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Total synthesis of (−)-incarvilline and (−)-incarvillateine

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ABSTRACT

An enantioselective, concise total synthesis of (−)-incarvilline and (−)-incarvillateine has been achieved in longest linear 9 steps (24.3% overall yield) and in 11 steps (16.5% overall yield) from (−)-carvone, respectively. The present synthesis features a notable Favorskii rearrangement of the *O*-protected chlorohydrin derivative of (−)-carvone to construct four of the five contiguous stereocenters on the bicyclic piperidine moiety and DMAP-catalyzed esterification of incarvilline with α-truxillic acid anhydride to generate incarvillateine skeleton.

1. Introduction

Since 1990, a new class of monoterpene alkaloids (Fig. 1) have been isolated and identified by Chi and co-workers from the plant *Incarvilla sinensis*, which has been used in treating rheumatism and relieving pain in Traditional Chinese Medicine (TCM).[1] Incarvillateine **1**, one of the novel monoterpene alkaloids, has been found to exhibit more potent antinociceptive activity comparable to that of morphine in a formalin-induced pain model in mice. The mechanism of action was also regarded to be different from that of morphine.[2] So, incarvillateine has potential to become an important lead compound for developing new nonopioid analgesic drugs. The structural characteristics of **1** include a unique dimeric structure, and five contiguous stereocenters on the bicyclic piperidine moiety. The unique structural features and interesting biological profile of **1** make it an attractive target for total synthesis.[3] Kibayashi's and Ellman's groups have achieved its total synthesis. Both of them took the same strategy to first construct the precursor 6-*epi*-incarvilline, from which incarvilline **3** and/or incarvillateine **1** was prepared via Mitsunobu reaction with complete inversion of the configuration at C6. However, the synthesis of 6-*epi*-incarvilline either required a number of steps or employed expensive heavy metal catalysts.[3a,b] In connection with our interest of investigating structure-antinociceptive activity relationship related to incarvillateine, an effective and practical asymmetric synthesis for **1** is highly desirable. Herein, we report a concise and practical asymmetric synthesis of (−)-incarvilline **3** and (−)-incarvillateine **1** employing (−)-carvone as a chiral starting material.

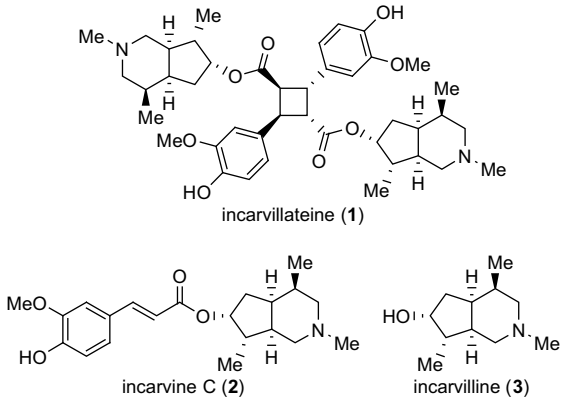

Figure 1. Structures of incarvillateine and related alkaloids.

2. Results and discussions

Our retrosynthetic analysis is outlined in Scheme 1. (−)-Incarvillateine may be disconnected to incarvilline **3** and α-truxillic acid **4**. Incarvilline **3** can be obtained from known cyclopentane **5** which has been prepared in four steps as a single diastereoisomer via a Favorskii rearrangement from carvone, and has been used in the total synthesis of cladantholide, estafiatin, and thapsigargin.[4] The synthesis of **4** can be accomplished in two steps from commercially available ferulic acid **7**.[3a]

Our synthesis of incarvilline **3** commenced with known cyclopentane **5** which was prepared from commercially available monoterpene (*R*)-(−)-carvone **6** through epoxidation, opening the resulting oxirane, protection of the chlorohydrin, and Favorskii rearrangement.[4] Stereoselective hydroboration of **5** with disiamylborane followed by oxidation with basic hydrogen peroxide to give the primary alcohol **10** has been reported.[4a] However, there is no operational procedure available. Treatment of **5** with the

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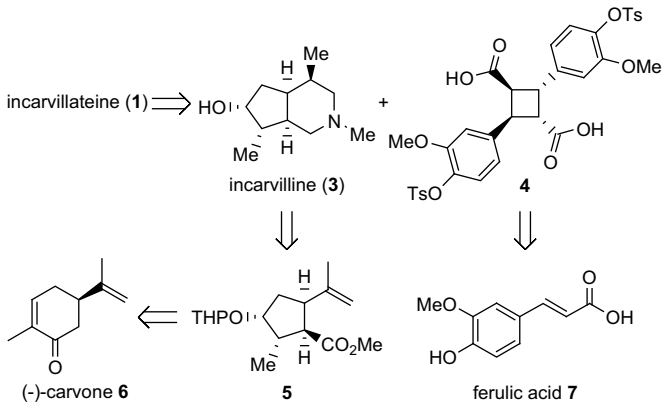
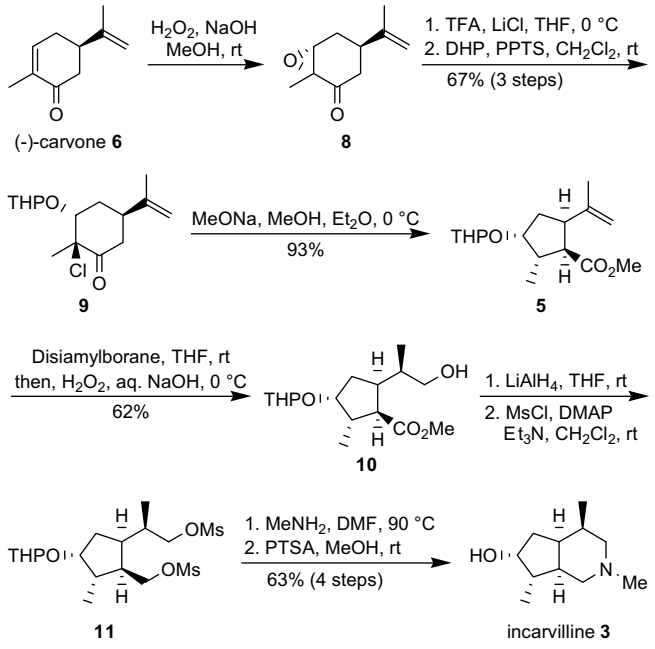


Scheme 1. Retrosynthesis of incarvillateine and incarvilline.

standard hydroboration–oxidation condition did not afford **10**. A range of temperatures and equivalents of disiamylborane were investigated, it was soon revealed that it is necessary to use at least 8 equiv of disiamylborane to get the desired hydroxyl ester **10** in satisfactory yield (62%) (Scheme 2).



Scheme 2. Synthesis of (−)-incarvilline **3**.

On the basis of the high diastereoselectivity, the plausible transition state in the hydroboration of **5** is proposed as an ester-directed process (Fig. 2). Chelating of the oxygen atom of the carbonyl group to the boron atom of disiamylborane directs the B–H bond to add to the terminate alkene from the *si* face, succedent oxidation affords the primary alcohol **10**.

Reduction of **10** and treatment of the resultant diol with mesyl chloride in the presence of TEA gave dimesylate **11**. Treatment of **11** with aqueous methylamine (6 equiv) solution in DMF at 90 °C resulted in piperidine formation, which was followed by acid treatment to give incarvilline **3**. It's noteworthy that just the final operation of this four-step sequence from **10** requires column chromatography purification with the overall yield as high as 63%.

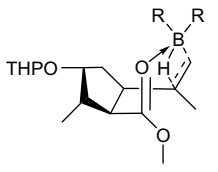
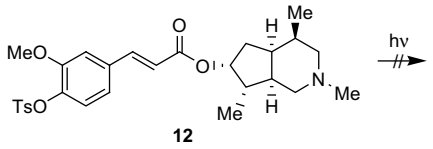


Figure 2. Plausible transition state in the hydroboration of **5**.

With rapid access to large quantities of **3**, the synthesis of (−)-incarvillateine was firstly explored by photochemical dimerization of Ts-protected incarvine C derivative **12**, prepared by coupling 4-Ts-protected ferulic acid (2 equiv) and **3** in quantitative yield. Although Kibayashi's group failed to dimerize **2** under UV irradiation, they have revealed that the 4-*O*-tosyl protection group in ferulic acid derivatives played a significant role in achieving an appropriate packing arrangement for α-dimerization to occur.[3a] Unfortunately, this approach resulted in recovering of **12** and no desired product was obtained (Scheme 3).



Scheme 3. Photodimerization of **12**.

We then turned our attention to direct esterification between **3** and **4**. However, we quickly realized it was a formidable synthetic challenge. It is known that there are problems for the esterification of amino alcohols. A careful review of the literature revealed that acid chlorides are usually used as acylation reagent, and large excess amounts of either acid chlorides or amino alcohols are used in this kind of condensation to give esters in only moderate yield.[5] Chi et al. have also reported that coupling between incarvilline **3** and α-truxillic acid dichloride provided 3,3′-demethoxy-4,4′-dehydroxy-incarvillateine in 33% yield based on the more valuable incarvilline **3**.[5d] In fact, all the standard coupling conditions that we had attempted gave the desired **13** in low yield (20–40%). Fortunately, the DMAP-catalyzed conditions for mixed-anhydride acylation of alcohols recently developed by Ishihara provided a satisfactory result, and more importantly, ester condensation can be conducted with equimolar amounts of carboxylic acids and alcohols.[6] Thus, reaction of **4** with triethylamine (2.2 equiv) and pivaloyl chloride (2.2 equiv) afforded the corresponding mixed anhydride, which was allowed to react with **3** in the presence of catalytic amount of DMAP at room temperature for 3 days to afford **13** in 80% yield. Finally, removal of the tosyl groups employing the conditions optimized by Ellman and co-workers completed the total synthesis of (−)-incarvillateine **1**.[3b]

It is noteworthy that during the course of preparation of **13** by direct esterification of **3** with **4**, we noticed some differences in the ^{1}H NMR spectra of **13** comparable to those reported. Moreover, the ^{1}H NMR spectra of **13** were slightly different from one another which were obtained via different esterification conditions. This is probably due to the trace acid effect. In fact, after these samples were washed with 0.2 N aqueous NaOH solution, the ^{1}H NMR spectrum of **13** was almost identical to those reported. However, we were still puzzled by the chemical shifts of 6 and 6′-H moved to lower ppm values while that of other protons moved to higher ppm values, since it is normal that the chemical shifts of protons in alkaloids would move to higher ppm values in the presence of acid.[7] This phenomenon promoted us to further investigate the acid effect on the ^{1}H NMR spectra of incarvilline **3**, **13**, incarvillateine **1**, respectively (see Supplementary data). It revealed that **3** and **1** followed line broadening effect, just only 6 and 6′-H of **13** shifted to high field, which was probably ascribed to the shielding effect of aromatic rings of the tosyl groups (Scheme 4).