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NOVEL AND FACILE ROUTE TO (±)-PHYSOVENINE VIA INTRAMOLECULAR [2+2]CYCLOADDITION REACTION

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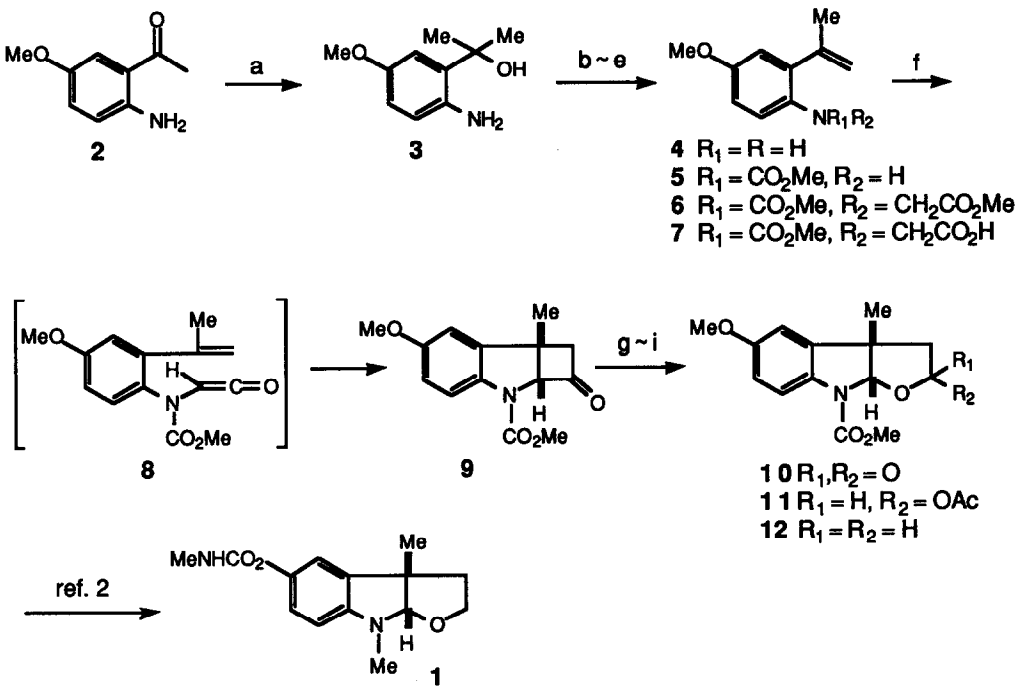
Abstract : A formal total synthesis of (±)-physovenine **1** from 2-amino-5-methoxyacetophenone **2** via an intramolecular [2+2]cycloaddition reaction is described.

The intramolecular [2+2]cycloaddition reactions[1] of a variety of ketenes with alkenes have been widely used for forming complex arrays of carbo- and heterocyclic rings including fused cyclobutanones. In this paper, we report *the first example of the reaction of carbamoylketene with alkene* and demonstrate the utility of this method by describing an efficient formal total synthesis of the Calabar bean alkaloid physovenine **1**.[2,3]

The starting 2-amino-5-methoxyacetophenone **2**[4] was readily prepared from *m*-hydroxyacetophenone via the six-step sequence in 63 % overall yield. Treatment of **2** with methyl lithium gave the amino alcohol **3** which was then dehydrated by heating at 230 °C for 5 min without solvent[5] to provide **4** in 69 % overall yield from **2**. Methoxycarbonylation of **4** gave the carbamate **5**, which was alkylated with methyl bromoacetate in the presence of sodium hydride to provide the ester carbamate **6** in 86 % yield for the two steps. The crucial [2+2]cycloaddition reaction was effected by treatment of the carboxylic acid **7**, derived from **6** by hydrolysis with lithium hydroxide in 98 % yield, with oxalyl chloride to give the corresponding acid chloride, which was immediately treated with triethylamine in refluxing benzene for 1 hr. Subsequent purification by column chromatography afforded the single tricyclic ketone **9**[6], which is assumed to be formed via the olefinic ketene **8**, in yield of 82 %. Baeyer-Villiger oxidation of **9** with *m*-chloroperbenzoic acid cleanly produced the lactone **10** in 97 % yield. The final transformation of **10** to **12** was achieved by using the method developed by Kraus.[7] Thus , sequential reduction with diisobutylaluminium hydride and acetylation gave the acetate **11** as a mixture of diastereoisomers, which was treated with triethylsilane in the presence of boron trifluoride etherate to furnish the furo[2,3-b]indole **12** in 63 % overall yield from **10**. The IR, ^{1}H NMR, and mass spectral data of the material prepared in this way were identical with those of the authentic sample of **12**. Since the compound **12** has already been converted into physovenine by Fukumoto,[2] the present synthesis means the formal total synthesis of it.

In summary, we have shown a new version of the intramolecular [2+2]cycloaddition reaction which should be a convenient method for preparation of alkaloids as well as nitrogen containing heterocycles, and have applied the method to the synthesis of (±)-physovenine.



Reagents: a, MeLi, 92 %; b, 230 °C, 75 %; c, $ClCO_2Me$, NaH, 90 %; d, $BrCH_2CO_2Me$, NaH, 95 %; e, LiOH, 98 %; f, $(COCl)_2$ then NEt_3, benzene, reflux, 82 %; g, MCPBA, 97 %; h, DIBAH then Ac_2O, pyridine, 79 %; i, Et_3SiH, BF_3OEt_2, 80 %.

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References and Notes

1. For an excellent review, see B.B. Snider, *Chem. Rev.*, **88**, 793 (1988).
2. K. Shishido, E. Shitara, H. Komatsu, K. Hiroya, K. Fukumoto, and T. Kametani, *J. Org. Chem.*, **51**, 3007 (1986).
3. For a recent synthetic effort, see J.P. Marino, M.W. Kim, and R. Lawrence, *J. Org. Chem.*, **54**, 1784 (1989), references cited therein.
4. A.R. Osborn and K. Schofield, *J. Chem. Soc.*, **1955**, 2100.
5. R. Smith and T. Livinghouse, *Tetrahedron*, **41**,3559 (1985).
6. Compound **9** : IR ($CHCl_3$) : 1790, 1705 cm^{-1} ; ^1H NMR (200MHz, $CDCl_3$) : δ 1.74 (3H, s), 3.20 (1H, dd, J=18.0 and 2.4 Hz), 3.37 (1H, dd, J=18.0 and 2.9 Hz), 3.79 (3H, s), 3.84 (3H, br s), 5.17 (1H, br s), 6.80 (2H, m), 7.76 (1H, br) ; MS (*m/z*) : 219 (100%), 261 (M^+).
7. G.A. Kraus, K.A. Frazier, B.D. Roth, M.J. Taschner, and K. Neuenschwander, *J. Org. Chem.*, **46**, 2417 (1981); G.A. Kraus, M. Taschner, and M. Shimagaki, *ibid.*, **47**, 4271(1982).

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