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Total Synthesis of (−)-Cardiopetaline

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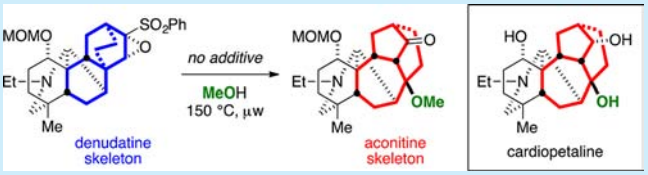
Supporting Information

ABSTRACT: The total synthesis of (−)-cardiopetaline, an aconitine-type natural product, has been accomplished. Our synthesis involved a Wagner−Meerwein rearrangement of a sulfonyloxirane that enabled, in a single step, the construction of the bicyclo[3.2.1] system in the aconitine skeleton and effective introduction of oxygen functional groups at the appropriate positions.



Norditerpenoid alkaloids,[1] isolated predominantly from the genera *Aconitum* and *Delphinium*, are known for their extremely high bioactivities and have been harnessed as poisons or medicines. For example, aconitine (Figure 1, **1**)[2] is one of the most toxic plant poisons, as it strongly activates voltage-dependent sodium ion channels.[3] The blockage of sodium ion channels enables lappaconitine (**2**)[4] to be used as an antiarrhythmic drug.[5] The attractive bioactivities of the norditerpenoid alkaloids have motivated extensive structure−activity relationship (SAR) studies, and these compounds continue to be important scaffolds in the field of pharmaceutical sciences.[6] Although these studies require a variety of synthetic derivatives, all the compounds examined in SAR studies so far depend on a supply from the natural sources and the derivatives synthesized through simple modifications of the natural products.

The hexacyclic skeleton of norditerpenoid alkaloids, known as the aconitine skeleton, contains two bicyclo[3.2.1]octane and one 2-azabicyclo[3.3.1]nonane moieties that are highly oxygenated. The complex structure has attracted the attention of many organic chemists over the past several decades. Although numerous syntheses of the aconitine skeleton have been reported,[7,8] the total syntheses of natural products comprising the entire aconitine skeleton have only been achieved by Wiesner's group for talatisamine (Figure 1, **3a**),[9] chasmanine (**3b**),[10] and 13-desoxydelphonine (**3c**)[10,11] by Gin's group for neofinaconitine (**4**)[12] and by Sarpong's group for weisaconitine D (**5**) and liljestrandinine (**6**).[13]

The biosynthesis of norditerpenoid alkaloids appears to proceed through a Wagner−Meerwein-type rearrangement of a bicyclo[2.2.2]octane moiety into a bicyclo[3.2.1]octane skeleton. Wiesner and co-workers employed the Wagner−Meerwein rearrangement as the key step in their syntheses of talatisamine (**3a**), chasmanine (**3b**) and 13-desoxydelphonine (**3c**) (Scheme 1). Sarpong and co-workers also have recently reported a concise total syntheses of weisaconitine D (**5**) and liljestrandinine (**6**) using a similar strategy. In these syntheses, tosylate, bromide or triflate was used as the substrate for the Wagner−Meerwein rearrangement. An *anti* relationship between the leaving group and the migrating carbon−carbon bond is required for the smooth progress of the rearrangement.

We also intended to synthesize norditerpenoid alkaloids via the Wagner−Meerwein rearrangement and found that a sulfonyloxirane was a good substrate for the rearrangement. Herein, we disclose a novel approach to constructing the aconitine skeleton via the Wagner−Meerwein rearrangement of a sulfonyloxirane, leading to a total synthesis of cardiopetaline (Figure 1, **7**).[14]

Our synthesis commenced with the preparation of a requisite sulfonyloxirane from a synthetic intermediate **9** prepared for our total synthesis of lepenine (Figure 1, **8**)[15] (Scheme 2). Protection of the hydroxy group of **9** with a MOM group, followed by reductive removal of the two methoxy groups at the α-position of the ketone using samarium(II) iodide,[16] furnished **10**. A selective reduction of the carbon−carbon double bond was achieved using palladium(II) hydroxide on carbon.[17] The resulting ketone **11** was converted to the corresponding silyl enolate, which was then treated with phenylsulfenyl chloride to give α-phenylsulfenylketone **12** as the sole diastereomer.[18] Stereoselective reduction of **12** afforded a secondary alcohol, which was protected as its acetate **13**. Oxidation of the sulfide moiety in **13** was achieved with Oxone while keeping the tertiary amine moiety intact. The resulting β-acetoxysulfone was treated with potassium *tert*-butoxide to provide vinyl sulfone **14**. Nucleophilic epoxidation with an anion derived from *tert*-butyl hydroperoxide occurred stereoselectively to afford sulfonyloxirane **15**.[19] A NOESY experiment revealed that the stereochemistry of the oxirane ring of **15** was suitable for a Wagner−Meerwein rearrangement. To clarify the stereoselection of the reaction, the conformation of a simplified model of **14** was obtained by using DFT calculations (Figure 2).[20] These calculations implied that the bicyclo[2.2.2]octane moiety was distorted by the fused ring system, and the distortion rendered the α face at C15 more accessible to reagents than the β face.[21]

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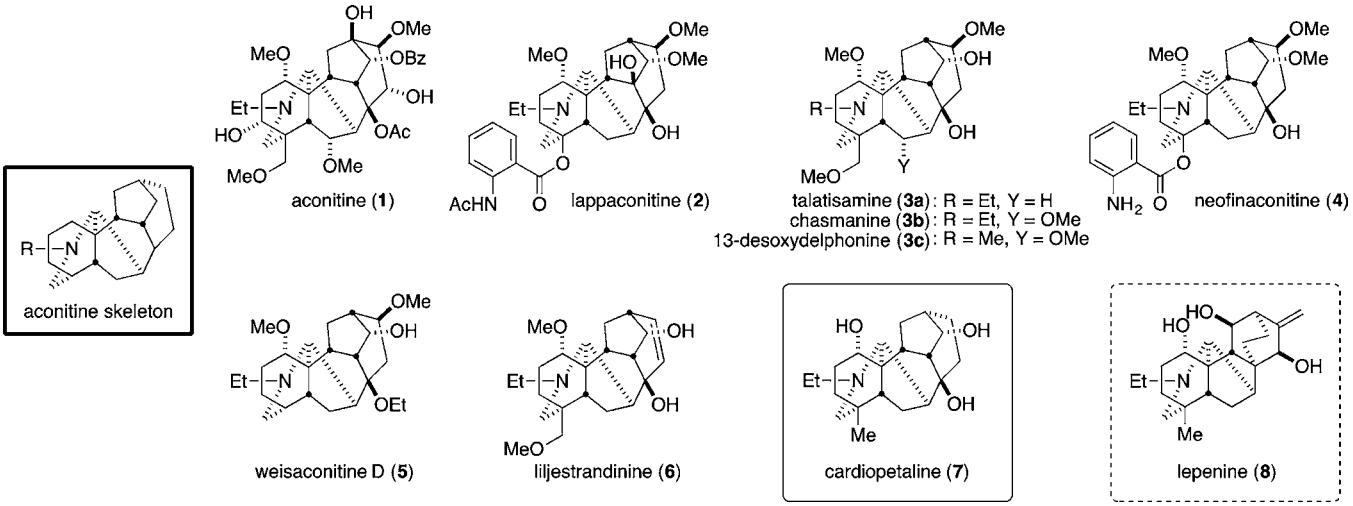
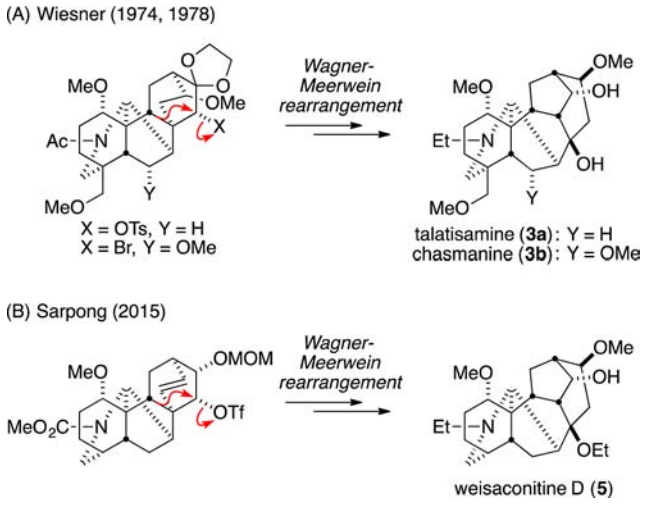


Figure 1. Selected structures of the norditerpenoid alkaloids **1**–**7** and the structure of lepenine (**8**).

Scheme 1. Selected Total Syntheses of Norditerpenoid Alkaloids



The sulfonyloxirane **15** was used to investigate the construction of the aconitine skeleton via the Wagner–Meerwein rearrangement. We first tried to activate the oxirane ring with a variety of acids.[22] Even the treatment of **15** with sulfuric acid in THF at 60 °C, however, did not cause the rearrangement, leaving the oxirane intact. The abnormal stability of the oxirane ring appeared to stem from the electron-withdrawing properties of the sulfonyl group. Heating **15** in toluene at 150 °C also did not bring about the rearrangement, and the reaction at 200 °C gave a complex mixture. We next attempted the reactions in neutral protic solvents, which have been used to cleave oxirane rings.[23] Heating **15** in water or *tert*-butyl alcohol, however, resulted only in decomposition. Much to our delight, when **15** was heated in methanol at 150 °C under microwave irradiation, the desired Wagner–Meerwein rearrangement proceeded smoothly (Scheme 3). The cation generated by the rearrangement was efficiently captured by methanol, and as expected, the elimination of benzenesulfinic acid liberated the ketone moiety. The product **17** proved to be rather unstable and was immediately reduced by $NaBH(OAc)_3$ to give the alcohol **18**. The MOM group and the methyl ether in **18** could be simultaneously cleaved by heating in aqueous sulfuric acid,[12]

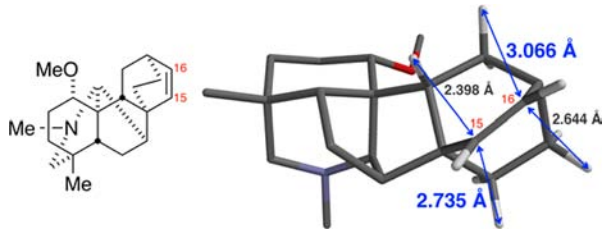
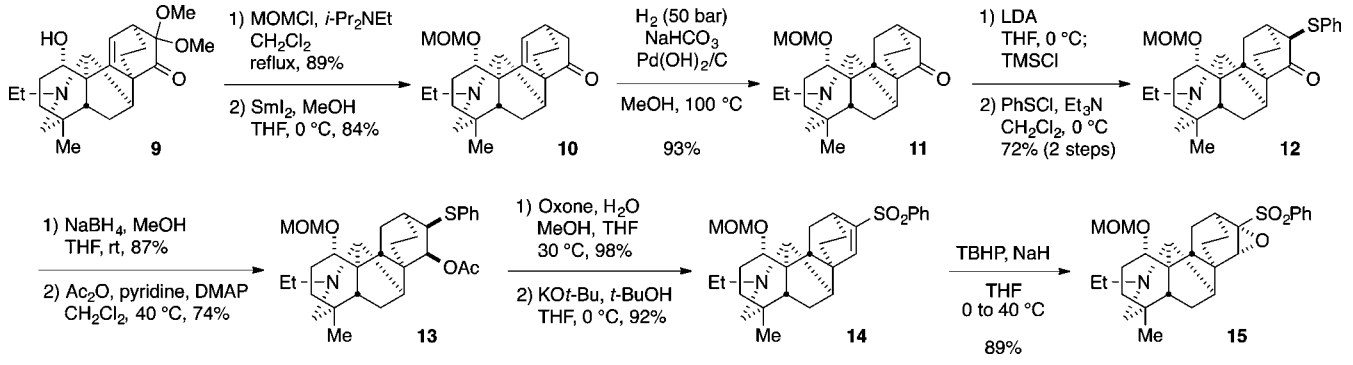


Figure 2. Conformation of a simplified model of **14** and distances between C15 (or C16) and the surrounding hydrogen atoms.

Scheme 2. Preparation of the Sulfonyloxirane



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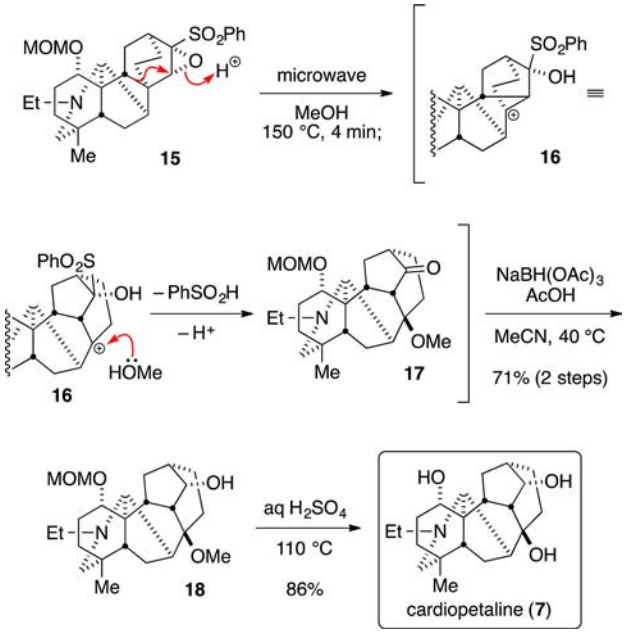
Scheme 3. Total Synthesis of Cardiopetaline via Wagner–Meerwein Rearrangement of the Sulfonyloxirane



completing the first total synthesis of (−)-cardiopetaline (**7**). The synthetic cardiopetaline was identical in all respects to the corresponding natural product.

In summary, we have achieved a concise synthesis of (−)-cardiopetaline by means of a Wagner–Meerwein rearrangement of a sulfonyloxirane. The synthetic strategy, via rearrangement of the sulfonyloxirane, offers the following advantages: (1) the oxygen functionalities could be easily introduced through the stereoselective nucleophilic epoxidation, (2) the sulfonyl group stabilized the oxirane ring under acidic conditions and may facilitate the regioselective cleavage of the oxirane ring,[24] and (3) the rearrangement could be carried out in methanol, which efficiently captured the cationic intermediate, leading to the introduction of the oxygen atom of the tertiary alcohol in the natural product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00789.

Experimental procedures, spectroscopic data, results of DFT calculations, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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