the solvent removed on the rotovap. The residue was partitioned between water and ether and the aqueous phase separated and again washed with ether. The aqueous layer was acidified with concentrated HCl to give an off-white solid that was filtered, throughly washed with water, and recrystallized from 2-methoxyethanol to yield 1.02 g (46%) of **23** as white crystals: mp 295 °C dec; NMR (Me_2SO-d_6) δ 9.95 (s, 1 H, H-2), 8.57 (d, J = 5.5, 1 H, H-6), 7.96 (d, J = 5.5, 1 H, H-5), 1.28 (s, 9 H, *tert*-butyl); IR (KBr) 3210 (br), 2980, 1687 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.06; H, 6.36; N, 12.52.

2,2-Dimethyl-*N*-(4-(hydroxyphenylmethyl)-3-pyridinyl)-propanamide (24). The metalation mixture obtained from 3.56 g (20 mmol) of **20** and 50 mmol of *n*-butyllithium as described for **21** and **22** was cooled to −78 °C and a solution of 3.18 g (30 mmol) of benzaldehyde in 5 mL of THF was added. The mixture was warmed to room temperature and poured into water, and upon addition of ether a solid precipitated, which was removed by filtration. The filtrates were separated into two layers, and the aqueous phase was extracted twice with ether. The combined ether layers and the filtered solid were recombined and evaporated to dryness. The residue was taken up in $CHCl_3$ and the resulting solution was washed with water, dried over $MgSO_4$, and evaporated to leave an oily orange solid. The solid was triturated with ether and filtered to leave colorless **24** (3.02 g, 53%): mp 199–204 °C. One recrystallization from ethyl acetate gave 2.84 g (50%) of **24**: mp 206–209 °C. (lit.[14] mp 200–202 °C). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.78; H, 7.04; N, 9.83.

Registry No. **1**, 86847-59-8; **2**, 70298-89-4; **3**, 86847-60-1; **4**, 86847-61-2; **5a**, 86847-62-3; **5b**, 86847-63-4; **5c**, 86847-64-5; **5d**, 86847-65-6; **5e**, 86847-66-7; **5f**, 86847-67-8; **5g**, 86847-68-9; **6a**, 86847-69-0; **6b**, 86847-70-3; **6c**, 86847-71-4; **6d**, 86847-72-5; **6e**, 86847-73-6; **9**, 86847-74-7; **10**, 86847-75-8; **11**, 86847-76-9; **12a**, 86847-77-0; **12b**, 86847-78-1; **12c**, 86847-79-2; **13a**, 86847-80-5; **13b**, 86847-81-6; **13c**, 86847-82-7; **14a**, 86847-92-9; **14c**, 86847-93-0; **15a**, 86847-83-8; **15b**, 86847-84-9; **16a**, 86847-85-0; **16b**, 86847-86-1; **17**, 86847-87-2; **18**, 86847-88-3; **19**, 86853-52-3; **20**, 70298-88-3; **21**, 86847-89-4; **22**, 86847-90-7; **23**, 86847-91-8; **24**, 82791-70-6; trimethylacetyl chloride, 3282-30-2; 2-aminopyridine, 504-29-0; 4-aminopyridine, 504-24-5; 3-aminopyridine, 462-08-8; deuterium oxide, 7789-20-0; chlorotrimethylsilane, 75-77-4; dimethylformamide, 68-12-2; dimethyl disulfide, 624-92-0; methyl iodide, 74-88-4; benzaldehyde, 100-52-7; ethyl chloroformate, 541-41-3; 2-amino-3-pyridinecarboxaldehyde, 7521-41-7; 4-amino-3-pyridinecarboxaldehyde, 42373-30-8; 4-methyl-2-aminopyridine, 695-34-1; 5-methyl-2-aminopyridine, 1603-41-4; 6-methyl-2-aminopyridine, 1824-81-3; 2-amino-5-chloropyridine, 1072-98-6; 6-chloro-2-aminopyridine, 45644-21-1; 6-fluoro-2-aminopyridine, 1597-32-6.

Synthetic Applications of Heteroatom-Directed Photoarylation. Benzo[*b*]furan Ring Construction

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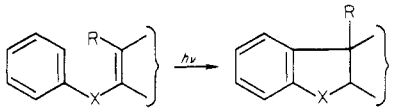
The preparation of several α-phenoxy-α,β-unsaturated carboxylic acid esters via condensation of phosphonate **3c** with ketones and an aldehyde is described. The resulting aryl vinyl ethers undergo photocyclization to give 2,3-dihydrobenzo[*b*]furan-2-carboxylic acid esters, which are converted to benzo[*b*]furans by (1) saponification to the carboxylic acid, (2) oxidative decarboxylation to the 2-acetoxy-2,3-dihydrobenzo[*b*]furan, and (3) solvolytic rearrangement with titanium tetrachloride in methylene chloride; thus, **8**, **9**, **11**, and **14** are prepared. Oxidative cleavage of 3-cyclohexylbenzo[*b*]furan **14** gives keto formate **15a** (saponification of **15a** gives **15b**), which demonstrates that the method can be used for conversion of phenols to *o*-acyl derivatives.

We have been involved in the development of synthetic methods based on photocyclization of aryl vinyl heteroatom systems (heteroatom-directed photoarylation; A → B).[1] An important feature of the photoreaction is the

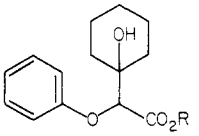


A B

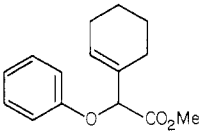
formation of a carbon–carbon bond between an aromatic ring and a quaternary carbon atom. On the other hand, benzo-fused heteroaromatic ring systems also are available by a subsequent elimination process (R = OH, OCH_3, OAc) to give indoles (X = NR),[2] benzothiophenes (X = S),[3] benzofurans (X = O),[3] and a benzoselenophene (X = Se).[4] In this paper, we report a new photochemically derived benzofuran synthesis, which features the oxidative rearrangement of 2,3-dihydrobenzo[*b*]furan-2-carboxylic acids; e.g., **5b** → **6a** → **8**.

Results and Discussion[5]

At the onset of this work, we desired a reliable method for preparation of α-(aryloxy)-α,β-unsatured carboxylic acid derivatives; e.g., **4**. Condensation of lithium α-phenoxy-α-lithioacetate[6] with cyclohexanone gives carbinol **1a**,



1a, R = H
b, R = Me



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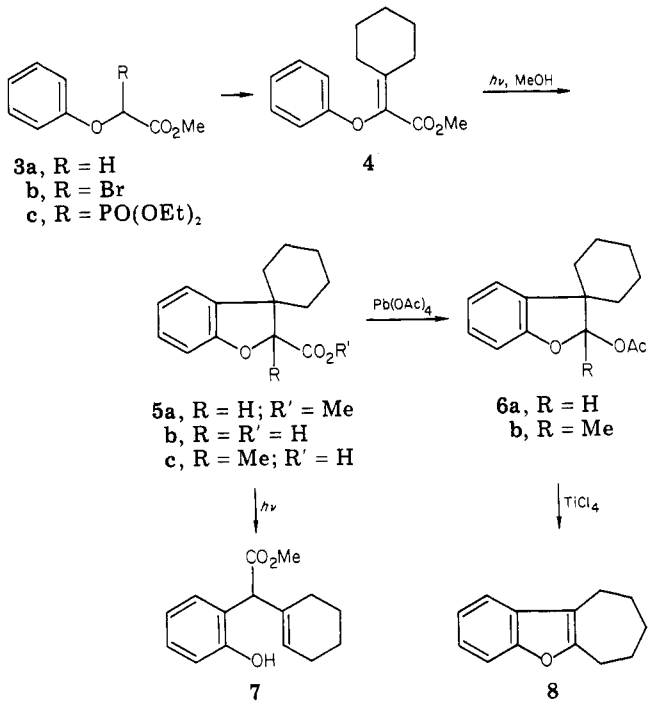
and this can be esterified to give **1b** in excellent overall yield. As anticipated,[7] however, dehydration of **1b** results in formation of mixtures of **2** and **4** with the β,γ-unsaturated isomer **2** predominating.

(1) For a recent application, see: Schultz, A. G.; Sha, C.-K. *Tetrahedron* **1980**, *36*, 1757.
(2) (a) Schultz, A. G.; Hagmann, W. K. *J. Org. Chem.* **1978**, *43*, 3391. (b) Schultz, A. G.; Hagmann, W. K. *J. Chem. Soc., Chem. Commun.* **1976**, 726. (c) Schultz, A. G.; Hagmann, W. K. *J. Org. Chem.* **1978**, *43*, 4231.
(3) Hagmann, W. K. Ph.D. Dissertation, Cornell University, 1978.
(4) Schultz, A. G. *J. Org. Chem.* **1975**, *40*, 3466.
(5) Taken in part from: Napier, J. Ph.D. Dissertation, Cornell University, 1981.
(6) Adam, W.; Fick, H.-H. *J. Org. Chem.* **1978**, *43*, 4574.
(7) Cope, A. C.; D'Addieco, A. A.; Whyte, D. E.; Glickman, S. A. "Organic Syntheses"; Wiley: New York; 1963; Collect. Vol. IV, p 234.

0022-3263/83/1948-3408$01.50/0

Scheme I



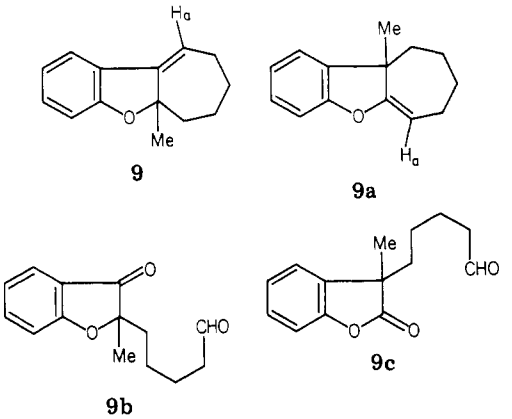
A solution to the problem of unfavorable aldol dehydration was at hand in phosphonate **3c** (Scheme I). This reagent is prepared by bromination of methyl phenoxyacetate (**3a**) (*N*-bromosuccinimide (NBS) in benzene, 87% distilled yield) to give α-bromo ester **3b**, followed by reaction of **3b** with triethyl phosphite (89% yield). The choice of benzene solvent in the bromination step is critical in that NBS in CCl_4 results in mainly aromatic ring bromination.[8]

Generation of the sodium salt of **3c** with sodium hydride in DME and condensation with cyclohexanone gives **4** in 72% isolated yield, with none of the isomeric **2** observed.[9] Phosphonates of type **3c** undergo condensation with a variety of aldehydes and ketones and therefore are to be considered very useful precursors of α-(aryloxy)-α,β-unsatured carboxylic acid esters (vide infra).

Pyrex-filtered irradiation of **4** in benzene–methanol solution gives 2,3-dihydrobenzo[*b*]furan **5a** in 88% isolated yield. In contrast to our reported photocyclizations of α-(aryloxy)-α,β-unsaturated ketones,[10] the conversion of **4** to **5a** requires excessive irradiation time (~70 h). This must be due in part to the fact that with Pyrex equipment, **4** absorbs relatively little of the incident light and, as the reaction proceeds, must compete with the product **5a** for light absorption. This observation is important because 2,3-dihydrobenzo[*b*]furan **5a** undergoes a photorearrangement to phenol **7**.[11] Fortunately, the relative quantum efficiencies for the two processes are such that when nearly all of **4** is consumed only about 5% phenol **7** has formed; phenol **7** is conveniently removed by aqueous base extraction to give analytically pure **5a** after crystallization. Despite this potential for a secondary 2,3-dihydrobenzo[*b*]furan photorearrangement, we find that by carefully following the progress of α-(aryloxy)-α,β-unsaturated carboxylic acid ester photocyclization, 2,3-dihydrobenzo[*b*]furans can be obtained in high yield.

Reaction of carboxylic acid **5b** with lead tetraacetate/pyridine in THF gives 2-acetoxy-2,3-dihydrobenzo[*b*]furan **6a** in 92% yield. Alkylation (methyl iodide) of the dianion derived from **5b** gives **5c**, and this undergoes oxidative decarboxylation to give **6b** in >90% overall yield.

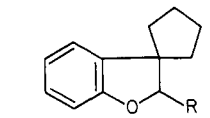
We expected that solvolysis of 2-acetoxy-2,3-dihydrobenzo[*b*]furan **6a** would generate an oxonium ion, from which rearrangement followed by deprotonation would give annelated benzofuran **8**. In fact, treatment of **6a** with excess titanium tetrachloride in CH_2Cl_2 gives benzofuran **8** in 92% isolated yield. Reaction of the blocked derivative **6b** with $TiCl_4/CH_2Cl_2$ gives the fused-tricycle **9** (72% yield).



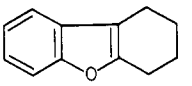
NMR and IR spectral data for **9** are fully in accord with the proposed structure. Another possible rearrangement product (**9a**) would be expected to have similar spectral properties; however, the chemical shift for H_a at δ 6.18 is compatible with the styrene-like chromophore in **9** but at much lower field than that expected for enol ether **9a**.

A simple chemical conversion provides a definitive confirmation of the assignment of structure. Oxidative cleavage of the carbon–carbon double bond in **9** would produce the aryl conjugated ketone **9b**, while **9a** would give the γ-lactone **9c**. The carbonyl absorption at 5.83 μm obtained for the product of ozonolysis of **9** is compatible only with ketonic structure **9b**. Thus, rearrangement of **6b** is uncomplicated by methyl group migration and results in the formation of **9** in good yield.

The generality of the benzofuran synthesis is demonstrated by additional examples. Spirocyclopentane **10a**



10a, R = CO_2Et
b, R = CO_2H
c, R = OAc



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is prepared by the photocyclization method outlined for **5a**, and this is converted to 2-acetoxy-2,3-dihydrobenzo[*b*]furan **10c** by oxidative decarboxylation; $TiCl_4$-initiated solvolytic rearrangement of **10c** gives the annelated benzofuran **11** in good overall yield.

Phosphonate **3c** reacts with cyclohexane carboxaldehyde to give **12** as a mixture of two isomers. Photocyclization of **12** gives **13a** (Scheme II), and this is converted to **13c** in the usual way. Elimination of acetic acid rather than migration of the cyclohexyl group occurs on treatment of **13c** with $TiCl_4$. The structure of **14** is firmly established

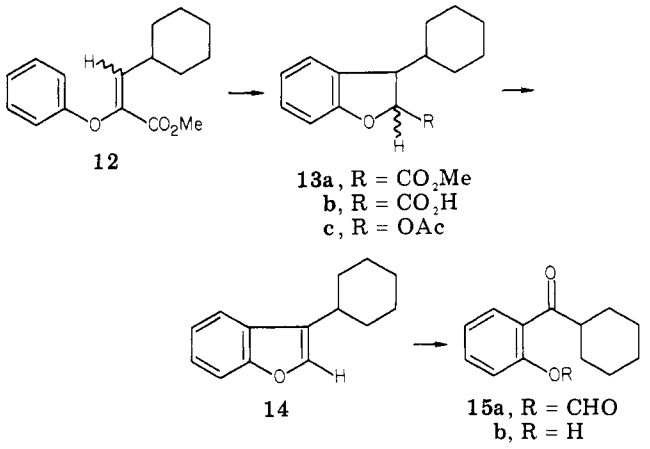
(8) For another report of an advantageous benzene solvent effect during NBS bromination, see: Dinizo, S. E.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 2846.

(9) For an alternative preparation of **4** (as the carboxylic acid) from (2,2,2-trifluoroethoxy)benzene, see: Tanaka, K.; Nakai, T.; Ishikawa, N. *Chem. Lett.* **1977**, 1379.

(10) For example, see: Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150.

(11) The photorearrangement of **5a** to phenol **7** has been communicated: Schultz, A. G.; Napier, J. J.; Lee, R. *J. Org. Chem.* **1979**, *44*, 663.

Scheme II



by the oxidative cleavage of the furan ring to give keto formate **15a**; saponification of **15a** gives keto phenol **15b**.

The last transformation demonstrates the conversion of phenol (the precursor of phenoxyacetic acid) to an *o*-acyl derivative. This might be of use in situations where the Fries or photo-Fries rearrangements of aryl esters are not applicable. Significantly, the conversion is regiospecific and the acyl group is stored in the form of the relatively stable furan ring.

Thus, a variety of benzo[*b*]furans should be available from (aryloxy)acetic acid derivatives and the appropriate aldehyde or ketone. The process incorporates all carbon atoms of the reactants except for the carboxylic acid carbon atom; this carbon atom is excised in the oxidative decarboxylation step. The method demonstrated here complements our previously reported phenol annelation with epoxides derived from 2-cycloalken-1-ones.[12]

Experimental Section

General Methods. A Hanovia 450-W medium-pressure mercury arc lamp placed in a water-cooled Pyrex immersion well was used as a light source for all photochemistry. Small-scale photoreactions generally were performed in sealed Pyrex tubes degassed by four freeze–pump–thaw cycles with an oil-diffusion-pump vacuum. Preparative-scale photoreactions were performed under an argon atmosphere in a conventional 350-mL-capacity photoreactor fitted to the immersion well. Irradiation solvents were spectral or reagent grade and were used without further purification. Microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, MI.[13]

Preparation of Methyl Bromophenoxyacetate (3b). A solution of methyl phenoxyacetate (**3a**, 20.0 g, 0.120 mol) and *N*-bromosuccinimide (25.6 g, 0.144 mol) in benzene (500 mL) was irradiated with a sunlamp for 30 min. The solution was cooled to 5 °C, and the precipitated succinimide was removed by filtration. Removal of solvent and distillation gave **3b** (25.8 g, 87%): bp 85–87 °C (0.35 mm); IR (neat) 3.30, 3.35, 5.69, 5.80 (w), 6.25 μm; ^{1}H NMR δ 7.60–7.00 (5 H, m), 6.53 (1 H, s), 3.93 (3 H, s).

Preparation of Methyl (Diethylphosphono)phenoxyacetate (3c). A mixture of **3b** (23.2 g, 0.095 mol) and triethyl phosphite (15.7 g, 19.6 mL, 0.095 mol) was heated on a steam bath for 12 min and allowed to stir at room temperature overnight. Distillation gave **3c** as a colorless liquid (25.4 g, 89%) bp 145–147 °C (0.25 mm); IR (neat) 3.40, 3.71, 6.26 μm; ^{1}H NMR, δ 7.50–6.80 (5 H, m), 5.05 (1 H, d, J = 19 Hz), 4.30 (4 H, q, J = 7 Hz), 3.98 (3 H, s), 1.37 (3 H, t, J = 7 Hz).

Preparation of Methyl Cyclohexylidenephenoxyacetate (4).[11] To a suspension of sodium hydride (0.802 g, 99%, 0.0334 mol) in DME (10 mL) was added a solution of **3c** (10.0 g, 0.0331 mol) in DME (20 mL) over 30 min. The mixture was warmed to 70 °C for 45 min and cooled to room temperature, after which cyclohexanone (3.45 g, 0.0352 mol, 1.05 equiv) was added and the solution was refluxed for 6 h. The reaction was cooled to room temperature, poured into water (120 mL) and extracted with ether (2 × 100 mL). The combined ether solution was washed with 1 N sodium hydroxide (2 × 20 mL) and brine (50 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave a yellow solid (7.69 g, 94%). Crystallization from hexane gave **4** (5.83 g, 72%): mp 51.5–53 °C; IR (KBr) 3.40, 5.79, 6.10, 6.17 μm; ^{1}H NMR δ 7.40–6.80 (5 H, m), 3.61 (3 H, s), 2.90–2.70 (2 H, m), 2.40–2.20 (2 H, m), 1.80–1.50 (6 H, m); UV (methanol) λ_{max} nm (ε) 270 (1990), 223 (18000); electron-impact mass spectrum, m/e 246 (23%), 77 (100%).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.36. Found: C, 73.07; H, 7.30.

Preparation of Methyl Spiro[benzofuran-3(2*H*),1′-cyclohexane]-2-carboxylate (5a).[11] An argon-purged solution of **4** (4.00 g, 0.016 mmol) in benzene–methanol (1:1, 300 mL, 0.055 M) was irradiated with Pyrex-filtered light for 72 h. The solution was concentrated under vacuum and the residue dissolved in ether. The ether layer was washed with ice-cold 1 N sodium hydroxide (3 × 30 mL) and brine (30 mL) and dried over anhydrous magnesium sulfate. Removal of solvent and Kugelrohr distillation gave **5a** as a colorless oil (3.52 g, 88%): bp 140 °C (0.25 mm); IR (neat) 3.40, 5.78, 6.25, 6.82, 6.91 μm; ^{1}H NMR δ 7.20–6.70 4 H, m), 4.88 (1 H, s), 3.72 (3 H, s), 1.90–1.20 (10 H, m), UV (methanol) λ_{max} nm (ε) 284 (2060), 277 (2300), 214 (5300); UV (ether) λ_{max} nm (ε) 285 (3350), 279 (3620). VPC analysis (6 ft, 10% SE-30 on Chromosorb W, isothermal 175 °C) indicated a single peak of R_f 13.6 min (under these conditions **4** has R_f 11.5 min).

Preparation of Spiro[benzofuran-3(2*H*),1′-cyclohexane]-2-carboxylic Acid (5b).[11] To a solution of **5a** (1.50 g, 6.10 mmol) in methanol (10 mL) was added 1 N sodium hydroxide (10 mL), and the resulting solution was stirred at room temperature for 6 h. The solution was poured into ether (50 mL) and water (25 mL). The ether layer was washed with 1 N sodium hydroxide (2 × 25 mL), and the combined aqueous washes were acidified with 10% hydrochloric acid. The aqueous phase was extracted with ether (3 × 50 mL). The final three ether washes were combined, washed with brine (25 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave **5b** as a crystalline solid (1.21 g, 86%); mp 137–139 °C. Recrystallization from ethyl acetate–hexane gave **5b** (1.06 g, 75%): mp 138–139 °C; IR (Nujol) 3.00–3.90, 5.79, 5.91, 6.23, 8.37, 13.34, 14.52 μm; ^{1}H NMR δ 9.36 (1 H, s), 7.40–6.60 (4 H, m), 4.80 (1 H, s), 1.90–1.40 (10 H, m).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.29; H, 7.04.

Preparation of 2-Methylspiro[benzofuran-3(2*H*),1′-cyclohexane]-2-carboxylic Acid (5c). To a solution of tetramethylpiperidine (0.390 mL, 2.2 mmol) in THF (1 mL) at 0 °C was added *n*-butyllithium (1.00 mL of 2.20 M in hexane, 2.2 mmol). After 30 min the solution was cooled to −78 °C and a solution of **5b** (232 mg, 1.0 mmol) in THF (1.5 mL) was added dropwise. The solution was stirred at −78 °C for 10 min and 0 °C for 30 min and cooled to −78 °C. Methyl iodide (0.093 mL, 1.5 mmol) was added, and the solution was stirred at −78 °C for 6 h and at room temperature overnight. The solution was poured into ether (30 mL) and 0.5 N hydrochloric acid (25 mL). The aqueous phase was extracted again with ether (25 mL). The combined organic solution was washed with brine (20 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave a yellow crystalline solid (242 mg, 98%). Recrystallization from ether–hexane gave **5c** (216 mg, 89%): mp 168–175 °C dec; IR (chloroform) 3.00–4.00, 3.45, 5.84, 6.24 μm; ^{1}H NMR δ 10.92 (1 H, s), 7.60–6.70 (4 H, m), 2.20–1.20 (10 H, m), 1.53 (3 H, s). An analytical sample was prepared by crystallization from ethyl acetate and hexane, mp 110–111 °C.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.38. Found: C, 73.25; H, 7.33.

Preparation of 2-Acetoxyspiro[benzofuran-3(2*H*),1′-cyclohexane] (6a). To a solution of **5b** (50 mg, 0.22 mmol) and pyridine (0.050 mL, 0.62 mmol) in THF (0.5 mL) was added lead

(12) Schultz, A. G.; Erhardt, J.; Hagmann, W. K. *J. Org. Chem.* **1977**, *42*, 3459. See ref 10 for additional detail.
(13) For additional general detail, see ref 1.
(14) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 192.

tetraacetate (96 mg, 0.22 mmol). The resulting yellow solution was stirred at room temperature for 3.5 h. At this time the solution was colorless with a white precipitate present. Water (20 mL) and ether (40 mL) were added. The ether layer was washed with 1 N hydrochloric acid (15 mL), 1 N sodium bicarbonate (2 × 15 mL), and brine (15 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave **6a** as a colorless oil (49 mg, 92%): IR (neat) 3.40, 5.76, 6.82, 6.95, 8.29 μm; ^{1}H NMR δ 7.20–6.70 (4 H, m), 6.53 (1 H, s), 2.03 (3 H, s), 2.10–1.10 (10 H, m).

Preparation of 7,8,9,10-Tetrahydro-6*H*-benzo[*b*]cyclohepta[*d*]furan (8). To a solution of **6a** (38 mg, 0.15 mmol) in methylene chloride (4 mL) at −78 °C was added titanium tetrachloride (0.070 mL, 0.60 mmol). The dark red-brown solution was stirred at −78 °C for 1 h; water (1 mL) was added and the mixture was allowed to warm to room temperature. The mixture was poured into ether (30 mL) and 1 N hydrochloric acid (10 mL). The ether phase was washed with 1 N sodium bicarbonate (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvent and filtration through a short column of silica gel gave **8** as a colorless oil (27 mg, 92%): R_f (analytical TLC, silica gel, benzene) 0.31; IR (neat) 3.41, 6.95, 13.42 μm; ^{1}H NMR δ 7.50–7.00 (4 H, m), 3.10–2.60 (4 H, m), 2.10–1.40 (6 H, m); electron-impact mass spectrum, *m/e* 186 (100%), 170 (15%), 143 (65%), 144 (45%).

Rearrangement of 6a in Trifluoroacetic Acid. A solution of **6a** (25 mg, 0.10 mmol) in trifluoroacetic acid was stirred at room temperature for 9 h. The solution was diluted with ether (30 mL). The ether solution was washed with 1 N sodium bicarbonate (2 × 10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave a yellow oil (15 mg, 79%); ^{1}H NMR analysis indicated that **8** was present (~50%) along with polymer.

Preparation of 2-Methyl-2-acetoxyspiro[benzofuran-3-(2*H*),1′-cyclohexane] (6b). To a solution of **5c** (26 mg, 0.11 mmol) and pyridine (0.060 mL, 0.74 mmol) in THF (1 mL) was added lead tetraacetate (49 mg, 0.11 mmol), and the mixture was stirred at room temperature for 4 h, in the dark. The mixture was dissolved in ether (50 mL) and 1 N hydrochloric acid (15 mL). The ether phase was washed with 1 N sodium bicarbonate (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvent gave **6b** as a pale yellow oil (28 mg, 98%): IR (neat) 3.40, 5.75, 6.85, 6.95, 8.15, 11.27 μm; ^{1}H NMR δ 7.60–6.70 (4 H, m), 2.10–1.20 (10 H, m), 1.93 (3 H, s), 1.84 (3 H, s).

Preparation of 5a*H*-6,7,8,9-Tetrahydro-5a-methyl-6*H*-benzo[*b*]cyclohepta[*d*]furan (9). To a solution of **6b** (28 mg, 0.11 mmol) in methylene chloride (2 mL) at −78 °C was added titanium tetrachloride (0.060 mL, 0.55 mmol). The solution was stirred at −78 °C for 10 min and 0 °C for 20 min. Water (1 mL) was added, and the mixture was dissolved in methylene chloride (30 mL) and 1 N hydrochloric acid (10 mL). The methylene chloride phase was washed with 1 N sodium bicarbonate (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvent and chromatography (silica gel, hexane–methylene chloride (1:1)) gave **9** as a colorless oil (15 mg, 72%) R_f 0.32; IR (neat) 3.40, 6.21, 6.87, 8.01, 13.42 μm; ^{1}H NMR δ 7.40–6.70 (4 H, m), 6.18 (1 H, t, *J* = 8 Hz), 2.50–1.20 (8 H, m), 1.53 (3 H, s).

Preparation of 2-Methyl-2-(4-formylbutyl)benzofuran-3-(2*H*)-one (9b). To a solution of **9** (21.0 mg, 0.10 mmol) in dry dichloromethane (1 mL) cooled to −78 °C was added a saturated solution of ozone in dichloromethane. The pale-blue reaction mixture was stirred at −78 °C for 10 min and was then warmed to room temperature over 1 h. Dimethyl sulfide (0.5 mL, large excess) was added and the solution stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in dichloromethane and washed with water, dried, and evaporated to give 20.0 mg of a pale-yellow oil. Flash column chromatography (SiO_2, 3:1 hexane–ethyl acetate) afforded **9b** (10.0 mg, 41%); IR ($CHCl_3$) 3.38, 3.41, 5.83 and 6.19 μm; ^{1}H NMR δ 9.74 (1 H, s), 7.58–7.72 (2 H, m), 7.02–7.16 (2 H, m), 2.38 (2 H, t, *J* = 6 Hz), 1.86 (2 H, t, *J* = 6 Hz), 1.46–1.88 (4 H, m), 1.42 (3 H, s); electron-impact mass spectrum, *m/e* 232 (14%), 148 (100%).

Preparation of Ethyl Cyclopentylidenephenoxyacetate. Prepared from ethyl (diethylphosphono)phenoxyacetate (bp 160 °C (0.15 mm)) and cyclopentanone by the method used for the synthesis of **4**: bp 100 °C (0.6 mm); ^{1}H NMR δ 7.50–6.80 (5 H, m), 4.08 (4 H, q, *J* = 7 Hz), 3.10–2.70 (2 H, m), 2.70–2.10 (2 H, m), 2.00–1.50 (4 H, m), 1.07 (3 H, t, *J* = 7 Hz).

Preparation of Ethyl Spiro[benzofuran-3(2*H*),1′-cyclopentane]-2-carboxylate (10a). Prepared from ethyl cyclopentylidenephenoxyacetate by the method used for the synthesis of **5a**: oil, 77% yield; ^{1}H NMR δ 7.40–6.80 (4 H, m), 4.95 (1 H, s), 4.30 (2 H, q, *J* = 7 Hz), 2.10–1.40 (8 H, m), 1.33 (3 H, t, *J* = 7 Hz).

Preparation of Spiro[benzofuran-3(2*H*),1′-cyclopentane]-2-carboxylic Acid (10b). Prepared from **10a** by the method used for the synthesis of **5b**: crystalline solid, quantitative crude yield; recrystallized from ethyl acetate–hexane (80%, mp 96–98 °C).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.36; H, 6.30.

Preparation of 2-Acetoxyspiro[benzofuran-3(2*H*),1′-cyclopentane] (10c). Prepared by the method used for the synthesis of **6a**: colorless oil (73%); ^{1}H NMR δ-7.40–6.70 (4 H, m), 6.45 (1 H, s), 2.07 (s) together with 2.20–1.20 (m, total 11 H).

Preparation of 1,2,3,4-Tetrahydrodibenzofuran (11). Prepared by the method used for the synthesis of **8**; colorless oil (82%); ^{1}H NMR δ 7.50–7.00 (4 H, m), 2.90–2.40 (4 H, m), 2.20–1.60 (4 H, m).

Preparation of Methyl 2-Phenoxy-3-cyclohexyl-2-propenoate (12). To a suspension of sodium hydride (236 mg, 9.74 mmol) in tetrahydrofuran (10 mL) was added a solution of **3c** (10 mL). After being stirred for 15 min, the mixture was heated under reflux for 30 min and cooled to room temperature. A solution of freshly distilled cyclohexane carboxaldehyde (2.18 g, 2.36 mL, 19.5 mmol) was added dropwise, and the mixture was heated under reflux for 5 h. After cooling, water (50 mL) was added, and the mixture extracted with dichloromethane. The organic extract was dried over anhydrous magnesium sulfate and evaporated to give 2.64 g of a brown oil, which was chromatographed on a silica gel column (4:1 hexane–ethyl acetate) to give 1.91 g of **12** as a mixture of *Z* and *E* (1:4) olefins (65%). A portion of this mixture was subjected to preparative thick-layer chromatography on silica gel (9:1 hexane–ethyl acetate), and after four developments, pure *Z* and *E* isomers were isolated.

(*Z*)-**12**: oil; IR ($CHCl_3$) 3.41, 3.51, 5.81, 6.29, 8.23 μm; ^{1}H NMR δ 0.80–2.00 (m, 10 H), 2.20–2.70 (br, 1 H), 3.67 (s, 3 H), 6.47 (d, 1 H, *J* = 12 Hz), 6.80–7.40 (m, 5 H); UV (MeOH) λ_{max} (log ε) 217 nm (4.31), 270 (3.42); mass spectrum, *m/e* 260 (M^+).

(*E*)-**12**: oil; IR ($CHCl_3$) 3.41, 3.51, 5.81, 6.29, 8.16, 8.27 μm; ^{1}H NMR δ 0.50–2.10 (m, 10 H), 2.60–3.40 (br, 1 H), 3.70 (s, 3 H), 5.80 (d, 1 H, *J* = 9 Hz), 6.60–7.60 (m, 5 H); UV (MeOH) λ_{max} (log ε) 219.7 nm (4.09), 270 (3.31); electron-impact mass spectrum, *m/e* 260 (M^+).

Preparation of 2-(Methoxycarbonyl)-3-cyclohexyl-2,3-dihydrobenzo[*b*]furan (13a). Prepared from **12** by the method used for the synthesis of **5a**; chromatographic separation of the reaction mixture on a Waters Prep LC 500 (using silica cartridges; 22:1 hexane–ethyl acetate) gave unreacted **12** and **13a** as a mixture of isomers (1:3) in 62% yield: IR ($CHCl_3$) 3.40, 5.65, 6.25 μm; ^{1}H NMR δ 0.75–2.20 (m, 11 H), 3.30–3.65 (m, 1 H), 3.80, 3.90 (s, 3 H), 5.00, 5.25 (d, 1 H, *J* = 5.0, 9.0 Hz), 6.75–7.50 (m, 4 H); electron-impact mass spectrum, *m/e* 260 (M^+).

Preparation of 2-Carboxy-3-cyclohexyl-2,3-dihydrobenzo[*b*]furan (13b). To a solution of **13a** (1:3 mixture of isomers, 312 mg, 1.20 mmol) in methanol (5.0 mL) was added a 2 N NaOH solution (1.20 mL, 2.40 mmol). After being stirred at room temperature for 12 h, the solution was acidified with 6 N HCl. The mixture was extracted with dichloromethane, and the organic extract was dried and evaporated to give **13b** (285 mg, 97%): mp 112–114 °C (ether–hexane); IR ($CHCl_3$) 3.03–4.00 (br), 3.43–3.51, 5.80, 6.25, 8.33 (br) μm; ^{1}H NMR δ 0.60–2.30 (m, 11 H), 3.30–3.80 (m, 1 H), 4.95, 5.30 (d, 1 H, *J* = 4.3, 9.0 Hz), 6.80–7.50 (m, 4 H), 8.60 (br s, 1 H); electron-impact mass spectrum, *m/e* 246 (M^+).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.38. Found: C, 72.91; H, 7.20.

Preparation of 2-Acetoxy-3-cyclohexyl-2,3-dihydrobenzo[*b*]furan (13c). Prepared from **13b** by the method used for the synthesis of **6a**: colorless oil (88%; of sufficient purity for the next reaction); IR ($CHCl_3$) 3.29, 3.36, 3.43, 3.51, 5.75 μm;

^{1}H NMR δ 0.50–2.30 (a broad envelope with a sharp singlet at 2.05, 14 H), 3.05–3.25 (m, 1 H), 6.60 (br, 1 H), 6.60–7.49 (m, 4 H); electron-impact mass spectrum, *m/e* 260 (M^+).

Preparation of 3-Cyclohexylbenzofuran (14). Prepared in quantitative crude yield from **13c** by the method used for the synthesis of **8**; thick-layer chromatography on silica gel (hexane) gave pure **14** (65%): IR ($CHCl_3$) 3.41, 3.50, 6.87, 8.40 (br) μm; ^{1}H NMR δ 0.70–2.30 (m, 10 H), 2.50–3.00 (br, 1 H), 7.00–7.90 (m, 5 H); electron-impact mass spectrum, *m/e* 200 (M^+).

Preparation of Cyclohexyl 2-(Formyloxy)phenyl Ketone (15a). To a solution of **14** (15.0 mg, 0.08 mmol) in dry dichloromethane (1 mL) cooled to −78 °C was added a saturated solution of ozone in dichloromethane over 5 min. The pale-blue reaction mixture was allowed to stir at −78 °C for 10 min and was then warmed to room temperature over 1 h. Dimethyl sulfide (0.5 mL, large excess) was added and the solution stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in ether, washed with water, dried and evaporated to give **15a** (15.1 mg, 86%): IR ($CHCl_3$) 5.75, 5.94 μm; ^{1}H NMR δ 0.90–3.50 (m, 1 H), 7.00–8.00 (m, 4 H), 8.30 (s, 1 H).

Preparation of Cyclohexyl 2-Hydroxyphenyl Ketone (15b). To a solution of crude formate ester **15c** (10.6 mg, 0.05 mmol) in methanol (1 mL) was added 1 N NaOH (0.5 mL). The resulting purple reaction mixture was stirred at room temperature for 12 h, acidified with 1 N HCl, and extracted into ether. The organic layer was washed with water, dried, and evaporated to give **15b** (9.0 mg, 100%): IR ($CHCl_3$) 6.13, 6.75, 6.94, 8.26 μm; ^{1}H NMR δ 1.00–2.12 (m, 10 H), 3.30 (br, 1 H), 6.70–7.90 (m, 4 H), 8.80 (s, 1 H); electron-impact mass spectrum, *m/e* 204 (M^+).

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Registry No. **3a**, 2065-23-8; **3b**, 86728-16-7; **3c**, 86728-17-8; **4**, 69515-13-5; **5a**, 80548-39-6; **5b**, 86728-18-9; **5c**, 86728-19-0; **6a**, 86728-20-3; **6b**, 86728-21-4; **7**, 86728-22-5; **8**, 5010-79-7; **9**, 86728-23-6; **9b**, 86728-24-7; **10a**, 86728-25-8; **10b**, 86728-26-9; **10c**, 86728-27-0; **11**, 13130-19-3; (*E*)-**12**, 86728-28-1; (*Z*)-**12**, 86728-29-2; *cis*-**13a**, 86728-30-5; *trans*-**13a**, 86728-31-6; *cis*-**13b**, 86728-32-7; *trans*-**13b**, 86728-33-8; *cis*-**13c**, 86728-34-9; *trans*-**13c**, 86728-35-0; **14**, 53707-88-3; **15a**, 86728-36-1; **15b**, 18066-52-9; ethyl (diethylphosphono)phenoxyacetate, 86728-37-2; ethyl (cyclopentylidene)phenoxyacetate, 86728-38-3; benzene, 71-43-2.

Stereoselective Reductions of Substituted Cyclohexyl and Cyclopentyl Carbon–Nitrogen π Systems with Hydride Reagents[1]

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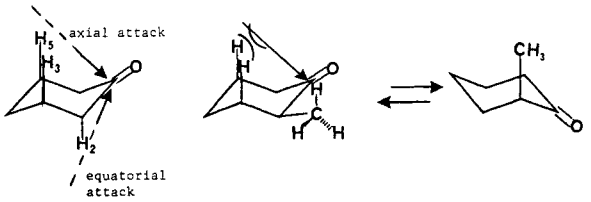
Reductions of 3- and 4-substituted cyclohexyl imines, iminium salts, and enamines (via iminium ions) with various hydride reagents reveal that while small reagents ($NaBH_4$, $NaBH_3CN$) favor axial approach as observed with the corresponding ketones, even moderately bulky reagents (i.e., acetoxyboranes) attack preferentially from the equatorial side. This is in direct contrast to the results observed for the same reagents with the corresponding ketones and is interpreted as implying that additional steric interactions induced by the nitrogen substituents encumber axial attack by substituted hydride reagents and force approach from the equatorial direction. The very bulky tri-*sec*-butylborohydride anion affords highly stereodiscriminating equatorial attack. Reductions of 2-alkylcyclohexyl and 2-alkylcyclopentyl imines and enamines also proceed with high stereoselectivity to give *cis*-2-alkyl cyclic amines with both hindered and unhindered reagents. This is interpreted to be the result of (1) augmented steric interactions between nitrogen substituents and equatorial 2-alkyl groups (1,3-allylic strain) which induces conformational changes to favor the axial 2-alkyl conformer and (2) hindrance toward equatorial approach by reagents induced by axial alkyl substituents. The result is that equatorial approach is favored with equatorial 2-alkyl conformers and preferential axial approach with axial 2-alkyl conformers, leading to stereoselective production of *cis*-2-alkylamines. *trans*-2-*n*-Propyl-4-*tert*-butylcyclohexanone is reduced by $LiBH(sec\text{-}Bu)_3$ preferentially from the axial direction in contrast to the usual highly selective equatorial attack observed with other cyclohexanones.

Unraveling the mechanism and stereochemistry of cyclic ketone reductions has occupied the interests of chemists for almost 3 decades and has been the subject of numerous and diverse investigations.[2] Although several explanations have been suggested to account for the observed trends in stereoisomer profiles obtained, none are completely satisfactory for all situations. Nevertheless, several general conclusions emerge which allow at least qualitative predictions of the expected stereochemistry outcome in the reductions of cyclohexanones. Thus, the preferred direction of ring attack (axial or equatorial) depends on both the bulkiness of the hydride reagent and the steric environment surrounding the carbonyl. With simple, unhindered cyclohexanones, small reagents such as $NaBH_4$ and $LiAlH_4$ favor approach from the axial direction, leading to a predominance of the equatorial alcohols. For instance, 4-*tert*-butylcyclohexanone affords 83–92% *trans*-4-*trans*-

Chart I



(1) Presented at the 14th Central Regional Meeting of the American Chemical Society, Midland, MI, June 1982.

(2) For recent, excellent reviews concerning the mechanism and factors controlling the stereochemistry of ketone reductions see: (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (b) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. (c) Hajos, A. "Complex Hydrides"; Elsevier: New York, 1979; Chapter 12. (d) See also: Giddings, M. R.; Hydec, J. *Can. J. Chem.* **1981**, *59*, 459. (e) Cieplak, A. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

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