The Mitsunobu Reaction of Some Indan Amino Alcohols

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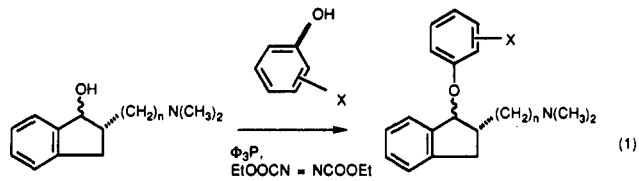
The Mitsunobu reaction, utilizing several phenols, has been applied to a series of indan amino alcohols. An interesting example of configurational retention as a result of an aziridinium intermediate was discovered.

The Mitsunobu reaction is a useful method for nucleophilic displacement of alcohol groups.[1] Although inversion of configuration is the rule, examples of the formation of mixtures resulting from a partial retention pathway have been noted.[2] In this regard, we report our results upon application of this reaction to a variety of amino alcohols of the indan series.

Results and Discussion

The Mitsunobu reaction of an aminoindanol with a phenol (eq 1) produced modest yields of aryl ether. The products were isolated as oxalate salts and analyzed by NMR spectroscopy for stereochemical composition.

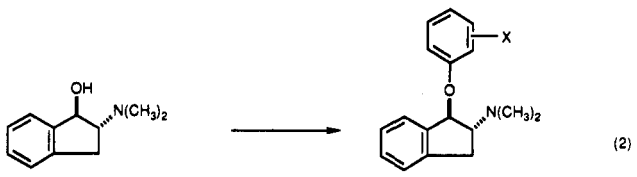
The cis amino alcohols **1a** and **1b** produced the inverted trans products. However, a most unexpected result was obtained with the trans amino alcohol **2a** in that complete retention was observed in the reaction with phenol or 2-methoxyphenol (eq 2). None of the ether corresponding to structure **3a** was observed. The products were the same as those obtained from the cis amino alcohol **1a** as well as from the arylation of **2a** with the corresponding aryl fluoride and NaH.



(1)

1a, CIS, n=0
b, CIS, n=1
2a, TRANS, n=0
b, TRANS, n=1

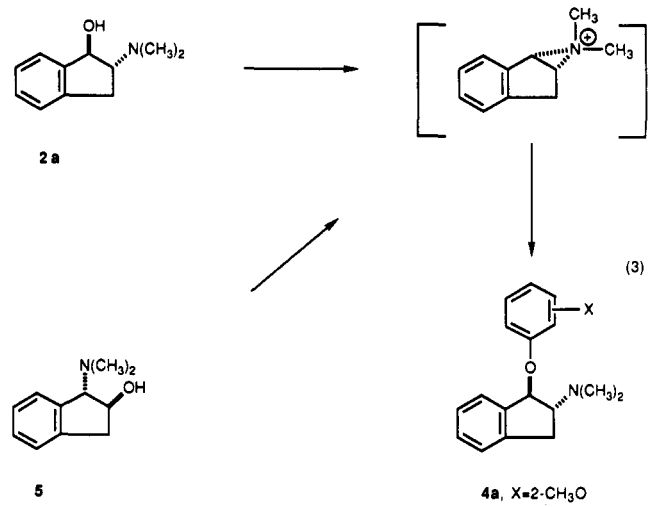
3a, CIS, n=0
b, CIS, n=1
4a, TRANS, n=0
b, TRANS, n=1



(2)

2a **4a**, X=H, 2-CH_3O

Since it has been shown that β-amino alcohols can be converted to aziridines under the conditions of the Mitsunobu reaction,[3] an aziridinium ion intermediate was considered as the basis for configurational retention (eq 3). To test this hypothesis, the isomeric amino alcohol **5** was prepared and subjected to the Mitsunobu reaction using 2-methoxyphenol. The product, isolated in greater than 80% yield, was identical with that formed from **2a** (eq 3). This finding supported the proposal that an aziridinium ion intermediate is the basis for configurational retention in this reaction. The regioselectivity of the ring opening of the aziridine is consistent with the expectation

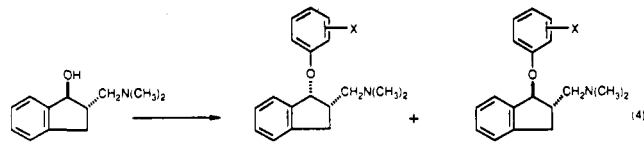


(3)

2a **5** **4a**, X=2-CH_3O

of preferential nucleophilic attack at the benzylic position of the indan ring.[4]

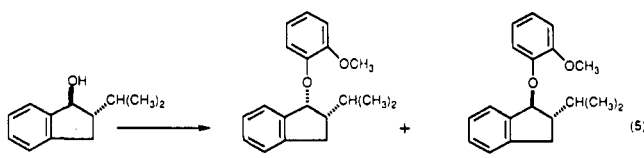
When the reaction was applied to **2b**, mixtures of aryl ethers were formed, with the cis isomer (inversion) predominant (eq 4). This result implies a duality of mechanism. The normal S_N2 process takes precedence, but hindrance to approach of the nucleophile allows a degree of dissociation to a benzyl carbocation. Such an ion would show a bias for nucleophile approach from the face opposite the (dimethylamino)methyl group, leading to the trans (retention) product. A lack of such hindrance to nucleophile approach in the cis isomer results in a clean S_N2 process.



(4)

2b **3b** (MAJOR) X= H, 4-CH_3O **4b** (MINOR) X= H, 4-CH_3O

To eliminate nitrogen participation as a factor in the latter results, the reaction was carried out with the 2-isopropylindanols **6** and **9**. These non-nitrogenous alcohols gave similar results to their nitrogen-containing counterparts, **1a**, **1b**, and **2b** (eqs 5 and 6).



(5)

6 **7** (3 parts) **8** (1 part)

(1) Mitsunobu, O. *Synthesis* **1981**, 1.
(2) Farina, V. *Tetrahedron Lett.* **1989**, *30*, 6445 and references therein.
(3) Pfister, J. R. *Synthesis* **1984**, 969.
(4) (a) Saito, M.; Kayama, Y.; Watanabe, T.; Fukushima, H.; Hara, T.; Koyano, K.; Takenaka, A.; Sasada, Y. *J. Med. Chem.* **1980**, *23*, 1364. (b) Lynas-Gray, J. I.; Stirling, C. J. M. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 341. (c) Tamura, Y.; Kawasaki, T.; Yasuda, H.; Gohda, N.; Yasuyuki, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1577.

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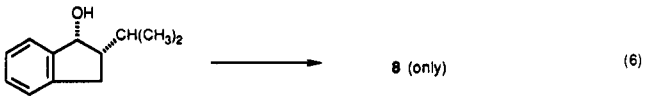

(6)

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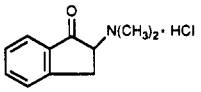
The requisite alcohols were prepared as follows. The trans amino alcohol **2a**[5] was oxidized with Jones' reagent to give the amino ketone **10**. Reduction of the latter with L-Selectride (Aldrich) gave the cis isomer **1a**.[5] The amino ketone 11,[6] on reduction with $NaBH_4$, gave a 5:1 mixture of isomers with the trans isomer **2b** predominant. The pure trans isomer was readily isolated by crystallization. Reduction of **11** with L-Selectride gave exclusively the cis isomer **1b**. Isomers **1b** and **2b** were differentiated using NOE difference spectroscopy. Thus, irradiation of the benzyl methine proton of the former produced a 6% NOE enhancement in the signal of the indan C-2 methine proton. Conversely, irradiation of the benzyl methine proton in **2b** produced a 3% enhancement in the signal of the side chain methylene protons and no enhancement of the C-2 methine proton. The isopropyl ketone **12**,[7] on reduction with LAH, gave a 1:1 mixture of alcohols **6** and **9**[8] which were separated by chromatography. Finally, the epoxide **13**[9] reacted with dimethylamine in toluene in a sealed tube to give amino alcohol **5**.



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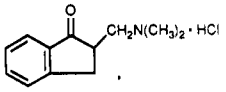

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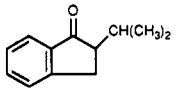

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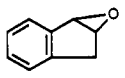

13

Our study of the Mitsunobu reaction of a series of amino indanols led to the discovery of a diversity of reaction pathways and their attendant stereochemical consequences. The ability to form an aziridinium ion intermediate can, as in the case of **5**, lead to rearrangement of functionality.

Experimental Section

General Methods. Melting points are uncorrected. Gas chromatography was performed using a 12-m capillary column packed with cross-linked methylsilicone with FID detection. TLC was accomplished on 0.25 mm precoated glass plates of silica gel 60A F-254 (Whatman) visualized by UV absorption. Flash chromatography was carried out using Merck silica gel (particle size 0.004–0.063 mm).

Solvents and starting materials were from commercial sources and used as received.

2-(Dimethylamino)-2,3-dihydroinden-1-one Hydrochloride (10). To an ice-cooled solution of 15.53 g (87.60 mmol) of **2a**[5] in 375 mL of acetone was added dropwise 70 g of Jones' reagent. The mixture was stirred at room temperature for 24 h, and the acetone was removed at reduced pressure. A saturated solution (100 mL) of potassium sodium tartrate was added followed by 4 N NaOH until basic. The mixture was then extracted with several portions of ether, and the extracts were dried with $MgSO_4$. Subsequent treatment with ethereal HCl gave an oil which solidified on trituration, first with ethyl acetate and then with acetone. The product (7.65 g, 41%) was recrystallized from methanol/ethyl acetate to give **10** as a white, crystalline solid: mp 173–175 °C dec; IR (KBr) 3425, 1724, 1610, 1470, 1220, 924, 765 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 7.88–7.53 (m, 4 H), 4.60 (dd, 1 H, J = 8.1, 5.3 Hz), 3.71 (dd, 1 H, J = 17.3, 8.2 Hz), 3.48 (dd, 1 H, J = 17.3, 5.3 Hz), 2.98 (s, 6 H). Anal. Calcd for $C_{11}H_{13}NO$·HCl: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.21; H, 6.82; N, 6.54.

***cis*-2-(Dimethylamino)-2,3-dihydroinden-1-ol (1a).**[5] The amino ketone hydrochloride **10** (7.21 g, 34.0 mmol) was added, via a solid addition funnel, to 80 mL of a 1 M solution of L-Selectride in THF while cooling in an ice bath. After 5 h, 50 mL of 10% NaOH was added cautiously, and the THF was removed at reduced pressure. The product was extracted into ether and from the ether into dilute HCl.[10] Treatment of the acidic extract with excess 10% NaOH gave **1a** as a solid (5.42 g, 90%). Recrystallization from cyclohexane gave a light tan powder: mp 121–122 °C; IR (KBr) 3425, 1470, 1084, 960, 904, 758 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.35–7.13 (m, 4 H), 4.75 (d, 1 H, J = 4.9 Hz), 4.45 (br s, 1 H, exchangeable), 2.95–2.80 (m, 2 H), 2.57 (m, 1 H), 2.28 (s, 6 H). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.58; H, 8.54; N, 7.64.

***cis*-2-((Dimethylamino)methyl)-2,3-dihydroinden-1-ol (1b).** The amino ketone hydrochloride **11**[6] (2.25 g, 10.0 mmol) was added, via a solid additional funnel, to 25 mL of an ice-cooled solution of 0.35 M L-Selectride in THF. After the mixture was stirred for 1.5 h, 25 mL of 10% NaOH was added cautiously and the mixture was concentrated at reduced pressure. The product was extracted into ether and from the ether into dilute HCl.[10] Treatment of the acidic extracts with 10% NaOH gave an oil which was purified by extraction and bulb-to-bulb distillation to give **1b** (0.92 g, 48%) as a colorless oil: bp 95–100 °C (0.4 mm); IR (film) 3365, 1455, 1255, 1100, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, 1 H, J = 7.2 Hz), 7.27–7.16 (m, 3 H), 6.86 (br s, 1 H, exchangeable), 5.33 (d, 1 H, J = 6.5 Hz), 2.99 (dd, 1 H, J = 15.8, 7.4 Hz), 2.84 (m, 1 H), 2.70 (t, 1 H, J = 12.1 Hz), 2.49 (dd, 1 H, J = 15.8, 7.4 Hz), 2.28–2.24 (m, 7 H). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.96; H, 9.03; N, 7.27.

***trans*-2-((Dimethylamino)methyl)-2,3-dihydroinden-1-ol (2b).** A solution of **11**[6] (33.7 g, 150 mmol) in 400 mL of water was added dropwise to an ice-cooled solution of 7.6 g (200 mmol) of $NaBH_4$ in 100 mL of water. The mixture was stirred for 5 h and then extracted with several portions of $CHCl_3$. The solvent was removed from the extracts to leave the product as an oil. Examination of the NMR spectrum showed it to be a mixture containing 85% of the trans isomer. The pure trans isomer (15.7 g, 55%) crystallized from heptane as colorless crystals: mp 65–67 °C; IR (KBr) 3390, 1453, 1227, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, 1 H, J = 6.7 Hz), 7.25–7.16 (m, 3 H), 4.95 (d, 1 H, J = 6.5 Hz), 4.02 (br s, 1 H, exchangeable), 2.98 (m, 1 H), 2.64 (m, 1 H), 2.50–2.43 (m, 3 H), 2.30 (s, 6 H). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.32; H, 8.96; N, 7.26.

2,3-Dihydro-2-(1-methylethyl)inden-1-ol. A solution of **12**[7] (3.35 g, 20.0 mmol) in 25 mL of ether was added dropwise to 35 mL of an ice-cooled 1 M solution of LAH in ether. The mixture was stirred at room temperature for 2 h, cooled in ice, and decomposed by cautious addition of 50 mL of water. After the mixture was stirred for 3 h, the ether layer was separated, washed with saturated NaCl solution, and dried over Na_2SO_4. Removal of the solvent left an oil which could be shown by NMR to be approximately a 1:1 mixture of isomers.

Flash chromatography on silica gel by elution with cyclohexane–ethyl acetate (3:2) gave the cis isomer **9**[8] which, on bulb-to-bulb distillation at 120–125 °C (0.3 mm), gave 0.74 g (22%) of an oil which solidified to a white solid: mp 45–48 °C; IR (KBr) 3378, 2956, 1478, 944, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ

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(10) Care should be taken at this point because of the presence of the flammable tris(1-methylpropyl)borane. Treatment of the ether after extraction of the product with oxidative workup conditions will destroy the borane. See: Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

7.43–7.18 (m, 4 H), 5.03 (t, 1 H, J = 5.4 Hz), 2.93 (dd, 1 H, J = 15.8, 7.2 Hz), 2.78 (dd, 1 H, J = 15.8, 9.7 Hz), 2.04–1.83 (m, 2 H), 1.25 (d, 1 H, J = 5.8 Hz, exchangeable), 1.13 (d, 3 H, J = 6.5 Hz), 1.03 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.93; H, 9.21.

Further elution with the same solvent gave the trans isomer **6**[8] which crystallized from hexane (1.31 g, 39%) as white needles: mp 70–72 °C; IR (KBr) 3260, 2958, 1480, 1460, 1050, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.17 (m, 4 H), 4.97 (t, 1 H, J = 7.6 Hz), 3.04 (dd, 1 H, J = 16.0, 8.7 Hz), 2.58 (dd, 1 H, J = 16.0, 9.0 Hz), 2.04–1.82 (m, 2 H), 1.75 (d, 1 H, J = 8.4 Hz, exchangeable), 1.11 (d, 3 H, J = 6.5 Hz), 0.99 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.58; H, 9.16.

***trans*-1-(Dimethylamino)-2,3-dihydroinden-2-ol (5).** A solution of 6.5 g (49 mmol) of **13**[9] in 75 mL of toluene was saturated with dimethylamine and heated at 80 °C overnight in a sealed tube. Removal of the solvent and bulb-to-bulb distillation of the residue at 90–95 °C (0.4 mm) gave a light brown oil which solidified. Recrystallization from cyclohexane gave **5** (6.1 g, 70%) as a white crystalline solid: mp 63–66 °C; IR (KBr) 3422, 3112, 2942, 1460, 1058, 1018, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.17 (m, 4 H), 4.60 (m, 1 H), 4.07 (d, 1 H, J = 4.7 Hz), 3.27 (dd, 1 H, J = 16.1, 7.0 Hz), 2.80 (dd, 1 H, J = 16.1, 5.4 Hz), 2.39 (s, 6 H). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.41; H, 8.63; N, 8.00.

General Procedure for the Mitsunobu Reaction of the Amino Indanols.[1] A solution of the amino indanol (50 mmol), the appropriate phenol (55 mmol), and triphenylphosphine (55 mmol) in 50 mL of benzene was stirred, and a solution of 55 mmol of diethyl azodicarboxylate in 25 mL of benzene was slowly added dropwise. The addition was mildly exothermic, and the temperature was maintained below 35 °C. Stirring was continued until gas chromatography indicated the absence of amino indanol. The mixture was then concentrated, and the residue was triturated with 50 mL of a 1:1 mixture of cyclohexane and ether. After overnight refrigeration at 0 °C, the solids were filtered and the solvent was removed from the filtrate. A small portion of the residue was dissolved in ether, and this solution was treated with ethereal oxalic acid. The resulting precipitate was triturated with several portions of ether and analyzed by NMR spectroscopy to determine the isomer ratio.

The remainder of the crude mixture was subjected to flash chromatography, monitoring the separation by thin-layer chromatography. In general, the purified isomers were also converted to oxalates for analytical purposes.

***trans*-*N*,*N*-Dimethyl-2,3-dihydro-1-phenoxyinden-2-amine (4a, X = H) Oxalate.** Starting with either **1a** or **2a** and phenol, this was the only product isolated. The respective yields were 59% and 72% of a white crystalline solid: mp 175–177 °C (methanol); IR (KBr) 3434, 1720, 1644, 1598, 1588, 1492, 1230, 756 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.42–7.01 (m, 9 H), 6.30 (d, 1 H, J = 6.4 Hz), 4.02 (dt, 1 H, J = 6.3, 8.2 Hz), 3.39 (dd, 1 H, J = 16.0, 8.5 Hz), 3.16 (dd, 1 H, J = 16.0, 8.5 Hz), 2.72 (s, 6 H). Anal. Calcd for $C_{17}H_{19}NO{\cdot}C_2H_2O_4$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.23; H, 6.14; N, 3.98. The same product was isolated in 48% yield when **2a** was treated with fluorobenzene and NaH in DMSO overnight at 100 °C.

***trans*-*N*,*N*-Dimethyl-2,3-dihydro-1-(2-methoxyphenoxy)inden-2-amine (4a, X = 2-CH$_3$O) Oxalate.** Starting with **1a**, **2a**, or **5** and 2-methoxyphenol, this was the only product isolated. The respective yields were 53%, 78%, and 83% of a white crystalline solid: mp 175–176 °C (methanol–ethyl acetate): IR (KBr) 3438, 2964, 1508, 1259, 1225, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.37–6.93 (m, 8 H), 6.27 (d, 1 H, J = 5.8 Hz), 4.07 (m, 1 H), 3.77 (s, 3 H), 3.40 (dd, 1 H, J = 15.9, 8.3 Hz), 3.16 (dd, 1 H, J = 15.9, 7.9 Hz), 2.74 (s, 6 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.4, 149.7, 146.4, 139.8, 138.8, 129.3, 127.4, 125.0, 124.4, 122.7, 120.9, 116.3, 112.8, 82.1, 71.3, 55.6, 41.7, 32.1 ppm. Anal. Calcd for $C_{18}H_{21}NO{\cdot}C_2H_2O_4$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.29; H, 6.31; N, 3.66.

The same product was obtained in 38% yield when **2a** was treated with 2-fluoromethoxybenzene and NaH in DMSO overnight at 100 °C.

***N*,*N*-Dimethyl-2,3-dihydro-1-phenoxyindene-2-methanamine.** Starting with **2b** and phenol, NMR analysis of the crude oxalate showed it to be a mixture containing approximately 65% of **3b** (X = H) and 35% of **4b** (X = H). Flash chromatography of the residual crude product on silica gel and elution with toluene–ether (1:1) gave the cis isomer **3b** (X = H) as an oil. Bulb-to-bulb distillation at 120–125 °C (0.4 mm) gave, in 30% yield, a colorless oil: IR (film) 2958, 2776, 1605, 1497, 1230, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–6.92 (m, 9 H), 5.68 (d, 1 H, J = 6.0 Hz), 3.13–2.95 (m, 2 H), 2.85 (m, 1 H), 2.53–2.45 (m, 2 H), 2.21 (s, 6 H). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.67; H, 7.95; N, 5.17. The same product was isolated in 50% yield when **1b** was treated with fluorobenzene and NaH in DMSO overnight at 100 °C.

Further elution with the same solvent gave the trans isomer **4b** (X = H) as an oil. Bulb-to-bulb distillation at 110–114 °C (0.3 mm) gave, in 11% yield, a colorless oil: IR (film) 2958, 2780, 1605, 1497, 1230, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–6.92 (m, 9 H), 5.54 (d, 1 H, J = 3.2 Hz), 3.31 (dd, 1 H, J = 16.2, 7.3 Hz), 2.77 (m, 1 H), 2.66 (dd, 1 H, J = 16.2, 4.2 Hz), 2.37 (dd, 1 H, J = 12.2, 7.6 Hz), 2.29 (dd, 1 H, J = 12.2, 8.5 Hz), 2.25 (s, 6 H). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.58; H, 7.93; N, 5.01. The same product was isolated in 61% yield when **2b** was treated with fluorobenzene and NaH in DMSO overnight at 100 °C.

***N*,*N*-Dimethyl-2,3-dihydro-1-(4-methoxyphenoxy)indene-2-methanamine Oxalate.** Starting with **2b** and 4-methoxyphenol, NMR analysis of the crude oxalate showed it to be a mixture containing approximately 65% of **3b** (X = 4-CH$_3$O) and 35% of **4b** (X = 4-CH$_3$O). Flash chromatography of the residual oil on silica gel and elution with ethyl acetate–methanol (9:1) gave the cis isomer **3b** (X = 4-CH$_3$O) as an oil. Conversion to the oxalate gave a 20% yield of a white crystalline solid: mp 153–155 °C (methanol–ethyl acetate); IR (KBr) 3422, 2958, 1720, 1634, 1503, 1216 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.35–6.84 (m, 8 H), 5.71 (d, 1 H, J = 4.9 Hz), 3.71 (s, 3 H), 3.40 (dd, 1 H, J = 12.5, 4.5 Hz), 3.26 (dd, 1 H, J = 12.5, 6.9 Hz), 3.13–2.98 (m, 3 H), 2.79 (s, 6 H). Anal. Calcd for $C_{19}H_{23}NO{\cdot}C_2H_2O_4$: C, 65.10; H, 6.50; N, 3.62. Found: C, 64.72; H, 6.53; N, 3.57.

Further elution with ethyl acetate–methanol (4:1) gave the trans isomer **4b** (X = 4-CH$_3$O). Conversion to the oxalate gave a 12% yield of a white crystalline solid: mp 154–155 °C (methanol–ethyl acetate); IR (KBr) 3428, 2958, 1722, 1640, 1505, 1218 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.32–6.89 (m, 8 H), 5.62 (d, 1 H, J = 5.2 Hz), 3.73 (s, 3 H), 3.26 (dd, 1 H, J = 15.6, 7.4 Hz), 3.17 (d, 2 H, 7.3 Hz), 2.88 (m, 1 H), 2.79–2.67 (m, 7 H). Anal. Calcd for $C_{19}H_{23}NO{\cdot}C_2H_2O_4$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.04; H, 6.51; N, 3.45.

2,3-Dihydro-2-(1-methylethyl)-1-(2-methoxyphenoxy)indene. A mixture of **6** (0.70 g, 4.0 mmol), 2-methoxyphenol (0.55 g, 4.4 mmol), triphenylphosphine (1.16 g, 4.4 mmol), and 50 mL of benzene was stirred, and a solution of diethyl azodicarboxylate (0.77 g, 4.4 mmol) in 10 mL of benzene was added dropwise. After 0.5 h, the mixture was concentrated and treated with 15 mL of a 1:1 mixture of cyclohexane and ether. After refrigeration at 0 °C overnight, the solids were filtered, and the filtrate was concentrated to an oil which, by gas chromatography, was shown to be a mixture containing approximately 75% of the cis isomer **7** and 25% of the trans isomer **8**.

Flash chromatography on silica gel and elution with cyclohexane–ether (95:5) gave **7** (0.32 g, 28%) as a white amorphous powder: mp 58–60 °C; IR (KBr) 2956, 1500, 1254, 1222, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–6.78 (m, 8 H), 5.54 (d, 1 H, J = 5.1 Hz), 3.72 (s, 3 H), 3.05 (dd, 1 H, J = 15.4, 6.7 Hz), 2.96 (dd, 1 H, J = 15.4, 7.4 Hz), 2.30 (m, 1 H), 2.08 (m, 1 H), 1.15 (d, 3 H, J = 6.8 Hz), 1.05 (d, 3 H, J = 6.8 Hz). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 81.09; H, 8.00.

Further elution with the same solvent gave the trans isomer **8** (0.09 g, 8%) as a colorless oil: IR (film) 2958, 1502, 1456, 1254, 1224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27–6.87 (m, 8 H), 5.59 (d, 1 H, J = 6.3 Hz), 3.82 (s, 3 H), 3.13 (dd, 1 H, J = 15.4, 7.9 Hz), 2.69–2.51 (m, 2 H), 1.87 (m, 1 H), 0.97 (d, 3 H, J = 6.8 Hz), 0.93 (d, 3 H, J = 6.8 Hz). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 81.12; H, 7.98.

The above ether (**8**) was the only product isolated when the cis alcohol **9** was reacted under the same conditions. It was also the product of the reaction of the trans alcohol **6** with 2-fluoromethoxybenzene and NaH in DMSO overnight at 100 °C.