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Total Synthesis of Incarviditone and Incarvilleatone**

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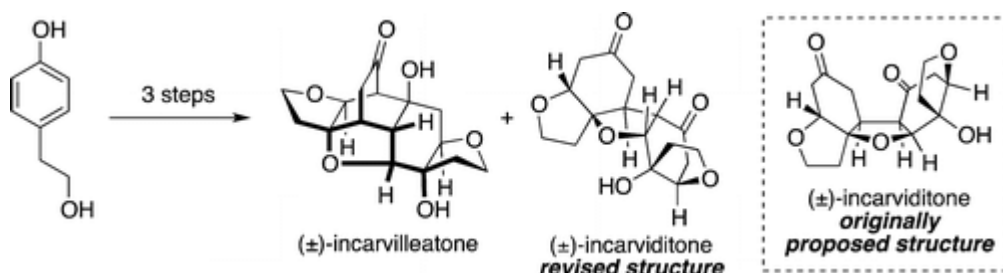
^[**]The authors would like to thank Prof. Zhang (School of Pharmacy, Second Military Medical University, Shanghai) for kindly providing copies of the original NMR data. We also thank Mr. Chris Blake (Australian National University) and Dr. Thomas Fallon (Australian National University) for NMR measurements. A.L.L. gratefully acknowledges financial support from the Australian Research Council, in the form of a Discovery Early Career Researcher Award (Project ID: DE120102113).

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Supporting information:

Experimental procedures and analytical data for all compounds, and atomic displacement ellipsoid plots for compound 9 (CCDC 897209). This material is available free of charge via the Internet at <http://pubs.acs.org>

Graphical abstract:

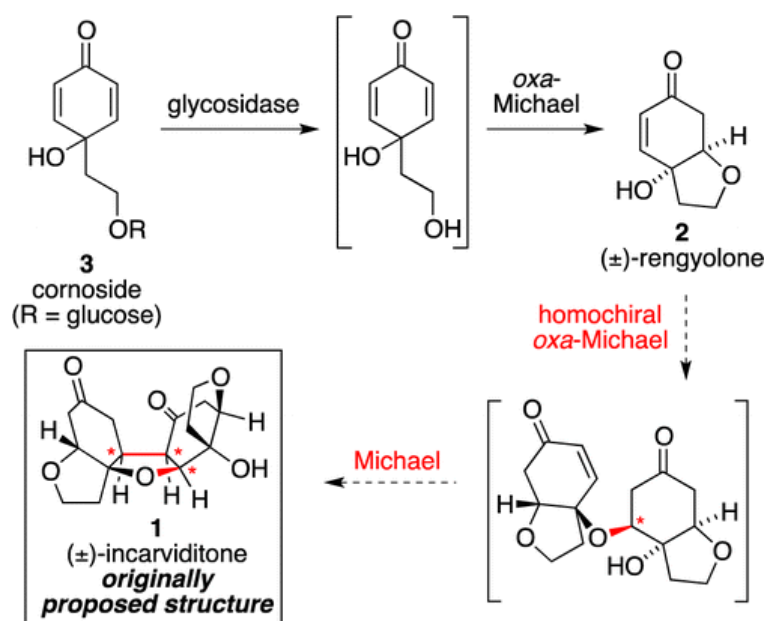


Abstract

The total synthesis of the racemic natural products (\pm)-incarviditone and (\pm)-incarvilleatone has been accomplished in three steps *via* biomimetic dimerization of (\pm)-rengyolone. Homochiral dimerization of (\pm)-rengyolone affords (\pm)-incarviditone through a domino *oxa*-Michael/Michael sequence. Heterochiral dimerization, involving a domino *oxa*-Michael/Michael/aldol reaction sequence, affords (\pm)-incarvilleatone. Single crystal X-ray analysis of a derivative of (\pm)-incarviditone has resulted in revision of the originally proposed structure.

Main text

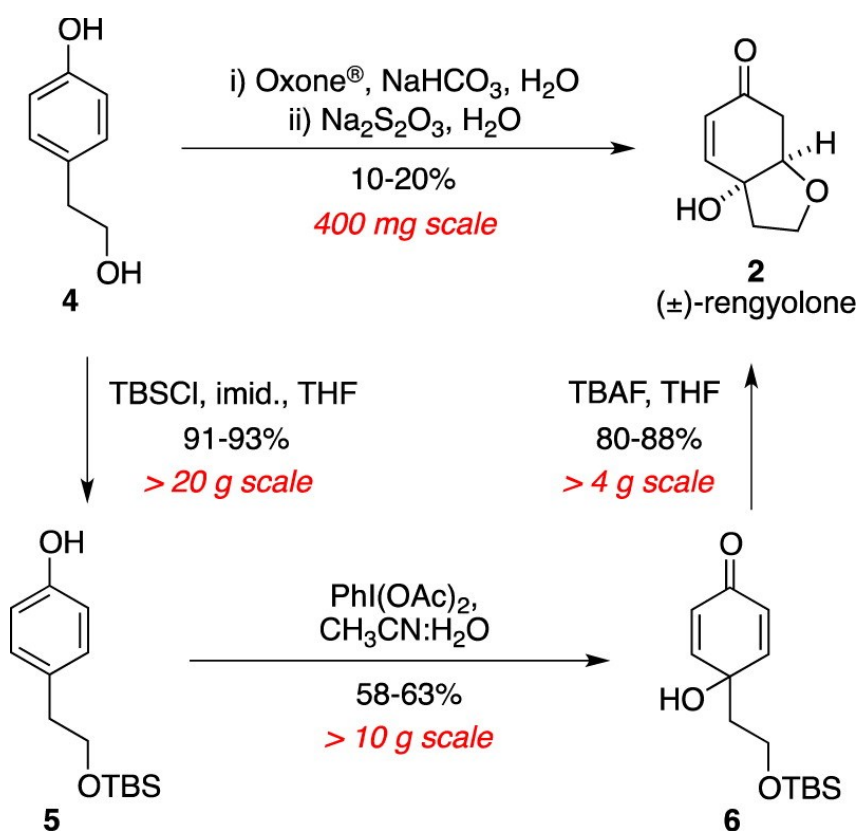
The racemic natural product (\pm)-incarviditone (**1**) was isolated in 2009 by Zhang and co-workers from *Incarvillea delevayi*.¹ In the isolation paper, Zhang noted that (\pm)-incarviditone (**1**) was a dimer of the co-isolated natural product (\pm)-rengyolone (**2**; synonyms: halleridone, cleroindicin F),² although no mechanism for this dimerization was presented. A plausible biosynthesis of (\pm)-incarviditone (**1**) from the *para*-quinolethanoid glycoside natural products, *e.g.* cornoside (**3**),³ is depicted in Scheme 1. Thus, upon cleavage of the glycosidic bond, the putative aglycone undergoes an intramolecular *oxa*-Michael reaction to afford (\pm)-rengyolone (**2**).⁴ Dimerization of (\pm)-rengyolone (**2**) then occurs through a domino *oxa*-Michael/Michael sequence to form (\pm)-incarviditone (**1**). This hypothesis involves two ‘like’ enantiomers reacting together (*i.e.* a homochiral dimerization) to afford a single diastereomeric product as a racemate (Scheme 1). The origin and magnitude of this apparent stereoselectivity, which presumably is non-enzymatic, was immediately intriguing to us. Therefore, we embarked upon a biomimetic synthesis of (\pm)-incarviditone (**1**).



Scheme 1. Proposed biogenesis of (\pm)-incarviditone (**1**).

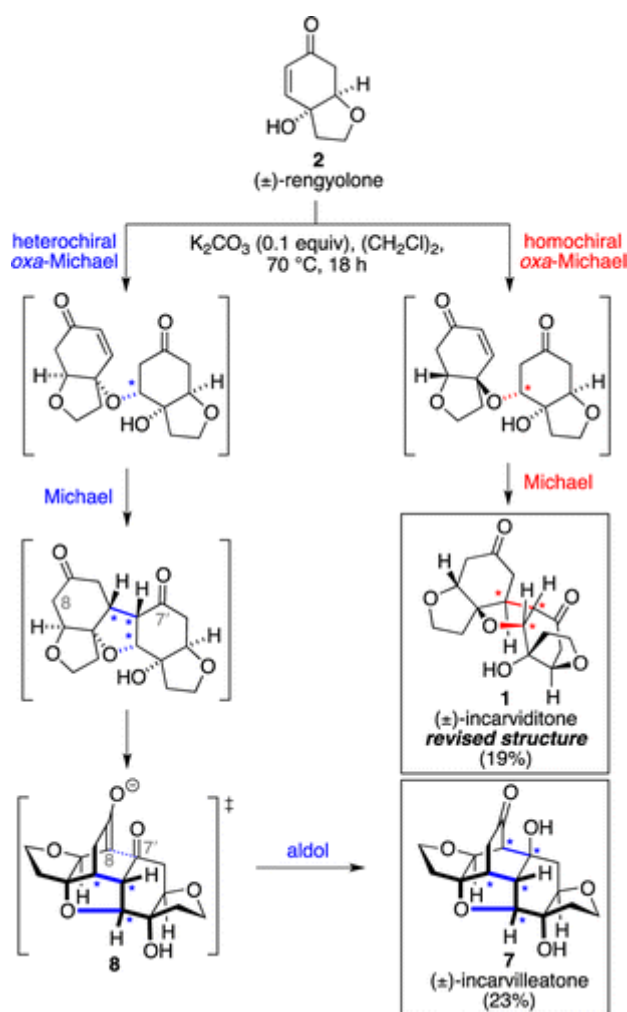
As noted by Nising and Bräse,⁵ the reversible nature of *oxa*-Michael reactions has precluded their general application in synthesis. Nevertheless, we were encouraged by the likelihood that our *oxa*-Michael adduct would be trapped through an essentially irreversible *carbo*-Michael reaction.⁵

Confident in our proposed domino Michael strategy we first required access to (±)-rengyolone (**2**). The synthesis of (±)-rengyolone (**2**) from commercially available phenol **4** has been reported by several groups.⁶ Photosensitized generation and addition of singlet oxygen has been explored in detail with only moderate yields of (±)-rengyolone (**2**) obtained.^{6a,b} Carreño and Urbano have described the same transformation using Oxone[®]/NaHCO₃ in water and, following a same-pot Na₂S₂O₃ reduction, obtained a 50% yield of (±)-rengyolone (**2**).^{6c} In our hands this protocol invariably gave low yields (10-20%) and was difficult to scale-up (Scheme 2);⁷ work is ongoing in our laboratory to optimize this one-pot procedure. With a need for larger quantities of (±)-rengyolone (**2**), we elected to devise a new practical, reliable and scalable synthetic route (Scheme 2). The PIDA oxidation of phenol **5** is a known transformation^{6d} and the resultant *para*-quinol **6** can be viewed as a synthetic equivalent of cornoside (**3**). Pleasingly, when treated with TBAF, *para*-quinol **6** afforded (±)-rengyolone (**2**) in high yield.⁸ This three step sequence was easily scaled up to afford multi-gram quantities of (±)-rengyolone (**2**).



Scheme 2. Synthesis of (±)-rengyolone (**2**).^{6c,d,7}

Our initial efforts at the biomimetic dimerization of (\pm)-rengyolone (**2**) using acid catalysis and iminium ion catalysis were unsuccessful. The likely explanation is the poor nucleophilicity of the tertiary alcohol. Following a screen of basic reaction conditions, including Taylor's stoichiometric LiOH/THF¹⁰ and Carreño's stoichiometric NaH/CH₂Cl₂ conditions,¹¹ we were delighted to find that catalytic K₂CO₃ in (CH₂Cl)₂ was sufficient for the dimerization of (\pm)-rengyolone (**2**). Thus, one gram of (\pm)-rengyolone (**2**) was treated to 10 mol % K₂CO₃ in 0.4 mL of (CH₂Cl)₂ at 70 °C for 18 h. Following flash chromatography, (\pm)-incarviditone (**1**) was isolated in 19% yield and the remaining (\pm)-rengyolone (**2**) was recovered in 6% yield (Scheme 3).

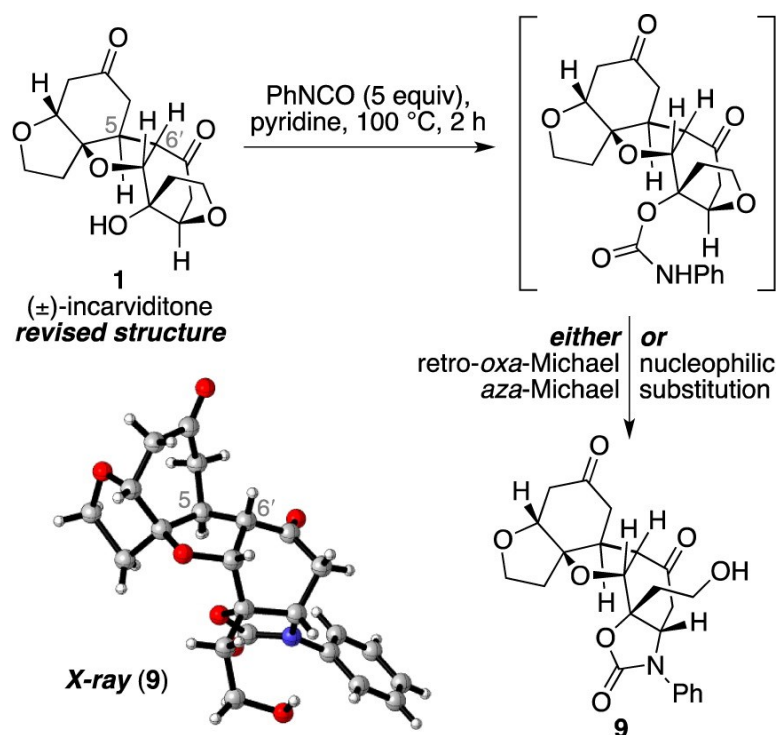


Scheme 3. Biomimetic synthesis of (\pm)-incarviditone (**1**) and (\pm)-incarvilleatone (**7**), with the proposed intermediates.

The spectroscopic data for our synthetic (\pm)-incarviditone (**1**) matched perfectly with that reported by Zhang and co-workers,^{1,8} thus confirming that the total synthesis had been achieved. The structure reported for the natural product by Zhang and co-workers was based on their analysis of NMR data. Upon re-evaluation of this

data we concluded that, although the connectivity of (\pm)-incarviditone (**1**) was secure, the relative stereochemistry could not be unequivocally established. After numerous attempts to grow crystals of (\pm)-incarviditone (**1**) and its derivatives, we finally discovered that treatment of (\pm)-incarviditone (**1**) to excess phenyl isocyanate in pyridine at 100 °C afforded crystalline oxazolidinone **9** (Scheme 4).⁹ Single crystal X-ray analysis of **9**, which is presumably formed through a sequence involving carbamate formation, retro-*oxa*-Michael addition and *aza*-Michael addition, revealed a *trans*-configuration between C5 and C6 at the central tetrahydrofuran ring. The structure originally assigned to (\pm)-incarviditone (**1**) (Scheme 1), with a *cis*-configuration between these two stereocentres is incorrect and must be revised to that shown in Schemes 3 and 4.

Compound **7**, a further isomeric dimer of (\pm)-rengyolone (**2**), was also isolated in 23% yield (Scheme 3). During the preparation of this manuscript, Zhang and co-workers disclosed the isolation of (\pm)-incarvilleatone (**7**) from *Incarvillea younghusbandii*.¹² The physical and spectroscopic data reported for this natural product matched perfectly with that of our synthetic dimer (Scheme 3).⁸ The structure of (\pm)-incarvilleatone (**7**) was secured by Zhang and co-workers using single crystal X-ray analysis.¹² Therefore, we report the first total syntheses of both these complex polycyclic natural products. The biosynthesis of (\pm)-incarvilleatone (**7**) involves the union of two ‘unlike’ enantiomers of rengyolone (**2**) (*i.e.* a heterochiral dimerization). We propose a domino *oxa*-Michael/Michael/aldol biosynthetic reaction sequence from rengyolone (**2**) to (\pm)-incarvilleatone (**7**) (Scheme 3).¹³ The difference in product outcome for the homochiral and heterochiral dimerization pathways appears to stem from the ability of the latter to adopt transition state **8** (Scheme 3).

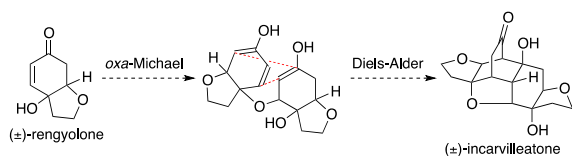


Scheme 4. Formation and crystal structure of compound **9**.

In summary, the synthetic work outlined in this communication provides strong evidence that (±)-rengyolone (**2**) undergoes domino sequences of nucleophilic addition reactions in nature to afford *both* (±)-incarviditone (**1**) and (±)-incarvilleatone (**7**).¹⁴ It is well established that imitating nature in synthesis has many anticipated benefits¹⁵ but this work also highlights an unexpected one. Our synthesis of (±)-incarvilleatone (**7**) is the more impressive of the two, with 7 new bonds, 4 new rings and 9 new stereocentres formed in just three steps, and yet was neither planned nor even considered at the outset.¹⁶ This serendipitous result is a direct result of following a biomimetic approach.

Notes and references

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- [13] Prof. Zhang proposed a different biosynthetic hypothesis for (±)-incarvilleatone, involving an *oxa*-Michael/intramolecular-Diels-Alder sequence.¹²



[14] The possibility that (±)-incarviditone (**1**) and (±)-incarvilleatone (**7**) are formed during the isolation process can not be ruled out. However, during our attempts to mimic the isolation conditions (rengyolone (**2**) in EtOH, 78 °C, 24 h) no trace of either dimer was observed *via* ^1H NMR.

[15] For a recent perspective on biomimetic syntheses see: Razzak, M.; De Brabander, J. K. *Nat. Chem. Biol.* **2011**, *7*, 865-875.

[16] For a recent example of a biomimetic approach yielding a natural product prior to isolation from natural sources see: Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. *Org. Lett.* **2010**, *12*, 1676-1679.