Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02880 • Publication Date (Web): 30 Dec 2019

Synthesis of CBD and Its Derivatives Bearing Various C4'-side Chains with a Late-Stage Diversification Method

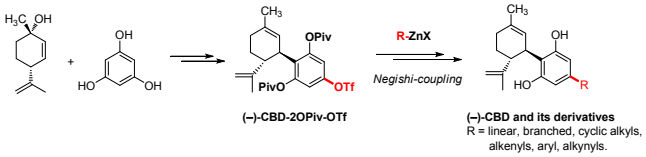
Xudong Gong,[†, ⊥] Changliang Sun,[§] Melkamu Alemu Abame,[‡] Wenqiang Shi,[‡] Yuanchao Xie[‡], Wanbin Xu,[‡] Fuqiang Zhu,[§] Yan Zhang,[‡] Jingshan Shen,*[, ‡] and Haji A. Aisa*[, †]

[†]The Key Laboratory of Plant Resources and Chemistry in Arid Regions and Key Laboratory of Xinjiang Indigenous Medicinal Plants Resource Utilization, Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, South Beijing Road 40-1, Urumqi, Xinjiang 830011, People's Republic of China

[⊥]University of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, People's Republic of China.

[§]Topharman Shanghai Co., Ltd., Building 1, No. 388 Jialilue Road, Zhangjiang Hitech Park, Shanghai 201209, People's Republic of China

[‡]CAS Key Laboratory for Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, People's Republic of China



Abstract

A novel synthetic route for making (−)-CBD and its derivatives bearing various C4'-side chains is developed by a late-stage diversification method. Starting from commercially available phloroglucinol, a key intermediate (−)-CBD-2OPiv-OTf is efficiently and regioselectively prepared and further undergoes Negishi cross-coupling to furnish (−)-CBD. This approach allowed an efficient synthesis of (−)-CBD in a five-step total 52% yield on a 10 g scale. Furthermore, diversification on the C4'-side chain with this method can be realized in a wide range.

Cannabinoids as the hallmark constituents of Cannabis and their analogs have been drawing keen attention from scientists due to their potential medical use.[1, 2] (−)-Cannabidiol ((−)-CBD) (**Figure 1**), a nonpsychotropic cannabinoid, has been approved for the treatment of seizures associated with Lennox–Gastaut syndrome and Dravet syndrome in patients 2 years

of age and older, by the United States Food and Drug Administration (U.S. FDA) in June, 2018.[3] Cannabidivarin (CBDV) is currently in phase II clinical trials for the treatment of epilepsy and in early clinical development for the treatment of autism spectrum disorders.[4] And other natural and synthetic derivatives of cannabidiol especially those with various C4'-side chains in place of the pentyl group, such as cannabidiorcol (CBD-C1) and KLS-13019, also demonstrate attractive biological activity.[1, 2, 5, 6] However, the bioactivities of many cannabinoids have not been well-studied, partially due to the lack of availability either by natural product separation or chemical synthesis.[5,7] Thus a synthetic way to obtain these cannabinoid compounds would enable more understanding of their pharmacological profiles.

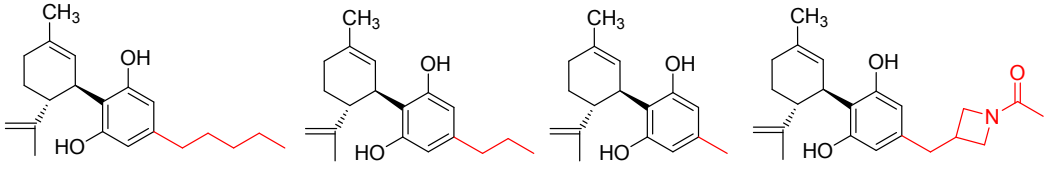
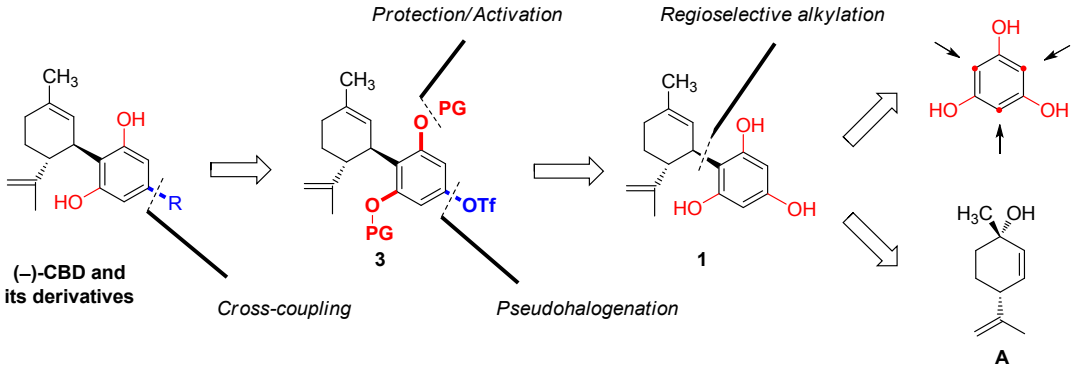


Figure 1. (−)-CBD and its natural or synthetic derivatives with various side chains in place of the pentyl group.

At present, CBD for pharmaceutical use is mainly extracted and purified from *Cannabis sativa L.* plants.[8] Though studies on CBD chemistry have been going on for about 80 years,[9–14] no significant progress has been made in this area till now. Conventionally, each of CBD and its derivatives is prepared by Friedel-Crafts alkylation of specific resorcinol which bears a side chain at C5 site with (+)-*p*-mentha-2,8-dien-1-ol (**A**). Condensation of olivetol with **A** in the presence of boron trifluoride as a weak acid gives the stereospecific CBD.[15] The acid condition required by this strategy and poor regioselectivity of the aromatic ring, inevitably, contributed to significant formation of byproducts, such as THC and abnormal cannabidiol (abn-cbd),[11] which is the reason for low yields and why cumbersome purification process is needed to obtain pure CBD.[9] Furthermore, a specific resorcinol derivative that has to be prepared by multiple steps is required as the starting material for each CBD derivative, which makes the structural modification work of CBD laborious. Hence, a generally applicable modular way allowing late-stage structural diversification would be suitable.

Through retrosynthetic analysis, we proposed our synthetic strategy for (−)-CBD and its C4'-substituted derivatives as outlined in **Scheme 1**. Considering that 5-substituted resorcinol displayed poor regioselectivity between the two nucleophilic substitution sites, we selected commercially available symmetric phloroglucinol, which has been used in the synthesis of THC and its analogs[16–19] as the starting material, to avoid the generation of positional isomers (abnormal CBDs) during the synthesis of **1**. In addition, the key intermediate **3** could be prepared from **1** in two steps through regioselective triflation and activation/protection. Finally, (−)-CBD and its derivatives could directly derive from **3** by late-stage cross-coupling chemistry. Herein, we reported a detailed study on this elegant approach to construct CBD and its analogs using (−)-CBD-2OPiv-OTf as a building block for the late-stage introduction of side chains by Negishi cross-coupling reaction.

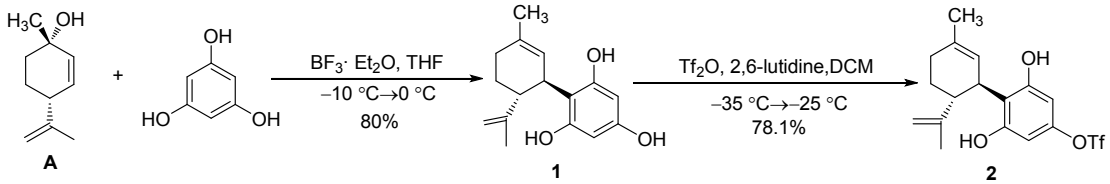
Scheme 1 Synthesis of (−)-CBD and its derivatives bearing various C4'-side chains with a late-stage diversification strategy



As Friedel-Crafts alkylation of phloroglucinol with **A** in a ratio of 1:1.5 gave the target compound **1** only in 50% yield, similar to the result of a patent method,[20] we started our study with the aim of improving the yield of this step. A considerable number of experiments have shown that double alkylation of phloroglucinol was the major side reaction, so a large excess of phloroglucinol (10 eq), which can be recovered after the reaction by simple filtration, was used to avoid double alkylation, leading to the desired product **1** in an excellent 80% yield (**Scheme 2**).

Regioselective triflation of the C4' phenolic hydroxyl group of **1** has never been reported previously, despite the fact that various ways of sulfonylation have been developed over the past years.[18, 19, 21–24] We hypothesized that the C4' phenolic hydroxyl group can be differentiated from the other two at C2' and C6' positions due to the steric hindrance of the terpenoid moiety and thus selective functionalization of the least hindered para-hydroxy group at C4' position would be possible. Accordingly, we performed an extensive investigation on the regioselective triflation. The result revealed that aryl triflate **2** could be smoothly prepared by treatment of **1** with Tf_2O in the presence of 2,6-lutidine at −30 to −20 °C in CH_2Cl_2. We used 1.5 equiv of **1**, which could be recycled after reaction, to prevent double triflation. Finally, triflate **2** was isolated by silica gel column chromatography in 78.1% yield (**Scheme 2**).

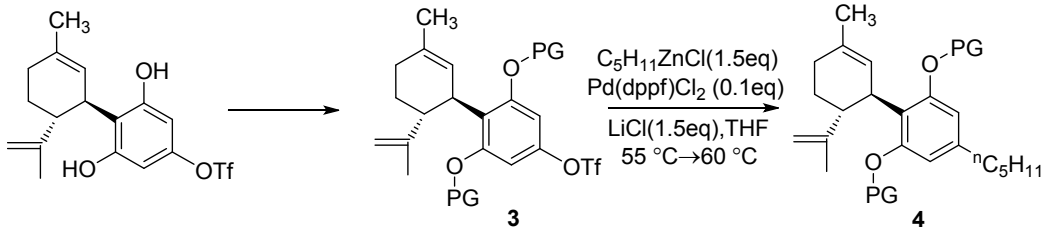
Scheme 2 The Synthetic Route of Triflate 2



Transition metal-mediated reactions such as Stille cross-coupling, Kumada cross-coupling, Suzuki-Miyaura cross-coupling, and especially Negishi cross-coupling reaction, which was discovered in the 1970s, have been widely utilized for carbon-carbon bond formation, including bond formation between trifluoromethanesulfonate and alkyl group.[25–32] To prepare CBD efficiently, initially, we attempted to introduce the pentyl side chain to **2** directly via sp^2-sp^3 bond formation (**Table 1**, entry 1**)**. Disappointingly, although cross-coupling reactions

using known Pd or Fe catalysts and various ligands and solvents have been carried out, unsatisfied yields were obtained (data not shown). The highest yield obtained was about 20% by treating **2** with excess $C_5H_{11}ZnCl$ (10 eq) in the presence of LiCl and a catalytic amount of $Pd(dppf)Cl_2$. We presumed that it was difficult to form the organopalladium intermediate state through the oxidative addition of a metal to the electron-rich phenolate state of **2** in the basic enviroment of the coupling reaction.[17, 33] Taking into account this problem, we adopted the phenolic hydroxyl protection strategy to investigate whether the Negishi cross-coupling could be influenced by the phenolic protecting groups of **3** (**Table 1**).

Table 1. Protecting group survey in Negishi cross-coupling reaction



entry	PG	products, yield(%)[a]	products, yield(%)[a, b]
1	H	/	**CBD**, 20
2	Me	**3a**, 80	**4aa**, 56 [c]
3	Ac	**3b**, 95	**4ba**, 20
4	*p*-NO_2-Bz	**3c**, 96	**4ca**, 0
5	Boc	**3d**, 99	**4da**, 50
6	Piv	**3e**, 95	**4ea**, 90 [d]
7	Ts	**3f**, 95	**4fa**, 81

[a] The isolated yields were calculated after purified by column chromatography unless otherwise mentioned. [b] The reactions were conducted on a 0.5−1 mmol scale unless otherwise noted. [c] Reaction was conducted with the same condition except using 3 equiv of $C_5H11ZnCl$ and 3 equiv of LiCl. [d] Reaction was performed on a 28 g scale.

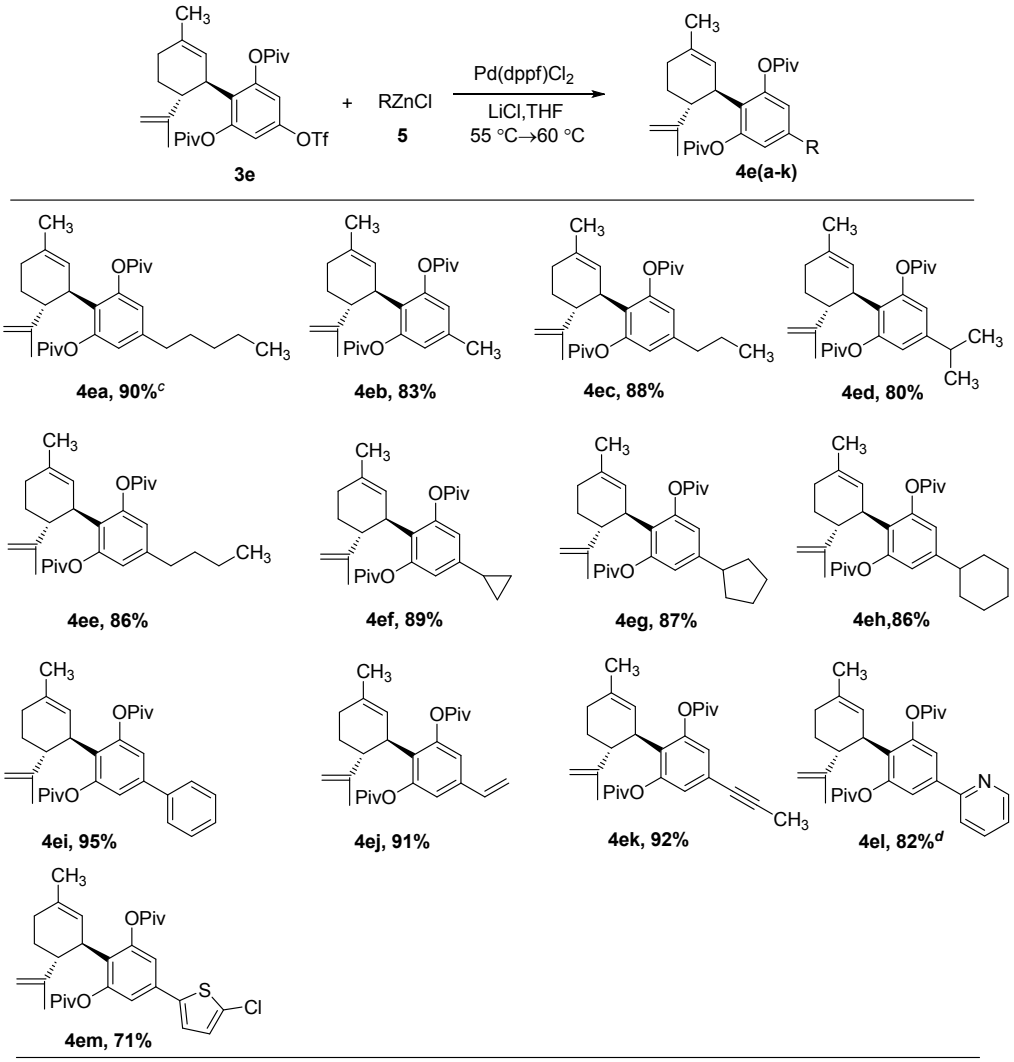
3a[9], **3b**[34], **3c**[35], **3d**[36], **3e**[37] and **3f**[38] were new compounds but could be prepared on the basis of the reference literature in yields of 80%, 95%, 96%, 99%, 95% and 95%, respectively. Methyl as an electron-donating protecting group was first employed to prepare **4aa (Table 1**, entry 2**)**. The reaction of methyl ether **3a** with $C_5H_{11}ZnCl$ in the presence of LiCl and a catalytic amount of Pd(dppf)Cl_2 gave **4aa** in a higher yield (56%) than that obtained by the direct preparation of CBD **(Table 1**, entry 1**)**. We hypothesized that the unsatisfied yield of Negishi cross-coupling as displayed in **4aa** is caused by the difficulty of oxidative addition in the presence of -OMe. Next, we explored the possibility of efficiently accessing **4** from **3** with electron-withdrawing protecting groups (**3b−f**).

Ac group (**3b**), p-NO_2-Bz group (**3c**), and Boc (**3d**) group as protecting groups were then utilized to prepare **4ba**, **4ca**, and **4da**, respectively (**Table 1**, entries 3−5); however, no acceptable yield was obtained. Particularly, when treating **3c** with $C_5H_{11}ZnCl$ in the presence of LiCl and a catalytic amount of Pd(dppf)Cl_2 in anhydrous THF at 55−60 °C, no trace of p-nitrobenzoic ester **4ca** was detected (**Table 1**, entry 4). Intermediates **3b**, **3c**, or **3d** were supposed to be preferentially hydrolyzed under the alkaline condition of the Negishi cross-coupling reaction, which resulted in low yields. Then we tried the "Piv" group (**3e**), which is a large sterically hindered protecting group and is relatively more stable than other protecting groups under basic conditions. To our delight, **4ea** was successfully obtained in an excellent yield (90%) **(Table 1**, entry 6**)**. Sulfonate ester **4fa (Table 1**, entry 7**)** was prepared by reaction of Ts ester **3f** with $C_5H_{11}ZnCl$ in the presence of LiCl and a catalytic amount of Pd(dppf)Cl_2 at 60 °C for 3 h in a little lower yield (81%) than that of **4ea**.

It seemed that a "stable" electron-withdrawing phenolic protecting group (**Table 1**, entry 6 *vs* entry 2) could promote the formation of the organopalladium intermediate state through the

electronic effect in the Negishi cross-coupling reaction. Obviously, the pivalate group was a more superior protecting group; thus, (−)-CBD-2OPiv-OTf (**3e**) as a building block was chosen to be applied to the late-stage introduction of side chains to the core of CBD by the Negishi cross-coupling reaction (**Table 2**).

Table 2. Negishi-coupling of the key intermediate with various organic zinc reagents[a,b].



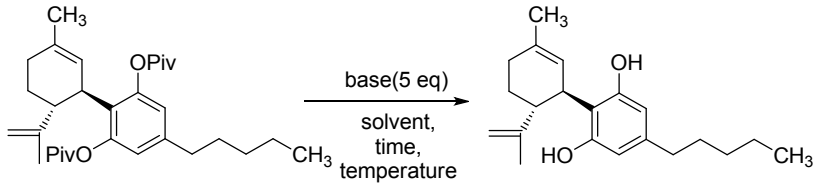
[a] The reactions were conducted on a 0.5 mmol scale under the conditions (0.1 equiv of $Pd(dppf)Cl_2$, 1.5 equiv of $C_5H_{11}ZnCl$ and 1.5 equiv of LiCl in anhydrous THF at 55−60 °C) unless otherwise noted. [b] The isolated yields were calculated after purified by column chromatography unless otherwise mentioned. [c] The reaction was performed on a 28 g scale to give the purified product in 90% isolated yield. [d] The reaction was performed on a 2.8 g scale to give the purified product in 82% isolated yield.

With the optimal protecting group confirmed, we surveyed the substrate scope of organic zinc reagent (**5**), which was prepared in one step by the transmetallation of the corresponding Grignard reagents or organolithium with zinc halide (ZnX_2) in anhydrous THF.[39, 40] To our delight, different pharmacologically interesting side chains were successfully coupled in good -to-high yields to the para position, including linear, branched, or cyclic alkyl groups, alkenyl groups, aryl groups, heteroaryl groups, and alkynyl groups. Among them, phenolic hydroxyl -protected derivatives **4e** with an alkyl group (**Table 2**, **4e(a−k)**) produced good yields

(80−90%). With an increase in steric hindrance, the reaction yield decreased (**4ed, 80%**). Compound **4e** with a cycloalkyl group (**Table 2, 4e(f−h))** could also be isolated in excellent yields, and the tension of the cycloalkyl ring does not affect the yield, as shown in the case of cyclopropyl (**4ec, 88%** *vs* **4ef, 89%**) and cyclopentyl groups (**4ea, 90%** *vs* **4eg**, **87%**). Interestingly, similar high yields for sp^2−sp^2 (**4ei** and **4eg**) and sp^2−sp (**4ek**) cross-couplings as that of sp^2−sp^3 cross-coupling were observed. In addition, **4el** and **4em** with heteroaryl groups were also obtained in satisfactory yields.

As CBD is unstable in the presence of acids,[41, 42] the removal of Piv groups was carried out under basic conditions.[43–47] Unexpectedly, subsequent de-protection of **4ea** to afford CBD in an acceptable yield turned out to be unsuccessful under normal basic conditions. To improve the yield of this step, we tried different bases. **4ea** was initially treated with 5 equiv KOH in different solvents (**Table 3,** entries 1 and 2) at reflux for 12 h. Disappointingly, CBD was only obtained in low-to-moderate yields. The yield of CBD got slightly improved when utilizing NaOMe in MeOH (**Table 3,** entry 3). By contrast, the use of NH_3 (5 equiv) as the base in MeOH afforded CBD in only 20% yield (**Table 3,** entry 4). Surprisingly, CH_3MgBr was found to be optimal among four different bases examined and provided CBD in an excellent 99% yield (**Table 3,** entry 5).

Table 3. Optimization of Reaction conditions for the Removal of Piv groups[a]



4ea **(–)-CBD**

entry	base	solvent	conditions	Yield(%)[b]
1	KOH	Water/MeOH 1:1	reflux, 12 h	63
2	KOH	DCM/MeOH 1:1	reflux, 12 h	30
3	NaOMe	MeOH	reflux, 12 h	75
4	NH_3	MeOH	rt, 12 h	20
5	CH_3MgBr	toluene	110 °C, 12 h	99

[a] The reactions were conducted on a 0.2 mmol scale under the conditions (5 equiv of base, solvent (2 mL), at reflux or room temperature for 12 h) unless otherwise noted. [b] The isolated yields were calculated after purified by column chromatography unless otherwise mentioned. [c] The reaction was performed on a 20 g scale.

With the optimized reaction conditions for the removal of Piv groups established, treatment of various phenolic hydroxyl-protected derivatives **4e**(**a**−**k**) with CH_3MgBr gave the corresponding free phenol products (**6a−k)** in almost quantitative yields. Notably, CBD was obtained with a total isolated yield of 52% on a 10 g scale. The structure of CBD was confirmed by NMR analysis and single-crystal X-ray analysis (See Supporting Info, Fig. S78).

In summary, we have developed a versatile (−)-CBD-2OPiv-OTf that can be used as a key intermediate for the late-stage introduction of C4'-side chains by cross-coupling chemistry. This intermediate was used to efficiently prepare a wide range of CBD analogs especially bearing biologically more relevant alkyl side chains under mild conditions by Negishi cross-coupling reaction. Following the presented approach, an efficient five-step synthesis of (−)-CBD from commercially available materials was achieved in 52% total yield on grams scale.

EXPERIMENTAL SECTION

General Information. All reactions were performed under a nitrogen atmosphere using anhydrous techniques unless otherwise noted. All commercially available reagents and solvents were used directly without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) visualized under ultraviolet light. TLC analyses were performed on silica gel 60 F254 plates. The ESI mass spectra were determined on a THERMOLTQ. All high-resolution mass spectra (HRMS) were measured on a mass spectrometer (Agilent Technologies 6520) by using electrospray ionization (ESI) quadrupole time-of-flight (Q-TOF). ^{1}H NMR ^{19}F NMR and ^{13}C{^{1}H} NMR data were recorded on 400 or 500 MHz instruments using TMS as an internal standard and are reported relative to their residual solvent signals. ^{1}H NMR data are presented as the chemical shift in ppm (multiplicity, coupling constant, and integration). The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. **Infrared spectra** (IR) were measured on a Thermo Scientific Nicolet iS5 *FT-IR Excalibur Series* spectrometer and the intensity of the signals is described with *w* (weak), *m* (medium) and *s* (strong). The position of the absorption bands is reported in wave numbers (cm^{-1}). Broad bands are labeled with *br*. **Melting points** (MP) were measured on a *WRR-Y* and are not corrected. **Optical rotation** measurements were recorded on an *Autopol VI* polarimeter and the sample concentration is given in g/100 mL.

(1'R, 2'R)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,4,6-triol (1). To a stirred mixture of phloroglucinol (83.0 g, 658 mmol) and boron trifluoride etherate (0.933 g, 6.58 mmol) in anhydrous tetrahydrofuran (100 mL) at (–10 to 0) ^{o}C was added a solution of (+)-*p*-mentha-2,8-dien-1-ol (10 g, 65.8 mmol) in anhydrous tetrahydrofuran. The reaction mixture was stirred at (–10 to 0) °C for 2 h, and TLC indicated the complete consumption of starting material. The reaction mixture was then treated with saturated aqueous $NaHCO_3$ (10 mL), and concentrated before the residue was dispersed in toluene (200 mL). The mixture was cooled to below 20 °C and filtered to recycle the excess phloroglucinol. And then the organic phase was diluted with toluene (200 mL) and washed with saturated $NaHCO_3$ solution (200 mL), water (200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography starting from PE to PE / EA (1:10, V/V) afforded the product **1** as a white solid (13.8 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.59 (br, 2H), 5.67 (s, 2H), 5.07 (s, 1H), 4.48 (m, 1H), 4.41 (m, 1H), 3.72 (d, J = 9.2 Hz, 1H), 2.97 (td, J = 10.8, 2.4 Hz, 1H), 2.08–2.04 (m, 1H), 1.91–1.87 (m, 1H), 1.68–1.61 (m, 2H), 1.58 (s, 3H), 1.57 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 157.2, 156.1, 149.8, 130.1, 128.1, 110.0, 108.4, 94.4, 44.4, 35.7, 30.8, 30.2, 23.8, 19.7. ESI-MS: m/z 261.33 $[M + H]^{+}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (br, 1H), 5.95 (s, 1H), 5.88 (s, 1 H), 5.54 (br, 1H), 4.92 (br, 2 H), 4.67 (s, 1 H), 4.57 (s, 1H), 3.77 (m, 1H), 2.34 (td, J = 11.7, 3.3Hz, 1H), 2.28–2.18 (m, 1 H), 2.14–2.06 (m, 1 H), 1.85–1.72 (m, 5 H), 1.66 (s, 3 H). **IR(neat):** 3380*br*, 2922*w*, 1629*m*, 1610*m*, 1523*w*, 1470*m*, 1304*w*, 1240*w*, 1224*w*, 1223*m*, 1152*m*, 1137*w*, 1054w, 1005*w*, 886*w*, 819*w*. **MP:**108.5–109.2 °C. $[\alpha]_D^{20}$ = –126.4° (*c* 1.014, MeOH). The ^{1}H NMR data are consistent with the literature.[20]

(1'R,2'R)-2,6-dihydroxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (2). A solution of Tf_2O (7.20 g, 25.5 mmol) in CH_2Cl_2 (8.00 mL) was added dropwise to a solution of 2,6-lutidine (5.46 g, 51 mmol) and **1** (9.95 g, 38.1 mmol) in CH_2Cl_2 (100 mL) at (–30 to –20) °C. After the mixture was stirred at (–30 to –20) °C for 30 min, the reaction was quenched with CH_2Cl_2 (80 mL) and washed with water (50 mL), 1M HCl (50 mL), sat. $NaHCO_3$ (30.0 mL), and brine (30.0 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford the pure product **2** as a white solid (7.81 g, 78.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (br,

2H), 6.24 (s, 2H), 5.08 (s, 1H), 4.46 (m, 1H), 4.44 (m, 1H), 3.87 (d, J = 6.4 Hz, 1H), 3.00 (td, J = 11.8, 2.8 Hz, 1H), 2.11–2.08 (m, 1H), 1.92–1.91 (m, 1H), 1.72–1.62 (m, 2H), 1.61 (s, 3H), 1.58 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 157.9, 149.1, 147.5, 131.4, 125.8, 118.8 (q, J = 321.3 Hz), 118.2, 110.4, 99.5, 43.8, 36.1, 30.7, 29.6, 23.6, 19.4. ESI-MS: m/z 783.13 $[2M - H]^-$. ^{19}F-NMR (470 MHz, DMSO-d_6): δ = –73.1. HRMS (ESI): calcd for $C_{17}H_{18}F_3O_5S$ $[M - H]^-$, 391.0833; found, 391.0823. **IR(neat):** 3381*br*, 2928*w*, 1614*s*, 1513*w*, 1445*m*, 1424*s*, 1378*w*, 1327m, 1291*w*, 1244*w*, 1211*m*, 1143*m*, 1103*w*, 1052w, 1010*w*, 981*m*, 896*w*, 854*m*, 825*w*, 613*m*, 589*w*. **MP:** 100–100.8 °C. $[\alpha]_D^{20}$ = –46° (*c* 1.005, DCM).

(1'R,2'R)-2,6-dimethoxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (3a).[9] Me_2SO_4 (946 mg, 7.5 mmol) was added dropwise at 0–10 °C to a mixture of **1** (1.18 g, 3.00 mmol) and K_2CO_3 (1.24 g, 9.00 mmol) in 10 mL of acetone. After the mixture was stirred at 25 °C for 12 h, the reaction mixture was diluted with EA (80 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford compound **3a** as a colorless oil(1.01 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.69 (s, 2H), 5.05 (s, 1H), 4.40 (m, 1H), 4.34 (m, 1H), 3.95–3.92 (m, 1H), 3.73 (s, 6H), 2.83 (td, J = 11.2, 3.2 Hz, 1H), 2.12–2.09 (m, 1H), 1.96–1.92 (m, 1H), 1.71–1.59 (m, 2H), 1.62 (s, 3H), 1.53 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 148.8, 148.6, 131.9, 124.9, 121.3, 118.7 (q, J = 322.6 Hz), 110.7, 56.8, 44.7, 36.1, 30.6, 29.3, 23.6, 19.1. ^{19}F-NMR (470 MHz, DMSO-d_6): δ = –72.9. HRMS (ESI): calcd for $C_{19}H_{24}F_3O_5S[M + H]^+$, 421.1292; found, 421.1298. **IR(neat):** 3071*w*, 3004*w* 2962*m*, 2924*s*, 2856*m*, 1642*w*, 1607*s*, 1463*m*, 1422*s*, 1376*w*, 1350*w*, 1247*s*, 1218*s*, 1142*s*, 1119*s*, 1082*w*, 972*s*, 888*w*, 859*w*, 844m, 798*w*, 762*w*, 613*m*, 509*w*.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl diacetate[34] **(3b).** A solution of acetic anhydride (766 mg, 7.50 mmol) in CH_2Cl_2 was added dropwise to a solution of dimethylaminopyridine (DMAP) (367 mg, 3.00 mmol) and **1** (1.18 g, 3.00 mmol) in pyridine (10 mL) at (–10 to 0) °C. After the mixture was stirred at 25 °C for 12 h, the reaction mixture was diluted with EA (80 mL) and washed with water (50 mL), 1M HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford compound **3b** as a yellow oil (1.36 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 (s, 2H), 4.95 (s, 1H), 4.46 (m, 1H), 4.34 (m, 1H), 3.57–3.55 (m, 1H), 2.62–2.57 (m, 1H), 2.28–2.11 (m, 7H), 2.00–1.96 (m, 1H), 1.73–1.67 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 169.1, 150.6, 147.5, 146.6, 133.9, 131.0, 123.3, 118.6(q, J=321.3 Hz), 111.7, 45.7, 37.9, 30.2, 28.2, 23.6, 21.0, 19.2. ESI-MS: m/z 494.41 $[M + NH_4]^+$. ^{19}F-NMR (470 MHz, DMSO-d_6): δ = –72.7. HRMS (ESI): calcd for $C_{21}H_{27}F_3NO_7S$ $[M + NH_4]^+$, 494.1455; found, 494.1460. **IR(neat):** 3075*m*, 2928*br*, 2833*s*, 1770*s*, 1644*w*, 1607*m*, 1470*w*, 1427*m*, 1287*w*, 1211*br*, 1141*w*, 1103*w*, 1038*w*, 980*w*, 900*w*, 829*w*, 799w, 755*w*, 702*w*, 608*w*, 523*w*, 506*w*.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(4-nitrobenzoate)[35] **(3c).** A solution of *p*-Nitrobenzoyl chloride (1.39 g, 7.51 mmol) in CH_2Cl_2 was added dropwise to a solution of DMAP (367 mg, 3.00 mmol) and **1** (1.18 g, 3.00 mmol) in pyridine (10 mL) at (0 to –10) °C. After the mixture was stirred at 25 °C for 12 h, the reaction mixture was diluted with EA (80 mL) and washed with water (50 mL), 1M HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford compound **3c** as a brown solid (1.98 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (d, J = 8.8 Hz, 4H), 8.37 (d, J = 8.8 Hz, 4H),7.74 (s, 2H), 5.05 (s, 1H), 4.58 (m, 1H), 4.45 (m, 1H), 3.66 (d, J = 10.4 Hz, 1H), 2.67 (td, J = 12.2, 2.8 Hz, 1H), 1.68–1.56 (m, 4H), 1.50 (s, 3H), 1.08 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 151.2, 150.5, 147.2, 146.9, 134.5, 134.1, 131.9, 131.8, 131.2, 124.5, 123.0, 118.7 (q, J = 321.3 Hz), 112.2, 46.0, 38.6,

29.8, 28.0, 23.3, 19.9. ^{19}F-NMR (470 MHz, DMSO-d_6): δ = –72.5. **MP:** 118–119.8 °C.

(1'R,2'R)-2,6-bis((tert-butoxycarbonyl)oxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate[36] (3d). A solution of Di-tert-butyl pyrocarbonate (1.64 g, 7.51 mmol) in CH_2Cl_2 was added dropwise to a solution of DMAP (367 mg, 3.00 mmol) and **1** (1.18 g, 3.00 mmol) in pyridine (10 mL) at (–10 to 0) °C. After the mixture was stirred at 25°C for 12 h, the reaction mixture was diluted with EA (80 mL) and washed with water (50 mL), 1M HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford compound **3d** as a white solid (1.76 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (s, 2H), 5.04 (s, 1H), 4.47 (m, 1H), 4.35 (m, 1H), 3.57 (d, J = 8.8 Hz, 1H), 2.62 (td, J = 11.8, 2.8 Hz, 1H), 2.17–2.10 (m, 1H), 2.00–1.96 (m, 1H), 1.74–1.64 (m, 2H), 1.63 (s, 3H), 1.53 (s, 3H), 1.47 (s, 18H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 150.5, 150.5, 147.3, 146.6, 134.5., 130.8, 121.7, 118.6 (q, J = 321.3 Hz), 111.7, 84.4, 45.5, 37.9, 30.2, 28.6, 27.6, 24.0, 19.2. ^{19}F-NMR (470 MHz, DMSO-d_6): δ = –72.7. ESI-MS: m/z 610.43 [M + NH_4]$^+$. HRMS (ESI): calcd for $C_{27}H_{39}F_3NO_9S$ [M + NH_4]$^+$, 610.2292; found, 610.2300. **IR(neat):** 2979*w*, 2938*w*, 1774*s*, 1763*s*, 1602*w*, 1472*w*, 1426*m*, 1398*w*, 1373*m*, 1328*w*, 1277*s*, 1242*s*, 1219*s*, 1149*s*, 1097*s*, 1023*w*, 971*s*, 867*m*, 850*m*, 831*m*, 777w, 765*w*, 757*w*, 641*w*, 588*w*. **MP:** 85.5–87.5 °C. $[\alpha]_D^{20}$ = –96.3° (*c* 1.019, DCM)

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) [37] (3e). A solution of pivaloyl chloride (904 mg, 7.50 mmol) in CH_2Cl_2 was added dropwise to a solution of DMAP (367 mg, 3.00 mmol) and **1** (1.18 g, 3.00 mmol) in pyridine (10 mL) at (–10 to 0) °C. After the mixture was stirred at 25 °C for 12 h, the reaction mixture was diluted with EA (80 mL) and washed with water (50 mL), 1M HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford compound **3e** as a white solid (1.60 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (s, 2H), 5.03 (s, 1H), 4.52 (m, 1H), 4.49 (m, 1H), 3.52 (d, J = 10 Hz, 1H), 2.68 (td, J = 11.4, 1.6 Hz, 1H), 2.14–2.01 (m, 2H), 1.79–1.76 (m, 1H), 1.71–1.60 (m, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 1.30 (s, 18H)**.** ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 176.3, 147.4, 146.8, 133.6., 130.8, 123.4, 118.6 (q, J = 321.3 Hz), 111.7, 45.1, 39.2, 38.3, 30.5, 29.1, 27.1, 23.5, 19.6. **^{19}F-NMR** (470 MHz, DMSO-d_6): δ = –72.8. ESI-MS: m/z 578.56 [M + NH_4]$^+$. HRMS (ESI): calcd for $C_{27}H_{39}F_3NO_7S$[M + NH_4]$^+$, 578.2394; found, 578.2396. **IR(neat):**2980*w*, 2932*w*, 1760*s*, 1600*w*, 1481*w*, 1468*w*, 1421*s*, 1396*w*, 1270*w*, 1241*s*, 1211*s*, 1144*m*, 1094*s*, 1035*w*, 983*m*, 893*w*, 875*m*, 839*w*. **MP:** 59.0–61.1 °C. $[\alpha]_D^{20}$ = –77.4° (*c* 1.007, DCM).

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(4-methylbenzenesulfonate)[38] (3f). A solution of p-toluenesulfonyl chloride (1.43 g, 7.5 mmol) in CH_2Cl_2 was added dropwise to a solution of DMAP (367 mg, 3.00 mmol) and **1** (1.18 g, 3.00 mmol) in pyridine (10 mL) at (–10 to 0) °C. After the mixture was stirred at 25 °C for 12 h, the reaction mixture was diluted with EA (80 mL) and washed with water (50 mL), 1M HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL).The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (PE / EA = 20:1) to afford compound **3f** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76 (d, J = 6.4 Hz, 4H), 7.51 (d, J = 6.4 Hz, 4H), 7.33 (s, 2H), 4.39 (s, 1H), 4.18 (s, 2H), 3.44 (d, J = 10.4 Hz, 1H), 2.43 (s, 6H), 2.32 (td, J = 11.8, 2 Hz, 1H), 1.75–1.71 (m, 1H), 1.55–1.44 (m, 3H), 1.48 (s, 3H), 1.40 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 149.2, 147.1, 146.9, 146.6, 133.4, 131.8, 130.9, 128.6, 121.3, 118.6(q, J = 322.6 Hz), 112.1, 45.7, 38.0, 29.6, 28.2, 23.6, 21.6, 18.5. ^{19}F-NMR (470 MHz, DMSO-d_6): δ = –72.4. ESI-MS: m/z 718.44 [M + NH_4]$^+$. HRMS (ESI): calcd for $C_{31}H_{35}F_3NO_9S_3$[M + NH_4]$^+$, 718.1421; found, 718.1433. **IR(neat):** 3108*w*, 2930*w*, 2895*w*, 1646*w*, 1596*m*, 1472*w*, 1428*s*, 1369*s*, 1243*m*, 1222*s*, 1211*m*, 1190*s*, 1140*m*, 1104*w*, 1015*m*, 980*m*, 884*m*, 765*m*, 758*m*, 738*m*, 705*w*, 657*w*, 589*w*, 553*m*, 533*w*. **MP:** 113.5–115.8 °C. $[\alpha]_D^{20}$ = –86.8° (*c* 1.008, DCM).

General Procedure for the preparation of 4 by Negishi cross-coupling reaction[39, 40]

Anhydrous zinc chloride (1.5eq) and anhydrous lithium chloride (1.5eq) was dissolved in anhydrous THF (5 mL) and cooled to –10 °C. $^{n}C_5H_{11}MgCl$ (1.0 M, 1.5eq) was added dropwise via a syringe, and the reaction mixture was stirred at –10 °C for 15 min and then warmed to room temperature and stirred for 1.5 h. In another flask, protected **3** (0.5–1 mmol, 1 eq) was dissolved in anhydrous THF and transferred to the $^{n}C_5H_{11}ZnCl$ solution via a cannula, and then $Pd(dppf)Cl_2$ (0.1 eq) was added into the flask. The resulting mixture was purged by nitrogen for 15 min, the mixture was stirred at 55–60 °C under oil bath. The reaction end point was monitored generally by TLC with the developing solvent of 40% CH_2Cl_2 in PE, visualized at UV254 nm. The reaction mixture was then cooled to room temperature and poured into ice NH_4Cl solution. Water and EA were added and the layers were separated. The aqueous phase was extracted with EA. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with PE / EA (50:1) as eluents to afford compound **4**.

(1'R,2'R)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl diacetate (4ba). Following the general procedure described above and starting from **3b** (476 mg, 1 mmol), the title compound **4ba** was prepared as a colorless oil (79.5 mg, 20% yield). ^{1}H NMR (400 MHz,DMSO-d_6): δ 6.76 (s, 2H), 4.96 (s, 1H), 4.46 (m, 1H), 4.38 (m, 1H), 3.45–3.42 (m, 1H), 2.66–2.60 (m, 1H), 2.53–2.50 (m, 2H), 2.20 (m, 7H), 1.99–1.95 (m, 1H), 1.71–1.66 (m, 2H), 1.62 (s, 3H), 1.56 (s, 3H), 1.55–1.49 (m, 2H), 1.31–1.23 (m, 4H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.5, 149.9, 147.9, 141.9, 132.9, 126.4, 124.5, 111.5, 45.7, 37.9, 34.7, 31.3, 30.4, 30.3, 28.6, 23.7, 22.4, 21.1, 19.4, 14.4. ESI-MS: m/z 416.51 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{25}H_{38}NO_4$ $[M + NH_4]^+$, 416.2795; found, 416.2797. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 2 H), 5.56 (br, 1 H), 4.67 (br. s, 1 H), 4.61 (br, 1 H), 3.92 (m, 1 H), 3.20 (m, 1 H), 2.51 (m, 2 H), 2.32 (s, 6 H), 2.21 (m, 2 H), 1.84 (m, 2 H), 1.80 (s, 3 H), 1.68 (s, 3 H), 1.56 (q, J = 7.6 Hz, 2 H), 1.30 (m, 4 H), 0.88 (t, J= 7.2 Hz, 3 H). **IR(neat):** 2958*w*, 2926*br*, 2857*m*, 1771*s*, 1429*m*, 1366*m*, 1200*s*, 1184*s*, 1149*w*, 153*m*, 1051*w*, 1032*m*, 888*w*. The ^{1}H NMR data are consistent with the literature.[48]

Di-tert-butyl ((1'R,2'R)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl) dicarbonate (4da). Following the general procedure described above and starting from **3d** (296 mg, 0.5 mmol), the title compound **4da** was prepared as a colorless oil (129 mg, 50% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.83 (s, 2H), 5.05 (s, 1H), 4.45 (m, 1H), 4.39 (m, 1H), 3.49–3.47 (m, 1H), 2.65 (td, J = 12, 2.4 Hz, 1H), 2.55–2.51 (m, 2H), 2.16–2.09 (m, 1H), 1.95–1.94 (m, 1H), 1.73–1.64 (m, 2H), 1.61 (s, 3H), 1.60–1.50 (m, 2H), 1.53 (s, 3H), 1.47 (br, 18H), 1.35–1.22 (m, 4H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 151.4, 149.9, 147.7, 142.1, 133.3, 126.4, 123.1, 111.4, 83.3, 45.5, 37.8, 34.7, 31.2, 30.6, 30.3, 29.0, 27.7, 24.0, 22.4, 19.3, 14.4. ESI-MS: m/z 532.52 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{31}H_{50}NO_6$ $[M + NH_4]^+$, 532.3633; found, 532.3628. **IR(neat):** 3073*w*, 2930*br*, 2858*s*, 1760*s*, 1643*w*, 1624*m*, 1574*w*, 1456*m*, 1394*w*, 1370*s*, 1243*s*, 1146*s*, 1102*m*, 1051*w*, 1037*w*, 971*w*, 944*w*, 884*m*, 861*m*, 777*m*, 460*w*.

(1'R,2'R)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ea). Following the general procedure described above and starting from **3e** (28 g, 50.0 mmol), the title compound **4ea** was prepared as a colorless oil (21.7 g, 90% yield). ^{1}H NMR (400 MHz,DMSO-d_6): δ 6.66 (s, 2H), 5.03 (s, 1H), 4.49–4.48 (m, 2H), 3.42–3.39 (m, 1H), 2.66 (td, J = 11.6, 2.4 Hz, 1H), 2.50 (t, J = 8 Hz, 2H), 2.06–1.98 (m, 2H), 1.76–1.73 (m, 1H), 1.67–1.58 (m, 1H), 1.55 (s, 3H), 1.51 (s, 3H), 1.55–1.48 (m, 2H), 1.28 (br, 22H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 176.6, 147.9, 142.2, 132.4, 126.4, 124.8, 111.3, 45.2, 39.1, 38.2, 34.7, 31.4, 30.7, 30.6, 29.4, 27.3, 23.5, 22.4, 19.8, 14.4. HRMS (ESI): calcd for $C_{31}H_{50}NO_4$ $[M + NH_4]^+$, 500.3734; found, 500.3742. **IR(neat):** 2962*s*, 2930*s*, 2872*m*, 1755*s*, 1643*w*, 1623*m*, 1573*w*, 1479*m*, 1456*w*, 1395*m*, 1368*w*, 1271*m*, 1216*w*, 1193*w*, 1105*s*, 1051*w*, 1033*m*, 982*w*, 890*m*, 765*m*, 757*m*.

(1'R,2'R)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(4-methylbenzenesulfonate) (4fa). Following the general procedure described above and starting from **3f** (350 mg, 0.5 mmol), the title compound **4fa** was prepared as an off-white solid (252 mg, 81% yield). ^{1}H NMR (400 MHz,DMSO-d_6): δ 7.74 (m, 4H), 7.51–7.49 (m, 4H), 6.86 (br, 2H), 4.41 (m, 1H), 4.38 (m, 1H), 4.26 (m, 1H), 3.48–3.46 (m, 1H), 2.48–2.35 (m, 3H), 3.43 (s, 6H), 1.74–1.71 (m, 1H), 1.54–1.51 (m, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.40–1.34 (m, 2H),1.29–1.22 (m, 2H), 1.18–1.11 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 149.1, 147.3, 146.4, 142.9, 132.5, 130.7, 128.5, 127.4, 122.8, 119.4, 111.7, 45.7, 37.8, 34.5, 30.9, 30.1, 29.7, 28.6, 23.6, 22.3, 21.6, 18.7, 14.3. ESI-MS: m/z 640.52 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{35}H_{46}NO_6S_2$ $[M + NH_4]^+$, 640.2761; found, 640.2755. **IR(neat):** 2959*s*, 2927*s*, 1617*m*, 1598*m*, 1436*w*, 1419*w*, 1377*s*, 1351*s*, 1191*s*, 1179*s*, 1104*s*, 1093*m*, 1016*w*, 983*m*, 958*m*, 815*m*, 765*m*, 741*m*, 675*m*, 564*m*, 527*w*. **MP:** 80.1–81.3 °C.

(1R,2R)-2',6'-dimethoxy-5-methyl-4'-pentyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1'-biphenyl (4aa). Anhydrous zinc chloride (408 mg, 3 eq) and anhydrous lithium chloride (128 mg, 3 eq) was dissolved in anhydrous THF (5 mL) and cooled to –10 °C. ^{n}C_5H_{11}MgCl (3 mL, 1.0 M, 3 eq) was added dropwise via a syringe, and the reaction mixture was stirred at –10 °C for 15 min and then warmed to room temperature and stirred for 1.5 h. In another flask, protected **3a** (420 mg, 1 mmol) was dissolved in anhydrous THF and transferred to the ^{n}C_5H_{11}ZnCl solution via a cannula, and then Pd(dppf)Cl_2 (73 mg, 0.1 eq) was added into the flask. The resulting mixture was purged by nitrogen for 15 min, the mixture was stirred at 55–60 °C under oil bath. The reaction end point was monitored generally by TLC with the developing solvent of 40% CH_2Cl_2 in PE, visualized at UV254 nm. The reaction mixture was then cooled to room temperature and poured into ice NH_4Cl solution. Water and EA were added and the layers were separated. The aqueous phase was extracted with EA. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with PE / EA (50:1) as eluents to afford compound **4aa** was prepared as a colorless oil (192 mg, 56% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.38 (s, 2H), 5.05 (s, 1H), 4.38 (m, 2H), 3.92–3.89 (m, 1H), 3.67 (s, 6H), 2.89 (td, J = 11.2, 3.2 Hz, 1H), 2.49 (t, J = 8 Hz, 2H), 2.12–2.09 (m, 1H), 1.95–1.91 (m, 1H), 1.70–1.63 (m, 2H), 1.61 (s, 3H), 1.59–1.55 (m, 2H), 1.53 (s, 3H), 1.35–1.27 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 158.7, 149.1, 141.9, 130.7, 126.5, 118.1, 110.3, 105.2, 56.2, 44.9, 36.2, 36.0, 31.6, 31.0, 30.7, 29.7, 23.7, 22.5, 19.4, 14.4. ESI-MS: m/z 343.49 $[M + H]^+$. ^{1}H NMR (400MHz, $CDCl_3$): δ 6.32 (s, 2 H), 5.20 (s, 1 H), 4.45–4.42 (m, 1 H), 4.42–4.40 (m, 1 H), 4.02–3.94 (m, 1 H), 3.72 (s, 6 H), 2.89 (td, J = 10.5, 4.7 Hz, 1 H), 2.52 (t, J = 7.8 Hz, 2 H), 2.25–2.11 (m, 1 H), 2.02–1.93 (m, 1 H), 1.78–1.69 (m, 2 H), 1.66 (s, 3 H), 1.63–1.56 (m, 5 H), 1.38–1.29 (m, 4 H), 0.89 (t, J = 6.8 Hz, 3 H). **IR(neat):** 2956*s*, 2927*s*, 2855*m*, 2833*w*, 1642*w*, 1608*m*, 1581*s*, 1453*s*, 1418*m*, 1375*w*, 1346*w*, 1233*m*, 1196*w*, 1158*w*, 1119*s*, 883*w*, 823*w*. The ^{1}H NMR data are consistent with the literature.[9]

General Procedure for the preparation of 4e by Negishi cross-coupling reaction

Anhydrous zinc chloride (1.5 eq) and anhydrous lithium chloride (1.5 eq) was dissolved in anhydrous THF (5 mL) and cooled to –10 °C. RMgX or RLi (1.5 eq) was added dropwise via a syringe, and the reaction mixture was stirred at –10 °C for 15 min and then warmed to room temperature and stirred for 1.5 h. In another flask, **3e** (0.7 mmol, 1 eq) was dissolved in anhydrous THF and transferred to the RZnCl solution via a cannula, and then Pd(dppf)Cl_2 (0.1 eq) was added into the flask. The resulting mixture was purged by nitrogen for 15 min, and then the mixture was stirred at 55–60 °C under oil bath. The reaction end point was monitored generally by TLC with the developing solvent of 40% CH_2Cl_2 in PE, visualized at UV254 nm. The reaction mixture was then cooled to room temperature and poured into satd. NH_4Cl (5 mL). Water and EA were added and the layers were separated.

The aqueous phase was extracted with EA. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with PE / EA (50:1) as eluents to afford compound **4e**.

(1'R,2'R)-4,5'-dimethyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4eb). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4eb** was prepared as a colorless oil (177 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 2H), 5.24 (s, 1H), 4.55 (m, 2H), 3.52–3.49 (m, 1H), 2.67 (td, J = 11.8, 2.8Hz, 1H), 2.27 (s, 3H), 2.11–1.98 (m, 2H), 1.83–1.79 (m, 1H), 1.74–1.63 (m, 1H), 1.60 (s, 3H), 1.55 (s, 3H), 1.33 (s, 18H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.8, 148.1, 136.9, 132.2, 126.2, 125.0, 110.8, 45.2, 39.2, 38.5, 30.8, 29.6, 27.2, 23.3, 20.9, 20.0. HRMS (ESI): calcd for $C_{27}H_{42}NO_4$ [M + NH_4]$^+$, 444.3108; found, 444.3110. **IR(neat):** 3072*w*, 2970*s*, 2928*s*, 2872*m*, 2833*w*, 1755*s*, 1643*w*, 1625*m*, 1575*m*, 1479*m*, 1455*m*, 1395*m*, 1368*m*, 1273*m*, 1217*w*, 1173*w*, 1104*s*, 1051*w*, 1035*m*, 980*w*, 890*m*, 844*w*, 757*w*.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-propyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ec). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4ec** was prepared as a colorless oil (200 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 2H), 5.26 (s, 1H), 4.55 (m, 2H), 3.53–3.50 (m, 1H), 2.67 (td, J = 12.2, 2.8 Hz, 1H), 2.51 (t, J = 8 Hz, 2H), 2.15–1.98 (m, 2H), 1.84–1.79 (m, 1H), 1.75–1.58 (m, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.33 (s, 18H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.2, 141.7, 132.1, 126.3, 125.1, 110.8, 45.2, 39.2, 38.6, 37.3, 30.8, 29.6, 27.3, 24.0, 23.3, 20.1, 13.8. HRMS (ESI): calcd for $C_{29}H_{46}NO_4$ [M + NH_4]$^+$, 472.3421; found, 472.3428. **IR(neat):** 3079*w*, 2964*s*, 2930*s*, 2872*m*, 2833*w*, 1755*s*, 1643*w*, 1622*m*, 1574*m*, 1479*m*, 1426*m*, 1395*w*, 1368*w*, 1273*m*, 1225*w*, 1104*s*, 1033*m*, 887*m*, 757*w*.

(1'R,2'R)-4-isopropyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ed). Following the general procedure described above and starting from **3e** (280 mg, 0.5mmol), the title compound **4ed** was prepared as a colorless oil (182 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 2H), 5.25 (s, 1H), 4.56 (m, 2H), 3.52–3.49 (m, 1H), 2.86–2.79 (m, 1H), 2.68 (td, J = 11.6, 2.4 Hz, 1H), 2.11–1.99 (m, 2H), 1.84–1.79 (m, 1H), 1.74–1.64 (m, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.34 (br, 18H), 1.21 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.2, 147.8, 132.1, 126.3, 125.1, 110.8, 45.1, 39.2, 38.6, 33.5, 30.8, 29.6, 27.3, 23.6, 23.3,20.2. HRMS (ESI): calcd for $C_{29}H_{46}NO_4$ [M + NH_4]$^+$, 472.3421; found, 472.3435. **IR(neat):** 3078*w*, 2963*br*, 2833*m*, 1755*s*, 1643*m*, 1622*s*, 1574*m*, 1479*s*, 1461*s*, 1461*s*, 1427*m*, 1396*m*, 1366*m*, 1271*m*, 1216*w*, 1168*w*, 1003*s*, 1050*w*, 1032*m*, 962*w*, 891*m*, 757*w*, 659*w*, 556*w*.

(1'R,2'R)-4-butyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ee). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4ee** was prepared as a colorless oil (202 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (s, 2H), 5.25 (s, 1H), 4.55 (m, 2H), 3.53–3.50 (m, 1H), 2.67 (td, J = 11.8, 2.8 Hz, 1H), 2.53 (t, J = 8 Hz, 2H), 2.11–2.02 (m, 2H), 1.84–1.79 (m, 1H), 1.74–1.67 (m, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.58–1.56 (m, 2H), 1.36–1.26 (m, 2H), 1.33 (br, 18H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.2, 141.9, 132.1, 126.2, 125.1, 110.8, 45.2, 39.2, 38.6, 35.1, 33.0, 30.8, 29.6, 27.2, 23.3, 22.5, 20.1, 14.0. HRMS (ESI): calcd for $C_{30}H_{48}NO_4$ [M + NH_4]$^+$, 486.3578; found, 486.3588. **IR(neat):** 2959*s*, 2927*s*, 2857*s*, 1752*s*, 1727*s*, 1622*m*, 1583*w*, 1479*w*, 1456*w*, 1429*m*, 1396*w*, 1376*w*, 1278*m*, 1240*w*, 1120*s*, 1051*w*, 1034*w*, 1014*w*, 891*m*, 811*w*, 575*w*.

(1'R,2'R)-4-cyclopropyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ef). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4ef** was prepared as a colorless oil (201 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (s, 2H), 5.23 (s, 1H), 4.55 (br, 2H), 3.50–3.47 (m, 1H), 2.67 (td, J = 12, 2.4 Hz, 1H), 2.10–1.98 (m, 2H), 1.84–1.78 (m, 2H), 1.73–1.62 (m, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.33 (br, 18H), 0.93–0.84 (m, 2H), 0.68–0.64 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.1, 143.2, 132.1, 126.1, 125.0, 110.8, 45.2, 39.2, 38.5, 30.8, 29.6, 27.2, 23.3, 20.1, 15.1, 9.2, 9.1. HRMS (ESI): calcd for $C_{29}H_{44}NO_4$ [M + NH_4]$^+$, 470.3265; found, 470.3273. **IR(neat):** 3079*m*, 2918*br*, 2726*w*, 1749*s*, 1650*m*, 1644*m*, 1621*m*, 1557*m*, 1470*m*, 1394*m*, 1271*m*, 1102*m*, 1033*w*, 968*m*, 889*m*, 814*w*, 757*w*, 738*w*, 648*w*, 557*w*.

(1'R,2'R)-4-cyclopentyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4eg). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4eg** was prepared as a colorless oil (214 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 2H), 5.25 (s, 1H), 4.56 (m, 2H), 3.52–3.49 (m, 1H), 2.95–2.87 (m, 1H), 2.68 (td, J = 11.8, 2.8 Hz, 1H), 2.14–1.99 (m, 4H), 1.84–1.62 (m, 6H), 1.60–1.49 (m, 2H), 1.60 (s, 3H), 1.54 (s, 3H), 1.33 (br, 18H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.2, 145.6, 132.1, 126.3, 125.1, 110.8, 45.2, 45.1, 39.2, 38.6, 34.2, 34.2, 30.8, 29.6, 27.3, 25.4, 23.3, 20.1. HRMS (ESI): calcd for $C_{31}H_{48}NO_4$ [M + NH_4]$^+$, 498.3578; found, 498.3590. **IR(neat):** 3073*w*, 2960*br*, 2871*s*, 2833*m*, 1755*s*, 1644*m*, 1622*m*, 1574*m*, 1479*m*, 1455*m*, 1396*m*, 1367*w*, 1272*m*, 1149*s*, 1103*m*, 1051*w*, 1033*m*, 890*m*, 757*w*.

(1'R,2'R)-4-cyclohexyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4eh). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4eh** was prepared as a colorless oil (213 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 2H), 5.25 (s, 1H), 4.55 (m, 2H), 3.52–3.49 (m, 1H), 2.67 (td, J = 12, 2.4 Hz, 1H), 2.46–2.40 (m, 1H), 2.11–1.98 (m, 2H), 1.89–1.79 (m, 5H), 1.74–1.63 (m, 2H), 1.60 (s, 3H), 1.53 (s, 3H), 1.37–1.29 (br, 23H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.2, 147.0, 132.1, 126.3, 125.1, 110.7, 45.1, 43.8, 39.2, 38.7, 34.0, 34.0, 30.8, 29.6, 27.3, 26.7, 26.0, 23.3, 20.2. HRMS (ESI): calcd for $C_{32}H_{50}NO_4$ [M + NH_4]$^+$, 512.3734; found, 512.3741**. IR(neat):** 2963*m*, 2928*s*, 2853*m*, 1756*s*, 1623*m*, 1574*w*, 1480*m*, 1450*w*, 1496*w*, 1364*w*, 1274*w*, 1105*s*, 1033*w*, 963*w*, 887*w*, 757*m.*

(1R,2R)-5-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-[1,1':4',1''-terphenyl]-2',6'-diyl bis(2,2-dimethylpropanoate) (4ei). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4ei** was prepared as a colorless oil (232 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.53 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.34–7.30 (m, 1H), 6.99 (s, 2H), 5.30 (s, 1H), 4.60–4.58 (m, 2H), 3.61–3.58 (m, 1H), 2.74 (td, J = 11.6, 2.4 Hz, 1H), 2.14–2.11 (m, 1H), 2.07–2.01 (m, 1H), 1.87–1.85 (m, 1H),1.77–1.66 (m, 1H), 1.63 (s, 3H), 1.59 (s, 3H), 1.36 (br, 18H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.7, 148.0, 140.1, 139.4, 132.5, 128.7 128.2, 127.7, 127.1, 124.7, 111.0, 45.2, 39.3, 38.7, 30.8, 29.6, 27.3, 23.3, 20.1. HRMS (ESI): calcd for $C_{32}H_{44}NO_4$ [M + NH_4]$^+$, 506.3265; found, 506.3270. **IR(neat):** 2971*m*, 2930*w*, 1754*s*, 1643*w*, 1621*w*, 1562*w*, 1479*m*, 1396*m*, 1367*w*, 1275*m*, 1203*w*, 1164*w*, 1102*s*, 1033*m*, 887*w*, 803*w*, 761*m*, 698*m.*

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-vinyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ej). Following the general procedure described above and starting from **3e**(280 mg, 0.5 mmol), the title compound **4ej** was prepared as a colorless oil (200 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (br, 2H), 6.61–6.54 (m, 1H), 5.67 (d, J = 17.2 Hz, 1H), 5.25–5.23 (m, 2H), 4.56 (m, 2H), 3.55–3.52

(m, 1H), 2.70 (td, *J* = 12, 2.4 Hz, 1H), 2.16–2.00 (m, 2H), 1.85–1.80 (m, 1H), 1.75–1.66 (m, 1H), 1.61 (s, 3H), 1.56 (s, 3H), 1.35 (br, 18H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 176.6, 147.9, 136.7, 135.3, 132.4, 128.8, 124.7, 115.0, 111.0, 45.20, 39.2, 38.7, 30.8, 29.6, 27.2, 23.3, 20.0. HRMS (ESI): calcd for $C_{28}H_{42}NO_4$ $[M + NH_4]^+$, 456.3108; found, 456.3118. **IR(neat):** 3073*m*, 2971*s*, 2914*s*, 2834*m*, 1755*s*, 1643*m*, 1618*m*, 1563*m*, 1479*m*, 1455*m*, 1396*m*, 1370*m*, 1270*m*, 1193*w*, 1173*w*, 1149*m*, 985*w*, 941*w*, 893*m*, 859*w*, 757*m*, 549*w*.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(prop-1-yn-1-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4ek). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4ek** was prepared as an off-white solid (207 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 5.23 (s, 1H), 4.54–4.53 (m, 2H), 3.53–3.50 (m, 1H), 2.66 (td, *J* = 11.6, 2.4 Hz, 1H), 2.15–2.03 (m, 2H), 1.99 (s, 3H), 1.83–1.78 (m, 1H), 1.73–1.64 (m, 1H), 1.60 (s, 3H), 1.53 (s, 3H), 1.32 (br, 18H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 176.5, 147.7, 132.5, 129.6, 124.4 122.7, 111.1, 87.0, 78.3, 45.2, 39.2, 38.7, 30.7, 29.4, 27.2, 23.3, 19.9, 4.2. HRMS (ESI): calcd for $C_{29}H_{42}NO_4$ $[M + NH_4]^+$, 468.3108; found, 468.3114. **IR(neat):** 2972*s*, 2930*s*, 1758*s*, 1644*w*, 1615*w*, 1557*m*, 1480*m*, 1460*w*, 1405*w*, 1396*m*, 1368*w*, 1274*w*, 1158*w*, 1099*s*, 1033*w*, 892*w*, 756*w*, 738*w*. **MP:** 68.2–69.3 °C.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4el). Following the general procedure described above and starting from **3e** (2.8 g, 5 mmol), the title compound **4el** was prepared an off-white solid (2.0 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 5 Hz, 1H), 7.72 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.43 (s, 2H), 7.23–7.17 (m, 1H), 5.29 (s, 1H), 4.58 (m, 1H), 4.54 (m, 1H), 3.63–3.58 (m, 1H), 2.77 (td, *J* = 13.0, 2.5 Hz, 1H), 2.18–2.11 (m, 1H), 2.07–2.02 (m, 1H), 1.89–1.80 (m, 1H), 1.76–1.67 (m, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.37 (s, 18H). $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$): δ 176.2, 155.0, 148.9, 147.3, 137.7, 136.5, 132.1, 129.8, 124.0, 122.0, 120.3, 110.6, 44.8 , 38.8, 38.3, 30.3, 29.1, 26.8, 22.8, 19.4. HRMS (ESI): calcd for $C_{31}H_{40}NO_4$ $[M + H]^+$, 490.2952; found, 490.2963. **IR(neat):** 3066*w*, 2970*s*, 2917*m*, 2836*w*, 2361*w*, 1755*s*, 1641*w*, 1617*w*, 1587*w*, 1561*w*, 1479*m*, 1460*w*, 1436*w*, 1396*w*, 1375*w*, 1273*w*, 1169*w*, 1100*s*, 1034*w*, 992*w*, 886*w*, 786*w*, 757*w*, 745*w*. **MP:** 188–189.4 °C.

(1'R,2'R)-4-(5-chlorothiophen-2-yl)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diyl bis(2,2-dimethylpropanoate) (4em). Following the general procedure described above and starting from **3e** (280 mg, 0.5 mmol), the title compound **4em** was prepared a vitreous solid (188 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 3.9 Hz, 1H), 6.88 (s, 2H), 6.84 (d, *J* = 3.9 Hz, 1H), 5.25 (s, 1H), 4.57 (m, 2H), 3.60–3.54 (m, 1H), 2.71 (td, *J* = 13.1, 2.6 Hz, 1H), 2.15–2.08 (m, 1H), 2.08–1.98 (m, 1H), 1.89–1.78 (m, 1H), 1.77–1.68 (m, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.35 (s, 18H). $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$): δ 176.5, 147.8, 141.0, 132.6, 129.6, 129.1, 127.0, 124.4, 123.1, 111.1, 45.2, 39.3, 38.7, 30.8, 29.5, 27.2, 23.3, 19.9. HRMS (ESI): calcd for $C_{30}H_{38}ClO_4S$ $[M + H]^+$, 529.5174; found, 529.5165. **IR(neat):** 3065*w*, 2973*s*, 2932*m*, 2835*w*, 2360*w*, 1759*s*, 1640*w*, 1618*m*, 1568*w*, 1477*m*, 1440*w*, 1415*w*, 1396*m*, 1369*w*, 1271*m*, 1159*w*, 1096*s*, 1034*w*, 995*w*, 886*w*, 836*w*, 797*w*, 756*w*, 737*w*. **MP:** 138–139.5 °C.

General Procedure for de-protection of 4e(a–k)

In a round-bottomed flask equipped with a stir bar was added **4e** (0.20 mmol) in anhydrous toluene (5 mL) under argon at rt. MeMgI (1 mmol, 3M in Et_2O) was added dropwise and the solution was heated to 110 °C under oil bath for 12 h under argon. The reaction mixture was then cooled to room temperature and poured into satd. NH_4Cl (5 mL). Water and EA were added and the layers were separated. The aqueous phase was extracted with EA. The

combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with PE / EA (50:1) to afford free phenol product **6**.

(1'R,2'R)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6a, CBD). Following the general procedure described above and starting from **4ea** (20 g, 41.4 mmol), the title compound **6a (CBD)** was prepared as an white solid (12.9 g, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (br, 2H), 6.01 (s, 2H), 5.09 (s, 1H), 4.49 (m, 1H), 4.41 (m, 1H), 3.84–3.82 (m, 1H), 3.03 (td, J = 8.4, 2.4 Hz, 1H), 2.30 (t, J = 6.4 Hz, 2H), 2.11–2.07 (m, 1H), 1.94–1.90 (m, 1H), 1.70–1.67 (m, 1H), 1.65–1.61 (m, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.50–1.44 (m, 2H), 1.32–1.23 (m, 4H), 0.86 (t, J = 5.6 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.7, 149.6, 140.6, 130.5, 127.3, 114.6, 110.1, 107.1, 44.1, 36.0, 35.4, 31.5, 30.8, 30.0, 23.8, 22.5, 19.7, 14.4. HRMS (ESI): calcd for $C_{21}H_{29}O_2$ [M – H]$^-$, 313.2173; found, 313.2169. The ^{1}H NMR data are consistent with the literature.[49]

(1'R,2'R)-4,5'-dimethyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6b). Following the general procedure described above and starting from **4eb** (85.3 mg, 0.2 mmol), the title compound **6b** was prepared as an a colorless oil (50.1 mg, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (br, 2H), 6.01 (s, 2H), 5.01 (s, 1H), 4.50 (br, 1H), 4.41 (br, 1H), 3.84–3.82 (m, 1H), 3.04 (td, J = 11.8, 2.8 Hz, 1H), 2.14–2.09 (m, 1H), 2.04 (s, 3H), 1.94–1.90 (m, 1H), 1.71–1.56 (m, 2H), 1.62 (s, 3H), 1.59 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.80, 149.6, 135.6, 130.5, 127.4, 114.4, 110.2, 107.7, 44.2, 35.9, 30.8, 30.0, 23.8, 21.3, 19.6. HRMS (ESI): calcd for $C_{17}H_{21}O_2$ [M – H]$^-$, 257.1547; found, 257.1543. **IR(neat):** 3439*br*, 3071*w*, 2964*s*, 2922*s*, 2856*m*, 2831*m*, 1631*s*, 1586*s*, 1515*w*, 1493*m*, 1445*m*, 1330*w*, 1312*w*, 1280*w*, 1218*w*, 1175*w*, 1079*w*, 1053*m*, 1035*m*, 987*m*, 889*m*, 823*m*, 584*w*, 523*w*.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-propyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6c). Following the general procedure described above and starting from **4ec** (90.9 mg, 0.2 mmol), the title compound **6c** was prepared as an off-white solid (56.6 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (br, 2H), 6.01 (s, 2H), 5.09 (s, 1H), 4.49 (m, 1H), 4.41 (m, 1H), 3.84–3.81 (m, 1H), 3.03 (td, J = 12.2, 2.8 Hz, 1H), 2.28 (t, J = 8 Hz, 2H), 2.12–2.07 (m, 1H), 1.93–1.89 (m, 1H), 1.70–1.62 (m, 2H), 1.60 (s, 3H), 1.59 (s, 3H), 1.53–1.44 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.7, 149.6, 140.4, 130.5, 127.4, 114.7, 110.1, 107.1, 44.1, 37.6, 36.0, 30.8, 30.0, 24.2, 23.8, 19.7, 14.3. HRMS (ESI): calcd for $C_{19}H_{25}O_2$ [M – H]$^-$, 285.1860; found, 285.1856. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.27 (s, 1H), 6.17 (s, 1H), 5.98 (s, 1H), 5.57 (s, 1H), 4.70–4.50 (m, 3H), 3.82–3.86 (m, 1H), 2.47–2.34 (m, 3H), 1.87–1.72 (m, 5H), 1.70–1.63 (m, 4H), 1.62–1.52 (m, 3H), 0.90 (t, J=7.3 Hz, 3H). **IR(neat):** 3387*br*, 2930*s*, 2866*m*, 1628*w*, 1586*m*, 1512*w*, 1443*m*, 1356*w*, 1323*m*, 1241*m*, 1217*w*, 1025*m*, 892*m*, 869*w*, 824*w*. **MP:** 118.1–119.1 °C The ^{1}H NMR data are consistent with the literature.[50, 51]

(1'R,2'R)-4-isopropyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6d). Following the general procedure described above and starting from **4ed** (90.9 mg, 0.2 mmol), the title compound **6d** was prepared as an off-white solid (56.2 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (br, 2H), 6.07 (s, 2H), 5.07 (s, 1H), 4.52 (m, 1H), 4.42 (m, 1H), 3.85–3.81 (m, 1H), 3.04 (td, J = 11.4, 2.8 Hz, 1H), 2.63–2.56 (m, 1H), 2.10–2.07 (m, 1H), 1.93–1.89 (m, 1H), 1.70–1.62 (m, 2H), 1.59 (s, 6H), 1.10 (d, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.7, 149.7, 146.7, 130.5, 127.3, 114.7, 110.2, 105.1, 44.1, 36.0, 33.4, 30.8, 30.1, 24.3, 24.2, 23.7, 19.7. HRMS (ESI): calcd for $C_{19}H_{25}O_2$ [M – H]$^-$, 285.1860; found, 285.1857. **IR(neat):** 3373*br*, 3076*w*, 2957*s*, 2932*m*, 2869*m*, 2824*w*, 1643*w*, 1626*m*, 1585*m*, 1521*w*, 1433*m*, 1378*w*, 1306*m*, 1236*w*, 1242*m*, 1147*w*, 1071*w*, 1050*w*, 1023*m*, 963*w*, 892*m*, 869*w*, 841*w*, 747*w*, 669*w*, 586*w*, 562*w*. **MP:** 115.9–117.1 °C.

(1'R,2'R)-4-butyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6e). Following the general procedure described above and starting from **4ee** (93.7 mg, 0.2 mmol), the title compound **6e** was prepared as a colorless oil (59.4 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (br, 2H), 6.01 (s, 2H), 5.08 (s, 1H), 4.49 (m, 1H), 4.40 (m, 1H), 3.84–3.81 (m, 1H), 3.03 (td, J = 11.8, 2.8 Hz, 1H), 2.31 (t, J = 7.6 Hz, 2H), 2.13–2.07 (m, 1H), 1.93–1.89 (m, 1H), 1.70–1.61 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.50–1.41 (m, 2H), 1.34–1.23 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.7, 149.6, 140.6, 130.5, 127.3, 114.6, 110.1, 107.1, 44.1, 36.0, 35.1, 33.3, 30.8, 30.0, 23.8, 22.3, 19.7, 14.3. HRMS (ESI): calcd for $C_{20}H_{27}O_2$ [M – H]$^-$, 299.2017; found, 299.2015. **IR(neat):** 3430*br*, 3072*w*, 2927*s*, 2857*s*, 1629*s*, 1584*s*, 1515*w*, 1444*s*, 1376*w*, 1339*w*, 1311*w*, 1236*w*, 1214*m*, 1174*w*, 1150*w*, 1131*w*, 1091*w*, 1051*w*, 1026*m*, 962*w*, 888*m*, 834*w*, 595*w*, 526*w*.

(1'R,2'R)-4-cyclopropyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6f). Following the general procedure described above and starting from **4ef** (90.5 mg, 0.2 mmol), the title compound **6f** was prepared as an off-white solid (55.7 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (br, 2H), 5.90 (s, 2H), 5.06 (s, 1H), 4.49 (m, 1H), 4.40 (m, 1H), 3.82–3.79 (m, 1H), 3.02 (td, J = 11.8, 2.8 Hz, 1H), 2.13–2.06 (m, 1H), 1.93–1.88 (m, 1H), 1.69–1.55 (m, 3H), 1.58 (s, 6H), 0.84–0.79 (m, 2H), 0.48–0.44 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.8, 149.6, 142.0, 130.5, 127.3, 114.5, 110.2, 104.2, 44.2, 36.0, 30.8, 30.0, 23.8, 19.6, 15.2, 9.1. HRMS (ESI): calcd for $C_{19}H_{23}O_2$ [M – H]$^-$, 283.1704; found, 283.1700. **IR(neat):** 3484*br*, 2930*s*, 1627*m*, 1580*m*, 1436*m*, 1314*m,* 1240*m*, 1227*w*, 1193*w*, 1046*w*, 1063*m*, 1025*m*, 970*m*, 899*m*, 817*w*, 610*w*, 547*w*. **MP:** 92.8 –94.5°C.

(1'R,2'R)-4-cyclopentyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6g). Following the general procedure described above and starting from **4eg** (96.2 mg, 0.2 mmol), the title compound **6g** was prepared as an off-white solid (61.8 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (br, 2H), 6.08 (s, 2H), 5.07 (s, 1H), 4.52 (m, 1H), 4.41 (m, 1H), 3.84–3.81 (m, 1H), 3.04 (td, J = 11.8, 2.8 Hz, 1H), 2.74–2.65 (m, 1H), 2.12–2.06 (m, 1H), 1.93–1.88 (m, 3H), 1.74–1.61 (m, 4H), 1.59 (s, 6H), 1.61–1.57 (m, 2H), 1.45–1.36 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.8, 149.6, 144.3, 130.5, 127.4, 114.7, 110.2, 105.7, 45.4, 44.1, 36.0, 34.3, 34.3, 30.8, 30.1, 25.4, 23.7, 19.7. HRMS (ESI): calcd for $C_{21}H_{27}O_2$ [M – H]$^-$, 311.2017; found, 311.2014. **IR(neat):** 3448*br*, 2933*s*, 2909*s*, 2867*m*, 1628*m*, 1585*m*, 1522*w*, 1435*m*, 1377*w*, 1307*m*, 1290*w*, 1227*w*, 1195*w*, 1050*w*, 1052*m*, 1006*w*, 890*w*, 863*w*, 821*w*, 669*w*, 597*w*, 652*w*, 524*w*, 487*w*. **MP:** 127.8–130.4 °C.

(1'R,2'R)-4-cyclohexyl-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6h). Following the general procedure described above and starting from **4eh** (98.9 mg, 0.2 mmol), the title compound **6h** was prepared as a colorless oil (64.5 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (br, 2H), 6.04 (s, 2H), 5.07 (s, 1H), 4.52 (m, 1H), 4.41 (m, 1H), 3.84–3.82 (m, 1H), 3.04 (td, J = 11.8, 2.8 Hz, 1H), 2.24–2.21 (m, 1H), 2.09–2.06 (m, 1H), 1.93–1.88 (m, 1H), 1.76–1.63 (m, 6H), 1.59 (s, 6H), 1.36–1.18 (m, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 156.6, 149.7, 146.0, 130.5, 127.3, 114.8, 110.2, 105.5, 44.1, 43.9, 36.0, 34.5, 34.4, 30.8, 30.1, 26.9, 26.3, 23.7, 19.7. HRMS (ESI): calcd for $C_{22}H_{29}O_2$ [M – H]$^-$, 325.2173; found, 325.2171. **IR(neat):** 3439*br*, 2918*m*, 2849*m*, 2358*s*, 2340*s*, 1643*m*, 1632*w*, 1614*m*, 1581*m*, 1574*m*, 1444*m*, 1434*m*, 1371*w*, 668*m*.

(1R,2R)-5-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-[1,1':4',1''-terphenyl]-2',6'-diol (6i). Following the general procedure described above and starting from **4ei** (97.7 mg, 0.2 mmol), the title compound **6i** was prepared as a colorless oil (60.8 mg, 95% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (br, 2H), 7.48–7.39 (m, 4H), 7.31–7.28 (m, 1H), 6.48 (s, 2H), 5.13 (s, 1H), 4.55 (m, 1H), 4.45 (m, 1H), 3.93–3.91 (m, 1H), 3.11 (td, J = 12, 3.2

Hz, 1H), 2.17–2.08 (m, 1H), 1.96–1.92 (m, 1H), 1.74–1.66 (m, 2H), 1.63 (s, 3H), 1.62 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ 157.4, 149.5, 141.0, 138.8, 130.9, 129.3, 127.5, 126.9, 126.6, 116.9, 110.3, 105.5, 44.1, 36.1, 30.8, 29.9, 23.8, 19.7. HRMS (ESI): calcd for $C_{22}H_{23}O_2$ $[M - H]^-$, 319.1704; found, 319.1700. **IR(neat):** 3435*br*, 3069*m*, 3034*w*, 2922*s*, 2855*m*, 2832*w*, 2358*s*, 2340*m*, 1643*m*, 1621*m*, 1641*w*, 1587*m*, 1572*m*, 1567*w*, 1461*m*, 1453*m*, 1426*w*, 1415*w*, 1346*w*, 1305*w*, 1274*w*, 1240*w*, 1189*w*, 1052*w*, 1027*m*, 890*w*, 846*w*, 761*m*, 696*m*, 668*w*, 652*w*, 546*w*, 424*w*.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-vinyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6j). Following the general procedure described above and starting from **4ej** (87.7 mg, 0.2 mmol), the title compound **6j** was prepared as an off-white solid (48.6 mg, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (br, 2H), 6.49–6.42 (m, 1H), 6.28 (s, 2H), 5.51–5.47 (d, J = 17.6 Hz, 1H), 5.11–5.10 (m, 2H), 4.49 (m, 1H), 4.41 (m, 1H), 3.87–3.85 (m, 1H), 3.05 (td, td, J = 12.2, 2.8 Hz, 1H), 2.11–2.08 (m, 1H), 1.95–1.90 (m, 1H), 1.70–1.67 (m, 2H), 1.60 (s, 3H), 1.59 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ 157.2, 149.5, 137.6, 135.6, 130.8, 126.8, 117.7, 112.8, 110.2, 105.0, 44.1, 36.2, 30.8, 29.8, 23.8, 19.6. HRMS (ESI): calcd for $C_{18}H_{21}O_2$ $[M - H]^-$, 269.1547; found, 269.1545. **IR(neat):** 3423*s*, 2964*s*, 2924*s*, 1624*m*, 1577*m*, 1511*w*, 1493*m*, 1439*m*, 1376*w*, 1312*w*, 1274*w*, 1238*w*, 1217*w*, 1150*w*, 1054*w*, 1026*m*, 985*w*, 891*w*, 847*w*, 550*w*. **MP:** 62.5–65.5 °C.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(prop-1-yn-1-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6k). Following the general procedure described above and starting from **4ek** (90.1 mg, 0.2 mmol), the title compound **6k** was prepared as an off-white solid (54.1 mg, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (br, 2H), 6.20 (s, 2H), 5.07 (s, 1H), 4.47 (m, 1H), 4.41 (m, 1H), 3.86–3.83 (m, 1H), 3.02 (td, J = 11.8, 2.8 Hz, 1H), 2.13–2.07 (m, 1H), 1.97 (s, 3H), 1.96–1.90 (m, 1H), 1.70–1.64 (m, 2H), 1.60 (s, 3H), 1.58 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ 157.0, 149.4, 130.9, 126.5, 121.2, 118.3, 110.3, 109.9, 84.8, 80.5, 44.0, 36.2, 30.8, 29.8, 23.7, 19.6, 4.3. HRMS (ESI): calcd for $C_{19}H_{21}O_2$ $[M - H]^-$, 281.1547; found, 281.1544. **IR(neat):**3407*s*, 3328*s*, 2931*s*, 1622*m*, 1571*s*, 1519*w*, 1434*m*, 1426*m*, 1377*w*, 1345*w*, 1310*w*, 1294*w*, 1243*m*, 1169*m*, 1049*w*, 1031*w*, 1023*w*, 966*w*, 903*w*, 874*w*, 847*m*, 828*m*, 634*w*, 607*w*, 542*w*, 516*w*. **MP:** 131.2–133.7 °C.

(1'R,2'R)-5'-methyl-2'-(prop-1-en-2-yl)-4-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6l) Following the general procedure described above and starting from **4el** (979 mg, 2 mmol), the title compound **6l** was prepared as a brown solid (585 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 2H), 8.65–8.53 (m, 1H), 7.82 (td, J = 7.7, 1.9 Hz, 1H), 7.63 (dd, J = 8.1, 1.1 Hz, 1H), 7.30–7.23 (m, 1H), 6.93 (s, 2H), 5.14 (s, 1H), 4.52 (d, J = 2.8 Hz, 1H), 4.43 (dd, J = 3.0, 1.6 Hz, 1H), 3.95–3.90 (m, 1H), 3.15–3.04 (m, 1H), 2.13–2.08 (m, 1H), 1.97–1.92 (m 1H), 1.73–1.64 (m, 2H), 1.62 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO): δ 157.4, 156.7, 149.8, 149.4, 137.5, 137.3, 130.9, 126.7, 122.6, 119.9, 118.7, 110.3, 105.4, 44.1, 36.2, 30.8, 30.1, 29.8, 23.8, 19.6. HRMS (ESI): calcd for $C_{21}H_{24}NO_2$ $[M + H]^+$, 322.1802; found, 322.1809. **IR(neat):** 3418*br*, 3069*w*, 2964*s*, 2923*m*, 1643*w*, 1622*w*, 1585*m*, 1563*m*, 1472*m*, 1443*m*, 1376*w*, 1346*w*, 1283*w*, 1252*w*, 1193*w*, 1154*w*, 1054*w*, 1031*w*, 1002*w*, 899*w*, 858*w*, 783*m*, 752*w*, 678*w*. **MP:** 85.1–86.9 °C.

(1'R,2'R)-4-(5-chlorothiophen-2-yl)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (6m). Following the general procedure described above and starting from **4em** (106 mg, 0.2 mmol), the title compound **6m** was prepared as a vitreous solid (70.8 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 2H), 7.08 (d, J = 3.9 Hz, 1H), 7.05 (d, J = 3.9 Hz, 1H), 6.41 (s, 2H), 5.10 (s, 1H), 4.51 (m, 1H), 4.43 (m, 1H), 3.90–3.86 (m, 1H), 3.05 (td, J = 11.5, 2.9 Hz, 1H), 2.18–2.09 (m, 1H), 1.96–1.91 (m, 1H), 1.73–1.61 (m, 2H), 1.60 (d, J = 2.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO): δ 157.6, 149.4, 143.5, 131.2, 131.0, 128.5, 126.7, 126.5, 122.5, 118.1, 110.3, 104.1, 44.1, 36.2, 31.2, 30.8, 29.8, 23.7, 19.5. HRMS (ESI): calcd for $C_{20}H_{22}ClO_2S$ $[M + H]^+$, 361.1024; found, 361.1023. **IR(neat):**3414*br*, 3070*w*, 2964*w*, 2923*s*, 2830*w*, 2360*m*, 2341*m*, 1623*m*, 1577*m*,

1541*w*, 1447*s*, 1376*w*, 1347*w*, 1300*w*, 1237*w*, 1222*w*, 1175*w*, 1027*m*, 993*m*, 891*w*, 866*w*, 792*m*, 668*w*, 542*w*, 498*w*. **MP:** 52.9–54.8 °C.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for the products and X-Ray crystallographic report for CBD. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: shenjingshan@simm.ac.cn.

*E-mail: haji@ms.xjb.ac.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the support from National Science Foundation for Young Scientists of China (Grant No. 81703338), the National Natural Science Foundation of China (U1703235) and National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (No: 2018ZX09711002). We thank the Central Asian Drug Discovery and Development Center of the Chinese Academy of Sciences for support of our research.

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