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Total Synthesis of (±)-Physovenine

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The Wittig olefination–Claisen rearrangement protocol was applied to the total synthesis of (±)-physovenine.

Introduction

The Wittig olefination–Claisen rearrangement protocol[1] is now well established in our laboratory for the preparation of 4-pentenals. These 4-pentenals have served as versatile intermediates for the synthesis of different natural products.[2] This protocol is quite useful for the construction of quaternary centers – an operation crucially required in many natural product syntheses.[3] Many indole alkaloids have a quaternary center at the C-3 position, and their syntheses have centered around the construction of such a quaternary center. This gave us an opportunity to apply the above protocol to the synthesis of physovenine, a representative of a group of indole alkaloids isolated from calabar beans. Physovenine, with a furoindoline ring system, is a minor component of the calabar bean alkaloids.[4] It has interesting and potent biological properties, such as anticholinergic and miotic activities.[5] Physovenine and its derivatives have been found to be clinically useful for relieving symptoms of Alzheimer's disease.[6] Furthermore, the pharmacological activity of physovenine is approximately equal to that of physostigmine. Physovenine was first isolated in 1911[7] and its structure was established in 1964.[8] As a result of its biological activities and unique structure, and the difficulty in generating the quaternary center, several methodologies have been applied to the synthesis of physovenine. These include Sharpless epoxidation,[9a] intramolecular arylation,[9b] Grignard reaction,[9c] [3,3]-sigmatropic rearrangement,[9d,9m,9q] catalytic asymmetric Heck reaction,[9g] Diels–Alder reaction,[9h] radical cyclization,[9f,9k] intramolecular Michael addition,[9l] [2+2] photocycloaddition,[9p] and catalytic asymmetric alkylations.[9i,9n,9o] In all, 21 total syntheses,[9] 12 diastereoselective and 9 enantioselective, of physovenine are documented in the literature. In spite of this voluminous work, even today the total synthesis of physovenine is an attractive goal for demonstrating the efficacy of newer synthetic protocols. We herein describe the successful application of the above protocol for the synthesis of the physovenine.

Results and Discussion

The Wittig olefination of *o*-nitroacetophenone (**2**) with allyloxymethylenetriphenylphosphorane under standard conditions[1] furnished the corresponding allyl vinyl ether **3**, which was found to be an inseparable mixture of *E* and *Z* isomers. However, the NMR signals of the *E* and *Z* isomers in the olefinic region were well separated,[10] which allowed us to estimate the ratio of these isomers as 5:1. The mixture of allyl vinyl ethers was heated in refluxing xylene to effect the Claisen rearrangement to get 4-pentenal **4** in 85% yield. After protecting the aldehyde group in **4** as its acetal, the double bond was ozonolyzed to get new aldehyde **5** in 88% yield. This aldehyde, upon reduction with sodium borohydride, in aqueous THF, afforded alcohol **6** in 92% yield. Further, reduction of the nitro group with Raney nickel in methanol gave the corresponding amino alcohol **7** in 80% yield. The hydrolysis of the acetal group in **7** with *p*-TSA in refluxing aqueous THF directly furnished the tricyclic skeleton of physovenine **8** in 89% yield. A singlet at δ = 5.2 ppm for C^{8a}-*H* confirmed the formation of the tetrahydrofuro[2,3-*b*]indole ring system of physovenine in one step. *N*-Methylation[11] of **8** by using aqueous formalin and 10% Pd/C furnished **9** in 87% yield. The relative stereochemistry between the 8a proton and the 3a methyl group was determined by NOE experiments (Figure 1). An NOE enhancement to the extent of 3.22% in the signal of the C-8a proton at δ = 5.02 ppm was observed upon irradiation of the C-3a methyl protons at δ = 1.44 ppm. Similarly, an NOE enhancement to the extent of 3.98% in the signal of the C-3a methyl protons at δ = 1.44 ppm was observed

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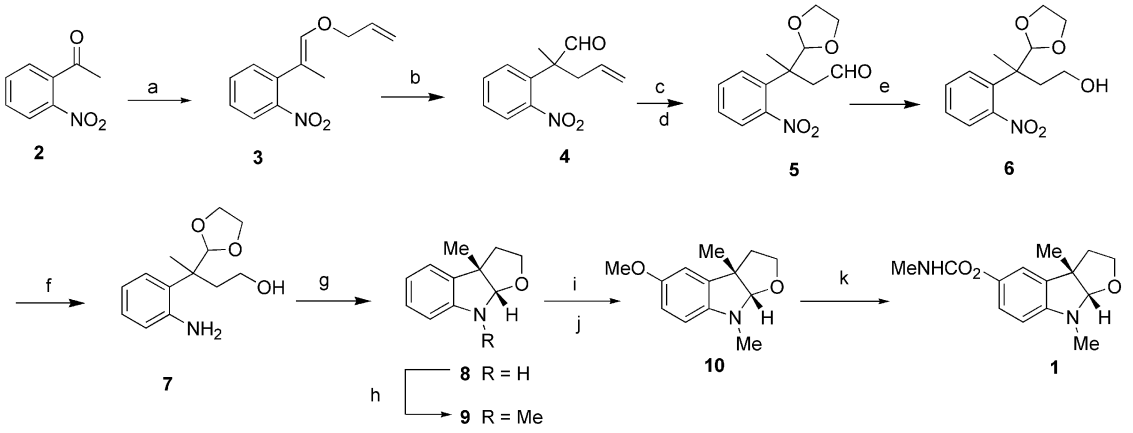

Scheme 1. Reagents and conditions: (a) $CH_2{=}CHCH_2OCH_2P^+Ph_3Cl^-$, tBuO$^-Na^+$, THF, 0 °C (65%); (b) xylene, reflux, (85%); (c) p-TSA, ethylene glycol, toluene, reflux, (89%); (d) O_3, dimethyl sulfide, DCM, (88%); (e) $NaBH_4$, aq. THF, (92%); (f) Raney nickel, [H_2], MeOH, (80%); (g) p-TSA, aq. THF, reflux, (89%); (h) aq. HCHO, 10% Pd/C, EtOAc, [H_2], room temp., (87%); (i) NBS, DMF, 0 °C; (j) CuI, NaOMe, reflux, (70%); (k) BBr_3, DCM, $MeNH_2$, $CO(COCl_3)_2$, toluene, reflux, NaH, MeNCO, (60%).

upon irradiation of the C-8a proton at δ = 5.02 ppm. This conclusively established that the two five-membered rings in compound **9** are *cis* fused. Upon treatment with *N*-bromosuccinimide, compound **9** gave the 5-bromo derivative, which upon heating with sodium methoxide in the presence of cuprous iodide[12] gave compound **10** in 70% yield. Finally, compound **10** was converted into physovenine (**1**) by effecting demethylation of **10** with boron tribromide and treatment of the resulting phenol with methyl isocyanate.[13] The spectroscopic data of the compound so obtained were identical with the reported data of physovenine (Scheme 1).

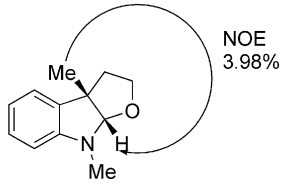

Figure 1. NOE of compound **9**.

Conclusions

In summary, we described a new and efficient synthesis of physovenine. Furthermore, it is possible to extend the present protocol developed for the synthesis of physovenine to the synthesis of other natural products with quaternary carbon centers at the benzylic position. On these lines, the total synthesis of other natural products like phenserine is being actively pursued.

Supporting Information (see footnote on the first page of this article): Complete experimental details, including characterization of the compounds.

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[10] The olefinic proton appearing as a singlet at δ = 6.10 ppm is due to the *E* isomer, whereas the singlet at δ = 6.04 ppm is due to the *Z* isomer. Similarly, the methyl signal at δ = 1.92 ppm is due to the *E* isomer and the signal at δ = 1.95 ppm is due to the *Z* isomer. The ratio of *E*-methyl to *Z*-methyl is 5:1, and the same ratio is observed for the olefinic *E*-H to *Z*-H. Further, the terminal and internal protons of the monosubstituted olefin and the allylic protons show two sets of the signals in a 5:1 ratio. This confirmed that the compound in hand is the mixture of the 5:1 ratio of *E* and *Z* isomers obtained from the Wittig reaction.

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