Recovered **46b** (0.66 g, 1.31 mmol) was dissolved in CH_2Cl_2 (13 mL), cooled down to -70 °C, and treated with gaseous BF_3 (165 mL, 6.5 mmol). The mixture was kept at this temperature for 20 min and then quenched with MeOH (absolute, 2 mL). After the usual treatment the mixture **46a,b** was isolated (0.56 g, yield ca. 85%, a:b = 3:1) and identified by ^1H NMR data comparison of the decomplexed material with the abovementioned sample.

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The Enantioselective Synthesis of (-)-Physostigmine via Chiral Sulfoxides

J. P. Marino,* S. Bogdan, and K. Kimura

Contribution from the Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055. *Received December 23, 1991*

Abstract: The total synthesis of naturally occurring (-)-physostigmine is described. The key element for the asymmetric induction is the chirality transfer from optically active 2-(alkylsulfinyl)indoles to indoline butyrolactones bearing two chiral centers. Novel features of this synthesis involve the use of a new class of sulfoxylating agents, *N*-(alkylsulfinyl)oxazolidinones, to prepare the starting indolyl sulfoxides and the correlation of the size of the alkyl group on the sulfoxide with the degree of asymmetric induction. The overall synthesis requires a dozen steps from commercially available 5-(benzyloxy)indole.

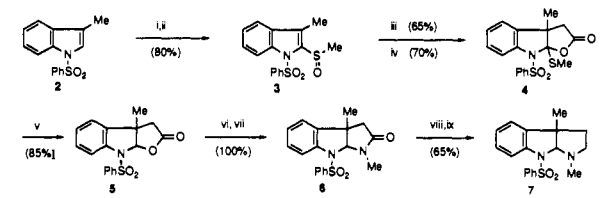
Introduction

A principal alkaloid of the Calabar bean, (-)-physostigmine (**1**), is a clinically useful anticholinesterase which has been used in the treatment of myasthenia gravis and glaucoma. More recently, analogues of (-)-physostigmine have also shown promise as therapeutic agents for Alzheimer's disease.[1,2] The importance of this class of alkaloids has elicited a large amount of synthetic work toward the total synthesis of the naturally occurring (-)-physostigmine. Earlier syntheses by and large produced only racemic physostigmine.[3] In recent years, a number of enantiocontrolled syntheses have been reported[4] for both the natural and unnatural physostigmine. Our interest in physostigmine emanated from the asymmetric synthesis of highly functionalized butyrolactones using chiral vinyl sulfoxides.

In a previous communication,[5] we showed that 2-(methylsulfinyl)indole **3** could serve as a unique precursor for the physostigmine alkaloids via lactonization with dichloroketene (Scheme I). Moreover, recent reports from our group[6] have established that the lactonization of chiral vinyl sulfoxides with dichloroketene occurs with complete control of the relative and absolute configuration.

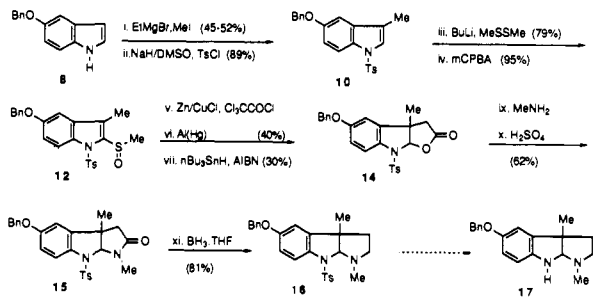
In this paper we want to summarize our earlier efforts toward racemic physostigmine and report a unique synthesis of optically active (-)-physostigmine, which involves the preparation of chiral indolyl sulfoxides and their use in the lactonization reaction.

Scheme I[a]

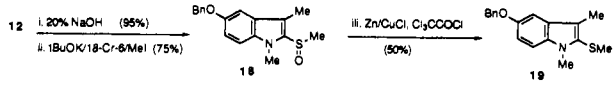


[a] Reagents: (i) 1.2 equiv of BuLi, THF, -23 °C. (ii) 5 equiv of MeSOCl, THF, -23 °C. (iii) 5 equiv of Cl_3CCOCl, 20 equiv of Zn-(Cu), THF, 0 °C. (iv) 20 equiv of Al(Hg), THF/H_2O/MeOH (10/1/1), room temperature. (v) *n*-Bu_3SnH, AIBN, benzene, 80 °C. (vi) Excess $MeNH_2$, 10 equiv of 1 N HCl, anhydrous MeOH, -78 °C; cat. concentrated H_2SO_4, DMF, 115 °C. (viii) $Et_3O^+BF_4^-$, CH_2Cl_2, room temperature, $NaBH_4$, EtOH, 0 °C → room temperature.

Scheme II



Scheme III



Synthesis of Racemic Physostigmine

Reaction of 5-(benzyloxy)indole (**8**) with ethylmagnesium bromide and methyl iodide afforded 5-(benzyloxy)-3-methylindole. Treatment with dimsyl sodium and tosyl chloride effected sulfonylation at the nitrogen. Deprotonation at the C-2 carbon (BuLi, -60 °C), followed by addition of dimethyl disulfide, produced the 2-(methylsulfenyl)indole derivative of **10**. The racemic sulfoxide **12** was easily obtained by oxidation with *m*-CPBA (Scheme II). The lactonization protocol calls for treatment of the vinyl sulfoxide

(1) Davis, K. L.; Mohs, R. C. *Am. J. Psychiatry* **1982**, *139*, 1421. Beller, S. A.; Overall, J. E.; Swann, A. C. *Psychopharmacology* **1987**, *87*, 145.
(2) Christie, J. E.; Shering, A.; Ferguson, J.; Glen, A. I. *Br. J. Psychiatry* **1981**, *138*, 46.
(3) For a review of synthetic approaches to the physostigmines, see: Takano, S.; Ogasawara, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 225-251.
(4) (a) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982-5984. (b) Node, M.; Hao, X.; Fuji, K. *Chem. Lett.* **1991**, 57-60. (c) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872-875. (d) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411-414. (e) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109-112. (f) Yu, Q.; Brossi, A. *Heterocycles* **1988**, *27*, 745-750. (g) Takano, S.; Goto, E.; Himara, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641-2643.
(5) Marino, J. P.; Kim, M.-W.; Lawrence, R. *J. Org. Chem.* **1989**, *54*, 1782-1784.
(6) (a) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643-7644. (b) Marino, J. P.; Fernandez de la Pradilla, R. *Tetrahedron Lett.* **1985**, *26*, 5382-5384. (c) Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *Synthesis* **1987**, 1088-1091. (d) Marino, J. P.; Laborde, E.; Paley, R. *J. Am. Chem. Soc.* **1988**, *110*, 966-968.

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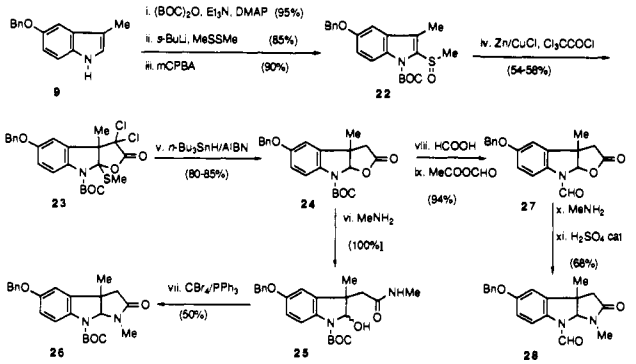
Scheme IV



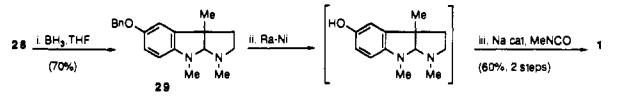
with an excess of trichloroacetyl chloride in the presence of a zinc–copper couple. Not all of the available procedures (i.e., $Zn/CuSO_4$,[7] $Zn/Cu(OAc)_2$,[8] $Zn/CuCl$[9]) are equally successful in producing a zinc–copper couple suitable for the lactonization reaction. For the reaction with the indolyl sulfoxides, the in situ production of the couple Zn/CuCl has given the best results. Thus, a suspension of zinc dust and dry cuprous chloride was heated at reflux in THF for 1 h and then cooled to −5 °C, and indolyl sulfoxide **12** was added, followed by fast addition[10] of trichloroacetyl chloride. The crude dichloro lactone was immediately treated with aluminum amalgam to effect dechlorination. Desulfenylation was achieved by treatment with tributyltin hydride (AIBN, toluene, reflux) to produce lactone **14**.

The moderate yield in the desulfenylation step (30%) in comparison to the same reaction on model compound **4** (Scheme I) was attributed to the electron-donating character of the 5-benzyloxy substituent that activates the sulfonamide toward reaction with the tin hydride. Lactone **14** was converted to lactam **15** by treatment with excess methylamine; closure of the resulting hydroxy amide was effected under acidic conditions. The lactam was reduced to the amine by treatment with borane/THF, followed by decomposition of the amine–borane complex with water. All attempts to deprotect the nitrogen met with failure. The conditions tried include reductive (Na/NH_3, Li/NH_3, sodium naphthalenide, Ra-Ni, Red-Al), basic (60% NaOH/THF, *t*-BuLi/HMPA), and acidic conditions (48% HBr/phenol). Although most of these conditions have been used to cleave indole sulfonyl groups, only a few methods have been successful in cleaving indolines (sodium naphthalenide[11]) or aliphatic (Red-Al[12]) sulfonamides.

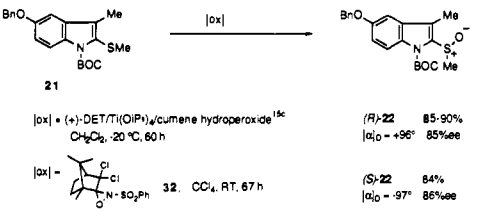
We also examined the possibility of introducing the N_1 methyl group earlier in the synthetic scheme. In such an event, the crucial step of the synthesis would be the lactonization. *N*-Methyl sulfoxide **18**, prepared in two steps from sulfoxide **12** (Scheme III), was submitted to the lactonization conditions. Only sulfide **19** (50%), which is the typical byproduct of the lactonization reaction, was obtained. For most of the examples, the ratio of products dichloro lactone/sulfide is strongly dependent on the reaction temperature. For this reaction, we have examined temperatures ranging from −40 °C to room temperature, with no success.

This result confirmed the need for an electron-withdrawing group on the nitrogen in order to reduce the conjugation between the nitrogen lone pair and the olefinic bond and allow the 3,3-sigmatropic rearrangement to take place. A carbamate group is well suited for assuming the double role of electron-withdrawing group for the lactonization and easily removable protecting group in the penultimate step of the synthesis.

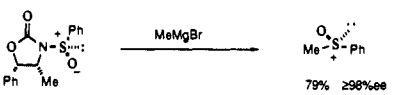
Scheme V



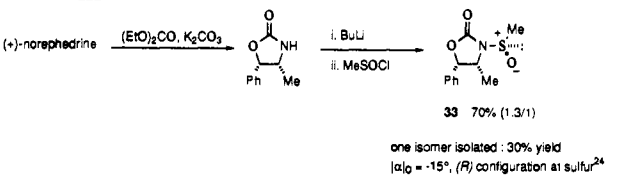
Scheme VI



Scheme VII



Scheme VIII



Sulfoxide **22** was prepared in a similar fashion as **12** and lactonized with dichloroketene (Scheme IV). Dechlorination and desulfenylation were performed in the same step by treatment with tributyltin hydride (AIBN, toluene, reflux).

Treatment of lactone **24** with methylamine gave hydroxy amide **25** as a mixture of diastereomers. The closure to the lactam could not be realized as before (acidic conditions) because of the lability of the BOC group. While the heating of **25** in methanol (50 °C, atmospheric pressure) gave back lactone **24**, the same treatment in a sealed tube[13] gave no reaction at all. The closure of hydroxy amide **25** could nevertheless be achieved by activation of the hydroxyl group under neutral conditions (CBr_4, Ph_3P) to give lactam **26** in a moderate yield. In an alternate route, the BOC group was replaced by a formyl group by treatment with formic acid and then acetic formic anhydride. Lactone **27** was then converted to lactam **28** under the standard conditions. Both lactone **27** and lactam **28** are mixtures of rotamers (4/1 and 2.3/1, respectively).[14]

Borane/THF reduced both the lactam and the formamide to afford *O*-benzyleseroline (**29**) in 70% yield (Scheme V). The benzyl group was cleaved with Raney nickel (THF, reflux), and the unstable phenol was immediately treated with methyl isocyanate in the presence of sodium to produce racemic physostigmine.[4f]

Optically Active Indolyl Sulfoxide

Very few methods of enantioselective oxidation of sulfides have been reported. One of these methods is a modified Sharpless oxidation reported at the same time by Kagan[15] and Modena.[16] Applied with further modifications[17] to sulfide **21**, this method

(7) (a) Brady, W. *Synthesis* **1971**, 415–422. (b) Simmons, H. E.; Smith, R. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 855–858.

(8) Le Goff, E. *J. Org. Chem.* **1964**, *29*, 2048–2050.

(9) Rawson, R. J.; Harrison, I. T. *J. Org. Chem.* **1970**, *35*, 2057–2058.

(10) The indolyl sulfoxide derivatives behave very different from the other type of vinyl sulfoxides in the lactonization reaction. Typical conditions for the lactonization call for a slow addition of trichloroacetyl chloride (over several hours).

(11) Magnus, P.; Katoh, T.; Matthews, I. R.; Huffman, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 6707–6711.

(12) Hoshino, O.; Ishizaki, M.; Saito, K.; Yumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 420–421.

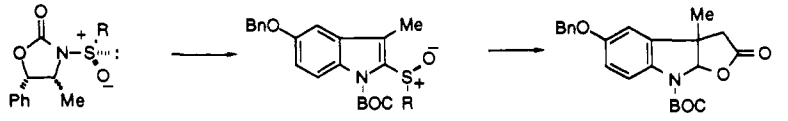
(13) Rosenmund, P.; Sotiriou, A. *Chem. Ber.* **1975**, *108*, 208–214. Recently, closure of a similar hydroxy amide was reported to occur at 180 °C in a sealed tube.[4a]

(14) Similar observations have been reported before: Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2399–2404 and references therein.

(15) (a) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193. (b) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135–5144.

(16) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325–326.

Table I. Preparation of Lactone **24** from the New Sulfinyloxazolidinones

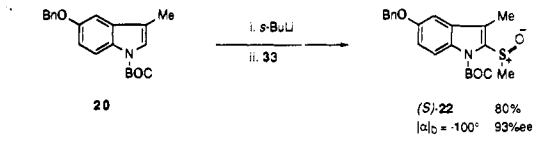


(*R*) at sulfur (*S*) at sulfur **24**

sulfinyl-oxazolidinone		sulfoxide				lactone **24**		
	R		yield, %	% ee	$[\alpha]_D$, deg	yield,[a] %	% ee	$[\alpha]_D$, deg
33	Me	**22**	80	93	−100	45	8	−1
34	iPr	**35**	80–90	≥97	−132	37	70–75	−13
36	tBu	**37**	unstable					
39	Ph	**40**	62	68 (93)[b]	−62[b]	traces		
41	CH_2tBu	**42**	78	≥97	−174	28	60	−10

[a] Yields from starting sulfoxides (lactonization + dechlorination + desulfenylation).[27] [b] After recrystallization.

Scheme IX



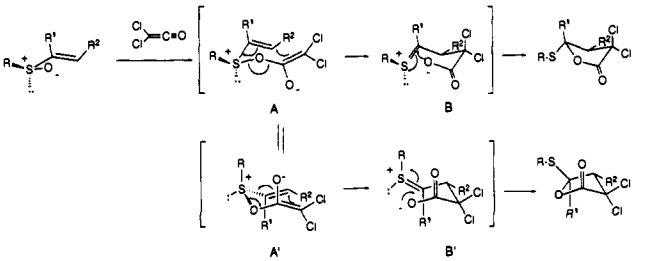
20 (*S*)-**22** 80% $[\alpha]_D$ = −100° 93%ee

gave us (*R*)-**22** with 85% ee[18] (Scheme VI). Another reagent used for the asymmetric oxidation of sulfides is the oxaziridine **32** recently described by Davis.[19] In our hands, it produced sulfoxide (*S*)-**22** with 86% ee (Scheme VI).

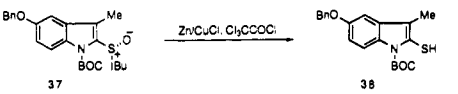
While investigating the direct asymmetric oxidation of the indolyl sulfide **21**, we sought a general sulfoxylation protocol for the preparation of alkyl indolyl sulfoxides. The classic Anderson method for the preparation of optically active sulfoxides involves the reaction of carbanions with menthyl sulfinates.[20] This method was unsuccessful with the indole system, probably due to the poor electrophilic character of menthyl methanesulfinate. Evans[21] has prepared a chiral sulfinyl electrophile that gives quantitative optical yields in reaction with Grignard reagents (Scheme VII).

Following this lead, we have prepared the methylsulfinyl derivative **33** in two steps from norephedrine[22] (Scheme VIII). Other chiral auxiliaries were also examined, but only the norephedrine resulted in an *N*-(methylsulfinyl)oxazolidinone that could be crystallized directly.[23] *N*-(Methylsulfinyl)oxazolidinone

Scheme X



Scheme XI



37 **38**

33 was reacted with a variety of Grignard reagents and gave sulfoxides with optical yields ranging from 90 to 97%.[22]

Being unsuccessful in producing the Grignard[25] of indole **20**, we resorted to the lithiated carbanion to prepare sulfoxide **22**. Thus, treatment of indole **20** with *sec*-butyllithium (THF, −78 °C) followed by quenching with a precooled solution (−78 °C) of enantiomerically pure *N*-(methylsulfinyl)oxazolidinone **33** produced sulfoxide (*S*)-**22** in 80% yield (Scheme IX). The absolute configuration of sulfoxide **22** was proposed to be *S*, assuming that inversion occurs at the sulfur during the displacement. This was also the same sulfoxide produced by Davis' oxaziridine oxidation.

Synthesis of Optically Active Physostigmine

The chiral sulfoxide (*S*)-**22** was submitted to lactonization and then dechlorination and desulfenylation as described earlier. The resulting lactone was analyzed by ^{1}H NMR spectroscopy in the presence of a chiral shift reagent. Although we could not achieve base line resolution of the enantiomers (the lactone is present as a partially collapsed mixture of rotamers), the result did not leave any doubt; to our surprise, we found that the lactone was essentially racemic! This was the first example of an optically active methyl sulfoxide subjected to the lactonization process.

This unexpected result prompted us to reexamine the arguments used to rationalize the enantiospecificity observed in the earlier work.[6] The proposed mechanism for this reaction involves a 3,3-sigmatropic rearrangement of intermediate A, followed by intramolecular trapping of B by the carboxylate anion. The enantiospecificity of the reaction was rationalized by assuming that intermediate A adopts a chairlike conformation in which the bulky aryl group is in an equatorial position and that the cycli-

(17) Kagan's modification involves the use of exactly 1 equiv of water in connection with titanium isopropoxide and diethyl tartrate. We have repeatedly tried to use these conditions to oxidize sulfide **21**, but we obtained sulfoxide **22** with only moderate enantiomeric excesses (ca. 50–70%).

(18) Enantiomeric excesses of all the sulfoxides prepared were determined using ^{1}H NMR spectroscopy (360 MHz) with chiral shift reagent Eu(hfc)$_3$.

(19) Davis, F. A.; ThimmaReddy, R.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964–5965. Davis, F. A.; ThimmaReddy, R.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428–1437.

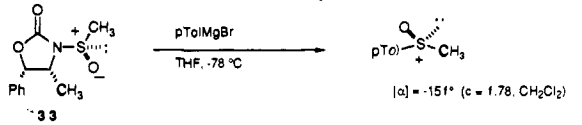
(20) (a) Anderson, K. K. *Tetrahedron Lett.* **1962**, 93–95. (b) Drabowicz, J.; Bujnicki, B.; Mikolayczik, M. *J. Org. Chem.* **1982**, *47*, 3325–3327.

(21) The (phenyl- and (tolylsulfinyl)oxazolidinones were first prepared by D. A. Evans and L. Columbo in 1985 at Harvard University. We became aware of these reagents through Professor Evans in May, 1988.

(22) Details on sulfinyloxazolidinone chemistry will be described elsewhere.

(23) *N*-(Phenylsulfinyl)oxazolidinone derivatives of norephedrine, *l*-phenylalanine, and *l*-valine are all crystalline.[21]

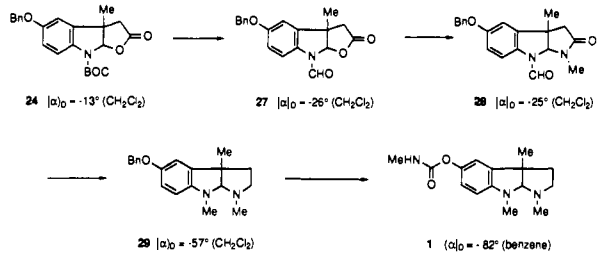
(24) The absolute configuration at the sulfur was determined as follows: *N*-(methylsulfinyl)oxazolidinone **33** was reacted with *p*-tolylmagnesium bromide to form methyl *p*-tolyl sulfoxide. The rotation was compared to values reported in the literature,[6] and the absolute configuration was determined to be *S*. Assuming that inversion occurs at sulfur during the displacement, the absolute configuration in **33** is *R* at the sulfur.



33 $[\alpha]$ = −151° (c = 1.78, CH_2Cl_2)

(25) According to Evans,[21] Grignard reagents give higher optical yields than lithiated carbanions.

Scheme XII



zation of intermediate B is faster than rotation about a carbon–carbon bond (Scheme X). The lack of selectivity observed with the methyl sulfoxide **22** suggested that the methyl group was not bulky enough to lock the first intermediate in conformation A, allowing for equilibration with conformation A′ and therefore formation of the enantiomeric lactones.

If the size of the R group on the sulfoxide was dictating the enantioselectivity of the lactonization, this could be put to the test. This hypothesis was confirmed by preparing bulkier sulfoxides and submitting them to the lactonization reaction (Table I). A series of new sulfinyloxazolidinones were prepared[22] and reacted in a similar manner as **33** to afford sulfoxides in quantitative optical yields.

Lactonization of isopropyl indolyl sulfoxide **35**,[26] followed by desulfenylation and dechlorination, gave lactone **24** with 70–75% ee. Such a dramatic improvement of the optical yield demonstrates the importance of the steric effect of the sulfoxide group in the lactonization. *tert*-Butyl sulfoxide **37** proved to be rather unstable and decomposed in the lactonization conditions to give thiol **38** (Scheme XI). Phenyl sulfoxide **40** gave very poor results in the lactonization step. This was attributed to the poor reactivity of a diaryl sulfoxide system toward electrophiles. In order to increase the sulfoxide nucleophilicity, preparation of the *p*-methoxyphenyl sulfoxide derivative was considered. This was, however, never achieved as the corresponding sulfinyloxazolidinone proved to be totally unstable. Neopentyl sulfoxide **42** was also prepared but did not increase the optical yield of the lactone over the isopropyl derivative.

At this stage, we decided not to search further for a sulfoxide that would give us a higher optical yield in the lactonization as it appeared that we might have uncovered one limitation of the lactonization reaction: in order to be totally enantiospecific, this reaction requires a chiral *aryl sulfoxide* group.

In order to confirm the optical yield of the lactonization and also the assignments we made for the absolute configurations, the synthesis was carried on to the end, using the lactone obtained from isopropyl sulfoxide (-)-**35**. According to earlier work,[6] we had assumed that the (*S*)-(-)-sulfoxides we used would give the (+)-physostigmine, which is the *unnatural* configuration. To our total surprise, we obtained a physostigmine with the *natural* configuration (Scheme XII).

This can nevertheless be rationalized if we examine again the proposed mechanism of the reaction (Scheme X). The assumption that conformation A would be favored with a bulky R group on the sulfur does not take into account the other substituents. With the indolyl sulfoxide system, the R^1 group is a (*tert*-butoxycarbonyl)amino group. Therefore, it is not unlikely that, in this particular case, the 1,2-diequatorial interaction between two bulky groups (BOC and isopropyl) makes conformation A less favorable than A′ where the two groups are in a trans-diaxial conformation. Thus, the stereochemistry observed for lactone **24** is controlled by conformation A′.

(26) The modified Sharpless oxidation (in the same conditions used for sulfide **21**) of the corresponding sulfide gave very poor chemical (34%) and optical yields (20% ee).

(27) The lactonization step gave increasing chemical yields going from the *S*-methyl derivative to the *S*-neopentyl (65%, 70%, and 79%, respectively, for *S*-methyl, *S*-isopropyl, and *S*-neopentyl). On the other hand, the desulfenylation step proved to be more difficult on neopentyl (80%, 54%, and 36%, respectively, for *S*-methyl, *S*-isopropyl, and *S*-neopentyl).

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a Brucker 360-MHz spectrometer in $CDCl_3$ at 360 MHz (^1H) and 90.4 MHz (^{13}C), respectively. Mass spectra were obtained on a Finnigan 4021 instrument, using electron impact ionization at 70 eV. High-resolution mass spectra were obtained on a VG 70-250-S mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using monochromatic sodium light. Bodman 230–400 mesh silica gel was used for flash column chromatography. All aprotic solvents were dried, and operations with them were carried out under nitrogen in flame-dried glassware. Zinc was sequentually washed with 3% HCl, H_2O, absolute ethanol, and absolute ether and dried in vacuo (P_2O_5); CuCl was dried in vacuo (P_2O_5).

5-(Benzyloxy)-3-methylindole (9). To 5-(benzyloxy)indole (8.2 g, 36 mmol) in dry THF (280 mL) cooled in an ice bath was added dropwise ethylmagnesium bromide (18.3 mL of 3 M in ether, 55 mmol). The mixture was stirred for 4 h at room temperature. Methyl iodide (6.85 mL, 110 mmol) was then added, and the stirring was continued for 18 h at room temperature. The reaction mixture was poured in ice/water and extracted with EtOAc (2 × 200 mL). The combined extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/CH_2Cl_2, 5/1–2/1) to afford **9** (4.47 g, 52%) as a white solid: mp 117.5–118.5 °C (MeOH); IR (CH_2Cl_2) 3472 s, 1624 w, 1588 w, 1483 s, 1454 s, 1380 s, 1288 s, 1198 m, 1068 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (bs, 1 H), 7.49–6.91 (m, 9 H), 5.11 (s, 2 H), 2.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.00, 137.72, 131.62, 128.57, 128.42, 127.69, 127.57, 122.59, 112.59, 111.64, 111.18, 102.49, 71.09, 9.60; MS (EI) *m/z* 237 (M^+, 35), 146 (100), 118 (27), 91 (48), 65 (13); HRMS (EI) calcd 237.1153, found 237.1146. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.00; H, 6.38; N, 5.89.

5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methylindole (20). To a solution of **9** (3.37 g, 14 mmol) and Et_3N (2.37 mL, 17 mmol) in dry THF (350 mL) were added $(BOC)_2O$ (5.2 mL, 18 mmol) and DMAP (0.34 g, 2.8 mmol) at room temperature. After stirring for 4 h at room temperature, the mixture was poured in H_2O and extracted with EtOAc. The extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 15/1) to afford **20** (4.7 g, 98%) as a white solid: mp 79–79.5 °C (MeOH); IR (CH_2Cl_2) 3066 w, 3057 w, 3046 w, 2986 w, 1724 s, 1604 w, 1476 m, 1452 m, 1392 s, 1373 s, 1288 m, 1256 s, 1224 m, 1161 m, 1081 m cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (bs, 1 H), 7.48–7.31 (m, 6 H), 7.03–6.97 (m, 2 H), 5.11 (s, 2 H), 2.21 (s, 3 H), 1.64 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.87, 149.58, 137.30, 132.17, 130.30, 128.36, 127.66, 127.35, 123.40, 115.94, 115.70, 113.24, 103.38, 82.82, 70.64, 28.09, 9.41; MS (EI) *m/z* 337 (M^+, 26), 281 (61), 264 (5), 237 (18), 190 (19), 146 (62), 118 (14), 91 (100), 65 (11), 57 (58), 41 (19); HRMS (EI) calcd 337.1677, found 337.1678. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.85; H, 6.86; N, 4.10.

5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(methylsulfenyl)-indole (21). To a solution of **20** (3.76 g, 11.1 mmol) in dry THF (110 mL) at -78 °C was slowly added *sec*-BuLi (8.5 mL of 1.3 M in hexane, 11.1 mmol). After 10 min of stirring at -78 °C, the solution was added to a solution of dimethyl disulfide (1.3 mL, 14.4 mmol) in dry THF (110 mL) at -78 °C. The mixture was stirred for 1 h at -75 °C and then poured into saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (2 × 100 mL). The extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 15/1) to afford **21** (3.6 g, 85%) as a white solid: mp 76–76.5 °C (EtOH); IR (CH_2Cl_2) 2981 m, 2930 m, 2871 m, 1728 s, 1610 m, 1452 s, 1371 s, 1245 s, 1161 s, 1102 s, 1016 m, 836 m cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 1 H), 7.43–7.26 (m, 5 H), 7.01–6.97 (m, 2 H), 5.05 (s, 2 H), 2.35 (s, 3 H), 2.33 (s, 3 H), 1.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.81, 149.75, 137.19, 131.79, 130.25, 129.71, 128.45, 127.79, 127.41, 124.96, 116.20, 114.47, 102.84, 83.57, 70.55, 28.18, 20.23, 10.09; MS (EI) *m/z* 383 (M^+, 23), 327 (23), 283 (54), 236 (5), 192 (100), 164 (26), 149 (14), 91 (61), 65 (9), 57 (66), 41 (25); HRMS (EI) calcd 383.1555, found 383.1551. Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.89; H, 6.57; N, 3.65. Found: C, 69.08; H, 6.63; N, 3.63.

5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(methylsulfinyl)-indole (22). To a solution of **21** (0.642 g, 1.67 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added *m*-CPBA (0.32 g of *m*-CPBA 80%, 1.5 mmol) in portions over 30 min. After stirring for an additional 30 min, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 3/1) to afford **22** (0.60 g, 90%) as a white solid: mp 99–100 °C (benzene/hexanes); IR (CH_2Cl_2) 3058 w, 3046 w, 2988 w, 1718 s, 1610 w, 1453 m, 1417 m, 1371 m, 1330 m, 1253 m, 1242 m, 1157

m, 1106 m, 1057 m cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (d, J = 9.77 Hz, 1 H), 7.48–7.25 (m, 5 H), 7.07 (m, 2 H), 5.13 (s, 2 H), 3.09 (s, 3 H), 2.62 (s, 3 H), 1.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.22, 149.59, 136.89, 135.44, 131.68, 130.09, 128.43, 127.82, 127.34, 123.06, 115.92, 115.82, 102.82, 85.33, 70.53, 42.70, 28.07, 8.33; MS (EI) m/z 399 (M^+, 12), 299 (69), 284 (77), 236 (11), 208 (85), 183 (33), 176 (13), 164 (4), 148 (7), 104 (4), 91 (100), 65 (17), 57 (47), 41 (40); HRMS (EI) calcd 399.1504, found 399.1493. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.30; N, 3.50. Found: C, 66.21; H, 6.33; N, 3.48.

5-(Benzyloxy)-8-(*tert*-butoxycarbonyl)-3a-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one (24). Zinc powder (1.48 g, 22.6 mmol) and CuCl (4.15 g, 41.9 mmol) in dry THF (28 mL) were heated at reflux for 1 h. The suspension was cooled to 0 °C, and a solution of sulfoxide **22** (0.838 g, 2.1 mmol) in dry THF (42 mL) was added. The suspension was vigorously stirred, and trichloroacetyl chloride (1.17 mL, 10.49 mmol) was added dropwise over 2.5 min. After the mixture was stirred for 5 min at 0 °C, the suspension was filtered through Celite into ice-cold saturated aqueous $NaHCO_3$. The filtrate was stirred for 5 min in an ice bath and then decanted, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 15/1) to afford dichloro lactone **23** (0.627 g, 58%) as a yellow oil (IR (CH_2Cl_2) 1812 cm^{-1}). The oil was immediately treated with n-Bu_3SnH (0.99 mL, 3 equiv) and a catalytic amount of AIBN in a reflux of toluene (15 mL). After 1 h, a second portion of n-Bu_3SnH (0.33 mL, 1 equiv) and AIBN was added, and the reflux was maintained for another hour. The mixture was concentrated under reduced pressure, and the residue was partitioned between acetonitrile and light petroleum ether. After separation, the acetonitrile layer was washed several times with light petroleum ether and then concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/EtOAc, 5/1) to afford **24** (0.40 g, 84%, 48% from sulfoxide) as a white foamy solid: mp 134–135 °C (MeOH); IR (CH_2Cl_2) 2977 w, 1783 s, 1712 s, 1492 s, 1392 m, 1370 m, 1355 m, 1273 s, 1161 s, 1078 m, 990 m, 944 m, 731 s cm^{-1}; ^1H NMR ($CDCl_3$) (partially collapsed mixture of rotamers) δ 7.75 and 7.35 (2 bs, 1 H), 7.43–7.30 (m, 6 H), 6.87 (m, 1 H), 6.78 (d, J = 2.5 Hz, 1 H), 6.22 and 6.05 (2 bs, 1 H), 5.02 (s, 2 H), 2.95 and 2.80 (AB, J = 17.8 Hz, 2 H), 1.58 (s, 9 H), 1.50 (s, 3 H); MS (EI) m/z 395 (M^+, 9), 339 (34), 322 (3), 295 (23), 250 (3), 204 (52), 176 (3), 160 (40), 91 (100), 65 (9), 57 (47), 41 (20); HRMS (EI) calcd 395.1732, found 395.1726. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.93; H, 6.60; N, 3.49.

5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-2-hydroxy-3-methyl-3-[2-oxo-2-(methylamino)ethyl]indoline (25). Excess methylamine (10 mL) was condensed at −30 °C in a flask containing **24** (0.041 g, 0.103 mmol). The cooling bath was removed, and the reaction mixture was stirred until the excess methylamine had evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/EtOAc, 3/1) to afford **25** (0.043 g, 100%) as a 1.5/1 mixture of diastereomers. The major isomer could be crystallized out with ether/hexanes: mp 159–160 °C; IR (CH_2Cl_2) 3453 w, 2978 w, 1697 s, 1655 m, 1536 w, 1492 s, 1454 w, 1393 m, 1369 m, 1323 w, 1263 m, 1167 m, 1073 m, 1010 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7 (bs, 1 H), 7.41–7.31 (m, 5 H), 6.79 (m, 1 H), 6.68 (bs, 1 H), 6.35 (bs, 1 H), 5.51 (bs, 1 H), 4.99 (s, 2 H), 2.82 and 2.67 (AB, J = 14.3 Hz, 2 H), 2.75 (d, J = 4.7 Hz, 3 H), 1.58 (s, 9 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.41, 154.96, 152.69, 137.91, 137.07, 133.36, 128.44, 127.83, 127.45, 115.45, 113.43, 110.09, 91.00, 81.46, 70.60, 47.06, 40.82, 28.37, 26.71, 26.32; MS (EI) m/z 426 (M^+, <1), 326 (7), 308 (6), 235 (30), 217 (57), 176 (11), 91 (100), 57 (47); HRMS (EI) calcd 426.2154, found 426.2158. Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.55; H, 7.08; N, 6.56. Found: C, 67.66; H, 7.06; N, 6.52. Minor isomer: ^1H NMR ($CDCl_3$) δ 7.7 (bs, 1 H), 7.41–7.31 (m, 5 H), 6.81 (m, 1 H), 6.76 (m, 1 H), 5.90 (bs, 1 H), 5.15 (bs, 1 H), 5.02 (s, 2 H), 2.63 (d, J = 4.7 Hz, 3 H), 2.31 (collapsed AB, 2 H), 1.58 (s, 9 H), 1.45 (s, 3 H).

5-(Benzyloxy)-8-(*tert*-butoxycarbonyl)-1,3a-dimethyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (26). Hydroxy amide **25** (17 mg, 0.04 mmol) was treated with carbon tetrabromide (26 mg, 0.08 mmol) and triphenylphosphine (21 mg, 0.08 mmol) in dry ether (1 mL) at 0 °C. After 15 min, the ice bath was removed and the mixture was stirred for 4 h at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc, 5/1) to afford **26** (8 mg, 50%) as an oil that solidified upon standing (partially collapsed mixture of rotamers): mp 161–162 °C; IR (CH_2Cl_2) 2975 w, 1696 s, 1490 m, 1377 m, 1276 m, 1253 m, 1157 m, 1073 w, 1013 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (bm, 1 H), 7.42–7.32 (m, 6 H), 6.81 (m, 1 H), 6.77 (m, 1 H), 5.60 (bm, 1 H), 5.02 (s, 2 H), 2.89 (s, 3 H), 2.79 and 2.62 (AB, J = 17.1 Hz, 2 H), 1.60 (s, 9 H), 1.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.01, 155.87, 139.27, 136.86, 133.17, 128.52, 127.93, 127.39, 117.19, 114.47, 110.45, 84.39, 82.12, 70.70, 45.14, 43.24, 29.60, 28.30, 27.58, 25.75; MS (EI) 408 (M^+, 1), 352 (7), 308 (9), 217 (77), 91 (100), 84 (24), 57 (86); HRMS (EI) calcd 408.2049, found 408.2038.

5-(Benzyloxy)-8-formyl-3a-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one (27). Lactone **24** (0.651 g, 1.64 mmol) was treated for 1 h at room temperature with 99% HCOOH (8 mL).[28] To this solution was added at 0 °C acetic formic anhydride[29] (preformed by heating 1 mL of acetic anhydride and 0.5 mL of 99% HCOOH for 1 h at 50–60 °C), and the mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/EtOAc, 5/1) to afford **27** (0.50 g, 94%) as a mixture of rotamers (4/1): mp 180–181 °C (CH_2Cl_2/MeOH); IR (CH_2Cl_2) 3062 w, 3048 w, 2929 w, 1972 s, 1692 s, 1602 w, 1494 m, 1395 w, 1337 w, 1283 w, 1228 m, 1164 m, 1001 m, 947 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.90 (minor) and 8.67 (major) (2 s, 1 H), 7.97 (major) and 7.72 (minor) (2 d, J = 8.7 Hz, 1 H), 7.43–6.83 (major+minor) (m, 7 H), 6.30 (minor) and 5.95 (major) (2 s, 1 H), 5.05 (major+minor) (s, 2 H), 3.00 and 2.86 (major) and 2.96 and 2.85 (minor) (2 AB, J = 18, 16.7 Hz, 2 H), 1.55 (major) and 1.52 (minor) (2 s, 3 H); MS (EI) m/z 323 (M^+, 12), 204 (3), 91 (100), 65 (6); HRMS (EI) calcd 323.1157, found 323.1159. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.86; H, 5.21; N, 4.21.

5-(Benzyloxy)-1,3a-dimethyl-8-formyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (28). Excess methylamine (15 mL) was condensed at −30 °C in a flask containing **27** (0.50 g, 1.54 mmol). When the solid dissolved, the cooling bath was removed. The reaction mixture was allowed to warm to room temperature and the excess methylamine to evaporate. The residue was heated for 1 h at 115 °C in DMF (20 mL) in the presence of concentrated H_2SO_4 (0.2 mL). The mixture was then poured into 1 N HCl and extracted with EtOAc. The extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford **28** (0.354 g, 68%) as a mixture of rotamers (2.3/1): IR (CH_2Cl_2) 3056 w, 2928 w, 1680 s, 1497 m, 1452 w, 1400 w, 1363 w, 1331 w, 1273 m, 1238 m, 1027 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.88 (major) and 8.61 (minor) (2 s, 1 H), 7.43–7.34 (major+minor) (m, 5 H), 7.90 (minor) and 7.09 (major) (2 m, 1 H), 6.86 (major+minor) (m, 2 H), 5.74 (major) and 5.26 (minor) (2 s, 1 H), 5.04 (major+minor) (s, 2 H), 2.93 (major) and 2.87 (minor) (2 s, 3 H), 2.86 and 2.67 (minor) and 2.80 and 2.67 (major) (2 AB, J = 17 Hz, 2 H), 1.50 (minor) and 1.47 (major) (2 s, 3 H); ^{13}C NMR ($CDCl_3$) δ major 171.86, 159.32, 157.25, 139.69, 136.45, 131.80, 128.80, 128.02, 127.32, 118.17, 115.16, 111.39, 81.67, 70.74, 45.49, 43.25, 28.11, 25.57, minor 171.47, 158.37, 157.18, 139.90, 136.56, 131.69, 128.49, 127.96, 127.32, 118.17, 114.54, 110.47, 84.29, 70.61, 46.05, 42.90, 26.61, 25.17; MS (EI) m/z 336 (M^+, 30), 245 (10), 217 (19), 91 (100), 65 (7), 42 (12); HRMS (EI) calcd 336.1473, found 336.1477.

5-(Benzyloxy)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indole (29). To a solution of borane in THF (3.12 mL of 1 M, 3.12 mmol) at 0 °C was added a solution of **28** (0.210 g, 0.62 mmol) in THF (10 mL). The mixture was refluxed for 1 h and then cooled to room temperature. Water (10 mL) was added, and the mixture was heated at reflux for 2 h. After cooling to room temperature, the mixture was extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography ($CHCl_3$/acetone, 1/1) to afford **29** (0.123 g, 64%) as an oil that slowly solidified upon standing at room temperature: mp 72–73 °C; IR (CH_2Cl_2) 2961 m, 2866 m, 1594 w, 1496 s, 1453 w, 1270 m, 1208 m, 1121 m, 1024 m, 958 w, 872 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.30 (m, 5 H), 6.73 (m, 2 H), 6.35 (d, J = 8.6 Hz, 1 H), 4.97 (s, 2 H), 4.07 (s, 1 H), 2.89 (s, 3 H), 2.75–2.60 (m, 2 H), 2.53 (s, 3 H), 1.96–1.92 (m, 2 H), 1.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.18, 146.74, 138.18, 137.73, 128.38, 127.65, 127.49, 113.56, 111.06, 107.24, 98.36, 71.21, 53.19, 52.73, 40.72, 38.22, 37.64, 27.33; MS (EI) m/z 308 (M^+, 26), 271 (100), 160 (41), 132 (10), 98 (6), 91 (8), 65 (4). Fumarate salt:[4f] a saturated solution of fumaric acid (1.1 equiv) in ethanol was added to **29**, and the resulting solution was left overnight in the freezer. The filtered solid was recrystallized from methanol: mp 153–155 °C; ^1H NMR ($CDCl_3$) δ 7.41–7.28 (m, 5 H), 6.84 (m, 2 H), 6.71 (s, 2 H), 6.58 (d, J = 9.1 Hz, 1 H), 4.99 (s, 2 H), 4.89 (s, 1 H), 3.35 (m, 1 H), 3.07 (s, 3 H), 2.81 (s, 3 H), 2.80 (m, 1 H), 2.29 (m, 2 H), 1.49 (s, 3 H); HRMS (EI) calcd for $C_{20}H_{24}N_2O$: 308.1888, found 308.1893. Anal. Calcd for $C_{20}H_{24}N_2O \cdot C_4H_4O_4$: C, 67.90; H, 6.64; N, 6.60. Found: C, 67.75; H, 6.74; N, 6.53.

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Physostigmine (1). A solution of **29** (0.045 g, 0.146 mmol) in dry THF (5 mL) was treated with Raney nickel W-2[30] (excess, washed 3× with THF), at reflux for 1 h. The mixture was filtered through Celite, the filtrate was concentrated to ca. 5 mL, and a small piece of sodium was added. The mixture was stirred for 1 min at room temperature, methyl isocyanate (0.05 mL) was added, and the stirring was maintained for another 5 min. The mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography ($CHCl_3$/MeOH, 95/5) to afford **1** (0.025 g, 60%) as an oil which solidified upon standing. The spectroscopic properties of **1** were identical with those reported in the literature.

(+)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(methylsulfinyl)indole (22) (Sharpless). $Ti(OiPr)_4$ (0.97 mL, 3.26 mmol) was added at room temperature to a solution of (+)-diethyl tartrate (1.12 mL, 6.52 mmol) in dry CH_2Cl_2 (24 mL), and the mixture was stirred for 10 min. To this solution, cooled at −20 °C, were added cumene hydroperoxide (1 mL at 80%) and sulfide **21** (1.25 g, 3.26 mmol in 24 mL CH_2Cl_2), sequentially. The reaction mixture was kept at −20 °C, and aliquots of cumene hydroperoxide (1 mL) were added every 12 h until the starting sulfide was completely consumed (TLC) (about 60 h). The reaction was quenched at −20 °C with 6 mL of H_2O and warmed at room temperature. After 1 h, the mixture was decanted, and the organic layer was washed with water, stirred with 5% NaOH (50 mL) and brine (50 mL) for 2 h, and then separated. The organic layer was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/AcOEt, 7/1–1/1) to afford (+)-**22** (1.16 g, 89%) as a foamy solid (85% ee, $[\alpha]_D$ = +96.5° (*c* = 3.03, CH_2Cl_2)).

(−)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(methylsulfinyl)indole (22) (Davis). Sulfide **21** (0.039 g, 0.101 mmol) was treated with oxaziridine **32**[19] (0.038 g, 0.101 mmol) in carbon tetrachloride (2 mL) at room temperature for 67 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc, 6/1–3/1) to afford (−)-**22** (0.034 g, 84%) as a foamy solid (86% ee, $[\alpha]_D$ = −96.6° (*c* = 0.81, CH_2Cl_2)).

(−)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(methylsulfinyl)indole (22) (from sulfinyloxazolidinone). To a solution of **20** (0.135 g, 0.4 mmol) in dry THF (10 mL) at −78 °C was added dropwise *sec*-BuLi (0.30 mL, 1.3 M in hexanes, 0.4 mmol). The mixture was stirred for 5 min and then quenched with a precooled solution of 3-(methylsulfinyl)oxazolidin-2-one **33**[22] (0.239 g, 1 mmol) in solution in THF (10 mL, −78 °C). After 5 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 3/1) to afford (−)-**22** (0.128 g, 80%) as a foamy solid (93% ee, $[\alpha]_D$ = −100° (*c* = 1.37, CH_2Cl_2)).

(−)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-[(2-propyl)sulfinyl]indole (35). To a solution of **20** (0.947 g, 2.8 mmol) in dry THF (50 mL) at −78 °C was added dropwise *sec*-BuLi (2.16 mL, 1.3 M in hexanes, 2.8 mmol). The mixture was stirred for 5 min and then quenched with a precooled solution of 3-(isopropylsulfinyl)oxazolidin-2-one **34**[22] (0.938 g, 3.5 mmol) in THF (20 mL, −78 °C). After 5 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 1/1) to afford (−)-**35** (1.10 g, 92%) as a foamy solid (≥95% ee, $[\alpha]_D$ = −131° (*c* = 1.37, CH_2Cl_2)): mp 93–94 °C (hexanes/EtOAc); IR (CH_2Cl_2) 3053 w, 2980 w, 1718 s, 1610 w, 1451 m, 1383 m, 1371 s, 1321 m, 1258 m, 1245 m, 1158 m, 1106 s, 1055 m, 1026 m, 998 w, 936 w, 876 w, 835 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (m, 1 H), 7.48–7.33 (m, 5 H), 7.04 (m, 2 H), 5.13 (s, 2 H), 3.43 (m, 1 H), 2.59 (s, 3 H), 1.67 (s, 9 H), 1.45 (d, *J* = 7.0 Hz, 3 H), 1.32 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.19, 149.71, 136.97, 132.75, 131.85, 130.29, 128.46, 127.84, 127.37, 124.49, 116.12, 115.56, 102.77, 85.10, 70.58, 53.50, 28.15, 17.64, 13.40, 8.68; MS (EI) *m/z* 427 (M^+, <1), 372 (2), 329 (19), 285 (17), 284 (14), 194 (20), 176 (8), 91 (100), 57 (54), 41 (60); HRMS (EI) calcd 427.1817, found 427.1822. Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.41; H, 6.83; N, 3.27. Found: C, 67.58; H, 6.83; N, 3.22.

(−)-5-(Benzyloxy)-8-(*tert*-butoxycarbonyl)-3a-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one (24) from Sulfoxide (−)-(35). Zinc powder (1.39 g, 39.2 mmol) and CuCl (3.89 g, 39.2 mmol) in dry THF (26 mL) were heated at reflux for 1 h. The suspension was cooled to −5 °C, and a solution of sulfoxide (−)-**35** (0.840 g, 1.96 mmol) in dry THF (39 mL) was added. The suspension was vigorously stirred, and trichloroacetyl chloride (1.09 mL, 9.8 mmol) was added dropwise over 2.5 min. After the mixture was stirred for 5 min, the suspension was filtered through Celite into ice-cold saturated aqueous $NaHCO_3$. The filtrate was stirred for 5 min in an ice bath and then decanted, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 15/1) to afford the dichloro lactone (0.732 g, 70%) as a yellow oil (IR (CH_2Cl_2) 1812 cm^{-1}). The oil was immediately treated with *n*-Bu_3SnH (1.1 mL, 3 equiv) and a catalytic amount of AIBN at reflux of toluene (15 mL). After 1 h, a second portion of *n*-Bu_3SnH (0.33 mL, 1 equiv) and AIBN was added, and the reflux was maintained for another hour. The mixture was concentrated under reduced pressure, and the residue was partitioned between acetonitrile and light petroleum ether. After separation, the acetonitrile layer was washed several times with petroleum ether and then concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/EtOAc, 5/1) to afford **24** (0.286 g, 53%, 37% from sulfoxide) as a white foamy solid (70–75% ee, $[\alpha]_D$ = −13° (*c* = 1.1, CH_2Cl_2)).

The oil obtained, prior to treatment with *n*-Bu_3SnH and AIBN, could be recrystallized from hexanes/EtOAc to afford a white solid, 5-(benzyloxy)-8-(*tert*-butoxycarbonyl)-3,3-dichloro-3a-methyl-8a-[(2-propyl)-sulfenyl]-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one: mp 138–138.5 °C (hexanes/AcOEt); IR (CH_2Cl_2) 2982 w, 1812 s, 1709 s, 1490 s, 1369 s, 1320 m, 1287 m, 1202 m, 1156 s, 1074 m, 1027 m, 974 m, 883 w, 834 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (m, 1 H), 7.44–7.33 (m, 5 H), 6.94 (m, 2 H), 5.05 (s, 2 H), 3.15 (m, 1 H), 1.80 (s, 3 H), 1.60 (s, 9 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.25 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.92, 155.36, 150.37, 136.75, 136.14, 129.05, 128.61, 128.10, 127.58, 116.49, 115.91, 112.07, 110.37, 84.31, 83.26, 71.00, 63.69, 36.87, 28.33, 24.70, 24.40, 21.62; MS (EI) *m/z* 537 (M^+, 6), 437 (13), 361 (11), 346 (18), 299 (10), 268 (4), 242 (5), 219 (6), 177 (9), 91 (100), 57 (82), 41 (25); HRMS (EI) calcd 537.1142, found 537.1133. Anal. Calcd for $C_{26}H_{29}Cl_2NO_5S$: C, 57.99; H, 5.42; N, 2.60. Found: C, 58.04; H, 5.45; N, 2.57.

(−)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(*tert*-butylsulfinyl)indole (37). To a solution of **20** (0.200 g, 0.59 mmol) in dry THF (15 mL) at −78 °C was added dropwise *sec*-BuLi (0.455 mL, 1.3 M in hexanes, 0.59 mmol). The mixture was stirred for 5 min and then quenched with a precooled solution of 3-(*tert*-butylsulfinyl)oxazolidin-2-one **36**[22] (0.208 g, 0.74 mmol) in THF (5 mL, −78 °C). After 5 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 3/1) to afford (−)-**37** (0.216 g, 83%) as a foamy solid (unstable): ^1H NMR ($CDCl_3$) δ 7.92 (m, 1 H), 7.48–7.30 (m, 5 H), 7.06 (m, 2 H), 5.13 (s, 2 H), 2.64 (s, 3 H), 1.66 (s, 9 H), 1.35 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.27, 149.66, 137.09, 131.87, 131.05, 128.55, 127.93, 127.45, 127.07, 125.47, 116.63, 115.83, 102.78, 84.95, 70.71, 61.95, 28.24, 23.99, 9.60.

5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-2-mercapto-3-methylindole (38). Zinc powder (0.17 g, 2.6 mmol) and CuCl (0.24 g, 2.6 mmol) in dry THF (3 mL) were heated at reflux for 1 h. The suspension was cooled to 0 °C, and a solution of sulfoxide **37** (0.107 g, 0.242 mmol) in dry THF (5 mL) was added. The suspension was vigorously stirred, and trichloroacetyl chloride (0.135 mL, 1.3 mmol) was added dropwise over 2.5 min. After the mixture was stirred for 5 min, the suspension was filtered through Celite into ice-cold saturated aqueous $NaHCO_3$. The filtrate was stirred for 5 min in an ice bath and then decanted, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 95/5) to afford **38** (0.055 g, 62%) as a yellow solid: mp 127–129 °C (methanol); IR (CH_2Cl_2) 2981 w, 1723 s, 1611 w, 1451 m, 1384 m, 1369 m, 1331 m, 1271 m, 1251 m, 1160 m, 1102 m, 1025 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (d, *J* = 9.1 Hz, 1 H), 7.46–7.34 (m, 5 H), 7.07 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.8 (d, *J* = 2.4 Hz, 1 H), 5.08 (s, 2 H), 1.72 (s, 3 H), 1.63 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.05, 149.85, 137.28, 137.07, 129.85, 128.95, 128.55, 127.91, 127.82, 127.54, 116.65, 116.15, 103.35, 83.90, 70.83, 28.21, 9.48; MS (EI) *m/z* 369 (M^+, <1), 313 (39), 269 (11), 178 (37), 150 (7), 91 (100), 57 (22), 44 (31), 41 (42); MS (CI, NH_3) 370 $(M + H)^+$; HRMS (EI) calcd 369.1398, found 369.1384. Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.26; H, 6.27; N, 3.79. Found: C, 68.47; H, 6.02; N, 3.70.

(−)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-(phenylsulfinyl)indole (40). To a solution of **20** (0.896 g, 2.65 mmol) in dry THF (50 mL) at −78 °C was added dropwise *sec*-BuLi (2 mL, 1.3 M in hexanes, 2.65 mmol). The mixture was stirred for 5 min and then quenched with a precooled solution of (phenylsulfinyl)oxazolidin-2-one **39**[21] (1 g, 3.32 mmol) in THF (20 mL, −78 °C). After 5 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4/1) to afford **40** (0.758 g, 62%) as a yellow oil (68% ee). Crystallization from EtOAc/hexanes afforded 0.235 g of a white solid (20% ee) and 0.523 g of an oil (95% ee, $[\alpha]_D$ = −63.4° (*c* = 2.4, CH_2Cl_2)): IR (CH_2Cl_2) 2983

w, 1721 s, 1610 w, 1444 m, 1371 m, 1330 m, 1247 m, 1156 m, 1106 s, 1043 m cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (d, J = 9 Hz, 1 H), 7.76 (m, 2 H), 7.47–7.34 (m, 8 H), 7.10–7.05 (m, 2 H), 5.11 (s, 2 H), 2.47 (s, 3 H), 1.59 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.31, 149.49, 145.70, 136.97, 135.02, 131.34, 130.63, 130.30, 128.86, 128.58, 127.98, 127.48, 125.81, 124.82, 116.53, 116.28, 103.02, 85.42, 70.66, 28.12, 8.80; MS (EI) m/z 461 (M^+, 3), 445 (3), 406 (3), 389 (30), 361 (64), 345 (62), 313 (13), 270 (75), 254 (69), 237 (22), 226 (39), 146 (30), 91 (100), 77 (20), 65 (24); HRMS (EI) calcd 461.1660, found 461.1652. Anal. Calcd for $C_{27}H_{27}NO_4S$: C, 70.25; H, 5.89; N, 3.03. Found: C, 70.39; H, 5.84; N, 3.10.

(−)-5-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-methyl-2-[(2,2-dimethylpropyl)sulfinyl]indole (42). To a solution of **20** (0.456 g, 1.35 mmol) in dry THF (25 mL) at −78 °C was added dropwise *sec*-BuLi (1 mL, 1.3 M in hexanes, 1.30 mmol). The mixture was stirred for 5 min and then quenched with [(2,2-dimethylpropyl)sulfinyl]oxazolidin-2-one **41**[22] (0.5 g, 1.69 mmol) in solution in precooled THF (7 mL, −78 °C). After 5 min, the mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 5/1) to afford (−)-**42** (0.484 g, 78%) as a white solid (>95% ee, $[\alpha]_D$ = −174° (c = 1.1, CH_2Cl_2)): mp 155–156 °C (hexanes/EtOAc); IR (CH_2Cl_2) 2963 s, 2870 m, 1722 s, 1610 m, 1451 s, 1369 s, 1319 m, 1284 m, 1247 s, 1158 s, 1105 s, 1047 s, 1024 m, 999 w, 936 w, 879 w, 834 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 1 H), 7.48–7.33 (m, 5 H), 7.06–7.02 (m, 2 H), 5.13 (s, 2 H), 3.15 and 3.09 (AB, J = 12.9 Hz, 2 H), 2.61 (s, 3 H), 1.67 (s, 9 H), 1.23 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.08, 149.78, 136.93, 135.74, 131.90, 129.80, 128.57, 127.97, 127.50, 123.29, 115.97, 115.57, 102.68, 84.95, 70.55, 70.34, 31.86, 29.86, 28.17, 8.67; MS (EI) m/z 455 (M^+, 6), 355 (27), 329 (12), 284 (100), 194 (25), 176 (10), 91 (62), 57 (52), 43 (28); HRMS (EI) calcd 455.2130, found 455.2132. Anal. Calcd for $C_{26}H_{33}NO_4S$: C, 68.53; H, 7.30; N, 3.07. Found: C, 68.63; H, 7.70; N, 3.09.

(−)-5-(Benzyloxy)-8-(*tert*-butoxycarbonyl)-3a-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one (24) from Sulfoxide (−)-42. Zinc powder (0.31 g, 4.7 mmol) and CuCl (0.87 g, 8.78 mmol) in dry THF (6 mL) were heated at reflux for 1 h. The suspension was cooled to −5 °C, and a solution of sulfoxide (−)-**42** (0.2 g, 0.44 mmol) in dry THF (7 mL) was added. The suspension was vigorously stirred, and trichloroacetyl chloride (0.245 mL, 2.19 mmol) was added dropwise over 2.5 min. After the mixture was stirred for 5 min, the suspension was filtered through Celite into ice-cold saturated aqueous $NaHCO_3$. The filtrate was stirred for 5 min in an ice bath and then decanted, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 15/1) to afford the dichloro lactone (0.196 g, 79%) as a white solid. The solid was treated with *n*-Bu_3SnH (0.28 mL, 3 equiv) and a catalytic amount of AIBN at reflux of toluene (5 mL). The reaction was followed by TLC, and aliquots (0.1 mL) of *n*-Bu_3SnH and AIBN were added every 4 h. After 48 h, the mixture was concentrated under reduced pressure, and the residue was partitioned between acetonitrile and light petroleum ether. After separation, the acetonitrile layer was washed several times with petroleum ether and then concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 95/5) to afford **24** (0.05 g, 36%, 28% from sulfoxide) as a white foamy solid (60% ee, $[\alpha]_D$ = −10.3° (c = 0.96, CH_2Cl_2)).

The white solid initially obtained above was 5-(benzyloxy)-8-(*tert*-butoxycarbonyl)-3,3-dichloro-3a-methyl-8a-[(2,2-dimethylpropyl)-sulfenyl]-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one: mp 138–138.5 °C (MeOH); IR (CH_2Cl_2) 2962 w, 1818 s, 1716 m, 1490 s, 1368 m, 1319 w, 1272 m, 1249 w, 1201 w, 1158 m, 1074 w, 1026 w, 975 w cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, J = 8.1 Hz, 1 H), 7.43–7.32 (m, 5 H), 6.97–6.93 (m, 2 H), 5.04 (s, 2 H), 2.59 and 2.49 (AB, J = 10.8 Hz, 2 H), 1.83 (s, 3 H), 1.60 (s, 9 H), 0.98 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 165.92, 155.21, 150.42, 136.66, 136.09, 128.89, 128.62, 128.11, 127.59, 116.38, 115.81, 112.18, 109.99, 84.17, 83.24, 70.86, 63.58, 45.13, 31.83, 29.10, 28.27; MS (EI) m/z 565 (M^+, 5), 531 (5), 465 (11), 431 (11), 374 (16), 361 (10), 340 (14), 327 (7), 300 (9), 270 (9), 248 (12), 208 (6), 177 (7), 91 (100), 71 (14), 57 (69), 41 (23); HRMS (EI) calcd 565.1456, found 565.1458. Anal. Calcd for $C_{28}H_{33}Cl_2NO_5S$: C, 59.35; H, 5.87; N, 2.47. Found: C, 59.29; H, 5.82; N, 2.53.

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Supplementary Material Available: Listings of full synthetic details and spectroscopic and analytical characterizations of compounds **10**, **12**, **14**, **15**, **16**, **18**, and **19** as well as intermediates **11** (2-methylsulfenyl derivative of **10**) and **13** (2-methylsulfenyl derivative of **14**) (8 pages). Ordering information is given on any masthead page.