of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From Meisenheimer Complex B. The orange suspension obtained (see above) from NaOMe and Meisenheimer Complex B in MeOH after 1 h of stirring at room temperature was heated at reflux for 3 h. The yellow solid was collected by suction to afford 2-methoxy-3,5-dinitrobenzoic acid, Na salt: IR was identical with that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid. Treatment of 0.125 g of the salt with 20% HCl at 50 °C afforded 0.10 g of the acid **4g**: mp 164–165 °C; mmp 164–165 °C; IR was identical with that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid.

2-(Phenylthio)-3,5-dinitrobenzoic Acid (4b). From Meisenheimer Complex A. The orange-red suspension obtained by combining 0.20 g (0.000 58 mol) of A and 0.288 g (0.001 95 mol) of potassium thiophenoxide, each dissolved in 1 mL of absolute MeOH, was stirred at room temperature for 0.5 h and then at 50 °C for 0.5 h until all solid had dissolved. The clear orange solution was cooled in an ice bath and acidified with 5% aqueous HCl until a solid precipitated from the solution. This was collected by suction and recrystallized once from ethanol/water to afford 0.15 g (85%) of the acid **4b**: mp 200–202 °C; mmp 200–202 °C; IR and ^{1}H NMR (acetone-d_6) were identical with those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From Meisenheimer Complex B. A mixture of 0.15 g (0.000 46 mol) of B in 4 mL of absolute MeOH and a solution of 0.288 g (0.001 95 mol) of potassium thiophenoxide in 1 mL of absolute MeOH were combined and stirred at room temperature for 1 h and then at 50 °C for 15 min. After acidification and workup as above, the acid **4b** (95% crude yield) was identical with other samples (mmp, ^{1}H NMR).

2-Amino-3,5-dinitrobenzamide (4c) from Meisenheimer Complex A. A mixture of 0.20 g (0.000 58 mol) of Meisenheimer complex A and 5 mL of 30% aqueous NH_4OH was stirred for 1 h at room temperature, then at 60 °C until all the solid had dissolved, and then an additional 5 min, until a solid began to precipitate. The mixture was cooled in an ice bath and a bright yellow solid was collected by suction. After one recrystallization from water, 0.10 g (85%) of the amide **4c** was obtained: mp 280–282 °C; mmp 279–281 °C; IR and ^{1}H NMR (Me_2SO-d_6) were identical with those of material prepared from **1b**.

From Meisenheimer Complex B. A suspension of 0.15-g (0.000 47 mol) of Meisenheimer complex B and 5 mL of 30% aqueous NH_4OH was stirred at 50 °C until all solid had dissolved. After the solution had been cooled in an ice bath there was obtained 0.10 g (94%) of **4c**: mp (after one recrystallization from water) 280–282 °C; mmp 278–281 °C; IR and ^{1}H NMR were identical with those of material prepared from **1b**.

2-(Dimethylamino)-3,5-dinitro-*N*,*N*-dimethylbenzamide (4e) from Meisenheimer Complex B. A mixture of 7 mL of aqueous 25% dimethylamine and 0.15 g (0.000 47 mol) of Meisenheimer Complex B was stirred at room temperature for 12 h and then heated on a steam bath to concentrate the volume to 2 mL. The solid was collected by suction to afford 0.12 g (90%) of the amide **4e**, which was recrystallized from ethanol/water: mp 105–106 °C; mmp 106–107 °C; IR and ^{1}H NMR (acetone-d_6) were identical with those of material prepared from **1b**.

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Preparation of Potential Intermediates for the Synthesis of Yohimbine and Reserpine

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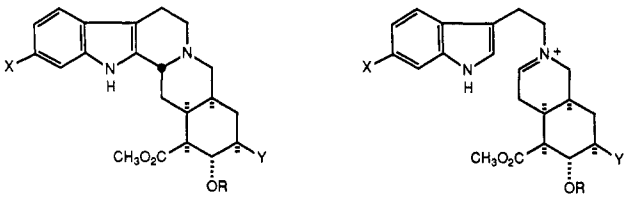
Norborn-5-ene-2-carboxaldehyde is converted by common synthetic intermediates into potential synthons for the ring D–E segment of 3-epi-α-yohimbine and reserpine.

The yohimbine alkaloids and reserpine represent molecules of challenging complexity and significant pharmacological importance.[3] Renewed synthetic interest in this area, as evidenced by several recent reports,[4] prompts us to disclose our own progress in this area.

We envisioned the stereospecific construction of reserpine[3a] (**1a**) and 3-epi-α-yohimbine[3b] (**1b**) from stereoelectronically allowed[5] capture of the tetrahydropyridinium ions **2a** and **2b** by the 2-position of the indole ring. This process would generate the 3-epialloyohimbane pentacyclic ring system. The tetrahydropyridinium salts **2** may be formed by condensation[6] of a suitably substituted trypt-



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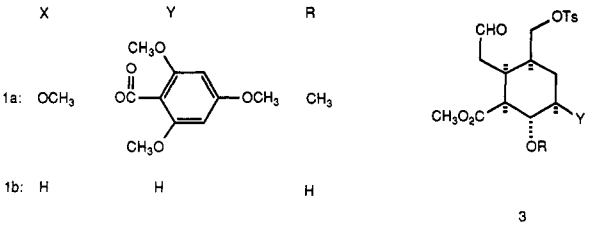

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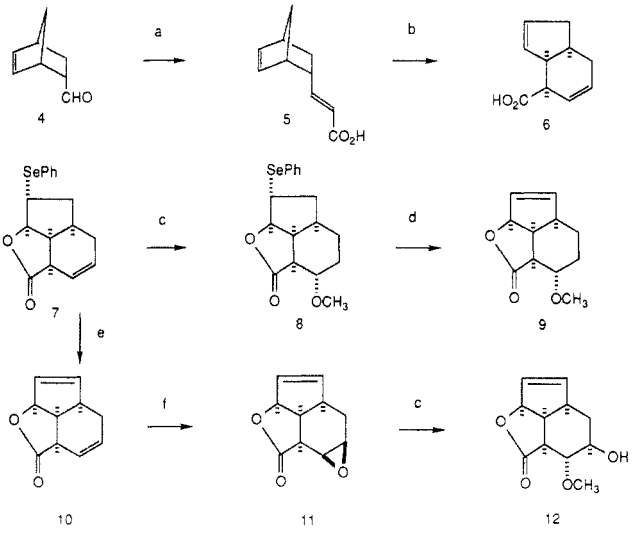
Scheme I[a]



[a] Reagents: (a) $(EtO)_2POCH_2CO_2SiMe_3$, *n*-BuLi, THF; (b) *o*-xylene, reflux, 4 h; (c) $NaOCH_3$, CH_3OH; (d) O_3, EtOAc, −78 °C, and then $(i\text{-}Pr)_2NH$, 25 °C, 24 h; (e) H_2O_2, THF, 0–25 °C; (f) Ag_2O, I_2, THF–H_2O.

amine with aldehyde **3**. This report describes our efforts toward preparation of intermediate **3**.

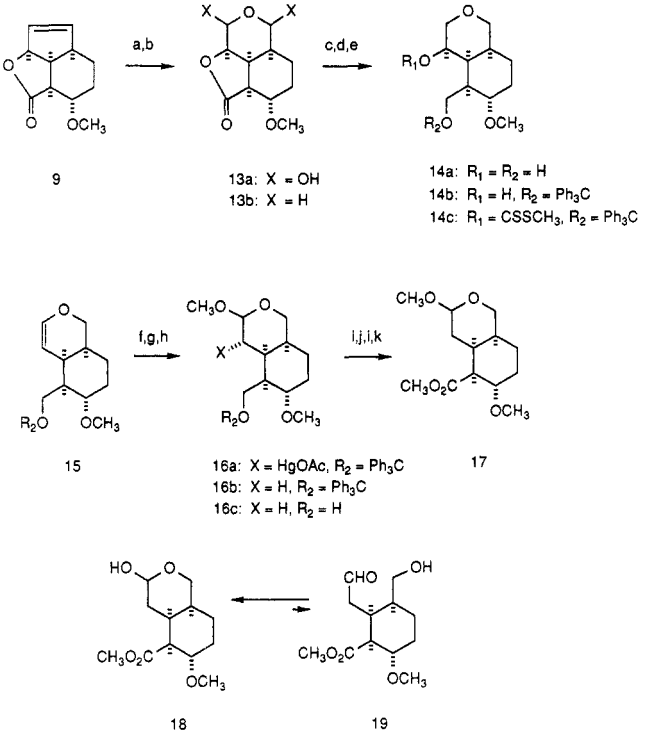
Results

Thermal Diels–Alder cycloaddition of cyclopentadiene and acrolein[7] produced norborn-5-ene-2-carboxaldehyde **4** in 95% yield as a 4:1 mixture of endo–exo isomers (Scheme I). Condensation of the aldehydes **4** with the lithium anion of diethyl [((trimethylsilyl)oxy)carbonyl]-methanephosphonate[8] generated the corresponding (*E*)-norborn-5-ene-2-acrylic acids **5** (endo–exo, 4:1). Crude **5** was dissolved in dry, nitrogen-saturated *o*-xylene and gently refluxed for 4 h. These conditions allowed the endo isomer to undergo a Cope rearrangement[9] to the functionalized hydrindane derivative **6**, whereas the exo isomer remained unchanged. The crude thermolysis mixture was concentrated and subjected to phenylselenyl chloride and triethylamine. These conditions[10] formed seleno lactone **7** selectively. Lactone **7** displayed an infrared stretching frequency of 1755 cm^{-1} characteristic of five-membered ring lactones. The unrearranged (*E*)-2-*exo*-norborn-5-ene-2-acrylic acid did not form a neutral lactone product, and separation was achieved by a simple base wash of the reaction mixture. Recrystallized seleno lactone **7** was obtained in 31% overall yield from aldehyde mixture **4**.

Exposure of seleno lactone **7** to a solution of sodium methoxide in methanol[11] resulted in isomerization of the double bond in **7** into conjugation with the lactone moiety followed by Michael addition of methoxide from the convex face to produce Michael adduct **8** in 60% yield. Oxidation of **8** with ozone to the corresponding selenoxide, followed by thermal syn elimination produced the unsaturated lactone **9** (84%).

Alternatively, seleno lactone **7** was oxidized with aqueous hydrogen peroxide[10] to its corresponding selenoxide, which upon thermal elimination formed diene lactone **10** in 66%

Scheme II[a]



[a] Reagents: (a) O_3, MeOH, −78 °C, and then H_2, Pd/C, MeOH, −78–25 °C; (b) TFA, $(Et)_3SiH$, 70 °C, 8 h; (c) LAH, ether; (d) Ph_3CCl, DMAP, $N(Et)_3$; (e) excess NaH, CS_2, 60 °C, and then excess CH_3I, 25 °C; (f) $Hg(OAc)_2$, MeOH; (g) $NaBH_4$, NaOH; (h) excess Na, NH_3, THF, and then NH_4Cl; (i) Me_2SO, oxalyl chloride, −78 °C, and then $N(Et)_3$; (j) acetone cyanohydrin, $N(Et)_3$, CH_2Cl_2; (k) MeOH quench.

yield. Selective epoxidation was achieved by employing a mixture of iodine and silver(I) oxide in aqueous THF.[12] The regiochemistry of the epoxidation was established by ^1H NMR decoupling experiments. Irradiation of the characteristic methine proton geminal to the oxygen of the lactone moiety in **11** split the olefinic multiplet at 5.97 ppm into a clean doublet, indicating the allylic lactone moiety had been maintained.[13] Subsequent exposure of epoxide **11** to a solution of sodium methoxide in methanol effected conversion to alcohol **12** (37%). It should be noted that intermediates **9** and **12** possess suitable functional groups in the correct relative stereochemical configurations for further elaboration into intermediates **3** for possible construction of 3-epi-α-yohimbine (**1b**) and reserpine (**1a**), respectively.

Addressing the yohimbine problem, ozonolysis of unsaturated lactone **9** in methanol at −78 °C (Scheme II), followed by reduction with hydrogen and palladium on carbon[14] produced a mixture of hemiacetals **13a**. Interestingly, no free aldehyde was observed in either IR or ^1H NMR spectra of **13a**. Further reduction of bishemiacetal **13a** with triethylsilane in trifluoroacetic acid,[15] conditions known to generate and reduce carbonium ions, produced tetrahydropyran **13b**, isolated in 66% overall yield from olefin **9**. Reduction of the lactone moiety in tetrahydropyran **13b** with lithium aluminum hydride[16] produced the

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corresponding diol **14a**, which was treated directly with triphenylmethyl chloride[17] to provide the corresponding trityl-protected derivative **14b** (47% overall). The monoprotected diol was converted to the xanthate ester under standard conditions (NaH, CS_2; MeI).[18] Xanthate pyrolysis[19] of **14c** at 210 °C (sublimation) resulted in regiospecific formation of dihydropyran **15** in 93% yield. Oxymercuration[20] of dihydropyran **15** produced organomercurial **16a**, which was reduced in situ with basic methanolic sodium borohydride to produce methyl pyranoside **16b** (71% overall). Deprotection of the primary alcohol was effected by dissolving metal reduction with excess sodium in ammonia[21] which formed alcohol **16c** in 82% yield. Oxidation of the primary alcohol to the ester stage was carried out according to a procedure described by Wender,[4d] an oxidation procedure compatible with an acid-sensitive functionality: (a) oxidation of the alcohol to the corresponding aldehyde under Swern[22] conditions, (b) conversion to the cyanohydrin,[23] (c) oxidation to the acyl cyanide,[24] employing the Swern[22] procedure, and (d) quenching the acyl cyanide with methanol. With this protocol, the methyl ester was obtained in 65% yield. Alternative procedures such as pyridinium dichromate were not pursued due to the anticipated acid lability of the methyl pyranoside linkage to the acid generated under such reaction conditions.

Finally, conversion of methyl pyranoside methyl ester **17** to the corresponding lactol **18** was effected with 1 N HCl–THF (76%). Lactol **18** appears to exist totally in the closed form **18**. Both IR and ^1H NMR show no evidence for the presence of ring opened tautomer **19**. This suggests that further manipulation of lactol **18** to intermediate **3** for 3-epi-α-yohimbine synthesis must proceed by some reaction which involves irreversible aldehyde trapping of tautomer **19**.

Conclusion

A convergent strategy to the synthesis of the indole alkaloids 3-epi-α-yohimbine and reserpine has been presented. Our efforts have resulted in the preparation of potential intermediate **18** for 3-epi-α-yohimbine synthesis. Common synthetic intermediates have produced unsaturated alcohol **12**, a potential reserpine precursor.

Experimental Section

Infrared spectra were recorded on a Beckmann IR 4210 infrared spectrophotometer. NMR spectra were taken on a Bruker WP200 spectrometer in dilute deuterochloroform solution with tetramethylsilane as internal standard. Mass spectra were determined on an AEI-MS9 mass spectrometer. Melting points and boiling points are uncorrected. Methanol was distilled from magnesium turnings, tetrahydrofuran (THF) from sodium–benzophenone, carbon disulfide from P_2O_5, and *o*-xylene from sodium–benzophenone. All chromatography was performed in open columns employing Baker analyzed reagent grade silica gel, 60–200 mesh.

6-(Phenylseleno)-7-hydroxy-*cis*-hydrind-2-ene-1-carboxylic Acid Lactone (7). To an ice-cooled, stirring solution of diethyl [((trimethylsilyl)oxy)carbonyl]methanephosphonate[8] (43.17 g, 0.13 mol) in dry THF (1200 mL) was added a solution of *n*-BuLi in hexane (80 mL, 1.6 M, 0.13 mol) dropwise and the resulting mixture stirred overnight. The mixture was then ice cooled, and a solution of 5-norbornene-1-carboxaldehyde[7] (**4**) (endo–exo, 4:1; 14.00 g, 0.12 mol) in dry THF (60 mL) was added dropwise and the solution stirred overnight at room temperature. The solution was poured onto 5% NaOH solution (1 L) and shaken vigorously for 15 min in a separatory funnel, the layers were separated, and the THF was discarded. The aqueous phase was washed three more times with ether, and the ether layer was discarded. The aqueous layer was ice cooled and acidified to pH 1 with concentrated HCl and extracted with ether (200 mL × 5), and the combined ether extracts were washed with water (2×), dried over $MgSO_4$, filtered, and concentrated.

The crude acid was dissolved in dry *o*-xylene (550 mL) and the solution saturated with N_2 for 30 min. The solution was gently refluxed under nitrogen in an oil bath at 155 °C for 4 h and cooled and solvent removed in vacuo (1–2 torr). The residue was dissolved in dry CH_2Cl_2 (500 mL), dry triethylamine (14.25 mL, 0.10 mol) added, and the solution stirred for 1 h. The solution was cooled to −78 °C and solid phenylselenyl chloride (13.40 g, 0.07 mol) added in one portion and stirred until the solid dissolved. The solution was then allowed to warm to room temperature, washed with saturated $NaHCO_3$ (2×) and brine, dried over Na_2SO_4, filtered, and concentrated and the resulting brown solid triturated 4× with hot hexane. On cooling, the triturate produced white needles, which were combined and recrystallized from ethyl acetate–hexane, affording the seleno lactone **7**: 11.01 g (30.1% overall); mp 122–123 °C; IR (KBr) 1758 (s), 1575 (m), 746 cm^{-1} (s); ^{13}C NMR 176.8, 133.4, 129.4, 129.0, 127.7, 125.8, 121.4, 89.3, 46.6, 37.3, 37.2, 34.8, 33.8, 24.0 ppm; ^1H NMR 7.54–7.51 (m, 2 H), 7.31–7.26 (m, 3 H), 5.81–5.90 (m, 2 H), 5.04 (d, J = 6.3 Hz, 1 H), 3.86 (d, J = 5.9 Hz, 1 H), 3.32–3.14 (m, 2 H), 2.83–2.64 (m, 1 H), 2.41–2.22 (m, 1 H), 2.16–1.86 (m, 2 H), 1.84–1.71 ppm (dd, 1 H); mass spectrum, exact mass (M^+) calcd 320.0331, found 320.0296.

2-Methoxy-6-(phenylseleno)-7-hydroxy-*cis*-hydrindan-1-carboxylic Acid Lactone (8). A solution of sodium methoxide in methanol from sodium (1.58 g, 69 mmol) and methanol (73 mL) was added rapidly to a solution of seleno lactone **7** (11.01 g, 34 mmol) in THF (146 mL) and the solution stirred 2 h under N_2. Saturated NH_4Cl solution (100 mL) was added, the mixture stirred for 15 min, organic solvent removed in vacuo, water added, and the mixture extracted with ether (3×, 200 mL total), the ether extracts were combined, washed with water, dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed (3×) over silica gel with 15:85 ethyl acetate–hexane to afford the seleno lactone methyl ether **8**: 7.28 g (60.0%); IR (film) 1752 (s), 7.32 cm^{-1} (s); ^{13}C NMR 176.8, 133.5, 129.2, 128.9, 127.6, 88.4, 73.6, 55.8, 45.8, 42.0, 36.1, 34.0, 33.4, 20.5, 18.2 ppm; ^1H NMR 7.48–7.57 (m, 2 H), 7.24–7.32 (m, 3 H), 4.87 (d, 1 H), 3.89 (d, 1 H), 3.83 (br s, 1 H), 3.33 (s, 3 H) 3.10–3.22 (m, 1 H), 2.93–3.01 (m, 1 H), 2.50–2.71 (m, 1 H), 1.73–2.12 (m, 4 H), 1.22–1.41 ppm (m, 2 H); mass spectrum, exact mass (M^+) calcd 352.0578, found 352.0588.

2-Methoxy-7-hydroxy-*cis*-hydrind-5-ene-1-carboxylic Acid Lactone (9). A solution of seleno lactone methyl ether **8** (3.26 g, 9.3 mmol) in ethyl acetate (120 mL) and CH_2Cl_2 (60 mL), cooled to −78 °C, was ozonized until the blue color persisted (30 min) and flushed with oxygen (30 min), diisopropylamine (1.4 mL, 10.0 mmol) added, and the solution warmed to room temperature and stirred for 3 days. The solvent was removed in vacuo, the residue dissolved in ether, washed with water and brine, separated, dried ($MgSO_4$), filtered, concentrated, and the residue chromatographed on silica gel with 25:75 ethyl acetate–hexane to afford the olefin as an oil, which was Kugelrohr distilled [150 °C (0.05 torr)]: 1.51 g (83.8%); IR (neat) 1759 cm^{-1} (s); ^{13}C NMR 176.7, 142.1, 127.9, 87.9, 74.4, 55.3, 41.8, 40.9, 34.1, 22.5, 20.5 ppm; ^1H NMR 5.93 (br s, 1 H), 5.49 (d, 1 H), 3.82–3.92 (m, 1 H), 3.37 (s, 3 H), 3.15–3.26 (m, 1 H), 2.94–3.09 (m, 2 H), 1.90–2.08 (m, 1 H), 1.61–1.78 (m, 1 H), 1.18–1.48 ppm (m, 2 H); mass spectrum, exact mass (M^+) calcd 194.0943, found 194.0936.

7-Hydroxy-*cis*-hydrin-2,5-diene-1-carboxylic Acid Lactone (10). A solution of H_2O_2 (30%, 10 mL in 20 mL THF) was added dropwise to an ice cold solution of seleno lactone **7** (2.25 g, 7 mmol) in THF (50 mL) and stirred at 0 °C for 3 h, gradually warmed to room temperature, and then stirred for 2 days. Ether (300 mL) was added, the mixture washed with water (2×), dried ($MgSO_4$), filtered, and concentrated, and the residue chromatographed on silica gel with 25:75 ethyl acetate–hexane to afford the diene lactone (0.82 g), which was Kugelrohr distilled [125 °C (0.1 torr)] to afford an oil, which solidified on standing: 0.76 g (66.6%); IR

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(NaCl, film) 3025 (w), 1755 cm^{-1} (s); ^{13}C NMR 177.4, 140.7, 129.2, 125.6, 123.1, 88.6, 39.3, 37.6, 25.4 ppm; ^1H NMR 5.77–5.92 (m, 4 H), 5.58 (d, J = 7.3 Hz, 1 H), 3.29–3.45 (m, 1 H), 3.08–3.20 (m, 2 H), 2.07–2.38 ppm (m, 2 H); mass spectrum, exact mass (M^+) calcd 162.0681, found 162.0684.

2,3-Epoxy-7-hydroxy-*cis*-hydrind-5-ene-1-carboxylic Acid Lactone (11). A mixture of lactone diene **10** (0.76 g, 4.7 mmol), THF (40 mL), water (10 mL), silver(I) oxide (3.27 g, 3 equiv), and iodine (3.57 g, 3 equiv) was stirred vigorously for 1 h, at which time second portions of silver(I) oxide (1.08 g, 1 equiv) and iodine (1.19 g, 1 equiv) were added. Stirring was continued for 24 h, the reaction mixture was filtered, and silver salts were washed thoroughly with ether. The combined filtrates were concentrated, and the residue was chromatographed on silica gel with 30:70 ethyl acetate–hexane, to afford the epoxide as a white solid: 0.37 g (44.0%); mp 116–118 °C; IR (KBr disk) 3060 (w), 1753 cm^{-1} (s); ^{13}C NMR 175.7, 144.5, 126.7, 87.1, 49.1, 48.8, 39.7, 37.8, 28.3 ppm; ^1H NMR 6.20–6.23 (unresolved dd, 1 H), 3.50–3.63 (m, 2 H), 3.22–3.29 (m, 1 H), 2.81–3.02 (m, 2 H), 2.42–2.59 (m, 1 H), 1.40–1.58 ppm (dd, 1 H); mass spectrum, exact mass (M^+) calcd 178.0630, found 178.0638.

2-Methoxy-3,7-dihydroxy-*cis*-hydrind-5-ene-1-carboxylic Acid Lactone (12). A solution of sodium (46.2 mg, 2 mmol) in methanol (5.6 mL) was added to an ice-cold solution of lactone epoxide **11** (369.2 mg, 2 mmol) in dry THF (17 mL), stirred for 25 min, and quenched with saturated NH_4Cl solution, the organic solvent removed in vacuo, the residue partitioned between ether and water, and the aqueous phase extracted several times with ether. The combined ether extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel with 60:40 ethyl acetate–hexane to afford a clear oil, which solidified on standing: 161.3 mg (37.0%); IR (KBr pellet) 3300 (br), 1750 and 1734 cm^{-1} (s); ^{13}C NMR 177.4, 142.3, 128.0, 88.3, 78.8, 65.2, 57.4, 42.3, 40.8, 34.4, 29.7 ppm; ^1H NMR 6.01–6.03 (dd, 1 H), 5.89–5.91 (d, 1 H), 5.50–5.52 (d, 1 H), 3.70–3.73 (br s, 2 H), 3.52 (s, 3 H), 3.21–3.28 (m, 2 H), 3.12–3.14 (d, 1 H), 2.33 (very br s, 1 H), 2.13–2.19 (m, 1 H), 1.32–1.37 ppm (m, 1 H); mass spectrum, exact mass (M^+) calcd 210.0892, found 210.0887.

3-Oxa-1-hydroxy-7-methoxy-*cis*-decalin-8-carboxylic Acid Lactone (13b). A solution of lactone methyl ether **9** (104.0 mg, 0.5 mmol) in dry methanol (3 mL) was ozonized for 30 min (an excess of O_3) at −78 °C and the solution flushed with oxygen for 30 min. The solution was then transferred to a prereduced slurry of 10% Pd on C in dry methanol kept at −78 °C under an atmosphere of H_2. After being stirred at −78 °C for 3 h, the mixture was warmed to room temperature, filtered through Celite, and concentrated in vacuo, the residue dissolved in trifluoroacetic acid (3 mL), and triethylsilane (1.5 mL) added. The solution was stirred at 70 °C under N_2 for 8 h and cooled, the volatile material removed in vacuo, and the residue chromatographed on silica gel with 40:60 ethyl acetate–hexane to afford a clear oil, which was Kugelrohr distilled [150 °C (0.1 torr)]: 74.8 mg (65.6%); clear oil; IR (neat) 1760 cm^{-1} (s); ^{13}C NMR 177.1, 75.5, 74.0, 70.0, 66.7, 56.2, 44.3, 32.4, 28.4, 25.1, 21.8 ppm; ^1H NMR 4.28–4.35 (dd, 1 H), 4.24 (d, J = 15 Hz, 1 H), 3.82–3.90 (dd, 1 H), 3.70 (dd, 1 H), 3.58 (dd, 1 H), 3.43 (dd, 1 H), 3.29 (s, 3 H), 3.14–3.21 (dd, 1 H), 2.69–2.82 (dd, 1 H), 1.37–2.08 ppm (m, 5 H); mass spectrum, exact mass (M^+) calcd 212.1049, found 212.1049.

3-Oxa-1-hydroxy-7-methoxy-8-[(triphenylmethoxy)methyl]-*cis*-decalin (14b). To a stirred suspension of lithium aluminum hydride (50.0 mg, 1.3 mmol) in dry ether (5 mL) at 0 °C under N_2 was added lactone oxodecalin **13b** in ether (2 mL). The cooling bath was removed and the suspension stirred 6 h at room temperature. Ethyl acetate (84 μL) was added and stirring continued for 15 min, and then 50 μL of water, 50 μL of 15% NaOH, and 150 μL of water were added sequentially. The mixture was filtered, the solid mass washed thoroughly with ether, and the filtrate dried ($MgSO_4$), filtered, and concentrated. The crude diol was of sufficient purity to be used for tritylation. However, a chromatographed sample of the diol (silica gel, ethyl acetate) provided the following analytical data for **14a**: IR (neat) 3400 (s), 1100 cm^{-1} (s); ^1H NMR 3.75–3.99 (m, 6 H), 3.52–3.60 (dd, 1 H), 3.42–3.49 (dd, 1 H), 3.37 (s, 3 H), 2.60 (br s, 2 H), 3.24–3.32 (m, 1 H), 1.91–2.14 (m, 2 H), 1.69–1.80 (m, 1 H), 1.46–1.58 (m, 2 H), 1.03–1.24 ppm (m, 1 H); mass spectrum, exact mass ($M^+ - H_2O$) calcd 198.1256, found 198.1252.

The crude diol from the previous experiment (132.0 mg) was dissolved in dry CH_2Cl_2 (2 mL), and trityl chloride (170.1 mg, 0.6 mmol), triethylamine (85 μL), and 4-(dimethylamino)pyridine (5.0 mg) were added; the solution was stirred overnight, poured onto water, and extracted with CH_2Cl_2, the organic phase washed with saturated NH_4Cl solution and water, then dried (Na_2SO_4), filtered, and concentrated, and the residue chromatographed on silica gel with 30:70 ethyl acetate–hexane to afford 169.1 mg (47.0%) of trityl ether as a white solid: IR (KBr) 3460 (s), 3020, 3050, 3090 (w), 707 cm^{-1} (s); ^1H NMR 7.21–7.52 (m, 15 H), 3.76–3.88 (m, 3 H), 3.31–3.61 (m, 5 H), 3.40 (s, 3 H), 2.33–2.42 (m, 2 H), 1.87–2.12 (m, 3 H), 1.46–1.56 (m, 2 H), 1.09–1.30 ppm (m, 1 H); mass spectrum, exact mass ($M^+ - C_{19}H_{15} - H_2O$) calcd 197.1178, found 197.1172.

3-Oxa-1-[(methyldithio)methoxy]-7-methoxy-8-[(triphenylmethoxy)methyl]-*cis*-decalin (14c). A mixture of NaH (50% dispersion in oil, prewashed 3× with hexane, 106.0 mg), oxadecalin trityl ether **14b** (100.0 mg), dry THF (6 mL), and dry CS_2 (1 mL) was stirred and heated under N_2 in an oil bath at 60 °C for 6 h, another 1 mL portion of CS_2 added, and heating continued for 2 h. The mixture was cooled, MeI added (1 mL), and stirring continued overnight. Water was added carefully and the xanthate isolated by ether extraction. The ether was washed with water and brine, dried ($MgSO_4$), and concentrated and the residue recrystallized from ethyl acetate–hexane to afford white prisms: 80.0 mg (61.0%); mp 199–200 °C; IR (KBr pellet) 3040, 3080, 3095 cm^{-1} (w); ^1H NMR 7.14–7.42 (m, 15 H), 5.63 (br s, 1 H), 4.21 (d, J = 13.1 Hz, 1 H), 3.86 (d, J = 11.5 Hz, 1 H), 3.65–3.72 (m, 2 H), 3.46, (d, J = 13.1 Hz, 1 H), 3.04–3.22 (m, 1 H), 3.12 (s, 3 H), 2.68–2.83 (m, 2 H), 2.47 (s, 3 H), 1.92–2.34 (m, 3 H), 1.51–1.73 (m, 2 H), 1.09–1.31 ppm (m, 1 H); mass spectrum, exact mass ($M^+ - C_{19}H_{15} - CH_3SH - COS$) calcd 197.1178, found 197.1178.

3-Oxa-7-methoxy-8-[(triphenylmethoxy)methyl]-*cis*-$\Delta^{2,3}$-octalin (15). The trityl xanthate **14c** (211.0 mg) was sublimed under a pressure of ca. 20 torr and a bath temperature of 210 °C for 8 h. The apparatus was cooled and dismantled and the white sublimed material washed off the cold finger with $CHCl_3$, concentrated, and chromatographed on silica gel with 10:90 ethyl acetate–hexane to afford a white solid: 158.0 mg (93.0%); IR (KBr pellet) 3045 cm^{-1} (w); ^1H NMR 7.18–7.55 (m, 15 H), 6.10–6.46 (dd, 1 H), 4.32–4.35 (m, 1 H), 4.00–4.06 (dd, 1 H), 3.84–3.89 (dd, 1 H), 3.53–3.60 (dd, 1 H), 3.13 (s, 3 H), 2.82–2.98 (m, 2 H), 1.53–2.28 (m, 6 H), 1.14–1.29 ppm (m, 1 H); mass spectrum, exact mass ($M^+ - C_{19}H_{15}$) calcd 197.1178, found 197.1171.

3-Oxa-2,7-dimethoxy-8-[(triphenylmethoxy)methyl]-*cis*-decalin (16b). Mercuric acetate (307.7 mg, 1.2 equiv) was added in one portion to a solution of trityl enol ether **15** (353.7 mg, 0.8 mmol) in methanol (3 mL) and THF (3 mL) under N_2. The solution was stirred for 1 h, and then 3 M NaOH (4 mL) and 3 M NaOH–0.5 M $NaBH_4$ (4 mL) solutions were added. After being stirred for an additional hour, the solution was extracted with ether (3×, 100 mL total) and the ether washed with water and $NaHCO_3$ solution, dried ($MgSO_4$), filtered, concentrated, and recrystallized (ethyl acetate–hexane), affording 245.0 mg (64.6%), mp 172–173 °C. The mother liquor was chromatographed (20:80 ethyl acetate–hexane) to afford 22.6 mg (5.7%): total yield, 70.3%; IR (CCl_4) 3030, 3059, 3093 (m), 1129 cm^{-1} (s); ^1H NMR 7.18–7.48 (m, 15 H), 4.61 (br s, 1 H), 3.98–4.04 (dd, 1 H), 3.43–3.50 (dd, 1 H), 3.34 (s, 3 H), 3.30–3.35 (m, 1 H), 3.14 (s, 3 H), 2.77–2.99 (m, 3 H), 2.13–2.21 (m, 1 H), 1.76–1.92 (m, 2 H), 1.46–1.59 (m, 4 H), 1.08–1.27 (m, 1 H); mass spectrum, exact mass ($M^+ - C_6H_5$) calcd 395.2222, found 395.2248.

3-Oxa-2,7-dimethoxy-8-(hydroxymethyl)-*cis*-decalin (16c). Liquid NH_3 (25 mL) was distilled from sodium and chilled to −78 °C under N_2. To the stirred ammonia was added trityl methoxyoxadecalin **16b** (267.6 mg, 0.6 mmol) in THF (6 mL). The mixture was warmed to −33 °C, at which time additional THF was added to solubilize the substrate. Sodium (135.5 mg, 5.9 mmol, 5 equiv) was added in one portion and stirring continued at −33 °C for 80 min, followed by addition of NH_4Cl (323.0 mg, 5.9 mmol). Ether (15 mL) was added, and the NH_3 allowed to evaporate under a N_2 stream overnight. The mixture was dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica with 50:50 ethyl acetate–hexane to afford the alcohol as a clear oil: 106.5 mg (81.7%); IR (CCl_4) 3520 cm^{-1} (br m); ^1H NMR 4.63–4.65 (m, 1 H), 3.90–3.97 (dd, 1 H), 3.72–3.82 (dd, 1 H),

3.41-3.55 (m, 1 H), 3.39 (s, 3 H), 3.32 (s, 3 H), 3.29-3.40 (m, 2 H), 2.23-2.46 (m, 2 H), 1.48-1.92 (m, 5 H), 1.13-1.41 ppm (m, 2 H); mass spectrum, exact mass (M^+) calcd 230.1518, found 230.1530.

3-Oxa-2,7-dimethoxy-8-carbomethoxy-*cis*-decalin (17). The primary alcohol **16c** was oxidized exactly according to the procedure of Swern[22] to provide the corresponding aldehyde in 84.5% yield as an oil: IR (CCl_4) 1726 cm^{-1} (s); ^1H NMR 9.74 (d, J = 2.0 Hz, 1 H), 4.64 (br dd, 1 H), 3.94-4.01 (dd, 1 H), 3.61-3.74 (td, 1 H), 3.38 (s, 3 H), 3.32 (s, 3 H), 3.15-3.40 (m, 1 H), 2.69-2.84 (m, 1 H), 2.27-2.44 (m, 2 H), 1.39-1.99 (m, 5 H), 1.10-1.31 ppm (m, 1 H); mass spectrum, exact mass ($M^+ - CH_3$) calcd 213.1127, found 213.1130.

To a solution of the aldehyde (89.1 mg, 0.4 mmol) and acetone cyanohydrin (71.4 μL, 2 equiv) in CH_2Cl_2 was added triethylamine (10 μL, 0.2 equiv) and the solution stirred under nitrogen overnight. Solvent was removed in vacuo, leaving a white solid (the cyanohydrin of the starting aldehyde). The cyanohydrin was used in this crude form and displayed no aldehydic proton in the ^1H NMR and was diastereomeric at the newly generated chiral center: IR (CCl_4) 3450 cm^{-1} (m); mass spectrum, m/e 224 ($M^+ - OCH_3$).

In a separate flask, oxalyl chloride (44 μL, 1.2 equiv was dissolved in CH_2Cl_2 (1.1 mL) and chilled to -78 °C and Me_2SO (110 μL, 4 equiv) added dropwise. After 15 min, a solution of the aldehyde cyanohydrin prepared as described above in CH_2Cl_2 was added. The solution was stirred at -78 °C for 30 min and at -25 °C for 30 min and chilled back to -78 °C and NEt_3 (271 μL, 5 equiv) added. After being stirred at -78 °C for 10 min, the mixture was warmed to -25 °C for 15 min and quenched with methanol (0.6 mL). After a gradual warming to room temperature, the solution was stirred overnight, poured onto water, and extracted with $CHCl_3$ (3×, 25 mL total), and the extracts were combined, washed with water, dried (Na_2SO_4), filtered, concentrated, and chromatographed on silica with 20:80 ethyl acetate-hexane to afford the methyl ester as a white solid in 65.0% yield: IR (CCl_4) 1737 cm^{-1} (s); ^1H NMR 4.66 (d, J = 1.3 Hz, 1 H), 3.88-3.95 (dd, 1 H), 3.68 (s, 3 H), 3.45-3.60 (m, 1 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 3.30-3.36 (m, 1 H), 2.46-2.67 (m, 2 H), 2.20-2.32 (m, 1 H), 1.71-1.96 (qd, 2 H), 1.47-1.62 (m, 2 H), 1.34-1.44 (dd, 1 H), 1.07-1.27 ppm (m, 1 H); mass spectrum, exact mass (M^+) calcd 258.1467, found 258.1475.

3-Oxa-2-hydroxy-7-methoxy-8-carbomethoxy-*cis*-decalin (18). A solution of 2-methoxy-3-oxadecalin **17** (18.2 mg) in THF (1 mL) and aqeuous 1 N HCl (1 mL) was stirred at room temperature for 21 h, poured onto brine (4 mL), and extracted with ethyl ether (3×, 25 mL total), the ether combined, washed with water, dried ($MgSO_4$), filtered, and concentrated, and the clear oily residue (homogeneous by TLC) chromatographed on silica with 50:50 ethyl acetate-hexane to afford a clear oil: 13.0 mg (76.0%); IR (neat) 3400 (br m), 1732 cm^{-1} (s); ^1H NMR 5.28 (br s, 1 H), 4.52-4.61 (m, 1 H), 4.17-4.23 (m, 1 H), 3.79 (d, 1 H), 3.70 and 3.71 (each a s, combined integral = 6 H), 3.46-3.68 (m, 3 H), 3.35 (s, 6 H), 3.32-3.40 (m, 1 H), 2.49-2.71 (m, 4 H), 1.09-2.35 (m, 14 H) [note: each proton of one anomer counts as 1 H]; mass spectrum, exact mass ($M^+ - H_2O$) calcd 226.1205, found 226.1208.

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Acyclic Stereoselection. 36. Simple Diastereoselection in the Lewis Acid Mediated Reactions of Enol Silanes with Aldehydes[1]

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The Lewis acid mediated aldol reactions of enol silanes with aldehydes have been investigated. The effects of enol silane structure, both nature of the ligand at the silyloxy carbon and the geometry of the double bond, the aldehyde structure, and the nature of the Lewis acid have been studied. In general, the reactions of prochiral enol silanes with prochiral aldehydes show little simple diastereoselection (Table I). An exception is *Z* enol silane **7**, derived from ethyl *tert*-butyl ketone, which shows synthetically useful anti selectivity. Enol silane **36** may therefore be used as an anti-selective propionate equivalent. The chiral α-alkoxy aldehyde **43** shows a high diastereofacial preference in its reactions with enol silanes **42c** and **42d** provided a Lewis acid capable of expanding its coordination beyond four is used ($TiCl_4$ or $SnCl_4$) (Table II). However, with the related ketene acetal **41b**, only modest diastereofacial selectivity is seen (Table II). Aldehyde **43** also shows a high diastereofacial preference, in the chelation-controlled sense, in its reactions with prochiral enol silanes **5-9**. However, the simple diastereoselection observed in the latter reactions (Table III) is quite different from that observed in the reactions of prochiral aldehydes with the same enol silanes. For example, enol silane **7**, which shows good anti selectivity in its reactions with prochiral aldehydes, gives a 1.5:1 mixture of the two syn aldols in its reaction with **43**; while the reverse is true with the propiophenone-derived enol silanes **8** and **9**. Finally, the results obtained in this study, along with those reported by other investigators, have been formulated into a coherent mechanistic rationale involving open transition states of the sort depicted in Figures 1 and 3.

In the last ten years there has been a resurgence of interest in the aldol addition reaction,[3] particularly from the standpoint of its stereochemistry.[4] Most of the stereochemical investigations to date have dealt with the uncatalyzed reactions of preformed enolates, mainly lithium, boron, and zinc,[4] with aldehydes. Recently, several groups have turned their attention to the analogous Lewis

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