

A Formal Asymmetric Synthesis of Calabar Bean Alkaloids¹⁾

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A total synthesis of (–)-eserethole (2) has been accomplished using the Diels–Alder reaction of (S)-(–)-2-methyl-2-[2-(E)-nitroethenyl]-δ-valerolactone (3) and Danishefsky's diene as a key step. The synthesis of optically pure (–)-eserethole (2) constitutes a formal synthesis of naturally occurring Calabar bean alkaloids, such as (–)-physostigmine (1), (–)-physovenine (17) and (–)-geneserine (18).

Key words (–)-eserethole; (–)-physostigmine; asymmetric nitroolefination; Diels–Alder reaction; nitro group; aromatization

(–)-Physostigmine (1), a major alkaloid from Calabar bean (*Physostigma venenosum* BALFOUR), is an acetylcholinesterase inhibitor,^{2a,b} and is used clinically to treat glaucoma³ and myasthenia gravis.⁴ More importantly, this alkaloid is a candidate agent for the treatment of Alzheimer's disease.⁵ This is reflected by a number of syntheses of this alkaloid^{6,7} since the first synthesis by Julian and Piki^{7a} in 1935. Some physostigmine analogues are more active than (–)-1 as acetylcholinesterase inhibitors.^{2c,d,8} The first asymmetric synthesis of naturally occurring (–)-physostigmine (1) was accomplished by Takano *et al.*^{7k} using (S)-O-benzylglycidol as a chiral building block. We have reported the synthesis of (–)-1 by asymmetric nitroolefination using a chiral β-sulfinyl-nitroolefin^{7m} or a chiral β-nitroenamine¹ through an addition-elimination process. (–)-Eserethole (2), which is a degradation product of (–)-physostigmine (1), is an important relay compound to Calabar bean alkaloids. Here we present a full account of an asymmetric synthesis of (–)-eserethole (2) utilizing (S)-(–)-2-methyl-2-[2-(E)-nitroethenyl]-δ-valerolactone (3), which was prepared by asymmetric nitroolefination of α-methyl-δ-lactone using a chiral nitroenamine.⁹

Results and Discussion

The (–)-nitroolefin 3 (87% ee) would be a suitable chiral building block for the construction of the aromatized

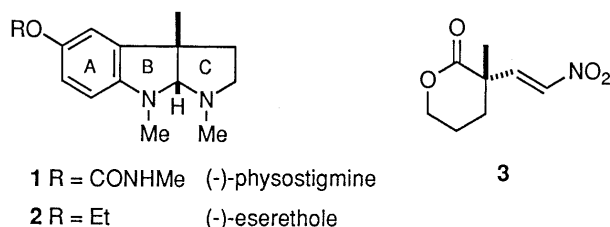


Chart 1

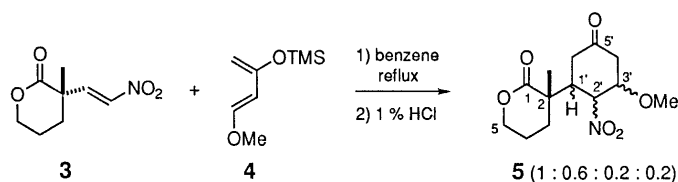


Chart 2

A-ring in (–)-eserethole (2), because a nitroolefin is a good dienophile in the Diels–Alder reaction. In particular, in the reaction with Danishefsky's diene,¹⁰ functional groups of the product are located at favorable positions for aromatization toward the A-ring and lactamization toward the B-ring. Indeed, the Diels–Alder reaction of the (–)-nitroolefin 3 with Danishefsky's diene (4) followed by protonation afforded the expected adducts 5 as a mixture of four diastereomers in 95% yield (Chart 2). The stereochemistries of the cyclohexane moieties in the two major diastereomers, 5a and 5b, were confirmed by ¹H–¹H correlation spectroscopy (COSY), ¹³C–¹H COSY and nuclear Overhauser effect (NOE) experiments as shown in Fig. 1. The major nitro ketone 5a having all-equatorial substituents was the *exo* product of the Diels–Alder reaction. The observed *exo* selectivity is unusual compared to the Diels–Alder reaction of other nitroolefins and dienes.¹¹

Though stereochemical control in the formation of 5 was poor, the regioselectivity in the products is suitable for further transformation without separation, because these diastereomers would converge to a single compound after aromatization of the resultant cyclohexane ring. There might be two pathways for further transformations: 1) aromatization of the cyclohexane ring followed by reduction of nitro group, and 2) the opposite sequence. The former pathway was difficult, because the *aci*-nitro intermediate 6A and its derivatives 6E and 6Z obtained from 5 (Chart 3) were not converted into the desired aromatized compound under oxidative conditions. Attempted aromatizations of the cyclohexane ring retaining the nitro or amino group failed.¹² We turned our attention to the reduction of the nitro group to an amino group in 5 in order to obtain a γ-lactam, because an amino-lactone, if formed, could be cyclized to a γ-lactam. However, the 2'-amino-5'-hydroxy derivative obtained from the reduction of 5 with palladium carbon in

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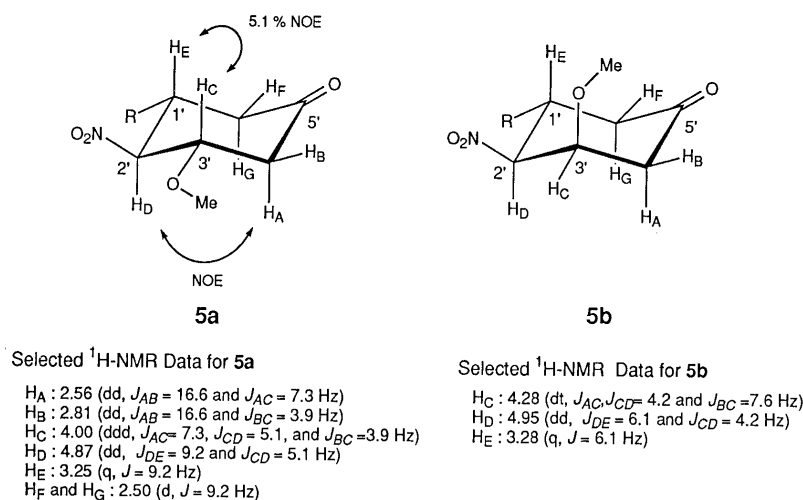


Fig. 1

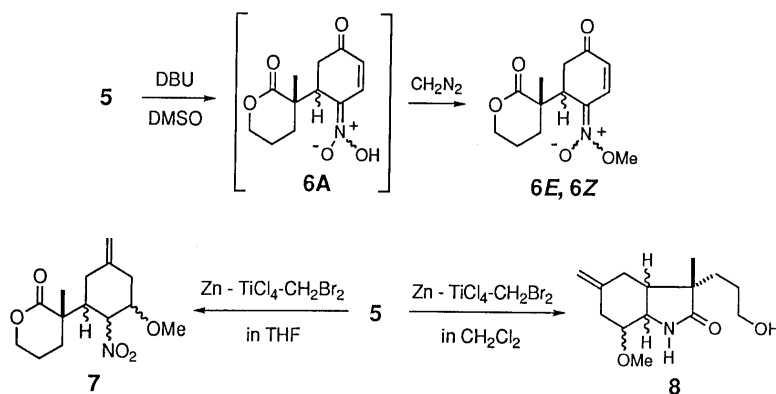


Chart 3

ammonium formate¹³⁾ could not be converted into a lactam. This difficulty of lactamization is presumably attributable to the formation of a *trans*-fused 5,6-ring system, which has a high strain energy. However, it might be possible to form the *trans*-5,6-ring system if an sp^2 carbon is present in the cyclohexane ring, which might then take a boat-like conformation to reduce the strain energy. These points led us to consider that an sp^2 carbon at C-5' of **5** would be essential for the γ -lactam cyclization. Therefore, we examined the methylenation of the carbonyl group of **5** as shown in Chart 3. The reaction of a diastereomeric mixture of **5** with the Nozaki reagent ($\text{Zn-TiCl}_4\text{-CH}_2\text{Br}_2$)¹⁴⁾ in tetrahydrofuran (THF) resulted in normal methylenation to give the *exo*-methylene product **7** in 47% yield. Fortunately, the same reaction in dichloromethane solution gave the diastereomeric mixture of lactams **8** in 82% yield, in which methylenation of the ketone and concomitant reduction of the nitro group occurred to give the desired lactam. Though the nature of the solvent effect of dichloromethane on this reaction is not clear at present, this result shortened the synthetic route to our goal.

The transformation of the lactam **8** to (–)-eserethole (**2**) is shown in Chart 4. Methylation of **8** followed by ozonolysis gave the cyclic ketone **10**. Elimination of methanol from **10** afforded a mixture of the conjugated and unconjugated cyclic ketone **11**, which was sub-

sequently oxidized with iodine¹⁵⁾ and ethylated with ethyl iodide to give a single aromatized compound **12** in 64% yield from **10**. Selective bond cleavage of the methyl ether **12** with a combination reagent system of aluminum chloride-sodium iodide¹⁶⁾ afforded the alcohol **13** in 85% yield. Recrystallization from hexane–ethyl acetate afforded optically pure **13**, as determined by means of a chiral shift NMR [400 MHz, $\text{Eu}(\text{hfc})_3$] experiment. Oxidation of the alcohol **13** with pyridinium dichromate (PDC) gave the carboxylic acid **14** in 62% yield. In order to transform the side chain of the 5-ethoxy-2-oxindole **14** from carboxylic acid to carbamate, the modified Curtius degradation with diphenylphosphoryl azide¹⁷⁾ was performed to give the carbamate **15**. Reductive cyclization of **15** with lithium aluminum hydride afforded the desired (–)-eserethole (**2**),¹⁸⁾ whose spectroscopic data and specific rotation $[\alpha]_\text{D}^{25} - 85^\circ$ ($c = 0.45$, EtOH) were identical with those reported.^{19a)} It is noteworthy that all of the carbons in the (–)-nitroolefin (**3**) have been utilized for this synthesis, because the carbonyl carbon of the carboxylic acid **14** rearranged in the Curtius reaction was converted into the *N*-methyl group of (–)-eserethole (**2**).

Since (–)-eserethole (**2**) has been converted into (–)-physostigmine (**1**)⁷⁾ via (–)-eseroline (**16**)^{7a,19b)} and into (–)-physovenine (**17**),^{20f)} and (–)-physostigmine (**1**) has been transformed to (–)-geneserine (**18**),^{19c,21c)} the total synthesis of optically pure (–)-eserethole constitutes a

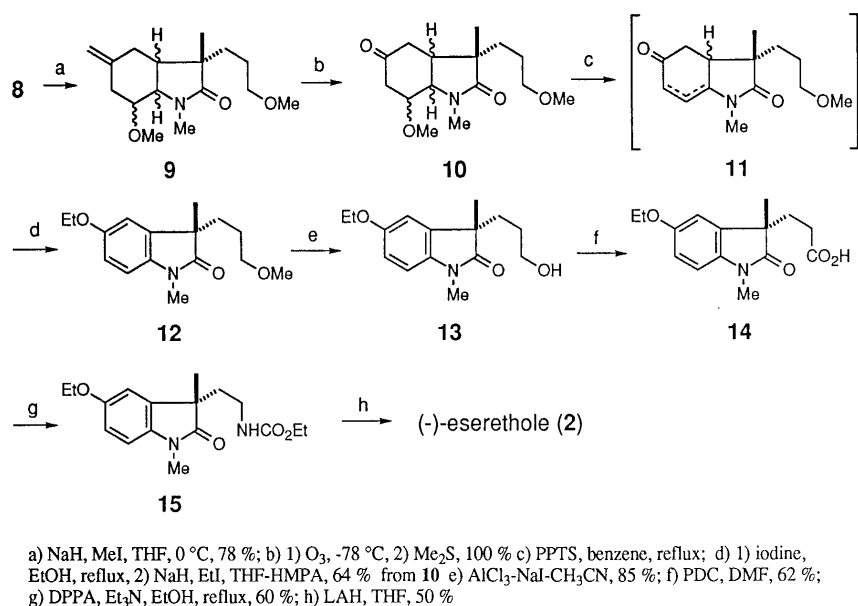


Chart 4. A Total Synthesis of (-)-Eserethole

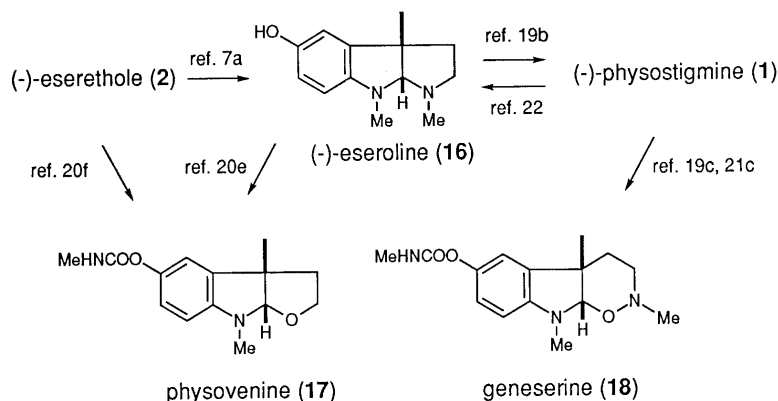


Chart 5

formal synthesis of these naturally occurring Calabar bean alkaloids (Chart 5).

Experimental

General Melting points were measured on a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer. ¹H-NMR spectra were measured in the indicated solvents with a Varian Gemini 200, JEOL JNM-GX-270, Varian XL-300, or JEOL JNM-GX 400 spectrometer. Signals are given in ppm using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 300 mass spectrometer. Combustion analyses were performed by a Yanaco CHN-corder MT-3. Optical rotations were recorded on a JASCO DIP-181 polarimeter in the indicated solvents. All reactions were monitored by TLC on silica gel plates (Kieselgel 60 F₂₅₄, 0.25 mm, Merck) with UV light or 10% ethanolic phosphomolybdic acid as the developing agent. Preparative TLC was performed on silica gel plates (Kieselgel 60 F₂₅₄, 0.5 mm × 20 cm × 20 cm, Merck). Short column chromatography was carried out on Merck Silica gel H (Type 60, Art. 7736). THF and benzene were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dichloromethane, hexamethylphosphoramide (HMPA), and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride. Methanol and ethanol were distilled after addition of sodium metal. Usual work-up means extracting with dichloromethane, washing the organic layer with brine, drying over Na₂SO₄, and evaporating under reduced pressure.

Material (2*S*)-2-Methyl-2-[(*E*)-2-nitroethenyl]-5-pentanolide [(−)-3] was prepared according to the literature procedure,⁹⁾ and its enantiomeric excess was determined to be 87% by 400 MHz ¹H-NMR

with Eu(hfc)₃.

(2*S*,1'*S**,2'*S**,3'*S**)-2-(3-Methoxy-2-nitro-5-oxocyclohexyl)-2-methyl-5-pentanolide (**5a**) and (2*S*,1'*S**,2'*S**,3'*R**)-2-(3-Methoxy-2-nitro-5-oxocyclohexyl)-2-methyl-5-pentanolide (**5b**) 1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**4**) (Danishefsky's diene)¹⁰⁾ (5.6 ml, 28.8 mmol) was added to a solution of (2*S*)-2-methyl-2-[(*E*)-2-nitroethenyl]-5-pentanolide [(−)-3] (4.6 g, 24.9 mmol) in dry benzene (100 ml) and the mixture was refluxed for 24 h under a nitrogen atmosphere. The diene **4** (4.1 ml, 21.2 mmol) was added and the reaction mixture was further continuously refluxed for 24 h. After the evaporation of benzene, THF (100 ml) and 1% hydrochloric acid solution (100 ml) were added and mixture was stirred for 30 min at 0 °C. Standard aqueous work-up gave a crude product, whose ¹H-NMR showed a diastereomeric mixture (**5a**:**5b**: other diastereomers = 1.0:0.6:0.2:0.2) based on integration of the signals of the methine proton (δ 4.87, 4.94, 5.40, 5.75) on carbon bearing the nitro group. Purification by column chromatography on silica gel (eluted with dichloromethane, then with ethyl acetate) gave a diastereomeric mixture **5** (6.7 g, 95%). A part of **5** (1.53 g) was subjected to short column chromatography (eluted with hexane: EtOAc = 3:1) to afford a major diastereomer **5a** (0.65 g) and **5b** (0.24 g). The optically pure **5a**¹²⁾ was obtained as a second crop in recrystallization from ethyl acetate and hexane. **5a**: colorless needles, mp 110–112 °C (AcOEt-hexane), [α]_D²⁴ −30.1° (*c* = 2.40, CHCl₃) (100% ee). ¹H-NMR (CDCl₃, 400 MHz) δ: 1.30 (3H, s), 1.77–1.91 (3H, m), 1.98–2.09 (1H, m), 2.50 (2H, d, *J* = 9.2 Hz), 2.56 (1H, dd, *J* = 16.5, 7.3 Hz), 2.81 (1H, dd, *J* = 16.7, 3.9 Hz), 3.25 (1H, q, *J* = 9.2 Hz), 3.40 (3H, s), 4.00 (1H, ddd, *J* = 7.3, 5.1, 3.9 Hz), 4.24 (1H, dt, *J* = 11.0, 3.3 Hz), 4.40–4.45 (1H, m), 4.87 (1H, dd, *J* = 9.2, 5.1 Hz). ¹³C-NMR (CDCl₃, 270 MHz): 204.58, 173.98, 86.29, 78.40, 70.06, 57.45, 45.09, 41.85, 41.38, 38.80, 28.81, 24.53, 20.38. IR

(CHCl₃) cm⁻¹: 2940, 1720, 1560, 1460, 1400, 1380, 1260, 1130, 1020. MS (M⁺) *m/z*: 285. *Anal.* Calcd for C₁₃H₁₉NO₆: C, 54.70; H, 6.71; N, 4.91. Found: C, 54.83; H, 6.66; N, 5.01. **5b**: amorphous solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 1.28 (3H, s), 1.65–2.15 (4H, m), 2.54–2.65 (2H, m), 2.72–2.89 (2H, m), 3.28 (1H, q, *J* = 6.1 Hz), 3.39 (3H, s), 4.28 (1H, dt, *J* = 7.6, 4.2 Hz), 4.31–4.39 (1H, m), 4.42–4.49 (1H, m), 4.95 (1H, dd, *J* = 6.1, 4.2 Hz). ¹³C-NMR (CDCl₃, 300 MHz): 206.01, 174.53, 85.07, 76.57, 70.19, 57.56, 45.60, 40.99, 39.68, 39.20, 30.77, 23.53, 20.04. FAB (+)-MS *m/z*: 286.1274 (M⁺ + 1) (Calcd for C₁₃H₂₀NO₆: 286.1291).

Ac-Nitro Methyl Ether 6E and 6Z A mixture of **5** (119 mg, 0.44 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.336 ml, 2.21 mmol) in THF (10 ml) was stirred overnight at room temperature. The reaction was quenched with 5% hydrochloric acid (15 ml), and usual work-up gave a residue, which was treated with diazomethane. The solvent was evaporated *in vacuo*. Purification of the residue by preparative TLC (eluted with ethyl acetate) gave a mixture of stereoisomers, **6Z** and **6E** (100 mg, 90%), in a ratio of 1.2:1. Major isomer: IR (CHCl₃) cm⁻¹: 1720, 1660, 1240. ¹H-NMR (CDCl₃) δ: 1.23 (3H, s), 2.55 (1H, A of ABX, *J* = 14 Hz), 2.73 (1H, B of ABX, *J* = 14, 7 Hz), 3.81 (3H, s), 3.96 (1H, d, *J* = 7 Hz), 5.87 (1H, d, *J* = 11 Hz), 7.55 (1H, d, *J* = 11 Hz). ¹³C-NMR (CDCl₃): 20.1, 24.4, 31.5, 38.8, 41.8, 48.5, 55.6, 70.5, 121.0, 126.8, 136.0, 174.6, 197.6. Minor isomer: ¹H-NMR (CDCl₃) δ: 1.24 (3H, s), 2.52 (1H, A of ABX, *J* = 14 Hz), 2.75 (1H, B of ABX, *J* = 14, 7 Hz), 3.78 (3H, s), 4.25 (1H, d, *J* = 7 Hz), 6.05 (1H, d, *J* = 11 Hz), 7.58 (1H, d, *J* = 11 Hz). ¹³C-NMR (CDCl₃): 20.3, 24.5, 31.3, 39.3, 40.9, 48.8, 54.3, 70.6, 122.5, 129.8, 138.2, 174.7, 197.7.

(2S)-2-(3-Methoxy-5-methylene-2-nitrocyclohexyl)-2-methyl-5-pentanolide (7) The Nozaki reagent¹⁴ (3 ml) was added to a THF (15 ml) solution of *dl*-**5a** (major diastereomer, 198 mg, 0.69 mmol), and the reaction mixture was stirred for 2 h at room temperature. After addition of 1% hydrochloric acid, usual work-up gave a residue, which was subjected to silica gel column chromatography (eluted with hexane: EtOAc = 4:1, then 1:1) to afford **7** (68 mg, 47%). IR (CHCl₃) cm⁻¹: 1720, 1660, 1550, 1260. ¹H-NMR (CDCl₃) δ: 1.29 (3H, s), 1.80–2.10 (6H, m), 2.40 (1H, dd, *J* = 7, 2 Hz), 2.70 (1H, dt, *J* = 6, 2 Hz), 2.87 (1H, dd, *J* = 7, 3 Hz), 3.35 (3H, s), 3.70 (1H, m), 4.20 (1H, m), 4.38–4.50 (2H, m), 4.90 (2H, s). ¹³C-NMR (CDCl₃): 20.3, 25.1, 28.0, 35.0, 37.3, 45.1, 45.9, 57.6, 70.3, 81.5, 90.3, 114.0, 139.9, 175.0.

(3S)-3-(3-Hydroxypropyl)-7-methoxy-3-methyl-5-methylenehexahydro-2-oxindole (8) Dibromomethane (4.04 ml, 57.5 mmol) was slowly added to a suspension of zinc powder (11.5 g, 176 mmol) in THF (100 ml). After dropwise addition of TiCl₄ (4.6 ml, 41.9 mmol) at -40 °C under a nitrogen atmosphere, the reaction mixture was stirred for 3 d at 0 °C to form the Nozaki reagent. To this Nozaki reagent was added compound **5** (3.2 g, 11.2 mmol) in dry CH₂Cl₂ (30 ml) over 1 h and the whole was stirred for 10 h at room temperature. Hydrochloric acid (1%, 200 ml) was added and the mixture was extracted with ethyl acetate. Salting out was followed by successive extraction with ethyl acetate. The organic layer was washed with water, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was subjected to short column chromatography (eluted with hexane: EtOAc = 1:1, EtOAc only, then EtOAc: MeOH = 1:1) to give the lactam **8** (2.4 g, 83%), which was again subjected to column chromatography on silica gel (eluted with EtOAc: MeOH = 25:1) to afford the major diastereomer of **8** (1.2 g). IR (CHCl₃) cm⁻¹: 3425, 1695, 1650. ¹H-NMR (CDCl₃) δ: 1.04 (3H, s), 1.50–1.80 (4H, m), 1.90–2.30 (4H, m), 2.85 (1H, dd, *J* = 14, 3 Hz), 3.20 (2H, m), 3.41 (3H, s), 3.63 (2H, br t, *J* = 5 Hz), 4.84 (2H, s), 6.12 (1H, s). ¹³C-NMR (CDCl₃): 17.5, 28.7, 32.7, 33.5, 39.7, 47.1, 48.0, 57.7, 61.0, 63.8, 83.3, 114.0, 144.8, 184.3. High-resolution MS *m/z*: 253.164 (Calcd for C₁₃H₂₃NO₃: 253.168).

(3S)-3-(3-Methoxypropyl)-7-methoxy-1,3-dimethyl-5-methylenehexahydro-2-oxindole (9) A solution of **8** (540 mg, 2.1 mmol) in THF (10 ml) was added to a suspension of sodium hydride (686 mg, 60% dispersion in mineral oil, 17 mmol) in THF (50 ml). The reaction mixture was stirred for 10 h at room temperature, then added dropwise into 2% hydrochloric acid (80 ml) solution. Standard aqueous work-up and column chromatography on silica gel (eluted with hexane: EtOAc = 1:1, then with EtOAc) afforded a diastereomeric mixture of dimethyl ethers **9** (455 mg, 76% yield). The diastereomeric mixture **9** (250 mg) was chromatographed on silica gel with hexane–EtOAc mixture (2:1) as an eluent to give the major diastereomer (140 mg). IR (CHCl₃) cm⁻¹: 1685, 1460, 1390. ¹H-NMR (CDCl₃) δ: 0.94 (3H, s), 1.40–1.70 (5H, s), 1.95 (2H, m), 2.20 (2H, m), 2.90 (1H, dd, *J* = 14, 3 Hz), 2.92 (3H, s), 3.02 (1H, t, *J* = 10 Hz), 3.25 (2H, m), 3.31 (3H, s), 3.39 (3H, s), 4.78 (2H,

br s). High-resolution MS *m/z*: 281.200 (Calcd for C₁₆H₂₇NO₃: 281.199).

(3S)-3-(3-Methoxypropyl)-7-methoxy-1,3-dimethyl-5-oxohexahydro-2-oxindole (10) Ozone was passed through a solution of **9** (125 mg, 0.4 mmol) in MeOH (7 ml) at -78 °C for 20 min. Dimethyl sulfide (0.2 ml) was added to the reaction mixture and the resulting mixture was stirred for 2 h at 0 °C. Methanol was evaporated, and the residue was chromatographed on SiO₂ with EtOAc to afford **10** (126 mg, 100% yield) as a diastereomeric mixture, which was subjected to preparative TLC to obtain the major diastereomer of **10** (65 mg). ¹H-NMR (CDCl₃) δ: 1.00 (3H, s), 1.40–1.75 (4H, m), 1.75–1.95 (2H, m), 2.20–2.45 (4H, m), 2.98 (3H, s), 3.05 (1H, dd, *J* = 14, 3 Hz), 3.31 (3H, s), 3.35 (2H, m), 3.39 (3H, s). IR (CHCl₃) cm⁻¹: 1720, 1690, 1390. High-resolution MS *m/z*: 283.176 (Calcd for C₁₄H₂₅NO₄: 283.178).

(3S)-5-Ethoxy-3-(3-methoxypropyl)-1,3-dimethyl-2-oxindole (12) A mixture of **10** (1.35 g, 4.8 mmol) and pyridinium *p*-toluenesulfonate (1.2 g, 4.8 mmol) in dry benzene (120 ml) was refluxed for 5 h under a nitrogen atmosphere (a molecular sieve tube was fitted on the reaction flask for absorption of the resulting methanol). After the addition of benzene (200 ml), the organic layer was washed with brine and dried over Na₂SO₄. Removal of the solvent afforded a crude product, **11** (1.3 g), which was dissolved in 95% ethanol (200 ml). The ethanol solution was treated with iodine (2.4 g, 9.6 mmol) and the mixture was refluxed for 48 h. After removal of the ethanol, dichloromethane (300 ml) was added and the solution was washed with saturated sodium thiosulfate (Na₂S₂O₃) and then with brine. The dichloromethane solution was dried over Na₂SO₄. Removal of the solvent gave a residue, which was dissolved in 20 ml of dry THF. This solution was added to a suspension of sodium hydride (286 mg, 7.16 mmol) in THF (80 ml) and HMPA (1.24 ml, 7.16 mmol) at 0 °C. The mixture was stirred for 2 h, then the reaction was quenched with 2% hydrochloric acid (50 ml). The product, after usual work-up, was subjected to chromatography and the oxindole **12** was eluted with ethyl acetate–hexane (1:2) to furnish a colorless oil (850 mg, 64%), [α]_D²² -5.4° (*c* = 0.95, CHCl₃). IR (CHCl₃) cm⁻¹: 1690, 1600, 1460. ¹H-NMR (CDCl₃) δ: 1.10–1.33 (2H, m), 1.35 (3H, s), 1.41 (3H, t, *J* = 7 Hz), 1.68–2.00 (2H, m), 3.18 (3H, s), 3.23 (3H, s), 3.23 (2H, t, *J* = 7 Hz), 4.01 (2H, q, *J* = 7 Hz), 6.69–6.80 (3H, m). High-resolution MS *m/z*: 277.168 (Calcd for C₁₆H₂₃NO₃: 277.168).

(3S)-5-Ethoxy-3-(3-hydroxypropyl)-1,3-dimethyl-2-oxindole (13) Sodium iodide (5.1 g, 28 mmol) was added to a solution of aluminum chloride (3.73 g, 28 mmol) in dry MeCN (55 ml), and the mixture was stirred for 1 h at room temperature. Then a solution of **12** (791 mg, 2.8 mmol) in MeCN (10 ml) was added, and the whole was stirred for 18 h at room temperature. Usual work-up followed by short column chromatography (eluted with CH₂Cl₂–EtOAc) afforded **13** (636 mg, 86%), which was recrystallized from EtOAc–MeOH to give optically pure **13** (420 mg, 65%) as colorless needles: mp 151.5–153.5 °C, [α]_D²² -23.6° (*c* = 0.87, CHCl₃). IR (CHCl₃) cm⁻¹: 3450, 1690, 1600, 1495. ¹H-NMR (CDCl₃) δ: 1.10–1.35 (2H, m), 1.35 (3H, s), 1.41 (3H, t, *J* = 7 Hz), 1.80 (1H, m), 2.00 (1H, m), 3.18 (3H, s), 3.47 (2H, m), 4.00 (2H, q, *J* = 7 Hz), 6.73–6.80 (3H, m). *Anal.* Calcd for C₁₅H₂₁NO₃: C, 68.40; H, 8.04; N, 5.32. Found C, 67.95; H, 8.04; N, 5.19.

(3S)-3-(2-Carboxyethyl)-5-ethoxy-1,3-dimethyl-2-oxindole (14) Pyridinium dichromate (3.4 g, 9.1 mmol) was added to a solution of **13** (400 mg, 1.5 mmol) in DMF (20 ml). The mixture was stirred for 20 h at room temperature. After addition of water (50 ml), the reaction mixture was extracted with ethyl acetate. The extract was dried over Na₂SO₄ and evaporated to give a residue, which was chromatographed on a silica gel column (eluted with EtOAc: MeOH = 10:1, then 2:1) to afford **14** (260 mg, 62%) as colorless needles, mp 100–102 °C (acetone–hexane), [α]_D²⁰ +15° (*c* = 1.0, CHCl₃). IR (CHCl₃) cm⁻¹: 3400, 1700, 1600, 1460. ¹H-NMR (CDCl₃) δ: 1.37 (3H, s), 1.41 (3H, t, *J* = 7 Hz), 1.85–2.30 (4H, m), 3.19 (3H, s), 4.01 (2H, q, *J* = 7 Hz), 6.71–6.82 (3H, m). High-resolution MS *m/z*: 277.129 (Calcd for C₁₅H₁₉NO₄: 277.131).

(3S)-5-Ethoxy-3-(2-ethoxycarbonylmethoxyethyl)-1,3-dimethyl-2-oxindole (15) Diphenylphosphoryl azide (356 μl, 1.6 mmol) and triethylamine (221 μl, 1.6 mmol) were added to a solution of **14** (220 mg, 0.8 mmol) in ethanol (50 ml). The mixture was refluxed for 48 h, then concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with EtOAc: MeOH = 1:3, then 1:1) to afford the carbamate **15** (153 mg, 60%) as a colorless oil, [α]_D¹⁸ -66.3° (*c* = 2.0, CHCl₃). IR (CHCl₃) cm⁻¹: 3450, 1710, 1700, 1240. ¹H-NMR (CDCl₃) δ: 1.21 (3H, t, *J* = 7 Hz), 1.38 (3H, s), 1.44 (3H, t, *J* = 7 Hz), 1.85–2.25 (2H, m), 2.95 (2H, m), 3.21 (3H, s), 4.01 (2H, q, *J* = 7 Hz), 4.04 (2H, q, *J* = 7 Hz), 6.75–6.87 (3H, m). *Anal.* Calcd for C₁₇H₂₄N₂O₄:

C, 63.44; H, 7.68; N, 8.44. Found C, 63.70; H, 7.55; N, 8.75.

(-)-Eserethole (**2**) Lithium aluminum hydride (16 mg, 0.44 mmol) was added to a solution of the carbamate **15** (34 mg, 0.11 mmol) in dry THF (8 ml). After having been stirred for 3 min at room temperature, the reaction mixture was refluxed for 30 min. Then 50% potassium hydroxide (10 ml) was added and the whole was extracted with ether. The extract was washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with CH₂Cl₂, then EtOAc:MeOH=10:1) to afford (-)-eserethole (**2**) (13 mg, 50%) as a colorless oil. [α]_D²¹ -85° (c=0.45, EtOH) (lit.^{19a}) -81, EtOH). IR (CHCl₃) cm⁻¹: 1600, 1500. ¹H-NMR (CDCl₃) δ : 1.37 (3H, t, J=7 Hz), 1.43 (3H, s), 1.94 (2H, m), 2.53 (3H, m), 2.68 (2H, m), 2.89 (3H, s), 3.96 (2H, q, J=7 Hz), 4.06 (1H, s), 6.35 (1H, m), 6.64 (1H, s), 6.66 (1H, m). High-resolution MS *m/z*: 246.173 (Calcd for C₁₅H₂₂N₂O: 246.173). The spectroscopic data for synthetic eserethole (**2**) were identical with literature values.^{7b}

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