A Novel Synthesis of 1-(2-Methyl-1-propenyl)-2-aminoindan Derivatives

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We developed a novel synthesis of 2-aminoindan derivatives, having a 2-methyl-1-propenyl group at the 1-position and oxygen functional groups in the benzene ring, in 8 or 9 steps from vanillin.

Key words 2-aminoindan; stereoselective cyclization; Heck reaction; 1-(2-methyl-1-propenyl)-2-aminoindan; vanillin

In the previous paper,[1] we reported a synthesis of a tricyclic ergot alkaloid analog, (±)-6-nor-6-propyl-6,7-secoagroclavine (KSU 1415, **1**, Fig. 1). It has a potent dopamine agonist activity[1] comparable to that of bromocryptine (**2**), which is used clinically as an anti-parkinsonian drug. We have also succeeded in synthesizing both enantiomers[2] of optically active KSU 1415 (**1**) for evaluation of their biological activities.

Much attention has been focused on 2-aminoindan derivatives,[3] such as RDS-127 (**3**),[3a] **4**,[3b] **5**,[3c] **6**,[3c] and **7**,[3d] due to their potent dopamine agonist activity,[3a,b] amphetamine-like activity,[3c] and inhibition of thromboses.[3d] 1-Aminoindan (OPC 14117, **8**)[4a] and an indan derivative (MDL 27777A, **9**)[4b] are a central nervous system (CNS)-stimulant[4a] and a serotonin uptake inhibitor,[4b] respectively. Comparing the structures of these compounds (**3**—**9**) with that of **1**, we have designed 2-propylaminoindan derivatives (**10**), having oxygen functional groups in the benzene ring and an appropriate side chain at the 1-position, as a novel type of mother skeleton for a dopamine agonist. In this paper, we wish to report a synthesis of 1-(2-methyl-1-propenyl)-2-aminoindan derivatives with the general formula **10**.

Several synthetic methods for 2-aminoindans have been reported,[5] but they are not suitable for producing 1-substituted 2-aminoindans. In our synthetic studies on ergot alkaloids, we have established two methods for stereoselective cyclization to generate the six-membered C ring of 4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole derivatives (**12**, **14a**), as illustrated in Chart 1. One is reductive cyclization of the nitrovinyl compound (**11**) with sodium borohydride ($NaBH_4$), giving the 4,5-*cis* compound (**12**).[6] The other is reaction of the nitrovinyl compound (**13**) with $NaBH_4$ and subsequent treatment with 2 N hydrochloric acid (HCl), giving the 4,5-*trans* compound (**14a**).[7] These methods seem to be promising for preparing a five-membered ring, culminating in the formation of 2-nitroindan derivatives, **17** and **18**, starting from the corresponding nitrovinyl derivatives, **15** and **16**.

First, 6-bromoveratraldehyde (**19**) and 4-benzyloxy-2-bromo-5-methoxybenzaldehyde (**20**) were prepared from vanillin in two steps in 78% and 77% overall yields, respectively, according to the known method.[8] Heck reaction of **19** with methyl acrylate in dimethylformamide (DMF) and triethylamine (Et_3N) in the presence of a catalytic amount of palladium acetate ($Pd(OAc)_2$) and triphenylphosphine (PPh_3) gave methyl 3-(2-formyl-4,5-dimethoxyphenyl)acrylate (**21**) in 51% yield (Chart 2). Heck reaction of **19** and **20** with 2-methyl-3-buten-2-ol gave 2-(3-hydroxy-3-methyl-1-butenyl)-4,5-dimethoxybenzaldehyde (**23**) and 4-benzyloxy-2-(3-hydroxy-3-methyl-1-butenyl)-5-methoxybenzaldehyde (**24**) in 77% and 54% yields, respectively. Unfortunately, the nitroaldol

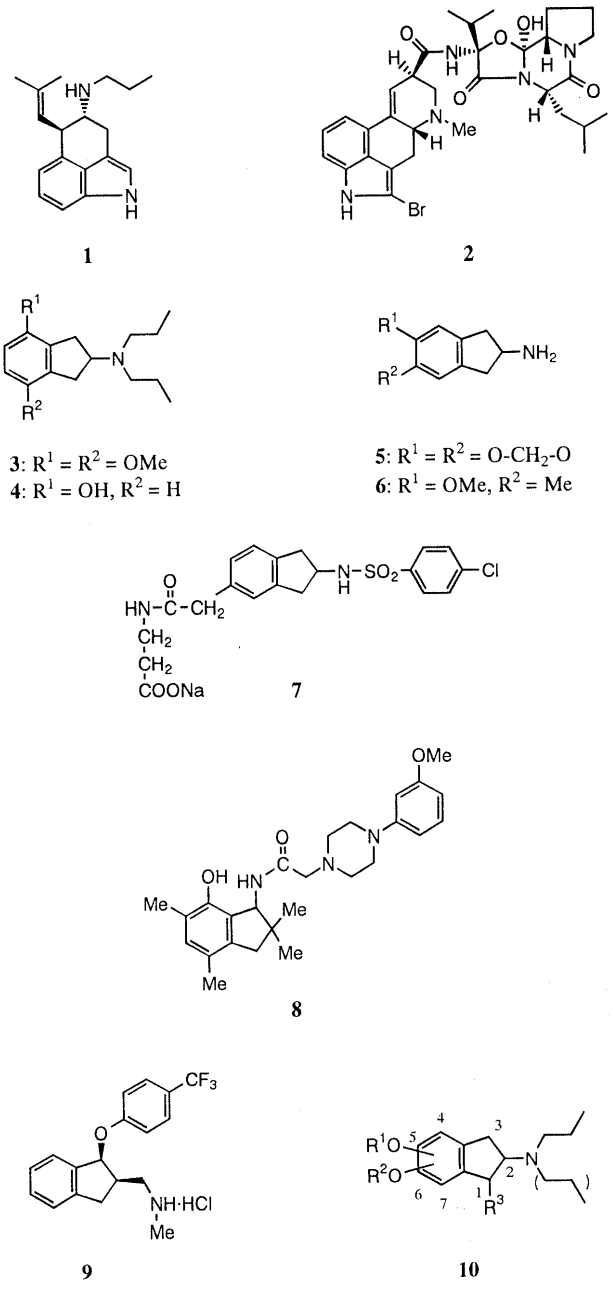

Fig. 1

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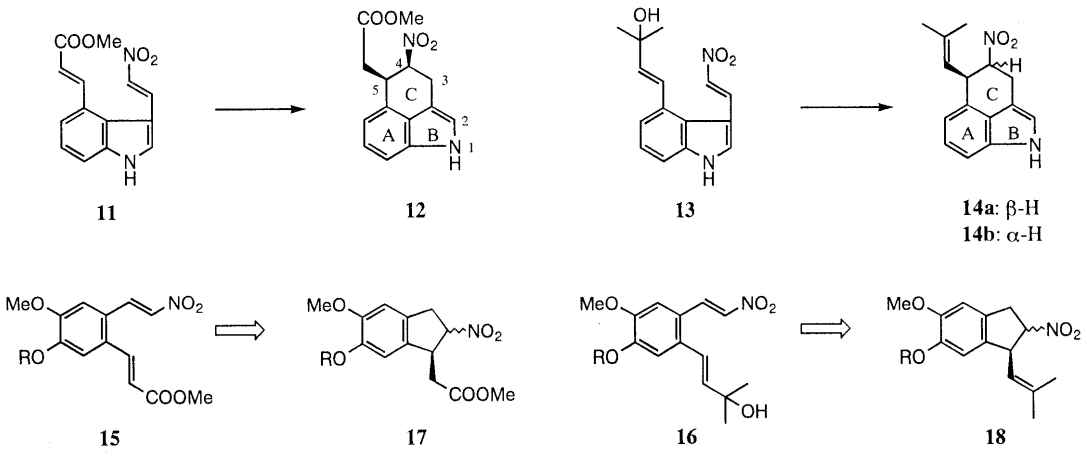


Chart 1

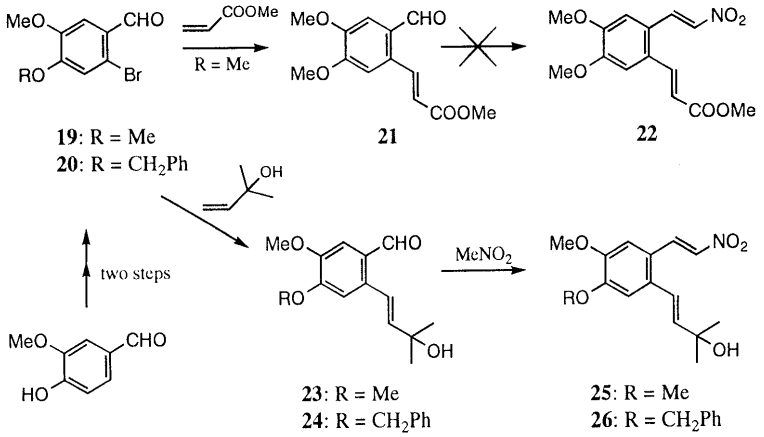
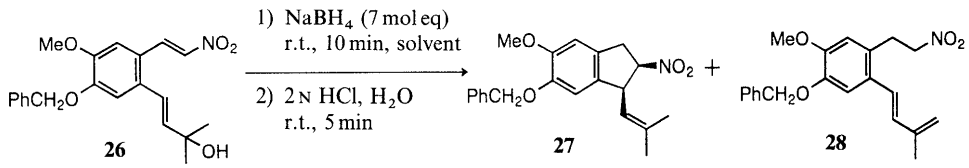


Chart 2

Table 1. Preparation of 1,2-*cis*-6-Benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-nitroindan **27** by the $NaBH_4$–HCl Method



Entry	Solvent	Yield (%) of		Total yield (%)
		27	**28**	
1	MeOH	40	12	52
2	Benzene–MeOH (1 : 2, v/v)	21	14	35
3	CH_3CN–MeOH (1 : 1, v/v)	37	6	43
4	THF–MeOH (1 : 1, v/v)	35	0	35
5	Dioxane–MeOH (1 : 1, v/v)	46	0	46

reaction of **21** with nitromethane (CH_3NO_2) failed to afford the desired nitrovinyl compound (**22**), though various reaction conditions were examined with NH_4OAc, NaOAc, Et_3N, and so on as a catalyst. Condensation of **23** and **24** with CH_3NO_2 in the presence of NH_4OAc occurred readily to afford 4-[4,5-dimethoxy-2-(2-nitrovinyl)phenyl]-2-methyl-3-buten-2-ol (**25**) and 4-[5-benzyloxy-4-methoxy-2-(2-nitrovinyl)phenyl]-2-methyl-3-buten-2-ol (**26**) in 94% and 78% yields, respectively.

With compounds **25** and **26** in hand, we next tried cyclization of **26**. Reduction of the nitrovinyl moiety of **26** with $NaBH_4$ (7.0 mol eq) in methanol (MeOH) followed by treatment with 2 N HCl[7] produced stereoselectively 1,2-*cis*-6-benzyloxy-5-methoxy-1-(2-methylpropenyl)-2-nitroindan (**27**) together with 1-[5-benzyloxy-4-methoxy-2-(2-nitroethyl)phenyl]-3-methyl-1,3-butadiene (**28**). The formation of the thermodynamically unstable 1,2-*cis*-nitroindan could be explained by orbital overlapping between the nitronate anion and the allyl cation, which lowers the activation energy of the transition state to the *cis* isomer relative to that of the transition state to the *trans* isomer. As can be seen from the typical results in

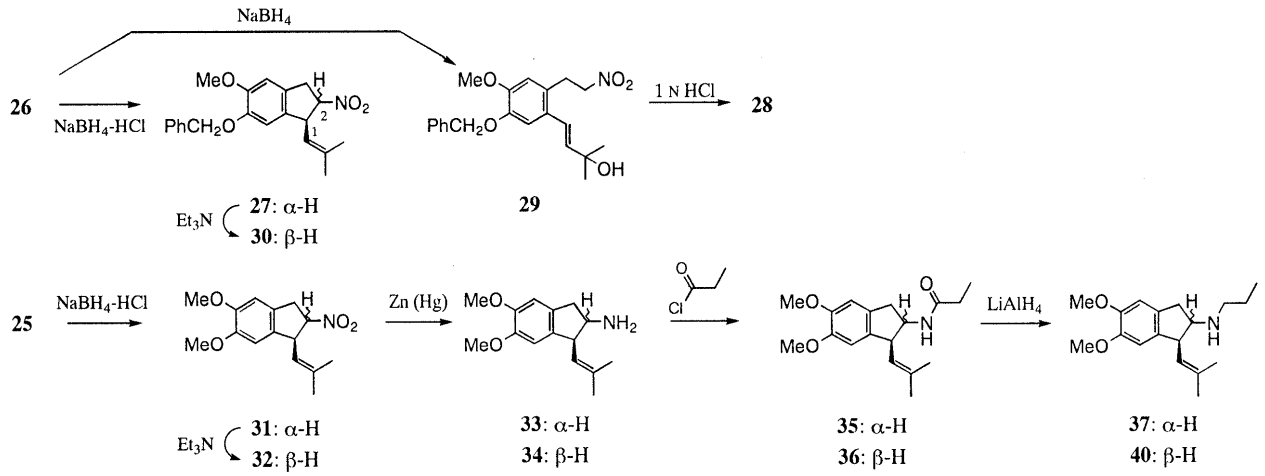


Chart 3

Table 1, the ratio of **27** and **28** changed significantly depending on the reaction solvent. Finally, using dioxane–MeOH (1 : 1, v/v) as described in entry 5, the desired compound **27** was obtained in 46% yield without concomitant formation of **28**.

Structural determination of **28** was carried out by employing a series of reactions as follows (Chart 3). The nitrovinyl compound **26** was initially reduced with $NaBH_4$ in MeOH to give 4-[5-benzyloxy-4-methoxy-2-(2-nitroethyl)phenyl]-2-methyl-3-buten-2-ol (**29**)[9] in 87% yield. Subsequent treatment of **29** with 1 N HCl in tetrahydrofuran (THF) produced an 80% yield of **28**, which was identical with **28** obtained as mentioned above.

Treatment of the dimethoxy compound **25** with $NaBH_4$–HCl[7] in MeOH gave 1,2-*cis*-5,6-dimethoxy-1-(2-methyl-1-propenyl)-2-nitroindan (**31**) as a single product in 62% yield without formation of the corresponding diene (Chart 3). The nitro group at the 2-position of **31** readily epimerized to 1,2-*trans*-5,6-dimethoxy-1-(2-methyl-1-propenyl)-2-nitroindan (**32**) in 82% yield in refluxing benzene with Et_3N. Similarly, the 1,2-*cis* compound (**27**) afforded 1,2-*trans*-6-benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-nitroindan (**30**) in 59% yield.

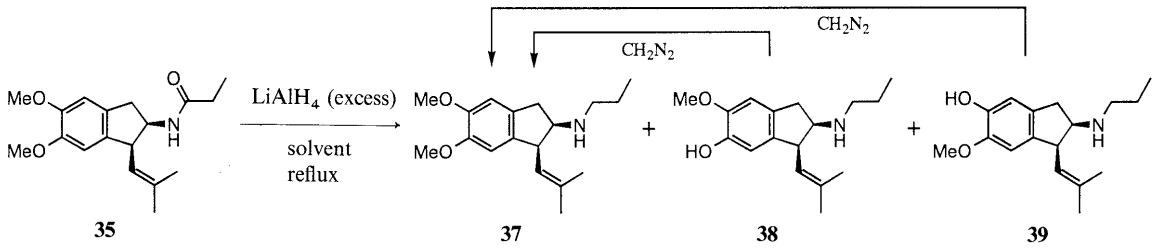
Although the stereochemistries of the six-membered cyclic compounds, **14a** and **14b**, were determined based on the differences in coupling constants between C_4- and C_5-H,[10] the same criteria could not be applied to the five-membered cyclic compounds, **31** and **32**, because the coupling constants between C_1- and C_2-H of the *cis* compounds, **27** and **31**, were 8.0 and 7.8 Hz, respectively, and almost the same as those of the *trans* compounds, **30** and **32** (8.0, 7.0 Hz, respectively). Their stereochemistries were determined unequivocally by X-ray crystallographic analysis as described later.

We have found that amalgamated zinc (Zn(Hg)) could reduce the nitro group in **14a** and **14b** to an amino group stereoselectively with retention of configuration.[11] Based on this fact, reduction of **31** and **32** with Zn(Hg) in methanolic HCl was applied to prepare 1,2-*cis*- (**33**) and 1,2-*trans*-2-amino-5,6-dimethoxy-1-(2-methyl-1-propenyl)indan (**34**) in 99% and 97% yields, respectively. Treatments of **33** and **34** with propionyl chloride in dichloromethane (CH_2Cl_2) in the presence of Et_3N gave 1,2-*cis*- (**35**) and 1,2-*trans*-5,6-dimethoxy-1-(2-methyl-1-propenyl)-2-propionylaminoindan (**36**) in 90% and 99% yields, respectively. Reduction of **35** with excess lithium aluminum hydride ($LiAlH_4$) in refluxing THF for 24 h produced 1,2-*cis*-5,6-dimethoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (**37**), 1,2-*cis*-6-hydroxy-5-methoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (**38**), and 1,2-*cis*-5-hydroxy-6-methoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (**39**) in 5%, 13%, and 15% yields, respectively, as shown in Table 2 (entry 1). To our knowledge, demethylation of such 1,2-dimethoxy benzene derivatives by reaction with $LiAlH_4$ has not previously been reported. Interestingly, change of the solvent from THF to ether (Et_2O) increased the yield of **37** and decreased the yields of **38** and **39** (entry 2). The yield of **37** was greatly improved by shortening the reaction time and finally a 73% yield of **37** was attained with $LiAlH_4$ in refluxing Et_2O for 5 h (entry 5). On the other hand, reduction of **36** with excess $LiAlH_4$ in refluxing Et_2O for 2 h gave 1,2-*trans*-5,6-dimethoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (**40**) in 86% yield without formation of the corresponding 5- or 6-hydroxy derivatives.

Both compounds, **38** and **39**, were independently transformed to the same compound **37** by methylation with diazomethane (CH_2N_2) in 66% and 75% yields, respectively. These results indicated that **38** and **39** are regioisomers of the methoxy and hydroxy groups at the 5- and 6-positions. However, the structures of **38** and **39** could not be determined based on the spectral data. Therefore, the hydroxy compound (**39**) was subjected to X-ray crystallographic analysis to establish the configurations at the 1- and 2-positions, as well as the positions of the methoxy and hydroxy groups in the benzene ring. The results (Fig. 2) clearly showed that the 2-methylpropenyl group and the propylamino group were *cis*, and the hydroxy and methoxy groups were at the 5- and 6-positions, respectively.

The structure of **38** was determined by converting it to 1,2-*cis*-6-benzyloxy-2-(*N*-benzylpropylamino)-5-methoxy-1-(2-methyl-1-propenyl)indan (**44**) in 67% yield by reaction with excess benzyl bromide (Chart 4). The same compound (**44**) was alternatively prepared by a sequence of reactions starting from **27**. Thus, reduction of **27** with

Table 2. Reduction of 1,2-*cis*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propionylaminoindan **35** with $LiAlH_4$



Entry	Solvent	Reaction time (h)	Yield (%) of			
			37	**38**	**39**	**35**
1	THF	24	5	13	15	0
2	Et_2O	24	29	0	5	0
3	Et_2O	12	49	0	5	6
4	Et_2O	6	70	0	4	18
5	Et_2O	5	73	0	1	20

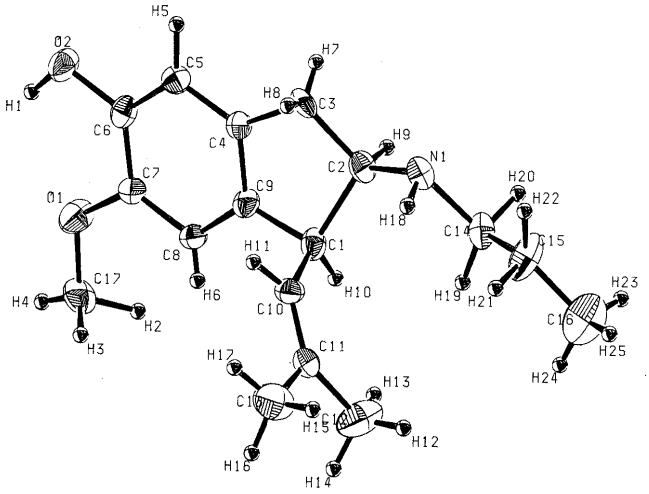


Fig. 2. ORTEP Drawing of **39**

Table 3. Positional Parameters and B_{eq} for **39**

Atom	*x*	*y*	*z*	B_{eq}
O1	0.2276 (4)	0.2172 (4)	0.7219 (6)	4.8 (4)
O2	0.3127 (4)	0.1688 (4)	0.9205 (6)	4.7 (4)
N1	0.1176 (5)	−0.2064 (5)	0.7980 (8)	3.8 (4)
C1	0.1118 (6)	−0.0579 (5)	0.723 (1)	3.5 (5)
C2	0.1577 (6)	−0.1312 (5)	0.772 (1)	3.6 (5)
C3	0.1955 (7)	−0.1015 (5)	0.895 (1)	3.8 (5)
C4	0.2098 (5)	−0.0146 (5)	0.8587 (9)	3.1 (4)
C5	0.2588 (5)	0.0406 (5)	0.9137 (8)	3.2 (4)
C6	0.2627 (5)	0.1165 (5)	0.8659 (8)	3.4 (4)
C7	0.2176 (5)	0.1399 (5)	0.7629 (9)	3.2 (4)
C8	0.1687 (6)	0.0855 (5)	0.711 (1)	3.1 (5)
C9	0.1640 (5)	0.0085 (5)	0.7601 (8)	3.1 (4)
C10	0.0381 (5)	−0.0486 (5)	0.785 (1)	3.4 (5)
C11	−0.0290 (6)	−0.0536 (5)	0.740 (1)	3.9 (5)
C12	−0.0488 (7)	−0.0726 (8)	0.606 (1)	7.3 (7)
C13	−0.0975 (7)	−0.0392 (7)	0.819 (1)	6.1 (7)
C14	0.0846 (6)	−0.2412 (6)	0.683 (1)	4.1 (5)
C15	0.0254 (8)	−0.3017 (7)	0.714 (1)	6.0 (7)
C16	−0.0133 (7)	−0.3339 (7)	0.599 (1)	7.6 (8)
C17	0.1818 (7)	0.2456 (7)	0.623 (1)	4.7 (6)
H1	0.316 (5)	0.221 (6)	0.87 (1)	6 (3)
H2	0.182 (5)	0.203 (6)	0.540 (9)	6 (2)
H3	0.125 (7)	0.236 (7)	0.65 (1)	9 (4)
H4	0.201 (6)	0.297 (7)	0.60 (1)	7 (3)
H5	0.290 (5)	0.018 (5)	0.98 (1)	5 (2)
H6	0.139 (4)	0.095 (4)	0.664 (7)	1 (2)
H7	0.236 (4)	−0.118 (4)	0.899 (7)	2 (2)
H8	0.157 (5)	−0.111 (4)	0.983 (8)	4 (2)
H9	0.200 (4)	−0.141 (4)	0.710 (7)	3 (2)
H10	0.103 (4)	−0.058 (4)	0.642 (6)	1 (1)
H11	0.047 (5)	−0.032 (5)	0.865 (7)	3 (2)
H12	−0.0732	−0.1230	0.6022	8.8
H13	−0.0047	−0.0745	0.5552	8.8
H14	−0.0810	−0.0323	0.5730	8.8
H15	−0.1243	−0.0879	0.8284	7.3
H16	−0.1280	−0.0006	0.7779	7.3
H17	−0.0835	−0.0199	0.9013	7.3
H18	0.076 (5)	−0.198 (5)	0.820 (8)	3 (3)
H19	0.064 (5)	−0.198 (5)	0.617 (8)	5 (2)
H20	0.126 (5)	−0.276 (5)	0.656 (8)	4 (2)
H21	−0.021 (6)	−0.281 (6)	0.76 (1)	7 (3)
H22	0.0311	−0.3323	0.8134	7.1
H23	0.0218	−0.3602	0.5452	9.1
H24	−0.0356	−0.2910	0.5528	9.1
H25	−0.0506	−0.3708	0.6244	9.1

Zn(Hg)–HCl gave a 67% yield of 1,2-*cis*-2-amino-6-benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)indan (**41**), which was then reacted with propionyl chloride to afford 1,2-*cis*-6-benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-propionylaminoindan (**42**) in 67% yield. Reduction of **42** with excess $LiAlH_4$ in refluxing Et_2O for 5 h produced 1,2-*cis*-6-benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (**43**) in 74% yield. Then, **43** was reacted with benzyl bromide in the presence of potassium carbonate (K_2CO_3) to give **44** in 83% yield.

In conclusion, we have developed a synthesis of 1-substituted 2-aminoindan derivatives by utilizing our stereoselective cyclization method as a key step. Biological evaluations of the 2-aminoindan derivatives described in this paper are in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with JEOL JNM-PMX60 and -FX100 spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{245} (Type 60) (SiO_2). Column

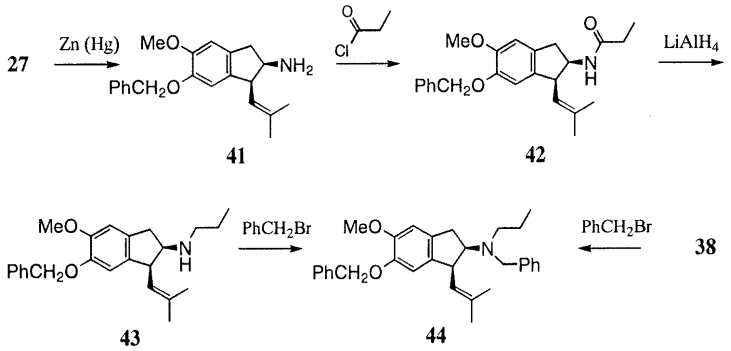


Chart 4

chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co., Inc.).

Methyl 3-(2-Formyl-4,5-dimethoxyphenyl)acrylate (21) A solution of methyl acrylate (613.6 mg, 7.13 mmol) in DMF (2 ml) was added to a solution of **19** (572.4 mg, 2.34 mmol), $Pd(OAc)_2$ (56.7 mg, 0.253 mmol), PPh_3 (183.5 mg, 0.707 mmol), and Et_3N (1 ml) in DMF (4 ml), and the mixture was heated at 110 °C for 23 h under argon. After evaporation of DMF *in vacuo*, brine was added to the residue and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2 as an eluent to give **21** (297.8 mg, 51%). **21**: mp 139.0—140.0 °C (yellow prisms from MeOH). IR (KBr): 1685, 1256 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 3.97 (3H, s), 3.99 (3H, s), 6.33 (1H, d, J=15.7 Hz), 7.03 (1H, s), 7.38 (1H, s), 8.45 (1H, d, J=15.7 Hz), 10.29 (1H, s). MS *m/z*: 250 (M^+). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.45; H, 5.60.

2-(3-Hydroxy-3-methyl-1-butenyl)-4,5-dimethoxybenzaldehyde (23) A solution of 2-methyl-3-buten-2-ol (14.34 g, 0.166 mol) in DMF (10 ml) was added to a solution of **19** (10.00 g, 40.8 mmol), $Pd(OAc)_2$ (946.5 mg, 4.22 mmol), PPh_3 (3.246 g, 12.4 mmol), and Et_3N (10 ml) in DMF (90 ml), and the mixture was heated at 100 °C for 19.5 h under argon. After work-up as described for the preparation of **21**, the crude product was purified by column chromatography with CH_2Cl_2–MeOH (99 : 1, v/v) as an eluent to give **23** (7.806 g, 77%). **23**: mp 75.0—77.0 °C (colorless needles from CH_2Cl_2–hexane). IR (KBr): 3390, 1667, 1652, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (6H, s), 2.15 (1H, s), 3.86 (3H, s), 3.90 (3H, s), 6.09 (1H, d, J=15.4 Hz), 6.79 (1H, s), 7.20 (1H, d, J=15.4 Hz), 7.21 (1H, s), 10.07 (1H, s). MS *m/z*: 232 ($M^+ - H_2O$). *Anal.* Calcd for $C_{14}H_{18}O_4 \cdot 1/3H_2O$: C, 65.61; H, 7.34. Found: C, 65.37; H, 7.31.

4-Benzyloxy-2-(3-hydroxy-3-methyl-1-butenyl)-5-methoxybenzaldehyde (24) A solution of 2-methyl-3-buten-2-ol (78.3 mg, 0.909 mmol) in DMF (1 ml) was added to a solution of **20** (65.2 mg, 0.204 mmol), $Pd(OAc)_2$ (6.8 mg, 0.03 mmol), PPh_3 (16.8 mg, 0.064 mmol), and Et_3N (0.3 ml) in DMF (1 ml), and the mixture was heated at 100 °C for 4 h under argon. After work-up and purification as described for the preparation of **23**, **24** (36.0 mg, 54%) was obtained. **24**: mp 91.0—92.0 °C (yellow prisms from Et_2O–hexane). IR (KBr): 3460, 1664, 1591 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H, s), 1.74 (1H, br s), 3.84 (3H, s), 5.11 (2H, s), 5.93 (1H, d, J=15.6 Hz), 6.81 (1H, s), 7.09—7.42 (6H, m), 7.12 (1H, d, J=15.6 Hz), 9.99 (1H, s). MS *m/z*: 308 ($M^+ - H_2O$). *Anal.* Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.41; H, 6.85.

4-[4,5-Dimethoxy-2-(2-nitrovinyl)phenyl]-2-methyl-3-buten-2-ol (25) NH_4OAc (148.2 mg, 1.92 mmol) was added to a solution of **23** (211.5 mg, 0.912 mmol) in CH_3NO_2 (10 ml) and the mixture was refluxed for 2 h. Brine was added to the mixture and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an orange solid. Recrystallization from MeOH afforded **25** (193.6 mg) as orange needles. The mother liquor was subjected to p-TLC with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give a further crop of **25** (39.1 mg). Total yield of **25** was 232.7 mg (93.9%). **25**: mp 141.0—142.0 °C. IR (KBr): 3370, 1616, 1592 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (6H, s), 1.72 (1H, s, OH, disappeared on addition of D_2O), 3.84 (3H, s), 3.87 (3H, s), 5.99 (1H, d, J=15.6 Hz), 6.77 (1H, d, J=15.6 Hz), 6.80 (2H, s), 7.30 (1H, d, J=13.2 Hz), 8.19 (1H, d, J=13.2 Hz). MS *m/z*: 293 (M^+). *Anal.* Calcd for $C_{15}H_{19}NO_5 \cdot 1/3H_2O$: C, 60.19; H, 6.62; N, 4.68. Found: C, 60.14; H, 6.43; N, 4.78.

4-[5-Benzyloxy-4-methoxy-2-(2-nitrovinyl)phenyl]-2-methyl-3-buten-2-ol (26) NH_4OAc (32.6 mg, 0.423 mmol) was added to a solution of **24** (124.0 mg, 0.380 mmol) in CH_3NO_2 (5 ml) and the mixture was refluxed for 3 h. After work-up and purification as described for the preparation of **25**, **26** (109.6 mg, 78%) was obtained. **26**: mp 184.0—186.0 °C (orange needles from MeOH). IR (KBr): 3440, 1617, 1592 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 1.40 (6H, s), 3.82 (3H, s), 5.09 (2H, s), 5.88 (1H, d, J=15.2 Hz), 6.72 (1H, d, J=15.2 Hz), 6.83 (2H, s), 7.08—7.41 (5H, m), 7.32 (1H, d, J=13.2 Hz), 8.15 (1H, d, J=13.2 Hz). MS *m/z*: 369 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.18; H, 6.37; N, 3.70.

1,2-*cis*-6-Benzyloxy-5-methoxy-1-(2-methylpropenyl)-2-nitroindan (27) and 1-[5-Benzyloxy-4-methoxy-2-(2-nitroethyl)phenyl]-3-methyl-1,3-butadiene (28) General Procedure $NaBH_4$ (7 mol eq) was added to a solution of **26** in an appropriate solvent (6 ml) and the mixture was stirred at room temperature for 10 min. Then water (H_2O, 6 ml) was added, and the resulting solution was added to 2 N HCl (6 ml) with stirring. Stirring was continued at room temperature for an additional 5 min, then the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to either column chromatography with CH_2Cl_2–hexane (7 : 3, v/v) or p-TLC with Et_2O–hexane (1 : 1, v/v), to afford **28** and **27** in increasing order of polarity.

Entry 1: In the general procedure, 72.5 mg (1.92 mmol) of $NaBH_4$ and 100.0 mg (0.271 mmol) of **26** were used, and MeOH was used as the solvent. After work-up and subsequent p-TLC as described above, 37.8 mg (40%) of **27** and 10.7 mg (12%) of **28** were obtained. **27**: mp 127.0—129.0 °C (colorless prisms from CH_2Cl_2–hexane). IR (KBr): 1547, 1503, 1314, 1218 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (6H, d, J=1.2 Hz), 3.21 (1H, dd, J=16.5, 7.5 Hz), 3.56 (1H, dd, J=16.5, 4.5 Hz), 3.85 (3H, s), 4.38 (1H, dd, J=9.0, 8.0 Hz), 4.90 (1H, br d, J=9.0 Hz), 5.05 (2H, s), 5.30 (1H, ddd, J=8.0, 7.5, 4.5 Hz), 6.57 (1H, s), 6.75 (1H, s), 7.08—7.48 (5H, m). MS *m/z*: 353 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.32; H, 6.48; N, 3.86. **28**: mp 103.0—104.0 °C (colorless leaves from CH_2Cl_2–hexane). IR (KBr): 1603, 1543, 1512, 1280, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (3H, s), 3.35 (2H, t, J=8.0 Hz), 3.86 (3H, s), 4.48 (2H, t, J=8.0 Hz), 5.07 (2H, s), 5.14 (2H, s), 6.56 (2H, s), 6.64 (1H, s), 7.04 (1H, s), 7.21—7.53 (5H, m). MS *m/z*: 353 (M^+), 262 ($M^+ - CH_2C_6H_5$). *Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.33; H, 6.49; N, 3.96.

Entry 2: In the general procedure, 74.5 mg (1.97 mmol) of $NaBH_4$ and 100.2 mg (0.272 mmol) of **26** were used, and a mixture of MeOH–benzene (2 : 1, v/v, 9 ml) was used as the solvent. After work-up and subsequent column chromatography as described above, 33.7 mg of a mixture of **27** and **28** was obtained. The yields of **27** (21%) and **28** (14%) were calculated by ^{1}H-NMR analysis.

Entry 3: In the general procedure, 73.4 mg (1.94 mmol) of $NaBH_4$ and 100.9 mg (0.273 mmol) of **26** were used, and a mixture of MeOH–CH_3CN (1 : 1, v/v) was used as the solvent. After work-up and subsequent column chromatography as described above, 41.1 mg of a mixture of **27** and **28** was obtained. The yields of **27** (37%) and **28** (6%) were calculated by ^{1}H-NMR analysis.

Entry 4: In the general procedure, 73.9 mg (1.95 mmol) of $NaBH_4$ and 101.2 mg (0.274 mmol) of **26** were used, and a mixture of THF–MeOH (1 : 1, v/v) was used as the solvent. After work-up and subsequent column chromatography as described above, **27** (33.7 mg, 35%) was obtained as a single product.

Entry 5: In the general procedure, 73.3 mg (1.94 mmol) of $NaBH_4$ and

100.5 mg (0.272 mmol) of **26** were used, and a mixture of MeOH–dioxane (1 : 1, v/v) was used as the solvent. After work-up and subsequent column chromatography as described above, **27** (44.4 mg, 46%) was obtained as a single product.

4-[5-Benzyloxy-4-methoxy-2-(2-nitroethyl)phenyl]-2-methyl-3-buten-2-ol (29) $NaBH_4$ (13.5 mg, 0.357 mmol) was added to a solution of **26** (49.9 mg, 0.135 mmol) in MeOH (8 ml) and the mixture was stirred at room temperature for 30 min. It was diluted with brine and then adjusted to pH 8 by adding 0.1% HCl. The whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2–MeOH (97 : 3, v/v) to give **29** (43.5 mg, 87%). **29**: mp 102.0—103.0 °C (colorless needles from CH_2Cl_2–hexane). IR (KBr): 3410, 2985, 1604, 1536, 1507 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s), 1.62 (1H, s), 3.28 (2H, t, J=7.5 Hz), 3.80 (3H, s), 4.44 (2H, t, J=7.5 Hz), 5.05 (2H, s), 5.93 (1H, d, J=15.6 Hz), 6.56 (1H, s), 6.62 (1H, d, J=15.6 Hz), 6.89 (1H, s), 7.11—7.47 (5H, m). MS m/z: 371 (M^+), 353 ($M^+ - H_2O$). *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.67; H, 6.87; N, 3.72.

1-[5-Benzyloxy-4-methoxy-2-(2-nitroethyl)phenyl]-3-methyl-1,3-butadiene (28) from 29 A 1 N HCl solution (0.5 ml) was added to a solution of **29** (10.2 mg, 0.027 mmol) in THF (1 ml) and the mixture was heated at 60 °C for 3.5 h, then extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2–hexane (7 : 3, v/v) to give **28** (8.4 mg, 80%) and recovered **29** (2.1 mg, 11%) in order of increasing polarity. All spectral data of **28** were identical with those of **28** obtained from **26**.

1,2-*trans*-6-Benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-nitroindan (30) A solution of **27** (41.9 mg, 0.119 mmol) in benzene–Et_3N (2 : 1, v/v, 12 ml) was refluxed for 21 h. The reaction mixture was evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2–hexane (7 : 3, v/v) to give **30** (24.9 mg, 59%). **30**: mp 106.0—107.0 °C (colorless prisms from MeOH). IR (KBr): 1606, 1534, 1505, 1295, 1216 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71 (3H, d, J=1.2 Hz), 1.77 (3H, d, J=1.2 Hz), 3.35 (1H, dd, J=15.5, 8.0 Hz), 3.53 (1H, dd, J=15.5, 8.0 Hz), 3.86 (3H, s), 4.53 (1H, dd, J=9.0, 8.0 Hz), 4.89 (1H, q, J=8.0 Hz), 5.05 (1H, br d, J=9.0 Hz), 5.07 (2H, s), 6.54 (1H, s), 6.72 (1H, s), 7.17—7.48 (5H, m). MS m/z: 353 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.39; H, 6.54; N, 3.92.

1,2-*cis*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-nitroindan (31) $NaBH_4$ (269.3 mg, 7.12 mmol) was added to a solution of **25** (303.7 mg, 1.04 mmol) in MeOH (9 ml) and the mixture was stirred at room temperature for 10 min. Then H_2O (9 ml) was added and the resulting solution was added to 2 N HCl (18 ml) with stirring. Stirring was continued at room temperature for an additional 5 min, then the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2–hexane (2 : 1, v/v) to give **31** (178.5 mg, 62%). **31**: mp 91.0—93.0 °C (colorless needles from MeOH–H_2O). IR (KBr): 1607, 1540, 1501 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (3H, d, J=1.2 Hz), 1.81 (3H, d, J=1.2 Hz), 3.27 (1H, dd, J=17.0, 7.3 Hz), 3.62 (1H, dd, J=17.0, 4.5 Hz), 3.85 (3H, s), 3.87 (3H, s), 4.49 (1H, dd, J=9.3, 7.8 Hz), 5.03 (1H, br d, J=9.3 Hz), 5.37 (1H, ddd, J=7.8, 7.3, 4.5 Hz), 6.59 (1H, s), 6.78 (1H, s). MS m/z: 277 (M^+). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.03; H, 7.06; N, 4.89.

1,2-*trans*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-nitroindan (32) Et_3N (1.8 ml) was added to a solution of **31** (106.1 mg, 0.383 mmol) in benzene (7 ml) and the mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with CH_2Cl_2–hexane (1 : 1, v/v) to give **32** (82.7 mg, 82%) and recovered **31** (18.8 mg, 18%) in order of increasing polarity. **32**: mp 65.5—66.0 °C (colorless needles from CH_2Cl_2–hexane). IR (KBr): 1609, 1537, 1500, 1294 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, d, J=1.2 Hz), 1.82 (3H, d, J=1.2 Hz), 3.39 (1H, dd, J=15.8, 8.1 Hz), 3.57 (1H, dd, J=15.8, 7.3 Hz), 3.85 (3H, s), 3.86 (3H, s), 4.63 (1H, dd, J=9.5, 7.0 Hz), 4.93 (1H, ddd, J=8.1, 7.3, 7.0 Hz), 5.15 (1H, br d, J=9.5 Hz), 6.55 (1H, s), 6.74 (1H, s). MS m/z: 277 (M^+). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.77; H, 6.90; N, 5.04.

1,2-*cis*-2-Amino-5,6-dimethoxy-1-(2-methyl-1-propenyl)indan (33) A solution of **31** (299.2 mg, 1.10 mmol) in MeOH (60 ml) and 2 N HCl (24 ml) was added to Zn(Hg), prepared from Zn powder (3.91 g, 59.8 mmol) and mercury(II) chloride ($HgCl_2$, 507 mg, 1.87 mmol) in 2 N HCl (24 ml), and the mixture was refluxed for 3 h. Unreacted Zn(Hg) was filtered off and the filtrate was evaporated under reduced pressure. The residue was basified with 20% aqueous sodium hydroxide (NaOH) and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography with $CHCl_3$–MeOH–29% NH_4OH (46 : 5 : 0.5, v/v) to give **33** (267.0 mg, 99%). **33**: mp 42.0—43.0 °C (colorless prisms from hexane). IR (KBr): 3350, 2910, 1608, 1496, 1299, 1216 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (3H, d, J=1.2 Hz), 1.84 (3H, d, J=1.2 Hz), 2.42 (2H, br s, NH_2, disappeared on addition of D_2O), 2.66 (1H, dd, J=15.5, 4.0 Hz), 3.08 (1H, dd, J=15.5, 5.5 Hz), 3.62—4.04 (2H, m), 3.86 (6H, s), 5.18 (1H, br d, J=9.0 Hz), 6.61 (1H, s), 6.76 (1H, s). MS m/z: 247 (M^+). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.70; H, 8.70; N, 5.55.

1,2-*trans*-2-Amino-5,6-dimethoxy-1-(2-methyl-1-propenyl)indan (34) A solution of **32** (173.5 mg, 0.633 mmol) in MeOH (20 ml) and 2 N HCl (7 ml) was added to Zn(Hg), prepared from Zn powder (1.55 g, 23.9 mmol) and $HgCl_2$ (250 mg, 0.921 mmol) in 2 N HCl (5 ml), and the mixture was refluxed for 3 h. After work-up and purification as described for the preparation of **33**, **34** (151.0 mg, 97%) was obtained. **34**: mp 50.0—51.0 °C (colorless prisms from hexane). IR (KBr): 3330, 3230, 3140, 1605, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, d, J=1.2 Hz), 1.84 (3H, d, J=1.2 Hz), 1.58—1.88 (2H, br, NH_2, disappeared on addition of D_2O), 2.61 (1H, dd, J=15.0, 8.5 Hz), 2.94—3.68 (3H, m), 3.84 (3H, s), 3.85 (3H, s), 5.08 (1H, br d, J=9.3 Hz), 6.50 (1H, s), 6.71 (1H, s). MS m/z: 247 (M^+). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.88; H, 8.77; N, 5.55.

1,2-*cis*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propionylaminoindan (35) A solution of propionyl chloride (474.1 mg, 5.12 mmol) in CH_2Cl_2 (10 ml) was added to a solution of **33** (851.5 mg, 3.45 mmol) and Et_3N (2.6 ml) in CH_2Cl_2 (40 ml) and the mixture was stirred at room temperature for 3 h. The whole was washed with saturated $NaHCO_3$, then with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2–MeOH (99 : 1, v/v) to give **35** (938.8 mg, 90%). **35**: mp 133.0—133.5 °C (colorless prisms from MeOH–H_2O). IR (KBr): 3380, 1669, 1536, 1502, 1464 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.5 Hz), 1.78 (3H, d, J=1.5 Hz), 1.80 (3H, d, J=1.5 Hz), 2.17 (2H, q, J=7.5 Hz), 2.68 (1H,dd, J=15.5, 6.6 Hz), 3.22 (1H, dd, J=15.5, 7.1 Hz), 3.85 (6H, s), 4.03 (1H, dd, J=9.5, 7.1 Hz), 4.79 (1H, ddt, J=8.5, 7.1, 6.6 Hz), 5.04 (1H, br d, J=9.5 Hz), 5.66 (1H, br d, J=8.5 Hz), 6.62 (1H, s), 6.74 (1H, s). MS m/z: 303 (M^+). *Anal.* Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.14; H, 8.50; N, 4.79.

1,2-*trans*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propionylaminoindan (36) A solution of propionyl chloride (109.1 mg, 1.18 mmol) in CH_2Cl_2 (1 ml) was added to a solution of **34** (138.0 mg, 0.559 mmol) and Et_3N (1 ml) in CH_2Cl_2 (3 ml) and the mixture was stirred at room temperature for 36 h. After work-up and purification as described for the preparation of **35**, **36** (166.9 mg, 99%) was obtained. **36**: mp 123.0—125.0 °C (colorless needles from CH_2Cl_2–hexane). IR (KBr): 3250, 1635, 1548, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 1.79 (6H, d, J=1.2 Hz), 2.19 (2H, q, J=7.5 Hz), 2.62 (1H, dd, J=15.5, 7.5 Hz), 3.29 (1H, dd, J=15.5, 7.5 Hz), 3.61—3.88 (1H, m), 3.84 (3H, s), 3.85 (3H, s), 4.34 (1H, f, J=7.5 Hz), 5.09 (1H, br d, J=9.3 Hz), 5.79 (1H, br d, J=7.5 Hz), 6.53 (1H, s), 6.69 (1H, s). MS m/z: 303 (M^+). *Anal.* Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.10; H, 8.35; N, 4.61.

1,2-*cis*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (37), 1,2-*cis*-6-Hydroxy-5-methoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (38), and 1,2-*cis*-5-Hydroxy-6-methoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (39)

Entry 1: $LiAlH_4$ (207.1 mg, 5.45 mmol) was added to a solution of **35** (78.9 mg, 0.259 mmol) in THF (4 ml) and the mixture was refluxed for 24 h. Excess $LiAlH_4$ was destroyed by adding MeOH at 0 °C and then saturated potassium sodium tartrate was added and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by p-TLC with CH_2Cl_2–MeOH (95 : 5, v/v). Under UV light, three bands were detected. Extraction from the

upper band with $CHCl_3$–MeOH–29% NH_4OH (46 : 5 : 0.5, v/v) gave **37** (3.5 mg, 5%). Extraction from the middle band with the same solvent as above gave **38** (9.0 mg, 13%). Extraction from the lower band with the same solvent as above gave **39** (10.8 mg, 15%). **37**: colorless oil. IR (film): 2950, 1609, 1500, 1460, 1299, 1219, 1088, 1028, 991, 846 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.0 Hz), 1.51 (2H, sex, J=7.0 Hz), 1.78 (3H, d, J=1.0 Hz), 1.83 (3H, d, J=1.0 Hz), 2.26 (1H, br s, NH, disappeared on addition of D_2O), 2.57 (2H, t, J=7.0 Hz), 2.76 (1H, dd, J=15.0, 8.0 Hz), 3.04 (1H, dd, J=15.0, 6.5 Hz), 3.61 (1H, ddd, J=8.0, 7.0, 6.5 Hz), 3.84 (6H, s), 4.01 (1H, dd, J=10.0, 7.0 Hz), 5.13 (1H, br d, J=10.0 Hz), 6.60 (1H, s), 6.72 (1H, s). High-resolution MS m/z: Calcd for $C_{18}H_{27}NO_2$: 289.2040. Found: 289.1986. The HBr salt of **37** was obtained by adding MeOH–47% HBr (95 : 5, v/v) to a solution of **37** in Et_2O. **37**·HBr: mp 193.0—194.0 °C (colorless prisms from Et_2O–MeOH). IR (KBr): 3490, 2960, 1607, 1559, 1501, 1452, 1303, 1243, 1216, 1086, 844 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.5 Hz), 1.85 (3H, d, J=1.0 Hz), 1.88 (3H, d, J=1.0 Hz), 1.98 (2H, sex, J=7.5 Hz), 2.68—3.04 (2H, m), 3.42 (1H, dd, J=15.0, 8.5 Hz), 3.66 (1H, dd, J=15.0, 7.5 Hz), 3.83 (6H, s), 3.91—4.29 (2H, m), 5.48 (1H, br d, J=10.0 Hz), 6.57 (1H, s), 6.68 (1H, s), 8.49 (1H, br s, NH, disappeared on addition of D_2O), 9.49 (1H, br s, NH, disappeared on addition of D_2O). *Anal.* Calcd for $C_{18}H_{28}BrNO_2 \cdot 1/2H_2O$: C, 56.99; H, 7.71; N, 3.69. Found: C, 57.00; H, 7.64; N, 3.75. **38**: mp 163.0—164.0 °C (colorless needles from MeOH–H_2O). IR (KBr): 2960, 2930, 1588, 1493, 1464, 1440, 1307, 1218, 1085 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.0 Hz), 1.43 (2H, sex, J=7.0 Hz), 1.75 (3H, d, J=1.0 Hz), 1.80 (3H, d, J=7.0 Hz), 1.88—3.02 (2H, m), 2.56 (2H, t, J=7.0 Hz), 2.74 (1H, dd, J=15.0, 8.0 Hz), 3.01 (1H, dd, J=15.0, 7.0 Hz), 3.58 (1H, dt, J=8.0, 7.0 Hz), 3.83 (3H, s), 3.98 (1H, dd, J=10.0, 7.0 Hz), 5.11 (1H, br d, J=10.0 Hz), 6.64 (1H, s), 6.69 (1H, s). MS m/z: 275 (M^+). *Anal.* Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.05; H, 9.38; N, 4.85. **39**: mp 136.0—137.0 °C (colorless prisms from MeOH–H_2O). IR (KBr): 2930, 1610, 1584, 1492, 1306, 1283, 1210, 1083, 832 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz), 1.48 (2H, sex, J=7.0 Hz), 1.76 (3H, d, J=1.0 Hz), 1.81 (3H, d, J=1.0 Hz), 2.28—3.86 (2H, m), 2.54 (2H, t, J=7.0 Hz), 2.68 (1H, dd, J=15.5, 8.0 Hz), 2.96 (1H, dd, J=15.5, 7.0 Hz), 3.55 (1H, dt, J=8.0, 7.0 Hz), 3.83 (3H, s), 3.98 (1H, dd, J=10.0, 7.0 Hz), 5.11 (1H, br d, J=10.0 Hz), 6.56 (1H, s), 6.71 (1H, s). MS m/z: 275 (M^+). *Anal.* Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.03, H, 9.43; N, 5.06.

Entry 2: $LiAlH_4$ (150.2 mg, 3.95 mmol) was added to a solution of **35** (52.8 mg, 0.174 mmol) in Et_2O (20 ml) and the mixture was refluxed for 24 h. After work-up and purification as described in entry 1, **37** (14.6 mg, 29%) and **39** (2.2 mg, 5%) were obtained.

Entry 3: $LiAlH_4$ (134.0 mg, 3.53 mmol) was added to a solution of **35** (49.4 mg, 0.163 mmol) in Et_2O (20 ml) and the mixture was refluxed for 12 h. After work-up and purification as described in entry 1, **37** (22.6 mg, 48%), **39** (2.2 mg, 5%), and **35** (3.1 mg, 6%) were obtained.

Entry 4. $LiAlH_4$ (134.0 mg, 3.53 mmol) was added to a solution of **35** (51.0 mg, 0.168 mmol) in Et_2O (20 ml) and the mixture was refluxed for 6 h. After work-up and purification as described in entry 1, **37** (33.9 mg, 70%), **39** (1.7 mg, 4%), and **35** (9.1 mg, 18%) were obtained.

Entry 5: $LiAlH_4$ (537.0 mg, 14.1 mmol) was added to a solution of **35** (200.0 mg, 0.660 mmol) in Et_2O (80 ml) and the mixture was refluxed for 5 h. After work-up and purification as described in entry 1, **37** (139.2 mg, 73%), **39** (2.1 mg, 1%), and **35** (40.8 mg, 20%) were obtained.

X-Ray Crystallographic Analysis of 39 The reflection data were collected on a Rigaku AFC-5 diffractometer over the range of $3° < 2\theta < 55°$ using Mo$K\alpha$ radiation (λ=0.71069 Å) and the ω–2θ scan method at a 2θ scan speed of 6°/min. The structure of **39** was solved by the direct method using MITHRIL[12] and refined by the full-matrix least-squares method with anisotropic thermal factors for non-hydrogen atoms and with isotropic ones for hydrogen atoms. The final R value was 0.081 for 1108 independent reflections [$I > 3\alpha(I)$]. The atomic parameters are listed in Table 3. Crystal Data for **39**: $C_{17}H_{25}NO_2$; M=275.39; Orthorhombic; Space group, *Pbca*; a=17.961 (7), b=16.704 (6), c=10.452 (3) Å; $\alpha=\beta=\gamma=90.0°$; V=3136 (3) Å^3, Z=8, D_c=1.17 g/cm^3.

1,2-*cis*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (37) from 38 Ethereal CH_2N_2 (1.2 M, 2 ml)[13] was added to a solution of **38** (8.1 mg, 0.029 mmol) in MeOH (2 ml) and the mixture was stirred at room temperature for 4 h. After evaporation of the solvent under reduced pressure, the residue was purified by p-TLC with CH_2Cl_2–MeOH (95 : 5, v/v) to give **37** (6.4 mg, 75%). All spectral data of **37** were identical with those of **37** obtained from **35**.

1,2-*cis*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (37) from 39 Ethereal CH_2N_2 (1.2 M, 2 ml)[13] was added to a solution of **39** (10.2 mg, 0.037 mmol) in MeOH (2 ml) and the mixture was stirred at room temperature for 3 h. After evaporation of the solvent under reduced pressure, the residue was purified by p-TLC with CH_2Cl_2–MeOH (95 : 5, v/v) to give **37** (7.1 mg, 66%). All spectral data of **37** were identical with those of **37** obtained from **35** and **38**.

1,2-*trans*-5,6-Dimethoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (40) $LiAlH_4$ (1.1598 g, 30.6 mmol) was added to a solution of **36** (407.5 mg, 1.34 mmol) in Et_2O (40 ml) and the mixture was refluxed for 2 h. Excess $LiAlH_4$ was destroyed by adding MeOH at 0 °C and then saturated potassium sodium tartrate was added. The whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography with CH_2Cl_2–MeOH (95 : 5, v/v) to give **40** (332.6 mg, 86%). **40**: colorless oil. IR (film): 2960, 2920, 1605, 1501, 1461, 1451, 1299, 1213, 1086 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.54 (2H, sex, J=7.2 Hz), 1.82 (6H, br s), 1.89 (1H, br s, NH, disappeared on addition of D_2O), 2.46—2.81 (1H, m), 2.64 (2H, t, J=7.2 Hz), 2.94—3.38 (2H, m), 3.58—3.88 (1H, m), 3.84 (6H, s), 5.11 (1H, br d, J=9.6 Hz), 6.50 (1H, s), 6.71 (1H, s). High-resolution MS m/z: Calcd for $C_{18}H_{27}NO_2$: 289.2040. Found: 289.2029. The HBr salt of **40** was obtained by adding MeOH–47% HBr (95 : 5, v/v) to a solution of **40** in Et_2O. **40**·HBr: mp 128.0—130.0 °C (colorless leaves from Et_2O–MeOH). IR (KBr): 3420, 2920, 1609, 1500, 1452, 1313, 1216, 1089 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.3 Hz), 1.64—2.19 (2H, m), 1.82 (3H, d, J=1.0 Hz), 1.88 (3H, d, J=1.0 Hz), 2.68—3.20 (2H, m), 3.24—3.87 (3H, m), 3.82 (6H, s), 4.36—4.64 (1H, m), 5.07 (1H, br d, J=9.5 Hz), 6.42 (1H, s), 6.66 (1H, s), 9.42 (2H, br s, NH_2, disappeared on addition of D_2O). *Anal.* Calcd for $C_{18}H_{28}BrNO_2$: C, 58.38; H, 7.62; N, 3.78. Found: C, 58.45; H, 7.73; N, 3.86.

1,2-*cis*-2-Amino-6-benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)indan (41) A solution of **27** (46.3 mg, 0.131 mmol) in MeOH–THF (1 : 1, v/v, 9 ml) and 2 N HCl (3 ml) was added to Zn(Hg), prepared from Zn powder (434.4 mg, 6.65 mmol) and $HgCl_2$ (37.9 mg, 0.140 mmol) in 2 N HCl (3 ml), and the mixture was refluxed for 3 h. Unreacted Zn(Hg) was filtered off and the filtrate was evaporated under reduced pressure. The residue was basified with aqueous 2 N NaOH and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by p-TLC with $CHCl_3$–MeOH–29% NH_4OH (46 : 5 : 0.5, v/v) to give **41** (28.3 mg, 67%). **41**: colorless oil. IR (KBr): 3360, 2920, 1601, 1500, 1450, 1295, 1216, 1208, 1084, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, d, J=1.0 Hz), 1.80 (3H, d, J=1.0 Hz), 2.30 (2H, br s, NH_2, disappeared on addition of D_2O), 2.67 (1H, dd, J=15.5, 3.5 Hz), 3.08 (1H, dd, J=15.5, 6.0 Hz), 3.63—3.95 (2H, m), 3.83 (3H, s), 4.93—5.21 (1H, m), 5.06 (2H, s), 6.63 (1H, s), 6.76 (1H, s), 7.18—7.49 (5H, m). High-resolution MS m/z: Calcd for $C_{21}H_{25}NO_2$: 323.1884. Found: 323.1902.

1,2-*cis*-6-Benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-propionylaminoindan (42) Propionyl chloride (0.4 ml, 1.18 mmol) was added to a solution of **41** (23.9 mg, 0.074 mmol) and Et_3N (0.3 ml) in CH_2Cl_2 (3 ml) and the mixture was stirred at room temperature for 16 h. The whole was washed successively with saturated $NaHCO_3$, then with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to leave an oil, which was purified by p-TLC with CH_2Cl_2–MeOH (95 : 5, v/v) to give **42** (24.4 mg, 87%). **42**: mp 142.0—143.0 °C (colorless needles from CH_2Cl_2–hexane). IR (KBr): 3250, 1636, 1548, 1496, 1446, 1309, 1219, 1086 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7.5 Hz), 1.71 (3H, d, J=1.0 Hz), 1.75 (3H, d, J=1.0 Hz), 2.13 (2H, q, J=7.5 Hz), 2.63 (1H, dd, J=15.5, 6.5 Hz), 3.18 (1H, dd, J=15.5, 7.0 Hz), 3.83 (3H, s), 3.95 (1H, dd, J=10.0, 7.5 Hz), 4.74 (1H, dddd, J=8.5, 7.5, 7.0, 6.5 Hz), 4.97 (1H, br d, J=10.0 Hz), 5.05 (2H, s), 5.56 (1H, br d, J=8.5 Hz, CONH), 6.62 (1H, s), 6.72 (1H, s), 7.17—7.46 (5H, m). MS m/z: 379 (M^+). *Anal.* Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 76.03; H, 7.78; N, 3.65.

1,2-*cis*-6-Benzyloxy-5-methoxy-1-(2-methyl-1-propenyl)-2-propylaminoindan (43) $LiAlH_4$ (67.8 mg, 1.79 mmol) was added to a solution of **42** (22.0 mg, 0.058 mmol) in Et_2O (10 ml) and the mixture was refluxed for 5 h. Excess $LiAlH_4$ was destroyed by adding MeOH at 0 °C, and then saturated potassium sodium tartrate was added. The whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by p-TLC with CH_2Cl_2–MeOH (92 : 8, v/v) to give **43**

(15.6 mg, 74%). **43**: colorless oil. IR (film): 2930, 1606, 1497, 1450, 1296, 1213, 1084 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.5 Hz), 1.50 (2H, sex, J=7.5 Hz), 1.75 (3H, d, J=1.5 Hz), 1.77 (3H, d, J=1.5 Hz), 1.88 (1H, br s, NH, disappeared on addition of D_2O), 2.54 (2H, t, J=7.5 Hz), 2.74 (1H, dd, J=15.0, 8.0 Hz), 3.02 (1H, dd, J=15.0, 7.0 Hz), 3.58 (1H, dt, J=8.0, 7.0 Hz), 3.83 (3H, s), 3.94 (1H, dd, J=10.0, 7.0 Hz), 5.06 (2H, s), 5.11 (1H, br d, J=10.0 Hz), 6.63 (1H, s), 6.74 (1H, s), 7.18—7.50 (5H, m). High-resolution MS m/z: Calcd for $C_{24}H_{31}NO_2$: 365.2353. Found: 365.2364.

1,2-*cis*-6-Benzyloxy-2-(*N*-benzylpropylamino)-5-methoxy-1-(2-methyl-1-propenyl)indan (44) i) From **43**: K_2CO_3 (53.5 mg, 0.388 mmol) was added to a solution of **43** (14.0 mg, 0.038 mmol) and benzyl bromide (0.009 ml, 0.076 mmol) in acetone (2 ml), and the mixture was stirred at room temperature for 38 h. The whole was diluted with H_2O and extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by p-TLC with CH_2Cl_2–MeOH (97 : 3, v/v) to give **44** (14.5 mg, 83%). **44**: mp 93.0—94.0 °C (colorless needles from MeOH). IR (KBr): 2920, 1602, 1599, 1450, 1293, 1233, 1212, 1109, 1085, 699 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, t, J=7.0 Hz), 1.42 (2H, sex, J=7.0 Hz), 1.71 (3H, d, J=1.5 Hz), 1.73 (3H, d, J=1.5 Hz), 2.22—2.58 (2H, m), 2.82 (1H, dd, J=15.0, 7.5 Hz), 3.01 (1H, dd, J=15.0, 7.5 Hz), 3.34—3.76 (3H, m), 3.83 (3H, s), 3.96 (1H, dd, J=10.0, 7.0 Hz), 5.06 (2H, s), 5.41 (1H, br d, J=10.0 Hz), 6.63 (1H, s), 6.72 (1H, s), 7.02—7.52 (10H, m). MS m/z: 455 (M^+). *Anal.* Calcd for $C_{31}H_{37}NO_2$: C, 81.72; H, 8.19; N, 3.07. Found: C, 81.62; H, 8.20; N, 3.02.

ii) From **38**: A solution of benzyl bromide (50.8 mg, 0.297 mmol) in acetone (1 ml) was added to a mixture of **38** (19.6 mg, 0.071 mmol) and K_2CO_3 (106.3 mg, 0.770 mmol) in acetone (5 ml), and the whole was stirred at room temperature for 44 h. After work-up as described above, the residue was purified by p-TLC with CH_2Cl_2–MeOH (93 : 3, v/v). Under UV light, two bands were detected. Extraction from the upper band with $CHCl_3$–MeOH–29% NH_4OH (46 : 5 : 0.5, v/v) gave **44** (21.7 mg, 67%). Extraction from the lower band with the same solvent as described above gave **38** (7.3 mg, 28%). All spectral data of **44** were identical with those of **44** obtained by the above procedure i.

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