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DIASTEREOSELECTIVE FISCHER-TYPE PYRROLOINDOLE SYNTHESIS AND ITS APPLICATION TO THE SYNTHESIS OF CHIRAL PYRROLOINDOLE ALKALOIDS

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Abstract – Facile access to optically active pyrroloindoles by Fischer-type pyrroloindole synthesis is investigated. The reaction using chiral hydrazines prepared from commercially available chiral amines proceeded with diastereoselective cyclization (up to 70% de), and a short-step conversion of the cycloadducts to (-)-desoxyeseroline and pyrroloindole alkaloids was achieved.

INTRODUCTION

Pyrroloindoles have been considered potential lead compounds in the search for drugs to treat Alzheimer disease (Figure 1), and their synthesis in an optically active form has been investigated.[1,2] Fischer-type pyrroloindole synthesis,[2] which is one of the most general methodologies for the synthesis of various pyrroloindole derivatives, is particularly useful because 1) the reaction can be carried out under mild reaction conditions, and 2) the reaction substrates are readily available. However, in the case of diastereoselective Fischer-type pyrroloindole synthesis, theire is no method available for the efficient removal of chiral auxiliaries.[3] Recently, we developed a method for the facile synthesis of pyrroloindoles[4] using *N*-methylhydrazine and reported its application to the synthesis of racemic physostigmine.[5] In this communication, we report the diastereoselective synthesis of pyrroloindoles using chiral hydrazines.

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

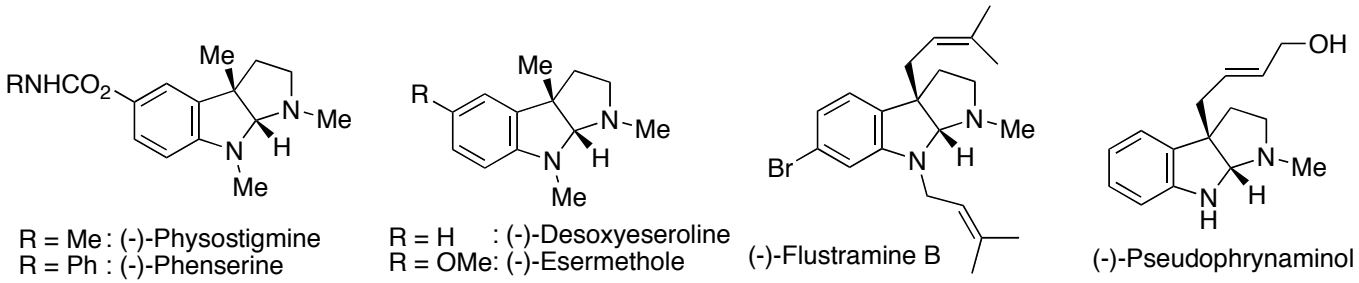
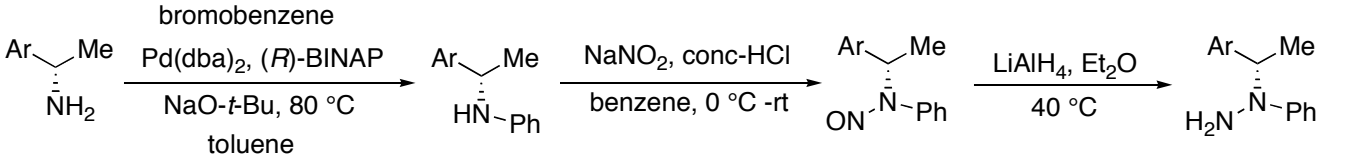


Figure 1 Representative examples of biologically important pyrroloindoles

RESULTS AND DISCUSSION

We initially prepared chiral hydrazines (**4a,b**) from commercially available chiral amines (**1a,b**), as follows; palladium-catalyzed arylation[6] of amines (**1a,b**) with bromobenzene, and subsequent nitrosylation and reduction gave **4a** and **4b**, respectively (Scheme 1).



1a : Ar = Ph
1b : Ar = α-Naphthyl

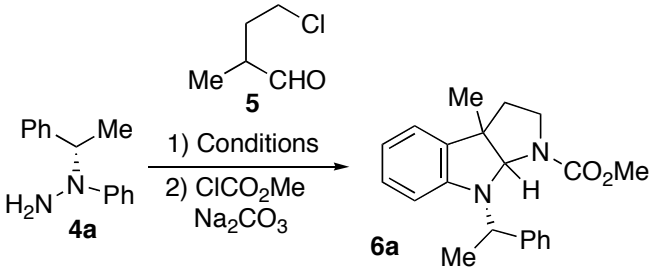
2a : Ar = Ph, 96%
2b : Ar = α-Naphthyl, quant

3a : Ar = Ph, quant
3b : Ar = α-Naphthyl, 96%

4a : Ar = Ph, 40%
4b : Ar = α-Naphthyl, 85%

Scheme 1 Synthesis of hydrazines (**4**)

In the synthesis of pyrroloindole (**6a**), the reaction of **4a** with chloroaldehyde (**5**) was investigated in protic solvents (Table 1). In a mixed solvent of ethanol and water (5:1), the reaction proceeded smoothly to give a *cis*-fused pyrroloindole (**6a)** through acylation with methyl chloroformate in 78% yield, although the diastereoselectivity was almost 1:1 (entry 1). In the case of methanol and isopropanol, **6a** was obtained in yields of 85 and 72%, respectively, with less than 14% de(entry 3).



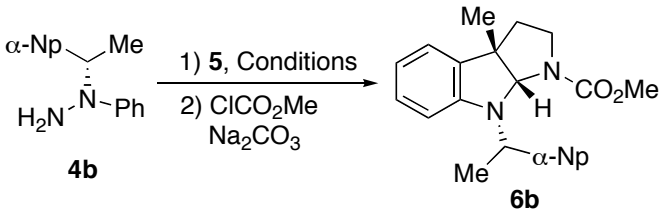
entry	solvent	**5** (eq.)	conditions	yield (%) of **6a**	de (%) of **6a**
1	EtOH-H_2O	2	reflux, 22 h	78	2
2	MeOH	1	40 °C, 25 h	85	7
3	*i*-PrOH	1.5	rt, 49 h	72	14

Diasetereoselectivity of **6a** was determined by HPLC and NMR spectral analysis.

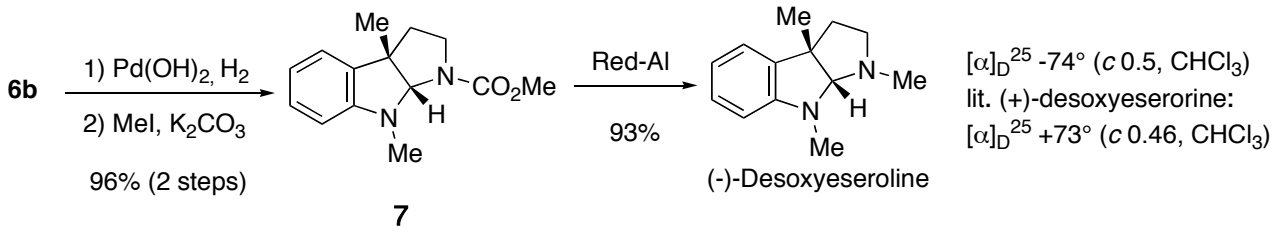
Table 1 Diastereoselective synthesis of **6a** using **4a**

In the reaction of **4b** in ethanol-water (5:1), **6b** was obtained in quantitative yield with an improved de (Table 2, entry 1). After we surveyed the protic solvents, we deteremined that isopropanol was the best solvent with regard to the diastereoselectivity of **6b** (entry 2).[7] The reaction without solvents in the presence of 15 eq. of **5** gave **6b** in 40% yield with 70% de (entry 3). We next investigated the synthesis of (-)-deoxyeseroline using the optically pure **6b**, which was obtained by purification of cyclized product from **4b** before acylation. Hydrogenation in the presence of $Pd(OH)_2$ and subsequent methylation gave **7** in 96% yield (2 steps). Finally, the carbamate (**7**) was converted to (-)-desoxyeseroline,[8] which is known to be a key intermediate to (-)-physostigmine,[5,9] by Red-Al in toluene under reflux conditions in 93% yield(Scheme 2).

Table 2 Reaction of **4b**



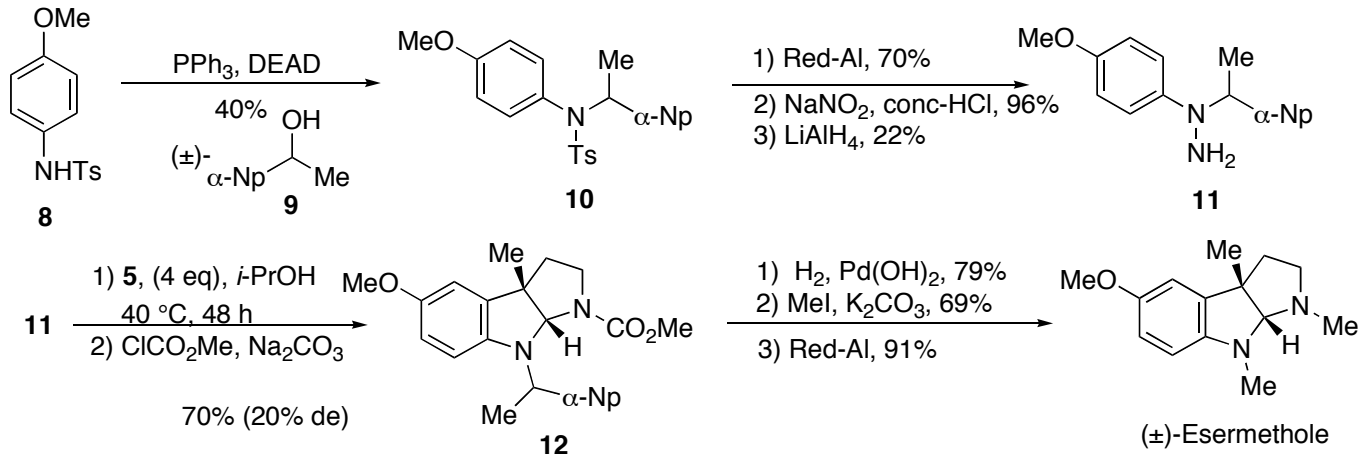
entry	solvent	**5** (eq.)	conditions	yield (%) of **6b**	de (%) of **6b**
1	EtOH-H_2O (5:1)	2	40 °C, 5 h	quant	17
2	*i*-PrOH	4	40 °C, 2 h	58	61
3	none	15	rt, 20 h	42	70



Scheme 2

Scheme 2 Conversion to (-)-desoxyeseroline

We next attempted to use a methoxy derivative (**11**) which is a more suitable substrate for the synthesis of physostigmine. Compound (**11**) was synthesized as follows. Treatment of tosylamide (**8**) with **(±)-9** under Mitsunobu conditions gave **10** in 40% yield. Subsequent reduction by Red-Al, nitrosylation with sodium nitrite and reduction with $LiAlH_4$ gave the desired hydrazine (**11**). With the substrate in hand, we performed the Fischer-type pyrroloindole synthesis under the optimized conditions (isopropanol at 40 °C). Unfortunately, **11** was not suitable for diastereoselective cyclization and gave **12** with only 20% de (70% yield), which was converted to racemic esermethole in three steps (Scheme 3).



Scheme 3 Synthesis and reaction of **11**, and conversion to **(±)**-esermethole

In conclusion, we have developed a facile preparation of optically active pyrroloindoles by diastereoselective Fischer-type pyrroloindole synthesis and have converted them to biologically important compounds. Further investigations to increase the de of products and the application of this method to the synthesis of various pyrroloindoles are currently in progress.

ACKNOWLEDGEMENTS

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7. Synthesis of **6b** (Table 2, entry 2): A solution of **4b** (40.0 mg, 0.15 mmol) and **5** (73.3 mg, 0.6 mmol) in isopropanol (3.0 mL) was refluxed for 2 h. After solvent was removed *in vacuo*, the crude mixture was dissolved in CH_2Cl_2:H_2O = 5:1 (3 mL). To this solution were added Na_2CO_3 (50

mg, 0.47 mmol) and $ClCO_2Me$ (0.29 mL, 0.34 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at rt. The mixture was extracted with $CHCl_3$ (10 mL X 3), and the extract was washed with brine and dried over Na_2SO_4. Afetr the solvent was removed, the crude mixture was purified by flash column chromatography with silica gel (hexane:AcOEt = 10:1) to give **6b** as a yellow oil (34.2 mg, 58%). The diastereoselectivity was determined by HPLC analysis (DAICEL CHIRALCEL AD-H, hexane:isopropanol = 95:5, flow rate:0.5 mL/min, 254 nm). The major isomer was obtained by another procedure; purification on a SiO_2 column before *N*-acylation and transformation of the resulting amine to **6b** with $ClCO_2Me$. Major isomer of **6b**: $[\alpha]_D^{25}$ –228.3° (*c*, 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz, 120 °C) δ: 1.21 (s, 3H), 1.75 (d, 3H, *J* = 6.8 Hz), 1.81-1.88 (m, 1H), 1.97-2.01 (m, 1H), 3.07-3.13 (m, 1H), 3.50 (s, 3H), 3.76-3.82 (m, 1H), 5.24 (s, 1H), 5.55 (q, 1H, *J* = 6.8 Hz), 6.26 (d, 1H, *J* = 7.6 Hz), 6.58 (t, 1H, *J* = 7.2 Hz), 6.85 (dt, 1H, *J* = 7.6, 1.2 Hz), 7.00 (dt, 1H, *J* = 7.2, 1.2 Hz), 7.36-7.45 (m, 2H), 7.49 (t, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 7.6 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 8.12 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, 120 °C) δ:15.0, 23.8, 38.3, 45.2, 50.9, 51.2, 51.5, 86.4, 107.4, 116.9, 121.5, 123.0, 123.9, 124.3, 124.7, 124.8, 126.9, 127.1, 127.8, 130.8, 133.0, 134.6, 137.1, 147.4, 154.5; IR (neat) ν: 3047, 2954, 1697, 1603, 1484 cm^{-1}; LRMS (EI) *m/z* 386 (M^+); HRMS (FAB) calcd for $C_{25}H_{27}N_2O_2$ 387.2065, found 387.2073.

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