Diversity-oriented synthesis of novel polycyclic scaffolds using polymer-bound reagents†

Domingo García-Cuadrado, Sofia Barluenga and Nicolas Winssinger*

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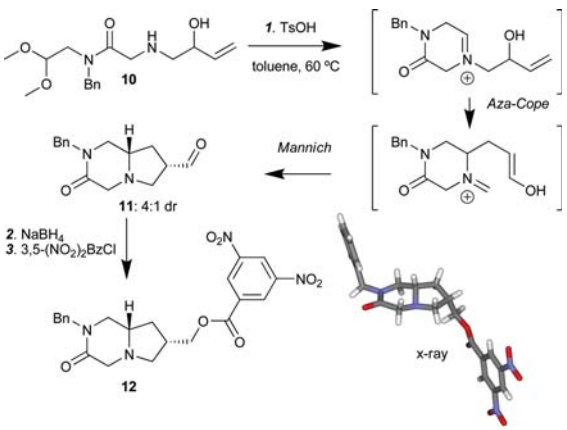
A concise sequence utilizing a Petasis three component reaction followed by a tandem aza-Cope–Mannich cyclization afforded novel polycyclic heterocycles in good yield; alternative iminium cyclization based on a Pictet–Spengler reaction or aminal formation led to divergent pathways affording skeletal diversity.

The search for new small molecules to perturb biological systems as chemical-genetic probes or drug leads has created a demand for efficient synthetic sequences leading to diverse "drug-like" structures.[1] Our attention was drawn to iminium cyclizations which offer a wide array of complexity-building cascade reactions[2] that have been the cornerstones of elegant natural product syntheses.[3,4] Herein we report short divergent pathways exploiting the reactivity of iminium intermediates to access heterocyclic frameworks **5**, **7** and **9** by cyclization through an aza-Cope–Mannich tandem reaction, aminal formation or Pictet–Spengler reaction to yield diverse bicyclic systems (Fig. 1). The key amino alcohol **2** was derived from a three component Petasis reaction.[5–7] To the best of our knowledge, heterocyclic systems **5** and **7** have not been reported previously whereas heterocycles such as **9** have been reported with an acyl or urea at the bridgehead nitrogen.[8]



Scheme 1 Aza-Cope–Mannich reaction sequence with unsubstituted compound **10**.

To evaluate the efficiency of the planned aza-Cope–Mannich cyclization, we subjected the unsubstituted compound **10**† to TsOH in toluene (Scheme 1). To our gratification, the bicyclic product **11** was obtained in good yield after three hours as a 4 : 1 mixture of diastereoisomers which could be separated upon reduction of the aldehyde to the corresponding alcohol. As neither diastereoisomer was

Laboratoire de Chimie Organique et Bioorganique, Institut de Science et d'Ingénierie Supramoléculaires, Université Louis Pasteur – CNRS, 8 allée Gaspard Monge, 67000 Strasbourg, France.
E-mail: winssinger@isis.u-strasbg.fr; Fax: (+33) 3 90 24 51 12

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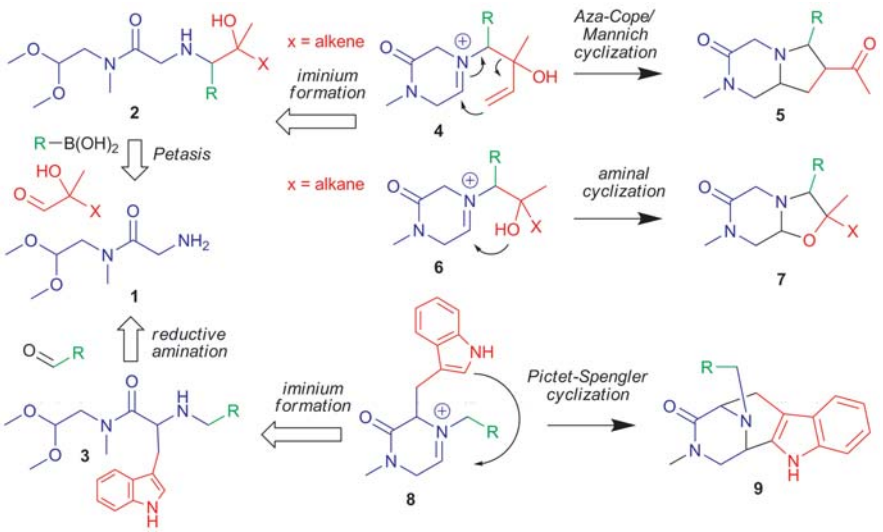
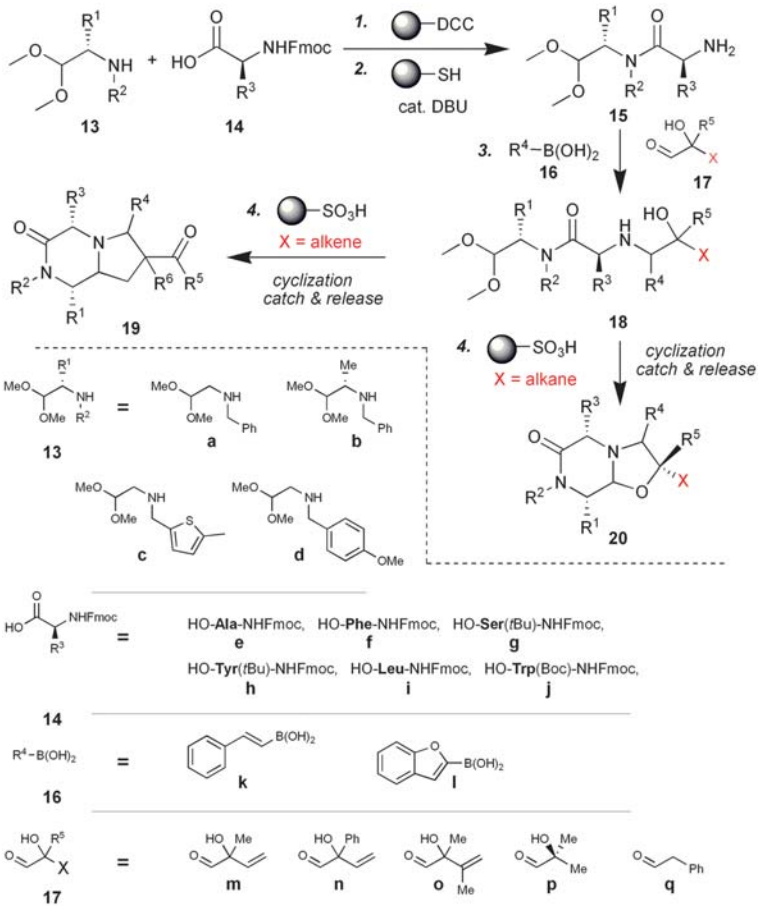


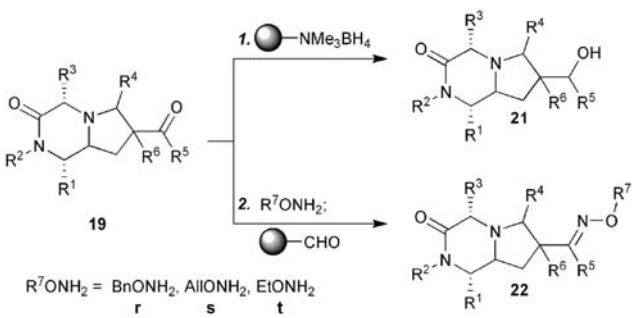
Fig. 1 Divergent pathways leading to heterocycles **5**, **7** and **9** based on alternative iminium cyclizations of intermediates **4**, **6** and **8**.



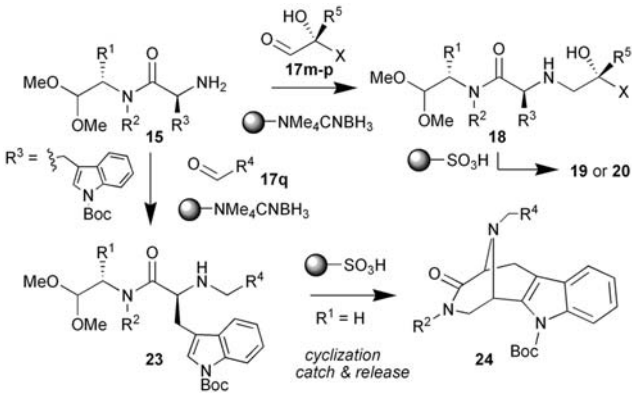
Scheme 2 Synthesis of bicyclic heterocycles **19** and **20**.

crystalline, the alcohols were acylated with 3,5-dinitrobenzoyl chloride thus yielding **12**. The major diastereoisomer afforded diffracting crystals which confirmed the postulated structure and defined the preferred relative stereochemistry among the two newly formed stereogenic centers as *anti*. Evaluation of tolerance of substitutions on the backbone of compound **10** suggested that this reaction sequence should be broadly applicable. The only substitution which was found to inhibit the desired cyclization pathway was at the terminal position of the alkene.

To facilitate the isolation of the products and make this chemistry amenable to high throughput synthesis, we explored the possibility of using supported reagents[9,10] for the sequence, mindful that the final cyclization could be carried out using sulfonic acid resin which would capture the final product. The ''catch-and-release'' strategy has been elegantly applied by Ley and coworkers in the final step of syntheses using solid supported reagents.[11–14] Starting from readily available amine **13** (Scheme 2), the peptide coupling with Fmoc-protected amino acid **14** was achieved with polymer bound carbodiimide (>90% yield, 11 examples) followed by an Fmoc deprotection using catalytic DBU and a thiol resin to sequester the fulvene byproduct.[15] Conveniently, the DBU remains associated with the resin and product **15** was obtained in excellent yield and purity (94–99% yield, 20 examples). Amine **15** was then converted to the amino alcohol **18** using the Petasis procedure with boronic acid **16** and hydroxyaldehyde **17** (83–96% yield, 16 examples).[16] A limitation on the part of the boronic acid is that alkyl boronic acids were not productive in our hands. Alternatively, the new carbon–nitrogen bond could also be made by reductive amination (*vide infra*). The crude product **18** was then treated with the sulfonic acid resin to obtain **19** by aza-Cope–Mannich reaction (36–77% yield, 15 examples) or **20** by aminal formation (65% yield, 1 example) depending on the nature of the substituent X in fragment **17**. As the product of either cyclization bears a tertiary amine, the product remained on the resin as a salt and was recovered by washing with a solution of ammonia in methanol. Any residual amine **15** from an incomplete Petasis reaction did not remain associated with the resin as it forms the cyclic imine which is less basic and can be washed off. The final products were thus



Scheme 3 Synthesis of bicyclic heterocycles **21** and **22**.



Scheme 4 Synthesis of key intermediate **18** and **23** by reductive amination and formation of heterocycle **24** by Pictet–Spengler.

generally obtained in >85% purity without a single traditional purification.

As shown in Scheme 3, compound **19** bearing a ketone could be further diversified by reduction using a polymer supported borohydride (**21**, >90%, 15 examples) or by oxime formation (**22**, >90%, 4 examples). The excess hydroxylamine used in the latter reaction was conveniently sequestered using an aldehyde resin.

Compound **18** could also be conveniently accessed from amine **15** and aldehyde **17** using a reductive amination with supported cyanoborohydride (Scheme 4, 53–80%, 7 examples) and subsequently cyclized to **19** or **20** using the aforementioned sulfonic acid procedure. If compound **15** was substituted with a nucleophilic aromatic system at R^3 such as an indole, the formation of the iminium would engender the Pictet–Spengler reaction. To this end, compound **15** was engaged in a reductive amination to obtain **23** (53–80%, 3 examples) which was subjected to sulfonic acid resin. As for the cyclization of **18**, the product of the reaction (**24**, 70–81%, 3 examples) remained associated with the resin and could be recovered cleanly following a wash with a solution of ammonia in methanol. Prolonged exposure at 60 °C afforded the product without Boc.

In conclusion, we report efficient synthetic pathways leading to diverse heterocycles in four steps containing up to five points of diversity. The starting materials are derived from amino acids, boronic acids and readily available hydroxyl aldehydes. The use of supported reagents greatly facilitates the isolation of the products and renders this chemistry amenable to high throughput synthesis. The utility of the novel heterocyclic frameworks as biological probes is currently being explored.

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