Article

SYNTHESIS OF CHIRAL 1,5-DIAMINES DERIVED FROM (*R*)-(+)-CAMPHOR

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In this work we described the synthesis and characterization of a series of novel chiral 1,5-diamines derived from (*R*)-(+)-camphor through simple procedures in moderate to good yields. These new enantiopure compounds constitute a new family of chiral diamines with potential applicability as chiral building blocks, bioactive products or chiral ligands for asymmetric transformations.

Keywords: camphor; chiral diamines; bioactive compounds.

INTRODUCTION

Chiral amines have found extensive applications as building blocks in natural product synthesis,[1-7] pharmaceutical agents[8-12] and bioactive compounds.[13-19] According to Yang and co-authors,[20] approximately 35% of the top 200 small molecule drugs sold in 2020 contained at least one chiral amine subunit.

Chiral amines also find applications in organic synthesis as organocatalysts[21-27] and chiral ligands for asymmetric catalysis.[28-36] In this scenario, the search for newly effective chiral amines is a continuous process and has attracted attention from both academia and industry. Enantiomerically pure amines have been synthesized through several methods including reductive coupling of ketimines,[37] metal-catalized asymmetric hydrogenation,[7] biocatalysis,[12,38-40] enantioselective reductive amination,[41] Mannich-type coupling,[42] diol diamination,[43] among many others. The Figure 1 shows examples of representative chiral amines and its applications.

Camphor is a powerful chiral pool building block readily available in both enantiomeric forms. Camphor chiral derivatives have been synthesized and used for several applications along the years such as ligands for asymmetric catalysis,[44-50] organocatalysts[51-56] and bioactive compounds.[57] The Figure 2 shows some examples of chiral amines derived from camphor and its applications.

Herein we describe the synthesis and characterization of a whole new series of chiral 1,5-diamines derived from (*R*)-(+)-camphor through simple methodologies. These new compounds represent a whole new family of chiral diamines with potential applicability as chiral building blocks, bioactive products or chiral ligands for asymmetric catalysis.

RESULTS AND DISCUSSION

The proposal begins with the synthesis of monotosylated-1,5-diamine **4** from (*R*)-(+)-camphor (Scheme 1). The treatment of (*R*)-(+)-camphor with potassium *tert*-butoxide followed by addition of butyl nitrite produced the keto-oxime **1** in 76% yield (76:24 *E/Z* ratio).[58] The reduction of compound **1** with sodium borohydride provided the alcohol **2** in 96% yield (83:17 *E/Z* ratio).[59] The aldehyde **3** was obtained in 88% yield by treatment of **2** with a 1:4 v/v sulfuric acid/water solution at 100 °C for 8 min.[59] The synthesis of monotosylated-1,5-diamine **4** was accomplished by the treatment of aldehyde **3** with tosylamine and tetraethyl orthosilicate at 160 °C[60] followed by lithium aluminium hydride (LAH) reduction.

The free amino group on compound **4** can be further derivatized providing a whole new family of chiral 1,5-diamines (Scheme 2).

The compounds **5**-**8**, were formed by reductive amination with the

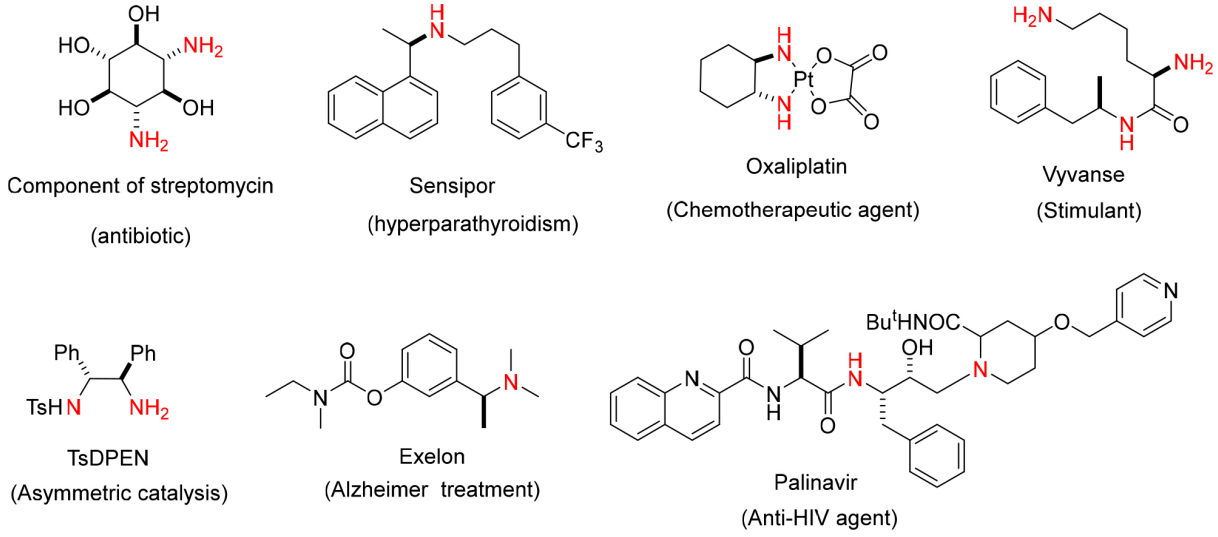

Figure 1. *Representative examples of bioactive compounds and chiral ligands based on amine motifs*

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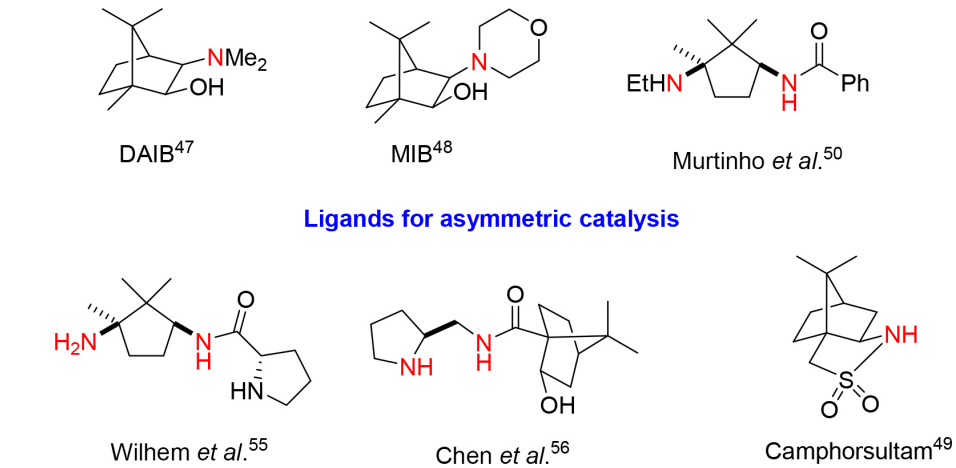
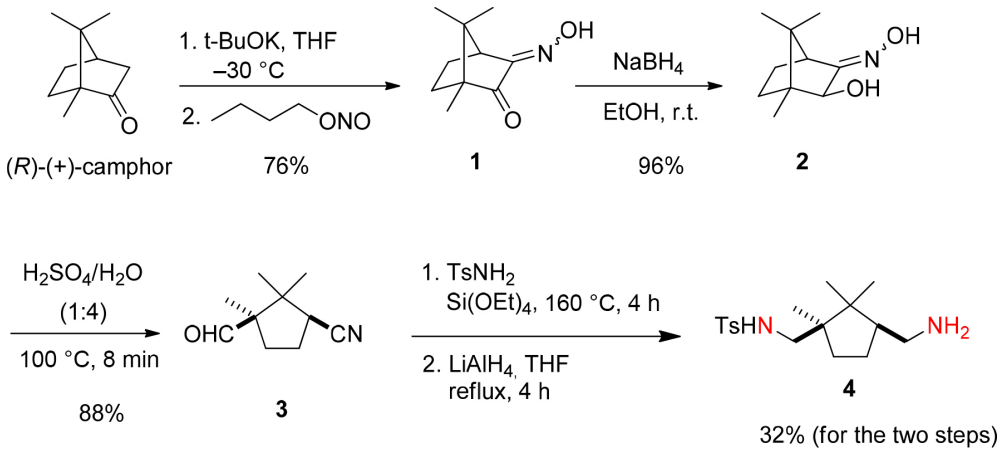


Figure 2. *Chiral amines derived from camphor and its applications*



Scheme 1. *Synthesis of chiral monotosylated-1,5-diamine (**4**)*

respective aldehydes using either sodium cyanoborohydride or sodium borohydride as reducing agent.[61-63] Ligand **9** was prepared by a two-steps process via acylation of **4** followed by LAH reduction. Ligand **10** was efficiently prepared by cyclization with 1,5-diiodopentane.[62] The compound **8** was submitted to Eschweiler-Clarke reaction providing the *N*-methylated product **11**.[64,65]

In another approach, the aldehyde **3** was submitted to reductive amination with 2-picolylamine furnishing the diamine **12** (Scheme 3).

All the new chiral amines were fully characterized by spectroscopic techniques.

CONCLUSIONS

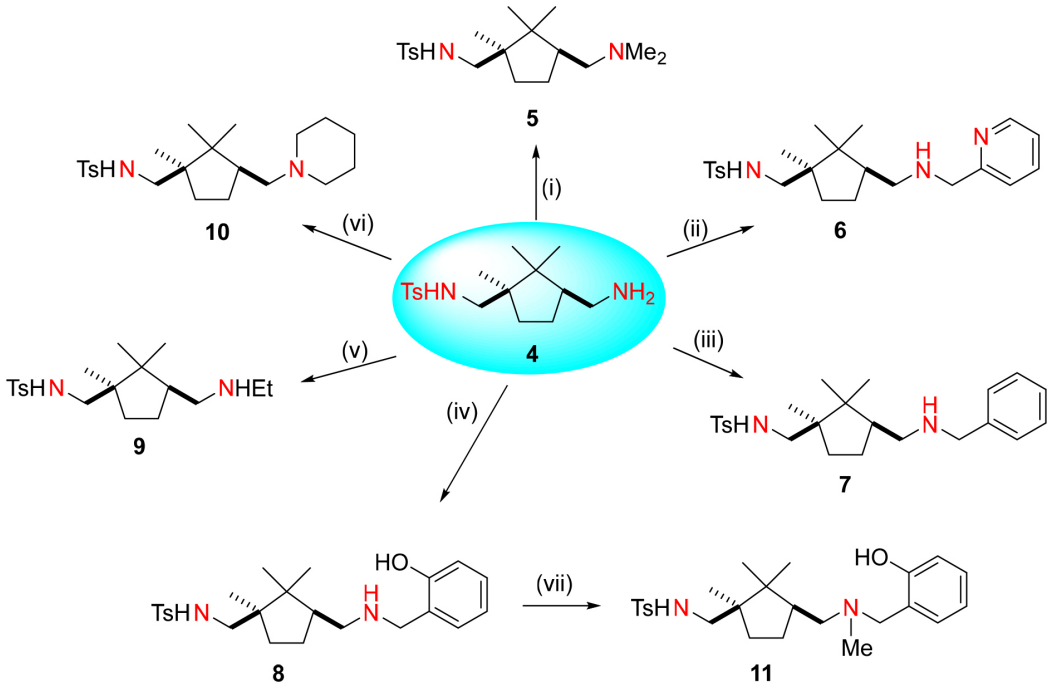
In this work we described the synthesis and characterization of a series of novel chiral 1,5-diamines derived from (*R*)-(+)-camphor through simple procedures in moderate to good yields. These new enantiopure compounds constitute a whole new family of chiral diamines with potential applicability as chiral building blocks, bioactive products or chiral ligands for asymmetric transformations. The studies are under way.

EXPERIMENTAL

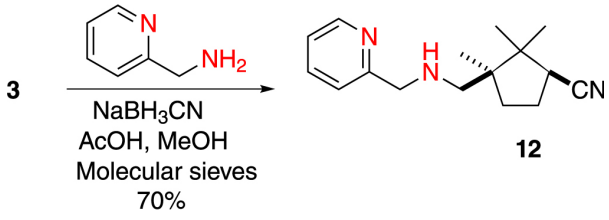
Unless indicated otherwise, all common reagents were used as obtained from commercial suppliers without further purification. Melting points were measured on a Stuart Scientific melting point apparatus. NMR spectra were measured with a Varian 400 MHz in $CDCl_3$ or CD_3OD solutions (Sigma-Aldrich Corp., St. Louis, USA). Chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and the *J* values are given in hertz. Infrared spectra (neat) were recorded with a Bruker Alpha ATR spectrometer. Optical rotations were measured with a Jasco P-2000 polarimeter. High resolution mass spectra were recorded with a Bruker Impact II UHPLC-QTOF mass spectrometer. Column chromatography was performed by using silica gel (230-400 mesh) or neutral aluminium oxide (70-230 mesh) when indicated according to the methods described by Still *et al.*[66] TLC was performed by using silica gel 60 with fluorescent indicator UV_{254} (0.20 mm thickness). For visualization, TLC plates were either placed under ultraviolet light, iodine cell or treated with ninhydrin followed by heating. Air and moisture sensitive reactions were conducted in flame or oven dried glassware equipped with tightly fitted rubber septa and under a positive pressure of dry nitrogen. Solvents were purified when necessary, using standard procedures.[67] All necessary chemicals were purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA) unless specified otherwise.

(1*S*,4*S*)-3-(hydroxyimino)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (1)

Adapted from literature.[58] A solution of (*R*)-(+)-camphor (1.0 eq, 20 g, 0.13 mol) in tetrahydrofuran (50 mL) was slowly added to a solution of potassium *tert*-butoxide (1.1 eq, 16.2 g, 0.14 mol) in



Scheme 2. *Synthesis of new chiral 1,5-diamine derivatives. Reagents and conditions: (i) H_2CO, AcOH, $NaBH_3CN$, MeOH, r.t. 75%; (ii) 2-pyridinecarboxaldehyde, AcOH, molecular sieves, $NaBH_3CN$, MeOH, r.t. 76%; (iii) benzaldehyde, AcOH, molecular sieves, $NaBH_3CN$, MeOH, r.t. 75%; (iv) salicylaldehyde, AcOH, molecular sieves, $NaBH_4$, MeOH, r.t. 76%; (v) (a) CH_3COCl, Et_3N, DCM; (b) $LiAlH_4$, THF, reflux, 46% (for two steps); (vi) 1,5-diiodopentane, K_2CO_3, CH_3CN, reflux, 79%; (vii) HCO_2H, H_2CO, reflux, 72%*



Scheme 3. *Synthesis of diamine **12** from aldehyde **3***

tetrahydrofuran (150 mL) at –30 °C. The mixture was stirred for 10 min at –30 °C and then butyl nitrite (1.0 eq, 17 mL g, 0,14 mol) was added dropwise. The mixture was stirred for 10 min, and then left stir overnight at room temperature. Tetrahydrofuran was removed under reduced pressure, after which water (100 mL) was added and the solution was extracted with diethyl ether (3 × 30 mL). The aqueous solution was acidified with acetic acid to pH 6 and then extracted with ethyl acetate (3 × 30 mL), dried over anhydrous K_2CO_3, filtered and concentrated by rotary evaporation providing the keto-oxime **1** (18g, 76%) as a light yellow solid, (mixture *E/Z* isomers, 74:26). $[\alpha]_D^{20}$ +119.6 (*c* 0.53, $CHCl_3$) [lit.[58] $[\alpha]_D^{26}$ +199 (*c* 1.41, $CHCl_3$)]; mp 115-118 °C [lit.[58] mp 116-119 °C]; IR (ATR) ν / cm^{-1} 3377, 2949, 1732, 1631, 1380, 993, 925, 875, 706; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 3.28 (d, *J* 4.48 Hz, 1H), 2.73 (d, *J* 4.22 Hz, 0.3H), 2.18-2.01 (m, 1H), 1.90-1.74 (m, 1H), 1.70-1.53 (m, 2H), 1.04 (s, 3H), 1.01 (s, 3H), 0.94 (s, 0.7H), 0.89 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.7, 204.0, 159.3, 156.1, 59.5, 58.4, 49.5, 46.5, 44.9, 30.6, 29.8, 24.9, 23.7, 20.6, 20.5, 8.9, 8.4.

(1*S*,3*S*,4*S*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime (2)

Adapted from literature.[59] The keto-oxime **1** (1.0 eq, 10 g, 54.5 mmol) was added on a 500 mL round bottom flask and dissolved in ethanol (150 mL). The system was cooled at 0 °C and then $NaBH_4$ (5.0 eq, 10.3 g, 272.2 mmol) was added in portions during 10 min. The system was allowed to reach room temperature and it was left overnight under stirring. The ethanol was evaporated under reduced pressure and 150 mL of water was added to the residue. The pH was adjusted to 4 using a 6 M sulfuric acid solution and then extracted with diethyl ether (3 × 60 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous K_2CO_3, filtered and concentrated by rotary evaporation providing the alcohol **2** (8.7 g, 86%) as a white solid, (mixture *E/Z* isomers, 92:08). $[\alpha]_D^{20}$ +77.2 (*c* 1.0, EtOAc); mp 156-158 °C [lit.[59] mp 156 °C]; IR (ATR) ν / cm^{-1} 3253, 2965, 2877, 1700, 1537, 1450, 1393, 1087, 955; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 3.96 (s, 1 H), 3.05 (d, *J* 4.39 Hz, 1H), 1.88-1.78 (m, 1H), 1.73-1.64 (m, 1H), 1.34-1.16 (m, 2H), 1.06 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 77.6, 49.5, 47.6, 47.0, 33.7, 22.8, 21.3, 19.0, 10.8.

(1*S*,3*R*)-3-formyl-2,2,3-trimethylcyclopentane-1-carbonitrile (3)

Adapted from literature.[59] Hydroxy oxime **2** (1.0 eq, 4.0 g, 24.2 mmol) was heated for 8 min at 100 °C with dilute sulfuric acid (60 mL; 1:4 v/v H_2SO_4/H_2O). The system was cooled in an ice bath and the acidic aqueous solution was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous K_2CO_3, filtered and concentrated under reduced pressure providing the aldehyde **3** (3.1 g, 88%) as a white solid. $[\alpha]_D^{20}$ +97.4 (*c* 1.1, EtOAc); mp 107-110 °C; IR (ATR) ν / cm^{-1} 2971, 2882, 2224, 1713, 1458, 1369, 915, 711; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 9.64 (s, 1H), δ 2.81 (t, *J* 9.71 Hz, 1H), δ 2.60-2.47 (m, 1H), 2.27-2.16 (m, 1H), 2.09-1.98 (m, 1H), 1.53-1.42 (m, 1H), 1,17 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.6, 120.0, 57.0, 46.9, 39.9, 30.4, 25.5, 22.5, 20.8, 18.3.

***N*-(((1*R*,3*S*)-3-(aminomethyl)-1,2,2-trimethylcyclopentyl) methyl)-4-methylbenzene sulfonamide (4)**

Adapted from literature.[60] On a 250 mL round bottom flask were

added the aldehyde **3** (1.0 eq, 3.0 g, 9.2 mmol), *p*-toluenesulfomamide (1.1 eq, 1.74 g, 10.1 mmol) and tetraethyl orthosilicate (1.0 eq, 2.0 mL, 9.2 mmol). The system was heated at 160 °C for 1 h then two more equivalents of tetraethyl orthosilicate were added (2.0 eq, 4.1 mL, 18.4 mmol) and the heating continued for additional 3 h. The excess of tetraethyl orthosilicate was removed under reduced pressure and the remaining solid was immediately dissolved in dry THF (30 mL). Lithium aluminum hydride powder was slowly added (5.0 eq, 1.7 g, 46.0 mmol) and the system was refluxed for 4 h under nitrogen atmosphere. The solution was cooled with an ice bath and quenched with 10% NaOH solution (~ 15 mL) and then ethyl acetate (50 mL) was added and the system was stirred for 1 h. The organic extract was separated and washed with brine (20 mL), dried over anhydrous K_2CO_3, filtered and evaporated under reduced pressure providing a brownish oil. Silica gel flash chromatography (0 → 5% v/v MeOH/DCM and then 1:1:0.1 v/v MeOH/DCM/Et_3N) afforded the pure monotosylated 1,5-diamine **4** (1.8 g, 31%) as a foamy yellow solid. $[\alpha]_D^{20}$ +20.8 (*c* 1.2, MeOH); mp 32-35 °C; IR (ATR) ν / cm^{-1} 3280, 2941, 2872, 1596, 1451, 1325, 1151, 1086, 1048, 809, 654, 555, 476; 1H NMR (400.1 MHz, $CDCl_3$) δ 7.72 (d, *J* 8.24 Hz, 2H), 7.28 (d, *J* 8.01 Hz, 2H), 2.41 (s, 3H), 1.98-1.76 (m, 2H), 1.56-1.16 (m, 7H), 0.81 (s, 6H), 0.62 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.2, 136.7, 129.6, 127.0, 51.2, 50.0, 47.1, 44.2, 43.7, 34.6, 26.1, 22.9, 21.5, 20.8, 18.3; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{17}H_{29}N_2O_2S$ $[M + H]^+$: 325.1944, found: 325.1950.

N-(((1*R*,3*S*)-3-((dimethylamino)methyl)-1,2,2-trimethylcyclopentyl)methyl)-4-methylbenzenesulfonamide (5)

Adapted from literature.[61] To a solution of diamine **4** (1.0 eq, 0.26 g, 0.81 mmol) in dry methanol (9 mL) was added 37% formaldehyde solution (4.5 eq, 0.3 mL, 3.70 mmol) and the mixture was stirred for 15 min at room temperature under inert atmosphere. To this solution, $NaBH_3CN$ (4.0 eq, 0.20 g, 3.30 mmol) was added slowly and the mixture was stirred for 15 min followed by addition of acetic acid (12.5 eq, 0.58 mL, 10.20 mmol). The reaction mixture was heated to 50 °C and stirred for 18 h, then cooled to room temperature. The solvent was evaporated under reduced pressure and chloroform (20 mL) was added to the residue. The mixture was washed with 1 M NaOH (3 × 20 mL), dried over anhydrous K_2CO_3, filtered and evaporated under reduced pressure providing a yellow oil. Chromatography on a short pad neutral aluminum oxide column (0 → 5% v/v MeOH/ DCM) afforded the pure *N*,*N*–dimethylated diamine **5** (0.21 g, 75%) as a light yellow oil. $[\alpha]_D^{20}$ +34.5 (*c* 0.7, $CHCl_3$); IR (ATR) ν / cm^{-1} 3294, 2964, 2859, 1607, 1458, 1329, 1142, 1082, 1045, 805, 655, 550; 1H NMR (400.1 MHz, $CDCl_3$) δ 7.72 (d, *J* 8.29 Hz, 2H), 7.29 (d, *J* 7.89 Hz, 2H), 2.87-2.71 (m, 2H), 2.41 (s, 3H), 2.17 (s, 6H), 2.02-1.84 (m, 2H), 1.60-1.44 (m, 2H), 1.37-1.21 (m, 4H), 0.89 (s, 3H), 0.87 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1, 136.8, 129.6, 127.0, 62.0, 50.0, 46.9, 45.9, 44.9, 44.4, 34.9, 27.3, 23.2, 22.5, 21.4, 20.9, 17.9; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{33}N_2O_2S$ $[M + H]^+$: 353.2257, found: 353.2262.

4-methyl-*N*-(((1*R*,3*S*)-1,2,2-trimethyl-3-(((pyridin-2-ylmethyl)amino)methyl)cyclopentyl)methyl) benzenesulfonamide (6)

To a stirred solution of *N*-tosyl diamine **4** (1.0 eq, 0.15 g, 0.47 mmol) and molecular sieves (0.7 g) in dried methanol (10 mL) was added 2-pyridinecarboxaldehyde (1.2 eq, 54 μL, 0.56 mmol) followed by three drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (3 h) and then sodium cyanoborohydride (3.0 eq, 0.090 g, 1.42 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered and the filtrate was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (15 mL), washed with saturated $NaHCO_3$ solution (20 mL) and then dried over anhydrous K_2CO_3. The system was filtered and the solvent was removed under reduced pressure to give a crude oil, which was purified by neutral aluminum oxide column chromatography (0 → 5% v/v MeOH/DCM) to afford the product **6** as a light-yellow oil (0.13 g, 70%). $[\alpha]_D^{20}$ +28.0 (*c* 0.5, EtOAc); IR (ATR) ν / cm^{-1} 3285, 2947, 2867, 1596, 1428, 1320, 1155, 1086, 1048, 908, 729, 664, 555; 1H NMR (400.1 MHz, $CDCl_3$) δ 8.62-8.54 (m, 1H), 7.75 (d, *J* 8.2 Hz, 2H), 7.73-7.63 (m, 1H), 7.33 (d, *J* 8.12 Hz, 2H), 7.30-7.15 (m, 2H), 4.32 (brs, 1H), 3.90 (s, 2H), 2.90-2.74 (m, 2H), 2.71-2.66 (m, 1H), 2.45 (s, 3H), 1.63-1.48 (m, 2H), 0.91 (s, 6H), 0.65 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.3, 149.2, 148.5, 143.2, 136.8, 136.7, 136.5, 129.6, 127.0, 122.3, 122.0, 55.5, 51.6, 50.0, 47.9, 47.0, 44.4, 34.8, 26.7, 22.8, 21.5, 20.9, 18.3; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{23}H_{34}N_3O_2S$ $[M + H]^+$: 416.2366, found: 416.2361.

N-(((1*R*,3*S*)-3-((benzylamino)methyl)-1,2,2-trimethylcyclopentyl)methyl)-4-methylbenzenesulfonamide (7)

To a stirred solution of monotosylated diamine **4** (1.0 eq, 0.16 g, 0.50 mmol) and molecular sieves (1 g) in dried methanol (10 mL) was added benzaldehyde (1.2 eq, 60 μL, 0.61 mmol) followed by three drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (3 h) and then sodium cyanoborohydride (3.0 eq, 0.095 g, 1.50 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered and the filtrate was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (15 mL), washed with saturated $NaHCO_3$ solution (20 mL) and then dried over anhydrous K_2CO_3. The system was filtered and the solvent was removed under reduced pressure to give a crude oil, which was purified by neutral aluminum oxide column chromatography (0 → 5% v/v MeOH/DCM) to afford the product **7** as a light yellow oil (0.15 g, 75%). $[\alpha]_D^{20}$ +35.0 (*c* 1.0, EtOAc); IR (ATR) ν / cm^{-1} 3286, 2956, 2868, 1596, 1452, 1315, 1137, 1089, 1057, 807, 695, 542; 1H NMR (400.1 MHz, $CDCl_3$) δ 7.73 (d, *J* 8.30 Hz, 2H), 7.37-7.20 (m, 7H), 4.51 (brs, 1H), 3.78 (m, 2H), 2.87-2.70 (m, 2H), 2.69-2.62 (m, 1H), 2.42 (s, 3H), 2.41-2.35 (m, 1H), 2.04-1.85 (m, 2H), 1.40-1.18 (m, 3H), 0.88 (s, 6H), 0.62 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.2, 140.2, 136.7, 129.6, 128.3, 127.9, 127.0, 54.4, 51.3, 50.0, 47.8, 46.9, 44.3, 34.7, 26.7, 22.8, 21.5, 20.8, 18.3; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{24}H_{35}N_2O_2S$ $[M + H]^+$: 415.2414, found: 415.2405.

N-(((1*R*,3*S*)-3-(((2-hydroxybenzyl)amino)methyl)-1,2,2-trimethylcyclopentyl)methyl)-4-methylbenzenesulfonamide (8)

Adapted from literature.[63] To a stirred solution of monotosylated-1,5-diamine **4** (1.0 eq, 0.4 g, 1.2 mmol) and molecular sieves (1.2 g) in absolute ethanol (15 mL) was added salicylaldehyde (1.2 eq, 0.15 mL, 1.5 mmol) followed by three drops of glacial acetic acid. The reaction was heated at 70 °C for 48 h and then sodium borohydride (3.0 eq, 0.14 g, 3.7 mmol) was added, and the reaction mixture was left to stir overnight. The molecular sieves were filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform (70 mL), washed with saturated $NaHCO_3$ solution (20 mL) and then dried over anhydrous K_2CO_3. The system was filtered and the solvent was removed under reduced pressure to give the crude solid **8** (0.4 g, 76%) which was used without further purification in the next step. $[\alpha]_D^{20}$ +37.7 (*c* 0.57, $CHCl_3$); mp 36-39 °C; IR (ATR) ν / cm^{-1} 3286, 2962, 2866, 1586, 1449, 1321,

1253, 1157, 1084, 1048, 811, 747, 651, 538; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.74 (d, *J* 8.29 Hz, 2H), 7.36 (d, *J* 8.00 Hz, 2H), 7.22-7.15 (m, 1H), 7.02-6.97 (m, 1H), 6.85-6.76 (m, 2H), 4.39 (brs, 1H), 3.99 (m, 2H), 2.92-2.71 (m. 3H), 2.45 (s, 3H), 1.98 (m, 2H), 1.6-1.5 (m, 1H), 1.42-1.25 (m, 3H), 0.91 (s, 6H), 0.67 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.4, 136.9, 129.7, 128.7, 128.2, 127.1, 122.5, 118.9, 116.3, 53.2, 50.9, 50.0, 47.9, 47.0, 44.4, 34.7, 26.7, 22.9, 21.5, 20.9, 18.4; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{24}H_{35}N_2O_3S$ [M + H]$^+$: 431.2363, found: 431.2354.

N-(((1*R*,3*S*)-3-((ethylamino)methyl)-1,2,2-trimethylcyclopentyl) methyl)-4-methylbenzenesulfonamide (9)

N-tosyl diamine **4** (1.0 eq, 0.2 g, 0.61 mmol) was dissolved in DCM (15 mL) and then acetic anhydride (1.1 eq, 64 µL, 0.67 mmol) and triethylamine (1.2 eq, 0.10 mL, 0.74 mmol) were added, and the reaction mixture was left to stir overnight at room temperature. The mixture was washed with water (20 mL) and then the organic layer was separated, dried over anhydrous K_2CO_3, filtered and concentrated under reduced pressure affording 0.17 g of a yellow oil which was immediately dissolved in anhydrous THF (10 mL). The system was cooled in an ice bath and a lithium aluminum hydride 1 M solution in THF (3.0 eq, 1.40 mL, 1.40 mmol) was added. The system was refluxed for 2 h under nitrogen atmosphere and then it was cooled with an ice bath and quenched with 10% NaOH solution (10 mL). Ethyl acetate (20 mL) was added and the system was stirred for 1 h. The organic extract was separated and washed with brine (15 mL), dried over anhydrous K_2CO_3, filtered and evaporated under reduced pressure providing a yellow oil which was purified by silica gel flash chromatography (1:9:0.1 v/v MeOH/DCM/Et_3N) to afford the product **9** as a light yellow oil (0.096 g, 46% for the two steps). $[\alpha]_D^{20}$ +35.4 (*c* 0.65, EtOAc); IR (ATR) ν / cm^{-1} 3302, 2967, 2874, 1618, 1450, 1316, 1148, 1081, 1056, 813, 654, 553; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.71 (d, *J* 8.30 Hz, 2H), 7.27 (d, *J* 8.14 Hz, 2H), 2.77 (m, 2H), 2.65-2.55 (m, 3H), 2.39 (s, 3H), 2.00-1.82 (m, 3H), 1.56-1.16 (m, 5H), 1.06 (t, *J* 7.11 Hz, 3H), 0.86 (s, 6H), 0.62 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.1, 136.7, 129.5, 126.9, 51.7, 49.9, 47.8, 46.8, 44.6, 44.3, 34.7, 26.7, 22.7, 21.4, 20.8, 18.2, 15.1; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{32}N_2O_2S$ [M + H]$^+$: 353.2257, found: 353.2257.

4-methyl-N-(((1*R*,3*S*)-1,2,2-trimethyl-3-(piperidin-1-ylmethyl) cyclopentyl)methyl) benzenesulfonamide (10)

Adapted from literature.[62] To a stirred solution of *N*-tosyl diamine **4** (1.0 eq, 0.16 g, 0.49 mmol) and potassium carbonate (2.6 eq, 0.17 g, 1.27 mmol) in acetonitrile (5 mL) was added 1,5-diiodopentane (1.1 eq, 83 µL, 0.54 mmol) and the reaction mixture was left to stir overnight under reflux. The reaction mixture was filtered and the acetonitrile was removed under reduced pressure. The residue was dissolved in chloroform (20 mL), washed with water (20 mL) and then dried over anhydrous K_2CO_3. The system was filtered and the solvent was removed under reduced pressure to afford a crude brown oil, which was purified by neutral aluminum oxide column chromatography (0 → 5% v/v MeOH/DCM) to afford the product **10** as a light yellow oil (0.15 g, 79%). $[\alpha]_D^{20}$ +33.7 (*c* 0.41, $CHCl_3$); IR (ATR) ν / cm^{-1} 3273, 2930, 2877, 2259, 2190, 1595, 1466, 1328, 1145, 1038, 916, 802, 725, 672, 542; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.74 (d, *J* 8.22 Hz, 2H), 7.28 (d, *J* 8.08 Hz, 2H), 4.65 (brs, 1H), 2.85-2.70 (m, 2H), 2.40 (s, 3H), 2.40-2.28 (m, 4H), 2.15-2.00 (m, 2H), 1.96-1.82 (m, 2H), 1.60-1.12 (m, 9H), 0.87 (s, 6H), 0.61 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.2, 136.7, 129.6, 127.0, 61.6, 55.0, 50.1, 46.8, 44.0, 34.9, 29.6, 27.8, 25.7, 24.2, 22.5, 21.5, 21.0, 17.8; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{22}H_{37}N_2O_2S$ [M + H]$^+$: 393.2570, found: 393.2574.

N-(((1*R*,3*S*)-3-(((2-hydroxybenzyl)(methyl)amino)methyl)-1,2,2-trimethylcyclopentyl)methyl)-4-methylbenzene-sulfonamide (11)

Adapted from literature.[64,65] To 0.19 g (1 eq, 0.44 mmol) of **8**, 0.10 mL of formaldehyde 36% H_2O solution (3 eq, 1.32 mmol) and 0.08 mL of 85% formic acid (5 eq, 2.2 mmol) were added. After refluxing for 24 h the resulting mixture was cooled to 0 °C, made alkaline by the addition of 20% sodium hydroxide (pH = 10) and extracted with diethylether (3 × 20 mL). The organic layer was dried over anhydrous K_2CO_3, filtered and the solvent was evaporated providing 0.13 g of **11** as a foamy light yellow solid (72%). $[\alpha]_D^{20}$ +31.6 (*c* 0.47, $CHCl_3$); mp 45-48 °C; IR (ATR) ν / cm^{-1} 3273, 2962, 2853, 1590, 1444, 1326, 1157, 816, 760, 661, 547; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.75 (d, *J* 8.2 Hz, 2H), 7.33 (d, *J* 8.0 Hz, 2H), 7.22-7.12 (m, 1H), 7.04-6.93 (m, 1H), 6.88-6.72 (m, 2H), 4.25 (brs, 1H), 3.85-3.70 (m, 1H), 3.64-3.52 (m, 1H), 2.96-2.88 (m, 1H), 2.82-2.74 (m, 1H), 2.45 (s, 3H), 2.44-2.37 (m, 2H), 2.26 (s, 3H), 2.16-1.96 (m, 4H), 0.93 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.2, 143.4, 136.7, 129.7, 128.7, 128.2, 127.1, 122.5, 118.9, 53.2, 50.9, 50.0, 47.9, 47.0, 44.4, 34.7, 26.7, 22.9, 21.5, 20.9, 18.4; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{24}H_{35}N_2O_3S$ [M + H]$^+$: 445.2519, found: 445.2514.

(1*S*,3*R*)-2,2,3-trimethyl-3-(((pyridin-2-ylmethyl)amino)methyl) cyclopentane-1-carbonitrile (12)

To a stirred solution of aldehyde **3** (1.0 eq, 1.60 g, 9.7 mmol) and molecular sieves (5 g) in dried methanol (40 mL) was added 2-picolylamine (1.1 eq, 1.1 mL, 10.6 mmol) followed by three drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (3 h) and then sodium borohydride (3.0 eq, 1.1 g, 29.0 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered and the solution was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (70 mL), washed with saturated $NaHCO_3$ solution (20 mL) and then dried over anhydrous K_2CO_3. The system was filtered and the solvent was removed under reduced pressure to give a crude oil, which was purified by neutral aluminum oxide column chromatography (0 → 5% v/v MeOH/DCM) to afford the product **12** as a light yellow oil (1.74 g, 70%). $[\alpha]_D^{20}$ +59.6 (*c* 0.80, $CHCl_3$); IR (ATR) ν / cm^{-1} 3341, 2964, 2870, 2226, 1598, 1456, 1110, 741; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 8.54-8.51 (m, 1H), 7.66-7.60 (m, 1H), 7.32-7.27 (m, 1H), 7.17-7.12 (m, 1H), 3.86 (m, 2H), (s, 2H) 2.78 (t, *J* 9.60 Hz, 1H), 2.53 (m, 2H), 2.15-2.03 (m, 1H), 1.93-1.71 (m, 3H), 1.59-1.50 (m, 1H), 1.06 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.9, 149.1, 136.4, 122.2, 121.9, 121.6, 56.4, 56.0, 46.5, 46.4, 39.9, 35.4, 25.3, 22.7, 21.1, 20.3; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{16}H_{24}N_3$ [M + H]$^+$: 258.1965, found: 258.1967.

SUPPLEMENTARY MATERIAL

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

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