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Enantiopure 2-(Trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1,2-diols from a Tartaric Acid Derived Scaffold

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The synthesis of the four stereoisomers of 2-(trifluoromethyl) tetrahydronaphthalene-1,2-diols and/or their 2-*O*-allyl derivatives is reported. Nucleophilic trifluoromethylation of a tartaric acid derived keto amide, and a one-pot hydrolysis/oxidative cleavage/intramolecular Friedel–Crafts transformation are the main features of this synthesis.

Introduction

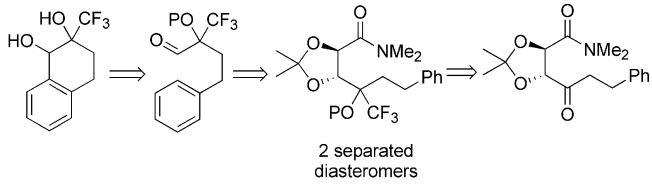
Organofluorine compounds have many applications in various fields, owing to their particular physicochemical and biological properties induced by the presence of the fluorine element.[1] Trifluoromethyl (Tfm) substituted compounds are of particular interest, because of the size, the high metabolic stability, and the hydrophobic character of the trifluoromethyl group.[2] We have recently reported diastereoselective methodologies to prepare enantiopure α-Tfm-α-alkoxy aldehydes from tartaric acid derived diketones[3] and keto amides[4] in only a few steps. The latter, more general, enabled us to prepare both aliphatic and aromatic derivatives, the former being limited to aromatic ones.

On the other hand, several recent patents disclosed the synthesis of Tfm-substituted tetrahydronaphthalene-1,2-diol[5] and 1,2-amino alcohol[6] derivatives as anti-inflammatory compounds. The synthesis was performed in racemic series, some amino alcohols derivatives having been resolved by classical selective crystallization of salt diastereomers. These naphthalenediols were prepared from α-Tfm-α-hydroxy aldehydes.

We report in this paper the synthesis of the enantiopure stereoisomers of the 2-*O*-allyl derivative of 2-(trifluoromethyl)naphthalene-1,2-diols and that of the corresponding diols.

Results and Discussion

The strategy for the asymmetric synthesis of the intermediate aldehydes and of the targeted compounds consists of the retrosynthetic scheme depicted in Scheme 1, which is based on our recently reported methodology,[4] where the key step is a nucleophilic trifluoromethylation of a tartaric acid derived keto amide.



Scheme 1. Retrosynthetic pathway.

O-Allyl trifluoromethylated intermediate **4** was first synthesized from keto amide **2** prepared from the bis(dimethylamide) of tartaric acid (**1**),[7] according to the one-pot procedure depicted in Scheme 2.[4] As previously observed, the trifluoromethylation step with aliphatic ketones is less diastereoselective than it was with aromatic ones, which is advantageous to have access to the whole set of stereoisomers. Unfortunately, the separation of the diastereomers of **4** proved to be difficult and a stepwise procedure had to be carried out. Thus, trifluoromethylation and subsequent desilylation led to carbinols **3**, the diastereomers of which were separated by silica gel chromatography (Scheme 3). Each diastereomer was then protected as the corresponding *O*-allyl ethers **4a** and **4b**. The *R* configuration was ascribed to the major diastereomer according to ^{19}F NMR spectroscopy correlation: the CF_3 signal of the major *R* isomer appears at upper field.[4]

Compounds **4a** and **4b** were then submitted to hydrolysis of the ketal moiety and subsequent oxidative cleavage according to the reported procedure.[4] Under these acidic conditions, the intramolecular Friedel–Crafts reaction was easily activated so that the intermediate aldehyde was directly converted into the final tetrahydronaphthalene derivative **5** as a mixture of easily separated diastereomers. As a

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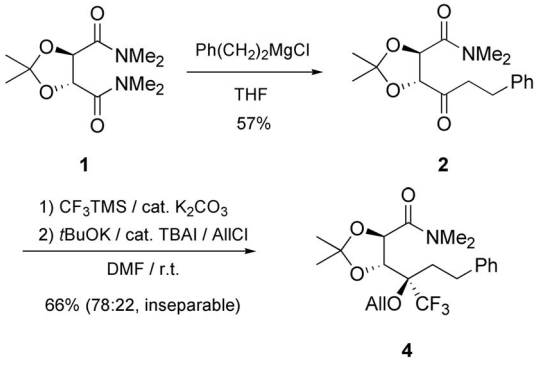
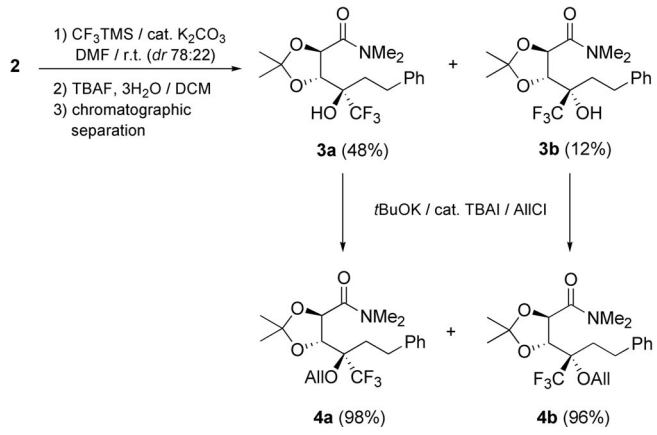
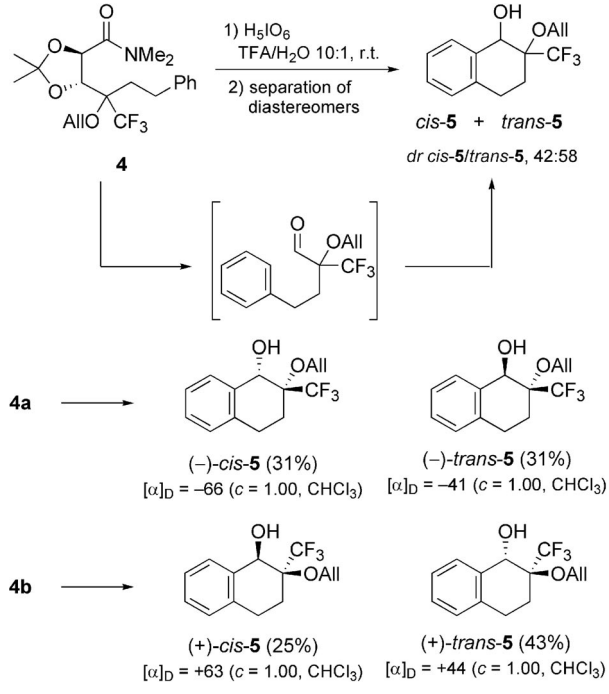


Scheme 2. Direct synthesis of intermediate **4**.



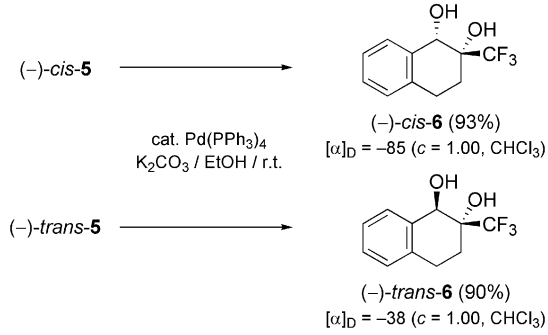
Scheme 3. Stepwise synthesis and separation of intermediates **4**.

result, the four stereoisomers of 2-*O*-allyl-2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1,2-diol were prepared in a one-pot process from intermediate **4** (Scheme 4).



Scheme 4. One-pot, three-step conversion of intermediate **4** into tetrahydronaphthalene derivatives **5**.

Finally, palladium-catalyzed deallylation[8] of (–)-*cis*-**5** and (–)-*trans*-**5** afforded the corresponding enantiopure 2-Tfm-tetrahydronaphthalene-1,2-diols (–)-*cis*-**6** and (–)-*trans*-**6** (Scheme 5).



Scheme 5. Conversion of intermediates **5** into 2-Tfm-tetrahydronaphthalene-1,2-diols (–)-*cis*-**6** and (–)-*trans*-**6**.

Conclusions

We have described the synthesis of enantiopure stereoisomers of 2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1,2-diol in a few steps from L-tartaric acid, a simple chiral-pool-derived starting material. The method is based on a fairly diastereoselective nucleophilic trifluoromethylation reaction with CF_3TMS, the separation of the diastereomers, and their subsequent one-pot transformation involving a sequential ketal hydrolysis/oxidative cleavage/intramolecular Friedel Crafts reaction. Taking into account that D-tartaric acid is also commercially available, the choice of the starting material may be adapted to the targeted stereoisomer.

Further applications of this strategy to the synthesis of valuable enantiopure trifluoromethylated building blocks are in progress and will be reported in a forthcoming paper.

Experimental Section

General Remarks: THF was distilled from sodium–benzophenone. DCM (dichloromethane) was distilled from CaH_2. Trifluoromethylation reactions were carried out in extra-dry DMF. Phenethylmagnesium chloride was titrated through the combined use of (+)-menthol and (1,10)-phenanthroline as indicator.[9] (Trifluoromethyl)trimethylsilane was distilled (b.p. 56 °C) before use. Others reagents and solvents were obtained from common commercial sources and used as received. Thin-layer chromatography using precoated aluminum-backed plates (Merck Kieselgel 60F254) were visualized by UV light and by an alcoholic solution of phosphomolybdic acid or an aqueous solution of potassium permanganate. Silica gel (Macherey–Nagel GmbH & Co KG, 40–63 μm, ASTM for column chromatography) was used for flash chromatography. Preparative centrifugal thin-layer chromatography was carried out on rotors coated with silica gel 60 PF_{254} containing gypsum, the layer thickness was 1 or 2 mm, depending on the amount of product to purify. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured at room temperature (ca. 20 °C). NMR spectra were recorded in $CDCl_3$, at fre-

quencies of 250 MHz or 500 MHz for ^{1}H, 235.3 MHz for ^{19}F, and 62.9 MHz or 125.8 MHz for ^{13}C nuclei. Chemical shifts are reported relative to TMS for ^{1}H and ^{13}C NMR spectra and to $CFCl_3$ for ^{19}F NMR spectra. In the ^{13}C NMR spectroscopic data, reported signal multiplicities are related to C-F coupling. The following abbreviations are used to indicate the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. s (broad singlet). The diastereomeric ratios (*dr*) were determined by ^{19}F NMR spectroscopic analysis of the crude mixture. HRMS (ESI+) were recorded with a spectrometer by using an electrospray source in positive mode. Elemental analysis were performed with a Perkin–Elmer CHN 2400 apparatus and analyses fell within ±0.4% of the calculated values. Isopropylidene-protected bis(amide) **1**[7] was prepared according to reported procedures from dimethyl 2,3-*O*-isopropylidenetartrate.[10]

(+)-(4*R*,5*R*)-2,2-Dimethyl-5-(3-phenylpropanoyl)-[1,3]-dioxolane-4-(dimethyl)carboxylamide (2): To a solution of amide **1** (9.77 g, 40.0 mmol) in THF (50 mL) was added, at –10 °C and under an atmosphere of argon, phenethylmagnesium chloride (44 mL, 44 mmol, 1.1 equiv.). After complete conversion of the starting amide (reaction monitored by GC), the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2×). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography [petroleum ether (PE)/EtOAc, 76:24] afforded keto amide **2** (6.95 g, 57%) as white crystals. M.p. 52 °C (PE/Et_2O). $[\alpha]_D$ = +7 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 2.95 (m, 4 H, CH_2CH_2), 2.98 (s, 3 H, NCH_3), 3.09 (s, 3 H, NCH_3), 4.69 (d, $^3J_{HH}$ = 6.0 Hz, 1 H, C*H*), 5.16 (d, $^3J_{HH}$ = 6.0 Hz, 1 H, C*H*), 7.20 (m, 2 H, *H* aryl), 7.25–7.27 (m, 3 H, *H* aryl) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.0 (*C*H_3), 26.3 (*C*H_3), 29.1 [C(O)*C*H_2], 36.0 (N*C*H_3), 37.1 (N*C*H_3), 41.0 (*C*H_2Ph), 74.9 (*C*H), 82.1 (*C*H), 112.2 [*C*(CH$_3$)$_2$], 126.1, 128.4, 128.5 (*C*H aryl), 140.9 (C_{IV} aryl), 168.0 [*C*(O)N], 208.3 (*C*=O) ppm. HRMS (ESI+): calcd. for [$C_{17}H_{23}NO_4$ + Na]$^+$ 328.1525; found 328.1515.

Preparation of (Trifluoromethyl)carbinols 3: To a solution of keto amide **2** (4.50 g, 14.7 mmol) and CF_3TMS (2.62 mL, 17.7 mmol, 1.2 equiv.) in DMF (30 mL) was added, at room temperature and under an atmosphere of argon, potassium carbonate (203 mg, 1.47 mmol, 0.1 equiv.). After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was diluted in CH_2Cl_2 and tetra *n*-butylammonium fluoride trihydrate (6 g, 19.1 mmol, 1.3 equiv.) was added. After 3 h, the reaction mixture was washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Preparative centrifugal thin-layer chromatography (PE/EtOAc, 90:10) afforded product **3a** (2.6 g, 48%), an intermediate fraction containing **3a** + **3b** (0.33 g, 6%), and product **3b** (0.66 g, 12%) as white crystals.

(–)-(4*R*,5*R*)-5-[(*R*)-1-Hydroxy-3-phenyl-1-(trifluoromethyl)propyl]-2,2-dimethyl-[1,3]-dioxolane-4-(dimethyl)carboxyl-amide (3a): M.p. 98–99 °C (PE/EtOAc). $[\alpha]_D$ = –20 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –78.9 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.99 (m, 1 H, CH_2), 2.17 (m, 1 H, CH_2), 2.87 (t, $^3J_{HH}$ = 8.6 Hz, 2 H, CH_2), 2.99 (s, 3 H, NCH_3), 3.18 (s, 3 H, NCH_3), 4.64 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, C*H*), 4.82 (s, 1 H, O*H*), 4.88 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, C*H*), 7.21–7.33 (m, 5 H, *H* aryl) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.4 (*C*H_3), 26.6 (*C*H_3), 28.9 (*C*H_2), 33.1 (*C*H_2), 36.3 (N*C*H_3), 37.5 (N*C*H_3), 73.7 (q, $^2J_{CF}$ = 27.0 Hz, *C*-CF_3), 74.9 (*C*H), 77.6 (*C*H), 111.1 [*C*(CH$_3$)$_2$], 124.4 (q, $^1J_{CF}$ = 287.0 Hz, *C*F_3), 126.0, 128.3, 128.4 (*C*H aryl), 142.1 (C_{IV} aryl), 170.5 (*C*=O) ppm. $C_{18}H_{24}F_3NO_4$ (375.38): calcd. C 57.60, H 6.40, N 3.73; found C 57.69, H 6.64, N 3.81.

(–)-(4*R*,5*R*)-5-[(*S*)-1-Hydroxy-3-phenyl-1-(trifluoromethyl)propyl]-2,2-dimethyl-[1,3]-dioxolane-4-(dimethyl)carboxyl-amide (3b): M.p. 110–111 °C (PE/EtOAc). $[\alpha]_D$ = –14 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –76.4 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.90–2.16 (m, 2 H, CH_2), 2.70–2.94 (m, 2 H, CH_2), 2.99 (s, 3 H, NCH_3), 3.17 (s, 3 H, NCH_3), 4.62 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, C*H*), 4.66 (d, $^3J_{HH}$ = 8.5 Hz, 1 H, C*H*), 5.37 (s, 1 H, O*H*), 7.19–7.31 (m, 5 H, *H* aryl) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.0 (*C*H_3), 26.4 (*C*H_3), 28.4 (*C*H_2), 34.9 (*C*H_2), 36.0 (N*C*H_3), 37.4 (N*C*H_3), 73.5 (q, $^2J_{CF}$ = 27.0 Hz, *C*-CF_3), 74.6 (*C*H), 77.8 (*C*H), 109.7 [*C*(CH$_3$)$_2$], 125.9 (q, $^1J_{CF}$ = 288.0 Hz, *C*F_3), 125.9, 128.3, 128.4 (*C*H aryl), 141.8 (C_{IV} aryl), 168.9 (*C*=O) ppm. $C_{18}H_{24}F_3NO_4$ (375.38): calcd. C 57.60, H 6.40, N 3.73; found C 57.52, H 6.67, N 3.92.

Preparation of *O*-Allyl Ethers 4: To a solution of carbinol **3** in DMF (≈1 mL/mmol) was added, at room temperature and under an atmosphere of argon, potassium *tert*-butoxide (2.0 equiv.), tetra-*n*-butylammonium iodide (TBAI, 0.10 equiv.), and allyl bromide (AllBr, 2.0 equiv.). After 4 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by preparative centrifugal thin-layer chromatography (PE/EtOAc, 90:10).

(–)-(4*R*,5*R*)-5-[(*R*)-1-Allyloxy-3-phenyl-1-(trifluoromethyl)propyl]-2,2-dimethyl-[1,3]-dioxolane-4-(dimethyl)carboxylamide (4a): According to the general procedure, **3a** (2.4 g, 6.4 mmol) was treated with *t*BuOK (1.44 g, 12.8 mmol, 2.0 equiv.), TBAI (236 mg, 0.64 mmol, 0.1 equiv.), and AllBr (1.04 mL, 12.8 mmol, 2.0 equiv.) in DMF (13 mL). Chromatography afforded **4a** (2.60 g, 98%) as a pale-yellow oil. $[\alpha]_D$ = –17 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –73.6 ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 2.24–2.31 (m, 2 H, CH_2), 2.83 (t, $^3J_{HH}$ = 8.5 Hz, 2 H, CH_2), 2.99 (s, 3 H, NCH_3), 3.15 (s, 3 H, NCH_3), 4.23 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, OC*H*$_a$H$_b$), 4.30 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, OCH$_a$*H*$_b$), 4.94 (d, $^3J_{HH}$ = 6.0 Hz, 1 H, C*H*), 5.16 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 10.5 Hz, 1 H, CH=C*H*$_{cis}$), 5.28 (d, $^3J_{HH}$ = 6.0 Hz, 1 H, C*H*), 5.32 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 17.0 Hz, 1 H, CH=C*H*$_{trans}$), 5.88 (m, 1 H, C*H*=CH$_2$), 7.20–7.23 (m, 3 H, *H* aryl), 7.29–7.32 (m, 2 H, *H* aryl) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.5 (*C*H_3), 26.6 (*C*H_3), 29.3 (*C*H_2), 31.2 (*C*H_2), 35.9 (N*C*H_3), 37.1 (N*C*H_3), 65.4 (O*C*H_2), 72.7 (*C*H-C-CF_3), 77.8 (*C*H-C=O), 79.1 (q, $^2J_{CF}$ = 25.0 Hz, *C*-CF_3), 110.7 [*C*(CH$_3$)$_2$], 116.0 (CH=*C*H$_2$), 125.4 (q, $^1J_{CF}$ = 289.0 Hz, *C*F_3), 126.1, 128.3, 128.5 (*C*H aryl), 134.3 (*C*H=CH$_2$), 141.8 (C_{IV} aryl), 168.9 (*C*=O) ppm. $C_{21}H_{28}F_3NO_4$ (415.45): calcd. C 60.72, H 6.74, N 3.37; found C 60.43, H 6.84, N 3.59. HRMS (ESI+): calcd. for [$C_{21}H_{28}F_3NO_4$ + Na]$^+$ 438.1868; found 438.1875.

(–)-(4*R*,5*R*)-5-[(*S*)-1-Allyloxy-3-phenyl-1-(trifluoromethyl)propyl]-2,2-dimethyl-[1,3]-dioxolane-4-(dimethyl)carboxylamide (4b): According to the general procedure, **3b** (0.80 g, 2.13 mmol) was treated with *t*BuOK (0.48 g, 4.27 mmol, 2.0 equiv.), TBAI (78 mg, 0.21 mmol, 0.1 equiv.), and AllBr (0.35 mL, 4.27 mmol, 2.0 equiv.). Chromatography afforded **4b** (0.85 g, 96%) as a pale-yellow oil. $[\alpha]_D$ = –8 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –70.4 ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.98 (m, 1 H, CH_aH$_b$), 2.22 (m, 1 H, CH$_a$*H*$_b$), 2.77–2.81 (m, 2 H, CH_2), 2.99 (s, 3 H, NCH_3), 3.14 (s, 3 H, NCH_3), 4.22–4.23 (m, 2 H, OCH_2), 4.95 (d, $^3J_{HH}$ = 6.0 Hz, 1 H, C*H*), 5.14 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 10.5 Hz, 1 H, CH=C*H*$_{cis}$), 5.25 (d,

$^3J_{HH}$ = 6.0 Hz, 1 H, C*H*), 5.28 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 17.0 Hz, 1 H, CH=CH_{trans}), 5.86 (m, 1 H, C*H*=CH_2), 7.19–7.21 (m, 3 H, *H* aryl), 7.26–7.30 (m, 2 H, *H* aryl) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.8 (*C*H_3), 26.5 (*C*H_3), 28.7 (*C*H_2), 32.3 (*C*H_2), 36.0 (N*C*H_3), 37.1 (N*C*H_3), 65.2 (O*C*H_2), 72.9 (*C*H-C-CF_3), 78.3 (*C*H-C=O), 79.2 (q, $^2J_{CF}$ = 25.0 Hz, *C*-CF_3), 111.4 [*C*$(CH_3)_2$], 116.0 (CH=*C*H_2), 125.7 (q, $^1J_{CF}$ = 291.0 Hz, *C*F_3), 126.1, 128.3, 128.5 (*C*H aryl), 134.3 (*C*H=CH_2), 141.5 (C_{IV} aryl), 169.1 (*C*=O) ppm. $C_{21}H_{28}F_3NO_4$ (415.45): calcd. C 60.72, H 6.74, N 3.37; found C 60.81, H 6.86, N 3.59. HRMS (ESI+): calcd. for [$C_{21}H_{28}F_3NO_4$ + Na]$^+$ 438.1868; found 438.1863.

Preparation of 2-*O*-Allyl Tetrahydronaphthalene Derivatives 5: To a solution of trifluoromethyl ether **4** in a mixture TFA/H_2O (10:1) was added, at room temperature and under an atmosphere of argon, periodic acid (1.4 equiv.). After 6.5 h the reaction was diluted with Et_2O, quenched with saturated aqueous Na_2CO_3 and extracted with Et_2O (3×). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by preparative centrifugal thin-layer chromatography (PE/Et_2O, 97:3).

(–)-(1*S*,2*R*)-2-(Allyloxy)-2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol [(–)-*cis*-5] and (–)-(1*R*,2*R*)-2-(allyloxy)-2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol [(–)-*trans*-5]: According to the general procedure, **4a** (1.8 g, 4.35 mmol) in a mixture of TFA/H_2O (5.5 mL) was treated with periodic acid (1.38 g, 6.07 mmol). Chromatography afforded successively the products (–)-*cis*-**5** (370 mg, 31%) as a pale-yellow oil and (–)-*trans*-**5** (365 mg, 31%) as white crystals.

(–)-*cis*-5: $[\alpha]_D$ = –66 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –73.5 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99 (ddd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.5 Hz, 1 H, C$H_a$$H_b$-$CH_2$Ar), 2.48 (ddd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H, $CH_a$$H_b$-$CH_2$Ar), 2.50 (br. s, 1 H, O*H*), 2.74–2.96 (m, 2 H, CH_2Ar), 4.23 (d, $^3J_{HH}$ = 5.5 Hz, 2 H, OCH_2), 4.94 (s, 1 H, C*H*OH), 5.10 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 10.5 Hz, 1 H, CH=CH_{cis}), 5.15 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 17.0 Hz, 1 H, CH=CH_{trans}), 5.83 (tdd, $^3J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, C*H*=CH_2), 7.10 (d, $^3J_{HH}$ = 6.5 Hz, 1 H, *H* aryl), 7.18–7.28 (m, 2 H, *H* aryl.), 7.64 (d, $^3J_{HH}$ = 6.5 Hz, 1 H, *H* aryl) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.8 (*C*H_2), 24.4 (*C*H_2), 65.6 (O*C*H_2), 69.7 (O*C*H), 77.1 (q, $^2J_{CF}$ = 25.0 Hz, *C*-CF_3), 117.0 (CH=*C*H_2), 125.9 (q, $^1J_{CF}$ = 290.5 Hz, *C*F_3), 126.7, 127.5, 127.7, and 128.1 (*C*H aryl), 133.7 (*C*H=CH_2), 134.5 and 136.8 (C_{IV} aryl) ppm. HRMS (ESI+): calcd. for [$C_{14}H_{15}F_3O_2$ + Na]$^+$ 295.0922; found 295.0930.

(–)-*trans*-5: M.p. 82–83 °C (PE/EtOAc). $[\alpha]_D$ = –41 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –73.3 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.90 (br. s, 1 H, O*H*), 2.18 (m, 1 H, C$H_a$$H_b$-$CH_2$Ar), 2.38 (m, 1 H, $CH_a$$H_b$-$CH_2$Ar), 2.89–2.98 (m, 2 H, CH_2Ar), 4.12 (d, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, OC$H_a$$H_b$), 4.19 (d, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, OC$H_a$$H_b$), 4.91 (s, 1 H, C*H*OH), 5.00 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 10.5 Hz, 1 H, CH=CH_{cis}), 5.02 (dd, $^2J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 17.0 Hz, 1 H, CH=CH_{trans}), 5.69 (tdd, $^3J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 5.0 Hz, 1 H, C*H*=CH_2), 7.13–7.38 (m, 4 H, *H* aryl) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.1 (*C*H_2), 24.3 (*C*H_2), 65.7 (d, $^4J_{CF}$ = 2.0 Hz, O*C*H_2), 69.1 (O*C*H), 78.1 (q, $^2J_{CF}$ = 25.0 Hz, *C*-CF_3), 116.3 (CH=*C*H_2), 126.4 (q, $^1J_{CF}$ = 290.0 Hz, *C*F_3), 126.7, 128.4, 128.7, 130.0 (*C*H aryl), 134.1 (*C*H=CH_2), 135.2 and 135.4 (C_{IV} aryl) ppm. HRMS (ESI+): calcd. for [$C_{14}H_{15}F_3O_2$ + Na]$^+$ 295.0922; found 295.0921.

(+)-(1*R*,2*S*)-2-(Allyloxy)-2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol [(+)-*cis*-5] and (+)-(1*S*,2*S*)-2-(Allyloxy)-2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol [(+)-*trans*-5]: According to the general procedure, **4b** (500 mg, 1.21 mmol) in a mixture TFA/H_2O (3.3 mL) was treated with periodic acid (384 mg, 1.69 mmol). Chromatography afforded successively the products (+)-*cis*-**5** (82 mg, 25%) as a pale-yellow oil and (+)-*trans*-**5** (140 mg, 43%) as white crystals. Data for (+)-*cis*-**5**: $[\alpha]_D$ = +63 (*c* = 1.00, $CHCl_3$). Data for (+)-*trans*-**5**: M.p. 84–85 °C (PE/EtOAc). $[\alpha]_D$ = +44 (*c* = 1.00, $CHCl_3$).

Preparation of Tetrahydronaphthalene-1,2-diol Derivatives 6: To a solution of 2-(allyloxy)-tetrahydronaphthalenols **5** (300 mg, 1.1 mmol) in EtOH (20 mL) was added, at room temperature and under an atmosphere of argon, tetrakis(triphenylphosphane)palladium (64 mg, 0.055 mmol, 0.05 equiv.) and potassium carbonate (453 mg, 3.3 mmol, 3 equiv.). The mixture was heated for 30 to 45 min, then cooled to room temperature. Et_2O (20 mL) was added, and the mixture was filtered through Celite. The filtrate was washed with brine (2×), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative centrifugal thin-layer chromatography (PE/EtOAc, 85:15).

(–)-(1*S*,2*R*)-2-(Trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1,2-diol [(–)-*cis*-6]: Prepared from (–)-*cis*-**5**; reaction afforded (–)-*cis*-**6** (237 mg, 93%) as white crystals. M.p. 90–91 °C (PE/EtOAc). $[\alpha]_D$ = –85 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –81.1 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.93 (m, 1 H, C$H_a$$H_b$-$CH_2$Ar), 2.27 (m, 1 H, $CH_a$$H_b$-$CH_2$Ar), 2.70 (m, 1 H, C$H_a$$H_b$-Ar), 2.94 (s, 1 H, O*H*), 3.13 (m, 1 H, $CH_a$$H_b$-Ar), 3.66 (s, 1 H, O*H*), 5.08 (s, 1 H, C*H*OH), 7.13 (m, 1 H, *H* aryl), 7.25–7.28 (m, 2 H, *H* aryl), 7.53 (m, 1 H, *H* aryl) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.6 (*C*H_2-Ar), 26.1 (*C*H_2-CH_2Ar), 66.6 (O*C*H), 72.4 (q, $^2J_{CF}$ = 26.0 Hz, *C*-CF_3), 126.2 (q, $^1J_{CF}$ = 286.7 Hz, *C*F_3), 126.7, 127.9, 128.1 and 128.4 (*C*H aryl), 134.4 and 135.8 (C_{IV} aryl) ppm. $C_{11}H_{11}F_3O_2$ (232.20): calcd. C 56.89, H 4.74; found C 56.51, H 4.47.

(–)-(1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(trifluoromethyl)naphthalene-1,2-diol [(–)-*trans*-6]: Prepared from (–)-*trans*-**5**; reaction afforded (–)-*trans*-**6** (229 mg, 90%) as white crystals. M.p. 128–129 °C (PE/EtOAc). $[\alpha]_D$ = –38 (*c* = 1.00, $CHCl_3$). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –78.9 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.96–2.01 (m, 2 H, $CH_a$$H_b$-$CH_2$Ar, O*H*), 2.28–2.35 (m, 2 H, C$H_a$$H_b$-$CH_2$Ar, O*H*), 2.92–2.98 (m, 2 H, CH_2-Ar), 4.69 (s, 1 H, C*H*OH), 7.15–7.35 (m, 4 H, *H* aryl) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.8 (*C*H_2-Ar), 23.9 (*C*H_2-CH_2Ar), 70.5 (O*C*H), 74.2 (q, $^2J_{CF}$ = 26.7 Hz, *C*-CF_3), 125.9 (q, $^1J_{CF}$ = 285.4 Hz, *C*F_3), 126.8, 128.6, 128.7 and 130.0 (*C*H aryl), 134.8 and 134.9 (C_{IV} aryl) ppm. $C_{11}H_{11}F_3O_2$ (232.20): calcd. C 56.89, H 4.74; found C 57.10, H 4.88.

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