2.67 (1 H, dd, $J = 14.0, 3.5$ Hz), 2.90 (1 H, dt, $J = 9.1, 3.3$ Hz), 3.03 (1 H, dd, $J = 17.1, 0.7$ Hz), 3.18 (1 H, d, $J = 18.4$ Hz), 3.29 (1 H, ddd, $J = 11.0, 7.5, 3.3$ Hz), 4.12 (2 H, q, $J = 7.1$ Hz); ^{13}C NMR δ 12.79, 14.14, 27.39, 28.70, 41.72, 42.60, 43.17, 48.05, 49.92, 51.79, 53.72, 56.07, 61.06, 84.55, 174.66, 210.71; MS, *m/z* 281, 221, 179, 147 (100%), 133, 91, 77, 55, 41. Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16; S, 10.82. Found: C, 64.83; H, 8.25; S, 10.86.

38b: IR ($CDCl_3$) 1035, 1200 (br), 1250, 1730, 1775; ^1H NMR δ 1.00 (3 H, s), 1.06 (3 H, s), 1.24 (3 H, t, $J = 7.1$ Hz), 1.21–1.28 (1 H, m), 1.36 (1 H, dd, $J = 12.0, 6.5$ Hz), 1.77 (2 H, s), 2.07 (3 H, s), 2.33 (1 H, dd, $J = 13.3, 6.5$ Hz), 2.48 (1 H, dd, $J = 13.3, 12.1$ Hz), 3.06–3.20 (4 H, m), 4.13 (2 H, q, $J = 7.1$ Hz); ^{13}C NMR δ 12.49, 14.25, 27.65, 28.81, 39.18, 40.66, 42.60, 42.71, 44.31, 50.39, 52.13, 55.31, 60.66, 83.44, 172.03, 210.17. Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16; S, 10.82. Found: C, 64.96; H, 8.18; S, 10.75.

Reaction of Cyclobutanones 38 with Diazomethane. A 25-mL round-bottomed flask fitted with a magnetic stirring bar was charged with a solution of 36 mg (0.12 mmoL) of cyclobutanones **38** (mixture of isomers) in 1 mL of anhydrous ether. The above solution was treated dropwise with 6 mL of ethereal diazomethane (ca. 0.1 M, generated from Diazald); no evolution of gas was observed. Addition of 1 drop of freshly distilled $BF_3\cdot Et_2O$ produced a vigorous evolution of gas and concomitant decolorization of the yellow solution. An additional 10 mL of diazomethane was added followed by 2 drops of methanol. After the reaction mixture was stirred for 48 h, the solvent was removed to give 32 mg of a yellow oil which, when subjected to TLC [hexane–ether (3:1)], showed four spots with very similar R_f values. Column chromatography on silica gel [hexane–ether (3:1)] was ineffective in separating the above-mentioned compounds. The ^1H NMR of the mixture was, consequently, too complicated to assign. On the other hand, the IR and MS of the mixture provided the following data: IR ($CDCl_3$) 1040, 1180–1210, 1250–1280, 1730; MS, GLC trace showed three peaks with *m/z* 310, one of them with higher intensity than the other two. The MS patterns of these three peaks, given in order on increasing retention times, are as follows: (a) 311, 310 (M), 263, 262, 217, 205, 189 (100%), 161, 147, 133, 119, 91, 77, 55, 41; (b) 311, 310 (M), 263, 262, 235, 221, 217, 189, 175, 147 (100%), 133, 190, 105, 91, 79, 55, 41; (c) 311, 310 (M), 263, 234, 219, 189, 161, 147 (100%), 131, 119, 105, 77, 55, 41.

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Zinc Salt Catalyzed Rearrangement of Acetals of Optically Active Aryl 1-Chloroethyl Ketones: Synthesis of Optically Active 2-Arylpropionic Acids and Esters[1]

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The preparation of (*S*)-2-(4′-isobutylphenyl)propionic acid ((*S*)-Ibuprofen) (82% optical purity) and (*S*)-2-(6′-methoxy-2′-naphthyl)propionic acid (Naproxen) (96% optical purity) has been accomplished by starting from optically pure (*S*)-2-chloropropionyl chloride. The investigation for finding the best experimental conditions and minimizing racemization phenomena is presented.

2-Arylalkanoic acids and derivatives are pharmaceutically[2] and agriculturally[3] useful products. Most of them contain a chiral carbon atom and one enantiomer usually shows higher biological or pharmaceutical activity. Well-known examples are 2-(6′-methoxy-2′-naphthyl)propionic acid, whose *S* isomer (Naproxen),[2,4] is 28 times as active as the *R* isomer as an antinflammatory agent, 2-(2′-(*p*-fluorophenyl)-5′-benzoxazolyl)propionic acid, whose *S* isomer (Flunoxaprofen)[5] is a new and interesting example of the same class of antiinflammatory drugs, and (*S*)-2-(4′-chlorophenyl)-3-methylbutanoic acid that is an intermediate for the synthesis of the insecticide Fenvalerate.[3,6]

For the preparation of optically active 2-arylalkanoic acids and/or their convenient precursors many different synthetic strategies have been reported as, for example, the use of (a) optically active bases for resolving racemates;[7a] (b) a second-order resolution of diastereomeric derivatives as salts,[7b] esters, anhydrides, amides, or oxazolines;[7c,d,e] (c) biochemical methods (asymmetric hydrolysis of esters[8a] or oxidation of aromatic hydrocarbons[8b]); (d) optically active catalysts in the asymmetric hydrogenation of prochiral unsaturated 2-aryl carboxylic

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acids,[9] in the asymmetric carbalkoxylation of aryl alkenes,[10a,b] in the asymmetric carbonylation of benzyl halides,[10c] in the asymmetric cross-coupling reactions of organometallic reagents either with aryl and vinyl halides or with allylic derivatives.[11] Other reported examples of asymmetric syntheses of this type of compounds are the reaction of optically active alcohols with ketenes, prepared in situ from racemic acid chlorides,[12] and Friedel–Crafts alkylation of an arene with optically active lactic acid derivatives.[13]

Recently Tsuchihashi and co-workers have described the base-catalyzed stereospecific rearrangement of optically pure diastereomeric 1-aryl-1,1-dimethoxy-2-((camphorsulfonyl)oxy)propanes (obtained by reaction of the corresponding racemic hydroxy acetals with camphorsulphonyl chloride and following separation of the two diastereomers) to afford enantiomerically pure methyl ester of 2-arylpropionic acids.[14a] This result suggested to us and to other groups of researchers to study and patent independently[14b–f] asymmetric syntheses of optically active 2-arylpropionic acids which use (*S*)-lactic acid and/or (*S*)-alanine as chiral starting materials. The stereospecific rearrangement of optically active acetals to esters is the key step (Scheme I), and, depending on the nature of X group,

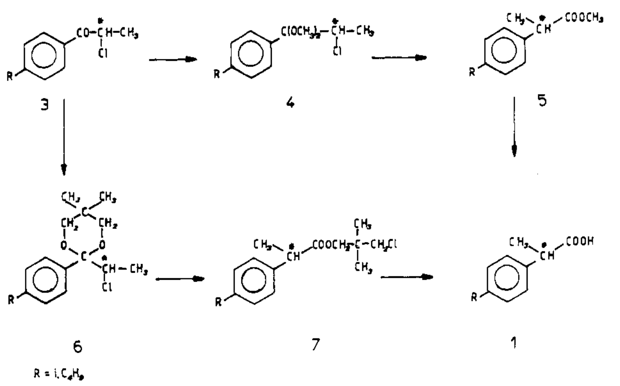
Scheme I

$$\mathrm{ArC(OR)_2C^*HXCH_3 \rightarrow ArC^*H(CH_3)COOR'}$$

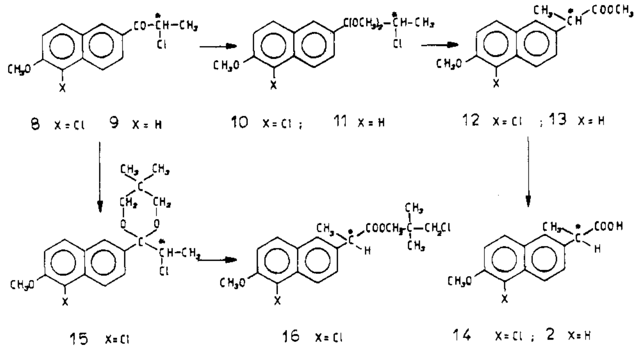
$$\mathrm{X = halide,\ OSO_2R,\ NH_2}$$

basic or acidic catalysts are used to catalyze this step. Here we report the details of our investigation on the use of derivatives containing a chlorine atom as the X group and zinc salts as catalysts for the synthesis of optically active 2-(4′-isobutylphenyl)propionic acid (Ibuprofen) **1** and 2-(6′-methoxy-2′-naphthyl)propionic acid (Naproxen) **2**. Under the best conditions compounds **1** and **2** of 82% and 96% optical purity, respectively, computed from maximum reported rotation values, were obtained. The synthetic routes are outlined in Schemes II and III. The values of the rotatory powers of intermediates and final products, obtained in different repeated synthetic procedures (runs), are presented in Tables I and II. For the preparation of some of the corresponding racemic compounds, see ref 15. A correlation between compound **2** and 2-(5′-chloro-6′-methoxy-2′-naphthyl)propionic acid (**14**) is outlined in Scheme IV.

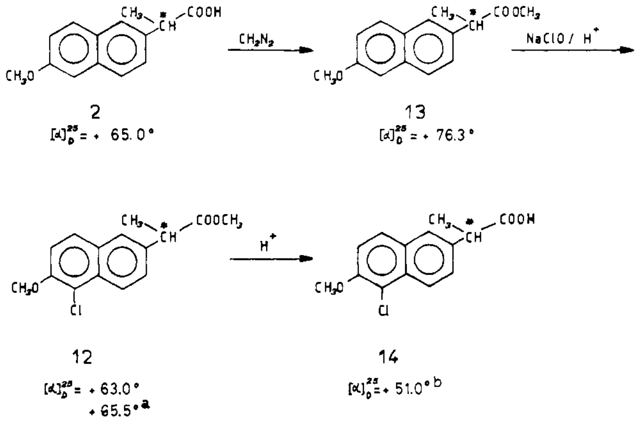
Scheme II



Scheme III



Scheme IV



[a] After two recrystallizations from methanol. [b] From **12** [α] +65.5°.

Results and Discussion

Optically pure (*R*)- and (*S*)-2-chloropropionic acid were prepared as previously described[16] starting from (*S*)-ethyl lactate and (*S*)-alanine, respectively, and converted by reaction with oxalyl chloride into the corresponding acid chlorides. These latter compounds afforded optically active aryl 1-chloroethyl ketones (aryl = 4′-isobutylphenyl (**3**), 5′-chloro-6′-methoxy-2′-naphthyl (**8**), and 6′-methoxy-2′-naphthyl (**9**)) by Friedel–Crafts reaction with isobutylbenzene and 1-chloro-2-methoxynaphthalene or by reaction with the Grignard reagent from 2-bromo-6-methoxy-naphthalene.[14b,c,f,17] In the synthesis of ketones **3**, **8**, and **9** we observed a slight and variable loss of en-

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Table I

	$[\alpha]^{25}_{\mathrm{D}}$ (c 1, $CHCl_3$) (% opt purity)	
compd	run 1[a]	run 2[a]
3	−30.5° (~96)[b]	+31.1° (~98)[b]
4	nd[c]	+12.7°
5	−51.5°	+55.7°[d]
6		+2.8°
7		+9.9°
1	−45.4° (75)[e]	+50.0° (82)[e–g] +9.2° (15)[e,h]

[a] Each run means an independent synthetic sequence we have carried out. [b] Based on maximum specific rotation obtained after repeated crystallizations of **3** from methanol. [c] Not determined. [d] A sample showed $[\alpha]^{20}_{\mathrm{D}}$ +70.5 (c 1, 8, benzene) [an erroneus value for maximum specific rotation of **5**, based on ^1H NMR using $Eu(dcm)_3$, was recently reported (see ref 11b)]. [e] Based on maximum specific rotation reported $[\alpha]^{25}_{\mathrm{D}}$ +60° (c 2, EtOH 95%) (Kaiser, D. G.; Vangiessen, G. J.; Reische, R. J.; Weckter, W. J. *J. Pharm. Sci.* **1976**, *65*, 269). [f] A sample showed $[\alpha]^{25}_{\mathrm{D}}$ +49.3° (c 2, EtOH 95%). [g] From compound **5**. [h] From compound **7**.

Table II

	$[\alpha]^{25}_{\mathrm{D}}$ (c 1, $CHCl_3$) (% opt. purity)		
compd	run 1	run 2	run 3
8	+108.5° (~100)[a]	+103.7° (~96)[a]	
9			+117.8 (~100)[b]
10	+25.2°[c]	+24.7°	
11			nd
12	+60.8° (~93)[d]	+57.0° (~87)[d,e]	
13		+66.1° (~86)[f]	+69.5° (~90)[f]
14	+48.6° (~95)[f]		
15		+3.3°[g]	
16		+7.0°	
2	+63.4° (96)[h]	+58.2 (88)[h]	+59.2 (90)[h]

[a] Based on maximum specific rotation obtained after repeated crystallization from n-heptane/methanol. [b] Based on maximum specific rotation obtained after repeated crystallization from methanol and confirmed by NMR using $Eu(tfc)_3$ as shift reagent. [c] Sample of **8**, $[\alpha]^{25}_{\mathrm{D}}$ +100.4°, was also recovered. [d] Based on maximum specific rotation obtained after two recrystallizations from methanol (Scheme IV). [e] A sample, after recrystallization from n-heptane, showed $[\alpha]^{25}_{\mathrm{D}}$ +62.9°. [f] Optical purity was confidentially calculated by using specific rotations observed in the sequence depicted in Scheme IV and assuming no racemization in the esterification with diazomethane and in the acidic hydrolysis. [g] A sample of **8**, $[\alpha]^{25}_{\mathrm{D}}$ +61.8°, was also recovered. [h] Maximum specific rotation $[\alpha]^{25}_{\mathrm{D}}$ +66° was reported (see ref 4).

antiomeric purity (<15%) related to the starting acids. Therefore we preferred to crystallize these ketones and evaluate their optical purities by comparison of their maximum rotatory powers with the highest rotation observed, after recrystallization, or, where possible (compound **9**), by NMR using europium shift reagents. Acetalyzation was then accomplished by acid catalyzed reaction of compounds **3**, **8**, and **9** with trimethyl orthoformate/methanol or with 2,2-dimethyl-1,3-propanediol (NPG) and azeotropic removal of water. Where recovered, the unreacted ketones were partially racemized. The rearrangement to esters was performed by using various zinc salts as the catalyst. Good chemical yields were generally observed, but the nature of the catalyst is very important for the optical yields, zinc chloride and zinc oxide giving the best results. The conversion to the corresponding acids was performed by treating the esters with 30–37% aqueous HCl in acetone or 1,2-dimetoxyethane because the optically active esters racemize partially or totally in the presence of bases before hydrolysis occurs. A sample of recovered optically active acid **2** was quantitatively converted either with diazomethane or with methanol and sulforic acid to the corresponding methyl ester **13** having the same rotatory power as the starting ester. This confirms that the acidic hydrolysis is not accompanied by racemization. It must be noted that if a partial conversion of the acid into ester is performed, a decrease in the optical purity of the unreacted acid is observed in the case of Naproxen, but an increase in the case of Ibuprofen. Two different routes to Naproxen were explored starting from methyl 2-(5′-chloro-6′-methoxy-2′-naphthyl)propionate (**12**). The first route involved treatment of compound **12** with hydrogen in the presence of Pd/C and then acidic hydrolysis of the intermediate **13**. In the second route the chlorine atom in compound **14**, obtained from **12** by acidic hydrolysis, was removed by using hydrazine hydrate and Raney Ni under alkaline conditions. In both cases no racemization was observed (Table II).

If we compare the optical purities of **1**, obtained via intermediates **5** and **7**, we note that a much higher degree of racemization is found in the latter case. This is attributable, in our opinion, to the acetalyzation step and not to the rearrangement step (at least when the catalyst used was $ZnCl_2$ or ZnO). This hypothesis is confirmed by the comparison of racemization found (7% vs. 40%, respectively) for unreacted ketone **8** in the reactions with trimethyl orthoformate or with NPG. On the other hand the optical instability of optically active ketones under acidic or basic conditions owing to the formation of an enol derivative was known. Our results show that when a cyclic acetal is formed under acidic conditions, the cycle formation and racemization rates become comparable. In the case of acetalyzation with NPG the formation of an achiral enol ether intermediate $ArC(OR){=}CClCH_3$ (($R = CH_2C(CH_3)_2CH_2OH$)) could also be involved in the racemization.

The nature of the X group bounded at the chiral carbon atom affects the rate of racemization. In the preparation of optically active 5′-chloro-6′-methoxy-2′-naphthyl 1-bromoethyl ketone, the optical instability of this derivative was observed. When X is a halogen atom, the racemization is even quicker under basic conditions. In fact, in the synthesis of optically active $ArC(OCH_3)_2CHOHCH_3$ by reacting $ArCOC^*HClCH_3$ with CH_3OH/CH_3ONa, the racemized hydroxy acetal is recovered in good chemical yield; on the contrary under the same experimental conditions $ArCOC^*HOMsCH_3$ affords, as reported,[14b,c] the same hydroxy acetal, stereospecifically with complete inversion of configuration.

We cannot give a clear cut explanation of the influence of the nature of catalyst on the stereospecificity of the rearrangement step. However a bigger substituent L on the zinc atom seems to favor the formation of near planar cationic intermediate $ArC(OCH_3)_2CH(CH_3)^+\ ZnClL_2^-$ so that the aromatic ring begins to be able to attack the chiral carbon atom from both sides in the rearrangement step, resulting in low stereospecificity. For example, starting from the same compound **4**, we obtained comparable chemical yields of compound **5**, but we observed the following rotatory powers of this ester, according to the catalyst used: +55.7° ($ZnCl_2$), +55.3° (ZnO), +44.0° (zinc 2-ethylhexanoate), and +28.0° (zinc bromocamphorsulfonate). Although as we have shown the reaction conditions are quite restricted to achieve optimum stereospecificity, this route to optically active 2-arylpropionic acids of high optical purity starting from commercially available chiral sources appears to be convenient and of some potentiality for an industrial application. Furthermore the racemization during the acetalyzation step, expecially with dioles, suggests the use of optically active diols as reagents in the acetalyzation of racemic 2-halo ketones to induce, by a second-order resolution, the formation of an optically active carbon atom bounded to the halogen atom. This hypothesis is currently under investigation and is connected to some reported experiences of second-order resolution of ketones containing a chiral carbon atom in the alpha position via optically active acetals.[18,19]

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. GLC analyses [2m × 0.6 cm columns packed with 10% methyl silicone polymer on AW Chromosorb W 60–80 mesh (SE 30), with 10% polyethylene glycol on AW Chromosorb W 60–80 mesh (C 20M), and with 10% fluoroalkylsiloxane on Gaschrom 80–100 mesh (QF_1)] were performed on a Carlo-Erba 2310 instrument with flame-ionization detectors and N_2 as carrier gas. Analytical TLC were performed on precoated Merck silica gel 60 plates. Column chromatography was performed using silica gel (70–230 mesh) or Florisil (100–200 mesh). ^{1}H NMR spectra were recorded on an EM 360 60-MHz Varian (in $CDCl_3/Me_4Si$; δ, ppm) or on a FT 220-MHz Bruker spectrometer. Eu(tfc)$_3$ was used as shift reagent. Optical rotations were taken with a Perkin-Elmer 142 polarimeter and refer to $CHCl_3$ 1% solution, at 25 °C and 589 nm, unless otherwise stated. Repeated preparations, we have carried out, are not here described, but in Tables I and II are reported the rotatory powers of intermediates and final products of the different preparations [(*R*)- and (*S*)-2-(4′-isobutylphenyl)propionic acid (runs 1 and 2, Table I) and (*S*)-2-(6′-Methoxy-2′-naphthyl)propionic acid (runs 1–3, Table II)]. (*S*)-2-Chloro-propionic acid, having [α] −16.5° and α (neat, $l = 1$) −17.6°, was prepared from (*S*)-alanine as described previously,[16b] and converted into the corresponding chloride, α (neat, $l = 1$) +5.34°. Also (*R*)-2-chloropropionic acid, α +17.1° (neat, $l = 1$), prepared starting from (*S*)-lactic acid ethyl ester,[16a] was used.

(*S*)-2-Chloro-1-(4′-isobutylphenyl)propan-1-one (3). To a mixture of 10.5 g (78.7 mmol) of $AlCl_3$ in 25 mL of methylene chloride at 0–5 °C were added 10 g (78.7 mmol) of (*S*)-2-chloropropionyl chloride, α +5.34° (neat, $l = 1$), and 9.8 g (73.0 mmol) of isobutylbenzene. The mixture was stirred for 5 h at 5 °C, hydrolyzed with ice and 50 mL of 10% HCl, and extracted with 3 × 50 mL of CH_2Cl_2. The organic phase was washed with 10% $NaHCO_3$ and with water and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 15.8 g (96%) of crude **3** that after crystallization from methanol (13.2 g; 80%) showed the following: mp 77 °C; [A] +30.5°; ^{1}H NMR 7.45 (4 H, dd, aromatic H), 5.15 (1 H, q, C*H*Cl), 2.55 (2 H, d, C*H*$_2$), 1.95 (1 H, m, C*H*(CH$_3$)$_2$), 1.75 (3 H, d, CHClC*H*$_3$), 0.95 (6 H, d, CH(C*H*$_3$)$_2$).

(*S*)-2-Chloro-1,1-dimethoxy-1-(4′-isobutylphenyl)propane (4). A mixture of 6 g (26.7 mmol) of **3** ([α] +30.5°), 7.6 g (69.3 mmol) of trimethyl orthoformate, 25 mL of methanol, and 0.2 mL of 96% H_2SO_4 was refluxed, under nitrogen, for 24 h. The mixture was then neutralized with CH_3ONa, cooled at room temperature, and diluted with 50 mL of CH_2Cl_2 and water. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to give 6.8 g (95%) of **4**. An analytical sample of **4**, purified by column chromatography (Florisil; eluent, *n*-hexane/ethyl acetate, 95/5), showed the following: +12.5°; ^{1}H NMR 7.24 (4 H, dd, aromatic H), 4.38 (1 H, q, C*H*Cl), 3.26 (6 H, 2s, OC*H*$_3$), 2.45 (2 H, d, C*H*$_2$), 1.88 (1 H, m, C*H*(CH$_3$)$_2$), 1.27 (3 H, d, CHClC*H*$_3$), 0.92 (6 H, d, CH(C*H*$_3$)$_2$).

(*S*)-Methyl 2-(4′-Isobutylphenyl)propanoate (5). A mixture of 3 g (11.1 mmol) of crude **4** ([α] +12.5°), 16 mg (0.96 mmol) of $ZnCl_2$, and 15 mL of toluene was refluxed for 8 h, then cooled at room temperature, diluted with 30 mL of toluene, and filtered. After evaporation of the solvent at reduced pressure, the crude **5** was purified by column chromatography (silica gel; eluent, *n*-hexane/ethyl acetate, 90/10) to afford 1.8 g (75%) of pure **5**: [α] +51.5; ^{1}H NMR 7.14 (4 H, m, aromatic H), 3.77 (1 H, q, C*H*CH$_3$), 3.67 (3 H, s, COOC*H*$_3$), 2.45 (2 H, d, C*H*$_2$) 1.83 (1 H, m, C*H*(CH$_3$)$_2$), 1.48 (3 H, d, CHC*H*$_3$), 0.92 (6 H, d, CH(C*H*$_3$)$_2$).

(*S*)-2-(4′-Isobutylphenyl)propionic Acid (1). Pure **5** (1.8 g; [α] +51.5°) was hydrolyzed by refluxing 3 h in the presence of 20 mL of 37% HCl and 20 mL of acetone to give, after recovering and purification by column chromatography (Florisil; eluent *n*-hexane/ethyl acetate, 80/20), 1.1 g (65%) of pure **1**: mp 49–52 °C; [α] +45.4°; ^{1}H NMR 7.06 (4 H, m, aromatic H), 3.67 (1 H, q, C*H*CH$_3$), 2.29 (2 H, d, C*H*$_2$), 1.82 (1 H, m, C*H*(CH$_3$)$_2$), 1.44 (3 H, d, CHC*H*$_3$), 0.80 (6 H, d, CH(C*H*$_3$)$_2$).

(*R*)-2-(1-Chloroethyl)-2-(4′-isobutylphenyl)-5,5-dimethyl-1,3-dioxane (6). A mixture of 6.0 g (26.7 mmol) of **3** ([α] −31.1°), 3.1 g (29.8 mmol) of 2,2-dimethyl-1,3-propanediol (NPG), 0.1 (0.53 mmol) of *p*-toluenesulfonic acid hydrate, and 50 mL of toluene was refluxed for 15 h with water removal. The mixture was then neutralized with Na_2CO_3, cooled at room temperature, washed with water, and dried over Na_2SO_4. After removal of the solvent, the crude **6** [7.9 g, 95%, 98% pure; [α] −2.8°; ^{1}H NMR 7.20 (4 H, dd, aromatic H), 4.04 (1 H, q, C*H*Cl), 3.46 (4 H, s, OC*H*$_2$), 2.50 (2 H, d, C*H*$_2$), 1.89 (1 H, m, C*H*(CH$_3$)$_2$), 1.36 (3 H, d, CHClC*H*$_3$), 1.23 (3 H, s, C(C*H*$_3$), 0.91 (6 H, d, CH(C*H*$_3$)$_2$, 0.56 (3 H, s, C(C*H*$_3$)] was recovered.

(*R*)-2-(4′-Isobutylphenyl)propionic Acid (1). Crude **6** in the presence of $ZnCl_2$ was converted, analogously to the procedure reported above, into the corresponding 3-chloro-2,2-dimethylpropyl ester of **1**, in a quantitative yield. The crude ester **7** ([α] −9.9°) afforded, after hydrolysis, **1** ([α] −9.2°).

1-Chloro-2-methoxynaphthalene. Sodium hypochlorite (30 mL, 68.9 mmol) was added dropwise to a mixture of 10.0 g (63.2 mmol) of 2-methoxynaphthalene, 15 mL of water, 2 g (36.7 mmol) of NaCl, 9 g (36.7 mmol) of 40% H_2SO_4, and 25 mL of CH_2Cl_2, under vigorous stirring at 15–17 °C. After 1 h, the organic layer was separated and the aqueous phase extracted with 2 × 25 mL of CH_2Cl_2. The combined organic layers were washed with 100 mL of water containing 0.5 g of Na_2SO_3, dried (Na_2SO_4), and concentrated under vacuum to give 12.1 g (94%, 95% pure) of 1-chloro-2-methoxynaphthalene.

(*S*)-2-Chloro-1-(5′-chloro-6′-methoxy-2′-naphthyl)-propan-1-one (8). To a mixture of 7.3 g (54.7 mmol) of $AlCl_3$ in 25 mL of CH_2Cl_2, at room temperature, were added 7.2 g (56.7 mmol) of (*S*)-2-chloropropionyl chloride, α +5.44° (neat, $l = 1$), and 7.0 g (36.4 mmol) of 1-chloro-2-methoxy-naphthalene. The mixture was stirred for 4 h at 25 °C, then hydrolyzed, and worked up as usual. After crystallization from *n*-heptane/methanol (3/2, V/V), 6.2 g of pure **8** (60%) were recovered: mp 123 °C; [α] +108.5°; ^{1}H NMR 8.35–7.13 (5 H, m, aromatic H), 5.24 (1 H, q, C*H*), 4.00 (3 H, s, OC*H*$_3$), 1.75 (3 H, d, CHC*H*$_3$); mass spectrum, *m/e* 284–282 (M^+, 21%), 221–219 (100%). By use of the same procedure (*S*)-2-bromo-1-(5′-chloro-6′-methoxy-2′-naphthyl)-propan-1-one was obtained (89%). Its highest rotation observed was [α] +118.3°; unfortunately some racemization of the product occurred on standing or during the crystallization from methanol.

(*S*)-2-Chloro-1-(6′-methoxy-2′-naphthyl)propan-1-one (9). A 75-mL THF solution of Grignard reagent (0.93 N, 69.7 mmol) prepared from 2-bromo-6-methoxynaphthalene was slowly added, under nitrogen, to 10.9 g (85.9 mmol) of (*S*)-2-chloropropionyl chloride, α +5.23° (neat, $l = 1$), diluted in 80 mL of THF, and cooled at −40 °C. The mixture was stirred for 2 h at this temperature and then hydrolyzed with ice and 50 mL of 10% HCl. After removal of THF under vacuum, the organic products were extracted with 3 × 70 mL of CH_2Cl_2. After the usual workup, a crude mixture containing 10.9 g (63%) of **9** was recovered. After crystallization from methanol, 9.9 g (57%) of pure **9** was obtained [mp 122 °C; [α] +117°; ^{1}H NMR 8.50–7.14 (6 H, m, aromatic H), 5.40 (1 H, q, C*H*), 3.95 (3 H, s, OC*H*$_3$), 1.80 (3 H, d, CHC*H*$_3$)].

(*S*)-2-Chloro-1,1-dimethoxy-1-(5′-chloro-6′-methoxy-2′-naphthyl)propane (10). A mixture of 6.2 g (21.9 mmol) of **8** ([α] +108.5°), 60 mL of methanol, 13 mL of toluene, 14.5 g (136 mmol) of trimethyl orthoformate, and 1.2 g of 96% H_2SO_4 was refluxed for 23 h while distilling about 25% of the solvent. The mixture was then neutralized with Na_2CO_3 and diluted with water and 50 mL of toluene. The toluene layer was separated and concentrated under vacuum to give 6.5 g (90%) of **10**. An analytical sample, purified by column chromatography (Florisil; eluent *n*-hexane/ethyl acetate, 90/10), showed the following: mp 106 °C; [α] +25.2°; ^{1}H NMR 8.25–7.10 (5 H, m, aromatic H), 4.25 (1

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[18] Mori, A.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5444.

[19] Giordano and co-workers patented a synthesis of optically active aryl alcanoic acids starting from optically active bromo acetals obtained by asymmetric bromination of acetals of alkyl aryl ketones (Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *Angew. Chem.* **1986**, *98*, 273 and references cited therein).

H, q, $\mathrm{C}H\mathrm{Cl}$), 3.95 (3 H, s, naphthyl $\mathrm{OC}H_3$), 3.35 (3 H, s, $\mathrm{OC}H_3$), 3.15 (3 H, s, $\mathrm{OC}H_3$), 1.30 (3 H, d, $\mathrm{CHC}H_3$). A sample of **8** was also recovered: [α] +100.4°.

(*S*)-Methyl 2-(5′-Chloro-6′-methoxy-2′-naphthyl)propanoate (12). A mixture of 6.0 g (18.2 mmol) of crude **10** ([α] +25.2°), 55 mg (0.4 mmol) of $ZnCl_2$, and 120 mL of toluene was refluxed while distilling the solvent until the internal temperature was about 120 °C. At the end of the reaction (3 h), the mixture was treated with charcoal, filtered, and concentrated to afford 5.1 g of **12** (85%). An analytical sample, purified by column chromatography (silica gel; eluent *n*-heptane/ethyl acetate, 95/5) showed the following: mp 102 °C; [α] +60.8°. The same sample, after crystallization from *n*-heptane, showed mp 106 °C; [α] +62.9°; ^{1}H NMR 8.30–7.15 (5 H, m, aromatic H), 4.00 (3 H, s, COOCH_3), 3.85 (1 H, q, $\mathrm{C}H\mathrm{CH}_3$), 3.65 (3 H, s, naphthyl $\mathrm{OC}H_3$), 1.55 (3 H, d, $\mathrm{CHC}H_3$).

(*S*)-2-(5′-Chloro-6′-methoxy-2′-naphthyl)propionic Acid (14). A mixture of 3.0 g (10.8 mmol) of **12** ([α] +60.8°), 20 mL of 37% HCl, and 20 mL of acetone was refluxed for 3 h and worked up as usual to give 2.6 g (91%) of **14**: mp 158 °C; [α] +48.6°; ^{1}H NMR 8.20–7.15 (5 H, m, aromatic H), 3.98 (3 H, s, naphthyl $\mathrm{OC}H_3$), 3.85 (1 H, q, $\mathrm{C}H\mathrm{CH}_3$), 1.56 (3 H, d, $\mathrm{CHC}H_3$).

(*S*)-2-(6′-Methoxy-2′-naphthyl)propionic Acid (2). Hydrazine hydrate (80%, 2 mL, 50.0 mmol) was added to a mixture of 0.94 g (3.6 mmol) of **14** ([α] +48.6°), 0.8 mL of 30% NaOH, and 90 mg of Raney Ni in 7 mL of water, at 75 °C, under vigorous stirring. After 6 h the mixture was diluted with water, filtered, and made acidic with 10% HCl. The product was extracted with ether, and after removal of the solvent and purification by column chromatography (silica gel; eluent *n*-heptane/diethyl ether, 25/75), 0.6 g (72%) of **2**, mp 156 °C [α] +63.4°, was recovered.

(*S*)-Methyl 2-(6′-Methoxy-2′-naphthyl)propanoate (13). A sample of 3.0 g (10.8 mmol) of **12** ([α] +57.0°) in 20 mL of methanol was hydrogenated at atmospheric pressure and room temperature in the presence of 0.3 g of 10% Pd/C to give after workup 2.4 g (91%) of **13**: mp 92 °C; [α] +66.1°; ^{1}H NMR 7.80–7.05 (6 H, m, aromatic H), 3.90 (3 H, s, $\mathrm{COOC}H_3$), 3.85 (1 H, q, $\mathrm{C}H\mathrm{CH}_3$), 3.65 (3 H, s, naphthyl $\mathrm{OC}H_3$), 1.55 (3 H, d, $\mathrm{CHC}H_3$).

(*S*)-2-(6′-Methoxy-2′-naphthyl)propionic Acid (2). **13** 2.0 g (8.2 mmol) ([α] +66.1°) was treated with 13 mL of 30% HCl in 20 mL of 1,2-dimethoxyethane for 5 h at 85 °C to give, after the usual workup, 1.3 g (69%) of **2**, [α] +58.2°.

(*S*)-2-(1-Chloroethyl)-2-(5′-chloro-6′-methoxy-2′-naphthyl)-5,5-dimethyl-1,3-dioxane (15). A mixture of 6.2 g (21.0 mmol) of **8** ([α] +103.7°), 2.5 g (24.4 mmol) of NPG, 0.1 g (0.53 mmol) of *p*-toluenesulfonic acid hydrate, and 50 mL of toluene was refluxed for 15 h with water removal. The mixture was then neutralized with Na_2CO_3, cooled at room temperature, washed with water, and dried. After removal of the solvent and purification by column chromatography (Florisil; eluent *n*-hexane/ethyl acetate, 80/20), 7.3 g of **15** [90%; mp 149 °C; [α] +3.3°; ^{1}H NMR 8.15–7.10 (5 H, m, aromatic H), 4.05 (1 H, q, $\mathrm{C}H\mathrm{Cl}$), 3.95 (3 H, s, naphthyl $\mathrm{OC}H_3$), 3.45 (4 H, s, $\mathrm{OC}H_2$), 1.28 (3 H, s, $\mathrm{C}(\mathrm{C}H_3)$), 0.57 (3 H, s, $\mathrm{C}(\mathrm{C}H_3)$)] were recovered. A sample of **8**, [α] +61.8°, was also obtained.

(*S*)-3-Chloro-2,2-dimethylpropyl Ester of 2-(5′-Chloro-6′-methoxy-2′-naphthyl)propionic Acid (16). **15** (4 g (10.8 mmol)), [α] +3.3°, in the presence of 55 mg (0.67 mmol) of ZnO, were quantitatively rearranged into **16**, [α] +7.0°.

(*S*)-Methyl 2-(6′-Methoxy-2′-naphthyl)propanoate (13). A mixture containing 3.8 g (15.2 mmol) of **9** ([α] +117.8°), 7.9 g (74.6 mmol) of trimethyl orthoformate, 50 mL of methanol, 10 mL of toluene, and 0.2 mL of 96% H_2SO_4 was refluxed for 25 h. After neutralization with $NaHCO_3$, the mixture was diluted with water and extracted with 3 × 30 mL of toluene. The organic phase was added to 22 mg (0.27 mmol) of ZnO and refluxed at 120 °C for 3 h with distilling of about 70% of the solvent. The residue was treated with charcoal, filtered, and concentrated to afford 3.1 g (84%) of **13**. An analytical sample, purified by column chromatography (Florisil; eluent *n*-heptane/diethyl ether, 95/5), showed [α] +69.5°.

(*RS*)-2-Hydroxy-1,1-dimethoxy-1-(6′-methoxy-2′-naphthyl)propane. To a stirred solution, at 25 °C, of 1.4 g (25.2 mmol) of sodium methoxide in 36 mL of methanol 3.6 g (14.3 mmol) of **9**, [α] +117.8°, was added portionwise. The mixture was stirred for 5 h, poured in water, and extracted with 3 × 30 mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated under vacuum to give 3.9 g (99%) of (*RS*)-2-hydroxy-1,1-dimethoxy-1-(6′-methoxy-2′-naphthyl)propane: ^{1}H NMR 8.35–7.10 (6 H, m, aromatic H), 4.18 (1 H, q, $\mathrm{C}H\mathrm{OH}$), 3.90 (3 H, s, naphthyl $\mathrm{OC}H_3$), 3.42 (3 H, s, $\mathrm{OC}H_3$), 3.25 (3 H, s, $\mathrm{OC}H_3$), 2.37 (1 H, b, $\mathrm{O}H$), 0.98 (3 H, d, $\mathrm{CHC}H_3$).

(*RS*)-2-Hydroxy-1,1-dimethoxy-1-(4′-isobutylphenyl)propane. With a similar procedure starting from 6.7 g (29.9 mmol) of **3** ([α] +31.2°) and 2.5 g (46.6 mmol) of sodium methoxide, 6.7 g (89%) of (*RS*)-2-hydroxy-1,1-dimethoxy-1-(4′-isobutylphenyl)propane was recovered [^{1}H NMR 7.23 (4 H, dd, aromatic H), 4.10 (1 H, q, $\mathrm{C}H\mathrm{OH}$), 3.36 (3 H, s, $\mathrm{OC}H_3$), 3.20 (3 H, s, $\mathrm{OC}H_3$), 2.45 (2 H, d, $\mathrm{C}H_2$), 2.37 (1 H, s, $\mathrm{O}H$), 1.83 (1 H, m, $\mathrm{C}H(\mathrm{CH}_3)_2$), 0.90 (3 H, d, $\mathrm{CHOHC}H_3$), 0.86 (6 H, d, $\mathrm{CH}(\mathrm{C}H_3)_2$)].

(*S*)-2-(5′-Chloro-6′-methoxy-2′-naphthyl)propionic Acid (14). **2** (10 g, 43.5 mmol) [α] +65.0°, was quantitatively converted into **13**, [α] +76.3°, by treatment with diazomethane in diethyl ether and the usual workup. After treatment of **13** with 6.5 g (87.8 mmol) of 16% sodium hypochlorite, 8.7 mL of 37% HCl in 50 mL of CH_2Cl_2, and 20 mL of water, at 15 °C for 1 h, and workup, 9.7 g (80%) of **12**, [α] +63.0°, was recovered. A sample of **12**, [α] +65.5°, obtained after recrystallization from methanol, was hydrolyzed, following the above reported procedure, to give **14**, [α] +51.0°.

Registry No. **1**, 15687-27-1; **2**, 22204-53-1; **3**, 105538-90-7; **4**, 105538-91-8; **5**, 81576-55-8; **6**, 105538-92-9; **7**, 105538-93-0; **8**, 102770-50-3; **9**, 102849-61-6; **10**, 105538-94-1; **12**, 103477-02-7; **13**, 26159-35-3; **14**, 89617-86-7; **15**, 105538-96-3; **16**, 105538-95-2; ZnClz, 7646-85-7; ZnO, 1314-13-2; (*S*)-2-chloropropionyl chloride, 70110-24-6; isobutylbenzene, 538-93-2; 2,2-dimethyl-1,3-propanediol, 126-30-7; 2-methoxynaphthalene, 93-04-9; 2-bromo-6-methoxynaphthalene, 5111-65-9; 1-chloro-2-methoxynaphthalene, 13101-92-3; (*S*)-2-bromo-1-(5′-chloro-6′-methoxy-2′-naphthyl)propan-1-one, 102770-51-4; (*R,S*)-2-hydroxy-1,1-dimethoxy-1-(6′-methoxy-2′-naphthyl)propane, 83022-48-4; (*R,S*)-2-hydroxy-1,1-dimethoxy-1-(4′-isobutylphenyl)propane, 105616-09-9.