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Total Synthesis of Gelsemiol

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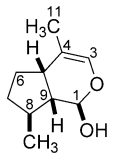
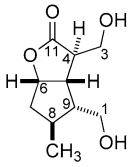
The power of natural products in controlling biological processes on a molecular level renders them ideal starting points for the discovery of new mechanisms of actions, as can be exemplified by the successful drugs vancomycin, quinine, and artemisinin.[1] To this end, identifying natural products that generate a desired phenotype in cell-based assays and understanding their structure/activity relationship is essential. In the therapeutic area related to neurodegenerative diseases, several natural products inducing (neuritogenic) or enhancing (neuritotrophic) neurite outgrowth have been studied for which the mechanism of action remains unclear.[2]



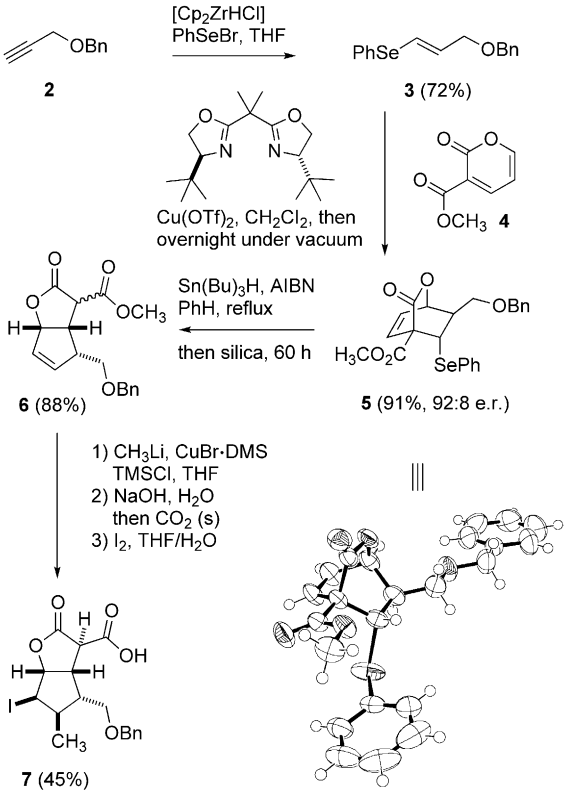
General Iridoid Structure



Gelsemiol (**1**)

Interesting biological activity, generally unidentified mechanisms of action combined with structural complexity render natural products ideal targets for organic synthesis combined with biological studies. In the context of our program on the synthesis and biological evaluation of neuritogenic natural products,[3] we became interested in gelsemiol (**1**), a C(6), C(11)-oxidized iridoid first isolated from *Gelsemium sempervirens* (Gentianales).[4] A subsequent publication by Ohizumi and co-workers reported the isolation of **1** from *Verbena littoralis* (Lamiales) and demonstrated its neuritotrophic properties in the PC-12D cell line in the presence of nerve-growth factor (NGF).[5] Attracted by the stereochemically complex, densely functionalized architecture of gelsemiol (**1**) combined with its striking biological activity, we embarked on a research program directed towards this natural product target. Herein, we report the first enantioselective total synthesis of gelsemiol (**1**) and its biological evaluation.

Although there have been several interesting approaches reported for the synthesis of related iridoids (e.g., by Grieco et al.,[6] Mangion and MacMillan,[7] Robertson et al.,[8] Makama,[9] and Zanoni, Vidari and co-workers[10]), we were intrigued by the radical cascade/skeletal rearrangement of Markó et al. on the oxabicyclo[3.3.0]octanone skeleton.[11] Modification of the starting materials and elaboration of the skeleton should result in a straightforward access to gelsemiol (**1**). The synthesis started out with a *trans*-selective hydrozirconation of alkyne **2** by using Schwartz's reagent and PhSeBr to give rise to the stable vinylselenide **3** (Scheme 1).[12–14] Separate preparation of the Schwartz's re-



Scheme 1. Preparation of intermediate acid **7**.

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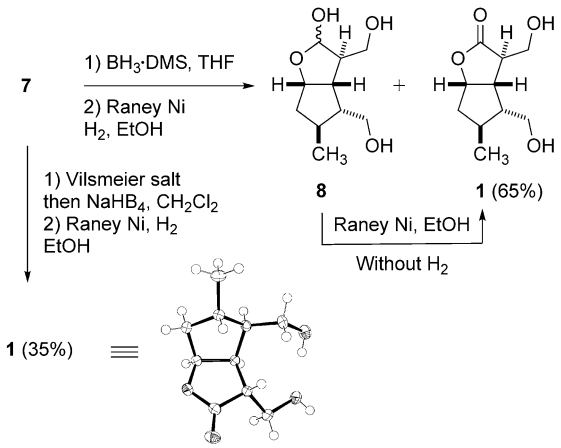
agent resulted in better yields and stereoselectivity compared with a in situ preparation procedure.[15] The preparation of bicyclic intermediate **5** proved to be more challenging than anticipated. We initially attempted to realize the inverse electron-demand Diels–Alder reaction (IEDDA) at ambient pressure and in the presence of a catalytic amount of the in situ formed Cu^{II}–*tert*-BuBox (Box = bis-oxazoline) complex, but mostly undesired byproducts were obtained. Interestingly, conducting the IEEDA reaction under reduced pressure and under neat conditions led to the bicyclic compound **5** in high yield and with a high enantioselectivity of 92:8 e.r. With **5** in hand, we were able to obtain the rearranged bicyclic lactone **6** in good yield via the radical reaction/skeletal rearrangement sequence developed by Markó et al.[11]

Preparation of bicyclic iodoacid **7** was realized from olefin **6** without purification or isolation of the different intermediates in a one-pot procedure (Scheme 2). Addition of the bicyclic lactone **6** and trimethylchlorosilane to a solution of in situ prepared methyl cuprate led the alkylation and opening of the lactone.[16] Saponification of the mono-ester malonate moiety under basic conditions was followed by mild pH adjustment of the mixture with solid CO_2, thereby preventing decarboxylation of the malonic acid under acid conditions. In situ iodolactonization[16,17] gave the desired iodocarboxylate **7** in 56% yield over three steps. The configuration of this bicyclic intermediate was confirmed by X-ray crystal-structure analysis (Figure 1).



Scheme 2. Two different synthetic approaches to access gelsemiol (**1**) from acid **7**.

Finding an efficient way to reduce the acid **7** became the most time-consuming part of the synthesis. After screening multiple reduction reagents, the best yields were obtained by making a detour via the lactol **8**. First, acid **7** was reduced with an excess of BH_3·DMS. After a solvent change from THF to EtOH, Raney nickel was added, and a hydrogen atmosphere applied to remove the benzyl group[18] and the iodo group,[10] which led to the desired natural product **1** and the lactol **8** in a 4:6 mixture. Interestingly, by exposing the product mixture of **1** and **8** to Raney nickel in the absence of H_2, it was observed that lactol **8** could be oxidized to lactone **1**. We were able to confirm this result by separating lactol **8** from lactone **1** and by demonstrating that the lactol **8** itself can be oxidized to gelsemiol (**1**) by using Raney nickel in the absence of H_2 in EtOH (Scheme 2). Raney nickel has been frequently utilized in transfer-hydrogenation reactions,[19] and oxidations of secondary alcohols to ketones by using Raney nickel are known.[20] To the best of our knowledge, this example represents the first Raney nickel mediated oxidation of an activated lactol at room temperature. The scope and limitations of this method are currently under investigation. Iridoid **1** can also be obtained without the formation of the lactol **8** by activation of the acid **7** by using the Vilsmeier salt, followed by $NaBH_4$[21] reduction and Raney nickel reduction by using H_2. The structure of **1** was confirmed by comparison of its spectral data with those reported in the literature.[4,5] Two chemical shift assignments were corrected, because C(4) and C(9) were mistakenly assigned. In addition, X-ray diffraction analysis of the synthetic sample of gelsemiol (**1**) confirmed its assigned structure.

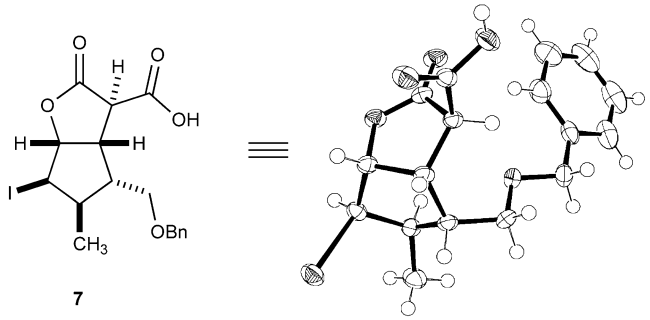


Figure 1. Assignment of the configuration of compound **7** by X-ray crystal-structure analysis.

After finding a synthetic route to the natural product secured, we wanted to profile its biological activity in a neurite outgrowth assay by using rat pheochromocytoma cells.[5,22] In addition, derivatives obtained along the synthesis were subjected to biological evaluation to profile the pharmacophore. Although for gelsemiol (**1**) the neuritotrophic activity described in the literature could be confirmed (Figure 2), none of the compounds obtained did induce the desired phenotype. After reproduction of the reported neuritotrophic activity by using PC-12 cells and NGF as was shown above, we attempted to find a similar morphological response by using primary granule cells from mice pups in combination with brain-derived neurotrophic factor (BDNF).[23] However, no activity could be observed.

In summary, the first total synthesis of gelsemiol (**1**) was accomplished in nine steps and an overall yield of 14%. Key features of the synthesis involve: 1) a stereoselective inverse electron-demand Diels–Alder reaction catalyzed by a chiral Cu Lewis acid; 2) a radical reaction/skeletal rearrangement cascade; and 3) a mild alkylation/iodolactonization procedure. A lactol oxidation by Raney nickel was en-

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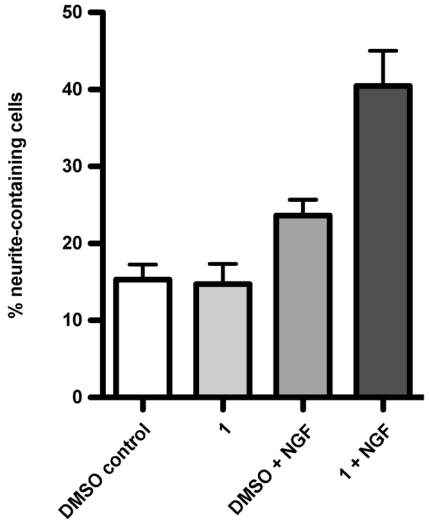

Figure 2. Neuritotrophic activity of **1** in combination with NGF in the PC-12 cell assay.

countered and allowed preparation of gelsemiol (**1**) with a subsequent crystallographic assignment of its structure. Although none of the derivatives of target structure were found to be active, gelsemiol (**1**) itself was confirmed to induce neurite outgrowth in a cellular model.

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Keywords: natural products · PC-12 cells · rearrangement · synthetic methods · total synthesis

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