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SYNTHESIS OF (±)-ESERMETHOLE VIA AN INTRAMOLECULAR CARBAMOYLKETENE-ALKENE [2+2] CYCLOADDITION

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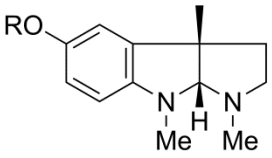
Abstract – A synthesis of (±)-esermethole (**2**), a synthetic precursor of physostigmine (**1**), has been accomplished by using an intramolecular carbamoylketene-alkene [2+2] cycloaddition followed by nitrone-mediated regioselective ring expansion for the construction of the basic carbon framework of **2** as the key steps.

Physostigmine (**1**)[1] is a representative of the Calabar bean alkaloid isolated from the African tropical vine *Physostigma venenosum*. Physostigmine is not only an important anticholinesterase compound with several clinical uses, but also a promising therapeutic agent for Alzheimer's disease.[2] Because physostigmine has a simple but intriguing molecular structure and biological profile, a number of synthetic efforts of the alkaloid and its synthetic precursor esermethole (**2**), which can readily be converted to **1** *via* a two-step sequence, have been reported in racemic[3] and optically active forms[4] so far (Figure 1).

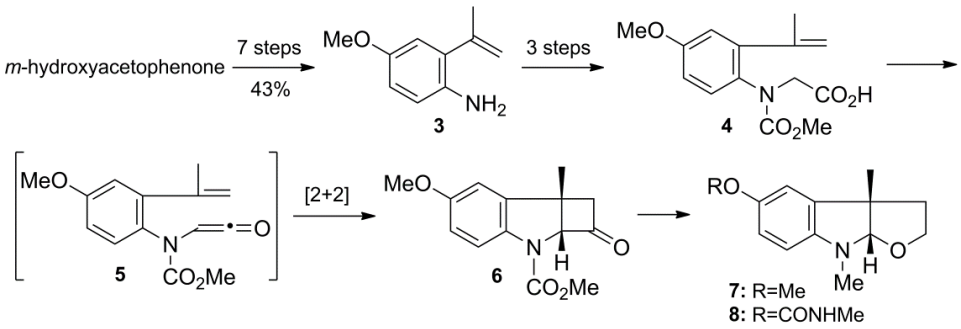


R=CONHMe: physostigmine (**1**)
R=Me: esermethole (**2**)

Figure 1. Physostigmine and esermethole

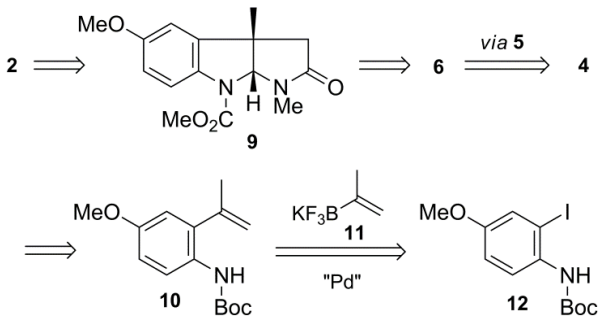
During the course of our synthetic studies directed towards the Calabar bean alkaloids,[5] we previously reported a synthesis of the tetrahydro-2*H*-furo[2,3-*b*]indole **7**, which has been converted to physovenine

(**8**) *via* a two-step sequence, employing an intramolecular carbamoylketene-alkene [2+2] cycloaddition reaction (**4→5→6**) followed by a Baeyer-Villiger oxidation as the key steps.[6] The originally developed [2+2] cycloaddition seemed to be a useful methodology not only for the synthesis of other Calabar bean alkaloids but also for related alkaloids,[7] however, its inefficiency for the preparation of 2-alkenylaniline derivatives, *e.g.* 2-isopropenyl-4-methoxyaniline **3** (in 43% overall yield for seven steps from *m*-hydroxyacetophenone)[6] remains a drawback. (Scheme 1) In this report, we describe a synthesis of (±)-esermethole (**2**) employing an intramolecular carbamoylketene-alkene [2+2] cycloaddition and a nitrone-mediated regioselective ring expansion of the cyclobutanone **6** to γ-lactam fused onto indoline as the key steps.



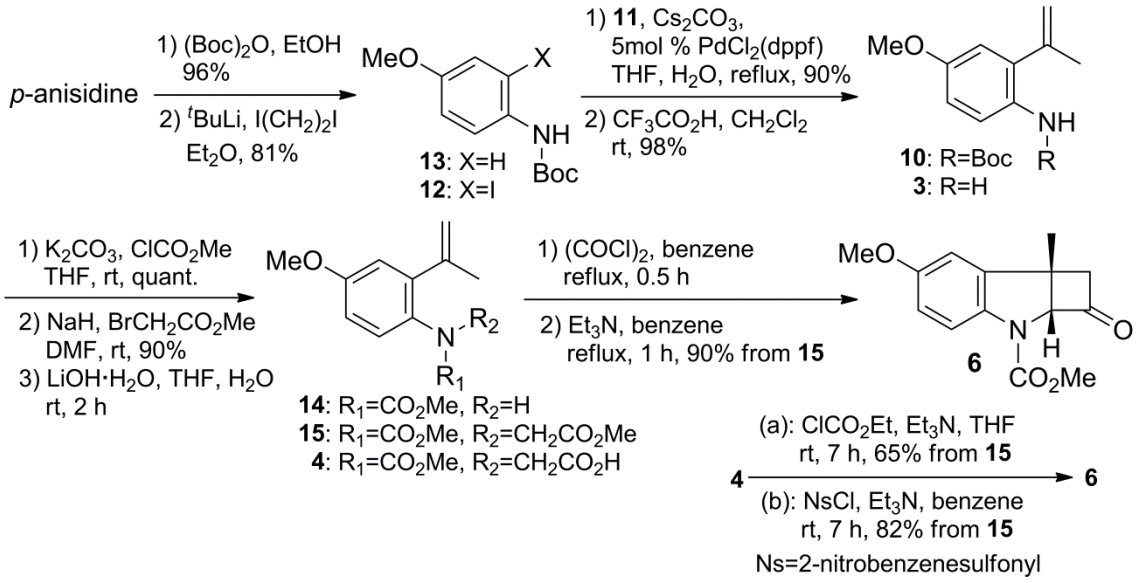
Scheme 1. Formal synthesis of physovenine *via* the intramolecular carbamoylketene-alkene [2+2] cycloaddition

Our retrosynthetic analysis is shown in Scheme 2. We envisaged that esermethole **2** might be derived from the lactam carbamate **9**, which would be assembled from the [2+2] cycloadduct **6** through a regioselective ring expansion. It was thought that the procedure to make the synthesis of **10** more efficient would be the Suzuki-Molander coupling of *t*-butyl 2-iodo-4-methoxyphenylcarbamate (**12**)[8] with potassium isopropenyltrifluoroborate (**11**)[9] (Scheme 2).



Scheme 2. Retrosynthetic analysis

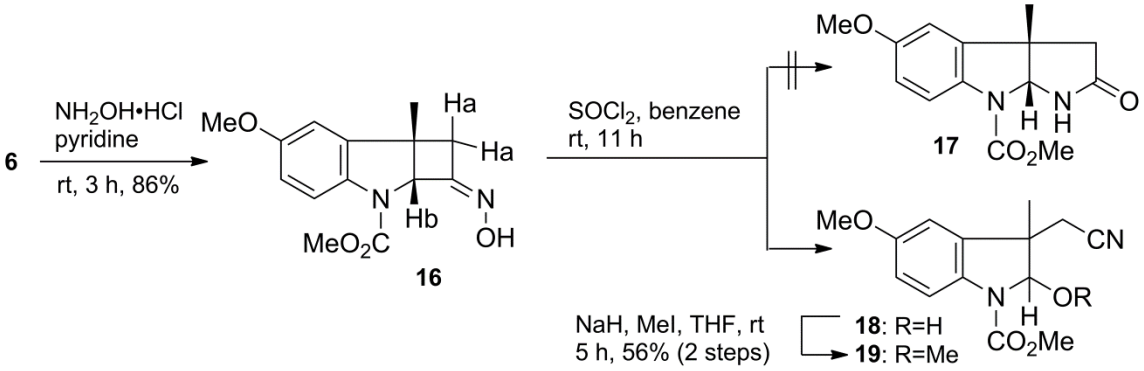
Ortho-lithiation of the *N*-Boc-*p*-anisidine **13** gave the iodide **12**, which was treated with potassium isopropenyltrifluoroborate **11** and 5 mol% of $PdCl_2$(dppf) in the presence of cesium carbonate in refluxing aqueous tetrahydrofuran (THF) to give the coupled product **10** in 90% yield. Removal of the Boc-group with trifluoroacetic acid provided **3** in four steps in 69% overall yield from *p*-anisidine and thus our objective of improvement of efficiency was achieved. Carbomethoxylation, alkylation with methyl bromoacetate followed by alkaline hydrolysis provided the carboxylic acid **4**, a precursor of the ketene. Treatment of **4** with oxalyl chloride in refluxing benzene produced the acid chloride which, after removal of excess reagent and the solvent by evaporation, was immediately treated with triethylamine in refluxing benzene in one pot[6,7] to give the cyclobutanone **6** in 90% overall yield from **15**. To explore a mild and efficient method for the [2+2] cycloaddition, we examined a procedure *via* a mixed anhydride.[10] Treatment of the carboxylic acid **4** with ethyl chloroformate and triethylamine at room temperature for seven hours produced **6** in 65% yield in a single operation (method a). The best result was obtained when **4** was treated with 2-nitrobenzenesulfonyl (nosyl) chloride[11] and triethylamine in benzene at room temperature providing **6** in 82% yield (method b) (Scheme 3).



Scheme 3. Synthesis of ketene precursor **4** and the [2+2] cycloaddition

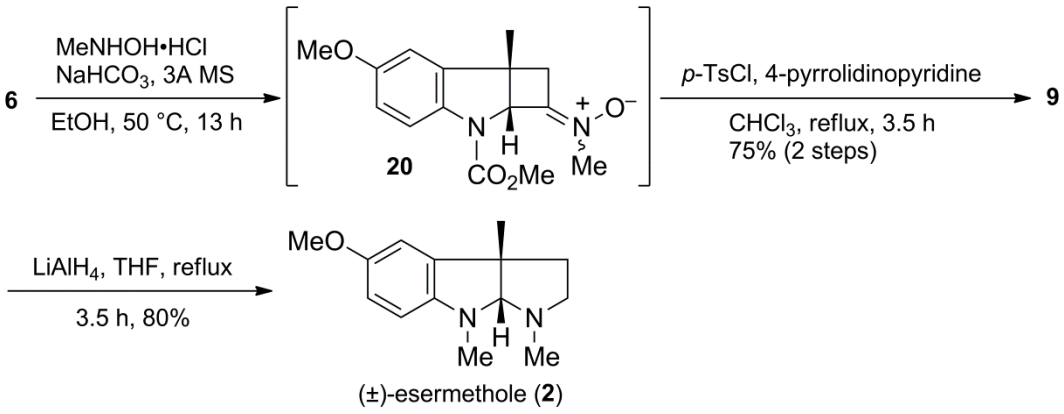
With the requisite tricyclic compound **6** in hand, we advanced to the key ring expansion. The cyclobutanone was converted to the oxime **16**,[12] the configuration of which, determined by ^{1}H NMR using a shift reagent Eu(dpm)$_3$,[13] proved to be *Z*.[14] On exposure of **6** to the conditions of Beckmann rearrangement ($SOCl_2$, benzene, rt, 11 h), the desired tricyclic lactam **17** was not obtained at all but the

ring-opened hemiaminal **18**, which was characterized as the methyl acetal **19**,[15] was produced in 56% yield for the two steps (Scheme 4).



Scheme 4. Attempted Beckmann rearrangement

Unsuccessful attempts at Beckmann rearrangement led us to find a regioselective ring expansion from **6** to the lactam. We found that a rearrangement through a nitrone[7,16] can be applied to the conversion; thus, treatment of **6** with *N*-methylhydroxylamine hydrochloride, $NaHCO_3$, and 3A molecular sieves in ethanol at 50 °C provided the nitrone **20**, which, without purification, was immediately reacted with *p*-toluenesulfonyl chloride (*p*-TsCl) and 4-pyrrolidinopyridine in refluxing chloroform to give the requisite γ-lactam **9** in 75% yield for the two steps. Thus, we were able to overcome a key hurdle and demonstrated that the procedure could be successfully applied to install the hexahydropyrrolo[2,3-*b*]indole backbone. Finally, reaction of **9** with lithium aluminum hydride (LAH) in refluxing THF produced esermethole (**2**) in 80% yield. The spectroscopic properties of synthetic **2** were completely identical with those reported in the literature[4a] (Scheme 5).



Scheme 5. Ring expansion *via* nitrone rearrangement and synthesis of esermethole

In summary, a synthesis of (±)-esermethole (**2**) has been accomplished in 12 steps in 33% overall yield from *p*-anisidine as an application of the intramolecular carbamoylketene-alkene [2+2] cycloaddition which has been developed in our laboratories. The unique features of this work include the use of originally developed [2+2] cycloaddition and a regioselective nitrone-mediated ring expansion for the construction of the basic carbon framework of the target molecule. We were also able to demonstrate that the mixed anhydride method using the nosyl group would be a mild (at room temperature) and efficient (by a single operation in one pot) alternative method for the generation of carbamoylketenes. The synthetic route developed here is general and efficient and can be applied to the synthesis of both Calabar bean alkaloids and related alkaloids.

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A JSPS Fellows Grant-in-Aid (22-9957) to T.O. is gratefully acknowledged. This work was supported financially by a Grant-in-Aid from the Program for Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

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12. IR (neat) 3336, 1708 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (s, 3H), 3.02 (d, 1H, J = 17.2 Hz), 3.13 (dd, 1H, J = 17.2 and 2.8 Hz), 3.81 (s, 3H), 3.85 (s, 3H), 5.11 (s, 1H), 6.75-6.79 (m, 2H), 7.81 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (CH_3), 44.0 (C), 44.1 (CH_2), 52.6 (CH_3), 55.6 (CH_3), 69.9 (CH), 109.3 (CH), 113.0 (CH), 115.8 (CH), 136.2 (C), 137.7 (C), 152.8 (C), 154.4 (C), 156.3 (C); HRMS (ESI) calcd for $C_{14}H_{16}N_2O_4Na$ [M+Na]$^+$: 299.1008, found 299.1005.
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15. IR (neat) 2928, 2360, 1714 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3H), 2.70 (d, 1H, J = 22.0 Hz), 2.85 (d, 1H, J = 22.0 Hz), 3.56 (s, 3H), 3.78 (s, 3H), 4.01 (s, 3H), 5.30 (s, 1H), 6.70 (s, 1H), 6.78 (d, 1H, J = 8.1 Hz), 7.61 (br, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, 60 ºC) δ 21.1 (CH_3), 25.2 (CH_2), 46.1 (C), 52.5 (CH_3), 55.3 (CH_3), 57.5 (CH_3), 97.0 (CH), 108.8 (CH), 112.8 (CH), 115.8 (CH), 118.5 (C), 132.4 (C), 137.1 (C), 153.3 (C), 155.9 (C); HRMS (ESI) calcd for $C_{15}H_{19}N_2O_4$ [M+H]$^+$: 291.1345, found 291.1348.
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