this may represent the first demonstration of strong coordination of a trifluoromethyl group to an organometallic compound.

Experimental Section

^{1}H NMR spectra were measured at 90 MHz on a Hitachi R-90H instrument. Chemical shifts were given relative to that of internal Me_4Si. Infrared spectra were recorded on a JASCO A-202 instrument. Mass spectra were recorded with a RMU-6MG instrument. High pressure liquid chromatography (HPLC) analyses were performed with a Tosoh PX-8010 instrument. All reactions were conducted under an atmosphere of dry argon. All solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; hexane and toluene were distilled from $LiAlH_4$; dichloromethane was distilled from calcium hydride. Preparative thin layer chromatography was performed with E. Merck silica gel plates (60F-254).

2-(Trifluoromethyl)propiophenone (1). To a solution of 3 mL (28.8 mmol) of 2-(trifluoromethyl)propanal in 30 mL of ether was added 14.4 mL of a 2.2 M solution of phenyllithium (31.7 mmol) in ether slowly at -78 °C. After being gradually warmed to room temperature, the mixture was quenched with 30 mL of 2 N HCl. The mixture was extracted with two 50-mL portions of ether, and the combined ether layers were dried and concentrated to give an oil. This crude product was chromatographed on silica gel, using 40:1 hexane/ethyl acetate as eluent, to obtain 4.57 g (78%) of a mixture of two diastereomers of 1-phenyl-2-(trifluoromethyl)-1-propanol. To a suspension of 5.3 g (24.6 mmol) of PCC and 5.3 g of Celite in 50 mL of dichloromethane was added 4.57 g (22.4 mmol) of the mixture of two diastereomers of 1-phenyl-2-(trifluoromethyl)-1-propanol without separation. After being stirred for 12 h, the reaction mixture was filtered through Florisil. The Florisil was washed with ether and the solvent was removed in vacuo. The residue was chromatographed on silica gel with 60:1 hexane/ethyl acetate as eluent to give 2.71 g (60%) of 1. IR (neat): 3100, 3050, 2950, 1695, 1600, 765, 705, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.3-8.1 (m, 5 H), 4.0-4.5 (m, 1 H), 1.47 (d, 3 H, J = 7.3 Hz). MS (70 eV): m/e (relative intensity) 202 (M^+, 2), 182 (4), 106 (8), 105 (100), 77 (51), 51 (16), 50 (5). Anal. Calcd for $C_{10}H_9OF_3$: C, 59.41; H, 4.49. Found: C, 59.42; H, 4.50.

General Procedure. Two general procedures were employed for the reduction of 1. The following experimental procedures are representative.

(1*S,2*R**)-1-Phenyl-2-(trifluoromethyl)-1-propanol (2).** To a solution of 26.9 mg (0.13 mmol) of 1 in 2 mL of ether was added 0.11 mL of a 1.77 M solution of $MeAlCl_2$ (0.19 mmol) in hexane slowly at -78 °C. After 15 min at -78 °C, 14.5 mg (0.67 mmol) of $LiBH_4$ was added. After being gradually warmed to room temperature, the mixture was quenched by the slow addition 2 mL of 2 N HCl. The mixture was extracted with two 2-mL portions of ether and the combined organic layers were dried and concentrated. The residue was chromatographed on preparative TLC with 4:1 hexane/ethyl acetate to give 20.4 mg (75%) of a 99:1 mixture of 2 and 3. IR (neat): 3450, 1465, 1260, 1170, 765, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32-7.40 (m, 5 H), 4.81 (dd, 1 H, J = 3.0, 8.1 Hz), 2.58-2.70 (m, 1 H), 2.17 (d, 1 H, J = 3.0 Hz), 0.87 (d, 3 H, J = 7.2 Hz). MS (70 eV): m/e (relative intensity) 204 (M^+, 1), 107 (100), 79 (47), 77 (25). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.82; H, 5.43. Found: C, 58.82; H, 5.33.

(1*R,2*R**)-1-Phenyl-2-(trifluoromethyl)-1-propanol (3).** To a solution of 15.6 mg (0.077 mmol) of 1 and 0.083 mL (0.31 mmol) of Bu_3SnH in 2 mL of toluene was added 0.14 mL of a 1.1 M solution of Et_3Al (0.15 mmol) in toluene slowly at -78 °C. After 2 h at -78 °C, 30 mg of NaF, a drop of water, and 1 mL of dichloromethane were added to the mixture. The mixture was warmed to room temperature and a precipitate was filtered. The filtrate was dried and concentrated. The residue was chromatographed on preparative TLC with 4:1 hexane/ethyl acetate to give 10.5 mg (67%) of a 15:85 mixture of 2 and 3. IR (neat): 3500, 1275, 1140, 990, 760, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.25-7.40 (m, 5 H), 5.24 (t, 1 H, J = 3.0 Hz), 2.40-2.52 (m, 1 H), 1.94 (d, 1 H, J = 3.5 Hz), 1.09 (d, 3 H, J = 7.1 Hz). MS (70 eV): m/e (relative intensity) 204 (M^+, 2), 108 (8), 107 (100), 79 (50), 77 (23), 28 (15). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.82; H, 5.43. Found: C, 58.78; H, 5.44.

Friedel-Crafts Synthesis of 4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenone, a Key Intermediate in the Preparation of the Antidepressant Sertraline

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Sertraline, a potent competitive inhibitor of synaptosomal serotonin uptake,[1] has demonstrated excellent efficacy as an antidepressant.[2] A key intermediate in the synthesis of sertraline is tetralone **5**, which was originally prepared in five steps and 8% overall yield from 3,4-dichlorobenzoyl chloride.[3] In this route, a Stobbe reaction on 3,4-dichlorophenyl ketone was utilized to assemble all of the necessary carbon atoms. Decarboxylation and subsequent reduction of the Stobbe product gave diaryl acid **4**, which was converted into **5** with a Friedel-Crafts cyclization. A more efficient preparation of **5** was conceived, which employed Friedel-Crafts reactions to construct all of the carbon-carbon bonds. Initially, this new synthesis of **5** was achieved in four steps but was further consolidated into three steps by performing a double Friedel-Crafts reaction.

Results and Discussion

Keto acid **2** had been prepared in 58% yield by the Friedel-Crafts reaction of 1,2-dichlorobenzene and succinic anhydride.[4] The reported yield of **2** was increased to 92% by using 3 equiv of aluminum chloride.[5] The regioisomeric keto acid **1** was prepared in modest yield by lithiation of 1,2-dichlorobenzene and condensation with succinic anhydride. Friedel-Crafts acylation was shown to be highly regioselective, with samples of **2** typically containing only 0.5% of **1** (esterification, GLC assay). Chemoselective ketone reduction of **2** was achieved by adding sodium borohydride to a basic aqueous solution of the keto acid. Lactonization of the resulting hydroxy acid occurred in situ upon destruction of the remaining hydride reagent with aqueous acid and heating. Initially, lactone **3** was converted into the tetralone **5** in a two-step process.[6] Friedel-Crafts reaction of the lactone with benzene and aluminum chloride yielded the known diaryl acid **4** in 77% yield from keto acid **2**.[3] This diaryl acid had previously been converted into tetralone **5** by conversion to the acid chloride with thionyl chloride and subsequent treatment with aluminum chloride.[3] Thus a four-step process was developed to afford the tetralone **5** in 38% overall yield (Scheme I).

A more efficient process would combine the Friedel-Crafts alkylation/acylation reactions of lactone **3** into tetralone **5**. Precedent exists for this direct conversion, an example being the conversion of γ-butyrolactone and benzene into α-tetralone.[7] However, it is also known that the interchange of the dichloro aromatic ring due to the reversible nature of the Friedel-Crafts reactions can occur. For example, reaction of 3,4-dichlorobenzyl chloride and benzene has been reported to yield 64% of the desired 3,4-dichlorodiphenylmethane and ~10% diphenylmethane.[8] In our case, it was discovered that a number of Lewis or protic acids converted the lactone **3** directly into the tetralone **5**, namely, aluminum chloride, ferric

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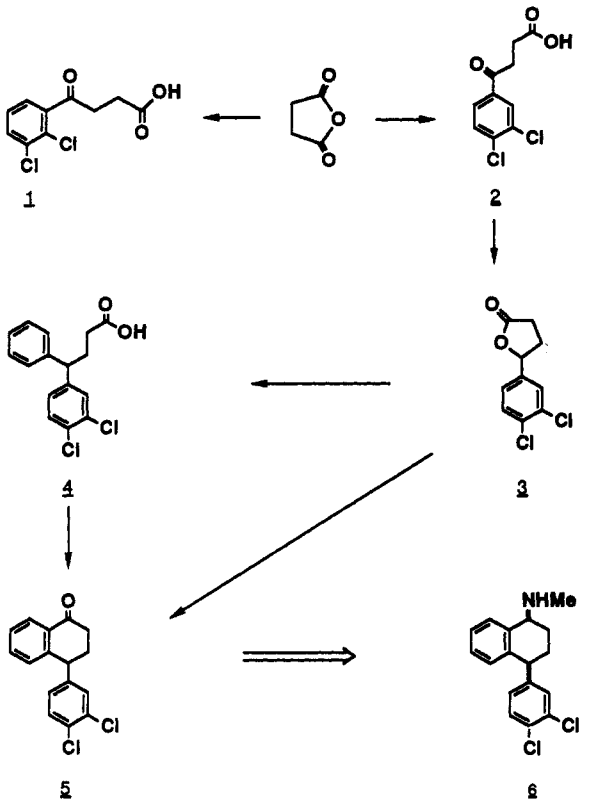
Scheme I



chloride, titanium tetrachloride, zirconium tetrachloride, polyphosphoric acid, phosphorus pentoxide, sulfuric acid, methanesulfonic acid, fluorosulfonic acid, chlorosulfonic acid, oleum (fuming sulfuric acid), triflic acid (trifluoromethanesulfonic acid), and anhydrous hydrogen fluoride. Diaryl acid 4 was an intermediate with all of these acids in the conversion of lactone 3 into the tetralone.

Protic acids proved superior to Lewis acids with respect to tetralone yield and purity. A number of observations are reported as follows. Zirconium tetrachloride provided clean and quantitative conversion to the diaryl acid 4, which could be slowly transformed into the tetralone on heating.[9] Sulfuric acid, methanesulfonic acid, and oleum produced the tetralone in 58–63% yield with the remainder of the materials being water-soluble compounds. Fluorosulfonic and chlorosulfonic acids by contrast yielded near quantitative formation of tetralone isolated with 7–20% diphenyl sulfone. The tetralone product 5 contaminated by diphenyl sulfone was purified by chromatography. High yields of pure tetralone 5 were obtained with triflic acid and anhydrous hydrogen fluoride. These protic acids generated tetralone in 91% and 97% yield, respectively.[10] Two other examples were conducted to demonstrate the generality of this double Friedel–Crafts reaction. Reaction of benzene and γ-phenyl-γ-butyrolactone with triflic acid provided a 90% yield of the known 4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone.[11] Triflic acid reaction of toluene and γ-phenyl-γ-butyrolactone yielded a 97% yield of isomeric products in a ratio of 30:3:1, with the major product identified as the known 4-phenyl-7-methyl-3,4-dihydro-1(2*H*)-naphthalenone.[12] See supplementary data for experimental details. In summary, an efficient synthesis of tetralone 5 was achieved in three steps and 82% overall yield by employing chemoselective ketone reduction and a double Friedel–Crafts alkylation/acylation reaction sequence.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 300 MHz in DMSO-d_6 unless noted otherwise. Infrared spectra were recorded in $CHCl_3$.

4-(3,4-Dichlorophenyl)-4-oxobutanoic Acid (2). Aluminum chloride (199 g, 1.5 mol) was added to a solution of succinic anhydride (50 g, 0.5 mol) in 1,2-dichlorobenzene (441 g, 3.0 mol) at ambient temperature. The reaction was heated to 60 °C for 2.5 h and then inverse quenched onto cold water (1200 mL), maintaining a temprature of <50 °C. After stirring the quenched reaction for 15 min, hexane (600 mL) was added and stirring continued for 1.5 h. The product was filtered off and dried in a vacuum oven to give the keto acid as a white solid, 113.9 g (92%), mp 165–66 °C (lit.[4] mp 165–66 °C): ^{1}H NMR 12.28 (br s, 1 H), 8.25 (d, J = 2 Hz, 1 H), 8.03 (dd, J = 2, J = 8 Hz, 1 H), 7.90 (d, J = 8 Hz, 1 H), 3.35 (t, J = 6 Hz, 2 H), 2.66 (t, J = 6 Hz, 2 H); ^{13}C NMR 197.0, 173.8, 136.6, 136.1, 131.9, 131.2, 129.9, 128.0, 33.4, 27.9. Anal. Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.7; O, 19.43. Found: C, 48.32; H, 3.14.

4-(2,3-Dichlorophenyl)-4-oxobutanoic Acid (1). *n*-Butyllithium (38.1 mL, 1.3 M, 0.05 mol, in hexanes) was added to tetrahydrofuran (THF, 50 mL), maintaining an internal temperature of below −60 °C during the addition. A solution of 1,2-dichlorobenzene (7.35 g, 0.05 mol) in THF (50 mL) was added dropwise over 45 min, maintaining the temperature below −60 °C. The resulting pale green solution was stirred at −60 to −70 °C for 45 min before addition of a solution of succinic anhydride (5.0 g, 0.05 mol) in THF (65 mL). This addition took 30 min, with the temperature kept below −60 °C. After stirring for 1 h, the temperature was allowed to rise over 1 h to ambient temperature. The reaction was poured into water (150 mL) and then acidified with 5 N HCl. The phases were separated and the aqueous phase extracted again with methylene chloride. The combined organic extracts were dried and evaporated to afford an oily solid, 10.6 g. The crude product (10.0 g) was mixed with water (50 mL), basified with 5 N sodium hydroxide, and extracted with CH_2Cl_2. The aqueous solution was acidified with 5 N HCl and extracted with CH_2Cl_2. The acidic extracts were evaporated to give a yellow sticky solid, 3.1 g (25%). The solid (3.0 g) was recrystallized from toluene and gave a pale yellow solid, 1.8 g (mp 112–14 °C): ^{1}H NMR 12.25 (br s, 1 H), 7.77 (dd, J = 1.4, J = 7.8 Hz, 1 H), 7.61 (dd, J = 1.4, 7.8 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 1 H), 3.12 (t, J = 6.3 Hz, H), 2.59 (t, J = 6.3 Hz, 2 H); ^{13}C NMR 201.2, 173.8, 141.6, 133.2, 132.6, 129.0, 127.8, 127.6, 37.8, 28.5. Anal. Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl 28.7; O, 19.43. Found: C, 48.69; H, 3.25.

5-(3,4-Dichlorophenyl)dihydro-2(3*H*)-furanone (3). A mixture of keto acid 2 (370.6 g, 1.5 mol) and demineralized water (1.5 L) was stirred and heated to 75–80 °C while aqueous NaOH (130 mL of 1.5 N solution) was gradually added in portions. The total time required for obtaining complete solution was about 1 h, with the pH of the final solution being 10.73 at 78 °C. Sodium borohydride (19.86 g, 0.52 mol) in demineralized water (100 mL) containing 1 mL of 1.5 N NaOH was added over 44 min. The reaction was stirred at the same temperature for 2 h. Aqueous hydrochloric acid (436 mL, 5.8 N) was added at 57–62 °C over 65 min, with particular care being taken during the first 30 min

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due to formation of a foam. Upon completion of the quench, the mixture was vigorously stirred and heated to 65–70 °C for 4 h. The mixture was then allowed to cool to ambient temperature and stirred for 16 h. The product was filtered off and dried under vacuum to afford the lactone as a white solid (320 g, 92%), mp 64–65 °C: ^{13}C NMR ($CDCl_3$) 176.2, 139.7, 133.0, 132.5, 130.8, 127.3, 124.5, 79.6, 30.8, 28.7; IR 2985, 1781, 1600, 1564, 1466, 1405, 1349, 1324, 1299, 1268, 1170, 1131, 1025 cm^{-1}. Anal. Calcd for $C_{10}H_8Cl_2O_2$: C, 51.98; H, 3.49; O, 13.85. Found: C, 52.03; H, 3.42.

4-(3,4-Dichlorophenyl)-4-phenylbutanoic Acid (4). To a well-stirred slurry of benzene (19.5 g, 0.25 mol), aluminum chloride (13.5 g, 0.10 mol), and CH_2Cl_2 (22.5 mL) was added a solution of lactone **3** (23.1 g, 0.10 mol) in CH_2Cl_2 (22.5 mL). The addition was carried out over 15 min, and the temperature rose from 23 to 35 °C. The mixture was stirred for 2 h at ambient temperature and then quenched on ice (100 g) containing hydrochloric acid (20 mL). The resulting acidic mixture was stirred for 15 min. The phases were separated, the organic layer was washed with water, and the methylene chloride was removed by atmospheric distillation. The residual liquid was treated with hexane and allowed to cool to ambient temperature, which resulted in precipitation of a light brown solid. After stirring for 1 h, the product was filtered off and washed with hexane to yield diaryl acid **4** (28.0 g, 91%), mp 121–122 °C: ^{13}C NMR 173.9, 145.9, 143.5, 131.0, 130.6, 129.6, 128.8, 128.7, 128.0, 127.6, 126.5, 48.8, 32.1, 29.5; IR 3665, 3506, 3001, 1711, 1601, 1558, 1491, 1466, 1452, 1399, 1229, 1130, 1027 cm^{-1}. Anal. Calcd for $C_{16}H_{14}Cl_2O_2$: C, 62.15; H, 4.56; O, 10.35. Found: C, 61.96; H, 4.39.

4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenone (5). A solution of lactone (1.0 g, 0.004 mol), benzene (4.0 mL, 0.045 mol), and sulfuric acid (96%, 5.0 mL, 0.094 mol) at ambient temperature was heated to 95 °C for 1 h and then 140 °C for 1.5 h. After cooling, the reaction was inverse quenched onto ice (40 g). The mixture was stirred for 18 h. The product was filtered off and dried under vacuum to afford the tetralone as a white solid (740 mg, 63%). Similar conditions were employed for methanesulfonic acid [lactone **3** (10.0 g, 0.04mol)], yielding tetralone **5** (7.24 g, 63%).

Reaction conditions for triflic acid are as follows: To a solution of lactone **3** (3.0 g, 0.012 mol) in benzene (6 mL, 0.067 mol) was added triflic acid (5.34 mL, 0.06 mol) at ambient temperature, and the solution was stirred for 5 min and then heated to 75 °C for 1.5 h. After cooling, the reaction was inverse quenched onto ice (20 g) and CH_2Cl_2 (30 mL) was added. The pH was then adjusted to 9.0 with aqueous NaOH (15 mL of a 4 N solution). The organic layer was then separated and the aqueous extracted again with CH_2Cl_2 (30 mL). The organic extracts were combined and dried with $MgSO_4$. The CH_2Cl_2 was distilled off at atmospheric pressure until the volume was reduced to ~40 mL. Hexane (40 mL) was added and the distillation continued until the distillate temperature reached 67 °C, at which point the heating mantle was removed and the contents allowed to crystallize for 16 h. The product was filtered off and dried in a vacuum oven to afford the tetralone **5** (3.22 g, 91%) as a white solid.

Reaction conditions for anhydrous hydrogen fluoride are as follows [*Note: hydrogen fluoride is a colorless, highly irritating, corrosive, and poisonous* gas.[13]]: To a 125-mL Daiflon [poly(trifluoromonochloroethylene)] vessel were added lactone **3** (3.0 g, 0.012 mol) and benzene (6 mL, 0.067 mol). The reaction vessel was then attached to a Daiflon manifold and anhydrous hydrogen fluoride (20 mL, 1.0 mol) was distilled into the vessel at −78 °C. The reaction mixture was then allowed to warm to ambient temperature and stirred for 18 h. The excess hydrogen fluoride and benzene were removed under vacuum and scrubbed with calcium oxide. Methylene chloride (30 mL) and water (15 mL) were added and the pH adjusted to 12 with aqueous NaOH (1.0 N, 13 mL) at 5 °C. The phases were separated, and the aqueous was extracted again with CH_2Cl_2 (30 mL). The combined organic extracts were dried $MgSO_4$, and the solvent was distilled off till the volume was reduced to ~30 mL. Hexane (40 mL) was added and distillation continued until the distillate reached a temperature of 67 °C. The solution was allowed to cool and stirred for 16 h at ambient temperature. The product was filtered off as a white solid and dried under vacuum to afford **5** (3.43 g, 97%), mp 102–3 °C: ^{13}C NMR ($CDCl_3$) 197.3, 144.9, 144.0, 133.9, 132.8, 132.7, 131.0, 130.6, 130.5, 129.3, 128.0, 127.6, 127.4, 44.6, 36.5, 31.7; IR 2997, 2942, 2865, 1682, 1598, 1559, 1466, 1452, 1397, 1345, 1330, 1285, 1132, 1026 cm^{-1}. Anal. Calcd for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.15; O, 5.49. Found: C, 65.83; H, 3.89.

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Supplementary Material Available: Experimental data for compounds not described in Experimental Section (1 page). Ordering information is given on any current masthead page.

(13) Merck index, Tenth Edition, 4703.

Isolation of Optically Active Oximes

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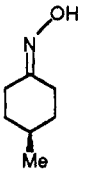
Since the failure of the first attempt of optical resolution of 4-(hydroxyimino)cyclohexanecarboxylic acid by the diastereomeric method using morphine as a chiral base,[1] because of the unstability of the optically active oxime,[1] no further effort for the resolution of the oxime had been carried out. Our success upon optical resolution of various compounds by complexation with optically active host compounds prompted us to attempt the resolution.[2] We now report the isolation of optically active 4-methyl-1-(hydroxyimino)cyclohexane (**1**) and *cis*-3,5-dimethyl-1-(hydroxyimino)cyclohexane (**2**). We also report Beckmann rearrangement of these optically active oximes to optically active ϵ-caprolactams.



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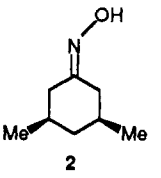

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For example, when a solution of racemic 4-methyl-1-(hydroxyimino)cyclohexane (**1a**) and (−)-1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**3b**)[3] in ether–petroleum ether was kept at room temperature, a 1:1 inclusion compound (**4**) of **3b** and (+)-oxime (**1c**) was obtained as colorless needles. Treatment of **4** with allylamine gave a 1:1 inclusion compound of **3b** and allylamine and optically active oxime **1c** of greater than 79% ee. Since the optical purity of the **1c** was not determined directly, its *O*-benzoyl derivative (**5c**) was prepared and its optical purity was determined to be 79% ee by HPLC using a column containing an optically active solid phase, Chiralcel

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