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Allyl vinyl ethers via Wittig olefination: a short and efficient synthesis of (±)-mesembrine

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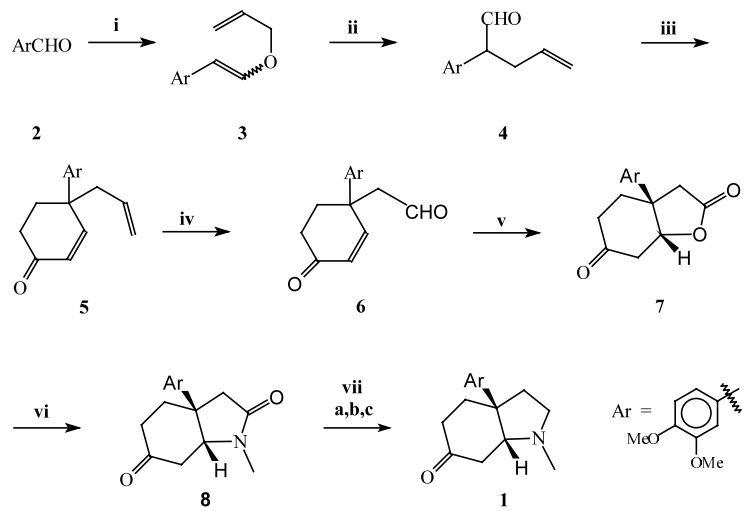
Abstract—A Wittig olefination-Claisen rearrangement approach has been successfully applied to a short and efficient synthesis of (±)-mesembrine.

Recently, we reported an efficient method for the preparation of allyl vinyl ethers.[1] Such allyl vinyl ethers once formed easily undergo Claisen rearrangement to give 4-pentenals. By taking advantage of this fact we have prepared[2] many 4-pentenals with built-in contiguous quaternary centers. Creation of such quaternary centers is a serious challenge in organic synthesis.[3–5] These 4-pentenals have served as key intermediates in the synthesis of natural products[6,7] with sterically crowded cyclopentanoid rings. Syntheses of several other natural products with sterically crowded ring systems carbocyclic or heterocyclic could be accessed through this methodology. The alkaloid mesembrine is an octahydroindole based natural product comprising 1% of the dry weight of plant material from certain plants of the *Sceletium* genus, namely *S. namaquense*, *S. strictum* and *S. tortuosum*.[8] Structure elucidation,[9,10] including the determination of the absolute configuration[11] of mesembrine spanned over 10 years and finally structure **1** was established for the compound. Pure mesembrine, though devoid of any interesting biological properties, has attracted enormous attention from synthetic chemists for the past three decades. As a direct result of this, in all, 28 syntheses[12–39] of



Scheme 1. *Reagents and conditions*: (i) CH_2:$CHCH_2OCH_2P^+Ph_3Cl^-$, $tBuO^-K^+$, THF, 0°C, 1 h (93%); (ii) xylene reflux, 7 h (98%); (iii) MVK, cat. ethanolic KOH, ether, 0°C–rt, 24 h (85%); (iv) cat. OsO_4 and 1.5 equiv. $NaIO_4$, 5 h (60%); (v) Jones' reagent CrO_3, H_2SO_4, acetone, 4 h (60%); (vi) $MeNH_2$ excess, MeOH, 80°C, 12 h in sealed tube (quantitative yield); (vii) a. 2-ethyl-2-methyl-1,3-dioxolane, *p*-TSA, reflux, 2 h, b. LAH excess, THF:Et_2O (2:1) reflux, 23 h, c. 10% HCl, rt, 2 days (72%).

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this compound are known. We herein report a short and efficient synthesis of (±)-mesembrine **1** (Scheme 1).

The reaction of veratraldehyde **2** with allyloxymethylenetriphenylphosphonium chloride[1] using potassium *t*-butoxide as a base furnished the allyl vinyl ether **3** as an inseparable mixture of *E*- and *Z*-isomers (^{1}H NMR) in good yield. The ill-resolved nature of the proton NMR spectrum of this mixture in the olefinic range (δ 5.6 to δ 6.7) prevented us from estimating the ratio of the geometric isomers. Nevertheless, this mixture of the allyl vinyl ethers **3** smoothly underwent Claisen rearrangement in refluxing xylene to furnish the 2-aryl-4-pentenal **4** in quantitative yield. The 4-pentenal **4** on treatment with methyl vinyl ketone and a catalytic amount of ethanolic KOH underwent tandem Michael addition–intramolecular aldol condensation[39] to give the allyl cyclohexenone **5** in 85% yield. This cyclohexenone has previously been prepared[20] in six steps with an overall yield of 10%. In the present case it was obtained in an overall yield of 80% in just three steps. The allyl cyclohexenone was treated with a catalytic amount of osmium tetroxide and 1.5 equivalents of sodium metaperiodate to give the unstable aldehyde **6** in 60% yield. As treatment of this aldehyde with basic Ag_2O did not lead to any meaningful isolable product, it was subjected to oxidation with Jones' reagent. To our pleasant surprise this resulted in the formation of the lactone **7** rather than the carboxylic acid. Apparently, the carboxylic acid formed on oxidation underwent in situ 1,4-addition to the enone to give the lactone **7**. Heating the lactone with excess methylamine in methanol at 80°C in a sealed tube for 12 h gave the lactam **8**. The conversion of this lactam **8** to (±)-mesembrine was achieved by the method reported by Oh-ishi.[17,18] Thus, the lactam was subjected to ketal exchange with 2-ethyl-2-methyl-1,3-dioxolane. The excess dioxolane was removed under vacuum and the crude lactam was reduced with excess lithium aluminium hydride in refluxing THF:Et_2O (2:1) for 23 h. Acid hydrolysis of the crude ketal amine so obtained gave (±)-mesembrine **1** in an overall yield of 72% from the lactam **8**. The protocol described here is a short and efficient route for the synthesis of (±)-mesembrine **1**.

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