72% isolated yield; $[\alpha]^{23}_D$ +25.2° (c 2, MeOH); 85% ee.

Hydroboration of 2-Methyl-4,5-dihydrofuran with 4-^{d}Icr$_2$BH. The reaction (25-mmol scale) was done as described under *cis*-3-hexene at 0 °C for 8 h. The trialkylborane (^{11}B NMR δ 86.4) was oxidized and the reaction mixture worked as described above to afford 1.9 g of *trans*-2-methyl-3-hydroxytetrahydrofuran, (74% isolated yield): bp 91–92 °C (15 mm); $[\alpha]^{23}_D$ −29.91° (c 2.5, MeOH); 70% ee.

Hydroboration of 3,4-Dihydro-2*H*-pyran with 4-^{d}Icr$_2$BH. To a stirred suspension of 4-^{d}Icr$_2$BH (25 mmol, 7.2 g) in 15.5 mL of THF was added 4.6 mL (50 mmol) of 3,4-2*H*-dihydropyran at 0 °C. The reaction mixture was stirred for 240 h at 0 °C, methanolyzed (80% of 4-^{d}Icr$_2$BH reacted), oxidized, and worked up as described under *trans*-3-hexene to afford 1.47 g of 3-hydroxytetrahydropyran (58% isolated yield), bp 90 °C (20 mm). Preparative GC was done using columns c and d to furnish GC-pure material: $[\alpha]^{23}_D$ +1.35° (neat), 11% ee.

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Chiral Synthesis via Organoboranes. 18. Selective Reductions. 43. Diisopinocampheylchloroborane as an Excellent Chiral Reducing Reagent for the Synthesis of Halo Alcohols of High Enantiomeric Purity. A Highly Enantioselective Synthesis of Both Optical Isomers of Tomoxetine, Fluoxetine, and Nisoxetine

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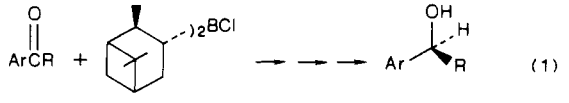
Diisopinocampheylchloroborane, ^{d}Ipc$_2$BCl, reduces ring and chain substituted haloaralkyl ketones to the corresponding halo alcohols in excellent enantiomeric excess. In certain cases these alcohols can be upgraded by simple methods to essentially 100% ee. For instance, (+)- or (−)-3-chloro-1-phenyl-1-propanol is initially obtained in 97% ee. Simple recrystallization then furnishes the pure enantiomers. These chiral halo alcohols are highly versatile intermediates. They can be readily cyclized to oxiranes and 2-substituted tetrahydrofurans with retention of chirality. Utilizing this methodology, we have developed an efficient, highly enantioselective synthesis of both optical isomers of the antidepressant drugs, Tomoxetine, Fluoxetine, and Nisoxetine, from the common intermediates (+)- or (−)-3-chloro-1-phenyl-1-propanol.

We[3-5] and others[6] have recently demonstrated the utility of chirally modified tri- and tetragonal boron compounds for the asymmetric reduction of prochiral ketones. In particular, we have shown that diisopinocampheylchloroborane, ^{d}Ipc$_2$BCl, (the symbol *d* indicates that the reagent is derived from (+)-α-pinene), enantioselectively reduces prochiral aralkyl ketones to the corresponding alcohols[3] (eq 1). We have further discovered that certain α-*tert*-



(1)

alkyl ketones can be similarly chirally reduced.[4] In these initial investigations we restricted ourselves to relatively simple ketones. However, difunctional chiral alcohols would be more valuable for the elaboration of complex compounds. With this in mind, we turned our attention to more suitably functionalized ketones, in particular, to various halo ketones.

Table I. Asymmetric Reductions of Haloaralkyl Ketones with ^{d}Ipc$_2$BCl in THF at −25 °C

	halo alcohol product[a]		cyclized product % ee
	% ee[b]	abs config	
2-chloroacetophenone	96	*R*[d]	96
2-bromoacetophenone	86[c]	*R*[d]	86
2-iodoacetophenone	67[c]	*R*	67
2′-bromoacetophenone	99	(*S*)[e]	
4′-bromoacetophenone	97	(*S*)[e]	
3-chloropropiophenone	97	(*S*)[e]	
4-chloropropiophenone	98	(*S*)[e]	
2,2′,4′-trichloroacetophenone	93	(*R*)[d,f]	
1-(4-bromophenyl)-4-chlorobutyrophenone	98	(*S*)[e]	98[f]

[a] Chemical yields of the alcohols were all in the 70–85% range. [b] Determined by capillary GC analysis of [*R*]-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate. [c] Determined by conversion to the epoxide and measuring the rotation. [d] See ref 9. [e] By analogy to the reduction of acetophenone and propiophenone: ref 3. [f] By analogy to the cyclization of 2-chloroacetophenone.

Results and Discussion

It has been demonstrated that the chiral reduction of 2-haloacetophenones with chirally modified boron reagents

(1) Part of this work was carried out at the Aldrich Chemical Company, Sheboygan Falls, WI.
(2) Postdoctoral research associate on ARO Grant DAAG 29-82-K-0047.
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(6) For leading references, see: (a) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollman, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402. (b) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, *2039*. (c) Soai, K.; Oyamada, H.; Yamanoi, T. *J. Chem. Soc., Chem. Commun.* **1984**, 413. (d) Midland, M. M. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 45. (e) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157. (f) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9.

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is influenced by the nature of the halogen substituent.[7,8] Thus in the reduction of 2-haloacetophenones with neat Alpine-Borane, the chlorohydrin is obtained in 96% ee, the bromohydrin in 93% ee, and the iodohydrin 83% ee.[7] In order to determine whether similar trends are operating with $^{d}Ipc_2BCl$, we initiated our present studies with the chiral reduction of 2-haloacetophenones. The results are summarized in Table I, entries 1–3. However, at this stage of the investigation, no attempt was made to isolate the compounds (vide infra), but rather to determine the extent and scope of chiral induction by unambiguous analytical methods.

The reduction of acetophenone with $^{d}Ipc_2BCl$ gives the *S* enantiomer predominantly.[3] The 2-haloacetophenones, however, give the *R* enantiomer.[9] The reduction of 2-chloroacetophenone in 95% ee is clearly superior to the results obtained with the bromide, 80% ee, or the iodide, 65% ee. This is not surprising and is in accord with the steric model proposed for this type of reduction.[3] As the steric requirements of the halide increases from chloride to iodide, the discrimination between R_L and R_S decreases, resulting in decreased selectivity in the transition state and decreased optical induction. On the other hand, placing the halide on the aromatic ring, as in 2-bromoacetophenone, would be expected to increase the steric demands of the ring and increase the % ee relative to the unsubstituted compound. This indeed is the case. The reduction of 2-bromoacetophenone with $^{d}Ipc_2BCl$ furnishes the alcohol in 99% ee (Table I, entry 4). However, placing the bromide in the para position furnishes the corresponding alcohol in 97% ee, identical with the parent compound[3] (Table I, entry 5).

We next investigated the effect on optical induction by varying the position of the halide substituent on the alkyl sidechain. Thus, reduction of 3-chloropropiophenone and 4-chlorobutyrophenone gave the corresponding alcohols in 97% ee and 98% ee, respectively (Table I, entries 6 and 7). From the above examples we conclude that halosubstitution in the α-position of the side chain exerts somewhat greater influence on optical induction than in the ortho position of the aromatic ring. This is further corroborated with 2,2′,4′-trichloroacetophenone, which is reduced in 93% ee (Table I, entry 8).

These halo alcohols can also be efficiently cyclized. For instance, the chlorohydrin obtained from the reduction of 2-chloroacetophenone is cyclized to [*R*]-phenyloxirane of the same enantiomeric purity as the starting material. Similarly, cyclization of 4-chloro 1-*sec*-alcohols leads to 2-substituted tetrahydrofurans. Thus, [*S*]-1-(4-bromophenyl)-4-chlorobutanol furnishes [*S*]-2-(4-bromophenyl)tetrahydrofuran of the same enantiomeric purity as the chloro alcohol.

Having demonstrated the utility of chiral reductions with $^{d}Ipc_2BCl$, we next turned our attention to the application of this methodology. Tomoxetine [[*R*]-(−)-*N*-methyl-γ-(2-methylphenoxy)benzenepropamine hydrochloride, Lilly, LY 139603] is a new drug currently undergoing evaluation as a potential antidepressant.[10] The (−)-optical isomer has been shown to be nine times more potent than the (+)-isomer. Unlike chemical tricyclic antidepressants, e.g., imipramine, (−)-Tomoxetine has been shown to inhibit specifically norepinephrine uptake in humans at doses which are clinically well tolerated and to be a relatively weak ligand for α-1, α-2, and β-adrenergic receptors.[10] The latter receptors are generally regarded as responsible for undesirable side effects associated with antidepressants. The patent literature preparation of (−)-Tomoxetine involves a long and tedious procedure, culminating in a highly inefficient resolution (20%) of the racemic mixture.[11,12] Clearly an enantioselective preparation of (−)-Tomoxetine would be desirable. We have demonstrated that diisopinocampheylchloroborane, $^{d}Ipc_2BCl$, reduces haloaralkyl ketones in a highly enantioselective and predictable manner, furnishing the [*S*]-halo alcohols. We now describe a simple synthesis based on our methodology of (−)-Tomoxetine and (+)-Tomoxetine, as well as both enantiomers of the cognant compounds, Fluoxetine and Nisoxetine.

Table II. Physical Properties and Absolute Configurations of Tomoxetine and Analogues

compound	$[\alpha]^{25}_D$, deg (conc, solv)	abs config	mp, °C
(−)-tomoxetine hydrochloride	−43.1 (*c* 5.9, MeOH)	*R*	160–162
(+)-tomoxetine hydrochloride	+42.9 (*c* 6, MeOH)	*S*	160–162
(−)-nisoxetine hydrochloride	−52.0 (*c* 5, MeOH)	*S*	149–151
(+)-nisoxetine hydrochloride	+51.88 (*c* 4.8, MeOH)	*R*	149–150
(−)-fluoxetine hydrochloride	−3.04 (*c* 5.9, MeOH) −15.52 (*c* 6, $CHCl_3$)	*R*	143–144
(+)-fluoxetine hydrochloride	+3.01 (*c* 5.8, MeOH) +15.83 (*c* 7.15, $CHCl_3$)	*S*	143–144

(−)-Tomoxetine Hydrochloride (9). [*S*]-(−)-3-Chloro-1-phenylpropanol is readily available by reduction of 3-chloropropiophenone with $^{d}Ipc_2BCl$, in 97% ee, $[\alpha]^{25}_D$ −25.26° (*c* 7.05, $CHCl_3$), mp 56–57 °C (Table I, 6). However, in the synthesis of biologically active compounds, it is desirable to attain enantiomerically pure compounds. We have found the simple recrystallization of the 97% ee [*S*]-(−)-3-chloro-1-phenylpropanol from hexane serves to upgrade the material to essentially 100% ee. Reaction of *o*-cresol in the presence of diethyl azodicarboxylate and triphenylphosphine (Mitsunobu conditions[13]) occurred with complete inversion at the benzylic carbon to furnish [*R*]-(−)-1-chloro-3-phenyl-3-(2-methylphenoxy)propane (**3**), $[\alpha]^{25}_D$ −21.7° (*c* 3.90, $CHCl_3$) as an oil in 70% yield. Treatment of this compound with excess aqueous methylamine in ethanol followed by conversion to the hydrochloride (ethereal hydrogen chloride) gave (−)-Tomoxetine hydrochloride (**9**), $[\alpha]^{25}_D$ −43.1° (*c* 5.9 MeOH), mp 158–160 °C (Scheme I). On the basis of our rotation, the compound reported in the literature is only 88% optically pure.[14] In a completely analogous manner we synthesized (+)-Tomoxetine starting with [*R*]-(+)-3-

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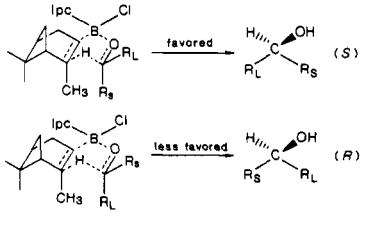
(8) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615.
(9) The *R* configuration of the product halohydrins is a consequence of the Cahn–Ingold–Prelog convention rather than a change in the mode of attack.



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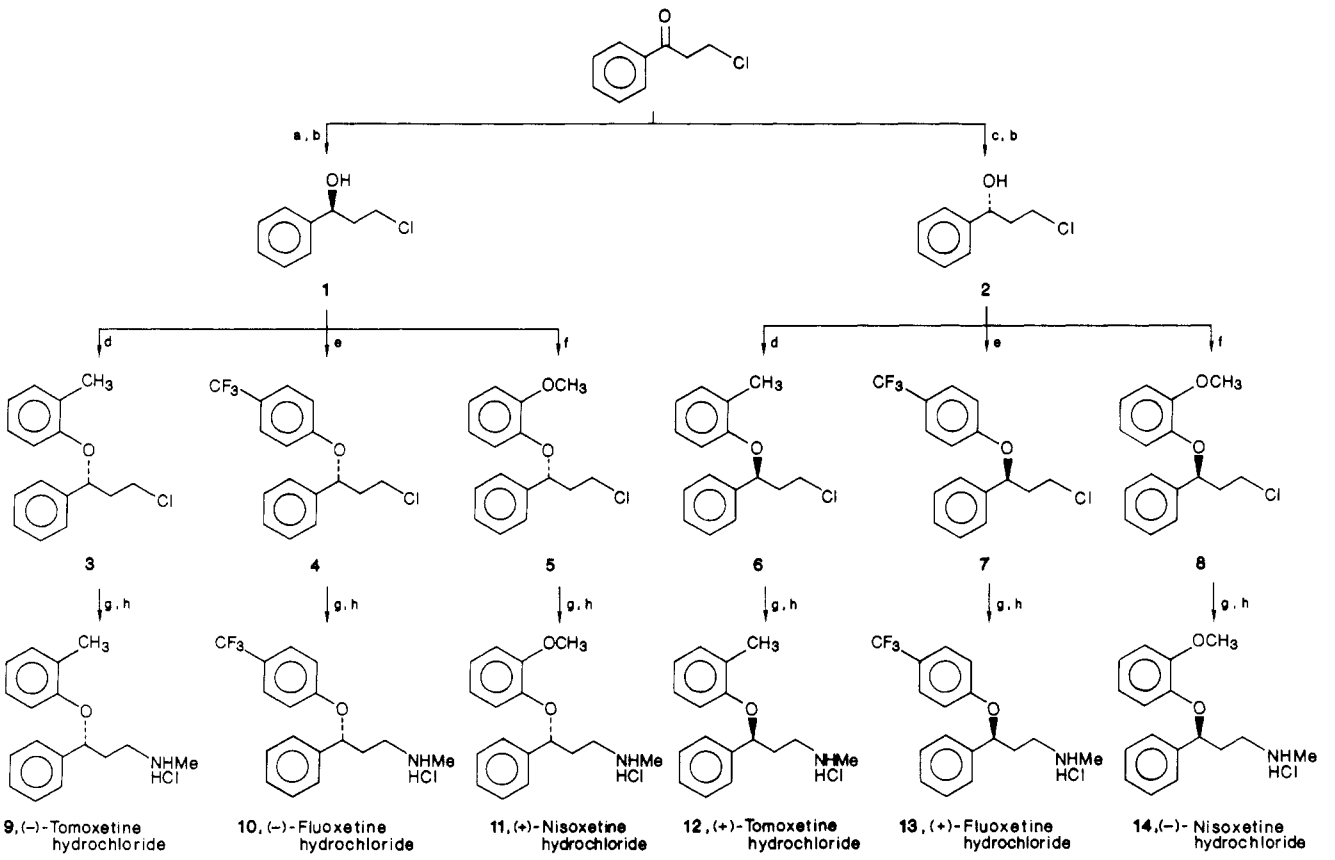
(11) Foster, B. J.; Lavagnino, E. R. Eur. Pat. 0052492, 1982; *Chem. Abstr.* **1982**, *97*, 215718d.
(12) Molloy, B. B.; Schmiegel, K. K. U. S. Pat. 4018895, 1977; *Chem. Abstr.* **1977**, *87*, 1345207.
(13) Mitsunobu, O. *Synthesis* **1981**, 1.
(14) Reference 12: $[\alpha]^{25}_D$ −38.1° (*c* 10, MeOH); mp 165–167 °C.

Scheme I[a]



[a] (a) $^{d}Ipc_2BCl$ (the symbol *d* refers to the reagent derived from (+)-α-pinene; (b) recrystallization; (c) $^{l}Ipc_2BCl$ (the symbol *l* refers to the reagent derived from (−)-α-pinene); (d) *o*-Cresol, DEAD, Ph_3P; (e) *p*-(trifluoromethyl)cresol, DEAD, Ph_3P; (f) Guaiacol, DEAD, Ph_3P; (g) aqueous $MeNH_2$, EtOH; (h) ethereal HCl.

chloro-1-phenylpropanol (Scheme I).

(−)-Fluoxetine Hydrochloride (10). (±)-*N*-Methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropamine hydrochloride is a widely used and selective inhibitor of serotonin uptake[15] and has been shown to be chemically effective for the treatment of mental depression.[16] In accord with the proposed mode of action, the (+)-enantiomer was found to be only slightly more active than the (−)-enantiomer. In a manner analogous to the preparation of (+)-Tomoxetine, we treated [*S*]-3-chloro-1-phenylpropanol with *p*-(trifluoromethyl)cresol to yield [*R*]-(+)-1-chloro-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propanol (**4**), $[\alpha]^{25}_{D}$ +2.3° (*c* 10.0, $CHCl_3$). Subsequent treatment with excess methylamine in ethanol, followed by ethereal hydrogen chloride, furnished (−)-Fluoxetine hydrochloride. The physical and optical properties of both enantiomers of Fluoxetine are summarized in Table II.

Nisoxetine Hydrochloride (11). The *o*-methoxy analogue of Tomoxetine is a potent inhibitor of norepinephrine and serotonin uptake.[17] Only recently has (±)-Nisoxetine been resolved into enantiomers and the optical isomers evaluated for norepinephrine uptake inhibition.[18] The absolute configuration of the enantiomers, however, has heretofore not been determined.[19] Applying our enantioselective synthesis to Nisoxetine hydrochloride, we have now correlated the absolute configurations and rotations. The results are summarized in Table II.

Conclusion

We have demonstrated that diisopinocampheylchloroborane,[20] $^{d}Ipc_2BCl$, is an excellent chiral reducing reagent for haloaralkyl ketones. The corresponding halo alcohols are generally obtained in >90% ee. In certain cases, i.e., 3-chloro-1-phenyl-1-propanol, which is initially obtained in 97% ee, can be upgraded to essentially 100% ee by simple recrystallization. In turn, 3-chloro-1-phenyl-1-propanol provides access to a highly enantioselective synthesis of the antidepressant agents Tomoxetine, Fluoxetine, and Nisoxetine. These halo alcohols can also be cyclized to oxiranes[21] and 2-substituted tetrahydrofurans[21] of the same enantiomeric purities as those of the starting alcohols.

Experimental Section

General Methods. Melting points and boiling points are uncorrected. ^{13}C NMR spectra were obtained on a Varian FT-80A spectrometer (20.00 MHz) relative to TMS. GC analysis was done on a Hewlett-Packard 58902 gas chromatograph using a Supelcowax glass capillary column (15 m) and integrated using a Hewlett-Packard 3390A integrator. Mass spectra were recorded

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(16) (a) Chovinard, G. A. *Clin. J. Psychiatry* **1985**, *46*, 32. (b) Stark, P.; Hardison, C. D. *Ibid.* **1985**, *46*, 53.
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(19) Oberlender, R.; Nichols, D. E.; Ramachandran, P. V.; Srebnik, M. *J. Pharm. Pharmacol.* **1987**, *39*, 1055.
(20) Both enantiomers of Ipc_2BCl are currently available from the Aldrich Chemical Company; see also ref 6f.
(21) Bartok, M.; Lang, K. L. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulfur Analogues*; Patai, S., Ed.; Wiley: Chichister, 1980; Supplement E, Chapter 14.

with a Finnigan gas chromatograph–mass spectrometer Model 4000. Elemental analyses were done in house. Optical rotations were recorded on a Rudolph Polarimeter Autopol III. Reduction of ketones were carried out as described in the literature.[3]

Materials. Tetrahydrofuran (Fisher), THF, was distilled from benzophenone ketyl and stored under nitrogen in an ampule. Diethyl ether (Mallinckrodt), ethyl acetate (Mallinckrodt), dichloromethane (Mallinckrodt), pentane (Phillips), hexane (Fisher) were used as received. Anhydrous ethereal hydrogen chloride was prepared from hydrochloric acid and sulfuric acid by using a Brown gasimeter.[22] *o*-Cresol, α,α,α-trifluoro-*p*-cresol, guaiacol, triphenylphosphine, diethyl azodicarboxylate, and aqueous methylamine were purchased from the Aldrich Chemical Company. Reactions were monitored wherever possible by TLC using Whatman precoated silica plates. Neutral alumina (J. T. Baker & Company, column chromatography) was used for column chromatography.

Determination of Enantiomeric Excess. The enantiomeric excess, ee, of the halo alcohols in the initial part of this study was determined by conversion to the MTPA esters, followed by analysis on a methyl silicone column (50 m) or Supelcowax column (15 m). In all cases racemic alcohols gave baseline separations and 1:1 ratios of integrated areas.

Recrystallization and Optical Upgrading of [*S*]-(−)-3-Chloro-1-phenylpropanol (1). [*S*]-3-Chloro-1-phenylpropanol (5 g, 29.3 mmol) (**1**) was dissolved in a minimum amount of hexane and allowed to stand at 0 °C overnight. The white crystals were filtered and washed with cold pentane to afford **1**: yield, 4.25 g, 85%; mp 60–62 °C; $[\alpha]^{23}_D$ −26.04 (*c* 7.00, $CHCl_3$). Analysis of the [*R*]-(+)-MTPA ester on methyl silicone (50 m, 180 °C) showed one peak.

[*R*]-(−)-1-Chloro-3-phenyl-3-(2-methylphenoxy)propane (3). Triphenylphosphine (5.25 g, 20 mmol) and ethyl azodicarboxylate (3.15 mL, 3.48 g, 20 mmol) were added to a solution of [*S*]-3-chloro-1-phenylpropanol (**1**) (3.4 g, 20 mmol) and *o*-cresol (2.06 mL, 2.16 g, 20 mmol) in THF (50 mL). The mixture was stirred at room temperature overnight when the reaction was complete (TLC). THF was removed under aspirator vacuum and the residue triturated with pentane (3 × 50 mL). The combined pentane fractions were concentrated, and the residue was chromatographed on neutral alumina. Elution with pentane and removal of solvent afforded 3.6 g (70%) of the chloro ether **3** as a thick liquid, which was found to be 99% pure by GC: bp 180–200 °C (0.5 mm); $[\alpha]^{23}_D$ −21.7° (*c* 3.9, $CHCl_3$); ^{13}C NMR δ 150.67, 147.81, 141.28, 128.76, 127.98, 125.32, 122.23, 120.96, 117.35, 112.71, 59.02, 56.07, 41.61; mass spectrum (EI), *m/z* (relative intensity) 260/262 (1, M^+), 224 (1, M − HCl), 153 (21, M − C_7H_8O), 91 (100, C_7H_7), (CI) 261 (7.4, M^+ + H), 153/155 (100, M^+ + H − C_7H_8).

[*R*]-(−)-Tomoxetine Hydrochloride (9). To the chloro ether **3** (2.6 g, 10 mmol) in a Paar "mini-reactor" was added aqueous methylamine (40%, 20 mL). Ethanol (10 mL) was added as cosolvent and the solution heated at 130 °C for 3 h. The solution was cooled to room temperature, and the mixture was poured on water (150 mL) and extracted with ether. The ether extract was washed with water and brine and dried ($MgSO_4$). HCl in EE (5 mL of 3.2 M, 16 mmol) was added to the decanted solution, and the solid which separated was crystallized from a mixture of dichloromethane and ethyl acetate: yield, 2.4 g (95%); mp 158–160 °C; $[\alpha]_D$ −43.1° (*c* 5.9, MeOH); ^{13}C NMR δ 155.45, 140.26, 130.85, 128.90, 128.10, 126.95, 126.72, 125.91, 120.91, 113.16, 77.08, 46.26, 34.59, 32.87, 16.53; mass spectrum (EI), *m/z* (relative intensity) 44 (100, CH_2NHMe), (CI) 312 (5, M^+ + C_4H_9), 256 (100). Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.98; H, 7.55; Cl, 12.18; N, 4.8. Found: C, 69.69; H, 7.73; Cl, 12.20; N, 4.72.

[*S*]-(+)-1-Chloro-3-phenyl-3-(2-methylphenoxy)propane (6). This chloro ether was prepared by using the same procedure as for the preparation of **3** using [*R*]-3-chloro-1-phenylpropanol (**2**) (3.4 g, 20 mmol), *o*-cresol (2.06 mL, 20 mmol), triphenylphosphine (5.25 g, 20 mmol), and diethyl azodicarboxylate (3.15 mL, 20 mmol) in THF (50 mL). Workup gave **6** (3.5 g, 68%) as a thick liquid: bp 180–200 °C (0.5 mm); $[\alpha]^{23}_D$ +21.7° (*c* 3.9, $CHCl_3$); ^{13}C NMR and the mass spectra were identical with those of **3**.

(22) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

[*S*]-(+)-Tomoxetine Hydrochloride (12). [*S*]-(+)-Tomoxetine hydrochloride was prepared by using the same procedure as for the preparation of the *R*-(−)-isomer using the chloro ether **6** and excess aqueous methylamine in a "mini-reactor" at 130 °C for 3 h. Workup provided 95% [*S*]-(+)-Tomoxetine hydrochloride: mp 158–160 °C, $[\alpha]^{23}_D$ +42.9° (*c* 6, MeOH). All spectral data are identical with those of [*R*]-(−)-Tomoxetine hydrochloride **9**. Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.98; H, 7.55; Cl, 12.18; N, 4.8. Found: C, 69.1; H, 7.9; Cl, 12.29; N, 4.91.

[*R*]-(+)-1-Chloro-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propane (4). Compound **4** was prepared by using a similar procedure as for the preparation of **3** using [*S*]-3-chloro-1-phenylpropanol (**1**) (2.57 g, 15 mmol), α,α,α-trifluoro-*p*-cresol (2.43 g, 15 mmol), triphenylphosphine (3.93 g, 14 mmol), and diethyl azodicarboxylate (2.36 mL, 15 mmol) in THF (40 mL) at room temperature. Workup gave **4** as a thick liquid: bp 180–200 °C (0.5 mm); $[\alpha]^{23}_D$ +2.3° (*c* 10, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 140.50, 129.39, 128.66, 127.56, 127.38, 127.19, 127.01, 126.34, 116.45, 77.82, 41.69, 41.38; mass spectrum (EI), *m/z* (relative intensity) 153/155 (45), 91 (100), (CI) 314/316, (1, M^+), 153/155 (100). Anal. Calcd for $C_{16}H_{14}ClNO$: C, 61.05; H, 4.45; Cl, 11.29; F, 18.12. Found: C, 61.06; H, 4.51; Cl, 11.16; F, 18.22.

[*R*]-(−)-Fluoxetine Hydrochloride (10). [*R*]-(−)-Fluoxetine hydrochloride was prepared by using a similar procedure as was used for [*R*]-(−)-Tomoxetine hydrochloride utilizing the chloro ether **4** (1.57 g, 5 mmol) and excess aqueous methylamine in ethanol as cosolvent in a "mini-reactor" at 130 °C for 3 h. Workup provided 1.55 g, 90%, of the recrystallized (CH_2Cl_2/EtOAc) Fluoxetine hydrochloride: mp 142–143 °C; $[\alpha]^{22}_D$ −3.01° (*c* 5.3, MeOH); $[\alpha]^{22}_D$ −15.52° (*c* 7.15, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 160.10, 139.46, 129.28, 128.66, 127.35, 127.16, 126.96, 126.77, 126.08, 116.26, 55.49, 46.32, 34.77, 33.13; mass spectrum (EI), *m/z* (relative intensity) 44 (100, CH_2NHMe), (CI) 310 (100, M^+ + H), 148 (12). Anal. Calcd for $C_{17}H_{19}ClF_3NO$: C, 59.05; H, 5.54; N, 4.05; F, 16.48; Cl, 10.25. Found: C, 59.02; H, 5.6; N, 4.13; F, 16.67; Cl, 10.5.

[*S*]-(−)-1-Chloro-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propane (7). The chloro ether **7** was prepared with [*R*]-(+)-3-chloro-1-phenylpropanol (**2**) (2.56 g, 15 mmol), α,α,α-trifluoro-*p*-cresol (2.43 g, 15 mmol), triphenylphosphine (3.93 g, 15 mmol), and diethyl azodicarboxylate (2.36 mL, 15 mmol) in THF (40 mL) at room temperature. Workup gave **7** as a thick liquid: yield, 3.07 g, 65%; bp 180–200 °C (0.5 mm); $[\alpha]_D$ −2.2° (*c* 12.5, $CHCl_3$); ^{13}C NMR and mass spectrum were identical with those of **4**.

[*S*]-(+)-Fluoxetine Hydrochloride 13. [*S*]-(+)-Fluoxetine hydrochloride was prepared by a similar procedure as was used for **10**, utilizing the chloro ether **7** (1.59 g, 5 mmol) and excess aqueous methylamine in ethanol as cosolvent in a "mini-reactor" at 130 °C for 3 h. Workup provided 1.55 g (93%) of the recrystallized (CH_2Cl_2/EtOAc) **13**, mp 142–143 °C; $[\alpha]^{22}_D$ +3.04° (*c* 5.9, MeOH), $[\alpha]^{22}_D$ +15.83° (*c* 6, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 160.08, 139.44, 129.26, 128.64, 127.30, 127.12, 126.76, 116.25, 77.48, 46.32; 34.77, 33.14; mass spectrum (EI), *m/z* (relative intensity) 44 (100, CH_2NHMe), (CI) 310 (100, M^+ + H), 148 (12). Anal. Calcd for $C_{17}H_{19}ClF_3NO$: C, 59.05; H, 5.54; N, 4.05; F, 16.48; Cl, 10.25. Found: C, 58.70; H, 5.58; N, 4.29; F, 16.38; Cl, 10.35.

[*R*]-(+)-1-Chloro-3-phenyl-3-(2-methoxyphenoxy)propane (5). The chloro ether **5** was prepared by a procedure similar to the one used for the preparation of **3** using [*S*]-(−)-3-chloro-1-phenylpropanol (**1**) (1.71 g, 10 mmol), guaiacol (1.1 mL, 10 mmol), Ph_3P (2.62 g, 10 mmol), and diethyl azodicarboxylate (1.57 mL, 10 mmol) in THF (40 mL) at room temperature. Workup and chromatography with neutral alumina (hexane/ethyl acetate, 97:3) gave 1.7 g, 62%, of **5** as a thick liquid, bp 180–200 °C (0.5 mm). The liquid, upon cooling, solidified and could be recrystallized from pentane: mp 59–61 °C; $[\alpha]^{23}_D$ +40.96° (*c* 7.8, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 150.67, 147.81, 141.28, 128.76, 127.98, 126.32, 122.23, 120.96, 117.35, 112.71, 79.02, 56.07, 41.61; mass spectrum (EI), 276/278 (1, M^+), 240 (M^+ − HCl), 260/262 (M − CH_4), 91 (100), 124 (82), (CI) 277/279 (13.6, M^+ + H), 153/155 (100). Anal. Calcd for $C_{17}H_{22}ClNO_2$: C, 69.44; H, 6.15; Cl, 12.84. Found: C, 69.67; H, 6.3; Cl, 12.65.

[*R*]-(+)-Nisoxetine Hydrochloride (11). [*R*]-(+)-Nisoxetine hydrochloride was prepared by a procedure similar to the one used for **4**, using the chloro ether **5** (1.35 g, 5 mmol) and excess aqueous methylamine in ethanol (1 mL) in a "mini-reactor" at 130 °C for

3 h. Workup gave 1.41 g (91%) of recrystallized (CH_2Cl_2/EtOAc) **11**: mp 149–150 °C; $[\alpha]_D$ +51.88° (*c* 4.8, MeOH); ^{13}C NMR δ 150.00, 140.18, 129.29, 129.07, 128.58, 126.14, 123.03, 121.32, 117.29, 112.23, 81.83, 56.44, 47.56, 34.20, 33.19; mass spectrum (EI), *m/z* (relative intensity) 167, 44 (100), 148 (8), (CI) 272 (100, M^+). Anal. Calcd for $C_{17}H_{22}ClNO_2$: C, 66.34; H, 7.15; N, 4.55; Cl, 11.5. Found: C, 66.08; H, 5.29; N, 4.66; Cl, 11.59.

[*S*]-(−)-Chloro-3-phenyl-3-(2-methoxyphenoxy)propane (8). Chloro ether **8** was prepared by a procedure similar to the one used for **5**: yield, 1.64 g (60%); mp 59–61 °C; $[\alpha]^{23}_D$ −41.6° (*c* 3, $CHCl_3$); ^{13}C NMR and mass spectrum were identical with those of **5**.

[*S*]-(−)-Nisoxetine Hydrochloride (14). [*S*]-(−)-Nisoxetine hydrochloride was prepared by a procedure similar to the one used for **11**: yield, 1.41 g (91%); mp 149–151 °C; $[\alpha]^{23}_D$ −52° (*c* 5, MeOH); ^{13}C NMR and mass spectra were identical with those of **11**.

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Registry No. **1**, 100306-34-1; **2**, 100306-33-0; **3**, 114446-47-8; **4**, 114446-48-9; **5**, 114446-49-0; **6**, 114446-50-3; **7**, 114446-51-4; **8**, 114446-52-5; **9**, 82248-59-7; **10**, 114247-09-5; **11**, 114446-53-6; **12**, 82857-39-4; **13**, 114247-06-2; **14**, 114446-54-7; $^dIpc_2BCl$, 85116-37-6; $^zIpc_2BCl$, 112246-73-8; 4′-bromo-4-chlorobutyrophenone, 4559-96-0; 2-chloroacetophenone, 532-27-4; 2-bromoacetophenone, 70-11-1; 2-iodoacetophenone, 4636-16-2; 2′-bromoacetophenone, 2142-69-0; 4′-bromoacetophenone, 99-90-1; 3-chloropropiophenone, 936-59-4; 4-chloropropiophenone, 6285-05-8; 2,2′,4′-trichloroacetophenone, 4252-78-2; [*R*]-2-chloro-1-phenylethanol, 56751-12-3; [*R*]-2-bromo-1-phenylethanol, 73908-23-3; [*R*]-2-iodo-1-phenylethanol, 85611-59-2; [*S*]-1-(2-bromophenyl)ethanol, 114446-55-8; [*S*]-1-(4-bromophenyl)ethanol, 100760-04-1; [*S*]-2-(4-bromophenyl)-tetrahydrofuran, 114446-56-9; [*S*]-4-chloro-1-phenylbutanol, 65488-06-4; [*R*]-1-(2,4-dichlorophenyl)-2-chloroethanol, 114446-57-0; [*S*]-1-(4-bromophenyl)-4-chlorobutanol, 114446-58-1; [*R*]-phenyloxirane, 20780-53-4; *o*-cresol, 95-48-7; α,α,α-trifluoro-*p*-cresol, 402-45-9; guaiacol, 90-05-1.

Relative Reactivities of Acetals and Orthoesters in Lewis Acid Catalyzed Reactions with Vinyl Ethers. A Systematic Investigation of the Synthetic Potential of Acetals and Orthoesters in Electrophilic Alkoxyalkylations of Enol Ethers

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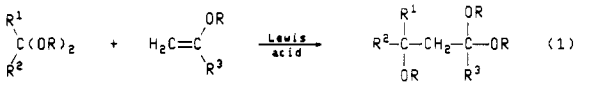
The relative reactivities of acetals and orthoesters in BF_3·OEt_2-catalyzed reactions with methyl vinyl ether (−78 °C, CH_2Cl_2) have been determined by competition experiments. A reactivity increase by 5 orders of magnitude was found in the series: saturated acetals < methyl orthoformate < benzaldehyde acetals < α,β-unsaturated acetals; formaldehyde acetals as well as orthoacetates and orthobenzoates did not react under these conditions. The k_{rel} values of the para-substituted benzaldehyde acetals follow a Hammett σ correlation (ρ = −4.6). Whereas the k_{rel} values of the aldehyde acetals are correlated with the corresponding rate constants of acid-catalyzed hydrolyses, ketals and orthoesters deviate from this correlation. It is concluded that the k_{rel} listing in Scheme II can be used to predict the results of Lewis acid catalyzed additions of acetals and orthoesters toward vinyl ethers: The formation of 1:1 addition products may only be expected, if the relevant functional group of the reactants is listed below the functional group of the potential 1:1 products.

Müller-Cunradi and Pieroh discovered in 1939 that acetals react with enol ethers in the presence of a Lewis acid to give 3-alkoxyacetals.[1] This reaction, which was later suggested to proceed via carbocationic intermediates,[2] has become an important method in organic synthesis.[3] Isler's carotine synthesis, for example, employs additions of unsaturated acetals to ethyl vinyl ether and ethyl propenyl ethers as key steps for the construction of the polyene fragment.[4]

Hoaglin and Hirsch[2] have already recognized that reaction 1 is not generally appplicable for the synthesis of 1:1 addition products, since the adducts **3** may add to the double bond of **2** in a similar manner as **1**, thus leading to the formation of higher adducts. As the yield of the



1 2 3

1:1 adducts **3** depends on the relative reactivity of the acetals **1** and **3** toward vinyl ethers, several papers were addressed to the relationship between structure and reactivity of acetals.[5] In an excellent review, Povarov has interpreted the results of acetal and orthoester additions to enol ethers in terms of relative reactivities of reactants and products using the qualitative reactivity sequence: saturated acetals < aromatic acetals ≈ ortho esters < α,-

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