Pergamon

Tetrahedron 56 (2000) 1469–1473

TETRAHEDRON

A New Efficient Route to (±)-Physostigmine and (±)-Physovenine by Means of 5-*exo* Selective Aryl Radical Cyclization of *o*-Bromo-*N*-acryloylanilides

Hiroyuki Ishibashi,* Tetsuya Kobayashi, Noriko Machida and Osamu Tamura

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

Received 16 December 1999; accepted 17 January 2000

Abstract—Bu_3SnH-mediated aryl radical cyclization of *o*-bromo-*N*-acryloylanilides **16** and **17** proceeded in a 5-*exo* manner exclusively to give, in high yields, oxindoles **3** and **4**, the key intermediates for the synthesis of (±)-physostigmine and (±)-physovenine, respectively.

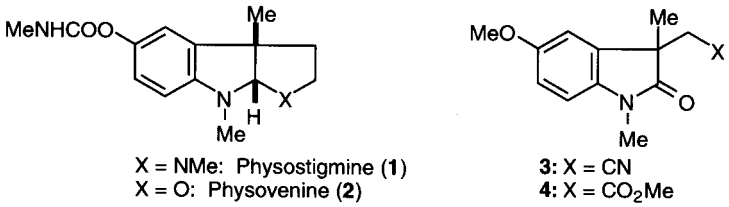
Introduction

Physostigmine (**1**) and physovenine (**2**), the alkaloids from the African Calabar bean, have interesting physiological effects such as anticholinergic and miotic activities.[1,2] More importantly, physostigmine and its derivatives have recently been found to be useful for relieving symptoms of Alzheimer's disease.[3] Therefore, the synthesis of this class of alkaloids has received renewed attention. The first synthesis of (±)-physostigmine was reported by Julian and Pikl[4] using the 5-ethoxy congener of 3,3-disubstituted oxindole **3** as an intermediate, and thereafter a number of methods have been reported for the preparation of (±)- and (−)-**3** and their analogs[5] and for the improvement in synthesis of physostigmine from these intermediates.[6] Herein we report a new synthesis of (±)-**3** using 5-*exo* selective aryl radical cyclization of *o*-bromo-*N*-acryloylanilides **16** as a key step. An application of this method to the synthesis of (±)-**4**, an intermediate for the synthesis of (±)-physovenine, is also presented (Scheme 1).

Results and Discussion

We began our investigation by examining the cyclization of **7**. The Horner–Emmons reaction of anilide **6**, prepared by acylation of *o*-iodo-*N*-methylaniline (**5**)[7] with pyruvyl chloride[8] (91%), with diethylphosphonoacetonitrile occurred effectively to give compound **7** in 95% yield. The ^1H NMR spectrum of **7** showed it to be a mixture of two isomers in a ratio of ca. 6:1, although it is unknown whether the mixture consists of the stereoisomers of olefin or the rotamers of amide (Scheme 2).

When a solution of anilide **7** in boiling benzene was treated slowly with a mixture of Bu_3SnH and AIBN, the 3,3-disubstituted oxindole (±)-**8** was obtained in 89% yield as a sole product. The spectral properties of (±)-**8** thus obtained were identical to the reported values.[5h] In the light of the previous work on other Bu_3SnH-mediated aryl radical cyclizations of anilides, the present result is of great interest. Thus, the anilides **9** having a methyl substituent on the carbon α to



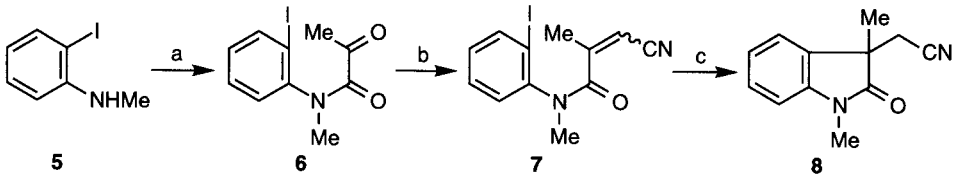
X = NMe: Physostigmine (**1**)
X = O: Physovenine (**2**)

3: X = CN
4: X = CO_2Me

Scheme 1.

Keywords: anilides; cyclization; indolines/indolinones; radicals and radical reactions.
* Corresponding author. Tel.: +81-76-234-4474; fax: +81-76-234-4476; e-mail: ishibashi@dbs.p.kanazawa-u.ac.jp

0040–4020/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(00)00051-X



Scheme 2. (a) MeCOCOCl, pyridine, CH_2Cl_2; (b) $(EtO)_2P(O)CH_2CN$, BuLi, THF, −78°C to r.t.; (c) Bu_3SnH, AIBN, benzene, reflux.

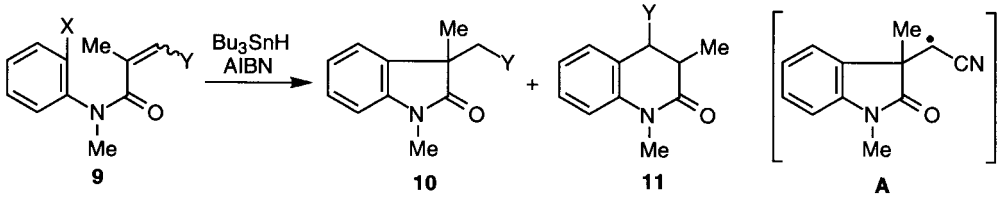
the carbonyl group were reported to usually provide mixtures of the 5-*exo* and the 6-*endo* cyclization products **10** (major) and **11** (minor).[9] This is also the case for cyclizations with Co(II)–RMgBr,[10a] SmI_2[10b] or Co(I)–salen complex.[11] The exclusive formation of oxindole **8** from **7** may be rationalized by assuming that the radical intermediate **A** formed by 5-*exo* cyclization of the aryl radical generated from **7** is highly stabilized by an adjacent nitrile group (Scheme 3).

Given the success in forming oxyindole **8** from the 5-*exo* selective aryl radical cyclization of **7**, we then applied the method to the synthesis of the key intermediate (±)-**3** for (±)-physostigmine.

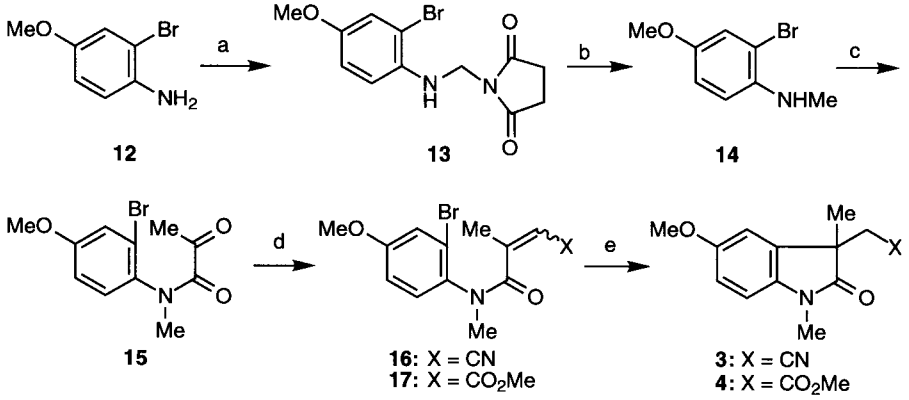
The starting 2-bromo-4-methoxyaniline (**12**)[12] was prepared by treating *p*-anisidine with Br_2 in AcOH in 44% yield. This compound was then converted into the corresponding *N*-methyl derivatives (**14**) (Scheme 4) using a procedure similar to that reported for the synthesis of **8** from *o*-iodoaniline.[7] Thus, condensation of **12** with formaldehyde and succinimide in boiling EtOH gave **13** in 84% yield, which was reduced by $NaBH_4$ in DMSO to give **14** in 91% yield. Sequential treatment of **14** with pyruvyl chloride followed by diethylphosphonoacetonitrile furnished the requisite radical precursor **16**. This compound was then treated with Bu_3SnH and AIBN in boiling benzene to give the expected oxindole (±)-**3** in 98% yield.

Next, we examined the cyclization of the ester congener **17**, which was prepared by reaction of **15** with methyl dimethylphosphonoacetate in 88% yield (Scheme 4). When a boiling solution of **17** in benzene was treated with Bu_3SnH and AIBN, oxindole-3-acetic ester (±)-**4**, whose physical data were identical with those of the literature values,[13] was obtained in 87% yield as a sole product. The exclusive formation of (±)-**4** from **17** might also be ascribed to a radical stabilizing effect of the ester group similar to that of the cyano group for the radical intermediate **A**. Since compound (±)-**4** has already been converted into (±)-physovenine (**2**),[13] the whole sequence of the reactions described herein means in a formal sense a synthesis of (±)-physovenine.

Thus, we revealed that anilides **16** and **17** having a nitrile or an ester group at the terminus of their acryloyl group underwent aryl radical cyclization in a 5-*exo* manner with a high degree of efficiency to enable a straightforward synthesis of the key intermediates (±)-**3** and (±)-**4** for (±)-physostigmine[14,15] and (±)-physovenine.[16,17]



Scheme 3.



Scheme 4. (a) 36% HCHO, succinimide, EtOH, reflux; (b) $NaBH_4$, DMSO, 50°C; (c) MeCOCOCl, pyridine, CH_2Cl_2; (d) $(EtO)_2P(O)CH_2CN$ (for **16**), $(MeO)_2P(O)CH_2CO_2Me$ (for **17**), BuLi, THF, −78°C to r.t.; (e) Bu_3SnH, AIBN, benzene, reflux.

Experimental

Melting points are uncorrected. IR spectra were recorded with a shimadzu FTIR-8100 spectrophotometer. ^{1}H NMR spectra were measured on a JEOL JNM-GSX 500 (500 MHz), a JEOL JNM-EX 270 (270 MHz), or a Hitachi R-1200 (60 MHz) spectrometer for solutions in $CDCl_3$. δ values quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102 instrument. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

Pyruvyl chloride. Dichloromethyl methyl ether (8.34 g, 72.5 mmol) was added dropwise to pyruvic acid (6.32 g, 71.8 mmol) at room temperature, and the mixture was heated at 50°C for 30 min. The reaction mixture was distilled to give pyruvyl chloride (4.02 g, 53%), bp 50–52°C/130 mmHg (lit.[8] bp 53°C/126 mmHg).

2-Iodo-*N*-methylpyruvanilide (6). A solution of pyruvyl chloride (53.4 mg, 0.50 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise to a solution of 2-iodo-*N*-methylaniline (**5**)[7] (79.9 mg, 0.36 mmol) and pyridine (47.8 mg, 0.57 mmol) in CH_2Cl_2 (1.5 ml) at 0°C, and the mixture was stirred at room temperature for 2 h. A saturated aq. $NaHCO_3$ solution (30 ml) was added to the reaction mixture and the whole was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give **6** (98.7 mg, 91%), mp 88–90°C (from hexane–AcOEt): IR ($CHCl_3$) ν 1725, 1655 cm^{-1}; ^{1}H NMR (60 MHz) δ 2.35 (3 H, s), 3.25 (3 H, s), 6.70–7.60 (3 H, m, ArH), 7.85 (1 H, d, *J*=8.0 Hz). Anal. Calcd for $C_{10}H_{10}INO_2$: C, 39.63; H, 3.33; N, 4.62. Found: C, 39.54; H, 3.24; N, 4.48.

2′-Iodo-*N*-methyl-3-cyano-2-methylpropenanilide (7). BuLi (1.57 M hexane solution) (1.53 ml, 2.41 mmol) was added to a solution of diethylphosphonoacetonitrile (417 mg, 2.45 mmol) in THF (6 ml) during 3 min at −78°C, and the mixture was stirred at the same temperature for 20 min. To this solution was added a solution of **6** (532 mg, 1.75 mmol) in THF (6 ml), and the mixture was stirred at room temperature for 2 h. A saturated aq. NH_4Cl solution (50 ml) was added to the reaction mixture, and the whole was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **7** (542 mg, 95%) as an oily mixture of two isomers in a ratio of ca. 6:1: IR ($CHCl_3$) ν 2225, 1655 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.93 (1/7×3 H, d, *J*=1.7 Hz), 2.07 (6/7×3 H, d, *J*=1.0 Hz), 3.26 (6/7×3 H, s), 3.32 (1/7×3 H, s), 5.12 (1/7 H, q, *J*=1.7 Hz), 5.46 (6/7 H, q, *J*=1.0 Hz), 7.05–7.66 (3 H, m), 7.90 (1 H, dd, *J*=7.9, 1.7 Hz). HRMS Calcd for $C_{12}H_{11}IN_2O$: 325.9916. Found: 325.9918.

2,3-Dihydro-1,3-dimethyl-2-oxo-1*H*-indole-3-acetonitrile (8). To a boiling solution of **7** (158.2 mg, 0.485 mmol) in benzene (48 ml) was added dropwise a solution of Bu_3SnH (189 mg, 0.65 mmol) and AIBN (10.1 mg, 0.06 mmol) in benzene (24 ml) via a syringe during 1 h. After evaporation of the solvent, Et_2O (50 ml) and an 8% aq. KF (50 ml) solution were added to the residue, and the whole was vigorously stirred at room temperature for 1 h. The organic phase was separated and the aqueous phase was further extracted with Et_2O. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give **8**[5h] (86.3 mg, 89%) as an oil: IR ($CHCl_3$) ν 2255, 1715 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.53 (3 H, s), 2.56 (1 H, d, *J*=16.5 Hz), 2.85 (1 H, d, *J*=16.5 Hz), 3.25 (3 H, s), 6.91 (1 H, d, *J*=7.3 Hz), 7.14 (1 H, td, *J*=7.3, 1.0 Hz), 7.36 (1 H, td, *J*=7.3, 1.0 Hz), 7.48 (1 H, d, *J*=7.3 Hz).

2-Bromo-4-methoxyaniline (12). To a solution of *p*-anisidine (5.0 g, 40.6 mmol) in AcOH (125 ml) was added dropwise a solution of bromine (6.51 g, 40.7 mmol) in AcOH (125 ml) during 2.5 h. After the solvent had been evaporated off, a 2 N aq. NaOH solution (100 ml) was added to the residue, and the whole was extracted with AcOEt. The extract was washed successively with an aq. $Na_2S_2O_3$ solution (50 ml) and brine (50 ml), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 7:1) to give **12**[12] (3.58 g, 44%) as an oil: ^{1}H NMR (270 MHz) δ 3.72 (3 H, s), 3.75 (2 H, br s), 6.70 (1 H, d, *J*=6.3 Hz), 6.73 (1 H, dd, *J*=6.3, 2.0 Hz), 6.99 (1 H, d, *J*=2.0 Hz).

***N*-(2-Bromo-4-methoxyanilinomethyl)succinimide (13).** To a solution of **12** (2.0 g, 9.9 mmol) in EtOH (15 ml) were added successively a formaldehyde solution (36% w/w) (1.0 ml) and succinimide (1.18 g, 11.95 mmol), and the mixture was heated at reflux for 4 h. An additional formaldehyde solution (0.5 ml) was added to the mixture, and the mixture was further heated at reflux for 1.5 h. After cooling the mixture at 0°C, the precipitates were collected by suction to give **13** (1.908 g). The filtrate was concentrated, and the residue was chromatographed on silica gel ($CHCl_3$) to give an additional **13** (711 mg, total 84% yield), mp 123–124°C (from EtOH–H_2O): IR ($CHCl_3$) ν 3425, 1705 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.67 (4 H, s), 3.72 (3 H, s), 5.00 (2 H, d, *J*=7.3 Hz), 5.10 (1 H, t, *J*=7.3 Hz), 6.80 (1 H, dd, *J*=9.0, 2.7 Hz), 7.02 (1 H, d, *J*=9.0 Hz), 7.03 (1 H, d, *J*=2.7 Hz). Anal. Calcd for $C_{12}H_{13}BrN_2O_3$: C, 46.03; H, 4.18; N, 8.95. Found: C, 45.87; H, 4.20; N, 8.82.

2-Bromo-4-methoxy-*N*-methylaniline (14). To a solution of **13** (233.8 mg, 0.75 mmol) in dimethyl sulfoxide (0.7 ml) was added sodium borohydride (28.7 mg, 0.76 mmol) by portions, and the mixture was stirred at 120°C for 30 min. After cooling the mixture, water (30 ml) was added, and the whole was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 7:1) to give **14** (146.4 mg, 91%) as an oil: IR ($CHCl_3$) ν 3430, 1515 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.83 (3 H, s), 3.71 (3 H, s), 3.95 (1 H, br s), 6.55 (1 H, d, *J*=8.9 Hz), 6.80 (1 H, dd, *J*=8.9, 3.0 Hz), 7.04 (1 H, d, *J*=3.0 Hz). Anal. Calcd for $C_8H_{10}BrNO$: C, 44.47; H, 4.66; N, 6.48. Found: C, 44.57; H, 4.74; N, 6.29.

2-Bromo-4-methoxy-*N*-methylpyruvanilide (15). Using a procedure similar to that described above for the preparation

of **6**, aniline **14** (127.6 mg, 0.59 mmol) was treated with pyruvyl chloride (92.3 mg, 0.87 mmol) in the presence of pyridine (81.6 mg, 0.97 mmol) in CH_2Cl_2 (3 ml). After work-up, the crude material was chromatographed on silica gel (hexane–AcOEt, 2:1) to give **15** (157.2 mg, 93%) as an oil: IR ($CHCl_3$) ν 1720, 1655 cm^{-1}; ^1H NMR (270 MHz) δ 2.30 (3 H, s), 3.24 (3 H, s), 3.81 (3 H, s), 6.85 (1 H, dd, J=8.6, 3.0 Hz), 7.12 (1 H, d, J=3.0 Hz), 7.22 (1 H, d, J=8.6 Hz). Anal. Calcd for $C_{11}H_{12}BrNO_3$: C, 46.18; H, 4.23; N, 4.90. Found: C, 45.94; H, 4.27; N, 4.76.

2′-Bromo-4′-methoxy-*N*-methyl-3-cyano-2-methylpropenanilide (16). Using a procedure similar to that described above for the preparation of **7**, diethylphosphonoacetonitrile (90.1 mg, 0.53 mmol) was treated with BuLi (1.57 M hexane solution) (0.3 ml, 0.47 mmol) and then with compound **15** (107.1 mg, 0.38 mmol). After work-up, the crude material was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **16** (82.8 mg, 72%) as an oily mixture of two isomers in a ratio of ca. 9:5: IR ($CHCl_3$) ν 2225, 1650 cm^{-1}; ^1H NMR (270 MHz) δ 1.93 (5/14×3 H, d, J=1.7 Hz), 2.05 (9/14×3 H, d, J=1.3 Hz), 3.23 (9/14×3 H, s), 3.29 (5/14×3 H, s), 3.83 (5/14×3 H, s), 3.84 (9/14×3H, s), 5.11 (5/14 H, q, J=1.7 Hz), 5.40 (9/14 H, q, J=1.3 Hz), 6.80–7.20 (2+9/14 H, m), 7.52 (5/14 H, d, J=8.6 Hz). Anal. Calcd for $C_{13}H_{13}BrN_2O_2$: C, 50.51; H, 4.24; N, 9.06. Found: C, 50.29; H, 4.35; N, 8.90.

Methyl 3-(2′-Bromo-4′-methoxyphenyl-*N*-methylcarbamoyl)-3-methyl-2-butenoate (17). Using a procedure similar to that described above for the preparation of **7**, methyl dimethylphosphonoacetate (84.5 mg, 0.46 mmol) was treated with BuLi (1.50 M hexane solution) (0.3 ml, 0.45 mmol) and then with compound **15** (100.1 mg, 0.35 mmol). After work-up, the crude material was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **17** (105.3 mg, 88%) as an oily mixture of three isomers in a ratio of ca. 10:5:3: IR ($CHCl_3$) ν 1715, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 1.85 (10/18×3 H, d, J=1.5 Hz), 2.14 (5/18×3 H, d, J=1.5 Hz), 2.22 (3/18×3 H, d, J=1.5 Hz), 3.16 (3/18×3 H, s), 3.23 (5/18×3 H, s), 3.28 (10/18×3 H, s), 3.63 (5/18×3 H, s), 3.76 (13/18×3 H, s), 3.81 (3 H, s), 5.55 (10/18 H, q, J=1.5 Hz), 5.87 (3/18 H, q, J=1.5 Hz), 5.90 (5/18 H, q, J=1.5 Hz), 6.70–7.60 (3 H, m). HRMS Calcd for $C_{14}H_{16}^{79}BrNO_4$: 341.0263. Found: 341.0275.

2,3-Dihydro-5-methoxy-1,3-dimethyl-2-oxo-1*H*-indole-3-acetonitrile (3). Using a procedure similar to that described above for the preparation of **8**, compound **16** (99.2 mg, 0.32 mmol) was treated with Bu_3SnH (114.6 mg, 0.39 mmol) in the presence of AIBN (6.4 mg, 0.04 mmol) in benzene (48 ml). After work-up, the crude material was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **3** (72.3 mg, 98%), mp 71–73°C (from Et_2O–hexane) (lit.[5h] mp 70–72°C): IR ($CHCl_3$) ν 2255, 1710 cm^{-1}; ^1H NMR (270 MHz) δ 1.52 (3 H, s), 2.55 (1 H, d, J=16.5 Hz), 2.84 (1 H, d, J=16.5 Hz), 3.22 (3 H, s), 3.82 (3 H, s), 6.81 (1 H, d, J=8.6 Hz), 6.86 (1 H, dd, J=8.6, 2.0 Hz), 7.09 (1 H, d, J=2.0 Hz). The ^1H NMR spectral data were identical with those reported.[5f]

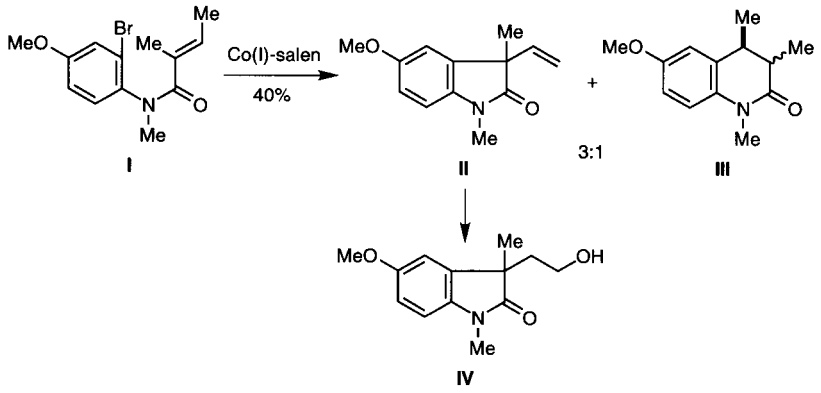
Methyl 2,3-dihydro-5-methoxy-1,3-dimethyl-2-oxo-1*H*-indole-3-acetate (4). Using a procedure similar to that described above for the preparation of **8**, compound **17** (105.3 mg, 0.31 mmol) was treated with Bu_3SnH (114.2 mg, 0.39 mmol) in the presence of AIBN (6.2 mg, 0.04 mmol) in benzene (45 ml). After work-up, the crude material was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **4** (70.1 mg, 87%), mp 83–84°C (from AcOEt–petroleum ether) (lit.[13] mp 83–84°C): IR ($CHCl_3$) ν 1740, 1700 cm^{-1}; ^1H NMR (270 MHz) δ 1.37 (3 H, s), 2.82 (1 H, d, J=16.5 Hz), 3.00 (1 H, d, J=16.5 Hz), 3.23 (3 H, s), 3.48 (3 H, s), 3.79 (3 H, s), 6.75–6.85 (3 H, m).

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

References

1. Takano, S.; Ogasawara, K. *The Alkaloids* **1989**, *36*, 225.
2. Brossi, A. *J. Med. Chem.* **1990**, *33*, 2311.
3. Grieg, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3.
4. Julian, P. L.; Pikl, J. *J. Am. Chem. Soc.* **1935**, *57*, 563 (see also p. 755).
5. For syntheses of racemic and optically acitive **3** and their 5-alkoxy derivatives, see (a) Robinson, B. *J. Chem. Soc.* **1965**, 3336. (b) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872. (c) Yu, Q.-S.; Luo, W.-M.; Li, Y.-Q.; Brossi, A. *Heterocycles* **1993**, *36*, 1279. (d) Yu, Q.-S.; Lu, B.-Y.; Pei, X.-F. *Heterocycles* **1994**, *39*, 519. (e) Pei, X.-F.; Bi, S. *Heterocycles* **1994**, *39*, 357. (f) Pallavicini, M.; Valoti, E.; Villa, L.; Lianza, F. *Tetrahedron: Asymmetry* **1994**, *5*, 111. (g) Pei, X.-F.; Brossi, A. *Heterocycles* **1995**, *41*, 2823. (h) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron* **1996**, *52*, 5339.
6. Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 1709. See also Refs. 5b, 5e and 5f.
7. Kihara, M.; Iwai, Y.; Nagao, Y. *Heterocycles* **1995**, *41*, 2279.
8. Ottenheijm, H. C. J.; de Man, J. H. M. *Synthesis* **1975**, 163.
9. Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115; Clark, A. J.; Jones, K. *Tetrahedron Lett.* **1989**, *30*, 5485; Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1992**, 1766; Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673; Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron Lett.* **1998**, *39*, 2331; Jones, K.; Brunton, S. A.; Gosain, R. *Tetrahedron Lett.* **1999**, *40*, 8935.
10. (a) Clark, A. J.; Davies, D. I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* **1994**, 41. (b) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949.
11. Jones reported that anilide **I**, upon treatment with Co(I)–salen complex, gave a mixture of the 5-*exo* cyclization product **II** and the 6-*endo* cyclization product **III** in a ratio of 3:1 and in 40% combined yield.[12] The product **II** was converted into **IV**, the intermediate for the synthesis of physovenine (**2**) (Scheme 5).
12. Clark, A. J.; Jones, K. *Tetrahedron* **1992**, *48*, 6875.
13. Luo, Y.-L.; Yu, Q.-S.; Chrisey, L.; Brossi, A. *Heterocycles* **1990**, *31*, 283.
14. For total or formal syntheses of (−)-physostigmine, see (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem Pharm. Bull.* **1982**, *30*, 2641. (b) Takano, S.; Moriya, M.; Iwabuchi, Y.;



Scheme 5.

Ogasawara, K. *Chem. Lett.* **1990**, 109. (c) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982. (d) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705. (e) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566. (f) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363. (g) Node, M.; Hao, X.-J.; Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715. (h) Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951. (i) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949. (j) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. See also Ref. 5b.

15. For recent total or formal syntheses of (±)-physostigmine by way of the intermediates other than **3**, see (a) Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559. (b) Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 3007.
16. For total syntheses of (−)-physovenine, see Refs. 14c and 14j.
17. For total syntheses of (±)-physovenine, see Refs. 13 and 15b.