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Novel anionic polycyclisation cascade. Highly stereocontrolled assembly of functionalised tetracycles akin to the middle core of the manzamines†

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Abstract—Substituted gramines, in the presence of *t*BuOK, react with acrolein and β-keto-phosphonates, via a novel sequence involving a multicomponent condensation followed by an anionic polycyclisation cascade, to afford in excellent overall yields, highly functionalised tetracyclic structures akin to the middle core of the manzamines. In this unique process, up to eight elementary transformations take place with remarkably high chemo- and stereocontrol. © 2002 Elsevier Science Ltd. All rights reserved.

Manzamine A **1** and B **2** (Fig. 1) are members of a growing family of unique indole alkaloids isolated by Higa and co-workers in 1986 from sponges of the genus *Haliclona* and *Pelina*.[1] The complex architectural framework of the manzamines, coupled with their remarkable biological activities[2] has stimulated considerable synthetic efforts towards their preparation,[3] culminating in 1998 with the first total synthesis of manzamine A **1**.[4] Most noteworthy among the structural features of the manzamines are the highly substituted, isoquinoline-based, tetracyclic core **3** and the 13-membered macrocyclic ring embodying a (*Z*)-alkene.

Our own interest in this area has prompted us to study and develop an efficient and flexible methodology towards the construction of **3** and related polycyclic analogues based upon a novel anionic polycyclisation cascade (Fig. 2).[5] Thus, addition of acrolein to gramine **4**, in the presence of catalytic amounts of DBU, smoothly generates the corresponding, highly unstable, β-amino-aldehyde.[6] Horner–Emmons olefination then

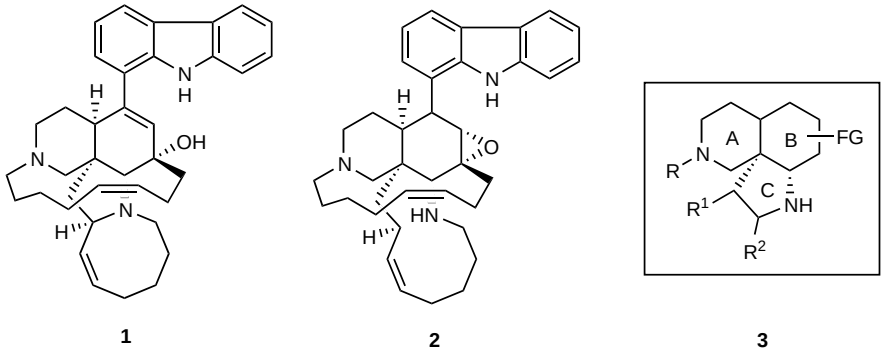

Figure 1.

Keywords: manzamines; anionic polycyclisation; perhydroisoquinoline; stereocontrol; β-keto-phosphonates.

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† Dedicated to the lasting memory of Dr. Antony Chesney, who left us far too soon.

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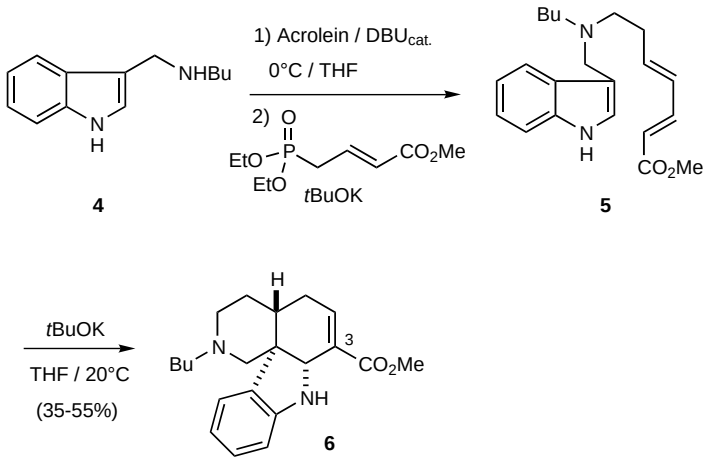


Figure 2.

affords the substituted sorbate derivative **5**.[7] In the presence of catalytic quantities of *t*BuOK, **5** undergoes a sequential anionic polycyclisation, ultimately leading to the tetracyclic system **6** in up to 55% yield.

Although this approach allowed us to assemble rapidly a variety of functionalised polycycles such as **6**, the introduction of the missing C_3–OH function (manzamine numbering) and the appendage of the bridging 13-membered macrocyclic ring proved to be a daunting task. In order to maintain the high convergency of our approach, we envisaged an alternative strategy in which a suitable precursor to the macrocycle would already be incorporated at the onset of the polycyclisation sequence. Our antithetic analysis is depicted in Fig. 3

We envisioned that ketone **7** might originate, via an anionic polycyclisation cascade, from the corresponding enone **8**. Subsequent disconnection of **8** reveals that it could be easily assembled from three readily available fragments: the gramine **9**, acrolein **10** and the β-keto-phosphonate **11**.

In order to validate this approach, indole **12** was reacted with acrolein, in the presence of catalytic

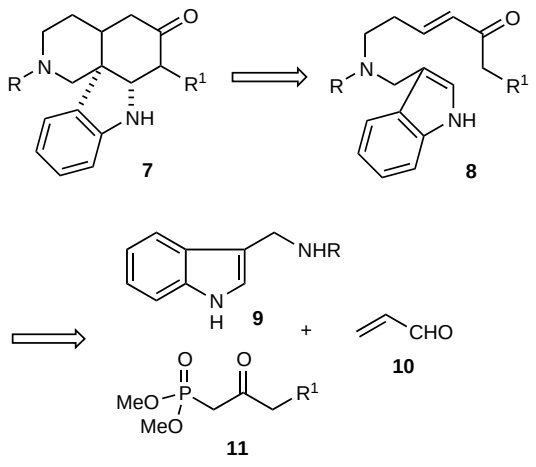


Figure 3.

amounts of DBU, to produce quantitatively adduct **13** which was not isolated but directly engaged in the subsequent Horner–Emmons olefination, affording the desired enone **15**, albeit in rather modest yields (Fig. 4).

With enone **15** in hand, the crucial anionic polycyclisation was attempted.[8] Gratifyingly, addition of catalytic quantities of *t*BuOK to **15** resulted in its smooth conversion into the diastereoisomerically pure, *trans*-fused, tetracyclic ketone **16** in 15% yield. The structure of **16** was unambiguously established by X-ray diffraction analysis (Fig. 5).

Closer examination of the individual steps of the anionic polycyclisation later revealed that the Horner–Emmons olefination of **13** proceeded quantitatively. However, the resulting enone **15** decomposed extensively during the purification step. It was therefore decided to combine the whole sequence as a one-pot procedure, without isolating any of the intermediates (Fig. 6).

Thus, gramine **12** was sequentially reacted with acrolein, the anion of β-keto-phosphonate **14** and finally with a small amount of *t*BuOK. Much to our delight, the desired adduct **15** was now isolated in a significantly improved yield of 55%! Some selected examples, illustrating the scope of this novel anionic cascade methodology, are collected in Table 1.

As can be seen from Table 1, the reaction tolerates various *N*-protecting groups and affords the desired adducts with a wide variety of substituted β-keto-phosphonates. In all cases, the tetracyclic structures, obtained as single diastereoisomers, possess a *trans*-ring junction and a B ring in a boat conformation. It is noteworthy that the newly introduced substituent at C_3 is orientated towards the most sterically crowded, α-face of the polycycle. Adducts **21**, **22** and **23** already bear the premises of the macrocyclic ring system that could be constructed later, either by intramolecular *N*-alkylation of the perhydroisoquinoline nitrogen by the acetylenic side-chain (entries 5 and 6)[4a] or by an intramolecular alkyne metathesis (entry 7).[9]

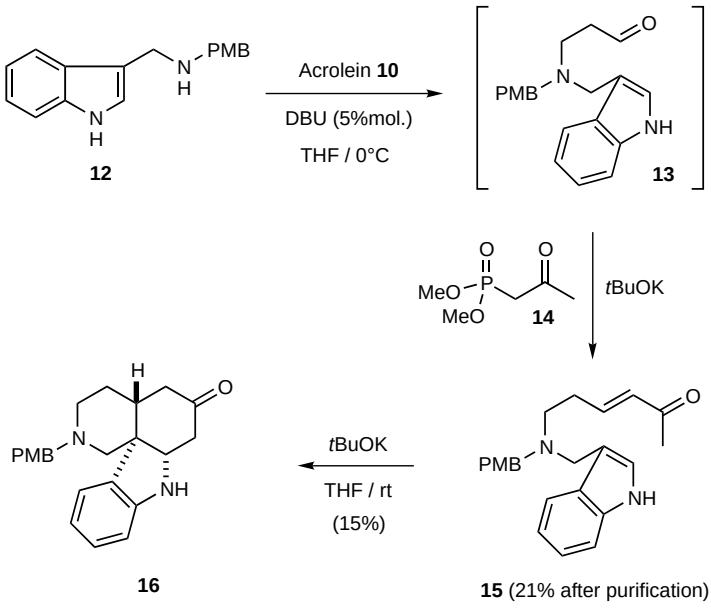


Figure 4.

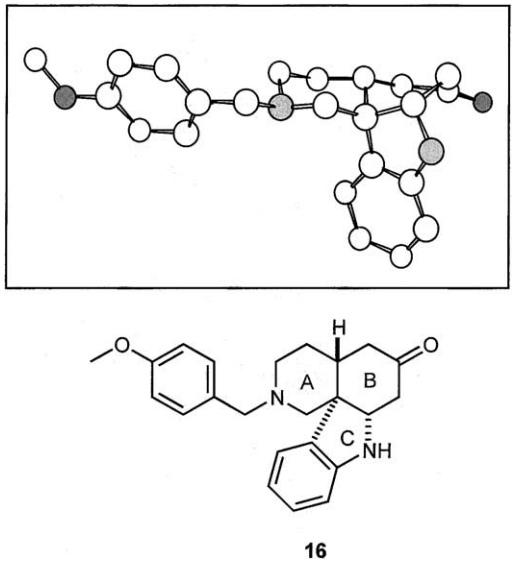


Figure 5.

Although the overall yields might appear modest, it is important to realise that up to eight successive elementary steps occur, in a highly chemo- and stereoselective manner, in this unique anionic polycyclisation cascade (Fig. 7).

Apart from the Michael addition of the gramine to acrolein, the deprotonation of the β-keto-phosphonate and the olefination step, the sequence involves the proton abstraction from the indole derivative **8**, followed by an intramolecular Michael addition of **24**, generating enolate **25**. Isomerisation of enolate **25** affords **26** which undergoes an intramolecular imino-aldol cyclisation to produce the indolenine anion **27**. Finally, proton exchange completes the cascade, affording adduct **28** and regenerating **24**.[10] Therefore, a 40% overall yield requires up to 90% yield for each elementary step occurring during the polycyclisation.

In summary, we have developed an efficient and concise methodology for the rapid construction of a variety of functionalised tetracyclic systems akin to the middle core of the manzamines.[11] This novel procedure embodies a multicomponent condensation sequence coupled with an anionic polycyclisation cascade. The reaction is highly chemo- and diastereoselective, allowing the control of up to four chiral centres.

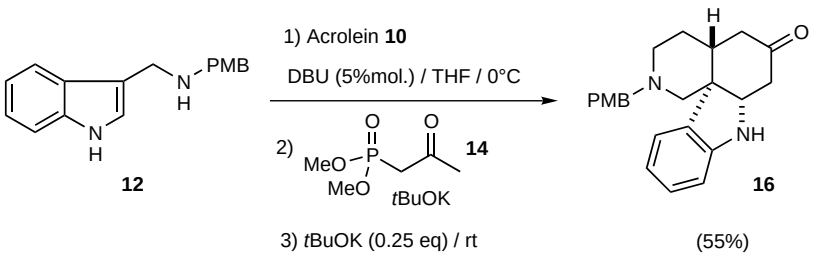
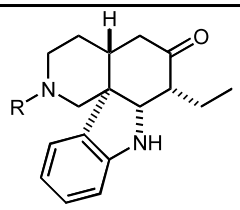
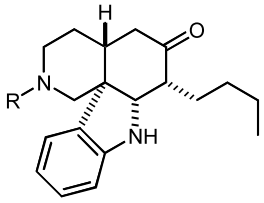
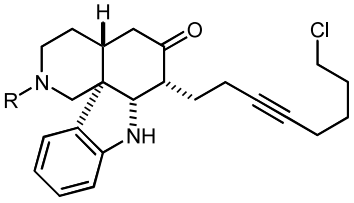
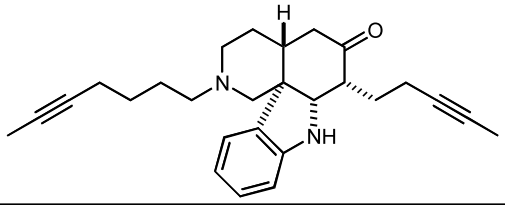


Figure 6.

Table 1. Preparation of substituted tetracycles

Entry	Products	R	Time[a]	Yields[b]
1		**17** : Allyl	150 min	35%
2		**18** : PMB	150 min	45%
3		**19** : Allyl	120 min	38%
4		**20** : PMB	60 min	60%
5		**21** : Allyl	120 min	49%
6		**22** : PMB	120 min	49%
7		**23**	120 min	36%

[a] Reaction time after the second addition of base. [b] All yields are for pure, isolated products.

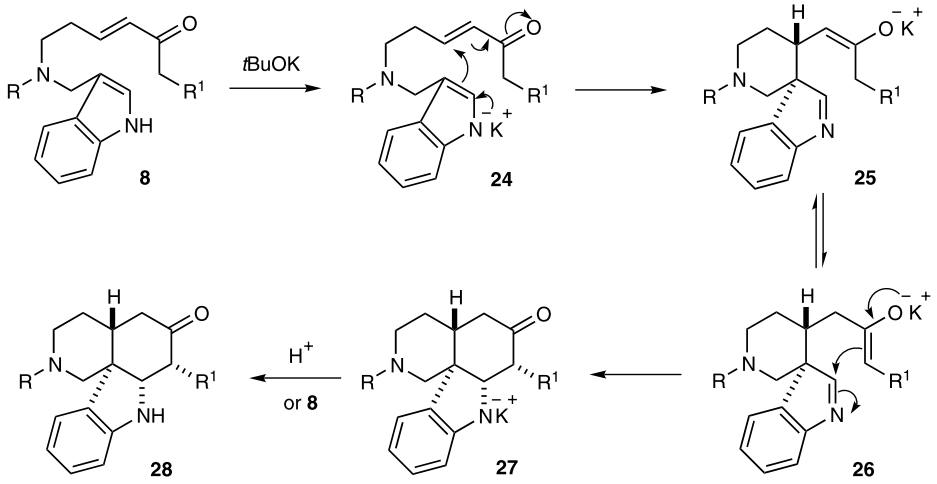


Figure 7.

Current efforts are now being directed towards delineating the full scope of this novel protocol and applying it to the total synthesis of manzamine A **1**.

Acknowledgements

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10. Proton exchange could occur either by direct deprotonation of **8** by **27** or by transfer from **27** to *t*BuOH.
11. **Typical experimental procedure**. Synthesis of tetracycle **20** (Table 1, entry 4).
In a dry, three-necked flask fitted with a magnetic stirrer was placed, under an atmosphere of argon, the gramine (13.18 g; 49.54 mmol; 1 equiv.) in dry THF (100 ml). DBU (0.74 ml; 2.47 mmol; 0.05 equiv.) was added and the solution was cooled to 0°C. Acrolein (3.31 ml; 49.54 mmol; 1 equiv.) was added dropwise within 5 min. The mixture was vigorously stirred for 30 min. During this time, in a dry, three-necked flask fitted with a magnetic stirrer, under argon, the β-keto-phosphonate (10.28 ml; 49.54 mmol; 1 equiv.) was diluted in dry THF (600 ml). At room temperature, *t*BuOK (5.55 g; 49.54 mmol; 1 equiv.) was added slowly and the mixture was stirred for 20 min. Then, the β-amino-aldehyde was quickly added to the phosphonate anion and the mixture was stirred during 2 h. Then, *t*BuOK (1.38 g; 12.38 mmol; 0.25 equiv.) was added and the mixture was vigorously stirred during 6 h. The reaction was followed by TLC (ethyl acetate/petroleum ether = 1:4). The reaction was stopped by the addition of water (200 ml). The aqueous layer was extracted twice with 400 ml of diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. The crude product was further purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1:4) to afford 12.6 g of the title compound (yield: 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.2 Hz, 3H), 1.2–1.5 (m, 7H), 1.8–2.2 (m, 7H), 3.04 (d, J = 10.8 Hz, 1H), 3.09 (m, 1H), 3.4 (d, J = 13.2, 1H), 3.49 (d, J = 13.2 Hz, 1H), 3.78 (s, 3H), 3.83 (d, J = 3.3 Hz, 1H), 6.46 (dd, J = 7.8, 1.5 Hz, 1H), 6.7 (dt, J = 7.8, 1.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.04 (dt, J = 7.8, 1.5 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.26; 23.14; 25.28; 26.78; 29.74; 38.98; 42.65; 49.48; 50.12; 53.45; 55.40; 62.52; 64.88; 65.60; 108.70; 113.70; 117.82; 128.47; 129.45; 130.09; 130.55; 130.91; 150.57; 158.72; 212.31. IR (neat) ν: 3378, 2933, 2792, 2749, 1714 cm^{-1}. MS (CI, CH_4–N_2O) m/z (relative intensity) 419.4 (100%), 418.4 (30%). Anal. calcd for $C_{26}H_{34}N_2O_2$: C, 77.48; H, 8.19. Found: C, 77.73; H, 8.21.