Total Syntheses of (±)-Physovenine and (±)-Physostigmine. An Application of Tandem Electrocyclic-[3,3]Sigmatropic Reaction of Benzocyclobutenes

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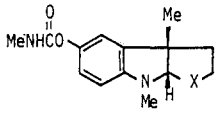
A high yield (40% overall yield) 14-step synthesis of (±)-physovenine and a formal synthesis of (±)-physostigmine, as applications of the tandem electrocyclic–[3,3]sigmatropic reaction of benzocyclobutenes, are described. The thermolysis of the benzocyclobutenyl allyl ester **6** gives quantitatively the isochromanone **7**, which can be elaborated to the key oxindole intermediate **8** in a seven-step sequence. (±)-Physovenine is obtained from **8** through a straightforward six-step sequence. The synthesis of (±)-physostigmine is formally accomplished by converting **8** into the amino lactam **25** by using the cyclic version of Grieco's cleavage of *N*-carbomethoxy γ-lactam. This represents a general strategy for an efficient construction of indole derivatives containing a quaternary center at the benzylic position.

In our previous communication[2] we had shown that the thermolyses of the benzocyclobutenes **1** with alkyl and allyl (or aryl) ester functionalities at C-1 position provided 4,4-disubstituted-isochroman-3-one **3** in high yield via tandem electrocyclic (ECR)–sigmatropic (STR) process of the (*Z*)-*o*-quinodimethane intermediate **2**, initial product of the thermolysis of **1** (Scheme I).

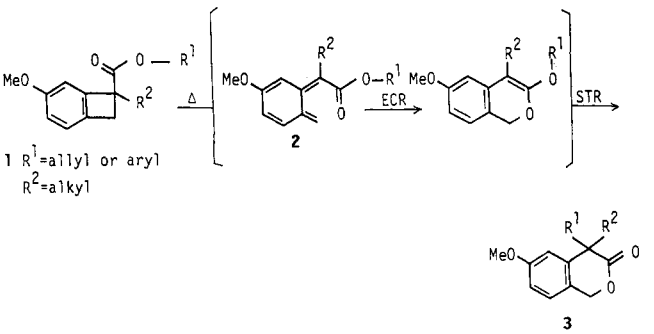
Since the resulting products (**3**) in the conversion contain two different functionalities, an allylic double bond and a lactone moiety, which may be manipulated into more complex products, this methodology provides a powerful tool for the construction of complex natural products especially those with a quaternary carbon at the benzylic position. Herein we demonstrate an application of the tandem ECR–[3,3]STR in the total syntheses of two kinds of Calabar bean alkaloids,[3] (±)-physovenine (**4**)[4] and (±)-physostigmine (**5**).[5]



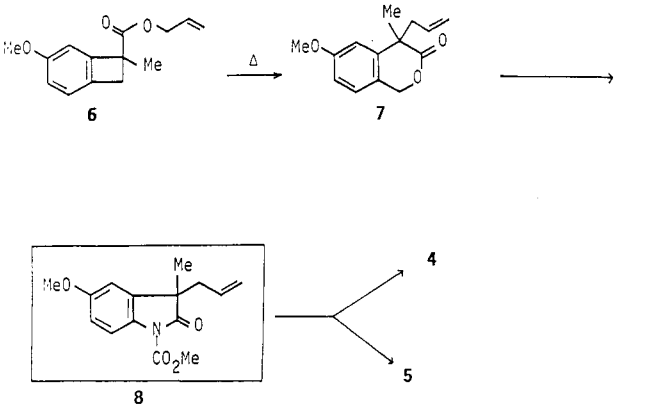
4 X=O
5 X=NMe

Our strategy for the synthesis of both alkaloids was to use a common precursor, oxindole compound (**8**), which would be derivable from the rearrangement product (**7**) of the readily available allyl 1,2-dihydro-5-methoxy-1-methylbenzocyclobutene-1-carboxylate (**6**). The key compound (**8**) contains an allyl side chain which may then be functionalized into the remainder of the targets without difficulty (Scheme II).

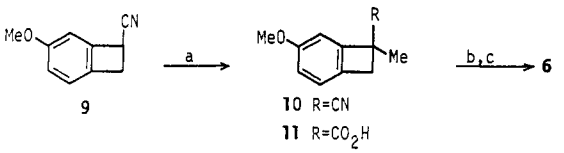
Scheme I



Scheme II



Scheme III[a]



[a] (a) LDA, HMPA, MeI, THF; (b) KOH, EtOH, H_2O; (c) allyl alcohol, DCC, 4-DMAP, CH_2Cl_2.

Results and Discussion

Total Synthesis of (±)-Physovenine. Preparation of the benzocyclobutene **6** from readily available 1-cyano-

(1) (a) Tohoku University. (b) Hoshi University.
(2) Shishido, K.; Shitara, E.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1985**, *107*, 5810.
(3) For reviews, see: (a) Robinson, B. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press; New York, 1968; Vol. X, Chapter 5. (b) Robinson, B. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press; New York, 1971; Vol. XIII, Chapter 4.
(4) Isolation: (a) Salway, A. H. *J. Chem. Soc.* **1911**, *99*, 2148. Structure: (b) Robinson, B. *J. Chem. Soc.* **1964**, 1503. Synthesis: (c) (±)-Physovenine: Longmore, R. B.; Robinson, B. *Chem. Ind. (London)* **1965**, 1297. (d) (-)-Physovenine: Longmore, R. B.; Robinson, B. *Chem. Ind. (London)* **1966**, 1638. (e) (+)-Physovenine: Dale, F. J.; Robinson, B. *J. Pharm. Pharmacol.* **1970**, *22*, 889. (f) (±)-Physovenine: Onaka, T. *Tetrahedron Lett.* **1971**, 4391.
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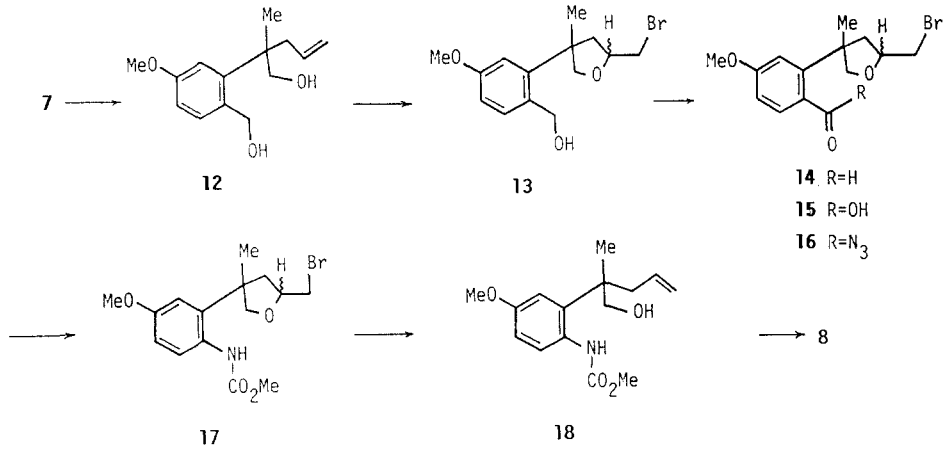
Scheme IV

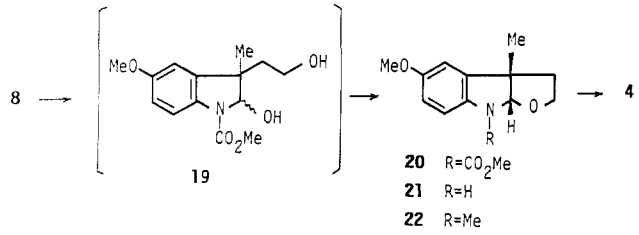


1,2-dihydro-5-methoxybenzocyclobutene (**9**)[6] was effected uneventfully in 85% overall yield by a standard series of reactions depicted in Scheme III. Full experimental details are reported in the Experimental Section.

A solution of **6** thus prepared in degassed *o*-dichlorobenzene was heated at 180 °C for 2 h to give 4-allyl-6-methoxy-4-methylisochroman-3-one (**7**), which contains all the requisite carbon units for the conversion into the natural products, quantitatively. After numerable unsuccessful trials at the conversion of **7** into **4**, we chose the following route that involved the oxindole intermediate **8**, a common precursor for both **4** and **5**. Assembling key compound **8** from **7** was achieved in 61% overall yield as shown in Scheme IV. Reduction of **7** with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) at room temperature gave the diol **12** which was then treated with *N*-bromosuccinimide in aqueous THF to give the bromo ether **13** as an inseparable mixture of diastereomers. Following oxidation of the primary alcohol moiety of **13** with Jones reagent in acetone at 0 °C, exposure of the resulting aldehyde **14** to oxidation conditions with sodium chlorite[8] in the presence of sulfamic acid produced the carboxylic acid **15**. The Curtius process, converting **15** into the carbamate **17**, was accomplished as follows. Treatment of **15** with *N,N*-dimethyl(chlorosulfino)methaniminium chloride, readily available in situ from dimethylformamide and thionyl chloride, and sodium azide, using the recently developed method by Palomo,[9] gave the acyl azide **16** which was heated in toluene followed by treatment with refluxing methanol to afford **17** in 48% yield. The low yield for this conversion was circumvented by using the well-established method of Shioiri.[10] Thus, exposure of the acid **15** to diphenylphosphoryl azide in refluxing benzene followed by refluxing with mthanol led to smooth rearrangement to give the carbamate, identical with the authentic material, quantitatively. Deprotection of the bromo ether with zinc–copper couple, and subsequent oxidation of the resulting alcohol **18** with pyridinium dichromate, provided the oxindole **8**, thus forming the key intermediate (Scheme IV).

Now the stage was set for introduction of the C-ring. Ozonolytic cleavage of **8** led to the diol **19**, a mixture of diastereomers, after reductive workup with sodium borohydride. This diol, without further purification, was then

Scheme V



treated with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane to furnish the furo[2,3-*b*]indole (**20**) in 86% yield. With a fully functionalized framework of physovenine available, we next addressed the task of introducing the *N*-methyl group. Reduction of **20** with LAH generated the labile decarbomethoxylated product **21** which was converted to **22** by a standard treatment with formalin and sodium cyanoborohydride[11] in 92% yield. Finally, cleavage of the methyl ether in **22** with boron tribromide in dichloromethane at 0 °C followed by treatment of the resulting phenol with methyl isocyanate in THF in the presence of a catalytic amount of sodium hydride afforded racemic physovenine in 83% yield. ^{1}H NMR, IR, and mass spectral as well as TLC behavior of our synthetic **4** were indistinguishable from those of a sample of the natural product generously provided by Professor Robinson (Scheme V).

Formal Total Synthesis of (±)-Physostigmine. With the successful synthesis of the oxindole **8** behind us we were ready to effect its conversion to physostigmine. In a previous paper, Grieco has reported the regioselective hydrolysis of *N*-*t*-Boc derivatives of lactams. Lithium hydroxide treatment or methanolysis under mild conditions gave the corresponding ω-amino acids or esters, respectively.[12]

Assuming that this reaction can also occur by intramolecular attack of a nitrogen nucleophile, reductive amination of the aldehyde, generated from **8** should provide the lactam carbamate **24** spontaneously. Since the amino lactam **25** has previously been converted into physostigmine in a four-step sequence,[5e,13] the preparation of **25** indicates the completion of the formal synthesis. Thus, oxidative cleavage of the double bond of **8** with sodium metaperiodate and osmium tetraoxide followed by reductive amination with methylamine hydrochloride and sodium cyanoborohydride provided the expected lactam

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(11) For a review, see: Lane, C. F. *Synthesis* **1975**, 135.
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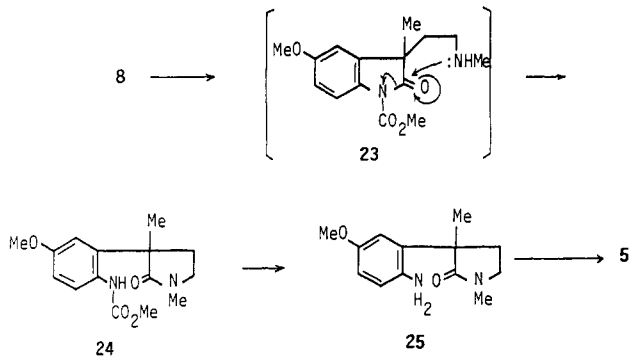
Scheme VI



carbamate **24**, via the initially formed secondary amine **23**, in 63% yield. Finally, treatment of **24** with dimethyl sulfide and aluminum trichloride[14] in dichloromethane at room temperature gave the amino lactam **25** in 63% yield. Comparison (IR, ^{1}H NMR, MS, and TLC) of material prepared in this way with a sample of the optically active **25** generously supplied by Professor Takano indicated that the formal synthesis was complete and our objectives had been achieved (Scheme VI).

Conclusion

We have described a high yield (40% overall yield), 14-step synthesis of (±)-physovenine and a formal synthesis of (±)-physostigmine using the intramolecular version of Grieco's cleavage from a common precursor that demonstrates the versatility and synthetic utility of the tandem ECR–[3,3]STR not only for the synthesis of Calabar bean alkaloids but also for the construction of indole derivatives containing a quaternary carbon at the benzylic position. Further applications of the tandem methodology are in progress and will be reported in due course.

Experimental Section

Melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL PMX-60 (60 MHz) or JEOL PS-100 (100 MHz) spectrometer in deuteriochloroform solution with tetramethylsilane as the internal standard. Chemical shifts are reported in δ units. When peak multiplicities are reported the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broadened. ^{13}C NMR spectra were obtained on a JEOL PS-100 spectrometer operating at a frequency of 25 MHz. Infrared spectra were obtained on a Hitachi 125 grating spectrophotometer as a chloroform solution. Ultraviolet spectra were recorded on a Hitachi 320 spectrophotometer in ethanol. Ordinary mass spectra were measured with a Hitachi M-52G instrument, while high-resolution mass spectroscopy was performed on a JEOL TMS-01SG-2 spectrometer. All reactions were run under an atmosphere of dry argon. Solvents were freshly distilled prior to use: tetrahydrofuran (THF) was distilled from $LiAlH_4$ and kept over sodium wire; dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide and kept over 4-Å molecular sieves. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous magnesium sulfate. Column chromatography was carried out with silica gel (Wako gel C-200). Preparative thin layer chromatography (preparative TLC) was performed on 20 × 20 cm plates coated with 1.75-mm thickness of silica gel (Kieselgel 60, Merck) containing PF254 indicator. All chromatography solvents were distilled prior to use.

1-Cyano-1,2-dihydro-5-methoxy-1-methylbenzocyclobutene (10). *n*-BuLi (41 mL, 1.47 M in hexane, 60.5 mmol) was added to a solution of diisopropylamine (8.8 mL, 60.5 mmol) in dry THF (200 mL) at −78 °C and the resulting mixture was stirred at the same temperature for 15 min. Then a solution of 1-cyano-1,2-dihydro-5-methoxybenzocyclobutene (**9**)[6] (8.0 g, 50.4 mmol) in dry THF (40 mL) was added dropwise to the mixture at −78 °C. After being stirred for 50 min, hexamethylphosphoric triamide[15] (8.8 mL, 50.4 mmol) was added and the stirring was continued for 20 min, then methyl iodide (3.8 mL, 60.5 mmol) was added in one portion. After being stirred at −78 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and the solvent was removed in vacuo. The residue was extracted with Et_2O, and the organic phase was washed with brine and dried. Evaporation of the solvent in vacuo gave a pale yellow solid which was recrystallized from Et_2O/*n*-hexane to yield 8.6 g (98%) of **10** as colorless prisms: mp 72–73 °C: IR ($CHCl_3$) cm^{-1} 2225; ^{1}H NMR (60 MHz) δ 1.75 (3 H, s), 3.10 (1 H, d, J = 13.0 Hz), 3.69 (1 H, d, J = 13.0 Hz), 3.73 (3 H, s), 6.70 (1 H, d, J = 2.0 Hz), 6.77 (1 H, dd, J = 8.0 and 2.0 Hz), 6.97 (1 H, d, J = 8.0 Hz); mass spectrum, m/e (relative intensity) 173 (M^+, 100); exact mass calcd for $C_{11}H_{11}NO$ 173.0839, found 173.0838. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40. Found: C, 76.49; H, 6.61.

1,2-Dihydro-5-methoxy-1-methylbenzocyclobutene-1-carboxylic Acid (11). A solution of the cyanide **10** (3.1 g, 17.9 mmol) in EtOH (45 mL) was mixed with water (9 mL) containing KOH (5.0 g, 89.3 mmol), and the mixture was heated at 100 °C for 11 h. After removal of the solvent in vacuo, water (10 mL) was added to the residue and the aqueous phase was extracted with CH_2Cl_2. The aqueous layer was then acidified with 10% H_2SO_4 and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated in vacuo to give a pale yellow solid which was recrystallized from Et_2O/*n*-hexane to yield 3.4 g (100 %) of **11** as colorless prisms: mp 69–70 °C: IR ($CHCl_3$) cm^{-1} 1700; ^{1}H NMR (60 MHz) δ 1.68 (3 H, s), 2.92 (1 H, d, J = 13.0 Hz), 3.63 (1 H, d, J = 13.0 Hz), 3.73 (3 H, s), 6.63–7.00 (3 H, m); mass spectrum, m/e (relative intensity) 192 (M^+), 163 (100). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.58; H, 6.16.

Allyl 1,2-Dihydro-5-methoxy-1-methylbenzocyclobutene-1-carboxylate (6). A solution of the carboxylic acid **11** (6.0 g, 31.3 mmol) in dry CH_2Cl_2 (120 mL) was mixed with dicyclohexylcarbodiimide (7.1 g, 34.4 mmol), allyl alcohol (2.32 mL, 34.4 mmol), and 4-(dimethylamino)pyridine (0.19 g, 1.56 mmol). The mixture was stirred at room temperature for 1 h and filtered through Celite. The filtrate was concentrated in vacuo to give the residue which was purified by column chromatography (eluting with 5:95 AcOEt/*n*-hexane) to yield 6.3 g (87 %) of **6** as a colorless oil: IR ($CHCl_3$) cm^{-1} 1720; ^{1}H NMR (60 MHz) δ 1.70 (3 H, s), 2.93 (1 H, d, J = 13.0 Hz), 3.67 (1 H, d, J = 13.0 Hz), 3.77 (3 H, s), 4.60 (2 H, d, J = 5.0 Hz), 5.03–6.23 (3 H, m), 6.67–7.07 (3 H, m); mass spectrum, m/e (relative intensity) 232 (M^+), 163 (100). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6, 94. Found: C, 72.32; H, 6.97.

4-Allyl-6-methoxy-4-methylisochroman-3-one (7). A solution of the benzocyclobutene **6** (13.5 g, 58.2 mmol) in degassed *o*-dichlorobenzene (1 L) was heated at 180 °C for 2.5 h. After removal of the solvent in vacuo, the residue, still containing *o*-dichlorobenzene, was purified by column chromatography (eluting with 25:75 AcOEt/*n*-hexane) to yield 13.7 g (100%) of **7** as a colorless oil: IR ($CHCl_3$) cm^{-1} 1730; ^{1}H NMR (100 MHz) δ 1.58 (3 H, s), 2.58 (2 H, m), 3.80 (3 H, s), 5.22 (1 H, d, J = 14.0 Hz), 5.44 (1 H, d, J = 14.0 Hz), 4.88–5.76 (3 H, m), 6.76 (1 H, d, J = 8.5 Hz), 6.79 (1 H, d, J = 3.0 Hz), 7.04 (1 H, d, J = 8.5 Hz); mass spectrum, m/e (relative intensity) 232 (M^+), 163 (100); exact mass calcd for $C_{14}H_{16}O_3$ 232.1100, found 232.1103. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.24; H, 6.75.

3-Methyl-3-(2-(hydroxymethyl)-5-methoxyphenyl)pent-4-en-1-ol (12). A solution of the isochromanone **7** (13.4 g, 57.8 mmol) in dry THF (220 mL) was added dropwise to a suspension of $LiAlH_4$ (3.30 g, 87.0 mmol) in dry THF (250 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, then cooled to 0 °C, and quenched by the slow addition of Et_2O containing water. After filtration through Celite, the filtrate was concentrated in vacuo to give 14.7 g (108%) of **12** as a colorless oil which was used for the next step without further purification. An analytical sample of **12** could be obtained by column chromatography

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(15) A highly toxic cancer suspect agent.

(eluting with 1:1 AcOEt/*n*-hexane): IR ($CHCl_3$) cm^{-1} 3580, 3400; ^1H NMR (60 MHz) δ 1.47 (3 H, s), 2.40 (2 H, br m, D_2O exchangeable), 2.47 (2 H, t, J = 8.0 Hz), 3.60 (1 H, d, J = 11.0 Hz), 3.80 (3 H, s), 4.03 (1 H, d, J = 11.0 Hz), 4.56–6.00 (5 H, m), 6.73 (1 H, dd, J = 8.0 and 2.5 Hz), 6.92 (1 H, d, J = 2.5 Hz), 7.23 (1 H, d, J = 8.0 Hz); mass spectrum, m/e (relative intensity) 218 ($M^+ - H_2O$), 149 (100). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.95; H, 8.67.

2-(Bromomethyl)-4-(2-(hydroxymethyl)-5-methoxyphenyl)-4-methyltetrahydrofuran (13). *N*-Bromosuccinimide (1.06 g, 5.96 mmol) was added to a solution of the diol **12** (1.28 g, 5.42 mmol) in THF (24 mL)–water (1.8 mL) at −78 °C. After being stirred at −78 °C for 2 h, the solvent was removed in vacuo to give the residue which was extracted with Et_2O. The organic phase was washed with saturated aqueous sodium thiosulfate and brine. The organic layer was dried and the solvent was evaporated in vacuo to give the residue which was purified by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) to yield 1.88 g (100%) of **13**, a mixture of diastereomers, as a colorless oil: IR ($CHCl_3$) cm^{-1} 3580; ^1H NMR (60 MHz) δ 1.46 (3 H, s), 2.30 (1 H, br s, D_2O exchangeable), 3.46 (2 H, t, J = 5.0 Hz), 3.80 (3 H, s), 4.63 (2 H, d, J = 2.0 Hz), 6.60–7.46 (3 H, m); mass spectrum, m/e (relative intensity) 316 and 314 (M^+), 160 and 162 (100); exact mass calcd for $C_{14}H_{19}O_3Br$ 314.0518 and 316.0496, found 314.0518 and 316.0496. Anal. Calcd for $C_{14}H_{19}O_3Br$: C, 53.51; H, 5.77. Found: C, 53.22; H, 5.84.

2-(Bromomethyl)-4-(2-formyl-5-methoxyphenyl)-4-methyltetrahydrofuran (14). The alcohol **13** (1.71 g, 5.43 mmol) in acetone (36 mL) at 0 °C was treated dropwise with Jones reagent (3.9 mL). After being stirred at 0 °C for 20 min an excess of isopropyl alcohol was added and the solution was warmed to room temperature. After removal of the solvent, water (10 mL) was added to the residue and the mixture was extracted with Et_2O. The organic phase was washed with brine and dried. Evaporation of the solvent gave 1.65 g (97%) of **14**, a mixture of diastereomers, as a colorless oil which was used for the next step without further purification. An analytical sample of **14** could be obtained by column chromatography (eluting with 3:7 AcOEt/*n*-hexane): IR ($CHCl_3$) cm^{-1} 1680; ^1H NMR (60 MHz) δ 1.60 (3 H, s), 3.87 (3 H, s), 6.83 (2 H, m), 7.87 (1 H, d, J = 8.0 Hz), 10.27 (1 H, d, J = 2.5 Hz); mass spectrum, m/e (relative intensity) 314 and 312 (M^+), 175 (100); exact mass calcd for $C_{14}H_{17}O_3Br$ 312.0362 and 314.0342, found 312.0377 and 314.0355.

2-(Bromomethyl)-4-(2-carboxy-5-methoxyphenyl)-4-methyltetrahydrofuran (15). A solution of the aldehyde **14** (6.16 g, 19.7 mmol) in *tert*-butyl alcohol (27 mL) was mixed with sodium chlorite (23.1 g, 256 mmol), sulfamic acid (24.9 g, 256 mmol), and water (214 mL). After being stirred at room temperature for 1 h, the mixture was extracted with Et_2O, then the organic phase was washed with brine, and dried. Removal of the solvent gave the residue which was taken up with CH_2Cl_2 and the organic phase was extracted with 5% NaOH. The alkaline phase was acidified with 10% H_2SO_4 and then extracted with Et_2O, and the organic layer was washed with brine and dried. Evaporation of the solvent yielded 5.47 g (84%) of **15**, a mixture of diastereomers, as a colorless oil which was used for the next step without further purification. An analytical sample of **15** could be obtained by column chromatography (eluting with 4:6 AcOEt/*n*-hexane) as colorless needles, mp 118–119 °C, after recrystallization from benzene/*n*-hexane: IR ($CHCl_3$) cm^{-1} 3500, 1700; ^1H NMR (60 MHz) δ 1.66 (3 H, s), 3.47 (2 H, t, J = 6.0 Hz), 3.83 (3 H, s), 6.77 (2 H, m), 7.80 (1 H, dd, J = 9.0 and 2.5 Hz), 11.75 (1 H, br s, D_2O exchangeable); mass spectrum, m/e (relative intensity) 330 and 328 (M^+), 175 (100); exact mass calcd for $C_{14}H_{17}O_4Br$ 328.0310 and 330.0290, found 328.0275 and 330.0265. Anal. Calcd for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.21. Found: C, 51.05; H, 5.29.

2-(Bromomethyl)-4-(2-((methoxycarbonyl)amino)-5-methoxyphenyl)-4-methyltetrahydrofuran (17). (a) The Curtius Rearrangement. In a 30-mL dropping funnel, dry benzene (10 mL), DMF (2 mL, 20.4 mmol), and thionyl chloride (1.6 mL, 22.0 mmol) were consecutively added; after 3–5 min, two phases were separated. *N,N*-Dimethyl(chlorosulfino)methaniminium chloride (lower layer) was added dropwise to a solution of the carboxylic acid **15** (4.2 g, 12.8 mmol), sodium azide (1.66 g, 25.6 mmol) tetrabutylammonium bromide (4.12 g, 12.8 mmol), and pyridine (1.93 mL, 12.8 mmol) in dry CH_2Cl_2 (100 mL) at room temperature. After being stirred for 1.5 h, the mixture was extracted with CH_2Cl_2, and the organic phase was washed with 10% HCl followed by brine and dried. Evaporation of the solvent in vacuo afforded 6.24 g of the crude keto azide **16** which was carried on to the next step without further purification. A solution of the crude **16** (6.24 g, 17.6 mmol) in dry toluene (60 mL) was heated under reflux for 7 h. After removal of the solvent in vacuo, the residue was taken up with MeOH (60 mL) and the solution was heated under reflux for 2 h. Evaporation of the solvent in vacuo followed by column chromatography (eluting with 1:3 AcOEt/*n*-hexane) yielded 2.18 g (48%) of **17**, a mixture of diastereomers, as a colorless oil: IR ($CHCl_3$) cm^{-1} 3430, 1725; ^1H NMR (60 MHz) δ 1.43 (3 H, br s), 2.10–2.80 (2 H, m), 3.27–3.60 (2 H, m), 3.74 (3 H, s), 3.78 (3 H, s), 3.97–4.57 (3 H, m), 6.37 (1 H, br s), 6.64 (1 H, d, J = 2.4 Hz), 6.73 (1 H, dd, J = 10.0 and 2.4 Hz), 7.29 (1 H, d, J = 10.0 Hz); mass spectrum, m/e (relative intensity) 359 and 357 (M^+), 220 (100); exact mass calcd for $C_{15}H_{20}NO_4Br$ 357.0576 and 359.0557, found 357.0576 and 359.0565. Anal. Calcd for $C_{15}H_{20}NO_4Br$: C, 50.43; H, 5.36; N, 3.92. Found: C, 50.28; H, 5.25; N, 4.20.

(b) The Shioiri Reaction. A solution of **15** (1.32 g, 4.02 mmol) in dry benzene (240 mL) was mixed with diphenylphosphoryl azide (4.8 mL, 22.1 mmol) and triethylamine (8.3 mL, 59.9 mmol), the mixture was heated under reflux for 1 h, and then MeOH (16.2 mL) was added and further refluxed for 3 h. After removal of the solvent in vacuo, the residue was extracted with Et_2O, and the organic phase was washed with brine and dried. Evaporation of the solvent in vacuo followed by column chromatography (eluting with 1:3 AcOEt/*n*-hexane) yielded 1.58 g (100%) of **17** which was identical with a sample prepared by the method a.

Methyl (2-(1-(Hydroxymethyl)-1-methyl-3-butenyl)-4-methoxyphenyl)carbamate (18). A solution of the carbamate **17** (0.30 g, 0.83 mmol) in EtOH (58 mL) was mixed with Zn–Cu couple (0.88 g) and water (1.5 mL) containing NH_4Cl (0.29 g, 5.41 mmol). The mixture was heated under reflux for 8 h; then the mixture was filtered through Celite. Evaporation of the filtrate in vacuo followed by column chromatography (eluting with 3:97 MeOH/$CHCl_3$) yielded 0.22 g (95%) of **18** as colorless needles, mp 106–107 °C, after recrystallization from Et_2O/*n*-hexane: IR ($CHCl_3$) cm^{-1} 3450, 3280, 1705; ^1H NMR (100 MHz) δ 1.32 (3 H, s), 2.24 (1 H, dd, J = 14.0 and 8.0 Hz), 2.54 (1 H, br s, D_2O exchangeable), 2.94 (1 H, dd, J = 14.0 and 6.0 Hz), 3.70 (2 H, m), 3.72 (3 H, s), 3.76 (3 H, s), 4.80–5.72 (3 H, m), 6.78 (2 H, m), 7.32 (1 H, m), 8.09 (1 H, br s, D_2O exchangeable); mass spectrum, m/e (relative intensity) 279 (M^+), 150 (100); exact mass calcd for $C_{15}H_{21}NO_4$ 279.1471, found 279.1478. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.48; H, 7.30; N, 4.83.

3-Allyl-1-carbomethoxy-5-methoxy-3-methyloxindole (8). The alcohol **18** (0.34 g, 1.24 mmol) was added to a solution of pyridinium dichromate (2.76 g, 7.32 mmol) in dry DMF (8.5 mL) at room temperature, and the mixture was further stirred for 22 h. After addition of Florisil, the mixture was diluted with Et_2O and filtered through Celite. Concentration of the filtrate in vacuo followed by column chromatography (eluting with 1:4 AcOEt/*n*-hexane) yielded 0.26 g (79%) of **8** as colorless needles, mp 80–81 °C, after recrystallization from Et_2O/*n*-hexane: IR ($CHCl_3$) cm^{-1} 1765, 1735; ^1H NMR (100 MHz) δ 1.41 (3 H, s), 2.54 (2 H, dd, J = 8.0 and 3.0 Hz), 3.80 (3 H, s), 3.98 (3 H, s), 4.84–5.64 (3 H, m), 6.73 (1 H, d, J = 2.5 Hz), 6.78 (1 H, dd, J = 9.0 and 2.5 Hz), 7.81 (1 H, dd, J = 9.0 and 1.0 Hz); ^{13}C NMR (25 MHz) δ 23.863 (q), 43.269 (t), 49.140 (s), 53.720 (q), 55.598 (q), 109.318 (d), 112.489 (d), 115.894 (d), 119.473 (t), 131.629 (d), 131.802 (s), 133.742 (s), 151.473 (s), 157.109 (s), 178.358 (s); UV λ_{max} (EtOH) 233 nm (ϵ 10719), 255 (2548), 290 (959); mass spectrum, m/e (relative intensity) 275 (M^+), 234 (100); exact mass calcd for $C_{15}H_{17}NO_4$ 275.1156, found 275.1120. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.14; H, 6.36; N, 5.10.

1-Carbomethoxy-2-hydroxy-3-(2-hydroxyethyl)-5-methoxy-3-methylindoline (19). A solution of the oxindole **8** (0.26 g, 0.94 mmol) in MeOH (10 mL)–CH_2Cl_2 (5 mL) was cooled to −78 °C and treated with ozone until a blue color persisted. After the excess ozone was discharged by bubbling nitrogen through the solution, $NaBH_4$ (0.25 g, 6.61 mmol) was added, and the solution was allowed to warm slowly to room temperature. After being stirred for 2 h, the solvent was removed to leave the residue which was extracted with $CHCl_3$; the organic phase was washed

with brine and dried. Concentration in vacuo gave 0.28 g (105%) of the diol **19**, a mixture of diastereomers [analytical sample could be obtained by column chromatography (eluting with 1:3 AcOEt/*n*-hexane)]: IR ($CHCl_3$) cm^{-1} 3575, 3400, 1700; ^1H NMR (100 MHz) δ 1.24 (3 H, s), 2.12 (2 H, m), 3.61 (2 H, m), 3.76 (3 H, s), 3.88 (3 H, s), 5.50 (1 H, s), 6.70 (2 H, m), 7.54 (1 H, d, J = 8.0 Hz); mass spectrum, m/e (relative intensity) 281 (M^+), 178 (100); exact mass calcd for $C_{14}H_{19}NO_5$ 281.1262, found 281.1262, as a colorless oil which was carried on to the next step without further purification.

3,3a,8,8a-Tetrahydro-8-carbomethoxy-5-methoxy-3a-methyl-2*H*-furo[2,3-*b*]indole (20). A solution of **19** (0.28 g, 1.0 mmol) in CH_2Cl_2 (11 mL) was mixed with a catalytic amount of *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 10 min. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 15:85 AcOEt/*n*-hexane) yielded 0.21 g (86 %) of **20** as a colorless oil: IR ($CHCl_3$) cm^{-1} 1700; ^1H NMR (100 MHz) δ 1.48 (3 H, s), 2.00–2.28 (2 H, m), 3.32–3.64 (1 H, m), 3.77 (3 H, s), 3.85 (3 H, s), 3.88–4.08 (1 H, m), 5.68 (1 H, br s), 6.69 (1 H, d, J = 2.7 Hz), 6.74 (1 H, dd, J = 8.0 and 2.7 Hz), 7.67 (1 H, m); mass spectrum, m/e (relative intensity) 263 (M^+ 100); exact mass calcd for $C_{14}H_{17}NO_4$ 263.1157, found 263.1158. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.63; H, 6.40; N, 5.13.

3,3a,8,8a-Tetrahydro-5-methoxy-3a-methyl-2*H*-furo[2,3-*b*]indole (21). A solution of $LiAlH_4$ (5 mg, 0.1 mmol) in dry THF (0.3 mL) was added dropwise to a solution of **20** (3.0 mg, 0.01 mmol) in dry THF (0.7 mL) at 0 °C. After being stirred for 1.5 h, the mixture was quenched with Et_2O containing water and extracted with AcOEt. The organic phase was washed with brine and dried. Concentration gave 2.3 mg (98%) of **21** as an unstable oil which was carried on to the next step without further purification: IR ($CHCl_3$) cm^{-1} 3400; mass spectrum, m/e 205 (M^+).

3,3a,8,8a-Tetrahydro-5-methoxy-3a,8-dimethyl-2*H*-furo[2,3-*b*]indole (22). $NaCNBH_3$ (0.92 mg, 0.02 mmol) was added to a solution of **21** (2.0 mg, 0.01 mmol) in MeOH (1.0 mL) at 0 °C; the mixture was then adjusted with 1% HCl to pH 4–5 and 35% aqueous formalin (0.3 mL, 3.5 mmol) was added. After being stirred at room temperature for 12 h, the solvent was removed in vacuo to give the residue which was treated with 28% aqueous NH_4OH to make the solution basic, and the resulting solution was extracted with AcOEt. The organic phase was washed with brine and dried. Evaporation of the solvent in vacuo followed by column chromatography on neutral alumina (eluting with 1:9 AcOEt/*n*-hexane) yielded 2.0 mg (94%) of **22** as a colorless oil: the picrate, mp 135–139 °C (lit.[4c] mp 136–139 °C); ^1H NMR (100 MHz) δ 1.44 (3 H, s), 1.90–2.24 (2 H, m), 2.87 (3 H, br s), 3.28–3.60 (1 H, m), 3.74 (3 H, br s), 3.80–4.04 (1 H, m), 5.01 (1 H, br s), 6.26 (1 H, d, J = 10.0 Hz), 6.58 (1 H, d, J = 3.2 Hz), 6.62 (1 H, dd, J = 10.0 and 3.2 Hz); mass spectrum, m/e (relative intensity) 219 (M^+, 100); exact mass calcd for $C_{13}H_{17}NO_2$ 219.1258, found 219.1251.

(±)-Physovenine (4). Boron tribromide (0.2 mL, 0.18 mmol) was added dropwise to a solution of **22** (6.0 mg, 0.04 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. After being stirred at room temperature for 3 h, saturated aqueous $NaHCO_3$ (1 mL) was added to the reaction mixture, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried. Evaporation of the solvent in vacuo gave 10 mg of the crude phenol as a colorless oil which was taken up with dry THF (1 mL), and a catalytic amount of sodium hydride was added to the solution at 0 °C. Then methyl isocyanate (0.1 mL, 1.7 mmol) was added dropwise to the mixture at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After quenching with water, removal of the solvent gave the residues which was extracted with $CHCl_3$; the organic phase was washed with brine and dried. Evaporation of the solvent followed by preparative TLC (developing with 15:85 MeOH/$CHCl_3$) yielded 6.0 mg (83%) of (±)-**4** as colorless prisms, mp 145–146 °C (lit.[4c] mp 142–143 °C), after recrystallization from Et_2O: IR ($CHCl_3$) cm^{-1} 3475, 1735; ^1H NMR (100 MHz) δ 1.43 (3 H, s), 2.08 (2 H, m), 2.86 (3 H, d, J = 4.0 Hz), 2.87 (3 H, s), 3.44 (1 H, m), 3.90 (1 H, m), 5.04 (1 H, s), 6.26 (1 H, d, J = 9.0 Hz), 6.78 (2 H, m); UV λ_{max} (EtOH) 252 nm (ϵ 12860), 310 (2950); mass spectrum, m/e (relative intensity) 262 (M^+), 205 (100).

1,3-Dimethyl-3-(2-((methoxycarbonyl)amino)-5-methoxyphenyl)-2-pyrrolidone (24). Sodium metaperiodate (198 mg, 0.93 mmol) was added dropwise to a solution of the oxindole **8** (26.5 mg, 0.10 mmol) and osmium tetraoxide (1.2 mg, 4.7 μmol) in Et_2O (1.1 mL)–water (1.1 mL) at room temperature. After being stirred for 2 h, the mixture was extracted with Et_2O; then the organic phase was washed with brine and dried. Evaporation of the solvent gave the residue which was taken up with MeOH (1.4 mL) and the solution was mixed with methylamine hydrochloride (13 mg, 0.19 mmol) and $NaCNBH_3$ (6.1 mg, 0.10 mmol). After being stirred at room temperature for 7 h, concentration gave the residue which was treated with K_2CO_3 to make the solution alkaline, and the resulting mixture was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over K_2CO_3, and evaporated to give the residue which was purified by column chromatography (eluting with $CHCl_3$) to yield 17.8 mg (63%) of **24** as colorless prisms, mp 150–151 °C, after recrystallization from benzene/*n*-hexane: IR ($CHCl_3$) cm^{-1} 3400, 1720, 1668; ^1H NMR (100 MHz) δ 1.57 (3 H, s), 2.08 (1 H, m), 2.62 (1 H, m), 2.89 (3 H, s), 3.41 (2 H, t, J = 7.0 Hz), 3.75 (3 H, s), 3.79 (3 H, s), 6.80 (2 H, m), 7.57 (1 H, d, J = 9.0 Hz), 9.32 (1 H, br s); mass spectrum, m/e 292 (M^+, 100); exact mass calcd for $C_{15}H_{20}N_2O_4$ 292.1423, found 292.1424. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.65; H, 7.03; N, 9.41.

3-(2-Amino-5-methoxyphenyl)-1,3-dimethyl-2-pyrrolidone (25). A solution of the carbamate **24** (13.0 mg, 0.045 mmol) in dimethyl sulfide (0.14 mL)–CH_2Cl_2 (0.04 mL) was added dropwise to a solution of freshly sublimed aluminum trichloride (19.8 mg, 0.015 mmol) in dimethyl sulfide (0.06 mL) at room temperature. After being stirred for 10 h, water (0.5 mL) was added and the solution was adjusted to slightly alkaline with K_2CO_3. The resulting mixture was extracted with CH_2Cl_2; the organic phase was washed with brine and dried over K_2CO_3. Evaporation of the solvent followed by preparative TLC (developing with AcOEt) yielded 3.5 mg (63%, based on consumed **24**) of **25** as a brownish oil, and 6.1 mg of recovered **24**: IR ($CHCl_3$) cm^{-1} 3425, 1675; ^1H NMR (100 MHz) δ 1.61 (3 H, s), 2.00 (1 H, sextet, J = 6.0 Hz), 2.30 (2 H, br s, D_2O exchangeable), 2.72 (1 H, m), 2.88 (3 H, s), 3.40 (2 H, m), 3.73 (3 H, s), 6.60–6.84 (3 H, m); mass spectrum, m/e (relative intensity) 234 (M^+), 177 (100); exact mass calcd for $C_{13}H_{18}N_2O_2$ 234.1368, found 234.1370.

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Registry No. (±)-**4**, 2520-34-5; (±)-**5**, 69926-97-2; (±)-**6**, 102615-89-4; (±)-**7**, 102615-90-7; (±)-**8**, 102615-91-8; (±)-**9**, 56221-52-4; (±)-**10**, 102615-92-9; (±)-**11**, 102615-93-0; (±)-**12**, 102615-94-1; (±)-**13** (isomer 1), 102615-95-2; (±)-**13** (isomer 2), 102616-05-7; (±)-**14** (isomer 1), 102615-96-3; (±)-**14** (isomer 2), 102616-06-8; (±)-**15** (isomer 1), 102615-97-4; (±)-**15** (isomer 2), 102616-07-9; **16**, 102615-98-5; (±)-**17** (isomer 1), 102615-99-6; (±)-**17** (isomer 2), 102616-08-0; (±)-**18**, 102616-00-2; (±)-**19** (isomer 1), 102616-01-3; (±)-**19** (isomer 2), 102616-09-1; (±)-**20**, 102616-02-4; (±)-**21**, 102616-03-5; (±)-**22**, 16641-65-9; (±)-**22**-ol, 102615-88-3; (±)-**24**, 102616-04-6; (±)-**25**, 102680-33-1; allyl alcohol, 107-18-6.