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Total Synthesis of Incarviditone and Incarvilleatone**

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

Main text

The racemic natural product (±)-incarviditone (1) was isolated in 2009 by Zhang and co-workers from Incarvillea delevayi. In the isolation paper, Zhang noted that (±)-incarviditone (1) was a dimer of the co-isolated natural product (±)-rengyolone (2; synonyms: halleridone, cleroidincin F), although no mechanism for this dimerization was presented. A plausible biosynthesis of (±)-incarviditone (1) from the para-quinolethanoid glycoside natural products, e.g. cornoside (3), is depicted in Scheme 1. Thus, upon cleavage of the glycosidic bond, the putative aglycone undergoes an intramolecular oxa-Michael reaction to afford (±)-rengyolone (2). Dimerization of (±)-rengyolone (2) then occurs through a domino oxa-Michael/Michael sequence to form (±)-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 (±)-incarviditone (1).

Scheme 1. Proposed biogenesis of (±)-incarviditone (1).
As noted by Nising and Bräse, 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.

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. Photosensitized generation and addition of singlet oxygen has been explored in detail with only moderate yields of (±)-rengyolone (2) obtained. 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). In our hands this protocol invariably gave low yields (10-20%) and was difficult to scale-up (Scheme 2); 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 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. This three step sequence was easily scaled up to afford multi-gram quantities of (±)-rengyolone (2).

Scheme 2. Synthesis of (±)-rengyolone (2).
Our initial efforts at the biomimetic dimerization of (±)-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/THF and Carreño’s stoichiometric NaH/CH\textsubscript{2}Cl\textsubscript{2} conditions, we were delighted to find that catalytic K\textsubscript{2}CO\textsubscript{3} in (CH\textsubscript{2}Cl\textsubscript{2}) was sufficient for the dimerization of (±)-rengyolone (2). Thus, one gram of (±)-rengyolone (2) was treated to 10 mol % K\textsubscript{2}CO\textsubscript{3} in 0.4 mL of (CH\textsubscript{2}Cl\textsubscript{2}) at 70 °C for 18 h. Following flash chromatography, (±)-incarviditone (1) was isolated in 19% yield and the remaining (±)-rengyolone (2) was recovered in 6% yield (Scheme 3).

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

The spectroscopic data for our synthetic (±)-incarviditone (1) matched perfectly with that reported by Zhang and co-workers, 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 (±)-incarviditone (1) was secure, the relative stereochemistry could not be unequivocally established. After numerous attempts to grow crystals of (±)-incarviditone (1) and its derivatives, we finally discovered that treatment of (±)-incarviditone (1) to excess phenyl isocyanate in pyridine at 100 °C afforded crystalline oxazolidinone 9 (Scheme 4). 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 (±)-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 (±)-rengyolone (2), was also isolated in 23% yield (Scheme 3). During the preparation of this manuscript, Zhang and co-workers disclosed the isolation of (±)-incarvilleatone (7) from Incarvillea younghusbandii. The physical and spectroscopic data reported for this natural product matched perfectly with that of our synthetic dimer (Scheme 3). The structure of (±)-incarvilleatone (7) was secured by Zhang and co-workers using single crystal X-ray analysis. Therefore, we report the first total syntheses of both these complex polycyclic natural products. The biosynthesis of (±)-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 (±)-incarvilleatone (7) (Scheme 3). 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). It is well established that imitating nature in synthesis has many anticipated benefits 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. This serendipitous result is a direct result of following a biomimetic approach.
Notes and references


[4] It has been shown that enzymatic hydrolysis of cornoside affords rengyolone directly.6b


[7] The yields we have obtained for the Oxone®/NaHCO3 reaction are in agreement with the yield reported by Prof. You.6e

[8] The NMR spectra of (±)-rengyolone (2), (±)-incarviditone (1) and (±)-incarvilleatone (7) all show concentration dependency in chemical shifts, see the Supporting Information for details.


[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 $^1$H NMR.
