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FORMAL TOTAL SYNTHESIS OF (–)-PHYSOSTIGMINE

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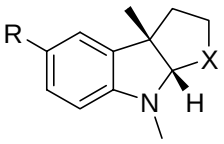
Abstract – The formal total synthesis of (–)-physostigmine via the chiral malonic acid mono-ester ((*R*)-2-(2-chlorophenyl)-2-methoxycarbonylpropanoic acid, 99% ee) newly prepared by the pig liver esterase (PLE) mediated asymmetric hydrolysis of the corresponding di-ester is described. The CuI-mediated intramolecular aryl amidation under modified Buchwald's conditions is a key reaction to constructing the oxindoline core in the target.



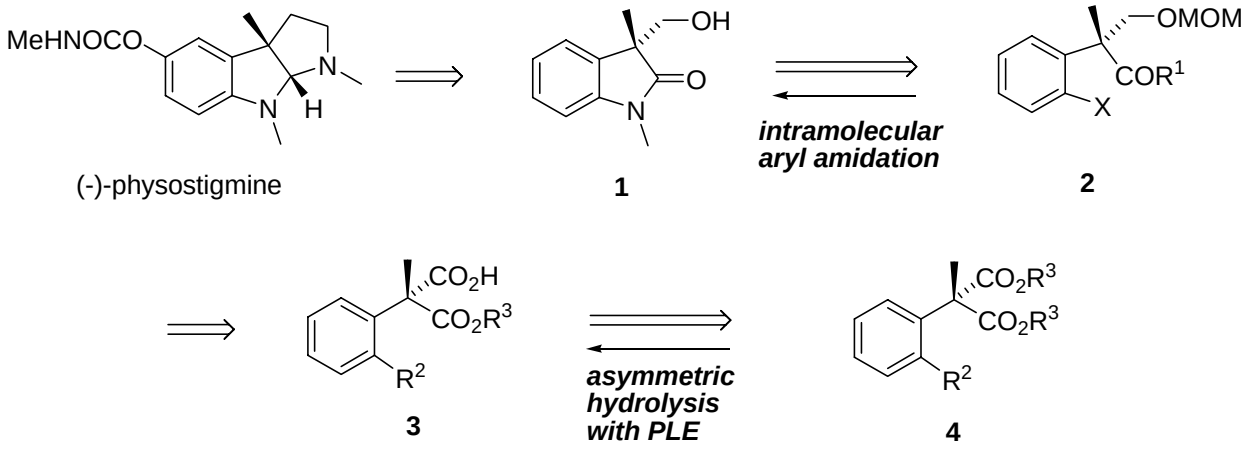
(-)-physostigmine	: R=OCONHMe, X=NMe
(-)-phenseline	: R=OCONHPh, X=NMe
(-)-esermethole	: R=OMe, X=NMe
(-)-eserethole	: R=OEt, X=NMe
(-)-eseroline	: R=OH, X= NMe
(-)-deoxyeseroline	: R=H, X=NMe
(-)-*N*^{8}-norphysostigmine	: R=OCONHMe, X=NH
(-)-physovenine	: R=OCONHMe, X=O

Figure 1. Structure of (–)-physostigmine and derivatives

(–)-Physostigmine (Figure 1)[1] was initially isolated from the seeds of *Physostigma venenosum* in 1864,[2] and its structural determination[3] disclosed its characteristic hexahydropyrrolo[2,3-*b*]indole core with a quaternary stereogenic center at its benzylic position. (–)-Physostigmine has been clinically used for the treatment of glaucoma, myasthenia gravis, atropine and organophosphate intoxication, and for the relief of intoxication induced by overdoses of tricyclic antidepressants, antihistamines, antipsychotics, and benzodiazepines.[1,4-6] Moreover, (–)-physostigmine has been evaluated in clinical trials for the symptomatic treatment of Alzheimer's disease.[1,4-6] (–)-Physostigmine is a potent inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), thereby showing wide biological activities. (–)-Physostigmine acts as a pseudosubstrate, transferring a carbamate residue to the enzyme's active site to bring about a stereoselective inhibition, but spontaneous hydrolysis regenerates the native

enzyme and function. Therefore, various derivatives of (–)-physostigmine with improved pharmacological profile against Alzheimer's disease have been prepared,[1,7] stimulating further synthetic studies. Indeed, although the first total synthesis of physostigmine was reported in 1935, a number of total syntheses as well as preparations of its derivatives have been reported to date.[8-10] Interestingly, the inhibition of AChE is found to be enantioselective through the studies using acetylcholinesterase obtained from human tissues;[11] that is, (–)-physostigmine is some 1000 times more potent than its (+)-enantiomer,[11] implying the importance of the enantioselective total synthesis of (–)-physostigmine and its derivatives.

The unique bioactivity and structural features of (–)-physostigmine described above make this compound a still-attractive target. We report herein a formal total synthesis of (–)-physostigmine via the chiral malonic acid mono-ester ((*R*)-2-(2-chlorophenyl)-2-methoxycarbonylpropanoic acid, 99% ee) newly prepared by the pig liver esterase (PLE) mediated asymmetric hydrolysis of the corresponding di-ester.

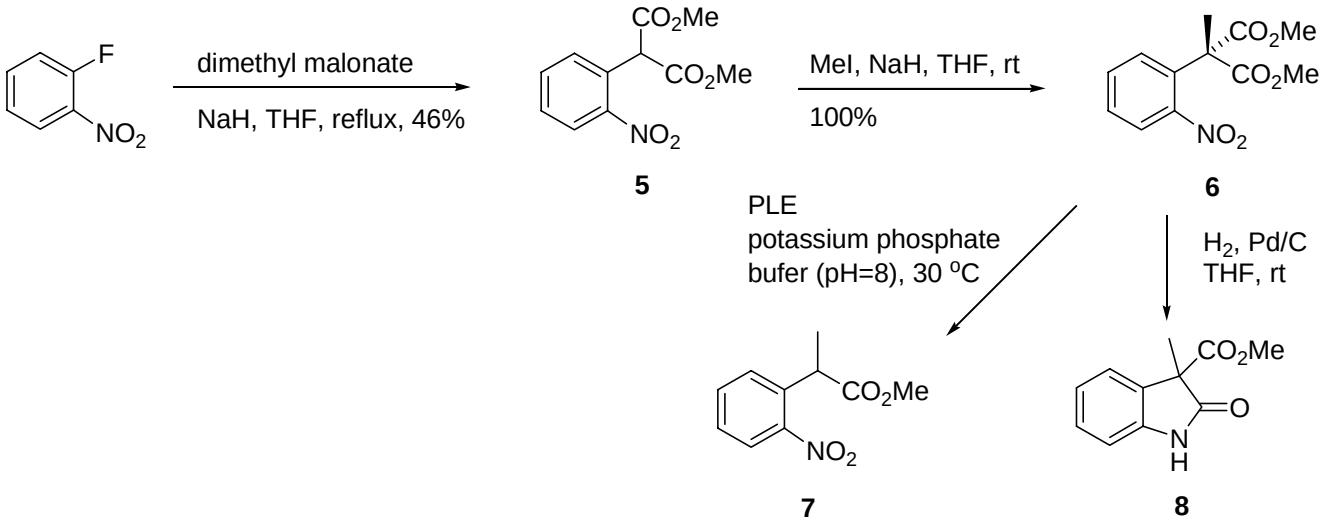


Scheme 1. Retrosynthetic analysis of (–)-physostigmine

The retrosynthetic analysis of (–)-physostigmine is shown in Scheme 1. The total synthesis of (–)-physostigmine presents some problems; 1) construction of the hexahydropyrrolo[2,3-*b*]indole core; 2) construction of a quaternary stereogenic center at the benzylic position; and 3) obtaining the chiral intermediate. Since lactam **1** has been converted to (–)-physostigmine,[9,10] we planned its formal total synthesis, namely, the enantioselective total synthesis of lactam **1**.

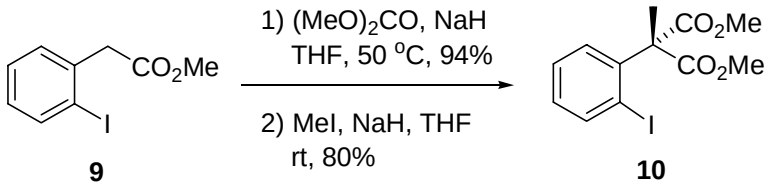
Although lactam **1** incorporates the oxindoline core with a quaternary stereogenic center at its benzylic position, the oxindoline core was expected to be constructed by the intramolecular lactam formation of compound **2**, which would be derived from mono-ester **3**. Chiral mono-ester **3** was thought to be obtained by asymmetric hydrolysis of the corresponding malonic acid di-ester **4** with pig liver esterase (PLE).[12] Mono-ester **3** would be a useful intermediate for the synthesis of congeners of (–)-physostigmine (Figure

1) and other compounds with a quaternary stereogenic center at the benzylic position. Consequently, preparation of di-ester **4** and its asymmetric hydrolysis with PLE was examined.



Scheme 2. Preparation of di-ester **6** and its attempted conversion

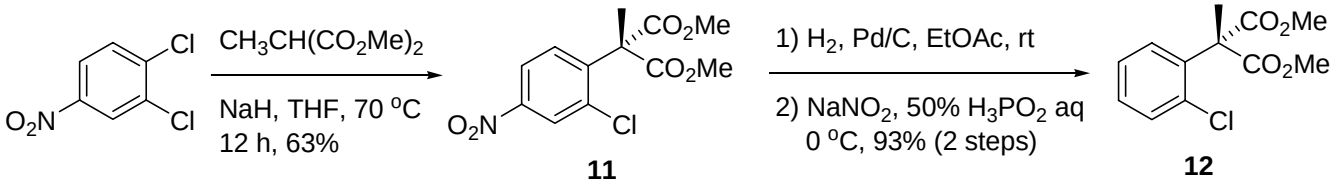
If substituent R^2 of di-ester **4** is an amine or its derivative, synthesis of lactam **1** via mono-ester **3** would be easy. Therefore, we first prepared di-ester **6** because a nitro group is easily reduced to an amine. Since *o*-fluoro nitrobenzene has been reported to undergo a nucleophilic substitution, dimethyl malonate was reacted with *o*-fluoro nitrobenzene using NaH as a base to afford diester **5**,[13] which was methylated to provide di-ester **6** (Scheme 2). Although asymmetric hydrolysis of di-ester **6** with PLE proceeded smoothly, the product obtained was not the corresponding mono-ester but, rather, decarboxylated methyl ester **7**. This result would be well explained by the fact that the anion at the benzylic position of the mono-ester, which was generated from di-ester **6**, could be stabilized by an electron withdrawing nitro group through the conjugation system. In addition, catalytic hydrogenation of a nitro group of di-ester **6** smoothly provided undesired lactam **8** even in the presence of acid or a trapping reagent such as acetic anhydride or Boc_2O, directing our attention to preparing another type of di-ester.



Scheme 3. Preparation of di-ester **10**

Next we examined the preparation of di-ester **4** with a halogen substituent as R^2, because the corresponding mono-ester would not undergo decarboxylation. Furthermore, the intramolecular aryl amidation of amide **2**, which would be easily prepared from mono-ester **3**, was expected to provide the oxindol core.

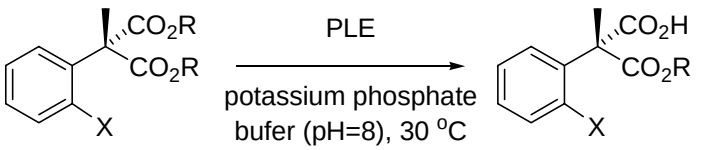
Iodide **10** was successfully prepared from known methyl ester **9**[14] by introduction of methyl ester[15] and subsequent methylation (Scheme 3).



Scheme 4. Preparation of di-ester **12**

Chloride **12** was prepared starting from 3,4-dichloronitrobenzene, which was easily obtained from *o*-dichlorobenzene (Scheme 4). As 3,4-dichloronitrobenzene was reported to react with dimethyl malonate with high regioselectivity,[16] we examined the reaction of 3,4-dichloronitrobenzene with an anion of dimethyl methylmalonate and found that the reaction in DMF proceeded at 70 °C, providing di-ester **11** in 63% after 12 h. The catalytic hydrogenation of di-ester **11** in methanol caused over-reduction, affording a product lacking no chlorine atom, but the reaction in ethyl acetate was chemoselective, cleanly providing the arylamine corresponding to compound **11**. The arylamine was treated with sodium nitrite in aqueous hypophosphorous acid solution, successfully giving di-ester **12**.

Table 1. PLE mediated hydrolysis of **10**, **10'**, and **12**



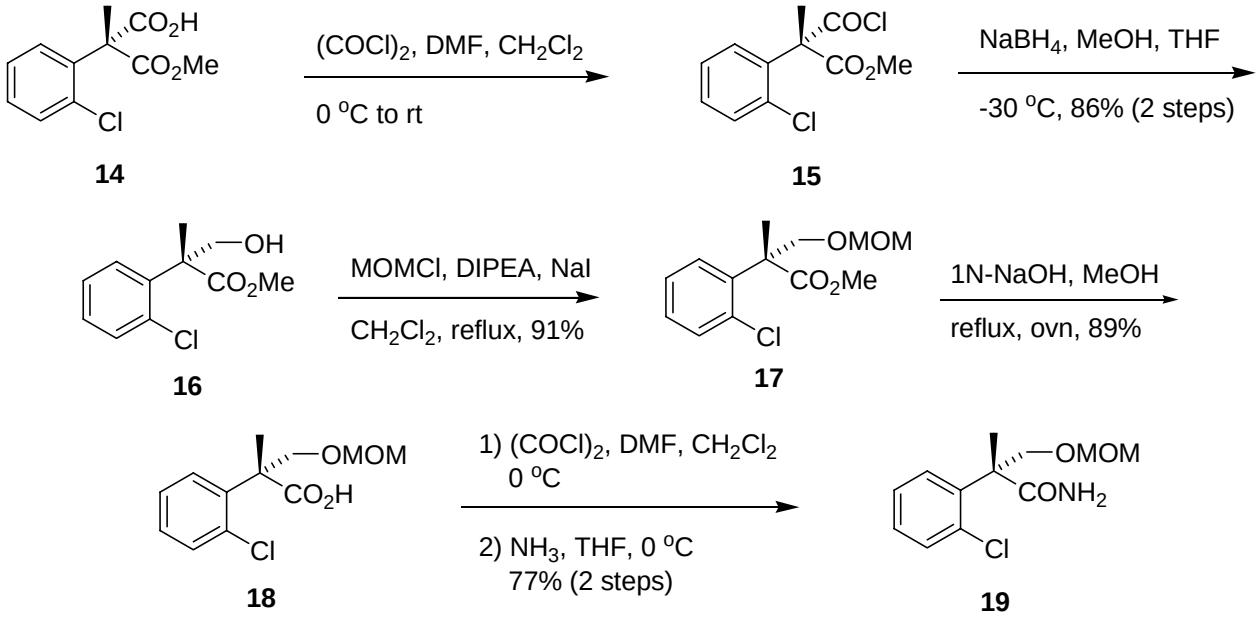
10 (R=Me, X=I)
10' (R=Et, X=I)
12 (R=Me, X=Cl)

13 (R=Me, X=I)
13' (R=Et, X=I)
14 (R=Me, X=Cl)

Entry	Substrate	Time (d)	Yield (%)[a]	Ee (%)[b]
1	**10**	2	78	99
2	**10'**	1	63	44
3	**12**	3	92	99

[a]Isolated yield. [b]Ee determined by HPLC using the corresponding anilide.

PLE-mediated asymmetric hydrolysis of di-esters **10**, **10'**,[17] and **12** was performed under the general conditions[12] (Table 1). The hydrolysis of dimethyl ester **10** proceeded with high enantioselectivity, affording the corresponding mono-ester **13** in 78% yield with 99% ee. Interestingly, the hydrolysis of diethyl ester **10'** gave the product **13'** with low ee (44% ee). On the other hand, the hydrolysis of dimethyl ester **12**, which was a chloride, provided mono-ester **14** with 92% yield and 99% ee. Comparing the preparation method of iodide **10** with that of chloride **12**, chloride **12** was easier to prepare and suitable for a large-scale synthesis. Consequently, we decided to employ mono-ester **14** for further transformations. Although the absolute configuration of **14** was undetermined at this point, the hidden symmetry in the structure of chiral mono-ester **14** implied that mono-ester **14** would be converted to both enantiomers of alcohol **1**. Hence, we continued further synthetic studies from **14** with assuming its absolute structure as shown in Scheme 5.



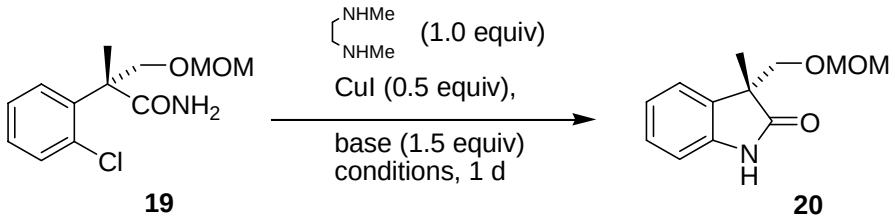
Scheme 5. Preparation of amide **19** from mono-ester **14**

Mono-ester **14** was converted to acid chloride **15** (Scheme 5), which was reduced with sodium borohydride to provide alcohol **16** in 86% yield (2 steps).[18] Alcohol **16** was converted to MOM ether **17**, which resisted conversion to amide **19** under any conditions. This can probably be attributed to the steric hindrance derived from the quaternary carbon adjacent to the ester group. Therefore, MOM ether **17** was subjected to hydrolysis, and the resulting carboxylic acid **18** was converted to the reactive acid chloride, followed by the reaction with ammonia to provide amide **19**.

In general, reaction of a functional group adjacent to a quaternary carbon is slow due to the steric hinderance. In addition, the copper(I)-mediated amidation of aryl chloride is slow. However, the reaction points of amide **19** are set closed; hence, its intramolecular aryl amidation was expected to provide lactam

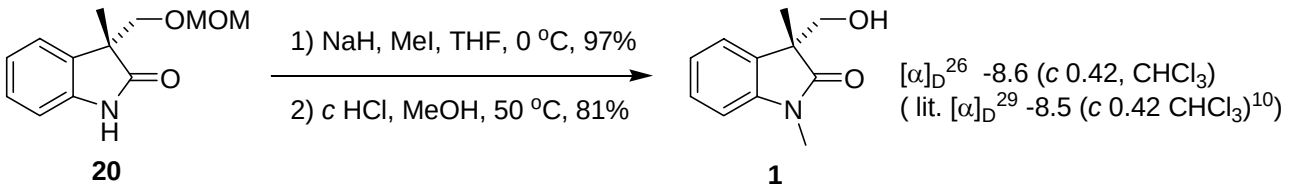
20. First, we examined the copper(I)-mediated intramolecular reaction of amide **19** under Buchwald's conditions, using *N*, *N'*-dimethyl ethylenediamine (Table 2).[19] The reaction carried out with potassium carbonate in toluene provided lactam **20** in 66% (entry 1), but a certain amount of amide **19** remained unreacted. Use of one equivalent of CuI did not improve the yield, and the reactions by use of potassium phosphate (entry 2) or cesium carbonate (entry 3) reduced the yield. The reaction in dioxane at reflux temperature (entry 4) lowered the yield. However, although the reaction in DMF at 100 °C (entry 5) was unsatisfactory, the reaction in DMF at reflux temperature (entry 6) gave lactam **20** in 76% yield.

Table 2. Intramolecular aryl amidation of amide **19**



Entry	Solvent	Base	Temp	Yield (%)[a]
1	toluene	K_2CO_3	reflux	66
2	toluene	K_3PO_4	reflux	33
3	toluene	Cs_2CO_3	reflux	57
4	dioxane	K_2CO_3	reflux	24
5	DMF	K_2CO_3	100 °C	53
6	DMF	K_2CO_3	reflux	76

[a]Isolated yield.



Scheme 6. Formal total synthesis of (–)-physostigmine

Lactam **20** thus obtained was *N*-methylated, and subsequent acid treatment successfully deprotected the MOM group, providing alcohol **1**. Synthesized alcohol **1** was identical with the known compound **1** in all respects (^{1}H-NMR, IR, MS, $[\alpha]_D$, and ^{13}C-NMR)[10], indicating that the formal total synthesis of (–)-physostigmine was achieved. This enantioselective total synthesis proved the absolute structure of

mono-ester **14** is as shown in Scheme 5, too.

In summary, we have developed the synthetic method of di-ester **12**, and the PLE-mediated asymmetric hydrolysis of di-ester **12** afforded chiral mono-ester **14** with 92% yield and 99% ee. The copper(I)-mediated intramolecular aryl amidation of amide **19** under modified Buchwald's conditions successfully provided lactam **20**, which was converted to known alcohol **1** to complete the formal total synthesis of (–)-physostigmine. Chiral mono-ester **14** possessing a stereogenic quaternary carbon center at the benzylic position could be used for enantioslective synthesis of other natural and unnatural products. All reactions in this synthesis can be carried out on a large scale, allowing supply of a considerable amount of alcohol **1,** which would be a key intermediate for the library of (–)-physostigmine.

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