SYNTHESIS OF 2-HYDROXY-8′-(HYDROXYMETHYL)-1,1′-BINAPHTHALENE (iso-HOMO-BINOL). A NEW STRUCTURAL PATTERN IN THE BINAPHTHYL REALM

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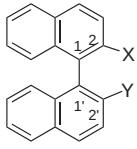
Dedicated to the memory of Professor Otakar Červinka, an inspiring mentor of one of us (P. K.).

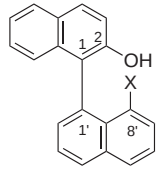
The title compound **7** has been synthesized in a racemic form, using Suzuki coupling (**8** + **15** → **16**) as the key step. Pure enantiomer (*S*)-(–)-**7** has been obtained by carbonylation of the known bromide (*S*)-(+)-**12** followed by reduction of the resulting methyl ester (*S*)-(+)-**18** with $LiAlH_4$.

Keywords: Biaryls; Binaphthyls; Axially chiral ligands; Alcohols; Phenols; Suzuki-Miyaura cross-coupling; NOBIN; Asymmetric reductions.

The classical 2,2′-disubstituted 1,1′-binaphthalenes[1] (Chart 1), such as the homobidentate BINOL [2] (**1**) and BINAP [3] (**2**), and heterobidentate NOBIN [4,5] (**3**), MOP [6] (**4**), and MAP [4i,7] (**5**), are established ligands for generating chiral transition metal catalysts that are utilized in asymmetric reactions.



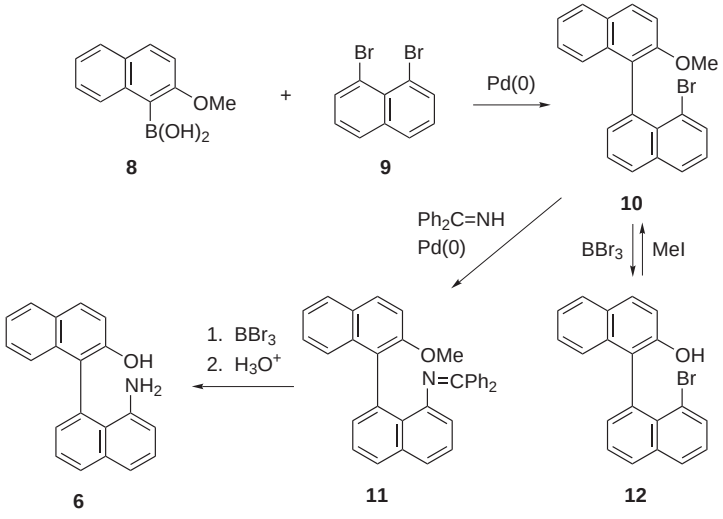
1, X = Y = OH
2, X = Y = PPh_2
3, X = NH_2, Y = OH
4, X = OMe, Y = PPh_2
5, X = NMe_2, Y = PPh_2



6, X = NH_2
7, X = CH_2OH

CHART 1

Recently, we have reported on the novel substitution pattern in the 1,1′-binaphthyl realm, with substituents in 2,8′-positions, in particular iso-NOBIN (**6**), and their application in asymmetric catalysis[8]. iso-NOBIN was synthesized *via* Suzuki coupling of boronic acid **8** with dibromide **9**, followed by Hartwig–Buchwald amination[4h] (**10** → **11**) and removal of the protecting groups[8] (Scheme 1). Enantiomerically pure iso-NOBIN (*S*)-(–)-**6** was prepared from intermediate **12** that was resolved into enantiomers. The absolute configuration of this new series was established by X-ray crystallography[8]. We have also demonstrated high configurational stability of the 2,8′-disubstituted 1,1′-binaphthalenes, which is in the same range as that of the classical 2,2′-disubstituted 1,1′-binaphthalenes[8].



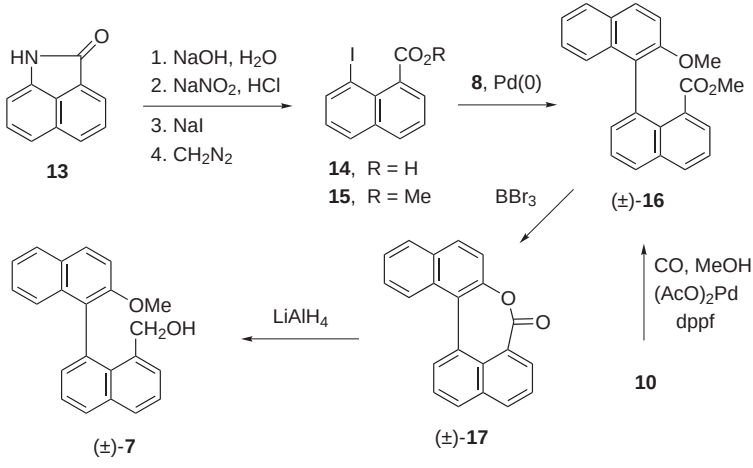
SCHEME 1

In this approach, the key Suzuki coupling proved to be a difficult step, since only the dibromide **9** was successfully coupled with boronic acid **8**. Attempted analogous coupling of **8** with the corresponding bromo derivatives carrying a Lewis basic group in the *peri*-position, such as 1-amino-8-bromonaphthalene or 1-acetamido-8-bromonaphthalene, proved unsuccessful and only a slow reduction of the C–Br bond was observed. Reversed polarity, *i.e.*, using the corresponding 1-boronic acid with a Lewis-basic substituent in 8-position, was also fruitless. For further discussion, see ref.[8]

Having completed the synthesis of iso-NOBIN **6**, we envisaged that a synthesis of the 2,8′-isomer of BINOL would be desirable. At this point, molecular modeling showed that when the potentially coordinating substituent is directly attached to 8-position of the naphthalene moiety, the expected

bidentate complex O–M–X would be too strained, so that chelation becomes unlikely. On the other hand, when a spacer is introduced between 8-position of the naphthalene and the ligating group, such as the CH_2 group in **7**, the geometry appeared much more favorable for the chelation.

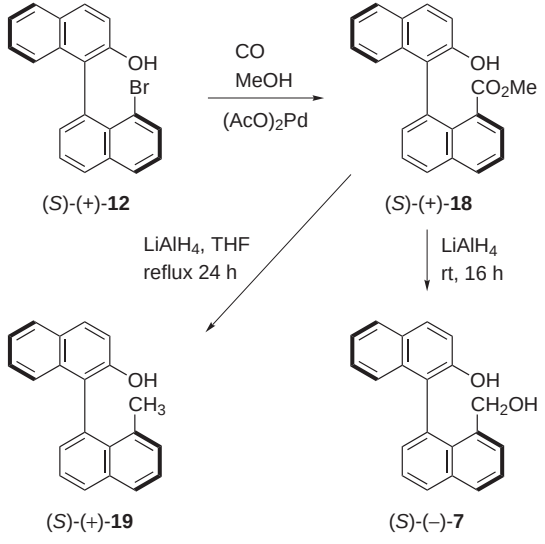
In the synthesis of **7**, we planned to employ the Suzuki coupling as a key step. Since aryl iodides are known to be more reactive than the corresponding bromides[9], we identified iodoester **15** (Scheme 2) as a suitable electrophilic partner for the coupling with boronic acid **8**. To this end, the commercially available benzoindolone **13** was hydrolyzed (NaOH, MeOH–H_2O 1:1, reflux, 20 h) and the resulting, unstable amino acid was immediately subjected to Sandmeyer reaction (HCl, $NaNO_2$, –5 °C, 15 min; then NaI, 0 to 50 °C)[10,11], which gave rise to the iodo acid **14** (43% overall). Esterification of the latter acid (CH_2N_2, Et_2O, 0 °C) afforded the required iodo ester[10] **15** (98%) as a fairly stable compound. Attempts at Suzuki coupling of the latter iodo derivative **15** with boronic acid **8** under our standard conditions employed for the preparation of **10** ($Pd(PPh_3)_4$, Na_2CO_3, DME–water, reflux) proved fruitless, as the reaction led to hydrolysis and dehalogenation of the starting iodo ester **15**. On the other hand, the use of the recent Buchwald protocol[12], designed for simple aromatic bromo and iodo esters, was successful. Under these conditions ($Pd(dba)_2$, dpePhos, K_3PO_4, toluene, 110 °C, 36 h), the desired 2,8′-disubstituted binaphthyl **16** was obtained in good yield (59%). Alternatively, the latter ester was also prepared by the palladium-catalyzed carbonylation of methoxy bromide **10** (CO, $(AcO)_2Pd$, dppf, MeOH, Et_3N, reflux 24 h; 69%). Deprotection of **16** (BBr_3, CH_2Cl_2, room temperature, 2 h) furnished lactone **17** (76%) rather than the expect-



SCHEME 2

ed hydroxy ester[13]. Lactone **17** was then converted into the racemic iso-homo-BINOL (±)-**7** on standard reduction ($LiAlH_4$, THF, room temperature, overnight; 92%). To date, we were not able to find a suitable method for resolution of (±)-**7** (or its precursors) into enantiomers. A small amount of the latter diol was resolved *via* HPLC of the corresponding dimenthyl carbonate, prepared from (±)-**7** by the reaction with (–)-menthyl chloroformate (2 equivalents). However, this method is hardly suitable for large-scale operations.

An alternative method, which also allowed to establish the absolute configuration of **7**, commenced with the palladium(0)-catalyzed carbonylation (Scheme 3) of (*S*)-(+)-**12** (≥99% ee)[8] in methanol (CO, MeOH, $(AcO)_2Pd$ (6 mole %), dppp, reflux, 24 h), which afforded methyl ester (*S*)-(+)-**18** (71%), whose reduction ($LiAlH_4$, THF, room temperature, overnight) produced the desired BINOL analogue (*S*)-(–)-**7** (96%). Interestingly, carrying out the latter reaction at reflux rather than at room temperature, led to the complete reduction of the ester group, affording the methyl derivative[14] (*S*)-(+)-**19**.



SCHEME 3

In conclusion, a new analogue of BINOL, namely diol **7**, with the novel 2,8-disubstitution pattern, has been synthesized in both racemic and enantiomerically pure form. The synthesis of the racemate relied on the Suzuki coupling of boronic acid **8** with iodo ester **15** as the crucial step, followed up by manipulation of the functional groups (Scheme 2). The key

steps in the synthesis of enantiopure (*S*)-(–)-**7** involved the Suzuki coupling of the same boronic acid (**8**) with *peri*-dibromide **9** (Scheme 1), resolution of the hydroxy bromide[8] **12**, and carbonylation of (*S*)-(+)-**12** (Scheme 3). The absolute configuration of the final diol **7** follows from the previously established[8] configuration of **10** and **12**. Applications of this novel diol in asymmetric catalysis will be reported in due course.

EXPERIMENTAL

General Methods

Melting points were determined on a Kofler block and are uncorrected. Boiling points (b.p.) of compounds obtained by kugelrohr (bulb-to-bulb) distillation correspond to uncorrected air bath temperatures. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated with an error less than ±0.1. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra (δ, ppm; *J*, Hz) were recorded in $CDCl_3$, ^1H at 400 MHz and ^{13}C at 100.6 MHz with $CDCl_3$-d_1 (δ 7.26, ^1H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra (ν, cm^{-1}) were recorded for a thin film between KBr plates or for $CHCl_3$ solutions or in a solid by the Golden Gate technique. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen (or argon where specified) in oven-dried glassware twice evacuated and filled with the nitrogen. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether from lithium aluminum hydride; tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane from calcium hydride. Standard workup of an ethereal solution means washing 3× with 5% HCl (aqueous), water, and 3× with 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range of 40–60 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior.

(±)-8′-Hydroxymethyl-1,1′-binaphthalen-2-ol (±)-(**7**)

$LiAlH_4$ (114 mg, 3 mmol) was added to a solution of lactone (±)-**17** (296 mg, 1 mmol) in dry THF (5 ml) and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous Na_2SO_4 solution (10 ml), acidified with 5% aqueous HCl (5 ml), and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (30 g) using toluene, followed by a toluene–ethyl acetate mixture (4:1) as eluent to afford pure (±)-**7** (276 mg, 92%) as a viscous oil. ^1H NMR (400 MHz, $CDCl_3$): 4.04 (d, *J* = 14.1, 1 H); 4.29 (d, *J* = 14.1, 1 H); 5.00 (s, 1 H); 7.01 (dm, *J* = 8.4, 1 H); 7.22–7.27 (m, 1 H); 7.30 (d, *J* = 8.8, 1 H); 7.30–7.35 (m, 1 H); 7.43 (dd, *J* = 6.9 and 1.4, 1 H); 7.51–7.57 (m, 1 H); 7.62 (dd, *J* = 8.2 and 7.00, 1 H); 7.66

(dm, *J* = 7.2, 1 H); 7.85 (dm, *J* = 8.0, 1 H); 7.90 (dd, *J* = 9.0 and 0.8, 1 H); 7.96 (dd, *J* = 8.5 and 1.5, 1 H); 8.06 (dd, *J* = 8.2 and 1.4, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): 63.79 t, 117.52 d, 122.92 s, 123.64 d, 124.55 d, 125.66 d, 126.13 d, 127.04 d, 127.26 d, 128.20 d, 128.79 s, 129.51 d, 129.81 s, 130.09 d, 130.78 s, 130.83 d, 132.17 d, 134.01 s, 135.65 s, 137.70 s, 150.37 s. IR ($CHCl_3$): 3538 (OH), 1621 and 1598 (arom.), 1468 (CH_2), 1055 (C–O). MS, *m/z* (%): 300 ($M^{\bullet+}$, 14), 282 (23), 281 (23), 266 (22), 265 (100), 253 (28), 252 (23), 239 (10), 126 (15), 119.5 (7). HRMS (EI): for $C_{21}H_{16}O_2$ calculated 300.1150, found 300.1148.

(*S*)-(–)-8′-Hydroxymethyl-1,1′-binaphthalen-2-ol (*S*)-(–)-(**7**)

Ester (*S*)-(+)-**18** (100 mg, 0.3 mmol) in dry THF (5 ml) was stirred with heating until a clear solution was obtained. The solution was cooled to room temperature, $LiAlH_4$ (23 mg, 0.6 mmol) was added, and the resulting mixture was stirred overnight at the same temperature. The reaction was quenched by stirring with crystalline $Na_2SO_4 \cdot 10H_2O$ (200 mg) for 5 min. The thick mixture was then filtered through silica gel (5 g), the adsorbent was washed with methanol (3 × 10 ml), and the solvent was evaporated under reduced pressure to afford diol (*S*)-(–)-**7** (88 mg, 0.3 mmol, 96%) as a foam: m.p. 81–82 °C ($CHCl_3$); $[\alpha]_D$ –2.4 (*c* 5.0, $CHCl_3$).

8-Iodo-1-naphthoic Acid (**14**)

1*H*-Benzo[*cd*]indol-2-one (**13**; 16.9 g, 0.1 mol) was suspended in a solution of NaOH (10 g, 0.25 mol) in aqueous methanol (1:1, 200 ml). The mixture was refluxed for 20 h, then cooled to room temperature, and concentrated HCl (50 ml, 0.6 mol) was slowly added[11]. The mixture was cooled to –5 °C and $NaNO_2$ (10 g, 0.145 mol) was slowly added, the mixture was stirred for 15 min and a solution of urea (8.4 g, 0.14 mol) in water (50 ml) was added, followed by a solution of NaI (30 g, 0.2 mol) in water (100 ml). The resulting mixture was stirred at 0 °C for 1 h, then at 20 °C for 2 h, and finally at 50 °C for 2 h. The product was taken up into toluene (4 × 100 ml), the organic extract was washed with 10% aqueous $Na_2S_2O_3$ (2 × 50 ml), brine (50 ml), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (150 g) using chloroform as eluent to give crude iodo acid **14** (13.3 g, 43%). This material was purified by crystallization from a 1:1 water–methanol mixture (100 ml) to give the pure iodo acid[10] **14** (10.8 g, 35%).

Methyl 8-Iodo-1-naphthoate (**15**)

8-Iodo-1-naphthoic acid (8.9 g, 0.03 mol) was dissolved in diethyl ether (200 ml) and cooled to 0 °C. An etheral soulution of freshly made diazomethane (made from Diazald, 12.8 g, 0.06 mol) was then added and the mixture was stirred at 0 °C for 1 h. The diazomethane excess was quenched with acetic acid (3 g) and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (100 g) using toluene–ethyl acetate 5:1 as eluent to give the pure iodo ester[10] **15** (9.17 g, 98%).

(±)-Methyl (2-Methoxy-1,1′-binaphthalenyl)-8′-carboxylate (±)-(**16**)

Method A. An oven-dried Schlenk tube was filled with $Pd(dba)_2$ (184 mg, 0.4 mmol, 10 mole %), dpePhos[12] (258 mg, 0.48 mmol, 12 mole %), iodo ester **15** (1.25 g, 4 mmol), boronic acid **8** (1.62 g, 8 mmol), and K_3PO_4 (2.55 g, 12 mmol). Activated 4Å molecular

sieves were then added, the tube was filled with argon, dry toluene was added (20 ml), and the resulting mixture was heated at 110 °C for 36 h. The mixture was then diluted with water, the organic phase was separated, and the water phase was extracted with ethyl acetate (2 × 20 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (30 g) using toluene as eluent to give pure (±)-**16** (807 mg, 59%): m.p. 164–165 °C (AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): 2.45 (s, 3 H); 3.73 (s, 3 H); 7.30–7.36 (m, 3 H); 7.41–7.52 (m, 4 H); 7.63 (dd, *J* = 8.2 and 6.9, 1 H); 7.81–7.84 (m, 1 H); 7.90 (dd, *J* = 9.1 and 0.8, 1 H); 7.96 (dd, *J* = 8.2 and 1.3, 1 H); 8.03 (dd, *J* = 7.3 and 2.2, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): 50.87 q, 56.24 q, 113.36 d, 123.49 d, 123.57 s, 124.45 d, 125.64 d, 126.02 d, 126.51 d, 127.17 d, 127.63 d, 128.38 s, 128.45 d, 129.05 s, 129.56 d, 131.34 d, 131.64 d, 132.04 s, 133.30 s, 134.19 s, 134.38 s, 154.33 s, 170.57 s. IR ($CHCl_3$): 1720 (CO), 1271. MS, *m/z* (%): 342 ($M^{\bullet+}$, 100), 295 (22), 252 (32), 239 (27), 83 (15). HRMS (EI): for $C_{23}H_{18}O_3$ calculated 342.1256, found 342.1255.

Method B. A stirred solution of (±)-**10** [8] (200 mg, 0.5 mmol), $(AcO)_2Pd$ (16 mg, 0.07 mmol), 1,1′-bis(diphenylphosphino)ferrocene (72 mg, 0.13 mmol) and triethylamine (0.4 ml) in dry methanol (2.0 ml) was heated to 65 °C under an atmosphere of carbon monoxide (from a ballon) for 24 h. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure to afford a brown residue. The crude product was purified using flash chromatography on a silica gel column (5 g) with toluene as the eluent to afford (±)-**16** (120 mg, 0.35 mmol, 64%) as a white solid, identical with the compound obtained by method *A*: m.p. 164–165 °C (AcOEt).

Lactone (±)-**17**

Boron tribromide (4.2 ml of 1 M solution in CH_2Cl_2) was slowly added to a solution of the binaphthyl derivative (±)-**16** (684 mg, 2 mmol) in dry CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h and quenched with brine (20 ml). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 g) using toluene as eluent to give pure (±)-**17** (450 mg, 76%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.48 (m, 2 H); 7.62 (dd, *J* = 8.1 and 7.2, 1 H); 7.62 (d, *J* = 8.8, 1 H); 7.73 (dd, *J* = 8.1 and 7.3, 1 H); 7.81 (dm, *J* = 8.5, 1 H); 7.90 (dm, *J* = 8.0, 1 H); 7.96 (dm, *J* = 8.5, 1 H); 7.97 (dd, *J* = 7.3 and 1.2, 1 H); 8.04 (dd, *J* = 8.2 and 1.4, 1 H); 8.18 (dd, *J* = 8.4 and 1.4, 1 H); 8.56 (dd, *J* = 7.2 and 1.4, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): 121.23 d, 125.06 d, 125.39 d, 125.48 d, 125.87 d, 126.43 s, 126.79 d, 127.06 s, 128.49 d, 129.32 d, 130.65 s, 131.17 d, 131.39 s, 132.57 s, 132.84 s, 133.11 d, 134.26 s, 135.26 d, 135.40 d, 147.29 s, 166.50 s. IR ($CHCl_3$): 1735 (C=O), 1604 (arom.). MS, *m/z* (%): 296 ($M^{\bullet+}$, 76), 294 (18), 269 (22), 268 (100), 252 (9), 251 (9), 240 (10), 239 (46), 237 (19), 148 (6), 134 (6), 133 (5), 120 (10), 119.5 (32), 119 (11), 118.5 (19), 106.5 (9). HRMS (EI): for $C_{21}H_{12}O_2$ calculated 296.0837, found 296.0833.

Methyl (*S*)-(+)-2-Hydroxy-1,1′-binaphthalene-8′-carboxylate (*S*)-(+)-(**18**)

A solution of (*S*)-(+)-**12** (640 mg, 1.8 mmol; ≥99% ee [8]), $(AcO)_2Pd$ (40 mg, 0.2 mmol), 1,1′-bis(diphenylphosphino)ferrocene (195 mg, 0.3 mmol) and triethylamine (1.2 ml) in dry methanol (6.0 ml) was heated to 65 °C while stirring under an atmosphere of carbon mon-

oxide (from a ballon) for 24 h. The mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to afford a brown residue. The crude product was purified using flash chromatography on a silica gel column (5 g) with dichloromethane, followed by a dichloromethane–methanol mixture (80:1) to furnish (*S*)-(+)-**18** (426 mg, 1.3 mmol, 71%) as a white solid: m.p. 236–237 °C (CH_2Cl_2); $[\alpha]_D$ +5.7 (*c* 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO): 2.46 (s, 3 H); 7.22–7.29 (m, 3 H); 7.38–7.41 (m, 3 H); 7.52–7.55 (m, 1 H); 7.66–7.70 (m, 1 H); 7.80–7.85 (m, 2 H); 8.07 (dd, *J* = 8.3 and 1.2, 1 H); 8.15 (dd, *J* = 8.3 and 1.3, 1 H); 9.46 (s, 1 H). ^{13}C NMR (100 MHz, DMSO): 50.83 t, 118.60 s, 120.17 q, 120.68 s, 124.89 s, 125.02 s, 126.37 s, 126.53 s, 127.09 s, 127.97 s, 128.28 q, 128.46 s, 129.33 s, 129.71 q, 131.40 s, 131.83 s, 132.44 q, 133.97 q, 134.42 q, 134.62 q, 152.96 q, 169.68 q. IR (solid): 3371 (OH), 1705 (C=O), 1273. MS, *m/z* (%): 328 ($M^{\bullet+}$, 25), 83 (100), 268 (66), 239 (30), 196 (21), 47 (19). HRMS (EI): for $C_{22}H_{16}O_3$ calculated 328.1099, found 328.1098.

(*S*)-(+)-8′-Methyl-1,1′-binaphthalen-2-ol (*S*)-(+)-(**19**)

A stirred mixture of ester (*S*)-(+)-**18** (180 mg, 0.55 mmol) and $LiAlH_4$ (42 mg, 1.1 mmol) in dry THF (5 ml) was refluxed for 24 h. The reaction mixture was cooled to 0 °C and quenched by stirring with crystalline $Na_2SO_4 \cdot 10H_2O$ (200 mg) for 5 min. The thick mixture was then filtered through silica gel (5 g), which was then washed with ether (3 × 30 ml). The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on a silica gel column (5 g) with a petroleum ether–diethyl ether mixture (10:1) to afford (*S*)-(+)-**19** (105 mg, 0.37 mmol, 67%) as a brown solid: m.p. 128–129 °C ($CHCl_3$); $[\alpha]_D$ +0.9 (*c* 3.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 3.13 (s, 3 H); 4.77 (s, 1 H); 6.95 (d, *J* = 8.3, 1 H); 7.10–7.23 (m, 4 H); 7.29–7.33 (m, 2 H); 7.48 (t, *J* = 7.1, 1 H); 7.72–7.77 (m, 3 H); 7.91 (dd, *J* = 8.2 and 1.1, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): 22.99 s, 117.57 s, 123.71 s, 123.98 q, 125.45 s, 125.85 s, 126.16 q, 126.47 s, 127.08 s, 128.34 s, 129.00 q, 129.94 s, 130.51 s, 131.13 s, 132.08 s, 132.82 q, 134.82 q, 135.80 q, 136.04 q, 150.77 q. IR (solid): 3502, 3433 (OH). MS, *m/z* (%): 284 ($M^{\bullet+}$, 55), 269 (30), 268 (13), 239 (12), 85 (65), 83 (100). HRMS (EI): for $C_{21}H_{16}O$ calculated 284.1201, found 284.1200).

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