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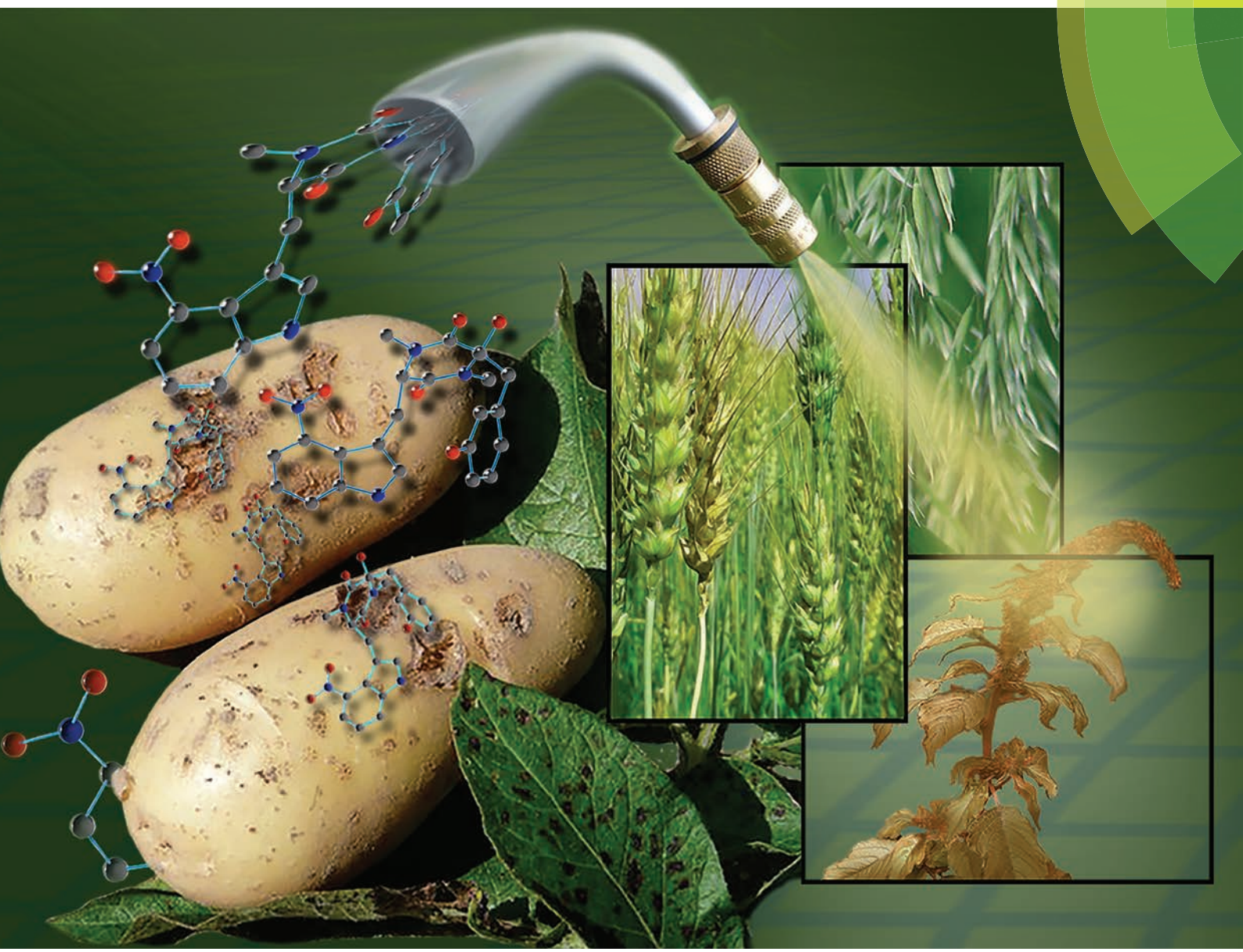

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A one-pot multicomponent coupling/cyclization for natural product herbicide (±)-thaxtomin A†

Jean Paul Bourgault, Amarendar Reddy Maddirala and Peter R. Andreana*

Herbicide (±)-thaxtomin A has been synthesized in a one-pot process with a 32% isolated yield. A multicomponent coupling reaction was utilized to prepare *in situ* a dipeptide precursor which then sequentially underwent an alkaline mediated keto-amide cyclization to provide the target molecule. Adjustment of diastereoselectivity was achieved using microwave-induced irradiation. The approach incorporates atom economy and reaction efficiency and allows for facile library development.

The use of herbicides in the years following World War II has proven to be more effective and less costly then hand removal or tillage for weed control. Furthermore, it is estimated that if these chemicals were discontinued the annual U.S. crop production would decrease by 20%.[1] The necessary control of unwanted foliage has been a tale of two damning stories; on one hand there is a constant threat of herbicide resistance and on the other there are great concerns regarding environmental effects.[2] Naturally occurring thaxtomin A (TA, *syn*-**1**) was first isolated in 1989 from *Streptomyces scabies*,[3] the soil bacteria responsible for common scab of potato disease, and since has attracted considerable attention from industrial[4] and academic[5] communities as a potent phytotoxin demonstrating activity similar to known cellulose inhibitors. TA has also been used to control weed growth and germination in the presence of grasses and cereal crops in the absence of toxicity.[4a] Interest is highly motivated by the environmentally benign and biodegradable properties of TA, which contains a cyclic dipeptide or 2,5-diketopiperazine (DKP) core, composed of a (*S*)-*N*-methyl-4-nitrotryptophan and (*R*)-2-hydroxy-3-(3-hydroxyphenyl)-*N*-methylalanine (Fig. 1). The unique 4-nitroindole has been confirmed as a requirement for the biological activity of this natural product.[6] While the art of total synthesis continues to evolve as an atom economical and highly efficient process aiming toward the limited use of protecting groups,[7] we planned to assemble TA in a one-pot process incorporative of all starting atoms exempt of only the loss of water.

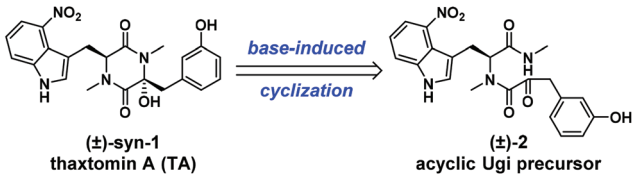

Fig. 1 Cyclization strategy to (±)-thaxtomin A.

DKPs and TA derivatives have been assembled through various strategies.[3,8] One strategy in particular takes advantage of dipeptides obtained *via* the Ugi reaction sequentially followed by an intramolecular aza-Michael addition/cyclization.[8b] While this exact approach does not directly allow for the synthesis of TA, a recent report[9] utilizing a base-induced cyclization of an amide onto a carbonyl has proven successful (Fig. 1). Therefore combined with a multicomponent coupling approach, a base-induced keto-amide cyclization would allow access to the desired DKP/TA scaffold including the essential hydroxyl at C12. Although examples of this amide-carbonyl cyclization are known,[10] only a lone report describes control of facial selectivity leading to enantiopure TA.[9]

Our approach requires the use of an α-keto carboxylic acid (Scheme 1) providing the necessary electrophile for the envisioned intramolecular cyclization. While there is precedent in employing assorted keto-carboxylic acids[10i,11] as starting materials in the Ugi reaction, there exists only sparse reports involving the utilization of keto-acids for the preparation of hydroxydiketopiperazines.[10b,h] In addition this motif has been generated *in situ* as a presumed transient intermediate for Pictet–Spengler reactions.[10a,12] Previously reported yields of Ugi reactions with highly enolizable α-keto-acids were low,[10a,12] however, we were eager to attempt the tandem Ugi/keto-amide cyclization strategy for the preparation of TA.

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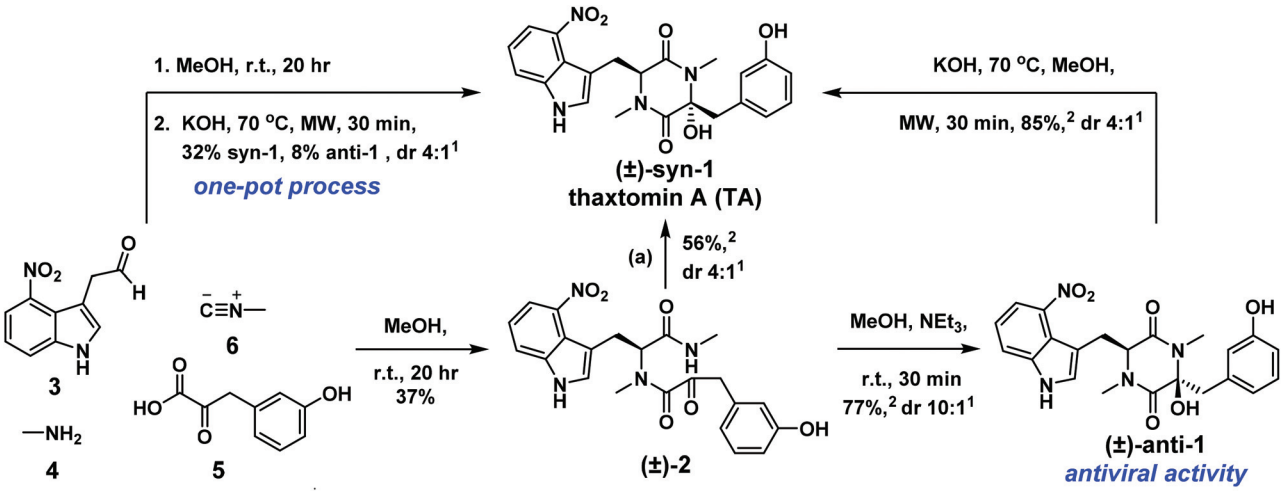
†Electronic supplementary information (ESI) available: NMR, HRMS, experimental procedures for *anti*-**1**, *syn*-**1**, **2**, **3**, **5**, and X-ray data for *anti*-**1** and *syn*-**1**. CCDC 1013566 and 1000681. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01148a



Scheme 1 Step-wise and one-pot preparation of TA.

In our synthesis of TA, the Ugi reaction was utilized to obtain the prerequisite dipeptide **2**. The reaction occurred between 4-nitroindolylacetaldehyde (**3**), methylamine (**4**), 3-hydroxyphenylpyruvic acid (**5**), and methyl isocyanide (**6**) which gave compound **2** in 37% yield (Scheme 1).[13] The acyclic product **2** was then subjected to base-mediated keto-amide cyclization using NEt_3 in MeOH at r.t. to afford an isolated 77% yield of two diastereomeric DKPs in a 10 : 1 dr, ultimately providing *anti*-**1**, the C12 epimer of TA as the major product. While *anti*-**1** is not a natural product this derivative has been demonstrated to possess activity against the tobacco mosaic virus.[9] The combined DKPs were then treated with KOH in methanol and heated to 70 °C under microwave irradiation for 30 minutes, which provided an 85% isolated yield in a 4 : 1 dr with *syn*-**1** being the major product. Alternatively **2** could be cyclized directly to *syn*-**1** by reaction with KOH in MeOH to give a 56% yield in a dr of 4 : 1.

Encouraged by the success of our initial studies involving the isolation and cyclization of the acyclic precursor (**2**) followed by the epimerization of *anti*-**1** to TA, we explored whether the formation of TA could occur in a sequential one-pot process. To this end, the multicomponent coupling reaction was conducted as previously noted with the exception of incorporating a cyclization/epimerization step (KOH, 70 °C) after the Ugi reaction was noted to have taken place. This two-step, one-pot sequence successfully provided a highly efficient approach to TA with an overall increase in yield, as compared to the stepwise strategies (**2** → *anti*-**1** → *syn*-**1**) or (**2** → *syn*-**1**), affording TA (*syn*-**1**) in 32% isolated yield as well as the minor diastereomer (*anti*-**1**) in 8% yield. The structures of *syn*-**1** and *anti*-**1** were confirmed by comparison of previously reported NMR data[6,9] and unequivocally by the crystal structures (Fig. 2 and 3).

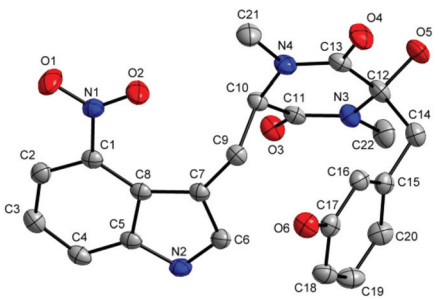


Fig. 2 ORTEP of (±)-thaxtomin A/*syn*-**1**.

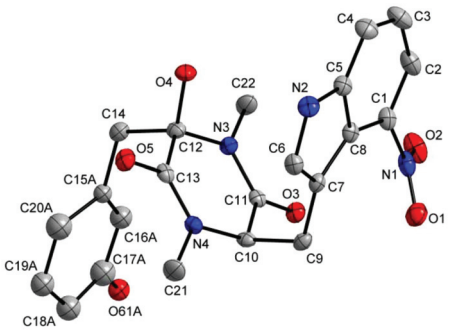


Fig. 3 ORTEP of (±)-*anti*-**1**.

Conclusion

In conclusion, we utilized 3-hydroxyphenyl pyruvic acid, 4-nitroindolylacetaldehyde, methylamine and methyl isocyanide in a tandem one-pot Ugi/DKP cyclization process for the synthesis of TA. While this synthesis is inherently limited by the Ugi reaction itself in that only racemic TA is obtained, it clearly demonstrates the power of multicomponent reactions to generate biologically validated scaffolds, including those embedded in naturally occurring products, in a limited

number of synthetic steps in the absence of protecting groups. While an asymmetric Ugi variant remains a top priority for our group, it must be noted that the approach described herein lends credibility for the preparation of various hydroxy DKP derivatives.[5]

Acknowledgements

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13 Methyl isocyanide (**6**) and 3-hydroxyphenylpyruvic acid (**5**) are available commercially from Priaxon Product List (1 g, $325) and Ryan Scientific Intermediate and Building Block Compounds (1 g, $690) respectively. However we chose to prepare these starting materials, the procedures/references for these compounds and 4-nitroindolylacetaldehyde (**3**) can be found in the ESI.†