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Total Synthesis of Incarviditone and Incarvilleatone

Patrick D. Brown, Anthony C. Willis,† Michael S. Sherburn, and Andrew L. Lawrence*

Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

allawrence@rsc.anu.edu.au

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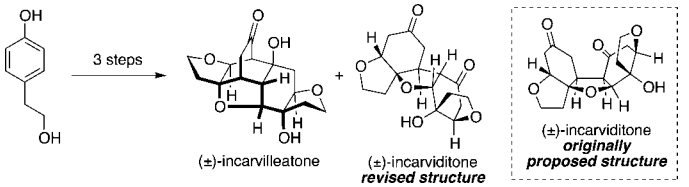
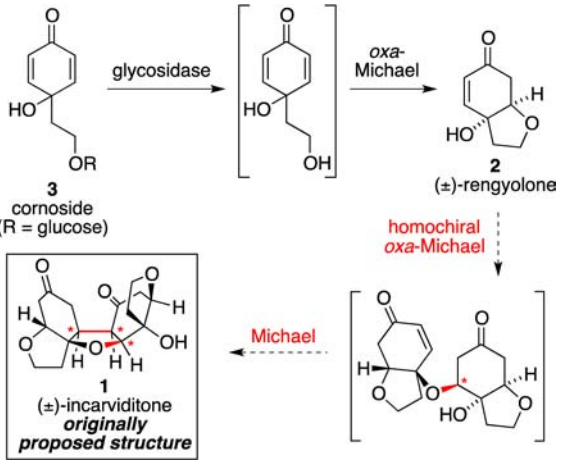
ABSTRACT



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.

The racemic natural product (±)-incarviditone (**1**) was isolated in 2009 by Zhang and co-workers from *Incarvillea delevayi*.[1] In the isolation paper, Zhang noted that (±)-incarviditone (**1**) was a dimer of the coisolated natural product (±)-rengyolone (**2**; synonyms: halleridone, clerodindicin F),[2] although no mechanism for this dimerization was presented. A plausible biosynthesis of (±)-incarviditone (**1**) from the *p*-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 (±)-rengyolone (**2**).[4] 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 nonenzymatic, 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,[5] the reversible nature of oxa-Michael reactions has precluded their general application in synthesis. Nevertheless, we were encouraged by the

† To whom correspondence regarding X-ray crystallography should be addressed. E-mail: willis@rsc.anu.edu.au.

(1) Chen, Y. Q.; Shen, Y. H.; Su, Y. Q.; Kong, L. Y.; Zhang, W. D. *Chem. Biodiversity* **2009**, *6*, 779–783.

(2) (a) Endo, K.; Hikino, H. *Can. J. Chem.* **1984**, *62*, 2011–2014. (b) Messana, I.; Sperandei, M.; Multari, G.; Galeffi, C.; Marini Bettolo, G. B. *Phytochemistry* **1984**, *23*, 2617–2619. (c) Tian, J.; Zhao, Q. S.; Zhang, H. J.; Lin, Z. W.; Sun, H. D. *J. Nat. Prod.* **1997**, *60*, 766–769.

(3) Isolation of cornoside: (a) Rosendal, J. S.; Kjaer, A.; Juhl, N. B. *Acta Chem. Scand.* **1973**, *27*, 367–369. For a review of C_6C_2 glycosides, see: (b) Jimenez, C.; Riguera, R. *Nat. Prod. Rep.* **1994**, *11*, 591–606.

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

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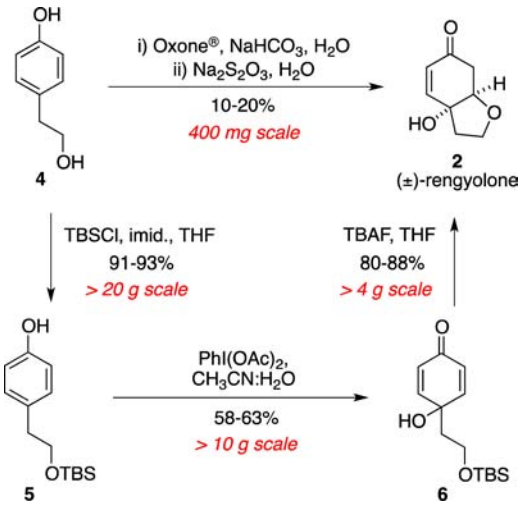
likelihood that our oxa-Michael adduct would be trapped through an essentially irreversible carbo-Michael reaction.[5]

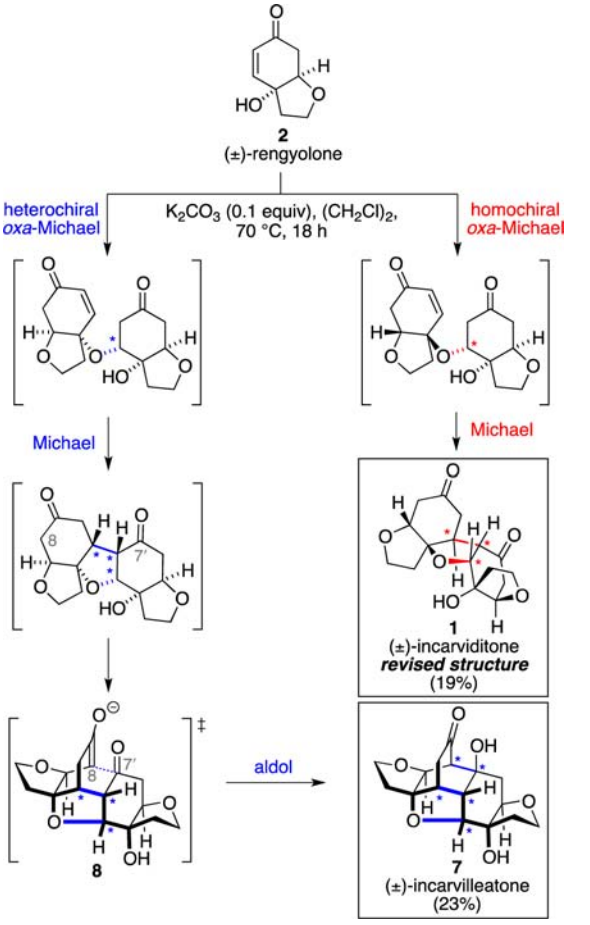
Confident in our proposed domino Michael strategy, we first required access to (±)-rengyolone (**2**). The synthesis of (±)-rengyolone (**2**) from commercially available phenol **4** has been reported by several groups.[6] Photosensitized generation and addition of singlet oxygen has been explored in detail with only moderate yields of (±)-rengyolone (**2**) obtained.[6a,b] Carreño and Urbano have described the same transformation using Oxone/$NaHCO_3$ in water and, following a same-pot $Na_2S_2O_3$ 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 *p*-quinol **6** can be viewed as a synthetic equivalent of cornoside (**3**). Pleasingly, when treated with TBAF, *p*-quinol **6** afforded (±)-rengyolone (**2**) in high yield.[8] This three-step sequence was easily scaled up to afford multigram quantities of (±)-rengyolone (**2**).

Scheme 2. Synthesis of (±)-Rengyolone (**2**)[6c,d,7]



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[10] and Carreño's stoichiometric NaH/CH_2Cl_2 conditions,[11] we were delighted to find that catalytic K_2CO_3 in $(CH_2Cl)_2$ was sufficient for the dimerization of (±)-rengyolone (**2**). Thus, 1 g of (±)-rengyolone (**2**) was treated to 10 mol % of K_2CO_3 in 0.4 mL of $(CH_2Cl)_2$ 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,[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

(5) (a) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37*, 1218–1228. (b) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2012**, *41*, 988–999.

(6) (a) Breton, J. L.; Llera, L. D.; Navarro, E.; Trujillo, J. *Tetrahedron* **1987**, *43*, 4447–4451. (b) Endo, K.; Seya, K.; Hikino, H. *Tetrahedron* **1989**, *45*, 3673–3682. (c) Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2737–2741. For asymmetric syntheses of rengyolone, see: (d) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem. Int. Ed* **2009**, *48*, 547–550. (e) Gu, Q.; Rong, Z. Q.; Zheng, C.; You, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057.

(7) The yields we have obtained for the Oxone/$NaHCO_3$ reaction are in agreement with the yield reported by Prof. You.[6e]

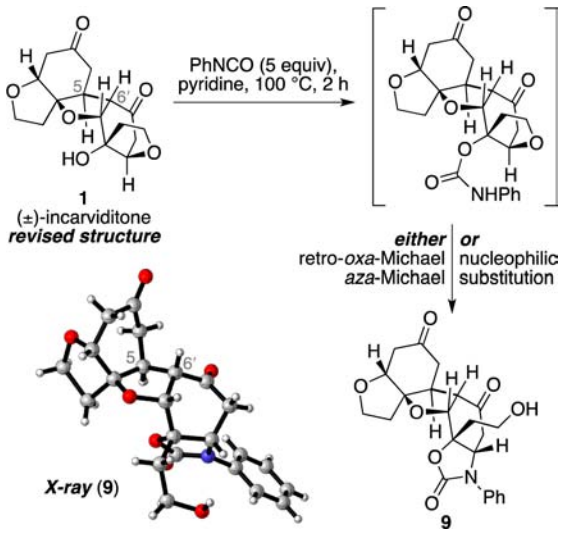
(8) The NMR spectra of (±)-rengyolone (**2**), (±)-incarviditone (**1**), and (±)-incarvilleatone (**7**) all show concentration dependency in chemical shifts; see the Supporting Information for details.

(9) Agarwal, K. L.; Khorana, H. G. *J. Am. Chem. Soc.* **1972**, *94*, 3578–3585.

(10) Greatrex, B. W.; Kimber, M. C.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2003**, *68*, 4239–4246.

(11) Cerrano, M. C.; Ribagorda, M. *Org. Lett.* **2003**, *5*, 2425–2428.

Scheme 4. Formation and Crystal Structure of Compound **9**



(±)-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).[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 (±)-incarviditone (**1**) (Scheme 1) with a *cis*-configuration between these two stereocenters 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*.[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 (±)-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 (±)-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).[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).

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 benefits,[15] but this work also highlights an unexpected one. Our synthesis of (±)-incarvilleatone (**7**) is the more impressive of the two, with seven new bonds, four new rings, and nine new stereocenters 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.

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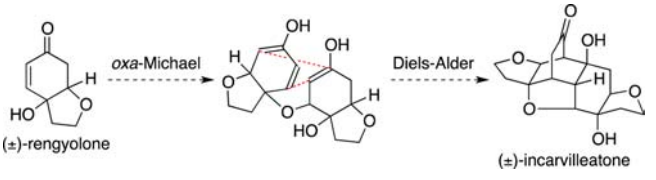
Supporting Information Available. Experimental procedures and analytical data for all compounds and atomic displacement ellipsoid plots for compound **9** (CCDC 897209). This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Gao, Y. P.; Shen, Y. H.; Zhang, S. D.; Tian, J. M.; Zeng, H. W.; Ye, J.; Li, H. L.; Shan, L.; Zhang, W. D. *Org. Lett.* **2012**, *14*, 1954–1957.

(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.

(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.

The authors declare no competing financial interest.