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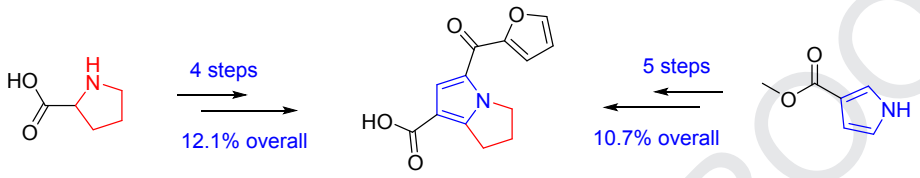

1, punicagranine

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Total synthesis of Punicagranine

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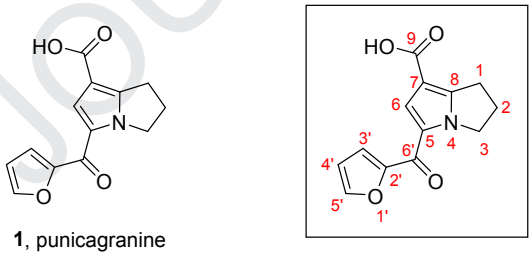
ABSTRACT

This communication details the first total synthesis of Punicagranine, a new pyrrolizine alkaloid isolated from the peels of the pomengranate, *Punica granatum*, the basis for traditional Chinese medicine, with anti-inflammatory activity. Two concise, 4-5 step routes were developed to rapidly prepare Punicagranine in 10.7 to 12.1% overall yields. One route features an intramolecular Heck reaction, while the other relies on a 1,3-dipolar cycloaddition. The latter route proceeds on scale to support future biological studies.

The peels of the pomegranate, *Punica granatum*, have been used in traditional Chinese medicine as an anti-inflammatory agent to treat a number of diseases, as well as possessing significant anticancer activities.[1-5] The report in 2019 by Du and Sun describing the isolation and identification of a novel pyrrolizine alkaloid, punicagranine (**1**) from the peels of *Punica granatum* with anti-inflammatory activity attracted our attention, as **1** represents an active component (**Figure 1**).[6] Moreover, the novel structure, drug-like features and potential for the generation of active metabolites (due to the furanyl ketone moiety) *in vivo* argued well for the synthesis of **1** and further biological evaluation.



1, punicagranine

Figure 1. Structure of punicagranine (**1**) and the numbering convention (inset). This unique skeleton has never before been reported in nature. The structure of **1** was determined by 1D- and 2D-NMR, and confirmed by single X-ray crystal structure.

We envisioned two distinct retrosynthetic approaches to access **1**, employing fundamentally distinct strategies as depicted in Figure 2, yet both requiring only four linear steps. Key bond disconnections in route A lead to intermediate **2**, which can be assembled through a 1,3-dipolar cycloaddition reaction with readily available/commercial materials **3** and **4**. Route B, in contrast disconnects the pyrrolidine ring juncture, **5**, which could be assembled via an intramolecular Heck reaction. An *N*-alkylation and Friedel-Crafts reaction sequence leads to commercial starting materials **6** and **7**.

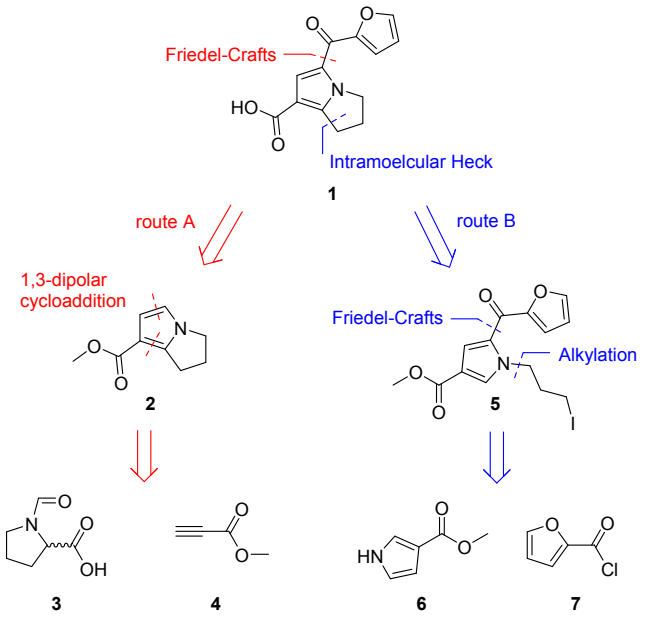


Figure 2. Retrosynthesis of **1**. Route A, features a final Friedel-Crafts acylation on the core **2**, which can be derived *N*-formyl protected D,L-proline **3** and methyl propiolate **4**. In Contrast, Route B features a final intramolecular Heck reaction to assemble the pyrrolidine ring from **5**, which can be assembled via alkylation and an initial Friedel-Crafts acylation, leading to **6** and **7**.

Route A was based on the work of Albonico,[7] wherein a 5,6 homologated congener of **2**, a 5,6,7,8-tetrahydroindolizine **9**, was prepared in 82% yield via a cycloaddition of methyl propiolate **4** and *N*-formyl-2-piperidine carboxylic acid **8** through a 1,3-dipolar intermediate (**Figure 3**). This approach had not been applied to 5,5-systems, such as the requisite methyl 2,3-dihydro-1*H*-pyrrolizine-7-carboxylate **2**.

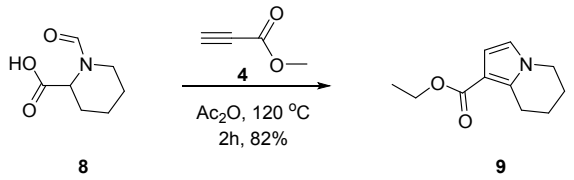
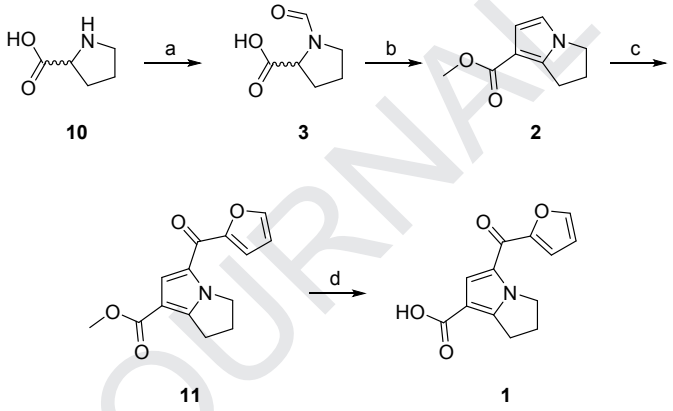


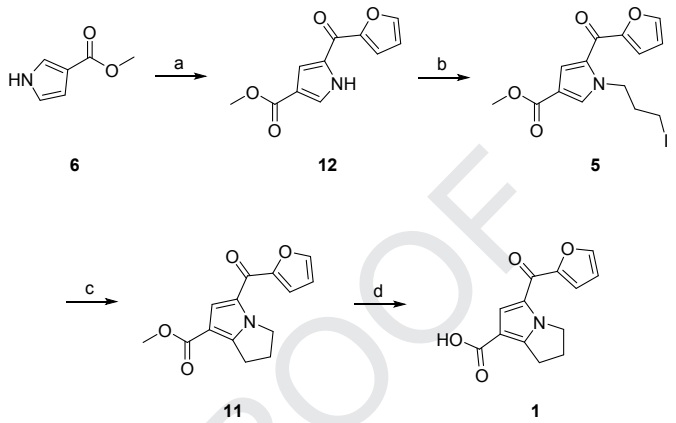
Figure 3. Albonico's 1.3-dipolar cycloaddition strategy to access a 5,6,7,8-tetrahydroindolizine **8**.

Thus, we found this attractive and elected to evaluate if this cycloaddition methodology would extend to a 5,5-system **2**. In the event, commercial D,L-proline **10** was converted to the *N*-formyl derivative **3** in quantitative yield (**Scheme 1**).[8] Following the literature conditions,[7] the reaction was sluggish, with little conversion after two hours. Extending the reaction time to 16 hours delivered the desired methyl 2,3-dihydro-1*H*-pyrrolizine-7-carboxylate **2** in a modest, unoptimized 39% yield. With **2** in hand, a Friedel-Crafts reaction with furan-2-carbonyl chloride **7** provided **11**. Finally, saponification of **11** under standard conditions gave punicagranine (**1**) in 87% yield. Overall, this route required only four steps and 12.1% overall yield; moreover, our synthetic **1** was in complete agreement with that of the natural product.[6,8]



Scheme 1. Route A Synthesis of **1**. Reagents and conditions: (a) CH_2O_2, Ac_2O, rt, 1 h, 99%; (b) methyl propiolate (**4**), Ac_2O, 120 °C, 16h, 39%; (c) furan-2-carbonyl chloride (**7**), $AlCl_3$, $ClCH_2CH_2Cl$, rt, 2h, 36%; (d) 2 N NaOH, EtOH, 60 °C, 1h, 87%.

In parallel, we also pursued alternative Route B (**Scheme 2**). Here, methyl 1*H*-pyrrole-3-carboxylate **6** undergoes a Friedel-Crafts reaction with **7** to provide the disubstituted pyrrole **12** in 63% yield. Alkylation of the pyrrole with 1,3-dibromopropane proceeded smoothly, followed by a Finkelstein reaction generating the alkyl iodide **5** which set the stage for an intramolecular Heck reaction. In this case, the intramolecular Heck reaction required forcing conditions[9] (i.e., refluxing *tert*-butylbenzene for 16 hours), but proceeded in 40% yield to deliver **11**. As in Route A, saponification of **11** under standard conditions gave punicagranine (**1**) in 87% yield. Overall, this route required only five steps from commercial materials and 10.7% overall yield; moreover, our synthetic **1** was in complete agreement with that of the natural product.[6,8]



Scheme 2. Route B Synthesis of **1**. Reagents and conditions: (a) furan-2-carbonyl chloride (**7**), $AlCl_3$, $ClCH_2CH_2Cl$, rt, 2h, 63%; (b) i) 1,3-dibromoethane, KOH, DMF, rt, 16h, 57%; ii) NaI, acetone, 60 °C, 1.5 h, 86%; (c) 10 mol % $Pd(PPh_3)_4$, K_3PO_4, *tert*-butylbenzene, 130 °C, 16 h, 40%; (d) 2 N NaOH, EtOH, 60 °C, 1h, 87%.

In conclusion, we have presented the first total synthesis of punicagranine (**1**) utilizing two distinct routes that require only four to five steps from commercial materials and proceed in 10.7-12.1% overall yields. In addition, our modular synthetic approach enables facile analog development, which will prove useful for the future exploration of anti-inflammatory SAR around related congeners, as well as target identification and metabolite identification studies.

Acknowledgments

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References and notes

[1] E. Shaygannia, M. Bahmani, B. Zamanzad, et al., J. Evid. Based Complementary Altern. Med. 21 (2016) 221–227.
[2] National Pharmacopoeia Committee, Pharmacopoeia of People's Republic of China, Part 1, Chemical Industry Press, Beijing, 2010, p. 87.
[3] S. Modaeinama, M. Abasi, M.M. Abbasi, et al., Asian Pac. J. Cancer Prev. 16 (2015) 5697–5701.
[4] E.P. Lansky, R.A. Newman, J. Ethnopharmacol. 109 (2007) 177–206.
[5] G.W. Plumb, S. De Pascual-Teresa, C. Santos-Buelga, J.C. Rivas-Gonzalo, G. Williamson, Redox Rep. 41 (2002) 41–46.
[6] H-y. Sun, N. Ma. T. Pan, et al., Tetrahedron Lett. 60 (2019) 1231-1233.
[7] M.T. Pizzorno, S.M. Albonico J. Org. Chem. 42 (1977) 909-910.
[8] See Supporting Information for full details.
[9] R.O. Alexander, P.T. Bohan, E.J. Alexanian J. Am. Chem. Soc. 137 (2015) 3731-3734.

Appendix A. Supplementary data

The following are the Supplementary data to this article:

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- First total synthesis of punicagranine
- Two distinct routes, only 4-5 steps and >10% overall yields
- Sufficient material to support mechanism of action studies