An Efficient Asymmetric Synthesis of a Liquid Crystal

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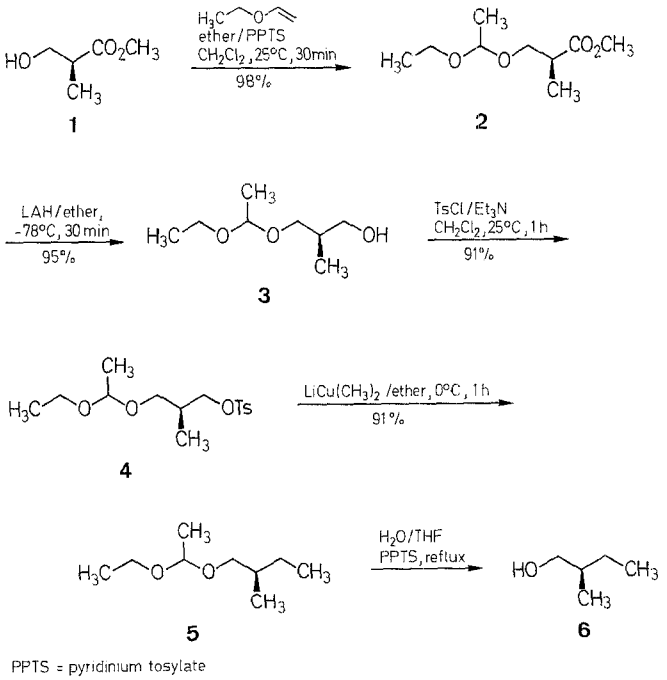
A synthesis of L-(−)-4-(2-methylbutyl)phenyl4′-(2-methylbutyl)biphenyl-4-carboxylate (CE2) and of related chiral liquid crystals has been reported; nevertheless, a detailed experimental and spectrometric characterization of both the intermediates and the final product has been lacking in the literature. We present here the first synthesis of the enantiomer of CE2 with full experimental details including spectroscopic data for each of the intermediates. The description of the synthesis of (*R*)-(+)-2-methylbutanyl will be broadly useful for preparing other liquid crystals with optically active (*R*)-2-methylbutyl side chains.

Chiral liquid crystals have been useful for both technological applications as well as for fundamental studies of phase transitions.[1] It is often desirable to choose a particular liquid-crystalline material on the basis of its phase-transition temperatures. One can subsequently adjust the pitch by mixing the liquid-crystalline material with its enantiomer or with its racemate, without substantially altering the other properties.

During our study of the so-called blue phases[2] of the commercially available tight-pitch cholesteric liquid crystal, 4-(2-methylbutyl)phenyl4′-(2-methylbutyl)biphenyl-4-carboxylate (CE2), we had a need for the racemate. The absolute configuration of both chiral centers in commercially available CE2 is (*S*). Unfortunately, the only "racemic" CE2 available to date is a mixture of equal amounts of the (*R*,*R*), (*S*,*S*), (*R*,*S*), and (*S*,*R*) isomers. A synthesis of CE2R, the enantiomer of commercially available CE2S, was therefore undertaken.[3]

The presence of two asymmetric C-atoms on CE2R makes the synthesis of racemic CE2 rather laborious. In the reported[4] synthesis of CE2S both of the 2-methylbutyl side chains were derived from commercially available (*S*)-(−)-2-methylbutanol. The first obstacle to the synthesis was the unavailability of (*R*)-(+)-2-methylbutanol from a commercial source.[5] Several attempts to resolve the diastereoisomeric esters of racemic 2-methylbutanoic acid with *l*-menthol, *l*-borneol, or *d*-mandelic acid methyl ester by chromatography did not appear promising. Although some separation of the diastereoisomeric esters could be observed, the preparation of several grams of material through this approach promised to be very laborious.

Commercially available methyl(*S*)-(+)-3-hydroxy-2-methylpropanoate (**1**) was converted to the (*R*)-(+) alcohol ***6*** *in five* steps (Scheme **A**). Hydroxyester **1** was converted to the 1-ethoxyethyl derivative **3** in 98% yield by treatment with ethyl vinyl ether in dichloromethane in the presence of pyridinium tosylate. The protection of the alcoholic hydroxy group of **1** as the tetrahydropyranyl derivative was not practical because the boiling points of 2-hydroxytetrahydropyran and 2-methylbutanol are very close. Reduction of ester **2** with lithium aluminum hydride produced alcohol **3** (95% yield) which was converted to tosylate **4** in 91% yield. Displacement of the tosyloxy group with



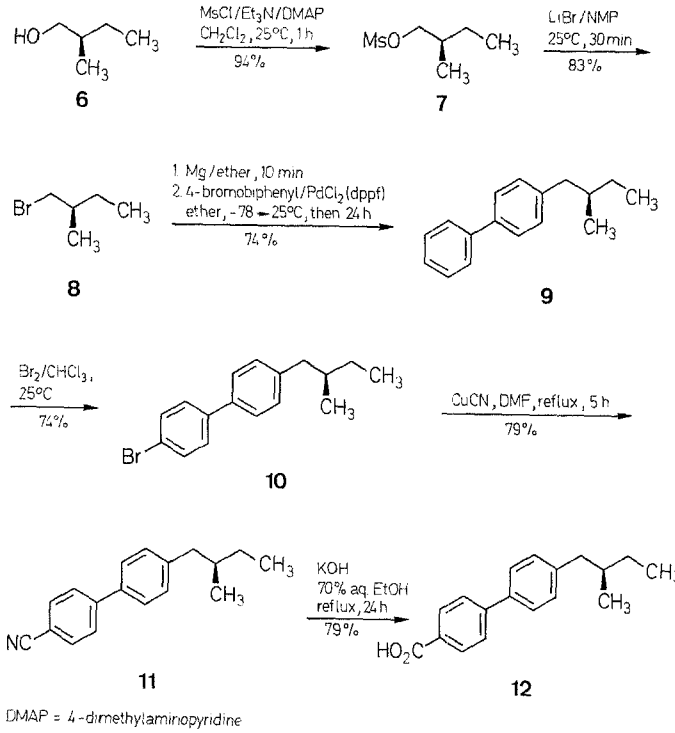
Scheme **A**

lithium dimethylcuprate produced the protected alcohol **5** (91% yield). Hydrolytic removal of the 1-ethoxyethyl protective group was accomplished in 88% yield with pyridinium tosylate in aqueous tetrahydrofuran.

The synthesis of (*R*)-(+)-2-methylbutanol was thus accomplished in 68% overall yield from commercially available hydroxyester. Although this is an efficient process, and is amenable to a large scale, the use of the method of Lit.[4] for coupling the chiral alkyl fragment to each of the aromatic moieties did not appear to be practical. The iron(III) chloride-catalyzed coupling reported[4] typically proceeds in rather modest yields (~ 50% in our hands). This is acceptable where the starting alcohol is the relatively cheap and commercially available (*S*)-(−)-2-methylbutanol. The iron(III) chloride-catalyzed coupling would lead to unacceptable losses of the valuable (*R*)-(+) isomer, therefore an alternative and more efficient coupling procedure was developed. It is worth pointing out that this improved procedure can be used for the coupling of either enantiomer and should be considered the method of choice for the synthesis of both CE2R and CE2S.

The next task prior to coupling was the conversion of (*R*)-(+)-2-methylbutanol to the corresponding bromide. Treatment with methanesulfonyl chloride and triethylamine[6] produced the mesylate in 94% yield. The mesylate was immediately converted to the bromide by stirring at room temperature in *N*-methylpyrrolidone with lithium bromide. The product was isolated by distillation from the reaction mixture in 83% yield. It is worth noting that displacement of the mesylate group by bromide in refluxing acetone led to a product that was contaminated with an impurity which interfered with the subsequent conversion to the Grignard reagent.

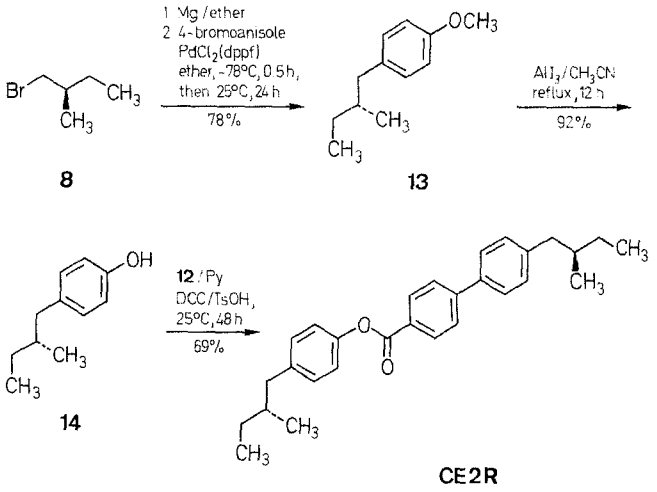
The major side reaction during the transition-metal catalyzed coupling of alkylmetal reagents bearing a hydrogen at C-2 with alkyl or aryl halides is the reductive elimination of a metal hydride. Consequently, the coupling of the Grignard reagent derived from **8** with 4-bromobiphenyl was accomplished with a catalytic amount of $PdCl_2$ (dppf),[7] a catalyst which is known to retard the reductive elimination of metal hydride (Scheme **B**). The yield of **9** from coupling reaction was 74–75%. Treatment of **9** with bromine in chloroform for 3 days at 25 °C produced bromobiphenyl **10** (74–93%). Copper(I) cyanide in refluxing dimethylformamide[8] produced nitrile **11** (79–89%) which was hydrolyzed with base to carboxylic acid **12** in 96–99% yield.



Scheme **B**

The synthesis of the phenol fragment of CE2R is summarized in Scheme **C**. 4-Bromoanisole was coupled with the Grignard reagent derived from **8** using catalytic amounts of $PdCl_2$(dppf)[7] (78% yield). Cleavage of the methyl ether of **13** was effected with aluminum iodide in acetonitrile[9] to produce phenol **14** in 92% yield. The esterification of carboxylic acid **12** with phenol **14** was accomplished with dicyclohexylcarbodiimide in pyridine in the presence of *p*-toluenesulfonic acid as catalyst in 69% yield.

This concludes the enantiospecific total synthesis of CE2R from (*R*)-(+)-2-methylbutanol. The optical purity of the (*R*)-(+)-2-methylbutanol[10] which was used for the preparation of CE2R was > 95% as determined by Mosher analysis.[11] The specific rotation of the neat alcohol was + 5.8°. Furthermore, expansion of the ^{1}H-NMR spectrum of CE2R revealed no shoulders on any of the peaks, from which we conclude that the purity was > 95%. It should be noted that the ^{1}H-NMR spectrum of the commercially obtained CE2S did exhibit shoulders on certain peaks, which we speculate is due to the presence of (*R,S*) and/or (*S,R*) isomers.



Scheme **C**

Flash chromatography was performed on Brinkmann silica gel (0.040–0.063 mm) using mixtures of EtOAc and hexane. TLC was performed on EM reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Electron-impact mass spectra were recorded on a Varian MAT-311 spectrometer. IR spectra were recorded on a Nicolet 5MX FT spectrometer or on a Beckman IR 10. ^{1}H-NMR spectra were recorded at 300 MHz on a Nicolet spectrometer equipped with an Oxford magnet.

Methyl (*S*)-(+)-3-(1-Ethoxyethoxy)-2-methylpropanoate (2):
A 250 mL round-bottom flask equipped with a magnetic stirrer is charged with methyl(*S*)-(+)hydroxymethylpropanoate (**1**; 24.03 g, 203.6 mmol) anhydrous CH_2Cl_2 (80 mL), and pyridinium tosylate (~ 100 mg). Freshly distilled ethyl vinyl ether (73 g, 5 equiv) is added at 25 °C under N_2. After 30 min, the mixture is extracted with aqueous

$NaHCO_3$, followed by H_2O and saturated NaCl solution, and is dried ($MgSO_4$). Solvent evaporation gives product **2**; yield: 37.86 g (199.3 mol, 98%); R_f 0.65 (30% EtOAc in hexane).

MS (70 eV): m/z = (no M^+), 145 ($M^+ - OCH_2CH_3$), 101 [$M^+ - OCH(CH_3)OCH_2CH_3$].

IR (neat): ν = 3005, 2960, 2910, 1735, 1460, 1390, 1350, 1260, 1210–1070, 1015 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$; mixture of ethoxyethyl diastereoisomers): δ = 1.22–1.17 (m, 6H); 1.28, 1.29 (diastereoisomeric CH_3 doublets, 3H, J = 5.3 Hz); 2.74 (m, 1H); 3.69 (s, 3H); 3.77–4.24 (m, 4H); 4.69 (q, 1H, J = 5.3 Hz).

(*R*)-3-(1-Ethoxyethoxy)-2-methylpropanol (3):

A 500 mL round-bottom flask equipped with a magnetic stirrer is charged with ester **2** (29.72 g, 156.4 mmol) and anhydrous Et_2O (175 mL). The solution is cooled to −78 °C and a 1 molar solution of $LiAlH_4$ in Et_2O (80 mL) is added under N_2. After 30 min, the reaction is quenched with the minimum volume of saturated aqueous KH_2PO_4. The Et_2O layer is separated and dried ($MgSO_4$), and the solvent is evaporated. Flash chromatography of the oily product (30% EtOAc in hexane) gives alcohol **3**; yield: 24.09 g (148.7 mmol, 95%); R_f 0.28 (30% EtOAc in hexane).

MS (70 eV): m/z = (no M^+), 147 ($M^+ - CH_3$), 117 ($M^+ - OCH_2CH_3$).

IR (neat): ν = 3400 (broad), 3000–2880 (broad), 1460, 1385, 1350, 1305, 1275, 1230, 1155, 1140, 1100, 1075, 1045 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$; mixture of ethoxyethyl diastereoisomers): δ = 0.81 (d, 3H, J = 7.0 Hz); 1.11 (t, 3H, J = 7.0 Hz); 1.21 (d, 3H, J = 5.3 Hz); 1.87 (m, 1H); 2.89 (br s, 1H); 3.61–3.25 (m, 6H); 4.58 (q, 1H, J = 5.3 Hz).

(*R*)-3-(1-Ethoxyethoxy)-2-methylpropyl Tosylate (4):

A 500 mL round-bottom flask equipped with a magnetic stirrer is charged with alcohol **3** (23.13 g, 142.8 mmol), anhydrous CH_2Cl_2 (125 mL), and Et_3N (25.2 g, 249.0 mmol) under N_2 at 25 °C. A solution of tosyl chloride (34.03 g, 178.5 mmol) in anhydrous CH_2Cl_2 (75 mL) is added to the mixture by cannula. After 1 h, the mixture is extracted with aqueous $NaHCO_3$, followed by H_2O. The organic phase is dried ($MgSO_4$) and the solvent is evaporated. The resulting solid is purified by flash chromatography on silica gel (15% EtOAc in hexane); yield of **4**: 41.13 g (130.2 mmol, 91%); R_f 0.53 (30% EtOAc in hexane).

MS (70 eV): m/z = 316 (M^+), 301 ($M^+ - CH_3$), 271 ($M^+ - OCH_2CH_3$).

IR (neat): ν = 3000, 2950, 2910, 1610, 1460, 1365, 1350, 1315, 1185, 1165, 1145, 1100, 1060, 1030 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$; ethoxyethyl diastereoisomers): δ = 0.89 (d, 3H, J = 6.9 Hz); 1.13 (m, 6H); 2.01 (octet, 1H, J = 6.0 Hz); 2.40 (s, 3H); 7.74 (d, 2H, J = 8.1 Hz); 3.56–3.18 (m, 4H); 3.95 (m, 2H); 4.53 (q, 1H, J = 5.1 Hz); 7.30 (d, 2H, J = 8.1 Hz).

***O*-(1-Ethoxyethyl-protected (*R*)-2-Methylpropanol [Acetaldehyde *O*-Ethyl *O'*-(*R*)-2-Methylpropyl Acetal, (5):**

A 1000 mL round-bottom flask equipped with a magnetic stirrer is charged with CuI (26.99 g, 141.7 mmol) and anhydrous Et_2O (50 mL). The mixture is maintained under N_2 at 0 °C and a 1 molar solution of methyllithium in Et_2O (284 mL, 284 mmol) is added to produce the grayish lithium dimethylcuprate. To this solution is added, at 0 °C *via* cannula, the tosylate **4** (37.33 g, 118.1 mmol) in anhydrous Et_2O (50 mL). After 1 h at 0 °C, the reaction is quenched by pouring the mixture onto ice. The Et_2O layer is dried ($MgSO_4$) and the solvent is evaporated to give product **5**; yield: 17.16 g (107.3 mmol, 91%); R_f 0.91 (30% EtOAc in hexane).

MS (70 eV): m/z = (no M^+) 145 ($M^+ - CH_3$), 115 ($M^+ - OCH_2CH_3$), 103.

IR (neat): ν = 2990, 2925, 2900, 1485, 1470, 1450, 1385, 1350, 1145, 1110, 1075 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$; ethoxyethyl diastereoisomers): δ = 0.84 (t, 6H); 1.11 (m, 2H); 1.15 (t, 3H, J = 7.0 Hz); 1.24 (d, 3H, J = 6.3 Hz); 1.54 (m, 1H); 3.63–3.10 (m, 4H); 4.61 (q, 1H, J = 5.3 Hz).

(*R*)-(+)-2-Methylbutanol (6):

A 250 mL round-bottom flask equipped with a magnetic stirrer is charged with acetal **5** (17.00 g, 106.3 mmol), THF (75 mL), and pyridinium tosylate (100 mg). The mixture is heated to reflux, and H_2O (5 mL) is slowly added in 1 mL portion. The reaction is monitored by TLC, and caution is exercised to insure that a separate aqueous phase does not form. Upon completion of the reaction (~ 2 h), solid $NaHCO_3$ (250 mg) is added to the mixture. Distillation gives alcohol **6**; yield: 8.265 g (93.8 mmol, 88%); bp 130 °C/760 Torr; R_f 0.50 (30% EtOAc in hexane).

MS (70 eV): m/z = 88 (M^+), 70 ($M^+ - H_2O$), 57.

IR (neat): ν = 3340 (broad), 2990, 2950, 2900, 1475, 1390, 1240, 1175, 1135, 1120, 1080, 1050, 1025 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.83 (m, 6H); 1.07 (m, 1H); 1.42 (m, 2H); 2.77 (s, 1H); 3.37 (ddd, 2H, J = 10.5, 6.4, 5.8 Hz).

(*R*)-1-Bromo-2-methylbutane (8):

(R)-1-Methylsulfonyloxy-2-methylbutane (**7**): A 100 mL round-bottom flask equipped with a magnetic stirrer is charged sequentially with (*R*)-(+)-2-methylbutanol (**6**; 8.00 g, 90.8 mmol), anhydrous CH_2Cl_2 (40 mL), Et_3N (16.04 g, 158.8 mmol), and 4-dimethylaminopyridine (75 mg). The reaction is conducted at 25 °C under N_2. To the solution is added methanesulfonyl chloride (13.51 g, 118.0 mmol). After 1 h, the mixture is extracted with aqueous $NaHCO_3$ followed by H_2O. The organic phase is dried ($MgSO_4$) and evaporated and the residue is purified by flash chromatography (15% EtOAc in hexane) to give mesylate **7**; yield: 14.21 g (85.6 mmol, 94%); R_f 0.58 (30% EtOAc in hexane). The mesylate **7** is immediately used in the next step.

MS (70 eV): m/z = (no M^+) 109 ($M^+ - C_4H_9$), 71 ($M^+ - CH_3SO_3$).

IR (neat): ν = 3050, 2960, 2900, 1470, 1420, 1360, 1180, 1115, 1100, 1045 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, J = 7.4 Hz); 0.93 (d, 3H, J = 6.8 Hz); 1.42 (m, 1H); 1.76 (sextet, 1H, J = 6.8 Hz); 1.91 (m, 1H); 2.95 (s, 3H); 4.00 (ddd, 2H, J = 9.4, 6.3, 5.9 Hz).

(R)-1-Bromo-2-methylbutane (**8**): A 100 mL round-bottom flask equipped with magnetic stirrer is charged with *N*-methylpyrrolidone (60 mL) and anhydrous LiBr (8.88 g, 102 mmol). The mixture is heated gently under N_2 to dissolve the LiBr. The flask is cooled to 25 °C and the mesylate **7** (11.32 g, 68.2 mmol) is added. After 30 min, product **8** is distilled from the reaction vessel under vacuum at 25 °C; yield: 8.53 g (56.3 mmol, 83%); bp ~ 25 °C/25 Torr.

MS (70 eV): m/z = 152 ($M^+ + 2$), 150 (M^+), 71 ($M^+ - Br$).

IR (neat): ν = 3000, 2960, 1460, 1390, 1305, 1285, 1220, 1160, 1130, 1055, 1000 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, J = 7.4 Hz); 0.98 (d, 3H, J = 6.7 Hz); 1.27 (quin, 1H, J = 7.4 Hz); 1.46 (quin, 1H, J = 6.0 Hz); 1.69 (m, 1H); 3.35 (ddd, 2H, J = 9.8, 6.0, 5.2 Hz).

(*R*)-4-(2-Methylbutyl)biphenyl (9):

A suspension of magnesium (117 mg, 4.8 mmol) in anhydrous Et_2O (5 mL) is stirred with (*R*)-1-bromo-2-methylbutane (**8**; 725 mg, 4.8 mmol) for 10 min (formation of the Grignard reagent). A solution of 4-bromobiphenyl (932 mg, 4 mmol) in anhydrous Et_2O (3 mL) containing $PdCl_2$(dppf) (34 mg, 0.04 mmol) is chilled to −78 °C. The Grignard solution is transferred by cannula to the cold solution of 4-bromobiphenyl. The mixture is allowed to warm to 25 °C and stirring is continued for 24 h. The reaction is quenched by the addition of 1 molar aqueous HCl (5 mL). The aqueous phase is extracted with Et_2O and the Et_2O layer is dried ($MgSO_4$) and evaporated. The residue is purified by flash chromatography (pentane) to give product **9**; yield: 665 mg (74%); R_f 0.53 (pentane).

MS (70 eV): m/z = 224 (M^+), 167 ($M^+ - C_4H_9$), 152, 115.

IR (neat): ν = 3060, 3030, 2960, 2920, 2880, 2860, 1490, 1460, 1410, 1380, 850, 810 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, 3H, J = 6.7 Hz); 0.93 (t, 3H, J = 7.2 Hz); 1.21 (m, 1H); 1.44 (m, 1H); 1.68 (m, 1H); 2.40 (dd, 1H, J = 13.4, 8.0 Hz); 2.67 (dd, 1H, J = 13.4, 6.2 Hz); 7.60–7.19 (m, 9H).

(*R*)-4-Bromo-4'-(2-methylbutyl)biphenyl (10):

A solution of bromine in $CHCl_3$ (10% v/v, 0.5 mL) is added to a stirred solution of (*R*)-4-(2-methylbutyl)biphenyl (**9**; 224 mg, 1.0 mmol) in

anhydrous $CHCl_3$ (4 mL) and stirring is continued for 36 h at 25 °C in the dark. After 12 h, additional bromine solution (0.5 mL) is added. When no further change in the composition of the mixture can be detected by TLC (~ 72 h), the mixture is diluted with Et_2O (50 mL), washed with aqueous $NaHCO_3$, and dried ($MgSO_4$), and the solvent is evaporated. Flash chromatography (pentane) gives product **10**; yield: 223 mg (74%); R_f 0.60 (pentane).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, 3 H, J = 6.5 Hz); 0.90 (t, 3 H, J = 7.4 Hz); 1.23 (m, 1 H); 1.42 (m, 1 H); 1.70 (m, 1 H); 2.39 (dd, 1 H, J = 13.4, 8.0 Hz); 2.66 (dd, 1 H, J = 13.4, 6.2 Hz); 7.60–7.20 (m, 8 H).

(*R*)-4-Cyano-4'-(2-methylbutyl)biphenyl (11):

A solution of (*R*)-4-bromo-4'-(2-methylbutyl)biphenyl (**10**; 2.27 g, 7.5 mmol) in anhydrous DMF (5 mL) containing CuCN (1.35 g, 15 mmol) is heated to gentle reflux for 5 h. The progress of the reaction is followed by TLC. The mixture is cooled to 25 °C and a mixture of $FeCl_3$ (4 g), concentrated HCl (1 mL), and H_2O (6 mL) is added. The mixture is warmed to 60–70 °C for 30 min to decompose the cyanide complex. Upon cooling to 25 °C, the mixture is extracted with benzene. The benzene extracts are combined, washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated. Flash chromatography (10% EtOAc in hexane) gives nitrile **11**; yield: 1.48 g (79%); R_f 0.43 (10% EtOAc in hexane).

MS (70 eV): m/z = 249 (M^+), 192 ($M^+ - C_4H_9$), 179, 155.

IR (neat): ν = 3000, 2970, 2920, 2260, 1630, 1520, 1480, 1400, 1310, 1200, 1090, 1030, 860 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, J = 6.3 Hz); 0.93 (t, 3 H, J = 7.2 Hz); 1.21 (m, 1 H); 1.42 (m, 1 H); 1.67 (m, 1 H); 2.42 (dd, 1 H, J = 13.4, 8.0 Hz); 2.64 (dd, 1 H, J = 13.4, 6.2 Hz); 7.25 (d, 2 H, J = 8.2 Hz); 7.50 (d, 2 H, J = 8.2 Hz); 7.68 (d, 4 H, J = 3.2 Hz).

***(R)*-4-Carboxy-4'-(2-methylbutyl)biphenyl (12):**

A solution of (*R*)-4-cyano-4'-(2-methylbutyl)biphenyl (**11**; 165 mg, 0.66 mmol) in a 5 molar solution (2 mL) of KOH in 70% EtOH is heated to gentle reflux for 24 h, then diluted with H_2O (~ 3 mL), acidified with concentrated HCl to pH 1, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts are combined, dried ($MgSO_4$), and concentrated. Flash chromatography (hexane/EtOAc 2:1) gives acid **12**; yield: 170 mg (96%); R_f 0.38 (hexane/EtOAc, 2:1); $[\alpha]_D^{19}$ −13.3° (c = 0.9020, $CHCl_3$).

MS (70 eV): m/z = 268 (M^+), 211 ($M^+ - C_4H_9$), 197, 166.

IR (neat): ν = 3600–2400, 2990, 1950, 1900, 1690, 1620, 1440, 1310, 1140, 1310, 1140, 960 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, 3 H, J = 6.5 Hz 3 H); 0.93 (t, 3 H, J = 7.5 Hz); 1.20 (m, 1 H); 1.41 (m, 1 H); 169 (m, 1 H); 2.43 (dd, 1 H, J = 13.4, 8.0 Hz); 2.69 (dd, 1 H, J = 13.4, 6.2 Hz); 7.26 (d, 2 H, J = 6.9 Hz); 7.56 (d, 2 H, J = 6.9 Hz); 7.70 (d, 2 H, J = 6.9 Hz); 8.17 (d, 2 H, J = 6.9 Hz).

(*R*)-1-Methoxy-4-(2-methylbutyl)benzene (13):

A suspension of magnesium (233 mg, 9.6 mmol, 1.2 equiv) in anhydrous Et_2O (10 mL) is stirred with (*R*)-1-bromo-2-methylbutane (**8**; 1.45 g, 9.6 mmol, 1.2 equiv). After the formation of the Grignard reagent is complete a suspension of $PdCl_2$(dppf) (68 mg, 0.08 mmol, 0.01 equiv) in anhydrous Et_2O (6 mL) containing *p*-bromoanisole (1.50 g, 8.0 mmol) is cooled to −78 °C. The Grignard solution is transferred to the suspension of the catalyst and *p*-bromoanisole by cannula, and the mixture is stirred at −78 °C for 0.5 h at 25 °C for 24 h. The reaction is quenched by the addition of 1 molar aqueous HCl (10 mL) and the aqueous layer is extracted with Et_2O. The combined organic extracts are dried ($MgSO_4$), evaporated, and purified by flash chromatography (pentane) to give product **13**; yield: 1.10 g (78%); R_f 0.50 (pentane; **13** stains dark with phosphomolybdic acid whereas *p*-bromoanisole does not stain with this reagent).

MS (70 eV): m/z = 178 (M^+), 177 ($M^+ - 1$), 147 ($M^+ - OCH_3$), 121 ($M^+ - C_4H_9$).

IR (neat): ν = 2950, 2900, 2860, 1610, 1520, 1300, 1250, 1180, 1050, 820 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, 3 H, J = 6.7 Hz); 0.89 (t, 3 H, J = 7.5 Hz); 1.14 (m, 1 H); 1.36 (m, 1 H); 1.57 (m, 1 H); 2.30 (dd, 1 H, J = 13.5, 8.0 Hz); 2.56 (dd, 1 H, J = 13.5, 6.2 Hz); 3.77 (s, 3 H); 6.81 (d, 2 H, J = 8.5 Hz); 7.05 (d, 2 H, J = 8.5 Hz).

(*R*)-4-(2-Methylbutyl)phenol (14):

Aluminum dust (375 mg, 13.9 mmol) is stirred with one drop of a saturated solution of $HgCl_2$ in Et_2O (10 mL) for 10 min. The resultant mixture is washed with anhydrous Et_2O (3 × 10 mL) and is suspended in Et_2O (5 mL). A solution of iodine (4.75 g, 37.4 mmol) in anhydrous Et_2O (20 mL) is added to the aluminum amalgam suspension and the mixture is stirred at 25 °C for 2 h. The solvent is evaporated under a current of dry N_2 and anhydrous acetonitrile (10 mL) is added. A solution of (*R*)-1-methoxy-4-(2-methylbutyl)benzene (**13**; 1.29 g, 7.25 mmol) in anhydrous acetonitrile (5 mL) is added and the mixture is heated to reflux for 12 h. The progress of the reaction is monitored by TLC. The mixture is cooled to 25 °C, 1 molar aqueous HCl (5 mL) is added, and the mixture is extracted with Et_2O. The combined organic phase is dried ($MgSO_4$), and evaporated. Flash chromatography (hexane/EtOAc 20:1) gives phenol **14**; yield: 1.10 g (92%); R_f 0.40 (hexane/EtOAc 10:1); $[\alpha]_D^{19}$ −7.0° (c = 1.554, $CHCl_3$).

MS (70 eV): m/z = 164 (M^+), 107 ($M^+ - C_4H_9$).

IR (neat): ν = 3300, 3050, 2950, 2900, 2870, 1610, 1520, 1460, 1380, 1240, 1130, 1030, 870 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, 3 H, J = 6.7 Hz); 0.90 (t, 3 H, J = 7.5 Hz); 1.15 (m, 1 H); 1.37 (m, 1 H); 1.58 (m, 1 H); 2.30 (dd, 1 H, J = 13.5, 8.0 Hz); 2.56 (dd, 1 H, J = 13.5, 6.2 Hz); 5.15 (s, 1 H); 6.76 (d, 2 H, J = 8.5 Hz); 7.02 (d, 2 H, J = 8.5 Hz).

(*R*)-4-(2-Methylbutyl)phenyl (*R*)-4'-(2-Methylbutyl)biphenyl-4-carboxylate (CE2R):

A solution of (*R*)-4'-(2-methylbutyl)biphenyl-4-carboxylate acid (**12**; 300 mg, 1.12 mmol) and (*R*)-4-(2-methylbutyl)phenol (**14**; 223 mg, 1.34 mmol, 1.2 equiv) in anhydrous pyridine (5 mL) is stirred with *p*-toluenesulfonic acid (20 mg). After a few minutes, dicyclohexylcarbodiimide (466 mg, 2.24 mmol, 2.0 equiv) is added to the solution and the mixture is stirred at 25 °C for 48 h. The mixture is filtered and the solid is washed thoroughly with cold $CHCl_3$. Evaporation of the solvent followed by flash chromatography (pentane/Et_2O, 100:1) gives **CE2R**; yield: 323 mg (69%). The product from chromatography is further purified by recrystallization from 95% EtOH to give colorless crystals; mp 101–102 °C; R_f 0.40 (hexane/EtOAc 20:1); $[\alpha]_D^{19}$ + 14.13° (c = 0.920, $CHCl_3$).

HRMS: exact mass calc. for $C_{29}H_{34}O_2$ 414.2559, found 414.2487.

MS (70 eV): m/z = 414 (M^+), 357, 251, 194, 166.

IR (CH_2Cl_2): ν = 3700, 3630, 2980, 2930, 2410, 1730, 1620, 1520, 1430, 1230, 940 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, 3 H, J = 6.5 Hz); 0.88 (d, 3 H, J = 6.5 Hz); 0.91 (t, 3 H, J = 7.5 Hz); 0.94 (t, 3 H, J = 7.5 Hz); 1.20 (m, 2 H); 1.41 (m, 2 H); 1.67 (m, 2 H); 2.40 (dd, 2 H, J = 13.4, 8.0 Hz); 2.67 (dd, 2 H, J = 13.4, 6.2 Hz); 7.20 (d, 2 H, J = 8.3 Hz); 7.26 (d, 2 H, J = 8.3 Hz); 7.56 (d, 2 H, J = 8.3 Hz); 7.71 (d, 2 H, J = 8.3 Hz); 8.24 (d, 2 H, J = 8.3 Hz).

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