Design, Synthesis, and Monoamine Transporter Binding Site Affinities of Methoxy Derivatives of Indatraline

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A series of methoxy-containing derivatives of indatraline **13a**−**f** and **17** were synthesized, and their binding affinities for the dopamine, serotonin, and norepinephrine transporter binding sites were determined. Introduction of a methoxy group to indatraline affected its affinity and selectivity greatly. Except for the 4-methoxy derivative **13a**,which had the same high affinity at the dopamine transporter binding site as indatraline, the other methoxy-containing analogues (**13b**−**f** and **17**) exhibited lower affinity than indatraline for the three transporter binding sites. However, some of the analogues were more selective than indatraline, and the 6-methoxy derivative **13c** displayed the highest affinity for both the serotonin and norepinephrine transporters. This compound retained reasonable affinity for the dopamine transporter and is a promising template for the development of a long-acting inhibitor of monoamine transporters. Such inhibitors have potential as medications for treatment, as a substitution medication, or for prevention of the abuse of methamphetamine-like stimulants.

Introduction

The abuse of stimulants, such as methamphetamine and amphetamine, is an outstanding national and international[1] public health problem;[2] a considerable number of adverse effects[3] derive from that abuse including the increased transmission of hepatitis and HIV/AIDS.[4,5] Drug therapy to prevent chronic stimulant abuse or to block the effect of a stimulant is the subject of considerable contemporary research by many research groups.[6] One approach, to find selective dopamine reuptake inhibitors, is currently being evaluated as a class of potential substitution medications for the treatment of cocaine and methamphetamine abuse.[7,8]

We considered a different approach and hypothesized that a compound that might be most useful as a treatment agent would eliminate the transport of the abused stimulant into nerve terminals.[6] Such a drug might be discovered by searching for a compound that displayed good affinity for all three monoamine transporters: the dopamine, serotonin, and norepinephrine transporters.[9−12] This high-affinity, nonselective drug might eliminate methamphetamine's reinforcing effects[12] by blocking the transporters which are thought to contribute to or modulate the effects of stimulant-like drugs. Furthermore, if this drug were capable of being converted to a long-acting depot medication,[13] it might also prevent craving and relapse for a considerable time.

Our present work is based on an indatraline template, since indatraline has been shown to be a nonselective monoamine reuptake inhibitor,[14−16] capable of antagonizing methamphetamine-induced [^{3}H]neurotransmitter release.[6] Herein we report the synthesis of a series of methoxy-containing derivatives of indatraline and their binding affinities for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) binding sites (Table 1). The methoxy function was chosen because it was amenable to being readily converted to the phenol from which long-acting inhibitors could be prepared.[13] However, since we had no way of predicting, a priori, which compound would prove best for our further purposes, we prepared a number of analogues.

Chemistry

Substituted 3,3-diphenylpropanoic acids **4a,b** were synthesized in three steps from commercially available benzaldehydes according to a modified literature method (Scheme 1).[15] Cyclization of **4a,b** occurred smoothly in polyphosphoric acid (PPA)[15] at 120 °C affording the desired indanones **5a**−**c** in good yield. It should be pointed out that treatment of the acid chlorides of **4a,b** with $AlCl_3$ gave a very low yield of indanones (12−27%). Cyclization of acid **4a** gave indanone **5a** in 68% yield along with a 17% yield of lactone which arose from demethylation and then intramolecular cyclization. Cyclization of the acid **4b** gave a 4:1 mixture of isomers **5b**,**c** in 75% overall yield with **5b** predominant. The structure of the indanone **5b** was confirmed by single-crystal X-ray analysis (Figure 1).

The 6-methoxyindanones **7a**−**c** were synthesized in good to excellent yields by heating the corresponding chalcones **6a**−**c** in neat trifluoroacetic acid (TFA) in a sealed tube (Scheme 2). Initial attempts to use PPA or TFA at room temperature or reflux to effect the cyclization were unsuccessful. The *trans*-chalcones **6a**−**c** were prepared by base-catalyzed condensation of the ap-

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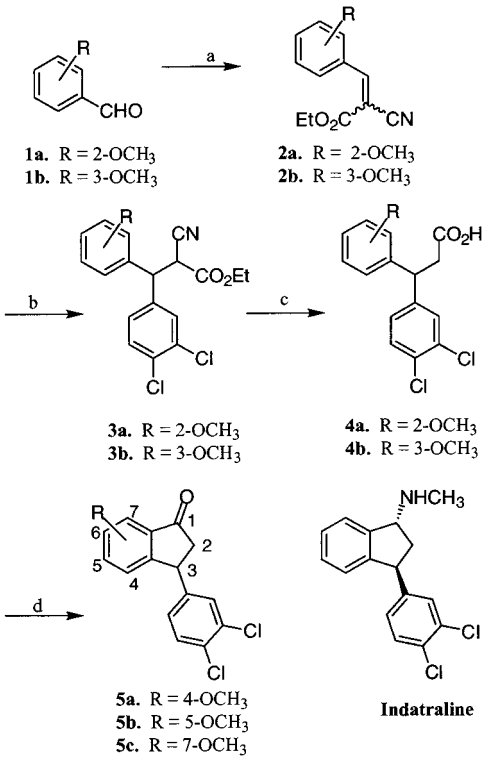
Scheme 1[a]



[a] (a) $CNCH_2CO_2Et$, piperidine, toluene, reflux; (b) 3,4-dichlorobromobenzene, Mg, toluene−ether; (c) $HOAc-H_2SO_4-H_2O$ (2:1:1), reflux; (d) PPA, 110−120 °C.

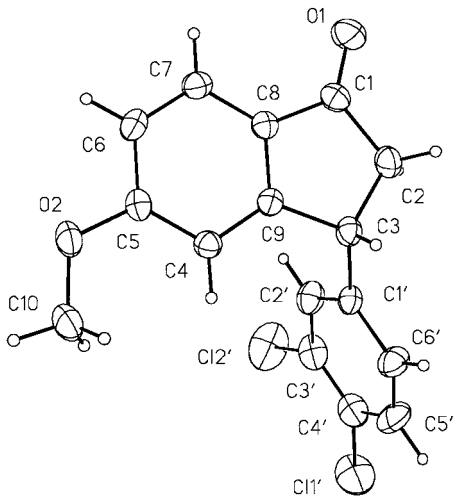
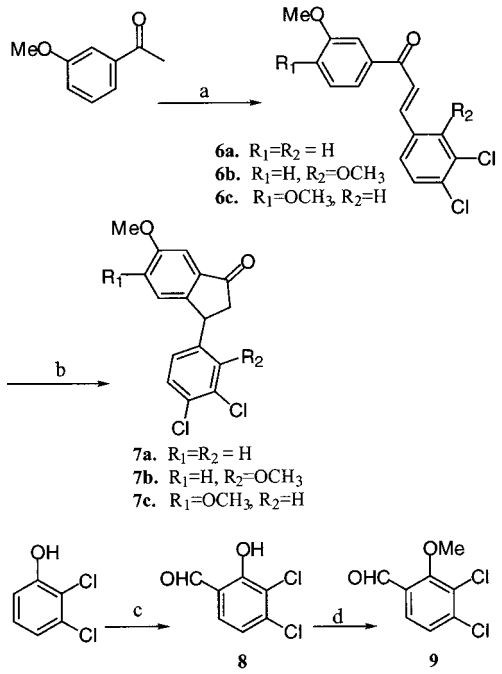


Figure 1. X-ray structure for 3-(3,4-dichlorophenyl)-5-methoxyindan-1-one (**5b**) with displacement ellipsoids drawn at the 30% probability level. The lower occupancy atoms of the disordered dichlorophenyl ring were omitted for clarity.

propriately substituted benzaldehydes and 3-methoxyacetophenone or 3,4-dimethoxyacetophenone.[17] The requisite benzaldehyde **9** was synthesized in 34% overall yield from commercially available 2,3-dichlorophenol by the Reimer−Tiemann reaction[18] to introduce a formyl group, followed by methylation of the hydroxyl group with MeI and K_2CO_3 in acetone. It should be noted that the 6-methoxyindanones **7a**−**c** were not able to be prepared by the same method as that described for indanones **5a**−**c**.

Reduction of the indanones **5a**−**c** and **7a**−**c** with sodium borohydride gave, as expected, almost pure *cis*-3-phenylindan-1-ols **10a**−**f** in nearly quantitative yield.

Scheme 2[a]



[a] (a) ArCHO, KOH, $EtOH-H_2O$; (b) TFA, sealed tube, 110−120 °C; (c) excess $CHCl_3$, 6 equiv NaOH, 2 equiv H_2O, reflux; (d) CH_3I, K_2CO_3, acetone, rt.

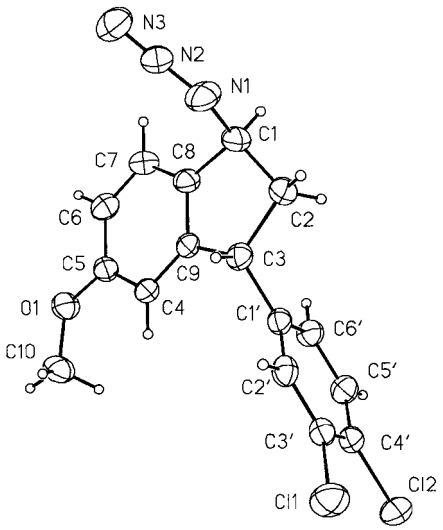
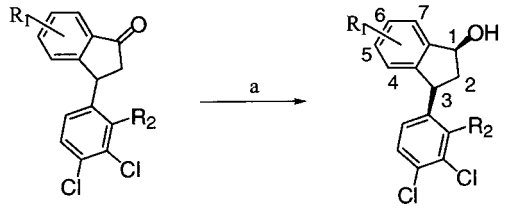


Figure 2. X-ray structure for *trans*-1-azido-3-(3,4-dichlorophenyl)-5-methoxyindan (**11b**) with displacement ellipsoids drawn at the 30% probability level.

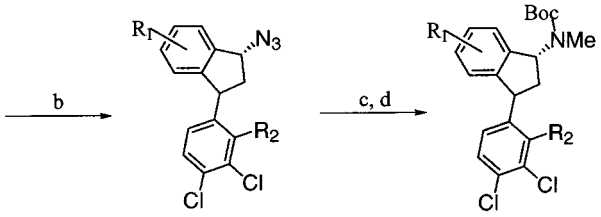
Others,[15] and we,[19] have shown that only the *trans* isomer of 3-phenyl-1-indanamine is a potent inhibitor for dopamine, serotonin, and norepinephrine uptake. Thus, we developed a selective synthetic strategy to obtain the desired *trans*-3-phenyl-1-indanamines. Treatment of the alcohols **10a**−**f** with diphenyl phosphorazidate (DPPA) in the presence of DBU following Thompson's procedure[20,21] gave predominantly the *trans*-azides **11a**−**f** in good yields (83−92%) and with high selectivity (95:5−85:15). The undesired *cis* isomers were removed by column chromatography. The *anti* configuration of the desired azide **11b** was unequivocally determined by single-crystal X-ray analysis (Figure 2).

With the desired substitution pattern in place, all that remained was to reduce the azide and methylate the

Scheme 3[a]

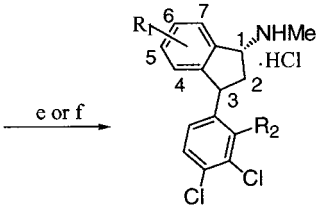


10a. R_1 = 4-OCH_3, R_2 = H
10b. R_1 = 5-OCH_3, R_2 = H
10c. R_1 = 6-OCH_3, R_2 = H
10d. R_1 = 7-OCH_3, R_2 = H
10e. R_1 = 6-OCH_3, R_2 = OCH_3
10f. R_1 = 5,6-$(OCH_3)_2$, R_2 = H



11a. R_1 = 4-OCH_3, R_2 = H
11b. R_1 = 5-OCH_3, R_2 = H
11c. R_1 = 6-OCH_3, R_2 = H
11d. R_1 = 7-OCH_3, R_2 = H
11e. R_1 = 6-OCH_3, R_2 = OCH_3
11f. R_1 = 5,6-$(OCH_3)_2$, R_2 = H

12a. R_1 = 4-OCH_3, R_2 = H
12b. R_1 = 5-OCH_3, R_2 = H
12c. R_1 = 6-OCH_3, R_2 = H
12d. R_1 = 7-OCH_3, R_2 = H
12e. R_1 = 6-OCH_3, R_2 = OCH_3
12f. R_1 = 5,6-$(OCH_3)_2$, R_2 = H



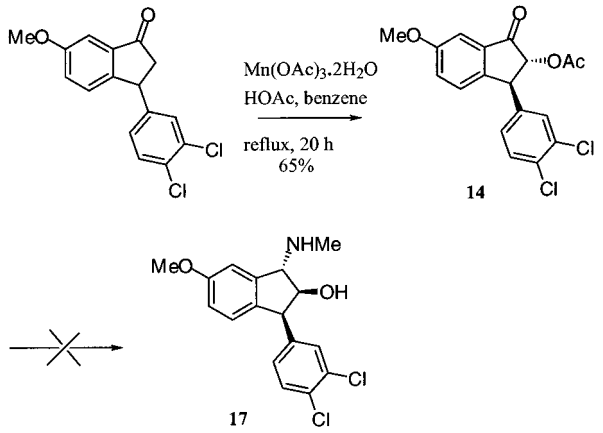
13a. R_1 = 4-OCH_3, R_2 = H
13b. R_1 = 5-OCH_3, R_2 = H
13c. R_1 = 6-OCH_3, R_2 = H
13d. R_1 = 7-OCH_3, R_2 = H
13e. R_1 = 6-OCH_3, R_2 = OCH_3
13f. R_1 = 5,6-$(OCH_3)_2$, R_2 = H

[a] (a) $NaBH_4$, MeOH, 0 °C−rt; (b) DPPA, DBU, THF, 0 °C−rt; (c) H_2, Boc_2O, 5% Pd/C, EtOAc; (d) CH_3I, NaH, DMF; (e) HCl−EtOAc, rt; (f) $ZnBr_2$, CH_2Cl_2, rt.

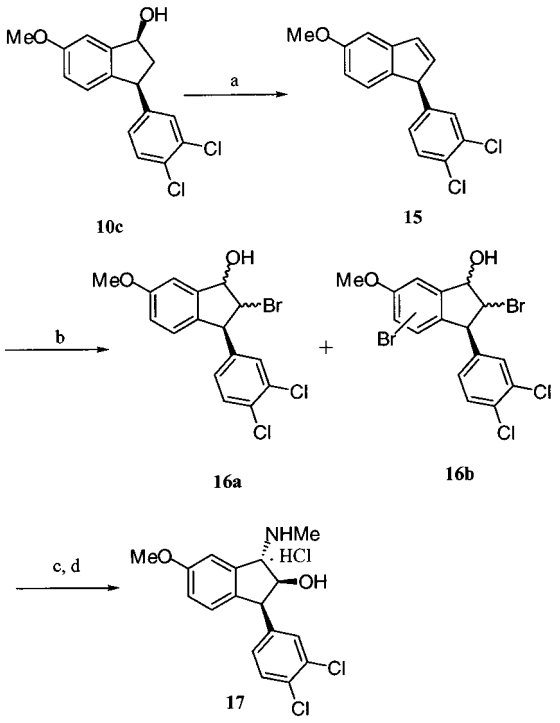
resulting amine. Hydrogenolysis of azides **11a**−**f** over Pd/C in the presence of $(BOC)_2O$[22] afforded the carbamates which were subsequently methylated with NaH and MeI in THF[23] to provide *N*-methylcarbamates **12a**−**f** in good yields. Initial attempts to use TFA to cleave the BOC group from **12a**−**f** were unsuccessful, and a complex mixture resulted. Removal of the BOC group from **12a**,**c**−**e** was achieved using a saturated solution of HCl in EtOAc.[24] However, this reagent afforded complex mixtures on attempts to deprotect the 5-methoxy-containing derivatives **12b**,**f**. The deprotection of **12b**,**f** was smoothly accomplished in high yield using $ZnBr_2$[25] in dry CH_2Cl_2. The HCl salts of **13a**−**f** were purified by recrystallization from a mixture of 2-propanol and isopropyl ether.

Initial attempts to synthesize compound **17** failed through the route shown in Scheme 4. Although indanone **7a** could be easily converted into compound **14** in 65% yield by treatment with $Mn(OAc)_3$ and AcOH,[26] we encountered great difficulty in transforming the carbonyl group in **14** to a methylamino group. Various reductive amination conditions were tried, but all failed to give the desired compound presumably because of the sensitivity of **14** to the reaction conditions.

Scheme 4. Unsuccessful Synthesis of **17**



Scheme 5[a]



[a] (a) *p*-TSA, PhH, reflux; (b) NBS, THF−H_2O, rt; (c) $MeNH_2$, EtOH−H_2O, reflux; (d) H_2, 5% Pd/C, NaOAc·$3H_2O$, MeOH, rt.

Finally, compound **17** was synthesized from indanol **10c** through the route shown in Scheme 5. Indanol **10c** was dehydrated with *p*-toluenesulfonic acid in refluxing benzene[27,28] to afford the unstable indene **15** as a colorless liquid in quantitative yield. Indene **15** was reacted immediately with NBS in aqueous THF[29] to give the expected bromohydrin **16a** along with unexpected ring-brominated bromohydrin **16b** in 50% yield. The latter was formed even when the amount of NBS was reduced to less than 1 equiv. The mixture of **16a**,**b** was treated with methylamine in refluxing aqueous ethanol[30] to give the desired amino alcohol in moderate yield. Subsequent brief hydrogenolysis in the presence of Pd/C

Table 1. Physical Properties and Binding Affinities of Indatraline Analogues[a]

compd	mp (°C)	formula	$K_i \pm$ SD (nM) DAT[b]	SERT[b]	NET[c]
13a	248−250 dec	$C_{17}H_{17}Cl_2NO\cdot HCl$	1.7 ± 0.05	63 ± 2	27 ± 1.7
13b	193−195	$C_{17}H_{17}Cl_2NO\cdot HCl$	9.4 ± 0.44	6.5 ± 0.5	76.5 ± 5.3
13c	240−242	$C_{17}H_{17}Cl_2NO\cdot HCl$	11.6 ± 0.3	1.1 ± 0.08	15 ± 0.6
13d	190−192 dec	$C_{17}H_{17}Cl_2NO\cdot HCl$	32 ± 2	108 ± 4	93 ± 9.3
13e	212−214	$C_{18}H_{19}Cl_2NO\cdot HCl\cdot 0.5H_2O$	788 ± 13	5.6 ± 0.5	122 ± 6.1
13f	220−222 dec	$C_{18}H_{19}Cl_2NO\cdot HCl\cdot 0.25H_2O$	3.6 ± 0.18	61 ± 2	102 ± 9.5
17	268−270 dec	$C_{17}H_{17}Cl_2NO_2\cdot HCl$	1133 ± 21	8.1 ± 0.5	1686 ± 93
indatraline[d]			1.7 ± 0.24[e]	0.42 ± 0.04[e]	5.8 ± 0.4[e]

[a] The K_i values of the test agents were determined using protocols previously established in ref 31. [b]DAT and SERT binding sites labeled with [^{125}I]RTI-55. [c]NET site labeled with [^{3}H]nisoxetine. [d]Physical data can be found in ref 15. [e]Data from ref 31.

and sodium acetate, selectively removing the aromatic bromine atom without affecting the aromatic chlorines, afforded compound **17** in 23% overall yield. The relative configuration of the three stereocenters was assigned through NOE. The observed cross-peaks between the CHOH at C2 and the Ar + indano CH at C3 and the lack of a cross-peak between the NHMeCH at C1 and any other proton in **17** except for the aromatic protons were unambiguously indicative of the *cis* relationship between the OH and the dichlorobenzene moiety and a *trans* relationship between the OH and the NHMe moiety. It was not possible to confirm the relative stereochemistry of **17** by X-ray analysis because it was not possible to grow a usable single crystal.

Pharmacology

The binding affinities (K_i) of compounds **13a**−**f** and **17** for the DAT, SERT, and NET are summarized in Table 1. Binding assays were determined in competition studies using [^{125}I]RTI-55 ([^{125}I]-3β-(4′-iodophenyl)tropane-2β-carboxylic acid methyl ester) to label the DAT and SERT and [^{3}H]nisoxetine to label the NET following known procedures.[31,32] For comparative purposes, binding data for indatraline are included.

Results and Discussion

In general, the binding affinity (K_i) of all the methoxy-containing indatraline-like compounds decreased relative to indatraline, although one of them maintained sufficiently high affinity for our purposes. A major loss in affinity for the DAT was observed with compounds **13e** and **17**. In those compounds, a second oxygen function was introduced in the molecule outside of the aromatic part of the indan moiety. Compound **13a**, with a methoxy group in the 4-position, exhibited the highest binding affinity for the DAT among these analogues (K_i = 1.7 nM, equivalent to indatraline) and showed high selectivity for DAT vs SERT or NET (37- and 16-fold, respectively). All the other compounds with methoxy substituents on the aromatic ring of the indan showed progressively less affinity for the DAT the further removed they were from that C4-position. Compound **13b**, with a methoxy group in the C5-position, possessed essentially equivalent, high binding affinities for the DAT and SERT, although it had 6- and 16-fold lower affinity than indatraline, respectively, at those transporters. Remarkably, introduction of a methoxy group in the 7-position (compound **13d**) resulted in an 18- and 257-fold decrease in binding affinity for the DAT and SERT, respectively. The 5,6-dimethoxy compound **13f** had higher affinity for the DAT than any of the monomethoxy derivatives except for the 4-methoxy analogue **13a**. The low binding affinity of compound **13e** for the DAT binding site was surprising considering that the difference between **13e**,**f** was only the transposition of a methoxy group from C5 to the dichlorobenzene ring. This clearly illustrated the sensitivity of the binding site in the DAT to structural modifications in the dichlorobenzene moiety of indatraline-like compounds. Compound **17** was a selective compound with high affinity for the SERT binding site and might prove useful as a template for compounds capable of blocking a single monamine transporter. From these SAR data it is apparent that substitution in the C2-position or in the dichlorobenzene ring inhibits binding at the DAT, but there is much less effect on the SERT.

Conclusions

Our results demonstrated that the introduction of a methoxy group into indatraline greatly influences its potency and selectivity for the three monoamine transporters. We have found that an oxygenated moiety outside of the aromatic ring in the indan skeleton is deleterious to the affinity of the compound for the transporters. Our synthesis of a series of methoxy-containing derivatives of indatraline afforded compounds that had high affinity for either the DAT or the SERT. Only one compound, however, the C6-monosubstituted methoxy compound **13c**, had high affinity for both of those transporters, as well as for the NET. This compound was formerly prepared and examined as an antidepressant by Bøgesø et al.[15] Its IC_{50} for synaptosomal uptake inhibition was noted to be 2.5, 0.67, and 0.62 nM at DA, NE, and 5-HT, respectively; it was not chosen for further pharmacological evaluation at that time. Compound **13c** will be the subject of our future research since we believe that it is theoretically capable of blocking the transport of methamphetamine-like substrates to all of the monamine nerve terminals. Furthermore, it can serve as a template for a potentially long-acting depot preparation, which may be suitable as a medication for the treatment or prevention of the sequelae resulting from the abuse of methamphetamine-like stimulants.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and were uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, and the results were within ±0.4% of the theoretical values for the elements indicated. Chemical ionization mass spectra (CIMS) were obtained using a Finnegan 1015 mass spectrometer. Electron ionization mass spetra (EIMS) were obtained using a V.G.

Micro Mass 7070F mass spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-300 spectrometer. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a tetramethylsilane (TMS) internal standard. Thin-layer chromatography (TLC) was performed on 250-μm Analtech GHLF silica gel plates. Flash column chromatography was performed with Fluka silica gel 60 (220−240 mesh). No attempt was made to optimize the reported yields.

2-Cyano-3-(2-methoxyphenyl)acrylic Acid Ethyl Ester (2a). The general method of Bøgesø[33] was used with slight modification. A solution of *o*-anisaldehyde (41 g, 0.3 mol), ethyl cyanoacetate (41 g, 0.36 mol) and piperidine (2.0 mL) in toluene (200 mL) was refluxed under a Dean−Stark trap for 1.5−2 h. After removal of the volatiles in vacuo, an orange oil was obtained in quantitative yield, which solidified when standing at ambient temperature. The product was used in the next reaction without further purification. A sample for analysis was obtained by recrystallization from EtOAc as pale-yellow needles: ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.31−6.95 (m, 4H), 4.38 (q, J = 8.05 Hz, 2H), 3.91 (s, 3H), 1.39 (t, J = 8.05 Hz, 3H); CIMS (NH_3) m/z 232 (MH^+, 100).

2-Cyano-3-(3-methoxyphenyl)acrylic Acid Ethyl Ester (2b). The title compound was prepared as a red oil in quantitative yield from *m*-anisaldehyde by a procedure similar to that described for **2a**. **2b** was used without further purification. A sample for analysis was obtained after purification by column chromatography on silica gel (petroleum ether/EtOAc 10:1): ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 8.7 Hz, 1H), 7.13−7.10 (dd, J = 2.1 Hz, 7.8 Hz, 1H), 4.39 (m, 2H), 3.87 (s, 3H), 1.40 (t, J = 8.7 Hz, 3H); CIMS (NH_3) m/z 232 (MH^+, 100).

2-Cyano-3-(3,4-dichlorophenyl)-3-(2-methoxyphenyl)-propionic Acid Ethyl Ester (3a). The general method of Bøgesø[33] was used with slight modification. A 250-mL two-necked flask was equipped with a dropping funnel and an efficient refluxing condenser attached to a potassium carbonate tube. In the flask were placed magnesium turnings (0.96 g, 0.04 g atom), a crystal of iodine and 30 mL of dry ether. A solution of 4-bromo-1,2-dichlorobenzene (9.0 g 40 mmol) in 50 mL of anhydrous ether was added at a rate which maintained rapid refluxing. The mixture was stirred and heated under reflux for an additional 1.5 h. A solution of **2a** (4.62 g, 20 mmol) in Et_2O (50 mL) was added to the above solution at ambient temperature. The mixture was refluxed for 1 h, then poured into a mixture of ice (200 g) and concentrated H_2SO_4 (20 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo to afford **3a** (10.16 g, 135%) as a red oil, which was used in the next reaction without further purification. A sample for analysis was obtained by column chromatography on silica gel (petroleum ether/EtOAc 10:1) as a pale-yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.47−6.88 (m, 7H), 5.00 (dd, J = 7.8 Hz, 10.8 Hz, 1H), 4.43 (dd, J = 7.8 Hz, 10.8 Hz, 1H), 4.13 (t, J = 8.1 Hz, 2H), 3.85 (s, 3H),1.13(q, J = 8.1 Hz, 3H); CIMS (NH_3) m/z 395 ($M^+ + NH_4$, 100), 361 (M − 17, 35); EIMS m/z 377(M^+, 18), 265 (M − 112, 95), 159 (100).

2-Cyano-3-(3,4-dichlorophenyl)-3-(3-methoxyphenyl)-propionic Acid Ethyl Ester (3b). As in the preparation of **3a**, magnesium turnings (2.76 g, 0.115 g atom), a crystal of iodine and 50 mL of dry Et_2O were placed in the flask. A solution of 4-bromo-1,2-dichlorobenzene (22.9 g, 100 mml) in 50 mL of anhydrous Et_2O was added at a rate which maintained rapid refluxing. The mixture was stirred and heated under reflux for 1 h after the addition. A solution of **2b** (10.5 g, 45.5 mmol) in dry toluene (50 mL) was added to the above solution at ambient temperature. The mixture was refluxed for 2 h, then poured into a mixture of ice (200 g) and concentrated H_2SO_4 (20 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was purification by column chromatography on silica gel (petroleum ether/EtOAc 10:1) to afford **3b** (14.2 g, 83%) as a pale-yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.45−6.77 (m, 7H), 4.67 (m, 1H), 4.24−4.11(m, 3H), 3.78(d, J = 2.1 Hz, 3H), 1.15(dd, J = 2.1 Hz 6.9 Hz, 3H); CIMS (NH_3) m/z 395 ($M^+ + NH_4$, 100).

3-(3,4-Dichlorophenyl)-3-(2-methoxyphenyl)propionic Acid (4a). The general method of Bøgesø[33] was used with slight modification. A mixture of crude **3a** (26 g, 6.9 mmol), AcOH (40 mL), concentrated H_2SO_4 (20 mL), and H_2O (20 mL) was refluxed with stirring for 26 h and then poured into ice. The brown crystalline acid was filtered, and washed thoroughly with H_2O. After coevaporation several times with toluene, the brown acid was recrystallized from EtOAc to afford **4a** (14.5 g, 65%) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 7.34−6.84 (m, 7H), 4.83 (t, J = 7.0 Hz, 8.16 Hz, 1H), 3.77 (s, 3H, OCH_3), 3.04 (m, 2H); CIMS (NH_3) m/z 342 ($M^+ + NH_4$, 100).

3-(3,4-Dichlorophenyl)-3-(3-methoxyphenyl)propionic Acid (4b). Prepared from **3b** in 72% yield as a white solid by a procedure similar to that described for **4a**: ^{1}H NMR ($CDCl_3$) δ 7.40−6.82 (m, 7H), 4.86 (t, J = 7.0 Hz, 8.2 Hz, 1H), 3.79 (s, 3H, OCH_3), 3.05 (m, 2H); CIMS (NH_3) m/z 342 ($M^+ + NH_4$, 100).

3-(3,4-Dichlorophenyl)-4-methoxyindan-1-one (5a). PPA (30 g) was placed in a dry flask and heated to 90 °C under an atmosphere of Ar. Acid **4a** (980 mg, 3 mmol) was added, and the reaction mixture was stirred at 110 °C for 3 h. The mixture was poured into ice−H_2O and extracted with EtOAc, The combined extracts were washed successively with H_2O, 5% NaOH solution and brine, dried over Na_2SO_4, and concentrated in vacuo to give a brown oil, which was purified by column chromatography on silica gel (petroleum ether/EtOAc 10:1→8:1) to afford **5a** (625 mg, 68%) as a pale-yellow syrup: ^{1}H NMR ($CDCl_3$) δ 7.48−6.87 (m, 6H), 4.33 (t, J = 6.8 Hz, 1H), 3.72 (s, 3H, OCH_3), 3.2 (q, J = 7.8 Hz, 19.5 Hz, 1H), 2.56 (m, 1H); EIMS m/z 306 (M^+, 45), 292 (M^+ − 15, 80), 215 (100).

3-(3,4-Dichlorophenyl)-5-methoxyindan-1-one (5b) and 3-(3,4-Dichlorophenyl)-7-methoxyindan-1-one (5c). A mixture of acid **4b** (7.0 g, 21.53 mmol) and PPA (28 g) was heated at 110 °C for 4 h under an atmosphere of Ar, then poured into a mixture of ice−H_2O and extracted with EtOAc. The combined extracts were washed successively with H_2O, 5% NaOH solution and brine, dried over Na_2SO_4, and concentrated in vacuo to give a brown solid, which was purified by column chromatography on silica gel (petroleum ether/EtOAc 8:1→3:1) to afford **5b** (3.902 g, 59%) as a pale-yellow solid. At the same time **5c** (0.847 g, 13%) was obtained as a yellow solid. **5b** (the less polar component): mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 9 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.00−6.94 (m, 2H), 6.63 (s, 1H), 4.47 (dd, J = 3.9 Hz, 7.8 Hz, 1H), 3.82 (s, 3H), 3.21 (dd, J = 7.8 Hz, 8.7 Hz, 1H), 2.59 (q, J = 3.9 Hz, 1H); EIMS m/z 306 (M^+, 100). **5c** (the more polar component): mp 124−126 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 2.1 Hz, 1H), 6.96 (dd, J = 2.1 Hz, 9 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 4.46 (dd, J = 3.9 Hz, 7.8 Hz, 1H), 4.00 (s, 3H), 3.2 (dd, J = 7.8 Hz, 8.7 Hz, 1H), 2.60 (dd, J = 3.9 Hz, 1H); EIMS m/z 306 (M^+, 100).

3-(3,4-Dichlorophenyl)-1-(3-methoxyphenyl)propenone (6a). To a stirred mixture of 3-methoxyacetophenone (15.1 g, 0.1 mol) and 3,4-dichlorobenzaldehyde (17.5 g, 0.1 mol) in EtOH (250 mL) was slowly added a solution of KOH (18.3 g) in H_2O (120 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 2 h. The pale-yellow solid product (27.52 g, 89%) was collected by filtration, washed with EtOH, and dried in air overnight: mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 7.74−7.14 (m, 9H), 3.89 (s, 3H); EIMS m/z 307 (M^+).

3-(3,4-Dichloro-1-methoxyphenyl)-1-(3-methoxyphenyl)-propenone (6b). Prepared in 69% yield from 3,4-dichloro-2-methoxybenzaldehyde as a yellow solid by a procedure similar to that described for **6a**: ^{1}H NMR ($CDCl_3$) δ 7.99−7.13 (m, 8H), 3.90 (s, 3H), 3.89 (s, 3H); EIMS m/z 336 (M^+, 15), 305 (M^+ − 31, 100).

3-(3,4-Dichlorophenyl)-1-(3,4-dimethoxyphenyl)propenone (6c). Prepared in 91% yield from 2,3-dimethoxyacetophenone as a yellow solid by a procedure similar to that

described for **6a**: ^{1}H NMR ($CDCl_3$) δ 8.05−7.10 (m, 8H), 3.93 (s, 3H), 3.88 (s, 3H); EIMS *m/z* 336 (M^+).

3-(3,4-Dichlorophenyl)-6-methoxyindan-1-one (7a).[15] A solution of **6a** (3.17 g, 10.3 mmol) in TFA (20 mL) in a sealed glass tube was heated at 120−130 °C for 4 h. After removal of the solvent in vacuo, the residual oil was poured into ice−H_2O and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4, and concentrated in vacuo to afford a yellow oil, which was crystallized from isopropyl ether to give **7a** (2.78 g, 88%) as a white solid: mp 80−82 °C (lit.[15] mp 67−69 °C); ^{1}H NMR ($CDCl_3$) δ 7.49−6.94 (m, 6H), 4.51−4.47 (m, 1H), 3.88 (s, 3H), 3.31−3.20 (m, 1H), 2.65−2.58 (m, 1H); EIMS *m/z* 307 (M^+).

3-(3,4-Dichloro-2-methoxyphenyl)-6-methoxyindan-1-one (7b). Prepared from **6b** in 58% yield as a white solid by a procedure similar to that described for **7a**: ^{1}H NMR ($CDCl_3$) δ 7.26−7.13 (m, 4H), 6.77 (d, J = 7.8 Hz, 1H), 4.84−4.80 (dd, J = 3.9 Hz, 7.8 Hz, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.28−3.19 (dd, J = 7.8 Hz, 19.5 Hz, 1H), 2.69−2.62 (dd, J = 3.9 Hz, 19.5 Hz, 1H); EIMS *m/z* 336 (M^+, 100), 321 ($M^+ - 15$, 75).

3-(3,4-Dichlorophenyl)-5,6-dimethoxyindan-1-one (7c). Crude **7c** was prepared from **6c** in 70% yield by a procedure similar to that described for **7a**. The residual oil was purified by column chromatography on silica gel (hexanes/EtOAc 8:1→3:1) to afford **7c** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 7.8 Hz, 1H), 7.23 (s, 2H), 6.95 (m, 1H), 6.61 (s, 1H), 4.46−4.43 (dd, J = 3.0 Hz, 7.8 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.25−3.16 (dd, J = 7.8 Hz, 18.6 Hz, 1H), 2.59−2.52 (dd, J = 3 Hz, 18.6 Hz, 1H); CIMS (NH_3) *m/z* 354 ($M^+ + NH_4$, 100), 337 (M^+, 50), 320 ($M^+ - 15$, 75); EIMS *m/z* 336 (M^+, 100).

3,4-Dichloro-2-hydroxybenzaldehyde (8).[34] NaOH (24 g, 0.6 mol) was added to a solution of 2,3-dichlorophenol (16.3 g, 0.1 mol), $CHCl_3$ (150 mL) and H_2O (3.6 mL, 0.2 mol) at ambient temperature. The reaction mixture was refluxed for 4 h, diluted with H_2O (250 mL) and EtOAc (100 mL), and the organic phase was separated. The aqueous phase was acidified with 1 N HCl to pH 1 and back-extracted with EtOAc. The combined extracts were washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo to give a brown oil, which was purified by column chromatography on silica gel (petroleum ether/EtOAc 10:1) to afford **8** (9.8 g, 51.3%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H, CHO), 7.45 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H); EIMS *m/z* 191 (M^+).

3,4-Dichloro-2-methoxybenzaldehyde (9). To a solution of **8** (5.8 g, 30.4 mmol) in dry acetone (100 mL) were added successively K_2CO_3 (8.42 g, 61 mmol) and MeI (8.8 g, 62 mmol). The reaction mixture was stirred at room temperature overnight. After removal of the volatiles in vacuo, the residue was partitioned between H_2O (150 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The brown residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 20:1) to afford **9** (4.86 g, 78.1%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.32 (s, 1H, CHO), 7.72 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 4.03 (s, 3H); CIMS (NH_3) *m/z* 222 ($M^+ +$ 17, 100).

***cis*-3-(3,4-Dichlorophenyl)-4-methoxyindan-1-ol (10a).** $NaBH_4$ (231 mg, 6.08 mmol) was added portionwise to a solution of ketone **5a** (1.868 g, 6.08 mmol) in 20 mL MeOH at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h, and the solvent was removed in vacuo. The residue was partitioned between H_2O and Et_2O. The aqueous phase was extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give crude **10a** (1.925 g, 100%) as a colorless syrup, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.38−6.45 (m, 6H), 5.23 (t, J = 6.9 Hz, 1H), 4.14 (t, J = 7.8 Hz, 1H), 3.78 (s, 3H), 3.06−2.94 (m, 1H), 1.93−1.82 (m, 1H); EIMS *m/z* 308 (M^+).

***cis*-3-(3,4-Dichlorophenyl)-5-methoxyindan-1-ol (10b).** Prepared from **9b** in 100% yield as a white solid by a procedure similar to that described for **10a**: ^{1}H NMR ($CDCl_3$) δ 7.40−7.35 (m, 3H), 7.10−7.06 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 6.89−6.86 (m, 1H), 6.44 (s, 1H), 5.25 (t, J = 6.9 Hz, 1H), 4.12 (t, J = 7.8 Hz, 1H), 3.73 (s, 3H), 3.05−2.96 (m, 1H), 1.94−1.85 (m, 1H); EIMS *m/z* 308 (M^+, 100), 291 ($M^+ - 17$, 45).

***cis*-3-(3,4-Dichlorophenyl)-6-methoxyindan-1-ol (10c).**[15] Prepared from **9c** in 97% yield as a white solid by a procedure similar to that described for **10a**: ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 2.1 Hz, 7.8 Hz, 1H), 7.01 (s, 1H), 6.83 (s, 2H), 5.24 (t, 7.8 Hz, 1H), 4.10 (t, J = 7.8 Hz, 1H), 3.83 (s, 3H), 3.06−2.97 (m, 1H), 1.92−1.82 (m, 1H); CIMS (NH_3) *m/z* 310 (MH^+, 100).

***cis*-3-(3,4-Dichlorophenyl)-7-methoxyindan-1-ol (10d).** Prepared from **9d** in 100% yield as a white solid by a procedure similar to that described for **10a**: ^{1}H NMR ($CDCl_3$) δ 7.37−6.46 (m, 6H), 5.21 (t, J = 6.9 Hz, 1H), 4.17 (t, J = 7.8 Hz, 1H), 3.05−2.91 (m, 1H), 1.90−1.85 (m, 1H); EIMS *m/z* 308 (M^+).

***cis*-3-(3,4-Dichloro-2-methoxyphenyl)-6-methoxyindan-1-ol (10e).** Prepared from **9e** in 95% yield as a white solid by a procedure similar to that described for **10a**: ^{1}H NMR ($CDCl_3$) δ 7.36−6.28 (m, 5H), 5.13 (t, J = 6.9 Hz, 1H), 4.11 (t, J = 7.8 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.2−2.86 (m, 1H), 1.89−1.83 (m, 1H); EIMS *m/z* 339(M^+).

***cis*-3-(3,4-Dichlorophenyl)-5,6-dimethoxyindan-1-ol (10f).** Prepared from **9f** in 100% yield as a white solid by a procedure similar to that described for **10a**: ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 2.1 Hz, 1H), 6.95 (s, 2H), 6.43 (s, 1H), 4.95−4.92 (dd, J = 1.8 Hz, 6.9 Hz, 1H), 4.50 (t, J = 7.8 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 2.65−2.59 (m, 1H), 2.34−2.27 (m, 1H); EIMS *m/z* 339 (M^+).

***trans*-1-Azido-3-(3,4-dichlorophenyl)-6-methoxyindan (11c).** Diphenyl phosphorazidate (2.463 g, 8.95 mmol) was added to a solution of **10c** (1.974 g, 6.39 mmol) in dry THF (30 mL). The mixture was stirred 10 min and cooled to 0 °C. DBU (1.34 mL, 8.95 mmol) was added dropwise via syringe and the reaction mixture was allowed to warm to room temperature overnight. The mixture was partitioned between H_2O (50 mL) and Et_2O (50 mL), and the aqueous phase was extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/EtOAc 30:1) to yield **11c** (1.982 g, 93%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 2.1 Hz, 1H), 6.98−6.89(m, 4H), 4.98−4.95 (dd, J = 1.8 Hz, 6.9 Hz, 1H), 4.67 (t, J = 7.8 Hz, 1H), 3.84 (s, 3H), 2.65−2.58 (m, 1H), 2.35−2.27 (m, 1H); EIMS *m/z* 333 (M^+), 304 ($M^+ - 28$), 291 ($M^+ - 43$).

***trans*-1-Azido-3-(3,4-dichlorophenyl)-4-methoxyindan (11a).** Prepared from **10a** in 87% yield as an oil by a procedure similar to that described for **11c**: ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 7.8 Hz, 1H), 7.29−7.23 (m, 2H), 7.00−6.98 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 5.25 (d, J = 6.9 Hz, 1H), 4.52 (t, J = 8.7 Hz, 1H), 3.86 (s, 3H), 2.58−2.52 (m, 1H), 2.65−2.12 (m, 1H); CIMS (NH_3) *m/z* 308 ($M^+ - 28$).

***trans*-1-Azido-3-(3,4-dichlorophenyl)-5-methoxyindan (11b).** Prepared from **10b** in 92% yield as a pale-yellow oil by a procedure similar to that described for **11c**: ^{1}H NMR ($CDCl_3$) δ 7.40−7.36 (dd, J = 3.9 Hz, 7.8 Hz, 2H), 7.25 (d, J = 1.8 Hz, 1H), 7.01−6.98 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 6.89−6.86 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 6.49 (s, 1H), 4.98 (m, 1H), 4.49 (t, J = 7.8 Hz, 1H), 3.75 (s, 3H), 2.64−2.56 (m, 1H), 2.34−2.25 (m, 1H); EIMS *m/z* 333 (M^+, 35), 304 ($M^+ - 28$, 45), 291 ($M^+ - 43$, 100).

***trans*-1-Azido-3-(3,4-dichlorophenyl)-7-methoxyindan (11d).** Prepared from **10d** in 85% yield as a colorless oil by a procedure similar to that described for **11c**: ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 7.8 Hz, 1H), 7.32−7.24 (m, 2H), 7.01−6.98 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 7.8 Hz, 1H), 5.28 (d, J = 6.9 Hz, 1H), 4.51 (t, J = 8.7 Hz, 1H), 3.91 (s, 3H), 2.59−2.52 (m, 1H), 2.67−2.16 (m, 1H); CIMS (NH_3) *m/z* 308 ($M^+ - 28$); EIMS *m/z* 333 (M^+, 10), 291 ($M^+ - 43$, 100).

***trans*-1-Azido-3-(3,4-dichloro-2-methoxyphenyl)-6-methoxyindan (11e).** Prepared from **10e** in 82% yield as a syrup

by a procedure similar to that described for **11c**: ^{1}H NMR ($CDCl_3$) δ 7.14 (d, J = 8.7 Hz, 1H), 6.99 (s, 1H), 6.89 (s, 2H), 6.75 (d, J = 8.7 Hz, 1H), 5.02−4.98 (m, 1H), 4.84 (t, J = 7.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.66−2.58 (m, 1H), 2.38−2.28 (m, 1H); EIMS m/z 363 (M^+, 20), 335 ($M^+ - 28$, 25), 320 ($M^+ - 43$, 53).

***trans*-1-Azido-3-(3,4-dichlorophenyl)-5,6-dimethoxyindan (11f).** Prepared from **10f** in 87% yield as a red oil by a procedure similar to that described for **11c**: ^{1}H NMR ($CDCl_3$) δ 7.41−7.39 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 2.1 Hz, 1H), 6.96 (s, 2H), 6.46 (s, 1H), 4.98−4.95 (dd, J = 1.8 Hz, 6.9 Hz, 1H), 4.49 (t, J = 7.8 Hz, 1H), 3.94 (s, 3H), 3.79 (s, 3H), 2.68−2.60 (m, 1H), 2.35−2.26 (m, 1H); EIMS m/z 363 (M^+, 13), 335 ($M^+ - 28$, 10), 321 ($M^+ - 43$, 100).

***trans*-[3-(3,4-Dichloro-2-methoxyphenyl)-6-methoxyindan-1-yl]methylcarbamic Acid *tert*-Butyl Ester (12e).** A solution of azide **11e** (1.85 g, 5.08 mmol) and BOC_2O (1.55 g, 7.11 mmol) in EtOAc (40 mL) was added to a mixture of 5% Pd/C in EtOAc (20 mL) which had been presaturated with hydrogen. The reaction mixture was shaken in a Parr hydrogenation apparatus at 35 psi for 3 h. After filtering off the catalyst, the filtrate was concentrated in vacuo to give a white solid, which was filtered through a short silica gel column (hexanes/EtOAc 10:1→6:1). The white foam was used in the next reaction.

The above product (1.49 g, 3.4 mmol) was dissolved in dry DMF (20 mL). To this solution was added NaH powder (429 mg, 17 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h, then CH_3I (3 mL) was added at 0 °C. The mixture was allowed to warm to room temperature overnight. The mixture was partitioned between H_2O and Et_2O. The aqueous phase was extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 10:1→5:1) to afford **12e** in 85% yield as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.83−6.76 (m, 2H), 6.64 (m, 1H), 6.02 (brs, 1H), 4.77- (m, 1H), 3.84 (s, 3H), 3.81(s, 3H), 2.62 (s, 3H), 2.51 (brs, 1H), 2.33−2.24 (m, 1H); CIMS (NH_3) m/z 469 ($M^+ + 17$), 452 (M^+).

***trans*-[3-(3,4-Dichlorophenyl)-4-methoxyindan-1-yl]-methylcarbamic Acid *tert*-Butyl Ester (12a).** Prepared from **11a** in 90% yield as a white foam by a procedure similar to that described for **12e**: ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 7.8 Hz, 1H), 7.14 (s, 1H), 6.88−6.74 (m, 4H), 6.07 (brs, 1H), 4.52 (d, J = 7.8 Hz, 1H), 3.69 (s, 3H), 2.59 (s, 3H) 2.49−2.41 (m, 1H), 2.28 (m, 1H). 1.50 (s, 9H); CIMS (NH_3) m/z 439 ($M^+ + 17$), 422 (M^+), 405 ($M^+ - 15$), 383 ($M^+ - 39$), 291 (100).

***trans*-[3-(3,4-Dichlorophenyl)-5-methoxyindan-1-yl]-methylcarbamic Acid *tert*-Butyl Ester (12b).** Prepared from **11b** in 87% yield as a pale-yellow syrup by a procedure similar to that described for **12e**: ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 6.93−6.83 (m, 2H), 6.52 (s, 1H), 4.45−4.40 (m, 1H), 3.74 (s, 3H), 2.57 (s, 3H), 2.48−2.43 (m, 1H), 2.36−2.27 (m, 1H), 1.50 (s, 9H); CIMS (NH_3) m/z 439 ($M^+ + 17$), 422 (M^+), 405 ($M^+ - 15$), 383 ($M^+ - 39$), 291 (100).

***trans*-[3-(3,4-Dichlorophenyl)-6-methoxyindan-1-yl]-methylcarbamic Acid *tert*-Butyl Ester (12c).** Prepared from **11c** in 93% yield as a white foam by a procedure similar to that described for **12e**: ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 7.8 Hz, 2H), 6.92−6.81 (m, 2H), 6.53 (s, 1H), 4.43−4.41 (m, 1H), 3.72 (s, 3H), 2.58 (s, 3H), 2.50−2.42 (m, 1H), 2.37−2.24 (m, 1H), 1.49 (s, 9H); CIMS (NH_3) m/z 439 ($M^+ + 17$), 291 (100).

***trans*-[3-(3,4-Dichlorophenyl)-7-methoxyindan-1-yl]-methylcarbamic Acid *tert*-butyl Ester (12d).** Prepared from **11d** in 86% yield as a white foam by a procedure similar to that described for **12e**: ^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.83−6.76 (m, 2H), 6.64 (m, 1H), 6.02 (brs, 1H), 4.77 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.62 (s, 3H, NCH3), 2.51 (brs, 1H), 2.33−2.24 (m, 1H), 1.41 (s, 9H); CIMS (NH_3) m/z 469 ($M^+ + NH_4$), 452 (M^+).

***trans*-[3-(3,4-Dichlorophenyl)-5,6-dimethoxyindan-1-yl]methylcarbamic Acid *tert*-Butyl Ester (12f).** Prepared from **11f** in 88% yield as a white foam by a procedure similar to that described for **12e**: ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 7.8 Hz, 1H), 7.32 (m, 1H), 7.06 (m, 1H), 6.75 (s, 1H), 6.48 (s, 1H), 4.44−4.39 (m, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.58 (s, 3H), 2.48 (brs, 1H), 2.34−2.28 (m, 1H), 1.51 (s, 9H); EIMS m/z 451 (M^+), 396 (100).

[3-(3,4-Dichlorophenyl)-4-methoxyindan-1-yl]methylamine (13a). HCl gas was bubbled into a solution of **12a** (601 mg, 1.43 mmol) in dry EtOAc (50 mL) at 0 °C for 5 min, and then the mixture was stirred at room temperature for 1 h. After removal of the solvent in vacuo, the residue was partitioned between H_2O and EtOAc. The aqueous phase was extracted once with EtOAc, then neutralized with 20% NaOH to pH 8, and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a viscous oil, which was converted into the HCl salt with 2 N ethereal HCl. The salt was recrystallized from 2-PrOH−^{i}Pr$_2$O to afford **13a** (428 mg, 83.4%) as a white solid: mp 248−250 °C dec; ^{1}H NMR (HCl salt, $CDCl_3$ + DMSO-d_6) δ 7.55 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 6.93−6.88 (m, 2H), 4.88 (t, J = 6.6 Hz, 1H), 4.71−4.66 (dd, J = 3.6 Hz, 8.4 Hz, 1H), 3.68 (s, 3H), 2.83−2.73 (m, 1H), 2.61 (s, 3H), 2.44−2.36 (m, 1H); CIMS (NH_3) m/z 322 (M^+). Anal. ($C_{17}H_{17}Cl_2NO$·HCl) C, H, N.

[3-(3,4-Dichlorophenyl)-6-methoxyindan-1-yl]methylamine (13c).[15] Prepared from **12c** in 86% yield by a procedure similar to that described for **13a**: mp 240−242 °C; ^{1}H NMR ($CDCl_3$) δ 7.41−6.78 (m, 6H), 4.44 (t, J = 7.2 Hz, 1H), 4.26−4.23 (m, 1H), 3.82 (s, 3H), 3.51 (s, 3H), 2.49−2.41 (m, 1H), 2.31−2.20 (m, 1H); CIMS (NH_3) m/z 322 (M^+). Anal. ($C_{17}H_{17}Cl_2NO$·HCl) C, H, N.

[3-(3,4-Dichlorophenyl)-7-methoxyindan-1-yl]methylamine (13d). Prepared from **12d** in 83% yield by a procedure similar to that described for **13a**: mp 190−192 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.38−6.70 (m, 4H), 6.75 (d, J = 8.7 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 4.53 (t, J = 7.8 Hz, 1H), 4.48−4.45 (m, 1H), 3.87 (s, 3H), 2.46 (s, 3H), 2.56−2.48 (m, 1H), 2.17−2.06 (m, 1H); CIMS m/z 322 (M^+), 288 ($M^+ - 34$). Anal. ($C_{17}H_{17}Cl_2NO$·HCl) C, H, N.

[3-(3,4-Dichloro-2-methoxyphenyl)-6-methoxyindan-1-yl]methylamine (13e). Prepared from **12e** in 81% yield by a procedure similar to that described for **13a**: mp 212−214 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (d, J = 8.7 Hz, 2H), 6.89−6.84 (m, 2H), 6.74 (d, J = 7.8 Hz, 1H), 4.88 (t, J = 8.7 Hz, 1H), 4.67 (dd, J = 3.0, 7.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.77−2.64 (m, 1H), 2.61 (s, 3H), 2.41−2.31 (m, 1H); EIMS m/z 352 (M^+), 336 ($M^+ - 15$), 320 ($M^+ - 31$). Anal. ($C_{18}H_{19}Cl_2NO_2$·HCl·0.5H_2O) C, H, N.

[3-(3,4-Dichlorophenyl)-5-methoxyindan-1-yl]methylamine (13b). A mixture of **12b** (1.69 g, 4 mmol) and anhydrous $ZnBr_2$ (1.81 g, 8 mmol) in dry CH_2Cl_2 (20 mL) was stirred at room temperature under Ar for 5 h. After evaporation of the solvent in vacuo, the residual syrup was purified by column chromatography on silica gel (hexanes/EtOAc 10:1−5:1, followed by CH_2Cl_2/MeOH 10:1) to yield a pale-yellow oil, which was converted into the HCl salt by treatment with ethereal HCl. The salt was recrystallized from 2-PrOH−^{i}Pr$_2$O to afford **13b** (1.31 g, 92%) as a pale-yellow solid: mp 193−195 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 7.05 (dd, J = 1.8, 8.1 Hz, 1H), 6.93 (dd, J = 2.1, 8.4 Hz, 1H), 6.51 (d, J = 1.8 Hz, 1H), 4.87 (d, J = 7.2 Hz, 1H), 4.70 (t, J = 8.1 Hz, 1H), 3.73 (s, 3H), 2.97−2.90 (m, 1H), 2.78 (s, 3H), 2.51−2.40 (m, 1H); CIMS (NH_3) m/z 322 (M^+). Anal. ($C_{17}H_{17}Cl_2NO$·HCl) C, H, N.

[3-(3,4-Dichlorophenyl)-5,6-dimethoxyindan-1-yl]methylamine (13f). Prepared from **12f** in 88% yield by a procedure similar to that described for **13b**: mp 220−222 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.65 (s, 1H), 7.51−7.48 (dd, J = 2.1, 8.7 Hz, 1H), 6.98 (s, 1H), 5.05 (t, J = 7.8 Hz, 1H), 4.30 (s, 3H), 4.12 (s, 3H), 3.71 (m, 1H), 3.23−3.18 (m, 1H), 3.15 (s, 3H), 2.92−2.84 (m,

1H); CIMS (NH_3) *m/z* 352 (MH^+), 321 ($M^+ - 31$). Anal. ($C_{18}H_{19}Cl_2NO_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

2-Acetoxy-3-(3,4-dichlorophenyl)-6-methoxyindan-3-one (14). A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (22 g, 80 mmol) and AcOH (14.4 g, 240 mmol) in 300 mL benzene was refluxed for 1 h. Solid **7a** (6.2 g, 20 mmol) was added, and the resulting mixture was refluxed overnight. After cooling to room temperature, the mixture was diluted with EtOAc and washed successively with 1 N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, and concentrated in vacuo to give 10.5 g of a red oil. The oil was purified by flash chromatography on silica gel (petroleum ether/EtOAc 6:1→4:1) to afford **14** (4.75 g, 65%) as a red syrup: ^{1}H NMR ($CDCl_3$) δ 7.45−7.03 (m, 6H), 5.34 (d, J = 5.1 Hz, 1H), 4.37(d, J = 1.2 Hz, 1H), 3.88 (s, 3H), 2.19 (s, 3H); CIMS (NH_3) *m/z* 382 ($M^+ + 17$, 100), 365 (M^+, 10), 324 ($M^+ - 41$, 100).

1-(3,4-Dichlorophenyl)-5-methoxy-1*H*-indene (15). A solution of **10c** (309 mg, 1 mmol) and *p*-toluenesulfonic acid (80 mg) in anhydrous benzene was refluxed for 30 min. The reaction mixture was washed twice with H_2O. The combined aqueous phases were extracted with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to afford **15** (310 mg, 100%) as a colorless oil, which was immediately used in the next reaction: ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 2.1 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.96−6.85 (m, 3H), 6.74−6.70 (dd, J = 2.1 Hz, 7.8 Hz, 1H), 6.54−6.51 (dd, J = 2.1 Hz, 6.0 Hz, 1H). 4.49 (s, 1H), 3.83 (s, 3H); EIMS *m/z* 291 (M^+).

2-Bromo-3-(3,4-dichlorophenyl)-6-methoxyindan-1-ol (16a). The indene **15** (1.07 g, 3.67 mmol) was dissolved in 50% (v:v) aqueous THF (50 mL), and NBS (382 mg, 2.14 mmol) was added to the above solution at 0 °C. The resulting reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 3 h. Additional NBS (240 mg, 1.35 mmol) was added to the mixture, and the mixture was stirred at room temperature overnight. After dilution with EtOAc, the reaction mixture was washed with water, 5% aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a brown oil, which was purified by flash chromatography on silica gel (hexanes/EtOAc 10:1→5:1). Compound **16a** (the least polar component) (200 mg, 14%) was obtained as a white solid along with dibrominated compound **16b** (the more polar component) (615 mg, 36%) as a white foam. **16a:** ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.12−7.08 (dd, J = 1.8 Hz, 7.8 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 6.88−6.84 (dd, J = 2.1 Hz, 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 5.32 (d, J = 7.8 Hz, 1H), 4.25 (d, J = 8.7 Hz, 1H), 3.96 (t, J = 8.7 Hz, 1H), 3.84 (s, 3H), 2.31 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 160.59, 143.35, 140.86, 133.33, 132.12, 131.08, 130.84, 128.35, 125.68, 116.33, 108.26, 81.78, 63.75, 55.86, 55.74; EIMS *m/z* 388 (M^+, 70), 307 (M^+ − Br, 100). **16b:** ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 1H), 7.09−7.03 (m, 2H), 6.93−6.83 (m, 2H), 5.35 (d, J = 7.8 Hz, 1H), 4.59 (d, J = 8.7 Hz, 1H), 4.22 (t, J = 8.7 Hz, 1H), 3.86 (s, 3H), 2.34 (brs, 1H); EIMS *m/z* 466 (M^+, 35), 388 (M^+ − Br, 90), 307 (M^+ − 2Br, 100).

1-(3,4-Dichlorophenyl)-5-methoxy-3-methylaminoindan-2-ol (17). A mixture of **16a**,**b** (1:2.57, respectively, 1.2 g) was dissolved in EtOH (40 mL), and 40% aqueous methylamine (40 mL) was added. The resulting solution was refluxed for 4 h. The volatiles were removed under reduced pressure, and the residue was partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was filtered through a short silica gel column to afford 550 mg of a yellow oil, which was taken up in MeOH (20 mL). 5% Pd/C (65 mg) and $NaOAc \cdot 3H_2O$ (330 mg, 2.4 mmol) were added to the above solution and the reaction mixture was shaken in a Parr hydrogenation apparatus at 35 psi for 25 min. After filtration off the catalyst, the filtrate was concentrated in vacuo. The residue was converted into the HCl salt by treatment with HCl−MeOH. The salt was recrystallized from 2-PrOH−^{i}Pr$_2$O to afford **17** as a white solid (238 mg, 23.3% overall yield): mp 268−270 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 7.00−6.93 (m, 3H), 6.87−6.83 (dd, J = 1.8 Hz, 7.8 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 4.44 (pseudo t, J = 4.8 Hz, 6.9 Hz, 1H), 4.01 (d, J = 4.8 Hz, 1H). 3.84 (s, 3H), 2.61 (s, 3H); NOE cross-peaks (DMSO) δ 4.5 (NMeCH, cross-peak with δ 3.3 (water), 3 cross-peaks with aromatic protons δ 6.9−7.2), 4.65 (Ar + indano CH, cross-peak with CHOH), 4.8 (CHOH, cross-peaks with Ar + indano CH and water); CIMS *m/z* 339 (MH^+). Anal. ($C_{17}H_{17}Cl_2NO_2 \cdot HCl$) C, H, N.

Single-Crystal X-ray Analysis of 3-(3,4-Dichlorophenyl)-5-methoxyindan-1-one (5b) and *trans*-1-Azido-3-(3,4-dichlorophenyl)-5-methoxyindan (11b). 3-(3,4-Dichlorophenyl)-5-methoxyindan-1-one (5b): $C_{16}H_{12}O_2Cl_2$, fw = 307.16, monoclinic space group $P2_1/c$; a = 8.444(2), b = 6.578(1), c = 26.081(4) Å; β = 98.74(1)°; V = 1431.7(4) Å^3, Z = 4, ρ_{calc} = 1.425 mg mm^{-3}; λ(Cu Kα) = 1.54178 Å, μ = 4.06 mm^{-1}, F(000) = 632, T = 295 K.

***trans*-1-Azido-3-(3,4-Dichlorophenyl)-5-methoxyindan (11b):** $C_{16}H_{13}N_3OCl_2$, fw = 334.19, triclinic space group $P\bar{1}$; a = 7.582(1), b = 9.940(1), c = 11.284(2) Å; α = 103.49(2), β = 106.38(2), γ = 95.22(2)°; V = 782.0(2) Å^3, Z = 2, ρ_{calc} = 1.419 mg mm^{-3}; λ(Cu Kα) = 1.54178 Å, μ = 3.772 mm^{-1}, F(000) = 344, T = 295 K. The following parameters are common to **5b** and **11b** and where different they are indicated by enclosure in brackets [ ] for [**11b**].

A clear colorless 0.54 × 0.52 × 0.15 [0.35 × 0.25 × 0.06] mm crystal was used for data collection on an automated Bruker P4 diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 30 [35] centered reflections within 11° < 2θ < 65° [10° < 2θ < 73°]. The data collection range had a $\{(\sin\theta)/\lambda\}_{max}$ = 0.55. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±1.9 [2.5]% during the data collection. A set of 3276 [2663] reflections was collected in the $\theta/2\theta$ scan mode and ω scan rate (a function of count rate) from 7.5 to 30.0°/min. There were 1964 [2133] unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL[35] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 varied 232 [199] parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2−1.5U_{eq}(C)]. Final residuals were $R1$ = 0.049 [0.055] for the 1764 [1763] observed data with $F_o > 4\sigma(F_o)$ and 0.054 [0.065] for all data. Final difference Fourier excursions of 0.31 and −0.21 [0.29 and −0.45] eÅ^{-3}.

In **5b** the dichlorophenyl group is disordered such that the atoms may be located on an alternate position with occupancies of 0.57 and 0.43 for the major and minor positions. Tables of coordinates, bond distances and angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge CB2 1EW, England.

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Supporting Information Available: Crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and torsion angles of **5b** and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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