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A Chiral Route to Both Enantiomers of Physostigmine and the First Synthesis of (-)-Norphysostigmine

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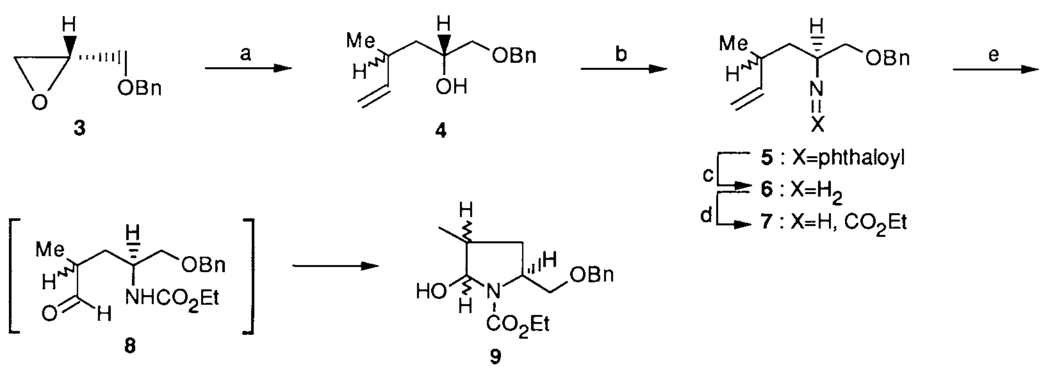
A chiral route to both enantiomers of esermethol, the key synthetic precursor of physostigmine, has been established starting from (S)-O-benzylglycidol via separation of the diastereomeric intermediates. (-)-Physostigmine obtainable from the (-)-enantiomer has been first transformed into (-)-norphysostigmine, the only unsynthesized member of the alkaloid group ever determined.

Besides the well-known anti-acetylcholinesterase,[1] it has recently been reported that the (-)-physostigmine (**1**), a major alkaloid constituent of the calabar bean, significantly improved memory in patients with Alzheimer's disease[2] and (-)-eseroline [(-)-**19**], the decarbamoyl derivative and a major metabolite of (-)-physostigmine (**1**), exhibited analgesic effect comparable to that of morphine.[3]

Fig. 1.

Moreover, it has also been reported that the unnatural (+)-physostigmine (ent-**1**) exhibited lower toxicity though its physiological effects were found to be not always comparable.[4] In this connection, we investigate a new chiral route leading to both enantiomeric forms of the alkaloid and the congeners via separation of



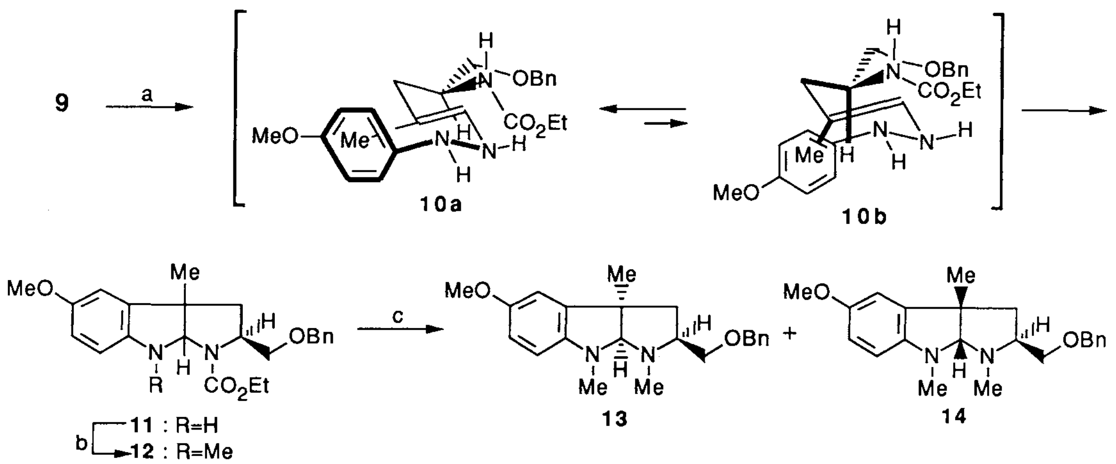
Scheme 1.

a, $CH_3CH{=}CHCH_2MgCl$, THF, 0 °C; b, phthalimide, PPh_3, diisopropyl azodicarboxylate; c, $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; d, EtOCOCl, Et_3N, CH_2Cl_2; e, 2% mol OsO_4, 2 equiv. $NaIO_4$, THF-H_2O (2:1) then $NaIO_4$.

diastereomeric intermediate starting from (S)-O-benzylglycidol[5] (**3**). We report herewith synthesis of the key intermediate esermethole (**19**) in both enantiomeric forms and the first synthesis of (-)-norphysostigmine[1c] (**2**), the only compound remained unsynthesized in the physostigmine alkaloids ever determined.

Reaction of (S)-O-benzylglycidol (**3**) with crotylmagnesium chloride[6] afforded the terminal olefin **4**, selectively, in 90% yield as an inseparable mixture of epimers. On the Mitsunobu reaction,[7] followed by sequential deacylation and carbamoylation **4** furnished the carbamate **7** in 72% overall yield as an inseparable mixture via the phthalimide **5** and the amine **6**. Treatment of **7** with a catalytic amount of osmium tetroxide and 2 equiv. of 1-methylmorphorine-1-oxide followed by sodium periodate[8] allowed cleavage at the terminal olefin to give the aldehyde **8** which was isolated as the hemiacetal form **9** in 94% yield (Scheme 1).

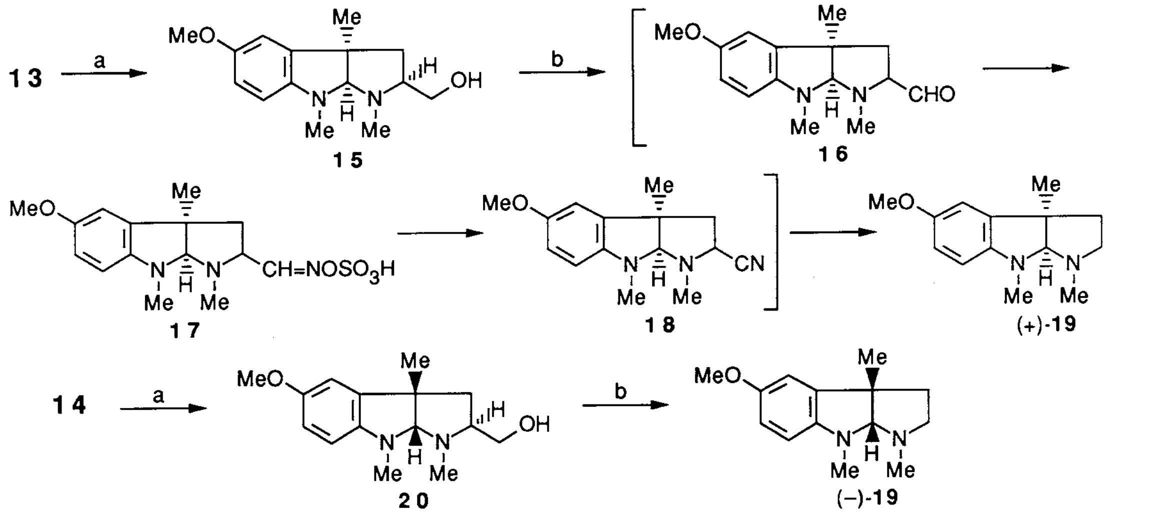
Upon the Fischer indolization with 4-methoxyphenylhydrazine hydrochloride in pyridine[9] at reflux **9** furnished an inseparable 2:1 mixture of products **11** in 95% yield which were later found to be consisted of the major isomer ("unnatural" configuration) by cyclization of conformer **10a** and the minor isomer ("natural" configuration) by cyclization of conformer **10b**. Fortunately, the N,N'-dimethylated derivatives obtained from the mixture **11** by sequential N-methylation and reduction were readily separated by silica gel column chromatography to give the "unnatural" amine **13**, $[\alpha]_D^{21.5}$ -2.6° (c 0.10, $CHCl_3$), in 53% overall yield and the "natural" amine **14**, $[\alpha]_D^{22}$ -107° (c 1.02, $CHCl_3$), in 29% overall yield, respectively, via **12** (Scheme 2).



Scheme 2.
a, 1 equiv. p-$MeOC_6H_4NHNH_2$·HCl, pyridine, reflux; b, 35% formalin, $NaBH_3CN$, MeOH; c, $LiAlH_4$, THF, reflux 5 min.

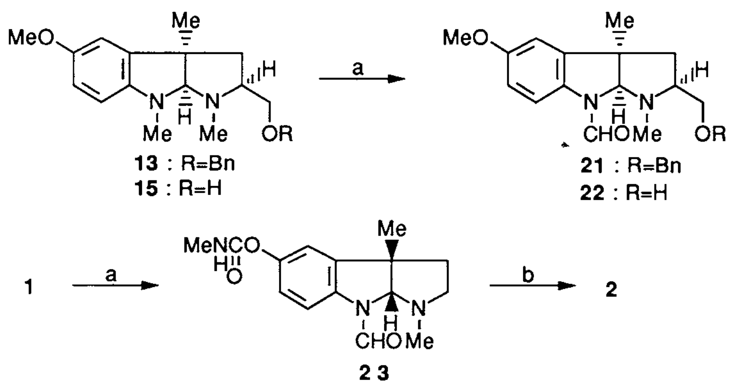
Having separated two diastereomers, the major isomer **13** was debenzylated under the Birch conditions to give the primary alcohol **15**, $[\alpha]_D^{30.5}$ +36.3° (c 1.01, $CHCl_3$), quantitatively. Since the aldehyde **16** obtained from **15** by the Swern oxidation was found to be extremely unstable,[10] the oxidation mixture of **13** was successively treated with hydroxylamine-O-sulfonic acid[11] and sodium borohydride[12] in the same reaction flask to give the "unnatural" (+)-esermethole [(+)-**19**], $[\alpha]_D^{28.5}$ +133° (c 0.35, benzene) [lit.[13] $[\alpha]_D$ -129° (c 0.33, benzene) for (-)-enantiomer], in 22% overall yield without isolation of the intermediates **16**, **17**, and **18**. On the same treatment, the isomeric alcohol **20**, $[\alpha]_D^{31}$ -118° (c 0.99,

$CHCl_3$), obtained in 92% yield from **14**, afforded the "natural" (-)-esermethole [(-)-**19**], $[\alpha]_D^{34}$ -134°. (c 0.35, benzene) [lit.[13] $[\alpha]_D$ -129° (c 0.33, benzene)], in 25% overall yield. Since (-)-**19** has already been converted into natural (-)-physostigmine (**1**) in two steps,[1,13] the present synthesis of (+)- and (-)-**19** constitutes a formal acquisition of both unnatural (ent-**1**) and natural (**1**) enantiomers of the alkaloid (Scheme 3).



Scheme 3.
a, Na, liq. NH_3; b, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 then NH_2SO_3H, evaporation of the solvent, then $NaBH_4$, EtOH, reflux.

During attempted oxidation of the alcohol **15** to the aldehyde **16**, it was observed that the N_8-formyl derivative **22** in place of the expected **16** was generated in 25% yield when pyridinium dichromate was used as oxidant in dichloromethane.[14] Application of the same conditions to the benzyl ether **13** and (-)-physostigmine (**1**) similarly led to the formation of the corresponding N_8-formyl derivatives, **21**, and **23**, in yields of 48 and 25%, respectively. The latter formamide **23**, on hydrolysis with diluted hydrochloric acid (10%), at room temperature furnished (-)-norphysostigmine[1c] (**2**), mp 152-153 °C, $[\alpha]_D^{28.5}$ -116° (c 0.40, EtOH) [lit.[1c] mp 151 °C, $[\alpha]_D^{21}$ -108.6° (EtOH), in 72% yield (Scheme 4).



Scheme 4.
a, PDC, CH_2Cl_2; b, aq. 10% HCl, room temp.

In conclusion a formal chiral route to both natural and unnatural forms of physostigmine (**1**) has been established starting from (S)-O-benzylglycidol (**3**) via separation of the diastereomeric intermediates. Furthermore, the first synthesis of (-)-norphysostigmine (**2**), the only unsynthesized member of the alkaloid group ever determined, has been accomplished based on the observation during the investigation. It has now been demonstrated that (-)-physostigmine (**1**) can be convertible into all other four members of the alkaloid group ever determined since the all but (-)-norphysostigmine (**2**) have been known to be convertible from **1**.[1)]

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