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A novel and efficient total synthesis of (±)-physostigmine

Mukund G. Kulkarni *, Attrimuni P. Dhondge, Ajit S. Borhade, Dnyaneshwar D. Gaikwad, Sanjay W. Chavhan, Yunnus B. Shaikh, Vijay B. Ningdale, Mayur P. Desai, Deekshaputra R. Birhade, Mahadev P. Shinde

Department of Chemistry, University of Pune, Ganeshkhind, Pune 411 007, Maharashtra, India

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ABSTRACT

Application of the Wittig olefination–Claisen rearrangement protocol for the total synthesis of (±)-physostigmine.

The *Physostigma* genus (Fabaceae) produces many indole alkaloids, of which Physostigmine **1** is one of the main constituents. It was first isolated in 1864 from the seeds of the African Calabar bean *Physostigma venenosum* and was structurally characterized in 1925.[1] The hexahydropyrrolo[2,3-*b*]indoline ring system, present in **1** is found in a large number of indole alkaloids with a wide variety of structural formats.[2–5] These alkaloids have interesting potent biological properties, such as anticholinergic and miotic activities.[6] These compounds and their derivatives have been found to be clinically useful for relieving symptoms of Alzheimer's disease.[7] Like many biologically important indole alkaloids, physostigmine **1** has a quaternary carbon center at the C-3a position. The effective construction of such a quaternary center has been one of the pivotal issues in the total synthesis of these alkaloids. As a result of their biological activities, unique structure and the difficulty of generating a quaternary center, several syntheses of physostigmine have been reported. Similarly, various racemic and/or chiral methods have been developed[8–10] for the construction of the core ring system of these alkaloids, namely, hexahydropyrrolo[2,3-*b*]indoline. These include a catalytic asymmetric Heck reaction, catalytic asymmetric alkylation and allylation, chiral auxiliary-induced asymmetric alkylation and rearrangement, asymmetric addition–cyclization, desulfurization–cyclization, [3,3] sigmatropic rearrangements, hetero-Pauson–Khand reaction, [4+1] cycloaddition reaction, intramolecular cyanoamidation, Diels–Alder reaction, Grignard reaction, intramolecular 1,3-dipolar addition, nucleophilic substitution, lipase-catalyzed desymmetrization protocol, domino reaction involving a sequence of olefination–isomerization, Claisen rearrangement and intramolecular Michael addition. After the pioneering synthesis of physostigmine by Julian in 1935,[9a] most of the above-mentioned methods for the construction of hexahydropyrrolo[2,3-*b*]indoline have been applied to the synthesis of physostigmine. An impressive total of 71 syntheses of physostigmine, 33 racemic[9]and 38 chiral,[10] have been reported in the literature. In spite of this voluminous work, even today the total synthesis of physostigmine is an attractive goal for demonstrating the efficacy of newer synthetic methodologies.

We have developed a methodology for the construction of a quaternary carbon center by using the Wittig olefination–Claisen rearrangement protocol.[11] This methodology provides a powerful tool for the synthesis of natural products especially those with a quaternary carbon center(s). Herein we describe the successful application of this protocol for the synthesis of the acetylcholinesterase inhibitor physostigmine **1**.

The Wittig olefination of *o*-nitroacetophenone **2** with allyloxymethylenetriphenylphosphorane under standard conditions[11] furnished the corresponding allyl vinyl ether **3**, which was found to be an inseparable mixture of *E*- and *Z*-isomer. However, the NMR signals of *E*- and *Z*-isomer in the olefinic region were well separated and it allowed us to estimate the ratio of these isomers[12] (5:1). The mixture of allyl vinyl ethers was heated in refluxing xylene to effect the Claisen rearrangement and 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 a new aldehyde **5**. This aldehyde on reduction with sodium borohydride in aqueous THF, gave alcohol **6** in a near quantitative yield. The conversion of alcohol **6** into amine **7** was achieved in two steps subjecting the alcohol to Mitsunobu conditions (DIAD, triphenylphosphine, and phthalimide) at room temperature and subsequently refluxing the intermediate phthalimide derivative in methylamine to get the corresponding amine **7** in 68% yield. Further, reduction of the nitro group with Raney nickel in methanol afforded diamine **8**. The hydrolysis of acetal in **8** with *p*-TSA in refluxing aqueous THF directly furnished the tricyclic compound **9** in 65% yield. A singlet at δ 5.0 for C_{8a}–*H* confirmed the formation of a hexahydropyrrolo[2,3-*b*]indole ring system of physostigmine in one step. Bis-*N*-methylation[13] of **9**, using aqueous formalin and 10% Pd–C furnished desoxyeseroline **10**. Following the known protocol[14], the compound **10** was converted to physostigmine. Compound **10** on treatment with N bromosuccinimide gave the 5-bromo derivative, which on heating with sodium methoxide in the presence of

* Corresponding author. Tel./fax: +91 020 2569 1728.
E-mail address: mgkulkarni@chem.unipune.ernet.in (M.G. Kulkarni).

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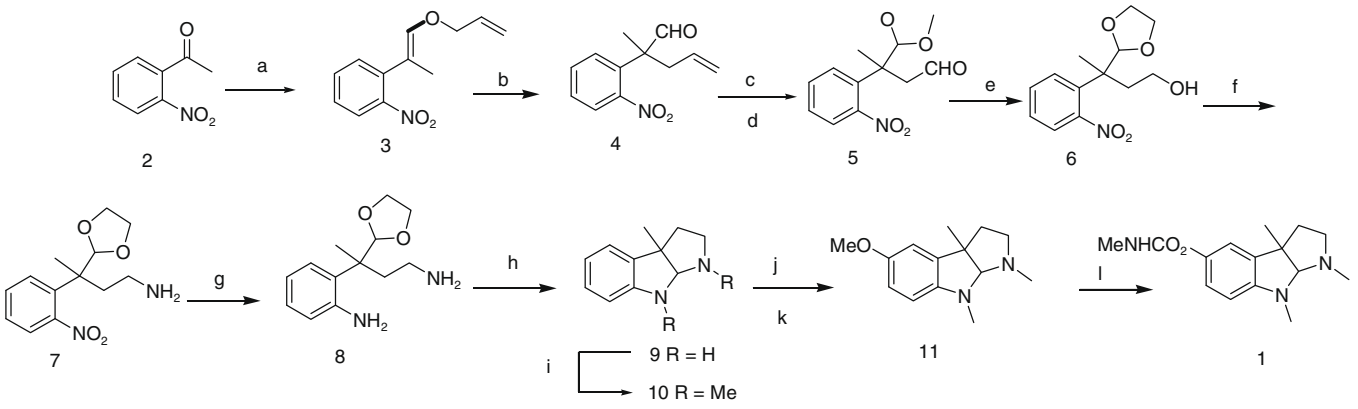

Reagents and condition: (a) CH_2=$CHCH_2OCH_2P^+Ph_3Cl^-$, t-BuO^-Na^+, THF, 0^oC; (b) Xylene, reflux; (c) *p*-TSA, ethylene glycol, Toluene, reflux; (d) O_3, dimethyl sulfide, 0^0C, DCM; (e) $NaBH_4$, aq. THF; (f) DIAD, PPh_3, phthalimide, methylamine, reflux; (g) Raney nickel, [H_2], MeOH; (h) *p*-TSA, aq. THF, reflux; (i) aq. HCHO, 10% Pd-C, EtOAc, [H_2]; (j) NBS, DMF, 0^0C; (k) CuI, NaOMe, reflux; (l) BBr_3, CH_2Cl_2, 0^0C- rt. NaH, MeNCO.

cuprous iodide gave esermethole **11.** Finally esermethole was converted to physostigmine **1** by effecting demethylation of **11** with boron tribromide and treatment of the resulting phenol with methylisocyanate.[10a–g] The spectral data of the compound so obtained were identical with the reported data for physostigmine. In summary, we have described a new and efficient synthesis of physostigmine. Further, it is possible to extend the present protocol developed for the synthesis of physostigmine to the synthesis of other natural products with quaternary carbon at the benzylic position. On these lines, the total syntheses of other natural products such as Physovenine and phenserine are being actively pursued.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.012.

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12. The olefinic proton appearing as a singlet at δ 6.10 ppm is due the *E*-isomer, while the singlet at 6.04 ppm is due the *Z*-isomer. Similarly, the methyl signal at 1.92 ppm is due the *E*-isomer and signal at 1.95 ppm is due the *Z*-isomer. The ratio of *E*-methyl to *Z*-methyl is 5:1, 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 ratio of 5:1. This confirmed that the compound in hand is the mixture of the 5:1 ratio of *E*-and *Z*-isomer obtained from the Wittig reaction.

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