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Serendipitous synthesis of cross-conjugated dienes by cascade deconstructive esterification of thiomorpholinone-tethered alkenoic acids†

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Functionalized 1,3-dienes are ubiquitous structural motifs in biologically pertinent molecules. They are frequently employed as precursors for a broad range of chemical transformations, including Diels–Alder reactions. The stereoselective construction of highly decorated 1,3-dienes therefore represents an important research objective. Medicinal chemists are becoming increasingly interested in synthetic methodologies that not only achieve expedient construction and peripheral editing of heterocycles, but also seek to modify their core framework in order to achieve skeletal remodeling. In a succinct manifestation of this 'scaffold hopping' concept, we herein describe a cascade reaction, which converts thiomorpholinone-tethered alkenoic acids to 1,1-disubstituted amino-1,3-dienes. This domino process involves esterification of the acid, base-assisted ring-opening, and concomitant 1,2-migration of the α-amino alkenyl group. Several control experiments have revealed that the alkenyl substituent is necessary for deconstruction to occur. Inherently more activated *N*-aryl-substituted thiomorpholinone acids react significantly faster than their less activated *N*-alkyl congeners.

Functionalized 1,3-dienes are omnipresent scaffolds in biologically pertinent molecules and also feature as precursors for a broad range of chemical transformations.[1] Examples include metathesis, ene reactions, reductive aldolization, or cycloaddition. Specifically, the increased reactivity of amino-substituted 1,3-dienes in the heteroatom-assisted Diels–Alder reaction allows for the facile preparation of functional arrays, which would otherwise be difficult to obtain through conventional modes of reactivity.[2] Indeed, bimolecular and intramolecular Diels–Alder reactions of 1-*N*-acylamino-1,3-dienes have been well-studied and typically proceed with a high degree of regioselectivity and facial selectivity.[3] It is now fully appreciated that the alkene geometry influences the stereochemical outcome and the efficiency of reactions involving 1,3-dienes.[4] Hence, several synthetic methods have been developed for the stereoselective construction of substituted 1,3-dienes.[5]

Sulfur-containing compounds are highly prevalent in natural and various biological systems.[6] The divalent sulfur atom introduces a metabolic liability from a drug discovery standpoint.[7,8] Specifically, the 1,4-thiomorpholine moiety has been widely encountered in a variety of bioactive products including DPP-IV inhibitors,[9] anti-inflammatory drugs,[10] antimycobacterial agents,[11] and hypolipidemic compounds.[12–15] We previously revealed that base-assisted methyl esterification of *N*-alkyl thiomorpholinone acids of type **1** (Fig. 1A) at room temperature, followed by Vilsmeier–Haack functionalization afforded dihydro-1,4-thiazines such as **2**.[16] During the course of the aforementioned studies, when a thiomorpholinone acid

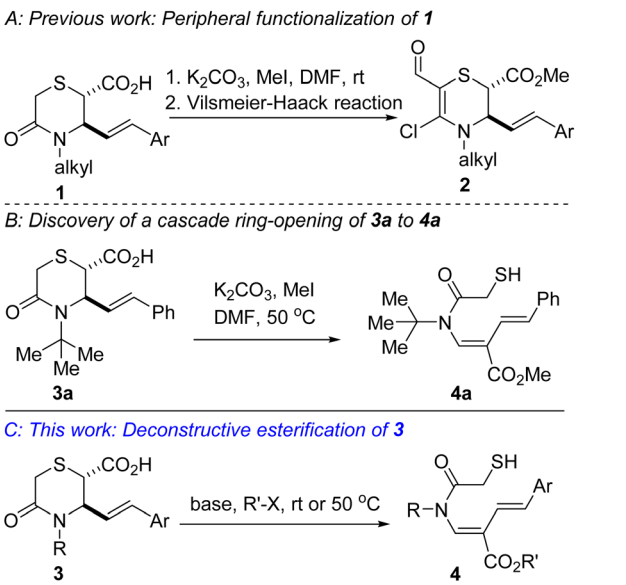

Fig. 1 (A) Peripheral functionalization of *N*-alkylated allylic thiomorpholinone acids, (B) serendipitous discovery of a deconstructive esterification protocol, (C) proposed plan for the synthesis of cross-conjugated aminodienes of type **4**.

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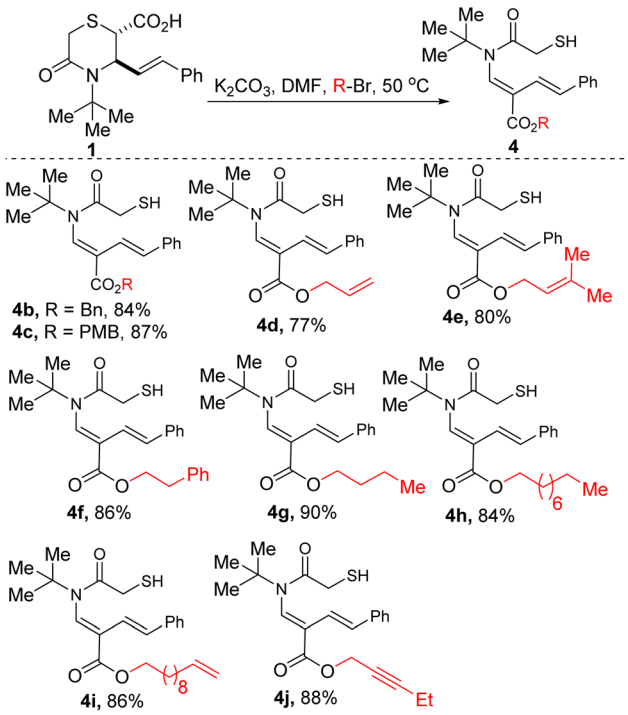
bearing a bulky *tert*-butyl group (*i.e.*, **3a**), was methylated at 50 °C, the expected lactam ester was not observed. Instead, ring-opened product **4a** was obtained (Fig. 1B). Notably, **4a** contains the β-enamino ester subunit, which is a well-recognized synthon for accessing azaheterocyclic architectures such as indoles, quinolines, pyridinones, and amino-furanones.[17] Additionally, **4a** harbors the highly versatile *N*,*N*-disubstituted-1,3-aminodiene motif.

Desiring an expedient and practical approach for accessing cross-conjugated aminodienes of type **4a**, as well as to gain a full understanding of the mechanistic underpinnings of the transformation, we sought to build on the aforementioned lone example by examining the scope of deconstructive esterification of thiomorpholinone-tethered alkenoic acids (Fig. 1C). Intrinsic to our design was the prospect of exploiting this cascade reaction, given that such domino processes are inherently step and atom-economical. Cascade reactions often lead to a reduction in the amount of waste and in the number of purification steps. Efforts toward the elicitation of our ideals are described herein.

We commenced these studies by benchmarking our optimization efforts toward the synthesis of cross-conjugated aminodienes with the reaction conditions described in Table 1. In the event, using acid **3a**, K_2CO_3 emerged as the most effective base and DMF emerged as the solvent of choice.

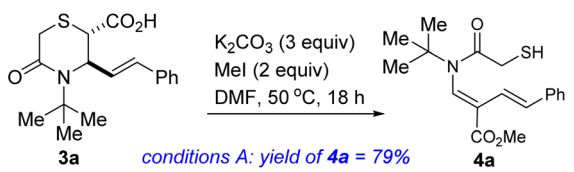
Under these mild conditions, the scope of this cascade esterification and ring-opening protocol with respect to the organic bromide was explored. In the event, the differentially substituted β-enaminoates depicted in Scheme 1 were obtained. Benzyl-, allyl-, alkyl-, and propargyl bromides are all competent electrophiles. The synthesis of ring-closing metathesis-suitable trienes such as **4d/e/i** sets the stage for the late-stage construction of medium- and large-sized lactones.

We have explored the scope of this deconstructive esterification protocol with respect to the electronic properties of the



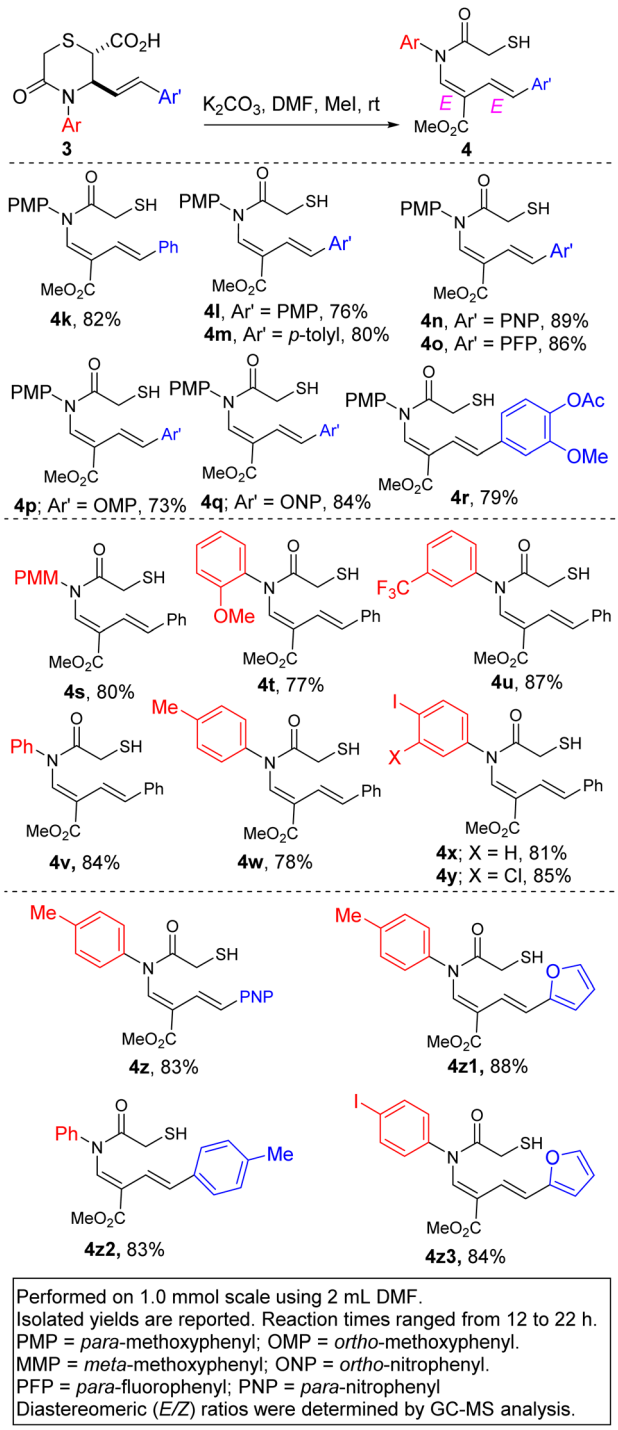
Scheme 1 Deconstructive esterification of allylic thiomorpholinone acid **3a** with various organic bromides.

Table 1 Optimization of the deconstructive functionalization of allylic thiomorpholinone acid **3a**



Entry	Deviation from conditions A	% Yield of **4a**
1	Tetrahydrofuran (THF) as solvent	66
2	2-Methyltetrahydrofuran (2-MeTHF) as solvent	70
3	Acetonitrile (MeCN) as solvent	52
4	*N*,*N*-Dimethylacetamide (DMA) as solvent	73
5	DMSO as solvent	59
6	Na_2CO_3 in place of K_2CO_3	75
7	Cs_2CO_3 in place of K_2CO_3	70
8	CsF in place of K_2CO_3	59
9	$NaHCO_3$ in place of K_2CO_3	38
10	$KHCO_3$ in place of K_2CO_3	57
11	After 48 h at room temperature	28

alkenyl moiety. After noticing that the *N*-aryl substituted thiomorpholinone acids underwent deconstructive methylation faster than **3a**, the former were used to evaluate the scope. In the event, we find that lactam acids harboring both electron-rich and electron-deficient styrenyl groups react competently (Scheme 2, **4k–r**). At present, the synthesis of alkenoic acid **3** is limited to cinnamaldehyde-derived α,β-unsaturated imines, which explains why we have not evaluated other alkene groups. Knowing that the nature of the nitrogen substituent present on a nitrogen-containing compound can have a dramatic effect on its biological activity and reactivity, lactam acids bearing diverse aryl substitution on nitrogen have been surveyed (see **4s–y**). The results show that electronically diverse *N*-aryl substituents are amenable to this deconstructive esterification protocol. Additionally, *ortho*-substituted aryl moieties can be installed (see **4t**). The incorporation of a fluorinated moiety (see **4o**) generally increases the solubility, lipophilicity, and metabolic stability of the parent molecules, thus, explaining why ~25% of existing preclinical drugs and 40% of agrochemicals contain at least one fluorine atom.[18] Specifically, the CF_3 group enjoys a privileged role because its incorporation often enhances efficacy by promoting electrostatic interactions with targets, improving cellular membrane permeability, and increasing robustness toward oxidative metabolism of the drug.[19] It is therefore noteworthy that diene **4u**, which bears a CF_3 group, is obtainable in good yield. Simultaneous variation of the *N*-aryl substituent and the styrenyl unit has also been achieved (see **4z–z3**).[21] Iodoarylated substituents are well tolerated in this transformation (see **4x**, **4y**, and **4z3**), which bodes well for late-stage



Performed on 1.0 mmol scale using 2 mL DMF.
Isolated yields are reported. Reaction times ranged from 12 to 22 h.
PMP = *para*-methoxyphenyl; OMP = *ortho*-methoxyphenyl.
MMP = *meta*-methoxyphenyl; ONP = *ortho*-nitrophenyl.
PFP = *para*-fluorophenyl; PNP = *para*-nitrophenyl
Diastereomeric (*E*/*Z*) ratios were determined by GC-MS analysis.

Scheme 2 Scope of deconstructive methylesterification of allylic thiomorpholinone acids.

diversification given that the iodo group is an excellent requisite group for cross-coupling purposes.[20]

A plausible mechanism for the deconstructive esterification, which takes advantage of the relatively weak C–S bond, involves base-assisted *O*-methylation of **3b** to arrive at **5**, which undergoes base-assisted elimination to furnish **6** (Fig. 2). The cascade process continues with concomitant 1,2-styryl migration to afford the 1,3-diene (*i.e.*, **4a**), following aqueous workup.

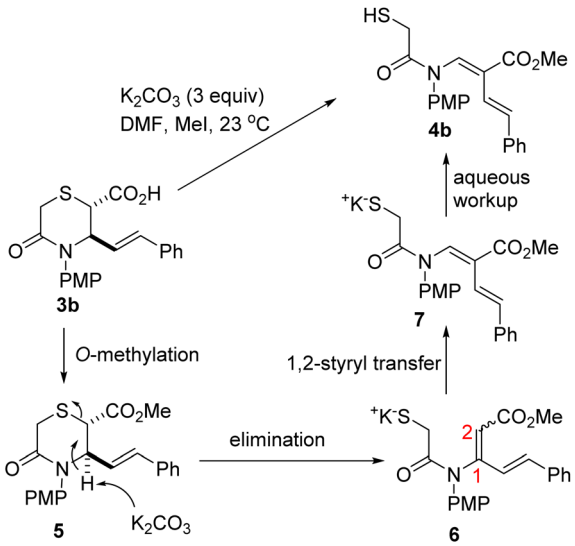
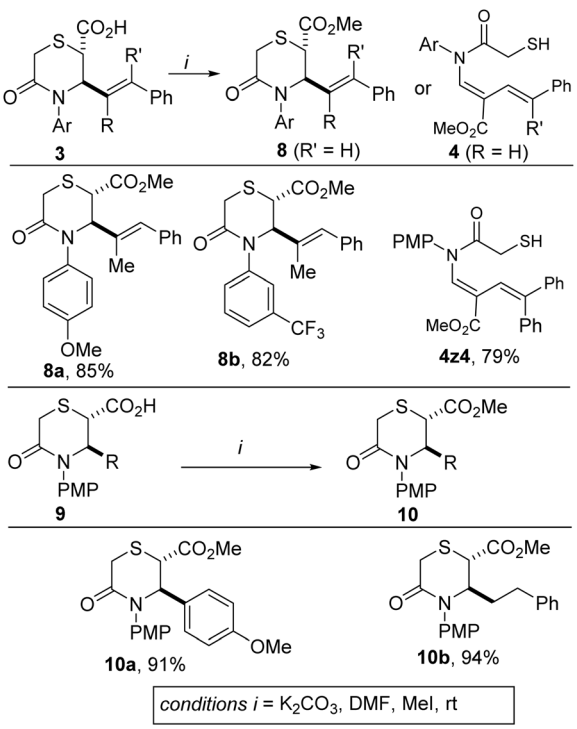


Fig. 2 Proposed pathway for the deconstructive esterification (substrate **3b** is chosen for simplicity).

Some mechanistically intuitive experiments have revealed that *N*-aryl-substituted thiomorpholinone acids bearing internally trisubstituted styrenes are not amenable to base-mediated ring-opening at room temperature (Scheme 3, see **8a**/**b**). However, a thiomorpholinone-tethered externally trisubstituted alkenoic acid does undergo successful deconstructive methylation (see **4z4**). We attribute the failure to observe ring-opening in **8a**/**b** to steric encumbrance imposed by the methyl group,



Scheme 3 Control experiments on the methylesterification of diverse thiomorpholinone acids.

which is closer to the reactive center. In the case of **4z4**, although the additional phenyl group is sterically more imposing than a methyl group, it is positioned further away from the reactive site. The sensitivity of the deconstructive esterification to steric congestion is further highlighted by the observation that no ring-opening occurs when the alkenyl group resident in **3b** is replaced by an electronically more suitable aryl group (see **10a**). An alkyl-substituted thiomorpholinone does not undergo ring-opening (see **10b**), probably because in this case, the α-amino proton is not acidic enough for deprotonation by K_2CO_3.

In summary, versatile cross-conjugated thiol-bearing aminodienes have been prepared in a stereocontrolled and modular manner, by engaging thiomorpholinone-tethered alkenoic acids in a cascade process featuring esterification, base-mediated ring opening and concomitant 1,2-styryl migration. Whereas *N*-arylated allylic thiomorpholinones readily undergo deconstructive esterification, the less activated *N*-alkylated congeners are less charitable substrates and require heating to 50 °C. The C6-alkenyl substituent is necessary for ring-opening to occur. However, the deconstructive esterification is quite sensitive to the stereoelectronic properties of the alkene. The interrogation of **4** in Diels–Alder reactions as well as the evaluation of their leishmanicidal activities are underway.

Author contributions

A. O. F. – investigation, data curation, validation; J. G. – investigation, methodology; C. B. – investigation, methodology; T. K. B. – conceptualization, project administration, investigation, supervision, writing – original draft, funding acquisition.

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references

1 (*a*) W. C. White, *Chem.-Biol. Interact.*, 2007, **166**, 10–14; (*b*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (*c*) M. S. McCammant, L. Liao and M. S. Sigman, *J. Am. Chem. Soc.*, 2013, **135**, 4167–4170; (*d*) Q.-A. Chen, D. K. Kim and V. M. Dong, *J. Am. Chem. Soc.*, 2014, **136**, 3772–3775; (*e*) Y. Zhu, R. G. Cornwall, H. Du, B. Zhao and Y. Shi, *Acc. Chem. Res.*, 2014, **47**, 3665–3678; (*f*) J. R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Rev.*, 2015, **115**, 5301–5365; (*g*) J. Han, A. X. Jones and X. Lei, *Synthesis*, 2015, **47**, 1519–1533; (*h*) S. Kotha, A. S. Chavan and D. Goyal, *ACS Comb. Sci.*, 2015, **17**, 253–302; (*i*) V. Saini, M. O'Dair and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 608–611; (*j*) Z.-L. Tao, A. Adili, H.-C. Shen, Z.-Y. Han and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2016, **55**, 4322–4326; (*k*) N. J. Adamson, E. Hull and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2017, **139**, 7180–7183; (*l*) A. H. Christian, Z. L. Niemeyer, M. S. Sigman and F. D. Toste, *ACS Catal.*, 2017, **7**, 3973–3978; (*m*) N. K. Mishra, S. Sharma, J. Park, S. Han and I. S. Kim, *ACS Catal.*, 2017, **7**, 2821–2847; (*n*) X.-H. Yang and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 1774–1777.

2 J. Barluenga, A. Suarez-Sobrino and L. A. Lopez, *Aldrichimica Acta*, 1999, **32**, 4.

3 (*a*) L. E. Overman and L. A. Clizbe, *J. Am. Chem. Soc.*, 1976, **98**, 2352; (*b*) L. E. Overman, G. F. Taylor, K. N. Houk and L. S. Domelsmith, *J. Am. Chem. Soc.*, 1978, **100**, 3182; (*c*) W. Oppolzer, L. Bieber and E. Francotte, *Tetrahedron Lett.*, 1979, **20**, 4537; (*d*) L. E. Overman, R. L. Freerks, C. B. Petty, L. A. Clizbe, R. K. Ono, G. F. Taylor and P. J. Jessup, *J. Am. Chem. Soc.*, 1981, **103**, 2816; (*e*) A. D. Brosius, L. E. Overman and L. Schwink, *J. Am. Chem. Soc.*, 1999, **121**, 700.

4 Y. N. Timsina, S. Biswas and T. V. RajanBabu, *J. Am. Chem. Soc.*, 2014, **136**, 6215–6218.

5 (*a*) T.-J. Hu, M.-Y. Li, Q. Zhao, C.-G. Feng and G.-Q. Lin, *Angew. Chem., Int. Ed.*, 2018, **57**, 5871–5875; (*b*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*c*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147–168; (*d*) M. W. Van Laren and C. J. Elsevier, *Angew. Chem., Int. Ed.*, 1999, **38**, 3715–3717; (*e*) B. M. Trost and T. Schmidt, *J. Am. Chem. Soc.*, 1988, **110**, 2301–2303; (*f*) C. Guo and X. Lu, *Tetrahedron Lett.*, 1992, **33**, 3659–3662; (*g*) C. Guo and X. Lu, *Synlett*, 1992, 405–406, DOI: 10.1055/s1992-21360; (*h*) B. M. Trost and U. Kazmaier, *J. Am. Chem. Soc.*, 1992, **114**, 7933–7935; (*i*) Y. Wang and F. G. West, *Synthesis*, 2002, 99–103, DOI: 10.1055/s-2002-19297.

6 (*a*) C. M. M. Santos and A. M. S. Silva, *Prog. Heterocycl. Chem.*, 2013, **25**, 409–453; (*b*) C.-V. T. Vo, G. Mikutis and J. W. Bode, *Angew. Chem., Int. Ed.*, 2013, **52**, 1705–1708; (*c*) L. Wang, W. He and Z. Yu, *Chem. Soc. Rev.*, 2013, **42**, 599–621; (*d*) Y.-Q. Wang, C.-B. Yu, D.-W. Wang, X.-B. Wang and Y.-G. Zhou, *Org. Lett.*, 2008, **10**, 2071–2074; (*e*) H. Zhang, X. Ye and M. Cai, *J. Chem. Res.*, 2008, 305–307; (*f*) M. Ichimaru, A. Kato and Y. Hashimoto, *J. Nat. Prod.*, 2000, **63**, 1675–1676; (*g*) D. Meng, W. Chen and W. Zhao, *J. Nat. Prod.*, 2007, **70**, 824–829; (*h*) Y. Fukata, K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2015, **137**, 5320–5323; (*i*) A. St-Gelais, J. Legault, V. Mshvildadze and A. Pichette, *J. Nat. Prod.*, 2015, **78**, 1904–1909; (*j*) W. Li, C. Schlepphorst, C. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2016, **55**, 3300–3303.

7 K. Shukla, D. V. Ferraris, A. G. Thomas, M. Stathis, B. Duvall, G. Delahanty, J. Alt, R. Rais, C. Rojas, P. Gao, Y. Xiang, C. V. Dang, B. S. Slusher and T. Tsukamoto, *J. Med. Chem.*, 2012, **55**, 10551–10563.

8 F. Pierre, C. F. Regan, M.-C. Chevrel, A. Siddiqui-Jain, D. Macalino, N. Streiner, D. Drygin, M. Haddach,

S. E. O'Brien, W. G. Rice and D. M. Ryckman, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3327–3331.

9 B. Han, J. L. Liu, Y. Huan, P. Li, Q. Wu, Z. Y. Lin, Z. F. Shen, D. L. Yin and H. H. Huang, *Chin. Chem. Lett.*, 2012, **23**, 297.

10 P. Theodosis-Nobelos, M. Kourti, A. Gavalas and E. A. Rekka, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 910.

11 M. Biava, G. C. Porretta, D. Deidda, R. Pompei, A. Tafi and F. Manetti, *Bioorg. Med. Chem.*, 2003, **11**, 515.

12 K.-K. Tooulia, P. Theodosis-Nobelos and E. A. Rekka, *Arch. Pharm.*, 2015, **348**, 629.

13 (*a*) M. H. Keylor, J. E. Park, C.-J. Wallentin and C. R. J. Stephenson, *Tetrahedron*, 2014, **70**, 4264–4269; (*b*) S. Marcaccini, R. Pepino, T. Torroba, D. Miguel and M. A. García-Valverde, *Tetrahedron Lett.*, 2002, **43**, 8591–8593; (*c*) A. J. Williams, S. Chakthong, D. Gray, R. M. Lawrence and T. Gallagher, *Org. Lett.*, 2003, **5**, 811–814; (*d*) S. Indumathi, S. Perumal and J. C. Menéndez, *Tetrahedron*, 2011, **67**, 7101–7105; (*e*) Z. Liu and A. Nefzi, *Tetrahedron Lett.*, 2012, **53**, 1013–1014; (*f*) A. Otto and J. Liebscher, *Synthesis*, 2003, **8**, 1209–1214.

14 (*a*) H. M. Davies and R. E. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2904; (*b*) R. Giri, B. F. Shi, K. M. Engle, N. Maugel and J. Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (*c*) R. H. Crabtree and A. Lei, *Chem. Rev.*, 2017, **117**, 8481–8482; (*d*) N. Y. S. Lam, K. Wu and J. Q. Yu, *Angew. Chem.*, 2021, **133**, 15901–15924; (*e*) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.

15 (*a*) J. R. Donald and W. P. Unsworth, *Chem.–Eur. J.*, 2017, **23**, 8780–8799; (*b*) J. B. Roque, Y. Kuroda, L. T. Gottemann and R. Sarpong, *Nature*, 2018, **564**, 244–248; (*c*) Y. Hu, D. Stumpfe and J. Bajorath, *J. Med. Chem.*, 2017, **60**, 1238–1246; (*d*) A. M. Szpilman and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 9592–9628; (*e*) Z. C. Cao and Z. J. Shi, *J. Am. Chem. Soc.*, 2017, **139**, 6546–6549.

16 T. K. Beng, A. O. Farah and V. Shearer, *RSC Adv.*, 2020, **10**, 37153.

17 (*a*) J. Maruyama, H. Yamashita, T. Watanabe, S. Arai and A. Nishida, *Tetrahedron*, 2009, **65**, 1327–1335; (*b*) N. Toyooka, M. Okumura and H. Nemoto, *J. Org. Chem.*, 2002, **67**, 6078–6081.

18 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264.

19 K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.

20 T. K. Beng and A. Moreno, *New J. Chem.*, 2020, **44**, 4257–4261.

21 The synthesis of alkenoic acid **3** using the 1,3-azadiene-anhydride reaction is currently limited to *N*-alkyl- and *N*-aryl-α,β-unsaturated imines. Strongly electron-withdrawing *N*-substituents such as *N*-Boc- and *N*-Cbz-α,β-unsaturated imines are not tolerated. See H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864–8872.