



# 2,7-Diazabicyclo[2.2.1]heptanes: novel asymmetric access and controlled bridge-opening†

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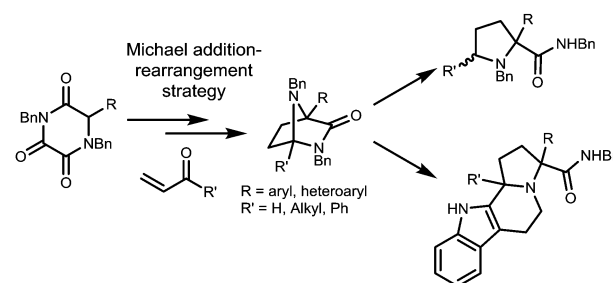
**Organocatalysed asymmetric Michael additions of substituted triketopiperazines to enones afford products in high yield and enantiomeric ratio (er). Further modification delivers products possessing natural product (NP) scaffolds including diazabicyclo[2.2.1]heptane, prolinamide and harmicine.**

For many years natural products have provided organic chemists with a multitude of synthetically challenging architectures, providing the stimulus for the development of new synthetic methods and strategies. An additional driving force in this field is provided by the diverse biological activities inherent in many natural products. The fact that around 30% of small molecule drugs developed in the last 30 years are either natural products, or their close relatives, is ample testament to the significance of this area.<sup>1,2</sup>

Traditionally, natural product synthesis is the exploration of a route towards a singular target compound<sup>3</sup> and with rapid access in mind, many research groups compete for the shortest linear sequence.<sup>4,5</sup> However, this approach often overlooks any potentially rewarding analogues or family members.<sup>6</sup> Therefore, a route in which multiple interesting scaffolds may be accessed from a common motif is highly desirable.<sup>7,8</sup>

In this report we describe how our newly developed asymmetric access to triketopiperazines (TKPs) can be utilised in this way to gain access to several interesting natural product-like motifs, as illustrated in Scheme 1.

We conceived that structures including various diazabicyclo[2.2.1]heptane core structures and proline amides would be available *via* initial asymmetric Michael addition of a TKP, followed by TKP manipulations involving ring-opening. The diazabicyclo[2.2.1]heptane structures are especially interesting as core components of biologically active products as shown in Fig. 1.<sup>9–15</sup>



Scheme 1 Michael addition-rearrangement strategy towards NP scaffolds.

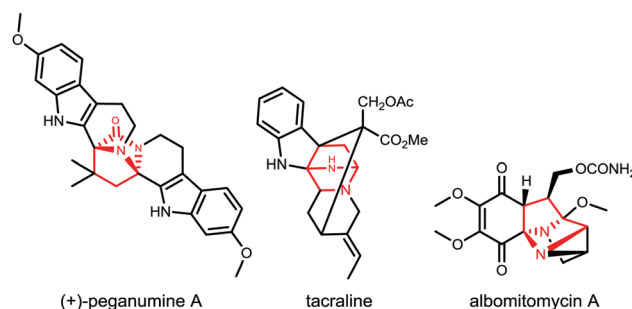


Fig. 1 NPs containing the diazabicyclo[2.2.1]heptane motif.

Recent reports from our group have described highly enantioselective Michael addition chemistry of various substituted TKP systems.<sup>16–18</sup> The chiral TKPs are generated in highly diastereo- and enantioselective form, and are amenable to fruitful regioselective manipulation to give attractive natural product like structures.

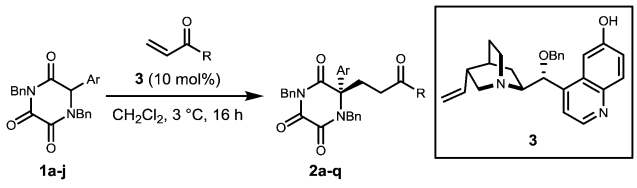
In the present research we opted to employ novel TKP structures in which R =  $\alpha$ -aryl and  $\alpha$ -heteroaryl, in order to achieve the objectives shown in Scheme 1. Initially,  $\alpha$ -aryl TKPs **1a–j** were readily prepared using previously established methods.<sup>16,18–24</sup> All optimisation was conducted with phenyl TKP **1a** employing methyl vinyl ketone (MVK) as the Michael acceptor (for details see ESI†).<sup>25</sup> Under the optimised conditions, using the *O*-benzylated cinchona derived catalyst **3**, the Michael additions of  $\alpha$ -aryl TKPs

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**Table 1** Michael additions of TKPs **1a–j** mediated by catalyst **3**


Entry	TKP	Ar	R	2 (%)	er
1	<b>1a</b>	Ph	Me	<b>2a</b> 90	92 : 8
2	<b>1b</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe	Me	<b>2b</b> 83	93 : 7
3	<b>1c</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub>	Me	<b>2c</b> 70	95 : 5
4	<b>1d</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	Me	<b>2d</b> 88	91 : 9
5	<b>1e</b>	Furan-2-yl	Me	<b>2e</b> 99	94 : 6
6	<b>1f</b>	Thiophen-2-yl	Me	<b>2f</b> 93	94 : 6
7	<b>1g</b>	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Br	Me	<b>2g</b> 88	55 : 44
8	<b>1h</b>	<i>N</i> -Methylpyrrol-2-yl	Me	<b>2h</b> 99	50 : 50
9	<b>1i</b>	<i>N</i> -Methylpyrrol-3-yl	Me	<b>2i</b> 63	77 : 23
10	<b>1j</b>	Indol-3-yl	Me	<b>2j</b> 91	73 : 27
11	<b>1a</b>	Ph	Et	<b>2k</b> 91	96 : 4
12	<b>1b</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe	Et	<b>2l</b> 75	97 : 3
13	<b>1c</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub>	Et	<b>2m</b> 63	97 : 3
14	<b>1a</b>	Ph	Ph	<b>2n</b> 90	85 : 15
15	<b>1b</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe	Ph	<b>2o</b> 95	87 : 13
16	<b>1c</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub>	Ph	<b>2p</b> 88	96 : 4
17	<b>1a</b>	Ph	H	<b>2q</b> 85	58 : 42 <sup>a,b</sup>

<sup>a</sup> –30 °C, 12 days. <sup>b</sup> HPLC conducted on the acetal derivative.

**1a–j** to MVK were explored and the results are shown in Table 1 (entries 1–10).

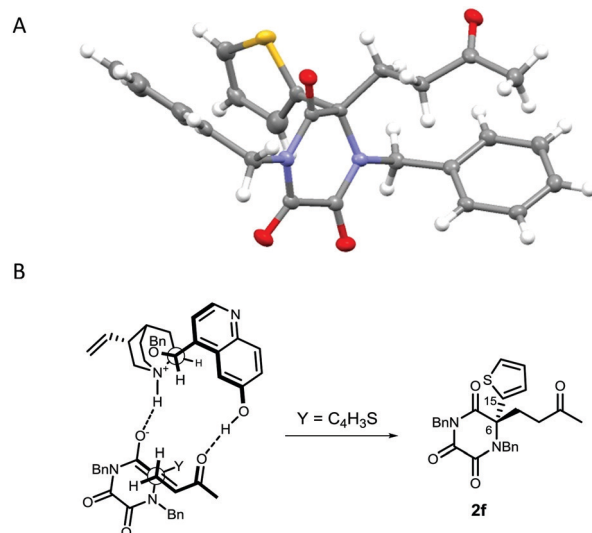
Addition products **2a–j** were isolated in good to excellent yields albeit with mixed levels of enantioselectivity. High levels of enantioselectivity were observed for substrates possessing either phenyl, *p*-substituted phenyl or unsubstituted 5-membered heterocycles (entries 1–6). Erosion of enantioselectivity appears to be the result of increased steric requirement proximal to the reacting enolate centre, *e.g.* with *o*-substituted aryl substrates (entries 7 and 8). This is exemplified by two *N*-Me pyrrole analogues (entries 8 and 9) in which moving the *N*-methyl group away from the reactive centre results in a significant increase in enantioselectivity.

When these conditions were employed with alternative enone acceptors, varied results were obtained (entries 11–17). Enantioselectivities remained high when employing ethyl vinyl ketone (entries 11–13) while a marked reduction in selectivity was observed with the use of phenyl vinyl ketone (entries 14 and 15) with the exception of entry 16 at 96 : 4 er. Selectivity was vastly reduced when using acrolein as the Michael acceptor, even when the reaction was performed at lower temperature (entry 17).

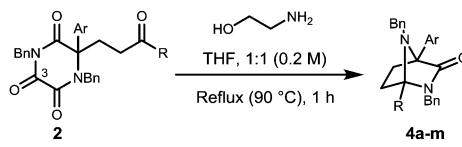
Following crystallisation, the absolute configuration of adduct **2f**, generated from reaction of TKP **1f** with MVK, was determined by X-ray crystallography (Fig. 2A).<sup>26</sup>

Our results are in accordance with the stereochemical model originally proposed by Deng for the dual activation and co-ordination, by the catalyst, of both the nucleophile and the electrophile, and with our group's previous works (Fig. 2B).<sup>16,17,27</sup>

With the Michael addition products **2** in hand, our attention turned to the removal of the oxalyl unit in an attempt to free the quaternary  $\alpha$ -amino acid. It was envisioned that the use of a



**Fig. 2** (A) Crystal structure of **2f** with ellipsoids drawn at the 50% probability level. The thiophene ring is disordered over two positions, which is the result of rotation around the C6–C15 bond, at a refined percentage occupancy ratio of 63.9(3) : 36.1(3), only the major position is shown for clarity. (B) Model for **3**-catalysed Michael addition generating **2f**.

**Table 2** Rearrangement of adducts **2** to diazabicyclo[2.2.1]heptanes **4a–m**


Entry	TKP	Ar	R	4 (%)
1	<b>2a</b>	Ph	Me	<b>4a</b> 87 <sup>a</sup>
2	<b>2b</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe	Me	<b>4b</b> 51
3	<b>2c</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub>	Me	<b>4c</b> 61
4	<b>2d</b>	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	Me	<b>4d</b> 60
5	<b>2e</b>	Furan-2-yl	Me	<b>4e</b> 75
6	<b>2f</b>	Thiophen-2-yl	Me	<b>4f</b> 50 <sup>a</sup>
7	<b>2g</b>	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Br	Me	<b>4g</b> 29
8	<b>2h</b>	<i>N</i> -Methylpyrrol-2-yl	Me	<b>4h</b> 26
9	<b>2i</b>	<i>N</i> -Methylpyrrol-3-yl	Me	<b>4i</b> 25
10	<b>2j</b>	Indol-3-yl	Me	<b>4j</b> 21
11	<b>2k</b>	Ph	Et	<b>4k</b> 50
12	<b>2n</b>	Ph	Ph	<b>4l</b> 84
13	<b>2q</b>	Ph	H	<b>4m</b> 28

<sup>a</sup> Enantioenriched substrates retain enantiopurity.

dinucleophile would achieve this goal through initial attack at the highly electrophilic C-3 carbonyl and subsequent cyclisation onto the neighbouring carbonyl.<sup>16</sup> After investigating a range of dinucleophiles, it was found that ethanolamine removed the oxalyl component, however, the free aminoamide was not isolated. Instead, direct access to products that possess the diazabicyclo[2.2.1]heptane (**4**) core framework was achieved, Table 2.

This process involves release of the TKP ring nitrogen functions from the oxalyl unit, and their convergent condensation with the ketone originating from the Michael acceptor to form an unusual bridged *N*-acyl aminal structure. Moderate to high yields were observed in most cases (entries 1–6, 11 and 12) with the exception



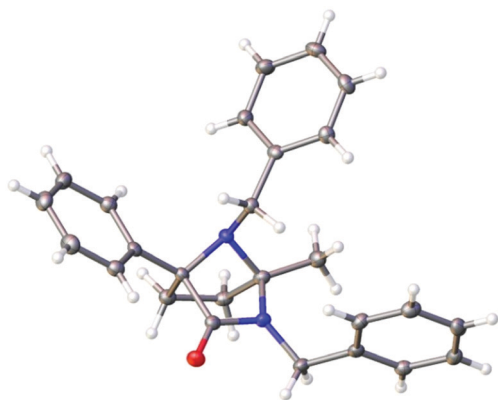


Fig. 3 Crystal structure of **4a** with ellipsoids drawn at the 50% probability level.

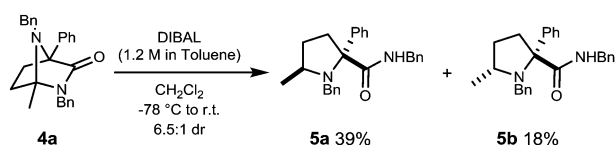
of substrates bearing *o*-substituents (entries 7–10) and the acrolein adduct (entry 13). As expected, the conversion of enantioenriched substrates proceeded with retention of enantiopurity, as demonstrated for entries 1 and 6. The structure of **4a** was unequivocally confirmed by single crystal X-ray analysis (Fig. 3).<sup>28</sup>

With diazabicyclic **4a** in hand, we endeavoured to break open the newly formed cyclic aminal to reveal a quaternary 2,5-disubstituted prolinamide. Several previously described reductive ring opening conditions were examined and details can be found in the ESI.<sup>†</sup><sup>29–31</sup>

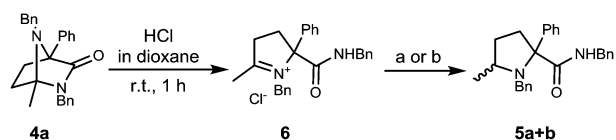
Reduction of diazabicyclic **4a** with DIBAL at  $-78\text{ }^{\circ}\text{C}$  affords prolinamides **5a** and **5b** in a modest 6.5 : 1 dr with a combined yield of 57% (Scheme 2).

Interestingly, the putative intermediate iminium ion involved in the process can be isolated in the form of **6** by treatment of diazabicyclic **4a** with HCl in dioxane. Preliminary investigations have found that this also undergoes reduction to give prolinamides **5a + b** (Scheme 3).

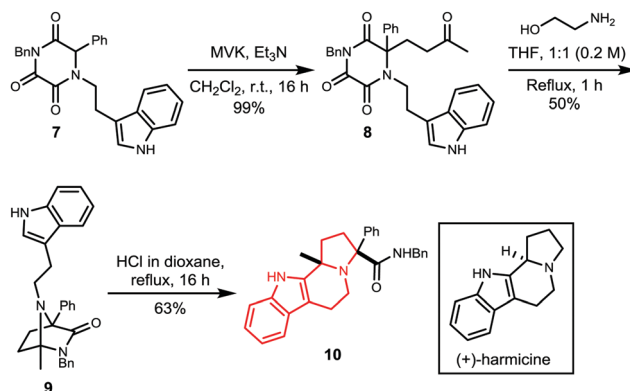
The potential to access further natural product skeletons was investigated by intramolecular trapping of the iminium intermediate. Thus, diazabicyclic **9** was synthesised from TKP **7** using our optimised methodology (Scheme 4). Treatment of **9** with HCl instigated a Pictet–Spengler reaction to yield product



Scheme 2 Reductive ring opening of **4a**.



Scheme 3 Reaction pathway to prolinamides **5a + b** (a) *L*-selectride, 1.0 : 1.3 dr; (b)  $\text{LiAlH}_4$ , 1.5 : 1.0 dr.



Scheme 4 Synthesis of harmicine derivative **10**.

**10**, as a single isomer, which possesses the scaffold of the natural product harmicine.<sup>32,33</sup>

In conclusion, we have demonstrated that  $\alpha$ -aryl TKPs can undergo asymmetric Michael additions with high selectivity and that manipulation of the TKP motif allows access to multiple products possessing NP scaffolds. We anticipate that additional biologically relevant and NP scaffolds can be accessed and investigations are currently on-going within our laboratory to unlock the further potential of the TKP motif.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- 1 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629–661.
- 2 A. L. Harvey, *Drug Discovery Today*, 2008, **13**, 894–901.
- 3 F. Saint-Dizier and N. S. Simpkins, *Chem. Sci.*, 2017, **8**, 3384–3389.
- 4 J. W. Reed and T. Hudlicky, *Acc. Chem. Res.*, 2015, **48**, 674–687.
- 5 P. S. Baran, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404–408.
- 6 J. Shimokawa, *Tetrahedron Lett.*, 2014, **55**, 6156–6162.
- 7 S. M. Geddis, L. Carro, J. T. Hodgkinson and D. R. Spring, *Eur. J. Org. Chem.*, 2016, 5799–5802.
- 8 J. T. Njardarson, C. Gaul, D. Shan, X. Y. Huang and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 1038–1040.
- 9 M. Kono, Y. Saitoh, K. Shirahata, Y. Arai and S. Ishii, *J. Am. Chem. Soc.*, 1987, **109**, 7224–7225.
- 10 J. E. Saxton, *Nat. Prod. Rep.*, 1997, **14**, 559.
- 11 C. Piemontesi, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2016, **138**, 11148–11151.
- 12 K. B. Wang, Y. T. Di, Y. Bao, C. M. Yuan, G. Chen, D. H. Li, J. Bai, H. P. He, X. J. Hao, Y. H. Pei, Y. K. Jing, Z. L. Li and H. M. Hua, *Org. Lett.*, 2014, **16**, 4028–4031.



- 13 T. A. Van Beek, R. Verpoorte, A. B. Svendsen and R. Fokkens, *J. Nat. Prod.*, 1985, **48**, 400–423.
- 14 S. R. Rajsiki and R. M. Williams, *Chem. Rev.*, 1998, **98**, 2723–2796.
- 15 P. D. Bass, D. A. Gubler, T. C. Judd and R. M. Williams, *Chem. Rev.*, 2013, **113**, 6816–6863.
- 16 A. Cabanillas, C. D. Davies, L. Male and N. S. Simpkins, *Chem. Sci.*, 2015, **6**, 1350–1354.
- 17 M. Rees, N. S. Simpkins and L. Male, *Org. Lett.*, 2017, **19**, 1338–1341.
- 18 R. W. Foster, E. N. Lenz, N. S. Simpkins and D. Stead, *Chem. – Eur. J.*, 2017, **23**, 8810–8813.
- 19 A. R. Katritzky, A. T. Cutler, N. Dennis, G. J. Sabongi, S. Rahimi-Rastgoo, G. W. Fischer and I. J. Fletcher, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1176–1184.
- 20 K. A. Mix and R. T. Raines, *Org. Lett.*, 2015, **17**, 2358–2361.
- 21 C. R. Whitlock and M. P. Cava, *Tetrahedron Lett.*, 1994, **35**, 371–374.
- 22 S. Crooke and C. Whitlock, *Molecules*, 2012, **17**, 14841–14845.
- 23 N. A. Petasis, A. Goodman and I. A. Zavialov, *Tetrahedron*, 1997, **53**, 16463–16470.
- 24 S. R. K. Pingali, S. K. Upadhyay and B. S. Jursic, *Green Chem.*, 2011, **13**, 928–933.
- 25 ESI†.
- 26 The CIF for the crystal structure of **2f** has been deposited with the CCDC and given the deposition number, CCDC 1880502†.
- 27 H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2005, **44**, 105–108.
- 28 The CIF for the crystal structure of **4a** has been deposited with the CCDC and given the deposition number, CCDC 1880503†.
- 29 M. Sannigrahi, P. Pinto, T. M. Chan, N. Y. Shih and F. George Njoroge, *Tetrahedron Lett.*, 2006, **47**, 4877–4880.
- 30 M. Kasai, M. Kono, S. Ikeda, N. Yoda and N. Hirayama, *J. Org. Chem.*, 1992, **57**, 7296–7299.
- 31 Y. Zhang, L. Zheng, F. Yang, Z. Zhang, Q. Dang and X. Bai, *Tetrahedron*, 2015, **71**, 1930–1939.
- 32 I. T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 13404–13405.
- 33 T.-S. Kam and K.-M. Sim, *Phytochemistry*, 1998, **47**, 145–147.

