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Asymmetric C–C bond formation by the mixed oxidative coupling of 1,1′-bi-2-naphthyl esters

Aurelio G. Csákÿ,* M. Belén Mula, Myriam Mba and Joaquín Plumet

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

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Abstract—Asymmetric C–C bond formation was effected by the oxidative coupling of two different ester enolates using (*R*)-(+)-1,1′-bi(2-naphthol) as a common tether which served to link together both ester moieties in an asymmetric environment. Reduction of the corresponding succinates afforded diastereomerically pure 2,3-disubstituted-1,4-butanediols. © 2002 Published by Elsevier Science Ltd.

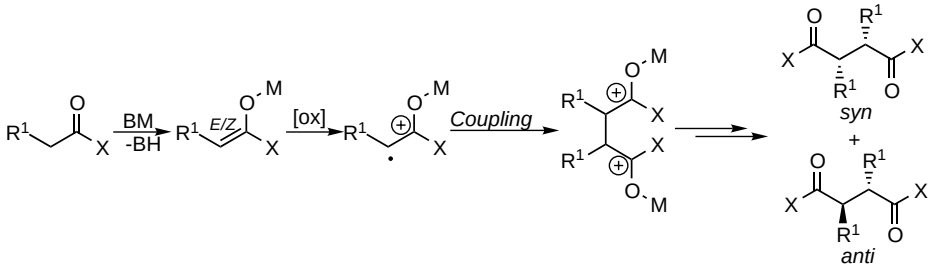
1. Introduction

Asymmetric C–C bond formation is one of the major concerns in modern organic synthesis. Therefore, a wide variety of procedures have been developed for this purpose. Among them, those that make use of enolates have been most amply used.[1]

The coupling of the enolates of carboxylic acid derivatives constitutes a useful extension of the many synthetic possibilities of the chemistry of enolates.[2] This procedure consists of enolization and subsequent oxidation of the enolate to a radical cation followed by an intermolecular coupling.[3] The method allows for a new C–C bond formation, affording 1,4-dicarboxylic acid derivatives (Scheme 1).

One of the key features of the oxidative dimerization reaction of carboxylic acid derivatives is the possibility of achieving a high degree of simple diastereoselectivity (*syn*:*anti* ratio) in the newly formed C–C linkage. All asymmetric variants thus far reported for this reaction make use of chiral amides or esters as starting materials in auxiliary controlled processes. High levels of induced diastereoselectivity have been achieved in this fashion for the homo-coupling of enolates, giving rise to symmetrical (either *meso* or C_2) 1,4-dicarbonyl compounds.

The oxidative mixed coupling of two different enolates would be a useful extension of this C–C bond forming process. However, this reaction is not possible in an intermolecular fashion due to competitive homo-coupling of each of the starting materials, which gives rise to mixtures of all possible homo- and mixed-coupling products.[4] We report herein the first asymmetric coupling of two different ester enolates in an intramolecular fashion, to afford, after reduction, diastereomerically pure 2,3-disubstituted 1,4-butanediols.



Scheme 1.

* Corresponding author. E-mail: csaky@quim.ucm.es

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2. Results and discussion

Our strategy makes use of (*R*)-(+)-1,1′-bi(2-naphthol)[5] (R_a)-**1** as a common tether in order to bring together both ester moieties in a chiral environment. This would allow the mixed coupling of both esters to take place in an intramolecular asymmetric fashion[6] (Scheme 2).

Therefore, (R_a)-**1** was first monoesterified with carboxylic acids **2** (1 equiv., DCC, DMAP, CH_2Cl_2) to give the monoesters **3**. The free hydroxyl group of compounds **3** was then esterified with a different carboxylic acid **2** (1 equiv., DCC, DMAP, CH_2Cl_2) to give the diesters **4**. With the diesters **4** in hand, the intramolecular coupling reaction ($TiCl_4$, Et_3N) was carried out. The results are gathered in Table 1.

The reaction took place without complications of intermolecular coupling, giving rise to the cyclic 1,4-diesters **5**, which were obtained as single diastereomers with *cis* relative stereochemistry between R^1 and R^2. This was evidenced by inspection of their ^1H NMR ($CDCl_3$, 200 MHz) spectra, which were compared with that of **5f** (R^1, R^2 = Ph).[7] High yields were obtained in the mixed coupling of arylacetic esters irrespective of the electron-donating or electron-withdrawing character of the aromatic moiety (entries 1–3).[8,9] Yields were lower when one of the ester counterparts was aliphatic (entry 4), and no mixed coupling reaction was observed when both esters were aliphatic (entries 5 and 6).[10]

Finally, compounds **5** were reduced ($LiAlH_4$, 4 equiv.) to the optically pure 2,3-diarylbutanediols **6**, with complete recovery of the chiral inducer (Table 1). The diastereomeric purity of compounds **6** was determined from the analysis of the ^{19}F NMR ($CDCl_3$, 141.2 MHz) spectra of the corresponding Mosher's diester derivatives. The (2*R*,3*R*)-absolute configuration of compounds **6** was deduced by correlation of the δ value exhibited in the ^{19}F NMR ($CDCl_3$, 141.2 HMz) spectra of the Mosher's diester of (−)-(2*R*,3*R*)-2,3-diphenyl-1,4-butanediol **6f** with previously reported RX data.[7]

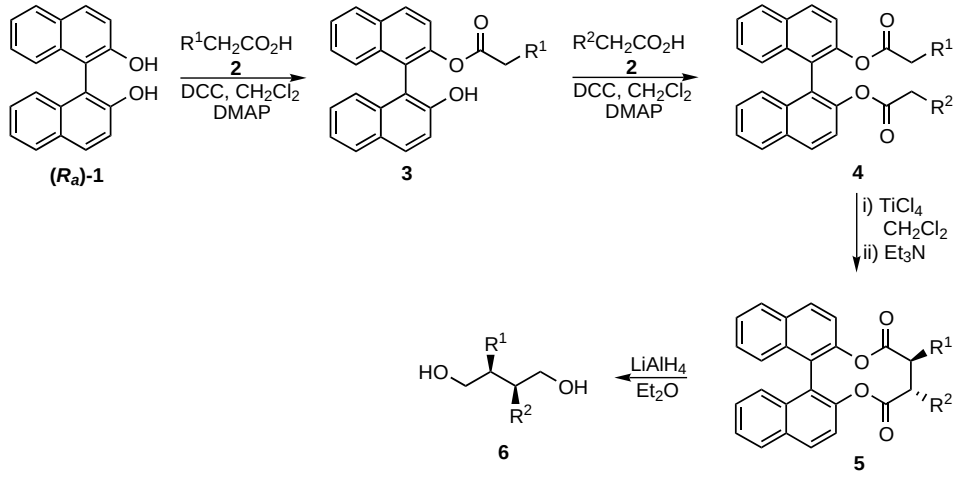
3. Conclusion

In conclusion, in this work we have put forward the scope and limitations of a new method of asymmetric C–C bond formation based on the mixed coupling of ester enolates, which allows for the formation of diastereomerically pure 2,3-disubstituted 1,4-butanediols.

4. Experimental

4.1. General

All starting materials were commercially available research-grade chemicals and used without further purification. CH_2Cl_2 was distilled after refluxing over $CaCl_2$ under Ar. Silica gel 60 F_{254} was used for TLC,



Scheme 2.

Table 1. Mixed intramolecular coupling of binaphthyl esters **4**

No.	**4**	R^1	R^2	**5** (%)[a]	**6** (%)[a]
1	**4a**	Ph	*p*-MeO–C_6H_4	(R_a,2*R*,3*R*)-**5a** (85)	(2*R*,3*R*)-**6a** (70)
2	**4b**	Ph	*p*-CF_3–C_6H_4	(R_a,2*R*,3*R*)-**5b** (85)	(2*R*,3*R*)-**6b** (70)
3	**4c**	*p*-MeO–C_6H_4	*p*-CF_3–C_6H_4	(R_a,2*R*,3*R*)-**5c** (85)	(2*R*,3*R*)-**6c** (70)
4	**4d**	Ph	Et	(R_a,2*R*,3*S*)-**5d** (70)[b]	(2*R*,3*R*)-**6d** (60)
5	**4e**	Et	Pr	**5e** (−)	**6e** (−)

[a] Isolated yields.
[b] The change in absolute stereochemistry corresponds with a change in the CIP-nomenclature rules.

and the spots were detected with UV or vanillin solution. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. ^1H, ^{13}C and ^{19}F NMR spectra were recorded at 200, 50.5 and 141.2 MHz, respectively in $CDCl_3$ solution. MS spectra were carried out by EI at 70 eV.

4.2. General procedure for the synthesis of (R_a)-1,1′-bi-2-naphthol monoesters of alkyl and aryl acids 3

A solution of DCC (1.1 mmol) and DMAP (0.06 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of (R_a)-(+)-1,1′-bi-2-naphthol (1.0 mmol) and the carboxylic acid (1.0 mmol) in CH_2Cl_2 (4 mL) at 0°C. The mixture was allowed to react at 25°C for 3–5 h. Addition of Et_2O, filtration of the precipitate formed and evaporation of the solvent under reduced pressure yielded an oil which was purified by flash chromatography (hexane/diethyl ether 5:1).

4.2.1. Data for (R_a)-phenylacetic acid 2′-hydroxy-[1,1]binaphthalenyl-2-ester 3a. White solid (95% yield), mp = 60–62°C (hexane–AcOEt). IR ($CHCl_3$): ν 3600–3500, 3065, 3034, 1750, 1240 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.35 (s, 2H), 6.40–8.00 (m, 17H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.8, 113.8, 118.2, 121.6, 123.1, 123.5, 124.5, 125.7, 126.3, 126.9, 127.4, 127.9, 128.2, 128.3, 128.8, 129.0, 130.4, 130.7, 132.3, 132.5, 133.5, 148.0, 151.7, 170.8 ppm. Anal. calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98. Found: C, 83.01; H, 5.23%.

4.2.2. Data for (R_a)-(4-methoxyphenyl)acetic acid 2′-hydroxy-[1,1]binaphthalenyl-2-yl ester 3b. White solid (95% yield), mp = 55–57°C (hexane–AcOEt). IR ($CHCl_3$) ν 3600–3500, 3063, 3038, 1758, 1235 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.37 (s, 2H), 3.68 (s, 3H), 5.25 (bs, 1H), 6.40–8.00 (m, 16H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.1, 55.2, 113.9, 117.9, 121.7, 123.3, 124.3, 124.7, 125.7, 126.8, 128.0, 129.1, 129.8 131.4, 133.5, 148.1, 151.7, 158.5, 171.2 ppm. Anal. calcd for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 79.95; H, 5.12%.

4.2.3. Data for (R_a)-propionic acid 2′-hydroxy-[1,1]binaphthalenyl-2-yl ester 3c. Colorless oil (90% yield). IR ($CHCl_3$) ν 3600–3500, 3065, 3030, 2985, 1736, 1224 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.55 (t, J = 7.2 Hz, 3H), 1.95 (q, J = 7.2 Hz, 1H), 2.03, (q, J = 7.2 Hz, 1H) 6.90–8.00 (m, 12H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.9, 27.5, 114.2, 118.4, 121.9, 123.6, 124.7, 125.8, 126.8, 128.4, 148.2, 151.9, 174.0 ppm. Anal. calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.41; H, 5.47%.

4.3. General procedure for the synthesis of (R_a)-1,1′-bi-2-naphthol diesters of alkyl and aryl acids 4

A solution of DCC (1.1 mmol) and DMAP (0.06 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of the corresponding (R_a)-(+)-1,1′-bi-2-naphthol monoester **3** and the carboxylic acid (1.0 mmol) in CH_2Cl_2 (4 mL) at 0°C. The mixture was allowed to react at 25°C for 3–5 h. Addition of Et_2O, filtration and evaporation of the solvent under reduced pressure yielded an oil which was purified by flash chromatography (hexane/diethyl ether 5:1).

4.3.1. Data for (R_a)-(4-methoxyphenyl)acetic acid 2′-phenylacetoxy-[1,1′]binaphthalenyl-2-yl ester 4a. White solid (95% yield), mp = 93–95°C (hexane–AcOEt). IR ($CHCl_3$) ν 3064, 3029, 1753, 1748, 1235 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.23 (s, 2H), 3.29 (2, 2H), 3.65 (s, 3H), 6.40–8.00 (m, 21H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 40.0, 40.8, 55.1, 121.8, 123.4, 125.6, 126.0, 126.7, 126.8, 127.9, 128.2, 129.1, 129.4, 130.0, 133.5, 133.3, 146.8, 158.3, 169.7, 170.0 ppm. Anal. calcd for $C_{37}H_{28}O_5$: C, 80.42; H, 5.11. Found C, 80.59; H 5.36%.

4.3.2. Data for (R_a)-phenylacetic acid 2′-[2-(4-trifluoromethyl-phenyl)acetoxy]-[1,1′]bi-naphthalenyl-2-yl ester 4b. White solid (90% yield), mp = 108–110°C (hexane–AcOEt). IR ($CHCl_3$) ν 3055, 3036, 1755, 1739, 1241 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.32 (s, 2H), 3.38 (s, 2H), 6.60–8.00 (m, 21H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.0, 41.1, 115.4 (q, $^2J_{CF}$ = 196 Hz), 121.6, 121.7, 125.3, 125.9, 126.1, 126.8, 127.0, 128.1, 128.4, 129.2, 129.4, 129.6, 129.7, 148.5, 167.9, 168.5 ppm. Anal. calcd for $C_{37}H_{25}F_3O_4$: C, 75.25; H 4.27. Found: C, 75.43; H 4.48%.

4.3.3. Data for (R_a)-(4-methoxyphenyl)acetic acid 2′-[2-(4-trifluoromethylphenyl)acetoxy]-[1,1′]binaphthalenyl-2-yl ester 4c. White solid (90% yield), mp = 104–106°C (hexane–AcOEt). IR ($CHCl_3$) ν 3053, 3025, 1758, 1753, 1240 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.25 (s, 2H), 3.37 (s, 2H), 3.67 (s, 3H) 6.40–8.00 (m, 20H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 40.0, 40.8, 55.1, 113.7, 115.5 (q, $^2J_{CF}$ = 196 Hz), 121.5, 123.1, 123.4, 125.4, 125.9, 126.8, 128.0, 129.2, 129.4, 130.0, 131.4, 131.6, 133.1, 133.2, 136.7, 146.7, 158.4, 168.8, 170.1 ppm. Anal. calcd for $C_{38}H_{27}F_3O_5$: C, 73.54; H, 4.39. Found C, 73.19; H, 4.47%.

4.3.4. Data for (R_a)-propionic acid 2′-[2-(4-methoxyphenyl)acetoxy]-[1,1′]binaphthalenyl-2-yl ester 4d. Colorless oil (90% yield). IR ($CHCl_3$) ν 3056, 3033, 1757, 1735, 1243, 1213 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.63 (t, J = 7.5 Hz, 3H), 1.97 (q, J = 7.5 Hz, 2H), 3.25 (s, 2H), 3.67 (s, 3H), 6.40–6.70 (m, 4H), 7.10–7.45 (m, 8 H), 7.75–8.02 (m, 4H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 8.7, 27.5, 40.1, 55.2, 113.7, 121.8, 123.4, 123.6, 125.1, 125.6, 126.1, 126.7, 128.0, 129.4, 130.1, 133.4, 146.8, 158.4, 170.1, 172.8 ppm. Anal. calcd for $C_{32}H_{26}O_5$: C, 78.35; H, 5.34. Found: C, 78.13; H, 5.13%.

4.3.5. Data for (R_a)-butyric acid 2′-propionyloxy-[1,1′]binaphthalenyl-2-yl ester 4e. Colorless oil (90% yield). IR ($CHCl_3$) ν 3058. 3031, 2985, 1736, 1218 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.48 (t, J = 7.4 Hz, 3H), 0.61 (t, J = 7.6 Hz, 3H), 1.03–1.30 (m, 2H), 1.95–2.20 (m, 4H), 7.10–8.00 (m, 12H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 8.7, 11.4, 17.9, 27.5, 35.7, 118.2, 121.9, 123.5, 125.6, 126.7, 127.9, 129.3, 133.5, 146.7, 171.8,

172.6 ppm. Anal. calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.64; H, 5.69%.

4.4. General procedure for the intramolecular oxidative coupling of diesters 4

A solution of the diester **4** (0.8 mmol) in dry CH_2Cl_2 (4 mL) was cooled down under argon at –45°C and $TiCl_4$ (3.2 mmol, 1.0 M solution in CH_2Cl_2) was added slowly. The mixture was stirred at –45°C for 30 min and Et_3N (3.2 mmol) was added dropwise. The red solution turned blue–violet, and was allowed to react for a further 3 h at –45°C. The mixture was quenched with HCl (0.5N) and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure yielded an orange solid, which was purified by flash chromatography (hexane/ether 10:1).

4.4.1. Data for (–)-(R_a,2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylsuccinic acid [1,1′]binaphtha-lenyl-2,2′-diol ester 5a. White solid (85% yield), mp = 145–147°C (hexane–AcOEt). $[\alpha]_D^{25} = -78.9$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) *v* 3064, 3034, 1774, 1224 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.60 (s, 3H), 4.36 (s, 2H), 6.50–8.00 (m, 21H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 55.3, 56.4, 56.7, 114.3, 121.3, 122.0, 125.4, 126.0, 127.3, 128.3, 128.5, 129.9, 130.4, 131.9, 133.7, 133.8, 148.2, 159.5, 169.8 ppm. MS (*m*/*z*, %) 550 (41), 237 (100), 209 (64). Anal. calcd for $C_{37}H_{26}O_5$: C, 80.71; H, 4.76. Found: C, 80.52; H, 4.81%.

4.4.2. Data for (–)-(R_a,2*R*,3*R*)-2-(4-trifluoromethyl-phenyl)-3-phenylsuccinic acid [1,1′]binaph-thalenyl-2,2′-diol ester 5b. White solid (85% yield), mp = 163–165°C (hexane–AcOEt). $[\alpha]_D^{25} = -88.2$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) *v* 3056, 3035, 1778, 1232 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.35 (B part of AB system, $J = 11.4$ Hz, 1H), 4.41 (A part of AB system, $J = 11.4$ Hz, 1H), 6.80–8.00 (m, 21H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 56.3, 56.7, 65.8, 120.7, 121.9, 125.9, 126.7, 127.1, 128.1, 128.6, 130.3, 131.7, 133.3, 133.5, 137.6, 147.9, 168.9, 169.1 ppm. MS (*m*/*z*, %) 588 (95), 286 (92), 268 (32), 247 (100). Anal. calcd for $C_{37}H_{23}F_3O_4$: C, 75.50; H, 3.94. Found: C, 73.62; H, 3.71%.

4.4.3. Data for (–)-(R_a,2*R*,3*R*)-2-(4-methoxyphenyl)-3-(4-trifluoromethylphenyl)succinic acid [1,1′]binaphthal-enyl-2,2′-diol ester 5c. White solid (85% yield), mp = 170–172°C (hexane–AcOEt). $[\alpha]_D^{25} = -78.1$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$) *v* 3053, 3034, 1776, 1224 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.68 (s, 3H), 4.38 (B part of AB system, $J = 11.3$ Hz, 1H), 4.50 (A part of AB system, $J = 11.3$ Hz, 1H), 6.50–8.00 (m, 20H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 55.1, 55.9, 56.3, 114.3, 115.5 (q, $^2J_{CF} = 196$ Hz), 120.7, 121.0, 124.6, 125.6, 126.0, 127.2, 128.3, 129.0, 129.7, 130.4, 131.7, 133.5, 147.9, 159.5, 169.6 ppm. MS (*m*/*z*, %) 618 (40), 305 (100), 277 (68). Anal. calcd for $C_{38}H_{25}F_3O_5$: C, 73.78; H, 4.07. Found: C, 73.57; H, 4.21%.

4.4.4. Data for (–)-(R_a,2*R*,3*S*)-2-(4-methoxyphenyl)-3-methylsuccinic acid [1,1′]binaph-thalenyl-2,2′-diol ester 5d. Colorless oil (70% yield). $[\alpha]_D^{25} = -45.7$ (*c* 0.7, $CHCl_3$). IR ($CHCl_3$) *v* 3060, 3034, 2985, 1774, 1748, 1230 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.6$ Hz, 3H), 3.22 (m, 1H) 3.70 (s, 3H), 3.80 (s, 1H), 6.80–8.00 (m, 16H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 8.9, 27.5, 46.2, 54.3, 114.6, 121.0, 121.9, 125.9, 126.7, 127.1, 128.1, 128.6, 130.3, 131.7, 133.3, 133.552, 147.9, 159.8, 170.7, 172.2 ppm. Anal. calcd for $C_{32}H_{24}O_5$: C, 78.67; H, 4.95. Found: C, 78.85; H, 4.71%.

4.5. General procedure for the reduction of diesters 5 into butanediols 6

A solution of diester **5** (0.5 mmol) in dry THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (8.0 mmol) in dry THF (3 mL). The mixture was allowed to react at rt until the reaction was completed (3–5 h, following the reaction by TLC). Ethyl acetate (3 mL), wet diethyl ether (3 mL), water (3 mL) and 0.5N HCl (3 mL) were added in that order to quench excess $LiAlH_4$. The organic layer was separated and the aqueous one was extracted twice with diethyl ether. All the organic layers were combined and dried over $MgSO_4$. Filtration and evaporation of the solvent gave rise to a colorless oil which was purified by flash chromatography (CH_2Cl_2/MeOH 20:1) to give two fractions: the first one was a white solid which was characterized as (R_a)-(+)1,1′-bi-2-naphthol, and the second one was a colorless oil which was characterized as the corresponding compound **6**.

4.5.1. Data for (–)-(2*R*,3*R*)-(4-methoxyphenyl)-3-phenyl-1,4-butanediol 6a. Colorless oil (70% yield). $[\alpha]_D^{25} = -37.2$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$) *v* 3300, 3065, 1603 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.12 (bs, 2H), 3.15 (m, 2H), 3.64 (s, 3H), 3.84 (m, 4H), 6.55–7.18 (m, 9H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 50.0, 51.0, 55.3, 65.6, 65.7, 113.7, 126.6, 128.3, 128.7, 131.5, 132.5, 140.7, 158.3 ppm. Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.83; H, 7.23%.

4.5.2. Data for (–)-(2*R*,3*R*)-2-phenyl-3-(4-trifluoro-methylphenyl)-1,4-butanediol 6b. Colorless oil (70% yield). $[\alpha]_D^{25} = -38.0$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$) *v* 3295, 3060, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.07 (bs, 2H), 3.23 (m, 2H), 3.90 (m, 4H), 6.85–7.15 (m, 9H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 50.8, 51.0, 65.4, 65.7, 115.5 (q, $^2J_{CF} = 196$ Hz), 125.1, 125.2, 126.9, 128.5, 129.1, 131.5, 140.3, 145.4 ppm. Anal. calcd for $C_{17}H_{17}F_3O_2$: C, 65.80; H, 5.52. Found: C, 66.01; H, 5.74%.

4.5.3. Data for (–)-(2*R*,3*R*)-2-(4-methoxyphenyl)-3-(4-trifluoromethylphenyl)-1,4-butanediol 6c. Colorless oil (70% yield). $[\alpha]_D^{25} = -35.5$ (*c* 0.7, $CHCl_3$). IR ($CHCl_3$) *v* 3302, 3057, 1604 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.14 (bs, 2H), 3.19 (m, 2H), 3.65 (s, 3H), 3.90 (m, 4H), 6.55–7.30 (m, 8H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 49.7, 51.0, 55.3, 65.3, 65.7, 113.9, 115.5 (q, $^2J_{CF} = 196$ Hz), 125.1, 125.2, 129.1, 129.5, 132.0, 144.3, 158.4 ppm. Anal. calcd for $C_{18}H_{19}F_3O_3$: C, 63.52; H, 5.63. Found: C, 63.75; H, 5.85%.

4.5.4. Data for (−)-(2*R*,3*R*)-2-(4-methoxyphenyl)-3-methyl-1,4-butanediol 6d. Colorless oil (60% yield). $[\alpha]_D^{25} = -28.5$ (*c* 0.7, $CHCl_3$). IR ($CHCl_3$) *v* 3295, 3055, 1599 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.65 (d, $J = 7.2$ Hz, 3H), 1.95 (m, 1H), 2.65 (m, 1H), 2.70 (bs, 2H), 3.48 (dd, $J = 10.6$, 6.4 Hz, 1H), 3.62 (dd, $J = 10.6$, 4.4 Hz, 1H), 3.71 (s, 3H), 3.79 (dd, $J = 6.3$, 1.1 Hz, 2H), 6.85–7.15 (m, 4H) ppm. ^{13}C NMR (25.5 MHz, $CDCl_3$) δ 19.3, 39.5, 50.8, 55.0, 65.4, 65.7, 113.1, 129.2, 152.6, 158.2 ppm. Anal. calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.71; H, 8.74%.

4.6. General procedure for the synthesis of Mosher's diesters of compounds 6

(+)-(*S*)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (1.25 equiv.), Et_3N (1.25 equiv.) and DMAP (0.015 equiv.) were added to a solution of **6** (0.02 mmol) in anhydrous CH_2Cl_2 (1 mL), and the solution was stirred for 12 h at 20°C. After washing with saturated $NaHCO_3$ (2×1 mL) and 5% HCl (2×1 mL), the organic phase was dried ($MgSO_4$) and evaporated to afford a pale yellow oil.

4.6.1. Data for Mosher's diester of (−)-(2*R*,3*R*)-6a. ^{19}F NMR (141.2 MHz, $CDCl_3$): δ −71.86, −71.89 ppm.

4.6.2. Data for Mosher's diester of (−)-(2*R*,3*R*)-6b. ^{19}F NMR (141.2 MHz, $CDCl_3$): δ −63.03, −71.78, −71.87 ppm.

4.6.3. Data for Mosher's diester of (−)-(2*R*,3*R*)-6c. ^{19}F NMR (141.2 MHz, $CDCl_3$): δ −62.99, −71.72, −71.80 ppm

4.6.4. Data for Mosher's diester of (−)-(2*R*,3*R*)-6d. ^{19}F NMR (141.2 MHz, $CDCl_3$): δ −71.77, −72.06 ppm

4.6.5. Data for Mosher's diester of dl-(2*R,3*R**)-6f**. ^{19}F NMR (141.2 MHz, $CDCl_3$): δ −71.85, −71.87 ppm

4.6.6. Data for Mosher's diester of (−)-(2*R*,3*R*)-6f. ^{19}F NMR (141.2 MHz, $CDCl_3$): δ −71.87 ppm

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