JOC Article

Application of Vicarious Nucleophilic Substitution to the Total Synthesis of *dl*-Physostigmine

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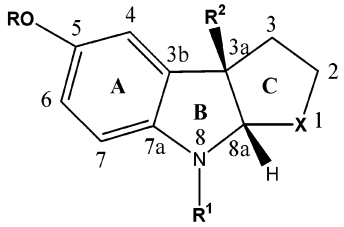
A concise, highly efficient formal total synthesis of *dl*-physostigmine is described, using a relatively simple method that should be adaptable to the synthesis of homologous members of this type of alkaloid. The key step in the synthesis is a new vicarious nucleophilic substitution reaction between *p*-nitroanisole and a C-silylated derivative of *N*-methylpyrrolidinone. Subsequent conversion of the initial adduct to the tricyclic framework of physostigmine follows a well-established protocol and provides the key intermediate **8** in high yield. The vicarious nucleophilic substitution reaction has also been extended to six-membered lactams, with encouraging results.

Introduction

Alkaloids isolated from the African calabar beans have shown encouraging pharmacological properties.[1] The simplest members of this family of compounds are (−)-physostigmine (**1**) and (−)-physovenine (**2**) (Figure 1). (−)-Physostigmine (***1***) was first isolated[2] from calabar beans as the principal base in 1864. It was later isolated from *Streptomyces* as an insecticidal compound. This type of alkaloid ring system has also been found in marine alkaloids such as the flustramines from broyoza *Flustra foliacea*.

The well-known pharmacological effects of (−)-physostigmine (**1**) are based on inhibiton of acetylcholinesterase.[3] (−)-Physostigmine (**1**) is used clinically in the treatment of glaucoma[4] and myasthenia gravis[5] and for protection against organophosphate poisioning.[6] It has also been reported that oral or intravaneous administration of (−)-physostigmine (**1**) significantly improved memory in patients with Alzheimer's disease;[7] however, opposite results have also been reported.[8]

Brossi and co-workers[9] have examined the anticholinesterase activity of natural (−) and unnatural (+) enantiomers of physostigmine (**1**) along with other related compounds. It was found that the unnatural (+)-antipode inhibits acetylcholinesterase from electric eel considerably less than the naturally occurring (−)-**1**, but



R= $CONHCH_3$, R^1= R^2= CH_3
X= NCH_3 : Physostigmine, **1**
X= O : Physovenine, **2**

FIGURE 1. Basic ring system for alkaloids isolated from calabar beans, *Streptomyces*, and *Flustra foliacea*.

the unnatural isomer exhibits lower toxicity and blocks the open channel of the nicotinic acetylcholine receptor.[10] Moreover, the unnatural antipode was found to prevent organophosphate-induced subjunctional damage at the neuromuscular synapse by a mechanism not related to cholinesterase carbamoylation.[11]

The first total synthesis[12] of (−)-physostigmine (**1**) was achieved by Julian and Pikl in 1935. Since then a

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[‡] Department of Pharmacological Sciences.

(1) For a review, see: Hino, T.; Nakagawa, M. *Alkaloids* **1989**, *34*, 1−75.
(2) Salway, A. H. *J. Chem. Soc.* **1911**, *99*, 2143−2148.
(3) Koelle, G. B. *The Pharmacological Basis of Therapeutics*, 5th ed.; Goodman, R. S., Gilman, A., Eds.; Macmillan: New York, 1975; pp 445−466.
(4) Axelsson, U. *Acta Ophthalmol.* **1969**, *47*, 1057−1067.
(5) Walker, M. B. *Proc. R. Soc. Med.* **1934**, *1*, 1200.
(6) Deshpande, S. S.;Viana, G. B.; Kauffman, F. C.; Rickett, D. L.; Albuquerque, E. X. *Fundam. Appl. Toxicol.* **1986**, *6*, 566−577.
(7) (a) Mohs, R. C.;Davis, B. M.; Johns, C. A.; Mathé, A. A.; Greenmald, B. S.; Horvath, T. B.; Davis, K. L. *Am. J. Psychiatry* **1985**, *142*, 28−33 and references therein. (b) Mohs, R. C.; Davis, B. M.; Greenmald, B. S.; Mathé, A. A.; Johns, C. A.; Horvath, T. B.; Davis, K. L. *J. Am. Geriatr. Soc.* **1985**, *33*, 749−757 and references therein. (c) Beller, S. A.; Overall, J. E.; Swann, A. C. *Psychopharmacology* **1985**, *87*, 147−151 and references therein.
(8) (a) Caltagirone, C.; Gainotti, G.; Masullo, C. *Int. J. Neurosci.* **1982**, *16*, 247−249 and references therein. (b) Jatkowitz, S. *Ann. Neurol.* **1983**, *14*, 690 and references therein. (c) Agnoli, A.; Martucci, N.; Manna, V.; Conli, L.; Fioravanti, M. *Clin. Neuropharmacol.* **1983**, *6*, 311.
(9) Brossi, A.;Schönenberger, B.; Clark, O. E.; Ray, R. *FEBS Lett.* **1986**, *201*, 190−192.
(10) Yu, R.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 1709−1712.
(11) Kawabuchi, M.;Boyne, A. F.; Despande, S. S.; Cintra, W. M.; Brossi, A.; Albuquerque, E. X. *Synapse (NY)* **1988**, *2*, 139−147.
(12) Julian, P. L.; Pikl, J. *J. Am. Chem. Soc.* **1935**, *57*, 563−566.

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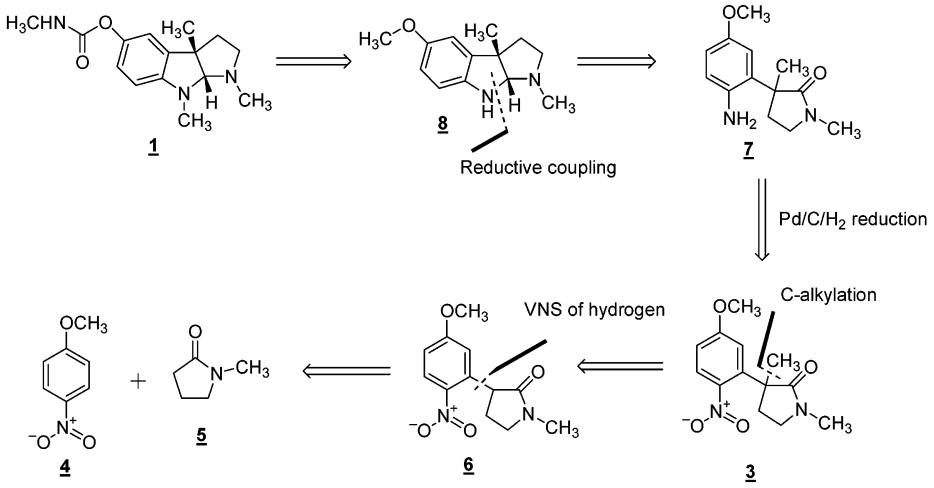
SCHEME 1. Retrosynthetic Analysis of Physostigmine



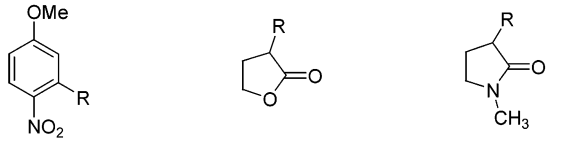
significant number of total syntheses[13] of this alkaloid have been reported. Unfortunately, a practical and efficient synthesis for this seemingly simple molecule has not been reported to date.

Results and Discussion

In reviewing the known methods for the synthesis of physostigmine we selected the *N*-methylpyrrolidinone (**7**) first reported by Takano and co-workers[14] in 1982, as the most desirable target. Although their synthesis (which is enantioselective) produces **7** in only low yield, completion of the total synthesis from **7** onward is simple and efficient. We thought that at least the racemic form of **7** might be synthesized by a more efficient three-step procedure starting from the commercially available and inexpensive *p*-nitroanisole (**4**) and *N*-methylpyrrolidinone (**5**), as indicated in the retrosynthetic analysis (Scheme 1).

The key to this proposed synthesis lies in coupling the two rings to obtain compound **6**. However, few examples of C-arylation[15] of a cyclic amide moiety have been reported in the literature. Stewart and co-workers[15a] have utilized an excess of strong base (lithium isopropylcyclohexylamide, 3.2−8.0 equiv) in the presence of aryl halides for the C3-arylation of ***5***. The reaction was thought to follow the benzyne mechanism, because it led to two isomeric products (yields 16−50%) in case of nonsymmetric substituted aryl halides. On the other hand, Alonso and co-workers[15b] have used 1-alkyl-2-pyrrolidinone enolate ions as nucleophiles to react with aryl halides under UV irradiation. The reaction apparently follows an $S_{RN}1$ mechanism and leads to a single product (yields 37−60%) for each of the three aryl halides that were examined.

Although no examples of the use of Pd-chemistry in the intermolecular construction of the physostigmine framework are known, intramolecular Pd-catalyzed chemistry has been utilized successfully by Overman[13b] (Heck reaction) and Zhang[13j] (C-arylation of acyclic amide) for the synthesis of (−)-physostigmine and *dl*-physovenine, respectively. Extension to cyclic amides of the intermolecular Pd-catalyzed C-arylation of ketones and esters, first developed by the groups of Buchwald[16] and Hartwig,[17] appeared an attractive possibility. The nitroarenes **13** and **14** were selected to examine this approach, and compounds **15**, **16**, **17**, and *5* were used as substrates. Despite significant variations (a) in the base that was used or (b) in the Pd/L system that was employed, we failed to achieve the desired reaction.



At this point, the "vicarious" nucleophilic substitution (VNS) of hydrogen developed by Makosza and co-workers[18] appeared to be the next best available methodology to achieve the needed carbon assembly. 1-Methyl-3-phenylsulfanylpyrrolidin-2-one[19] (**9**) was chosen initially as the nucleofuge. However, **9** was found to be unstable under the strong basic conditions needed for the VNS reaction, and this led only to the formation of thiophenol

(13) For a full discussion of synthetic aproaches to physostigmine before 1989, see: (a) Takano, S.; Ogasawara, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 225−251. For recent syntheses, see: (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (c) Kawahara, M.; Nishida, A.; Nakagawa, M.; *Org. Lett.* **2000**, *2*, 675−678. (d) Ishibashi, H.; Kobayashi, T.; Machida, N.; Tamura, O. *Tetrahedron* **2000**, *56*, 1469−1473. (e) Nakagawa, M.; Kawahara, M. *Org. Lett.* **2000**, *2*, 953−955. (f) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757−2759. (g) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049−1052. (h) Morales-Rios, M. S.; Santos-Sanchez, N. F.; Joseph-Nathan, P. *J. Nat. Prod.* **2002**, *65*, 136−141. (i) Robinson, B. *Heterocycles* **2002**, *57*, 1327−1352. (j) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363−1365.

(14) The only two examples noted in the literature are those reported by (a) Stewart, J. D.; Fields, S. C.; Kochhar, K. S.; Pinnick, H. W. *J. Org. Chem.* **1987**, *52*, 2110−2113. (b) Alonso, R. A.; Rodriguez, C. H.; Rossi, R. A. *J. Org. Chem.* **1989**, *54*, 5983−5985.

(15) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641−2643.

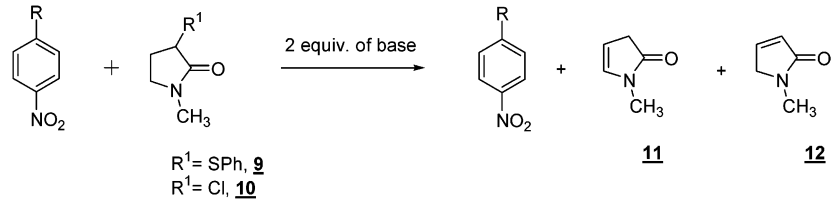
(16) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109.

(17) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383.

(18) Maksoza, M.; Wojceiechowski, K. *Liebigs Ann./Reueil* **1997**, 1805−1816 and references therein.

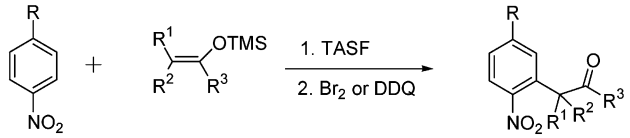
(19) Zoretic, P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587−3589.

SCHEME 2[a]



[a] Different cases investigated were R = OCH_3, NO_2, Cl, CH_3.

SCHEME 3



and the pyrrolenones **11** and **12** (detected in the reaction mixture by ^{1}H NMR) (Scheme 2). Again all of our attempts to use 3-chloro-1-methyl-2-pyrrolidinone[20] (**10**) in place of **9** met with the same fate. Also, during the course of attempting these VNS reactions it was observed that under a variety of conditions the color of the mixtures turned dark blue on the addition of the base. Such color changes are known to be associated with acid−base reactions of the nitronate ion, which lead to the destruction of the nitroarene.[21]

An alternative approach that proved to be more successful was the fluoride-assisted nucleophilic addition of enol silyl ethers to aromatic nitro compounds (Scheme 3) developed by RajanBabu and co-workers.[22] Oxidation of the resulting intermediate nitronate gives α-nitroaryl carbonyl compounds. Formally, this is a variation of the VNS of hydrogen, but because the C-arylation proceeds under nonbasic reaction conditions, it seemed likely that the destructive acid−base reactions noted above could be avoided.

The α-silylated derivative **18** of 1-methyl-2-pyrrolidinone (**5**) needed to follow this strategy was prepared in high yield by the method of Kramarova and co-workers.[23] It is well-established[23] in the literature that the cleavage of such α-silyl carbonyl compounds using fluoride anion leads to the generation of stabilized enolate anions. Indeed Kramarova and co-workers,[23] in studying the reactivity of 1-methyl-3-trimethylsilyl-2-pyrrolidinone (**18**), found that it reacts easily with a series of electrophilic reagents to give α-substituted pyrrolidin-2-ones. Following the exact experimental procedure by Rajan-Babu and co-workers,[22] the reaction of the silyl compound **18** with *p*-nitrotoluene (**19**) took place smoothly to give the coupled product **20** but in only 11% isolated yield. The remainder was the unreacted starting material. Better results were obtained in the case of *p*-nitroanisole (**4**) where a 50% isolated yield of compound **6** was obtained, again the remanider being unreacted starting material. Modification of the reaction conditions then led to more satisfactory results. When *p*-nitroanisole (**4**) was treated with excess of the silyl compound **18** in the presence of TASF at − 78 °C and the reaction mixture was then allowed to warm to room temperature and then stirred for 15 h before oxidizing the intermediate nitronate with DDQ, the expected product **6** was now obtained in 85% yield (Scheme 4). Attempts to use tetrabutylammonium fluoride (TBAF) instead of TASF failed. It is likely that the water normally present in TBAF hydrolyzes the silyl compound **18** prior to the Micheal reaction that leads to the nitronate ion. An annoying feature of TASF is that it is hydroscopic and in an attempt to avoid this the use of tetrabutylammonium triphenyldifluorosilicate (TBAT)[24] as a source of F^- was examined. Unfortunately, with this reagent a complex reaction mixture was obtained with only a partial consumption (25%) of the starting material.

We also examined the use of bromine in the place of DDQ as the oxidant in the second step of the process. This also proved to be satisfactory, although the desired product **6** (∼60% yield) was contaminated with 15% of 3-(6′-bromo-5′-methoxy-2′-nitro-2′,4′-cyclohexadienyl)-1-*N*-methylpyrrolidin-2-one (**31**). Nevertheless this did not constitute a problem because subsequent treatment with Et_3N led to **6** in approximately 73% overall yield

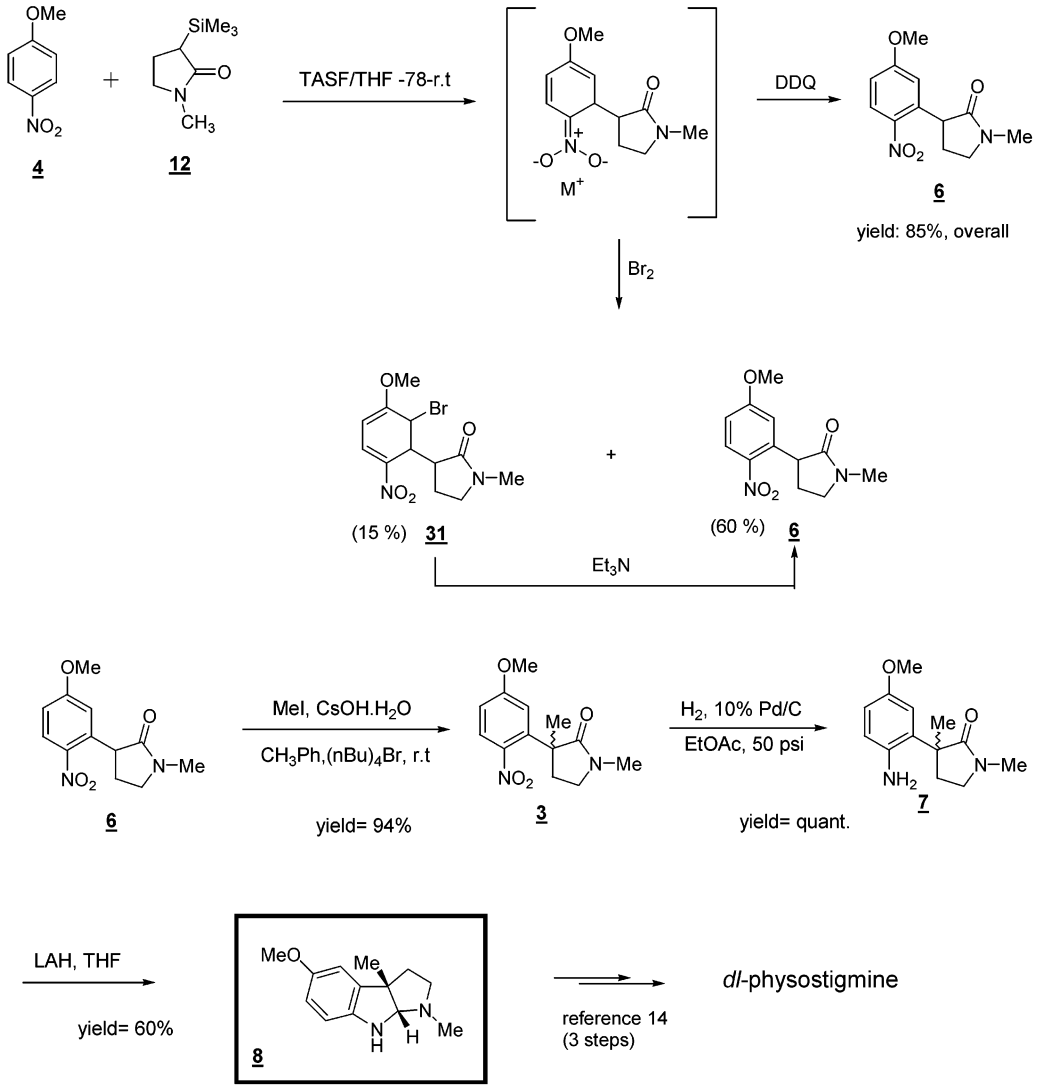
In continuing with the synthesis of **1**, an ion-pair-mediated reaction using the phase-transfer catalysis (PTC) method was employed to achieve methylation of ***6***. When the latter was treated with methyl iodide using tetrabutylammonium bromide as the catalyst, compound ***3*** was obtained in 95% yield (Scheme 4). Its structure was confirmed by X-ray crystallographic analysis.[27]

Encouraged by this result we attempted an asymmetric methylation using the dihydrocinchodinium salt developed by Corey and co-workers,[28] as the chiral catalyst for the alkylation reaction under PTC conditions. In our case the catalyst failed to give any selectivity whatsoever (as determined by chiral HPLC of compound **7** and the lack of optical rotation in the subsequent tricyclic compound **8**). A second attempt at enantioselective alkylation was made using a chiral tetradentate lithium amide developed by Matsuo and co-workers[29] as the base. However, in this case no alkylation occurred at all as judged by TLC analysis.

Compound **3** on catalytic reduction with 10% Pd/C in

(20) Vedejs E.; Galante R. J.; Goekjian P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3613−3622.
(21) Paradasi, C.; Scorrano, G. *Acc. Chem. Res.* **1999**, *32*, 958−968.
(22) RajanBabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473−5483.
(23) Kramarova, E. P.; Anisomova, N. A.; Baukov, Y.; I. *Zh. Obshch. Khim.* **1991**, *61*, 1406−1413.
(24) Pilcher, A. S.;Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166−5167.
(25) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 881−884.
(26) Maksoza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494−1499.
(27) Crystal data is available in Supporting Information.
(28) (a) Corey, E. J.;Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (b) Corey, E. J.; Bo, Y.; Busch-Peterson, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001.
(29) Matsuo, J.;Kobayashi, S.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 9723−9726.

SCHEME 4. Formal Total Synthesis of *dl*-Physostigmine



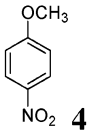
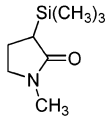
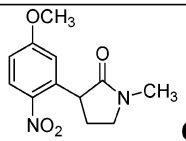
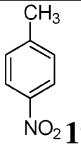
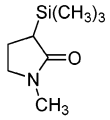
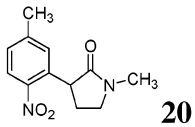
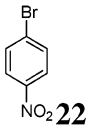
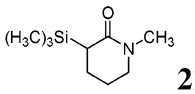
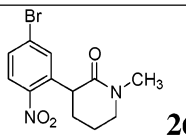
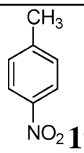
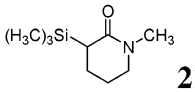
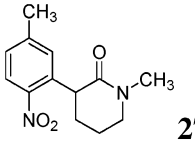
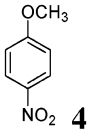
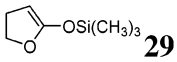
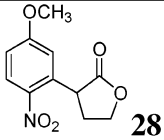
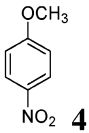
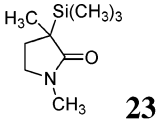
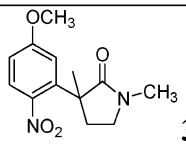
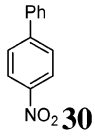
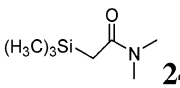
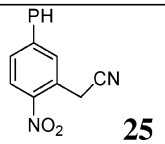
EtOAc then provided in quantitative yield the aminoarene **7**, whose spectroscopic data were identical to those previously reported in the literature.[30] Although the synthesis of compound **7** formally completes a new short total synthesis of *dl*-physostigmine **1**, we repeated the reductive cyclization of the amino compound **7** using lithium aluminum hydride. As reported by Takano and co-workers[14] the required tricyclic intermediate **8** was obtained in 60% yield. The final three steps to obtain **1** are efficient and well-established.[14]

The lack of a general method in the literature for the C-arylation of cyclic amides prompted us to explore the application of the VNS reaction to other systems. In this regard, the silyl derivative of the six-membered lactam **21** smoothly underwent coupling with *p*-nitrotoluene (**19**) and *p*-bromonitrobenzene (**22**) (entries 3 and 4, Table 1). As has been observed by RajanBabu and co-workers,[22] the halo groups of nitroarenes are stable under these reaction conditions (entry 3, Table 1). By contrast reaction of the silyl derivative of the seven-membered lactam, namely, *N*-methyl caprolactam, failed with several different nitroarenes to give any product on attempted reaction whatsoever. However, as expected, the coupling reaction itself is sensitive to steric effects. When the silyl compound **23** was allowed to react with *p*-nitroanisole (entry 6, Table 1), in comparison with the same reaction of **3** a dramatic decrease in the yield was observed (to around 15% as judged by ^{1}H NMR and GC/MS analysis of the crude product). Despite this low yield it is worth noting that the reaction does lead to the formation of a carbon quaternary center in one step. Interestingly and in constrast to the intramolecular case,[13j] when the reaction was applied to the acyclic amide **24**,[24] only compound ***25***[25] was isolated as the sole product (entry 7, Table 1).

In summary, we have developed a new procedure for the C-arylation of cyclic amides, application of which to the formal total synthesis of (±)-physostigmine leads to a substantially improved and much shorter route to this biologically important natural product. This approach should also provide easy access to other natural products having a similar framework and is versatile enough to allow significant variations in the basic structure of physostigmine itself.

(30) Shishido, K.;Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1982**, *51*, 3007−3011.

TABLE 1. Examples of the Vicarious Nucleophilic Substitution Reaction

S.No.	Nitroarene	Silyl compound	Product	Yield[a]
1.	 **4**	 **18**	 **6**	85 %
2.	 **19**	 **18**	 **20**	11% (92%)[b]
3.	 **22**	 **21**	 **26**	60 %
4.	 **19**	 **21**	 **27**	53% (70 %)
5.	 **4**	 **29**	 **28**	38% (68%)[b]
6.	 **4**	 **23**	 **3**	~15%[c]
7.	 **30**	 **24**	 **25**	39% (50%)

[a] Yield based on recovered starting material is reported in brackets. [b] Reaction carried out for 2 h at −40 °C [c] Yield on the basis of GC/MS analysis of crude reaction product.

Experimental Section

All reactions were performed under nitrogen gas in glassware that was flame-dried and equipped with a magnetic bar. Tetrahydrofuran (THF) was freshly distilled from the sodium complex of benzophenone before use. Acetonitrile was freshly distilled from CaH_2. All compounds were judged pure by TLC (single spot/ two solvent systems) using a UV lamp or an iodine chamber for detection purposes. Elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Wood-

side, NY. TLC analysis was performed on silica gel sheets containing a fluorescent indicator. Flash column chromatographic separation was carried out on 60 Å (230−400-mesh) silica gel. All experiments dealing with moisture-sensitive compounds were conducted under an atmosphere of dry nitrogen. TASF was transferred under an atmosphere of dry nitrogen in a glovebox.

1-Methyl-3-(trimethylsilyl)-2-pyrrolidinone (18). To 16.9 g (0.156 mol; 2 M solution in heptane/ethyl benzene/THF) of LDA in 78 mL of dry THF at −78 °C under an atmosphere of nitrogen was added 10.28 g (0.14 mol) of 1-methyl-2-pyrrolidinone (**5**) (freshly distilled from CaH_2) dropwise with stirring. When the addition was complete, the resulting mixture was stirred for an additional 10 min, at which point 24 mL (0.87 mol) of Me_3SiCl was rapidly added to the mixture. Stirring was then continued for 3 h, by which time the reaction mixture had warmed to room temperature. Solvent was then removed in vacuo by rotoevaporation, and then ca. 150 mL of cold (0 °C) pentane was added to the residue. Rapid filtration and evaporation of the filtrate in vacuo yielded the crude product. Fractional distillation at 55−60 °C (1 mm of Hg) gave pure product **18** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37−3.23 (m, 2H), 2.78 (s, 3H), 2.21−2.11 (m, 1H), 1.94−1.84 (m, 2H), 0.08 (s, 9H). Because the NMR data was identical to that previously reported,[23] the compound was used in the next step without further characterization.

General Procedure for Coupling Reaction Exemplified by Synthesis of 1-*N*-Methyl-3-(5′-methoxy-2′-nitrophenyl)pyrrolidin-2-one (6). (Note: An identical procedure was employed to synthesize compounds **20** and **26**−**29**). To a mixture of 555 mg (3.63 mmol) of *p*-nitroanisole (**4**) and 1.06 g (1.7 equiv, 6.16 mmol) of 1-methyl-3-(trimethylsilyl)-2-pyrrolidinone (**18**) in 5 mL of dry THF at −78 °C (dry ice and acetone) was added 1.0 g (3.63 mmol) of TASF dissolved in 3 mL of CH_3CN and 2 mL of THF. The mixture was stirred for 15 h, by which time it had reached room temperature. The mixture was then cooled to −78 °C, and 1.4 g of DDQ (6.16 mmol) in 5 mL of dry THF was added dropwise. After the addition was complete, the reaction mixture was brought to room temperature and stirred at room temperature for another hour. The volatiles were removed under reduced pressure, and the crude solid was dissolved in CH_2Cl_2 (15 mL) and washed with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with 5% NaOH (15 mL) and then brine (15 mL). The organic layer was dried ($MgSO_4$), and the solvent was evaporated. The crude product was chromatographed on a silica gel column (eluent ethyl acetate/hexanes 4:1) to give the pure product (***6***, 770 mg) in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 9 Hz, 1H), 6.85 (dd, J_1= 3 Hz, $J2$= 9 Hz, 1H), 6.78 (d, J = 3 Hz, 1H), 4.38 (t, J = 9 Hz, 1H), 3.87 (s, 3H), 3.50−3.44 (m, 2H), 2.96 (s, 3H), 2.75−2.71 (m, 1H), 2.07−2.00 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 175.9, 163.2, 142.4, 137.6, 127.5, 115.7, 112.2, 55.6, 47.2, 45.5, 29.8, 27.7. IR (KBr): 1521.65, 1696.19, 1706.32 cm^{-1}. GC/MS (EI) (M − NO_2) *m*/*z*: 204 (calcd for $C_{12}H_{14}NO_2$ − NO_2 204.11). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59, H, 5.64, N, 11.19. Found: C, 57.87, H, 5.62, N, 10.86

1-*N*-Methyl-3-(5′-methyl-2′-nitrophenyl)pyrrolidin-2-one (20). Compound **19** (497 mg) was allowed react with 750 mg of **18** and 1.0 g of TASF to obtain **20** (100 mg) (silica gel column chromatography, eluent 70% ethyl acetate in hexanes). Note: The reaction was stopped after 2 h at −40 °C. Yield: 11% (92% based on recovered starting material (brsm)). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.82 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.07 (s, 1H), 4.23 (t, J = 10 Hz, 1H), 3.46−3.40 (m, 2H), 2.92 (s, 3H), 2.73−2.63 (m, 1H), 2.61 (s, 3H), 2.36−2.96 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.4, 147.1, 144.6, 135.0, 130.9, 128.4, 124.9, 47.3, 45.1, 30.0, 28.1, 21.3. ES (M + H)$^+$ *m*/*z*: 235.1 (calcd for $C_{12}H_{14}N_2O_3$ 234.10). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53, H, 6.02, N, 11.96. Found: C, 62.67, H, 5.92, N, 11.63.

1-*N*-Methyl-3-(5′-bromo-2′-nitrophenyl)piperidin-2-one (26). Treatment of 450 mg of **22** with 530 mg of **21** and 680 mg of TASF resulted in 415 mg of **26** (silica gel column chromatography, eluent 70% ethyl acetate in hexanes). Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 6 Hz, 1H), 7.52 (dd, J_1 = 3 Hz, J_2 = 6 Hz, 1H), 7.465 (d, J = 3 Hz, 1H), 3.97 (q, J = 6 Hz, 1H), 3.61−3.52 (m, 1H), 3.39−3.32 (m, 1H), 2.98 (s, 3H), 2.24−2.12 (m, 1H), 2.05−1.96 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.4, 147.7, 138.5, 135.0, 130.8, 127.8, 126.7, 49.9, 47.3, 34.9, 29.7, 22.5. ES (M + H)$^+$ *m*/*z*: 313.1 (calcd for $C_{12}H_{13}BrN_2O_3$ 312.01). Anal. Calcd for $C_{12}H_{13}BrN_2O_3$: C, 46.03, H, 4.18, Br, 25.52, N, 8.95. Found: C, 46.23, H, 4.21, Br, 25.72, N, 8.90.

1-*N*-Methyl-3-(5′-methyl-2′-nitrophenyl)piperidin-2-one (27). Compound **19** (249 mg) was treated with 506 mg of **21** and 500 mg of TASF to obtain 237 mg of **27** (silica gel column chromatography, eluent 50% ethyl acetate in hexanes). Yield: 53% (70% brsm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 9 Hz, 1H), 7.18−7.15 (m, 1H), 7.09−7.08 (d, J = 3 Hz, 1H), 4.00−3.94 (m, 1H), 3.62−3.53 (m, 1H), 3.38−3.30 (m, 1H), 2.99 (s, 3H), 2.40 (s, 3H), 2.21−2.09 (m, 1H), 2.00−1.92 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 169.2, 146.3, 144.3, 136.7, 132.8, 128.2, 125.4, 50.0, 47.6, 34.8, 29.8, 22.4, 21.2. ES (M + H)$^+$ *m*/*z*: 248.9 (calcd for $C_{13}H_{16}N_2O_3$ 248.12). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89, H, 6.50, N, 11.28. Found: C, 63.07, H, 6.67, N, 11.28.

3-(5′-Methoxy-2′-nitrophenyl)butyrolactone (28). Reaction of 290 mg of **4** with 450 mg of *29* and 525 mg of TASF gave 150 mg of *28* (silica gel column chromatography, eluent 50% ethyl acetate in hexanes). Note: The reaction was stopped after 2 h at −40 °C. Longer reaction times gave side products with no substantial improvement in yield. Yield: 38% (68% brsm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 9 Hz, 1H), 6.92 (dd, J_1 = 3 Hz, J_2 = 9 Hz, 1H), 6.83 (d, J = 3 Hz, 1H), 4.58−4.37 (m, 3H), 3.89 (s, 3H), 2.92−2.81 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 175.97, 163.71, 142.31, 134.97, 128.50, 117.17, 113.28, 66.75, 56.05, 44.56, 30.97. GC/MS (EI) (M): 237.0 (calcd for $C_{11}H_{11}NO_5$: 237.06). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 59.73, H, 5.01, N, 6.33. Found: C, 55.96, H, 4.69, N, 5.90.

(4-Nitro-3-biphenylyl)acetonitrile (25). Treatment of 160 mg of **30** with 229 mg of **24** and 220 mg of TASF resulted in 70 mg of **25** (silica gel column chromatography, eluent 70% ethyl acetate in hexanes). Yield: 39% (50%, brsm). The spectroscopic data were identical to those previously reported.[26] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, J = 9 Hz, 1H), 7.92 (t, J = 1.05 Hz, 1H), 7.75 (dd, J_1 = 3 Hz, J_2 = 9 Hz, 1H), 7.66−7.63 (m, 2H), 7.52−7.26 (m, 3H), 4.30 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 147.52, 146.06, 137.67, 129.49, 129.32, 129.23, 127.76, 127.33, 126.51, 126.33, 22.99. IR (KBr pellet): 1344.31, 1513.07 (NO_2), 2235.04 (CN). The structure was also confirmed by X-ray analysis.

1,3-Dimethyl-3-(5′-methoxy-2′-nitrophenyl)pyrrolidin-2-one (3). To a mixture of 1-methyl-3-(5′-methoxy-2′-nitrobenzene)pyrrolidin-2-one (**6**) (250 mg, 1.0 mmol), ^{n}Bu$_4$NBr (32.23 mg, 10 mol %), and CsOH·H_2O (1.67 g, 10.0 mmol) in toluene (10 mL) was added methyl iodide (4 mL, 12.4 mmol) dropwise. The reaction was stirred rigorously at room temperature for 10 h, by which time complete consumption of the starting material was observed. The volatiles were removed under reduced pressure, the solid residue was dissolved in Et_2O (20 mL), and then the extract was washed with water (2×) and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude solid (253 mg) was purified by silica gel column chromatography (eluent ethyl acetate/hexanes 4:1) to give the required product 1,3-dimethyl-3-(5′-methoxy-2′-nitrophenyl)pyrrolidin-2-one (**3**) in 95% yield (246 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 9 Hz, 1H), 7.12 (d, J = 3 Hz, 1H), 6.82 (dd, J_1 = 3 Hz, J_2 = 9 Hz, 1H), 3.87 (s, 3H), 3.49−3.43 (m, 2H), 2.91 (s, 3H), 2.63−2.59 (m, 1H), 2.13−2.05 (m,1H), 1.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.67, 157.96, 138.07, 135.57, 123.73, 111.63, 106.64, 51.26, 43.71, 41.90, 29.68, 25.52, 20.15.

GC/MS (EI) (M − NO_2): 218 (calcd for $C_{13}H_{16}N_2O_4$ − NO_2 218.13). Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08, H, 6.10, N, 10.06. Found: C, 60.13, H, 6.72, N, 10.71. X-ray crystallographic data is available in Supporting Information.

1,3-Dimethyl-3-(2′-amino-5′-methoxyphenyl)pyrrolidin-2-one (7). An ethyl acetate solution (20 mL) of 1,3-dimethyl-3-(5′-methoxy-2′-nitrophenyl)pyrrolidin-2-one (**3**) (578 mg) was hydrogenated at 50 psi in the presence of 10% Pd/C (70 mg) for 3 h at room temperature. The reaction mixture was then filtered through a plug of Celite to remove the Pd/C. The Celite plug was thoroughly washed with ethyl acetate, and the washings and the filterate were combined and evaporated on a rotary evaporator to obtain almost pure **7**. This product was then subjected to silica gel column chromatography (eluent ethyl acetate) to give 1,3-dimethyl-3-(2′-amino-5′-methoxybenzene)-pyrrolidin-2-one (**7**) in quantitative yield (518 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (d, J = 3 Hz, 1H), 6.67−6.59 (m, 2H), 4.12−4.09 (m, 2H, NH_2), 3.73 (s, 3H), 3.44−3.29 (m, 2H), 2.86 (s, 1H), 2.76−2.67 9m, 1H), 2.00−1.91 (m, 1H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.18, 148.09, 134.84, 123.63, 114.82, 190.40, 107.98, 51.26, 43.39, 41.98, 28.83, 25.81, 17.08. The spectral data were identical to those previously reported.[30] FABMS (M + H)$^+$ *m*/*z*: 235.08 (calcd for $C_{13}H_{18}N_2O_2$ 234.14). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.63, H, 7.74, N, 11.96. Found: C, 66.30, H, 7.82, N, 11.76.

5-Methoxy-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole (8). To an ice-cooled 3 mL THF (dry) solution of 1,3-dimethyl-3-(2′-amino-5′-methoxybenzene) pyrrolidin-2-one (**7**) (270 mg, 1.16 mmol) was added 67 mg (1.75 mmol) of lithium aluminum hydride under a nitrogen stream in roughly three equal portions. The ice bath was removed, and the reaction mixture was stirred at room temperature for 40 min, by which time complete consumption of **7** had occurred (TLC analysis). The reaction mixture was then cooled to 0 °C, and 3 mL of EtOAc was added to destroy unreacted lithium aluminum hydride. The solution was then filtered through Celite, and the Celite plug was thoroughly washed with EtOAc. The filtrate and the washings (∼15 mL) were combined and washed with 1.0 N HCl (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 430 mg of crude material. Silica gel column chromatography (eluent 90% ethyl acetate in hexanes) then afforded compound **8** (140 mg) in 60% as reported by Takano and co-workers,[14] mp 70 °C (reported[14] 68−69 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65−6.51 (m, 3H), 4.39 (s, 1H), 4.22 (broad singlet, 1H, NH), 3.73 (s, 3H), 2.75−2.62 (m, 2H), 2.44 (s, 3H), 2.03−1.99 (m, 2H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 143.0, 138.2, 112.4, 109.9, 109.4, 89.8, 55.8, 53.8, 52.2, 40.1, 36.5, 26.5.

Acknowledgment. We thank Professor Joseph W. Lauher and Sean M. Curtis for the X-ray crystallographic analysis. Robert A. Rieger and Avalyn Lewis are also gratefully acknowledge for performing the mass analysis.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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