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Article

Chiral Amino and Imino-Alcohols Based on (*R*)-Limonene

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Derivatives of the natural occurring and inexpensive terpene (*R*)-limonene were synthetized and completely characterized. Starting from internal olefin epoxidation, followed by epoxide opening with sodium azide and azide reduction with $LiAlH_4$, two chiral amino-alcohols were obtained. The amino-alcohols were reacted with three different aldehydes, generating six new imino-alcohols, two of them yielding crystals suitable for X-ray diffraction characterization. The reduction of four of these compounds with $LiAlH_4$ led to new amino-alcohols. All derivatives were obtained with good overall yields through simple reaction protocols.

Keywords: natural products, *N*,*O* ligands, Schiff bases, sustainable chemistry, renewable sources

Introduction

Natural asymmetric molecules are excellent starting points for the synthesis of chiral compounds since they are usually enantiomerically pure, obtained from renewable sources and, for most of them, inexpensive. Terpenes are great natural asymmetric building blocks: mainly produced by a variety of plants, some exemplars can be transformed into more complex compounds with high aggregated value, used as ligands or catalyst for asymmetric reactions, for instance.[1] One good example of this type of compound is (*R*)-limonene (Scheme 1), which is present in high quantities on citric fruits, especially in orange peel. Since Brazil is the world top producer of orange and its juice (having the peel as a side product),[2] it is economically interesting to give (*R*)-limonene nobler applications compared to solvent for paint, additive to food, hygiene products or cosmetics and other classical uses of this terpene.[3]

(*R*)-Limonene has two chemically distinct double bonds that make possible a large number of chemical modifications in order to synthesize more complex molecules[4-6] with applications spread over medicinal chemistry,[7-13] total synthesis of natural products,[14-18] and others, including applications in catalysis. The first use of limonene-derived chiral ligands in catalytic systems was published by Lahuerta *et al.*[19] in 2000, where the researchers used $LiPPh_3$ to perform previously reported selective epoxide opening in limonene oxides,[20] generating phosphine-alcohols that induced low selectivity in Rh-catalyzed C–H insertion and cyclopropanation reactions. Since then, there was a narrow development in the ligand synthesis starting from limonene, having excellent results in terms of yield and stereoselectivity, however distributed into two main reactions: organozinc additions[21-25] and ruthenium catalyzed asymmetric hydrogen transfer reactions.[26-28] Usually, its internal *cis* and *trans*-oxides are used as substract for selective epoxide opening with amines in order to produce secondary or tertiary chiral amino-alcohols, although there are some divergent methodologies using amino-oximes[26,29,30] or aziridines.[28]

In order to increase structure variety, hoping this would widen the application of limonene-based chiral molecules, we present herein the synthesis of new amino- and imino-alcohols based on (*R*)-limonene through simple and high yielding reactions as epoxidation, epoxide opening, azide reduction, imine formation and reduction (Scheme 1).

Results and Discussion

In order to produce (*R*)-limonene based imines, it was necessary to synthesize its primary amines. We performed the epoxidation of the internal double bond using H_2O_2 as oxidant and methyltrioxorhenium ($MeReO_3$, MTO) as catalyst, as described by Rudler *et al.*,[31] producing a

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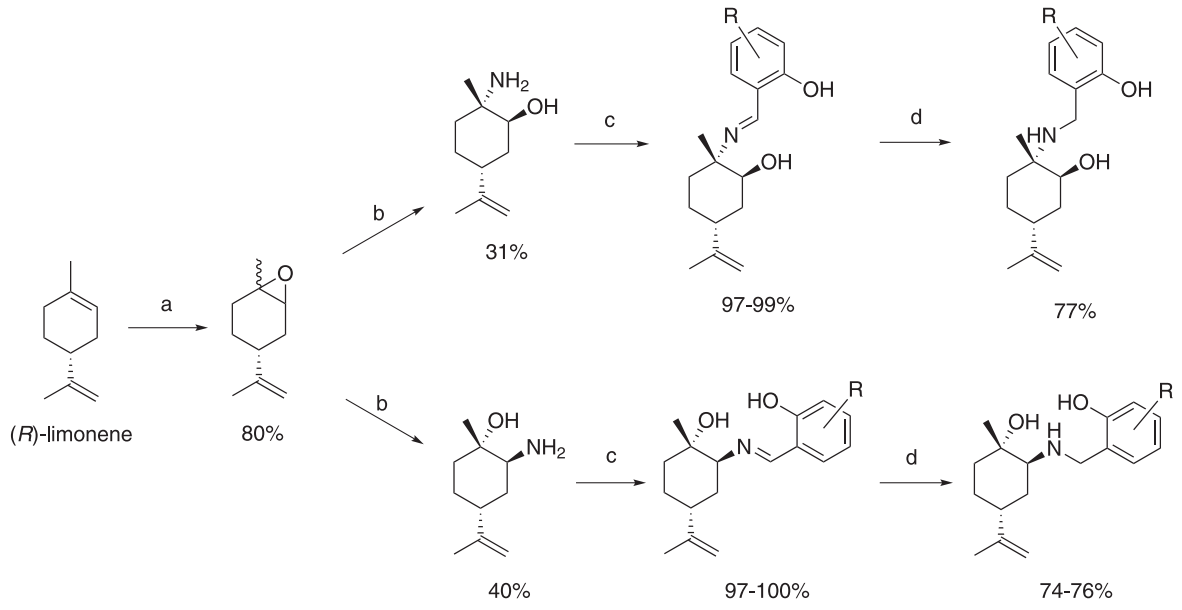
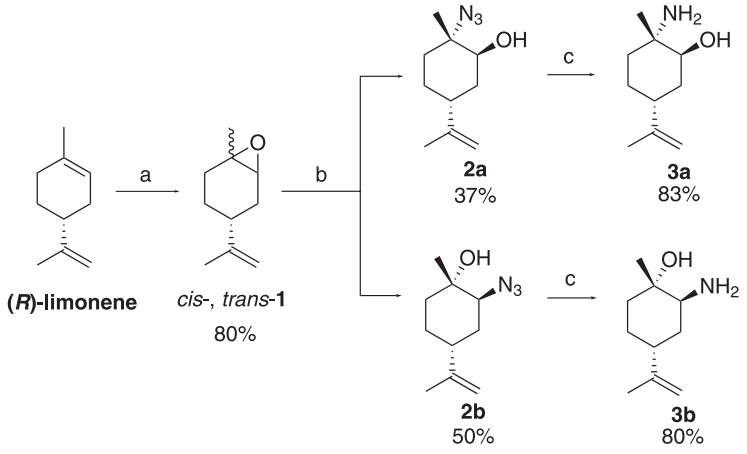


(a) H_2O_2, $MeReO_3$; (b) 1) NaN_3, 2) $LiAlH_4$; (c) ArCHO; (d) $LiAlH_4$.

Scheme 1. Present work overview.

mixture of *cis* and *trans*-limonene oxides **1** in good yield (Scheme 2). This mixture was then reacted with NaN_3, using an adaptation of the methodology of Cimarelli *et al.*[32] As described by these researchers, the reaction was highly stereosselective and yielded only two products, the azido-alcohols **2a** and **2b**, bearing *trans* carbon substituents in the cyclohexyl ring, which could be separated by flash column chromatography. This reaction pattern is very common for limonene oxide ring opening by nucleophiles and is due to the ring strain during the transition state and therefore is used for the kinetic separation of these oxides.[33,34] Through the reduction of the azide group with $LiAlH_4$ in tetrahydrofuran (THF), primary amines **3a** and **3b** were obtained in high yields. These derivatives were characterized by ^1H and ^{13}C nuclear magnetic resonance (NMR) and the spectra matched very well the ones of their enantiomers, which are described in the literature.[32]

With the primary amines **3a-b** in hands, we proceeded to the imine formation reaction with three different OH-substituted aromatic aldehydes. These reactions produced the desired Schiff bases (**4-6a** and **4-6b**) in excellent yields and in short reaction times (Scheme 3). It is worth pointing out that the acidity of the phenolic group itself was the catalyst for this reaction and provided an optimum pH for the reaction to take place, since there was no need to use another catalyst or water removal to dislocate



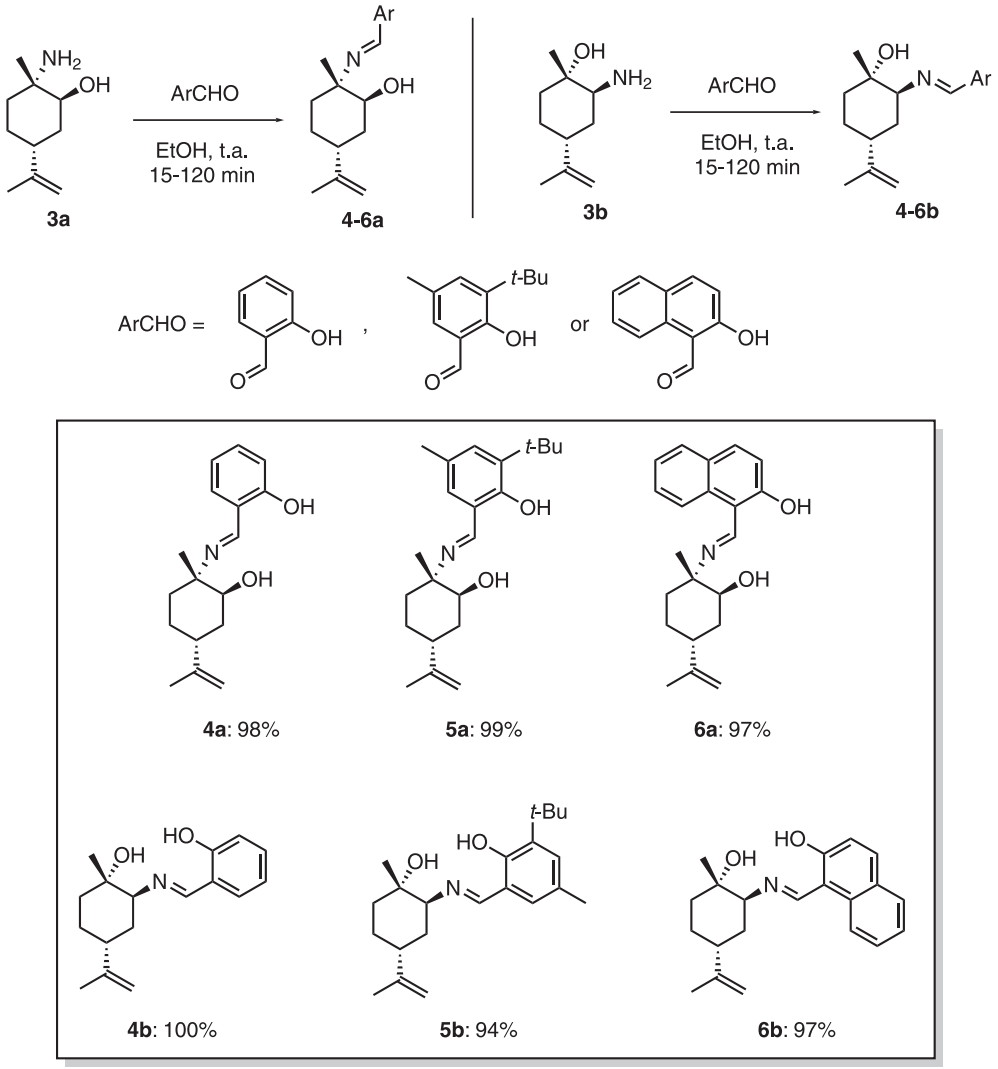
(a) 10% H_2O_2 (aq), 1 mol% MTO, DCM, 4 °C; (b) NaN_3, NH_4Cl, MeOH, reflux, 30 h; (c) $LiAlH_4$, THF, rt, 1 h, N_2(g).

Scheme 2. Chiral amino-alcohol synthesis using (*R*)-limonene as starting material.

the reaction equilibrium to the products. The phenolic OH group present in these compounds could be useful in catalysis or medicinal chemistry, by providing an additional number of possible interactions to metals or biomolecules active sites. All of these compounds were characterized by mass spectroscopy, polarimetry, infrared spectroscopy (IR), ^{1}H and ^{13}C NMR. The most important change on the ^{1}H NMR spectra of these compounds was the appearance of the imine N=C–H signal at about 8.5 ppm, along with the incorporation of the aromatic and phenolic hydrogens.

Single crystals of **5a** and **6a** suitable to X-ray diffraction studies were grown by slow evaporation of the solvent from a concentrated dichloromethane (DCM)/hexane solution of the compounds and provided additional information about their molecular structures. The molecular structures of **5a** and **6a** are shown in Figures 1 and 2, respectively. The main crystallographic data and structure refinement parameters are reported in the Supplementary Information (SI) section. Compound **5a** (Figure 1) has three stereogenic centers and the absolute configuration was determined to be C13(*S*), C14(*S*), C16(*R*) by considering the synthetic pathway and confirmed by the X-ray diffraction study. Moreover, the solid-state structure of **5a** reveals that the imine group are in *E* configuration and the torsion angle between C6–C12–N–C13 is 176.55(32). Compound **6a** (Figure 2) has also three chiral centers with the absolute configuration determined as C12(*S*), C15(*R*), C17(*S*), which is consistent with the synthetic pathway and confirmed by the X-ray diffraction analysis. Like **5a**, the imine group in **6a** are in *E* configuration and the torsion angle between C12–N1–C11–C10 is 175.38(14).

To increase the structural variation of the compounds, we performed the reduction of the imines with $LiAlH_4$ (Scheme 4). Although the reaction occurred in good yield with imines **4-5a** and **4-5b**, it was not the case for the naphtyl derivatives, which produced a complex mixture



Scheme 3. Synthesis of limonene-derived aromatic imines.

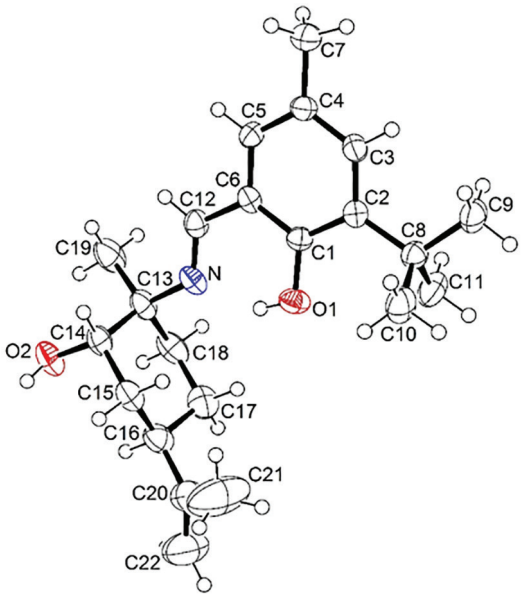


Figure 1. Molecular structure of **5a** with the key atoms labelled (thermal ellipsoids drawn at 50% probability level).

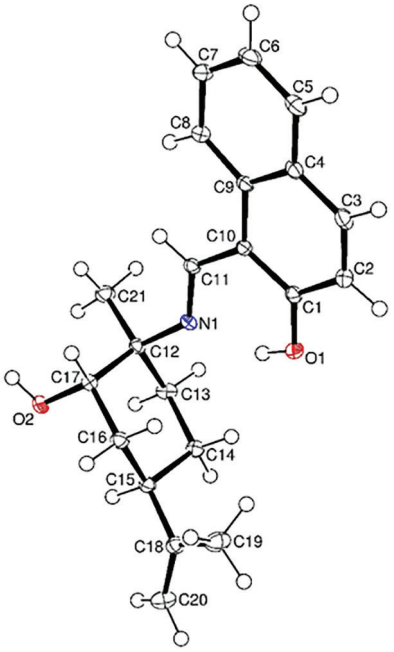


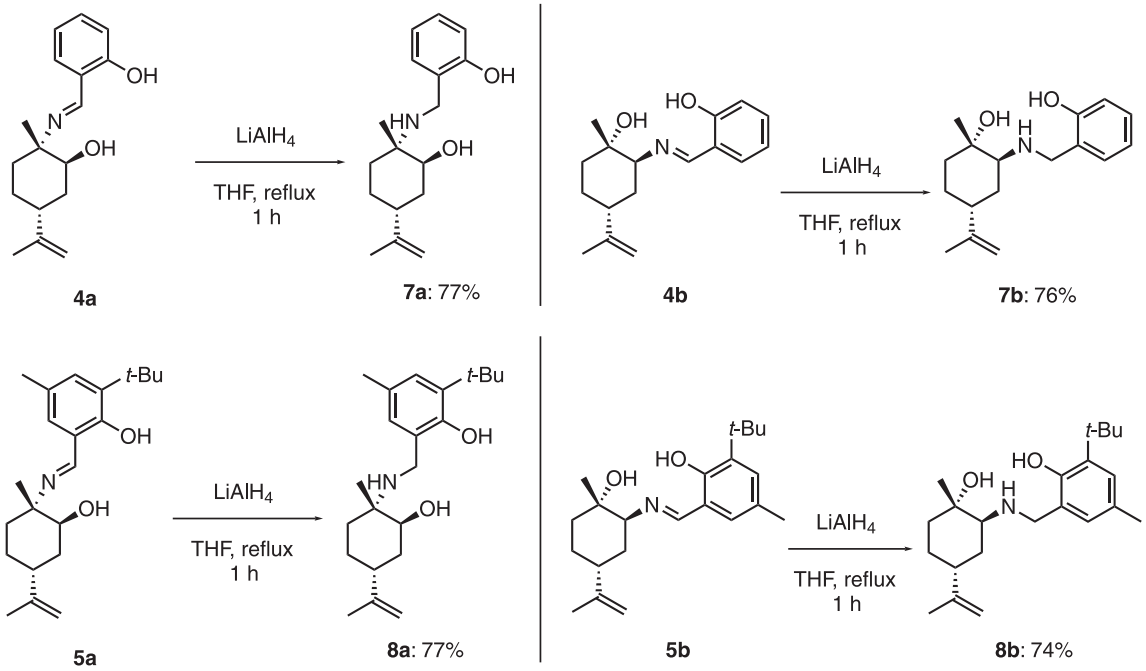
Figure 2. Molecular structure of **6a** with the key atoms labelled (thermal ellipsoids drawn at 50% probability level).

along with some unreacted starting material. All of these compounds were characterized by mass spectroscopy, polarimetry, infrared spectroscopy, ^{1}H and ^{13}C NMR. The most important change on the ^{1}H NMR spectra of these derivatives was disappearance of the imine N=C–H signal at about 8.5 ppm.

In summary, we obtained 4 enantiomers of compounds that were previously described in the literature (**2a-b** and **3a-b**).[32] We also described the synthesis of 6 new imino-alcohols and 4 new amino-alcohols, all based on the terpene (*R*)-limonene, through simple reactions with good overall yields.

Conclusions

Primary amino-alcohol ligands were obtained by epoxidation of (*R*)-limonene with MTO/H_2O_2, followed by epoxy-opening reactions with sodium azide and reduction



Scheme 4. Imine reduction reactions.

with $LiAlH_4$. From these, imines were formed by reacting with three aromatic salicylaldehydes in excellent yields. Some imines were reduced to secondary amino-alcohols. The compounds were extensively characterized by NMR, IR, high resolution mass spectroscopy (HRMS) and polarimetry, and it was possible to solve the crystal structure of two of them through single crystal X-ray diffraction (XRD). The reactions proceeded smoothly and with great yields. With these procedures, we were able to achieve new imino- and amino-alcohols, which could be useful in catalysis, medicinal chemistry or even in other applications. This study is under way.

Experimental

General

Unless otherwise stated, all reagents and solvents were used as received. THF was dried through distillation from Na-benzophenone. NMR experiments were performed in a 300 or 400 MHz Varian spectrometer. Fourier-transform infrared spectroscopy/attenuated total reflection (FTIR/ATR) analyses were performed in a Bruker alpha-P apparatus in ATR mode or Shimazdu IR Prestige-21 as thin films between KBr crystals. The NMR chemical shifts are given in ppm relatively to tetramethylsilane (TMS) and the FTIR wavenumbers are given in cm^{-1}. Mass spectra were recorded on a Micromass Q-TOF Micro operating in electrospray mode. Polarimetry analyses were performed in a Jasco P2000 polarimeter in chloroform.

Synthesis of *cis*- and *trans*-(+)-limonene oxides (**1**)

The procedure was based on the literature.[24] To 15.4 mg of MTO (0.0613 mmol), in an ice bath, 5 mL of dichloromethane (DCM) and 0.99 mL of (*R*)-limonene (6.13 mmol) were added. Then 2.90 mL of a 3.18 M aqueous H_2O_2 (1.5 equiv.) were added and the reaction was stirred in an ice bath for 1 h. Then, the oxidant excess was destroyed with a small amount of MnO_2. The organic phase was separated, and the aqueous layer was extracted with 1 × 10 mL and 2 × 5 mL of DCM. The organic layers were combined, dried with Na_2SO_4 and the solvent removed under vacuum. The product was purified by silica flash column chromatography using 5% ethyl acetate (EtOAc) in hexane as elutant (thin layer chromatography (TLC), t_R = 0.5, 5% EtOAc in hexane, using $KMnO_4$ basic solution as developer). The solvent was carefully evaporated in a rotatory evaporator to give **1** as a colourless volatile oil. Yield: 746 mg (80%).

(4*R*)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptane

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76-4.53 (m, 4H, *cis* + *trans*), 3.01 (t, 1H, *J* 2.0, *cis*), 2.95 (d, 1H, *J* 5.3, *trans*), 2.15-1.92 (m, 5H, *cis* + *trans*), 1.89-1.76 (m, 4H, *cis* + *trans*), 1.73-1.58 (m, 9H, *cis* + *trans*), 1.56-1.44 (m, 1H, *cis* + *trans*), 1.39-1.30 (m, 2H, *cis* + *trans*), 1.28 (s, 3H, *cis*), 1.27 (s, 3H, *trans*).

Synthesis of (1*S*,2*S*,4*R*)-2-azido-1-methyl-4-(pro-1-en-2-yl)cyclohexanol (**2a**) and (1*S*,2*S*,5*R*)-2-azido-2-methyl-5-(prop-1-en-2-yl)cyclohexanol (**2b**)

The procedure was based on the literature.[25] 1.52 g of **1** (10 mmol), 1.3 g of NaN_3 (20 mmol) and 0.54 g of NH_4Cl (10 mmol) were refluxed in 4 mL of methanol (MeOH) until all limonene oxide was consumed according to TLC (about 32 h). The mixture was allowed to cool to room temperature and the solvent removed. Then, DCM was added, and the mixture was filtered through Na_2SO_4 and evaporated. The azido-alcohols were separated by silica flash column chromatography using 10-30% ether in hexane as gradient elutant (TLC: t_R = 0.45 (**2a**) and 0.3 (**2b**), $KMnO_4$ as developer). After solvent removal, the azido-alcohols were obtained as pale-yellow oils. Yield: **2a** 594 mg (37%) and **2b** 822 mg (50%).

Compound **2a**

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76-4.70 (m, 2H), 3.64 (t, 1H, *J* 3.3), 2.25 (tt, 1H, *J* 10.8, 3.3), 1.95-1.40 (m, 10H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 109.1, 71.9, 63.1, 37.1, 34.1, 30.8, 26.4, 22.6, 20.8.

Compound **2b**

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 2H), 3.54 (s, 1H), 2.20 (ddd, 1H, *J* 14.8, 9.8, 3.9), 2.00 (ddd, 1H, *J* 14.8, 11.9, 3.0), 1.90-1.81 (m, 1H), 1.76 (s, 3H), 1.72- 1.61 (m, 1H), 1.62-1.36 (m, 5H), 1.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 109.2, 70.9, 66.4, 37.9, 33.9, 30.7, 27.6, 25.92, 20.95.

Synthesis of (1*S*,2*S*,5*R*)-2-amino-2-methyl-5-(prop-1-en-2-yl)cyclohexanol (**3a**)

The procedure was based on the literature.[25] Under argon atmosphere, 2 mL of dry THF were added on 200 mg of $LiAlH_4$ (5.26 mmol) in an ice bath. Then, a solution of 699 mg of **2a** (3.58 mmol) in 3 mL of dry THF was slowly added, causing N_2 evolution, and the mixture was stirred for 1 h in room temperature. The reaction was quenched with saturated Na_2SO_4 (aq), then 10 mL of DCM were

added, along with $MgSO_4$. The mixture was filtered and the solid washed with 5 × 5 mL of DCM. The filtrate was dried under vacuum to give **3a** as a white crystalline solid. Yield: 488 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 2H), 3.47 (s, 1H), 2.23 (ddd, 1H, *J* 14.7, 10.0, 3.9), 1.79 (dddd, 1H, *J* 13.8, 10.9, 3.0, 1.3), 1.72-1.49 (m, 9H + H_2O), 1.49-1.36 (m, 1H), 1.36-1.24 (m, 1H), 1.07 (d, 3H, *J* 1.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 109.1, 71.9, 55.4, 37.5, 34.4, 33.7, 26.2, 25.8, 21.2.

Synthesis of (1*S*,2*S*,4*R*)-2-amino-1-methyl-4-(prop-1-en-2-yl)ciclohexanol (**3b**)

The procedure was identical to the synthesis of **3a**, using 717 mg of **2b** (3.67 mmol). Yield: 519 mg (84%). The product was obtained as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 2H), 3.52-3.44 (m, 1H), 2.22 (td, 1H, *J* 10.3, 5.0), 1.85-1.50 (m, 9H + H_2O), 1.49-1.39 (m, 1H), 1.33 (dddd, 1H, *J* 13.3, 4.9, 3.6, 1.1), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 109.1, 74.5, 51.6, 37.6, 34.5, 33.7, 26.4, 26.1, 21.3.

Synthesis of 2-((*E*)-(((1*S*,2*S*,4*R*)-2-hydroxy-1-methyl-4-(prop-1-en-2-yl)cyclohexyl)imino)methyl)phenol (**4a**)

86.3 mg of **3a** (0.51 mmol) and 55 µL of salicylaldehyde (0.51 mmol) were stirred in 2 mL of EtOH at room temperature until **3a** was completely consumed according to TLC (20 min, 20% MeOH in DCM, t_R = 0.5, $KMnO_4$ as developer). The solvent was removed and the product purified with silica flash column chromatography using gradient elution with 5-20% EtOAc in hexane (TLC: 15% EtOAc in hexane, t_R = 0.35, using vanillin acidic solution as developer). Yield: 137 mg (98%) of a bright yellow oil.

$[\alpha]_D^{25}$ +31.7° (*c* 0.427, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.13 (s, 1H), 8.46 (s, 1H), 7.40-7.23 (m, 2H), 6.99 (d, 1H, *J* 8.2), 6.91 (t, 1H, *J* 7.4), 4.75 (s, 2H), 3.82 (s, 1H), 2.42 (tt, 1H, *J* 11.9, 3.9), 1.95 (ddt, 2H, *J* 14.4, 12.8, 2.2), 1.80 (td, 1H, *J* 3.9, 1.8), 1.78-1.70 (m, 5H), 1.69-1.47 (m, 2H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 161.6, 149.1, 132.3, 131.5, 118.9, 118.4, 117.2, 109.2, 74.2, 61.7, 37.4, 34.1, 32.4, 26.1, 23.8, 20.8; FTIR ν / cm^{-1} 3421, 3075, 2938, 1625, 889, 755; HRMS (FTMS + pESI) *m/z*, calculated for $C_{17}H_{23}NO_2H$ $[MH]^+$: 274.1807, found: 274.1807.

Synthesis of 2-((*E*)-(((1*S*,2*S*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl)imino)methyl)phenol (**4b**)

The procedure was identical to the synthesis of **4a**, using **3b** as substract. The product was purified with silica flash column chromatography using gradient elution with 5-20% EtOAc in hexane as elutant (TLC: 15% EtOAc in hexane, t_R = 0.35, vanillin as developer). Yield: 139 mg (100%) of a bright yellow oil.

$[\alpha]_D^{25}$ −166.3° (*c* 0.325, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H), 8.29 (s, 1H), 7.28-7.16 (m, 2H), 6.89 (d, 1H, *J* 8.2), 6.81 (td, 1H, *J* 7.5, 1.1), 4.68-4.61 (m, 2H), 3.20 (t, 1H, *J* 3.1), 2.33-2.21 (m, 1H), 2.08 (ddd, 1H, *J* 13.3, 12.2, 3.3), 1.89-1.75 (m, 1H), 1.22-1.54 (m, 6H), 1.50 (ddt, 1H, *J* 13.3, 3.7. 2.2) 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.1, 149.4, 132.4, 131.4, 118.8, 118.8, 117.0, 109.0, 74.3, 70.8, 38.2, 34.9, 34.8, 28.3, 26.5, 21.1; IR (KBr) ν / cm^{-1} 3425, 2929, 2864, 1631, 1496, 1276, 756, 433; HRMS (FTMS + pESI) *m/z*, calculated for $C_{17}H_{23}NO_2H$ $[MH]^+$: 274.1807, found: 274.1807.

Synthesis of 2-(*tert*-butyl)-6-((*E*)-(((1*S*,2*S*,4*R*)-2-hydroxy-1-methyl-4-(prop-1-en-2-yl)cyclohexyl)imino)methyl)-4-methylphenol (**5a**)

83 mg of **3a** (0.48 mmol) and 96 mg of 3-(*tert*-butyl)-2-hydroxy-5-methylbenzaldehyde (0.5 mmol) were stirred in 2 mL of EtOH until all **3a** was consumed according to TLC (1 h 30 min). The mixture was vacuum dried and purified by silica flash column chromatography using 0-10% EtOAc in hexane as elutant. Yield: 167.9 mg (99%) of a yellow crystalline solid.

$[\alpha]_D^{25}$ −17.0° (*c* 0.456, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (s, 1H), 8.40 (s, 1H), 7.13 (d, 1H, *J* 2.2), 6.95 (d, 1H, *J* 1.5), 4.78-4.68 (m, 2H), 3.83 (s, 1H), 2.47-2.33 (m, 1H), 2.29 (s, 3H), 2.02-1.85 (m, 2H), 1.78-1.74 (m, 1H), 1.57 (m, 7H), 1.43 (s, 9H), 1.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 158.3, 14.5, 137.3, 130.4, 129.8, 126.4, 118.6, 109.2, 74.4, 61.5, 37.5, 34.8, 34.1, 32.3, 29.4, 26.1, 23.9, 20.7, 20.6; IR (KBr) ν / cm^{-1} 3508, 2939, 2858, 1620, 1440, 876; HRMS (FTMS + pESI) *m/z*, calculated for $C_{22}H_{33}NO_2H$ $[MH]^+$: 344.2589, found: 344.2586; melting point: 110 ºC.

Synthesis of 2-(*tert*-butyl)-6-((*E*)-(((1*S*,2*S*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl)imino)methyl)-4-methylphenol (**5b**)

The procedure was identical to the synthesis of **6a**, using **3b**. The product was purified by silica flash column chromatography using 10-30% EtOAc in hexane as elutant. (t_R = 0.5, 20% EtOAc in hexane, vanillin as developer). Yield: 158 mg (94%) of a yellow viscous material.

$[\alpha]_D^{25}$ −24.8° (*c* 0.584, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.50 (s, 1H), 8.33 (s, 1H), 7.14 (d, 1H, *J* 1.8), 6.94 (d, 1H, *J* 1.8), 4.76-4.69 (m, 2H), 3.25 (t, 1H, *J* 2.9), 2.49-2.32 (m, 1H), 2.29 (s, 3H), 2.13 (ddd, 1H, *J* 13.2, 12.2,

3.3), 1.81-1.51 (m, 9H), 1.44 (s, 9H), 1.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 153.7, 148.3, 137.9, 134.0, 129.3, 128.0, 126.0, 125.5, 122.7, 117.5, 109.7, 106.5, 73.0, 59.7, 37.2, 34.1, 32.4, 25.8, 23.8, 21.0; IR (KBr) ν / cm^{-1} 3428, 2947, 1620, 1432, 888, 753; HRMS (FTMS + pESI) *m/z*, calculated for $C_{22}H_{33}NO_2H$ $[MH]^+$: 344.2589, found: 344.2589.

Synthesis of 1-((*E*)-(((1*S*,2*S*,4*R*)-2-hydroxy-1-methyl-4-(prop-1-en-2-yl)cyclohexyl)imino)methyl)naphtalen-2-ol (**6a**)

130.8 mg of **3a** (0.773 mmol) and 137.1 mg of 2-hydroxy-1-naphtaldehyde (0.77 mmol) were solubilized in 5 mL of EtOH and stirred at room temperature until all **3a** was consumed (about 15 min). The mixture was dried in vacuum and then purified by silica flash column chromatography using 20-40% EtOAc in hexane as elutant. Yield: 242 mg (97%) of an orange crystalline solid.

$[\alpha]_D^{25}$ +83.1° (*c* 0.596, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.99 (s, 1H), 8.80 (d, 1H, *J* 8.4), 7.81 (d, 1H, *J* 8.4), 7.66 (d, 1H, *J* 9.3), 7.58 (d, 1H, *J* 7.8), 7.41 (ddd, 1H, *J* 8.3, 7.1, 1.2), 7.25-7.17 (m, 1H), 6.90 (d, 1H, *J* 9.3 Hz), 4.76 (d, 2H, *J* 5.7), 3.89 (s, 1H), 3.34- 2.93 (m, 1H), 2.44 (ddd, 1H, *J* 14.5, 10.8, 3.6), 2.11-1.90 (m, 2H), 1.90-1.78 (m, 2H), 1.78-1.55 (m, 5H), 1.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 153.7, 148.3, 137.9, 134.0, 129.3, 128.0, 126.0, 125.5, 122.7, 117.5, 109.7, 106.5, 73.0, 59.7, 37.2, 34.1, 32.4, 25.8, 23.8, 21.0; IR (KBr) ν / cm^{-1} 3258, 2925, 2852, 1616, 1341, 759; HRMS (FTMS + pESI) *m/z*, calculated for $C_{21}H_{25}NO_2H$ $[MH]^+$: 324.1964, found: 324.1963; melting point: 138 ºC.

Synthesis of 1-((*E*)-(((1*S*,2*S*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl)imino)methyl)naphtalen-2-ol (**6b**)

The procedure was identical to the synthesis of **5a**, using 84.7 mg (0.50 mmol) of **3b**. Yield: 156.9 mg (97%) of an orange viscous material.

$[\alpha]_D^{25}$ +33.0° (*c* 0.562, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.17 (s, 1H), 8.88 (s, 1H), 7.93 (d, 1H, *J* 8.3), 7.72 (d, 1H, *J* 9.2), 7.64 (d, 1H, *J* 7.9), 7.46 (t, 1H, *J* 7.7), 7.26 (t, 1H, *J* 7.4), 6.99 (d, 1H, *J* 9.2), 4.77 (d, 2H, *J* 4.6), 3.49 (s, 1H), 2.43-2.30 (m, 1H), 2.23 (td, 1H, *J* 12.4, 3.2), 1.99-1.62 (m, 9H + H_2O), 1.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 157.9, 148.6, 136.9, 133.4, 129.3, 128.0, 126.5, 123.7, 123.0, 118.1, 109.5, 107.1, 70.7, 69.7, 38.2, 34.8, 33.7, 27.7, 26.2, 21.2; IR (KBr) ν / cm^{-1} 3319, 3058, 2950, 1616, 1027, 746; HRMS (FTMS + pESI) *m/z*, calculated for $C_{21}H_{25}NO_2H$ $[MH]^+$: 324.1964, found: 324.1964.

Synthesis of 2-((((1*S*,2*S*,4*R*)-2-hydroxy-1-methyl-4-(prop-1-en-2-yl)cyclohexyl)amino)methyl)phenol (**7a**)

Under Ar atmosphere, 16 mg of $LiAlH_4$ (0.42 mmol) were suspended in 1 mL of dry THF and to this 58.1 mg of **4a** (0.17 mmol) were added. The reaction was stirred at reflux temperature for 1 h and allowed to cool to room temperature. The reaction was quenched with saturated Na_2SO_4 (aq), then 10 mL of DCM were added, along with $MgSO_4$, the mixture was filtered and the solid washed with 5 × 5 mL of DCM. The filtrate was dried under vacuum to give **7a**. Yield: 36 mg (77%) of a yellow viscous material.

$[\alpha]_D^{25}$ +20.4° (*c* 1.632, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (td, 1H, *J* 7.9, 1.7), 7.01 (dd, 1H, *J* 7.4, 1.7), 6.84 (dd, 1H, *J* 7.9, 1.2), 6.78 (td, 1H, *J* 7.4, 1.2), 4.80-4.72 (m, 2H), 3.96-3.83 (m, 2H), 3.77-3.71 (m, 1H), 2.35 (tt, 1H, *J* 10.9, 4.0), 1.92-1.81 (m, 1H), 1.81-1.56 (m, 8H), 1.54-1.39 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 148.7, 128.8, 128.2, 123.2, 119.2, 116.5, 109.4, 72.1, 55.6, 44.8, 37.4, 33.8, 30.2, 25.7, 21.8, 21.1; IR (KBr) ν / cm^{-1} 3424, 3015, 2929, 1277, 765, 667, 466; HRMS (FTMS + pESI) *m/z*, calculated for $C_{17}H_{25}NO_2H$ $[MH]^+$: 276.1964, found: 276.1964.

Synthesis of 2-((((1*S*,2*S*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl)amino)methyl)phenol (**7b**)

The procedure was identical to the synthesis of **7a**, starting from 81 mg (0.31 mmol) of **4b**. Yield: 56 mg (76%) of a light yellow viscous material.

$[\alpha]_D^{25}$ +26.4° (*c* 1.028, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (td, 1H, *J* 8.0, 1.2), 7.01 (dd, 1H, *J* 7.4, 0.7), 6.84 (dd, 1H, *J* 8.0, 0.7), 6.79 (td, 1H, *J* 7.4, 1.2), 4.76 (d, 2H, *J* 7.5), 4.07 (d, 1H, *J* 13.6), 3.87 (d, 1H, *J* 13.6), 2.69 (t, 1H, *J* 4.0), 2.17-2.02 (m, 1H), 1.96 (ddd, 1H, *J* 14.0, 10.8, 3.3), 1.78-1.50 (m, 9H), 1.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 148.4, 128.9, 128.3, 123.0, 119.3, 116.4, 109.6, 71.5, 61.8, 51.0, 37.8, 35.0, 29.9, 28.8, 26.0, 21.2; IR (KBr) ν / cm^{-1} 3425, 3012, 2933, 1215, 761, 486; HRMS (FTMS + pESI) *m/z*, calculated for $C_{17}H_{25}NO_2H$ $[MH]^+$: 276.1964, found: 276.1962.

Synthesis of 2-(*tert*-butyl)-6-((((1*S*,2*S*,4*R*)-2-hydroxy-1-methyl-4-(prop-1-en-2-yl)cyclohexyl)amino)methyl)-4-methylphenol (**8a**)

The procedure was identical to the synthesis of **7a**, starting from 58 mg (0.16 mmol) of **5a**. Yield: 45 mg (77%) of a light yellow solid.

$[\alpha]_D^{25}$ +15.3° (*c* 0.180, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.71 (s, 1H), 4.76 (s, 2H), 3.85

(m, 2H), 3.74 (s, 1H), 2.43-2.29 (m, 1H), 2.24 (s, 3H), 1.95-1.79 (m, 2H), 1.72-1.45 (m, 10H), 1.40 (s, 9H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 148.9, 136.8, 127.2, 126.9, 126.6, 123.5, 109.5, 72.3, 55.4, 45.2, 37.6, 34.6, 33.8, 30.2, 29.6, 25.8, 22.1, 20.9, 20.8; IR (KBr) ν / cm^{-1} 3508, 2938, 1425, 1075, 1017, 859; HRMS (FTMS + pESI) *m/z*, calculated for $C_{22}H_{35}NO_2H$ $[MH]^+$: 346.2746, found: 346.2745; melting point: 104 ºC.

Synthesis of 2-(*tert*-butyl)-6-((*E*)-(((1*S*,2*S*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl)imino)methyl)-4-methylphenol (**8b**)

The procedure was identical to the synthesis of **7a**, starting from 103 mg (0.30 mmol) of **5b**. Yield: 76 mg (74%) of a yellow viscous material.

$[\alpha]_D^{25}$ +30.8° (*c* 1.478, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, 1H, *J* 2.2), 6.71 (d, 1H, *J* 2.2), 4.80-4.73 (m, 2H), 4.04 (d, 1H, *J* 13.2), 3.81 (d, 1H, *J* 13.2), 3.78-3.68 (m, 1H), 2.65 (t, 1H, *J* 3.8), 2.24 (s, 3H), 2.06 (t, 1H, *J* 10.4 Hz), 1.97-1.86 (m, 1H), 1.67-1.53 (m, 11H), 1.41 (s, 9H), 1.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 148.6, 136.7, 127.3, 127.1, 126.8, 123.1, 109.5, 71.6, 62.7, 61.2, 51.1, 37.8, 34.8, 34.6, 29.9, 29.6, 28.7, 26.9, 26.1, 21.2, 20.8; IR (KBr) ν / cm^{-1} 3406, 2951, 1639, 1436, 1213, 887, 767, 501; HRMS (FTMS + pESI) *m/z*, calculated for $C_{22}H_{35}NO_2H$ $[MH]^+$: 346.2746, found: 346.2744.

Single crystal X-ray diffraction studies

Single crystal of **5a** and **6a** suitable for X-ray diffraction studies were grown by slow evaporation of the solvent from a concentrated DCM/hexane solution of the compounds. A Bruker D8 Venture dual source diffractometer equipped with a Photon 100 complementary metal-oxide-semiconductor (CMOS) detector was used to collect X-ray data for the structural analysis of the compounds. Data were collected using Cu Kα (**5a**) and Mo Kα (**6a**) radiation, and a combination of φ and ω scans was carried out to obtain at least one unique data set. The crystal structures were solved using direct methods in the SHELXS program.[35] The final structures were refined using SHELXL,[35] where the remaining atoms were located from difference Fourier synthesis in which anisotropic displacement parameters were applied to all non-hydrogen atoms, followed by full-matrix least-squares refinement based on F^2. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. Additional structural information for **5a** and **6a** are provided in SI section.

Supplementary Information

Crystallographic data for the structures in this work (Table S1) were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1585565 and 1585568. Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

The full characterization spectra of new compounds are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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