J. Org. Chem.*, 1992, **57**, 2888–2902; (b) F. F. Paintner, G. Bauschke and M. Kestel, *Tetrahedron Lett.*, 2000, **41**, 9977–9980.
- 18 For other examples of the use of HFIP in Diels–Alder reactions, see: (a) E. Tzouma, I. Mavridis, V. P. Vidali and E. N. Pitsinos, *Tetrahedron Lett.*, 2016, **57**, 3643–3647; (b) C. Cativiela, J. I. García, A. J. Royo and L. Salvatella, *Tetrahedron: Asymmetry*, 1993, **4**, 1613–1618; (c) C. Cativiela, J. I. García, J. A. Mayoral and L. Salvatella, *Can. J. Chem.*, 1994, **72**, 308–311; (d) C. Cativiela, J. I. García, J. Gil, R. M. Martínez, J. A. Mayoral, L. Salvatella, J. S. Urieta, A. M. Mainar and M. H. Abraham, *J. Chem. Soc., Perkin Trans. 2*, 1997, 653–660; (e) For an interesting review on the uses of HFIP, see: I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, *Nat. Rev. Chem.*, 2017, **1**, 0088–0100.

