Synthesis and Structural Elucidation of Novel Camphor-Derived Thioureas

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ABSTRACT Nine novel (+)-camphor-derived thioureas have been prepared. 3-((Dimethylamino)methylene)camphor (**2**) served as the common precursor for the preparation of both, 2-thiourea **15–20** and 3-thiourea functionalized camphor derivatives **6**, **7**/**7′**, respectively. Starting from **2**, the latter were prepared in two or three steps whereas the former in five steps, respectively. Configuration of all novel compounds has been meticulously determined using NMR techniques and/or single crystal X-ray crystallography. *Chirality 24:307–317, 2012.*

KEY WORDS: camphor-derived oxime; camphor-derived amines; oxime reduction; enaminone reduction; enaminone methodology; X-ray analysis; 2,3-functionalized camphor derivatives

INTRODUCTION

Camphor is one of nature's privileged scaffolds, which is readily available in both enantiomeric forms. It undergoes a wide variety of chemical transformations which functionalize, at first glance, inactivated positions.[1,2] All of the above makes camphor a very desirable starting material for the preparation of a wide variety of compounds ranging from natural products[1,2] to chiral auxiliaries,[3,4] ligands in asymmetric synthesis,[5–9] NMR shift reagents,[10] etc.

Considering camphor's vast potential for chemical manipulation, it is fair to say it has not yet been fully exploited in the relatively immature field of organocatalysis. In the subfield of covalent organocatalysis, there are only a few reports of camphor-derived catalysts. Those are mainly five- and six-membered cyclic sulfonyl hydrazine derivatives prepared from camphor sulfonic acid.[11–14] However, there are also more noncovalent camphor-derived organocatalysts, the bulk of them comprised of pyrrolidinyl–camphor–derived bifunctional organocatalysts, where both camphor and pyrrolidine chiral frameworks, connected with an appropriate linker, act in synergy.[15–24] All the above mentioned camphor-derived organocatalysts have been prepared via derivatization of camphor i.e., camphorsulfonic acid at positions 2 and/or 10 (Fig. 1) in most cases in combination with "external chiral fragments" like pyrrolidine.

On the other hand, position 3 in camphor displays the reactivity of an active methylene group, which resulted in the preparation of a large number of C(3)-substituted camphor derivatives.[1,2] This, in turn, has not yet been translated into the preparation of the corresponding organocatalysts.

Thiourea derivatives are the workhorses of noncovalent organocatalysis working through double hydrogen-bonding interactions with a suitable substrate. The preferred substituent is the electron-poor 3,5-bis(trifluoromethyl)phenyl-group attached through thiourea functionality to a suitable chiral scaffold. Of special interest are the thiourea organocatalysts with bi-functionality which can achieve electrophile and nucleophile binding and activation (Fig. 2).[25–40]

To the best of our ability, we could not find any 3,5-bis(trifluoromethyl)phenyl thiourea derivatives with camphor as the exclusive chiral framework. This prompted us to investigate the possibility to prepare some mono-functional 2- and 3-thiourea camphor derivatives, preferably in a stereo divergent synthesis. Thus, herein, we report our preliminary results on the synthesis and structural characterization of novel 2-thiourea **15–20** and 3-thiourea **6**, **7**/**7′** functionalized camphor derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100 - Automated Melting Point System. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, and Bruker UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer and Agilent 6224 Accurate Mass TOF LC/MS, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyser 2400 II. Catalytic hydrogenations were performed in a Parr Pressure Reaction Hydrogenation Apparatus and in Berghof type RHS 175 autoclave. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size: 0.035–0.070 mm). Medium-pressure liquid chromatography (MPLC) was performed with Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChrosphere® Si 60 (12 μm) and/or LiChroprep® Si 60 (15–25 μm)); column dimensions (wet filled): 22 × 460 mm, 36 × 460 mm and 40 × 460 mm; backpressure: 10–20 Bar; detection: UV 254 nm.

(+)-Camphor, *tert*-butoxy bis(dimethylamino)methane, anhydrous DMF, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**5**) and 10% palladium on charcoal are commercially available (Sigma-Aldrich). (1*S*,4*S*,3*E*)-3-Benzylidene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**8**) was prepared following the literature procedure.[41]

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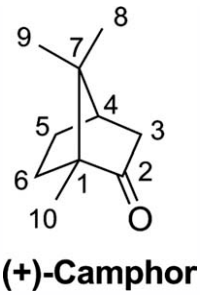


Fig. 1. The numbering system used in this article.[2]

Source of chirality: (+)-Camphor (**1**) (Fluka AG), product number 21300, purum, natural, ≈97.0% (GC, sum of enantiomers), $[\alpha]_D^{20}$ = +42.5 ± 2.5 (*c* = 10, EtOH), mp 176–180°C, ee not specified.

Syntheses

(1*S*,4*S*,3*E*)-3-((Dimethylamino)methylene)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (2).[42] To a solution of (+)-camphor (**1**) (456 g, 30 mmol) in anhydrous DMF (60 ml) under Argon *tert*-butoxy bis(dimethylamino)methane (12 ml, 58 mmol) was added, and the resulting mixture was heated under reflux for 24 h. The reaction mixture was cooled to room temperature and volatile components were evaporated in vacuo. The residue (100% conversion was achieved according to the ^{1}H-NMR of the raw reaction mixture) was purified by CC (Silica gel 60, EtOAc/petroleum ether = 1:1). Fractions containing the product were combined and volatile components evaporated in vacuo to give **2**. Yield: 4.79 g (77%) of yellowish-brown solid; mp 57–61°C (lit. 42: 59–62°C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.85 (*s*, Me); 0.89 (*s*, Me); 0.94 (*s*, Me); 1.29–1.46 (*m*, 2H of CH_2); 1.54–1.63 (*m*, 1H of CH_2); 1.94–2.04 (*m*, 1H of CH_2); 2.90 (*d*, *J* = 3.8 Hz, H—C(4)); 2.98 (*s*, NMe_2); 7.00 (*s*, H—C(3′)).

(1*S*,4*S*,3*E*)-3-(Aminomethylene)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one (3).[43] A mixture of NH_4OAc (156 g, 20 mmol) and **2** (0.5 g, 2.41 mmol) in EtOH (25 ml) was stirred at room temperature for 48 h. Volatile components were evaporated in vacuo, the residue dissolved/suspended in CH_2Cl_2 (150 ml), and washed with $NaHCO_3$ (aq. sat,) and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components were evaporated in vacuo. The residue was purified by CC (Silica gel 60, EtOAc/petroleum ether = 2:1). Fractions containing the product were combined and volatile components evaporated in vacuo to give **3**. Yield: 300 mg (69%); mp 147–151°C (lit. 43: mp 156°C). $[\alpha]_D^{20}$ = +275.0 (*c* = 0.09, CH_2Cl_2). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.82 (*s*, Me); 0.92 (*s*, Me); 0.94 (*s*, Me); 1.31–1.43 (*m*, 2H of CH_2); 1.60–1.68 (*m*, 1H of CH_2); 1.91–1.98 (*m*, 1H of CH_2); 2.50 (*d*, *J* = 3.7 Hz, H—C(4)); 4.24 (br *d*, *J* = 7.8 Hz, NH_2); 7.09 (*t*, *J* = 10.7 Hz, CH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.6, 19.0, 20.4, 26.7, 31.6, 45.6, 48.0, 57.9, 115.9, 133.8, 207.4. (Found C, 73.89; H, 9.85; N, 7.89. $C_{11}H_{17}NO$ requires: C, 73.70; H, 9.56; N, 7.81.); EI-HRMS: *m/z* = 179.13156 (M^+); $C_{11}H_{17}NO$ requires: *m/z* = 179.13101 (M^+); ν_{max} (KBr) 3389, 3207, 2952, 2360, 1684, 1645, 1575, 1389, 1304, 1071, 949 cm^{-1}.

Isomerization of (1*S*,4*S*,3*E*)-3-(aminomethylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3). A solution of **3**-(*E*) (25 mg) in $CDCl_3$ (0.7 ml) was left standing at room temperature for 5 days. Partial isomerization of the exocyclic double bond of **3**-(*E*) took place to give a mixture of *E*- and *Z*-isomers, **3**-(*E*)/**3**-(*Z*) = 83:17, respectively. ^{1}H-NMR (500 MHz, $CDCl_3$) for **3**-(*Z*): δ 0.88 (*s*, Me); 0.93 (*s*, Me); 2.31 (*d*, *J* = 3.6 Hz, H—C(4)); 6.44 (*t*, *J* = 10.3 Hz, H—C(3′)). ^{13}C-NMR (126 MHz, $CDCl_3$) for **3**-(*Z*): δ 9.3, 19.3, 20.5, 28.6, 30.4, 49.1, 49.9, 58.8, 113.5, 138.5, 208.9.

(1*S*,3*R*,4*R*)-3-(Aminomethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4)[44] **and (1*S*,3*S*,4*R*)-3-(aminomethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4′).**[44] To a solution of **3** (240 mg, 1.34 mmol) in anhydrous EtOH (100 ml) under Argon, Pd–C (10%, 100 mg) and HCl (five drops, 37%, ca. 2 mmol) were added. The reaction vessel was flushed with H_2 and the reaction mixture was hydrogenated in *Paar* hydrogenator (P = 4 Bar) at room temperature for 3 h. The reaction mixture was filtered through a plug of Celite® and washed with EtOH (100 ml). Volatile components were evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (200 ml) and washed with NaOH (aq., 0.2 M, 50 ml). The organic phase was dried owed anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo to give a crude mixture of amines **4**/**4′** (100% conversion). The amine mixture could not be separated using preparative chromatographic techniques and was used in the following transformation without further purification/separation. Yield: 213 mg (87%, **4**:**4′** = 68:32) of yellow oil. EI-HRMS: *m/z* = 182.1541 (MH^+); $C_{11}H_{20}NO$ requires: *m/z* = 182.1539 (MH^+). ^{1}H-NMR (500 MHz, $CDCl_3$) for **4**: δ 0.88 (*s*, Me); 0.90 (*s*, Me); 1.00 (*s*, Me); 1.27–1.34 (*m*, 1H of CH_2); 1.44–1.54 (*m*, 1H of CH_2, NH_2); 1.62–1.73 (*m*, 1H of CH_2); 1.75–1.84 (*m*, 1H of CH_2); 2.14 (*t*, *J* = 4.3 Hz, H—C(4)); 2.50 (br *dd*, *J* = 6.6; 12.2 Hz, H—C(3)); 2.68 (*dd*, *J* = 7.8; 12.6 Hz, Ha-C(3′)); 3.02 (*dd*, *J* = 7.2; 12.6 Hz, Hb-C(3′)). ^{1}H-NMR (500 MHz, $CDCl_3$) for **4′**: δ 0.83 (*s*, Me); 0.90 (*s*, Me); 0.94 (*s*, Me); 1.38–1.43 (*m*, 1H of CH_2); 1.95–2.00 (*m*, H—C(3), H—C(4)); 2.00–2.07 (*m*, 1H of CH_2); 2.72 (*dd*, *J* = 7.3; 12.7 Hz, Ha-C(3′)); 3.11 (*dd*, *J* = 6.8; 12.7 Hz, Hb-C(3′)). ^{13}C-NMR (126 MHz, $CDCl_3$) for **4**: δ 9.6, 19.2, 19.6, 20.5, 31.3, 40.8, 45.8, 53.0, 58.9, 59.0, 221.0. ^{13}C-NMR (126 MHz, $CDCl_3$) for **4′**: δ 9.4, 20.6, 21.8, 29.4, 29.5, 44.6, 46.0, 46.8, 58.0, 221.2.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*Z*)-((1*S*,4*S*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-ylidene)methyl)thiourea (6). To a suspension of **3** (184 mg, 1.03 mmol) in Et_2O (10 ml) under Argon 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**5**) (195 μL, 1.03 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. Volatile components were evaporated in vacuo and the residue was purified by CC (Silica gel 60; 1) EtOAc/petroleum ether = 1:40 to elute the unreacted **5**; 2) EtOAc/petroleum ether = 1:15 to elute the product **6**). Fractions containing the product were combined and volatile components evaporated in vacuo to give **6**. Yield: 130 mg (28%) of light yellow solid; mp 169–171°C. $[\alpha]_D^{20}$ = +178.3 (*c* = 0.07, CH_2Cl_2). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.80 (*s*, Me); 0.90 (*s*, Me); 0.95 (*s*, Me); 1.32–1.39 (*m*, 1H of CH_2); 1.41–1.47 (*m*, 1H of CH_2); 1.67–1.76 (*m*, 1H of CH_2); 2.04–2.11 (*m*, 1H of CH_2); 2.59 (*d*, *J* = 3.7 Hz, H—C(4)); 7.73 (*d*, *J* = 9.7 Hz, H—C(3′)); 7.77 (*s*, 1H of Arl); 7.96 (*s*, 2H of Arl), 8.65 (*s*, NH); 11.28 (*d*, *J* = 9.6 Hz, H—N(4′)). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.0, 18.7, 20.6, 27.6, 30.2, 48.9, 49.1, 59.3, 119.7–119.9 (*m*), 123.0 (*q*, *J* = 273.0 Hz), 123.4, 123.8–124.0 (*m*), 130.0, 132.8 (*q*, *J* = 33.8 Hz), 139.0, 178.6, 211.6. ($C_{20}H_{20}F_6N_2OS$ requires: C, 53.33; H, 4.48; N, 6.22. found C, 53.60; H, 4.33; N, 6.16); EI-HRMS: *m/z* = 449.1126 (M-H); $C_{20}H_{19}F_6N_2OS$

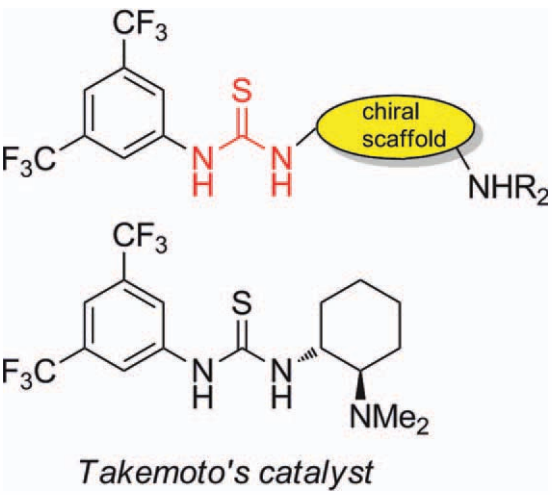


Fig. 2. General outline and an example of a bi-functional thiourea organocatalyst. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

requires: m/z = 449.1128 (M-H); ν_{max} (KBr) 3418, 2962, 1703, 1647, 1619, 1549, 1516, 1471, 1453, 1381, 1337, 1281, 1249, 1180, 1127, 1107, 1070, 1025, 959, 888 cm^{-1}.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(((1*R*,2*R*,4*S*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)methyl)thiourea (7) and 1-(3,5-bis (trifluoromethyl)phenyl)-3-(((1*R*,2*S*,4*S*)-4,7,7-trimethyl-3-oxobicyclo-[2.2.1]heptan-2-yl)methyl)thiourea (7′). To a solution of **4** (**4**:**4**′ ≈ 68:32, 183 mg, 1.01 mmol) in Et_2O (10 ml) under Argon 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**5**) (192 μL, 1.01 mmol) was added, and the resulting mixture was stirred at room temperature for 24 h. Volatile components were evaporated in vacuo and the residue (**7**/**7**′ = 69:31) was purified by CC (Silica gel 60; $CHCl_3$/MeOH = 150:1). No separation of diastereoisomers took place. Fractions containing the product were combined and volatile components evaporated in vacuo to give **7**/**7**′. The residue was dissolved in Et_2O (7 ml), *n*-heptane (50 ml) was added and the resulting solution was left open overnight for the Et_2O to evaporate. The precipitate was collected by filtration, washed with petroleum ether (10 ml) and dried on high vacuum. Yield: 300 mg (65%, **7**/**7**′ = 70:30) of white solid; mp 150–152°C. $[\alpha]_D^{20}$ = +4.8 (*c* = 0.19, CH_2Cl_2). ($C_{20}H_{22}F_6N_2OS$ requires: C, 53.09; H, 4.90; N, 6.19. found C, 53.12; H, 4.78; N, 6.13); EI-HRMS: m/z = 453.1421 (MH^+); $C_{20}H_{22}F_6N_2OS$ requires: m/z = 453.1435 (MH^+); ν_{max} (KBr) 3420, 1730, 1636, 1618, 1558, 1532, 1472, 1386, 1337, 1279, 1185, 1129, 959, 886, cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6) for **7**: δ 0.82 (*s*, 2xMe); 0.98 (*s*, Me); 1.20–1.28 (*m*, 1H of CH_2); 1.56–1.81 (*m*, 3H of CH_2); 2.13 (*s*, H—C(4)); 2.91–2.97 (*m*, H—C(3)); 3.53 (br *s*, Ha-C(3′)); 3.66–3.81 (*m*, Hb-C(3′)); 7.75 (*s*, 1H of Arl); 8.22 (*s*, 2H of Arl); 8.28 (br *s*, NH); 10.13 (br *s*, NH). ^{1}H-NMR (500 MHz, DMSO-d_6) for **7**′: δ 0.85 (*s*, Me); 0.92 (*s*, Me); 1.31–1.39 (*m*, 1H of CH_2); 1.40–1.46 (*m*, 1H of CH_2); 1.92–2.00 (*m*, 1H of CH_2); 2.33–2.38 (*m*, H—C(3)); 8.41 (br *s* NH). ^{13}C NMR (126 MHz, DMSO-d_6) for **7** and **7**′: δ 9.3, 9.4, 18.9, 19.2, 20.1, 21.1, 28.4, 28.6, 30.4, 41.9, 45.1, 45.2, 45.4, 45.5, 46.4, 48.4, 53.4, 57.1, 58.2, 116.1 (br *s*), 121.8 (br *s*), 122.0 (br *s*), 123.2 (*q*, *J* = 272.7 Hz), 130 (*q*, *J* = 32.3 Hz), 141.8, 180.3, 218.2, 218.3.

(1*S*,3*R*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (9) and (1*S*,3*S*,4*R*)-3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (9′). To a solution of (*E*)-3-benzylidene-camphor (**8**)[41] (5.34 g, 22.22 mmol) in anhydrous EtOH (150 ml) under Argon Pd–C (10%, 0.5 g) was added. The reaction vessel was flushed with H_2 and the reaction mixture was hydrogenated in *Paar* hydrogenator (P = 4 Bar) at room temperature for 10 min. The reaction mixture was filtered through a plug of Celite® and washed with CH_2Cl_2 (100 ml). Volatile components were evaporated in vacuo to give a mixture of ketones **9**/**9**′ (100% conversion). Yield: 5.12 g (95%, **9**:**9**′ = 66:34) of colorless oil. $[\alpha]_D^{20}$ = +52.7 (*c* = 0.26, CH_2Cl_2, **9**:**9**′ = 62:38). EI-HRMS: m/z = 243.1746 (MH^+); $C_{17}H_{23}O$ requires: m/z = 243.1743 (MH^+); ν_{max} (NaCl) 2959, 1741, 1604, 1496, 1453, 1391, 1372, 1323, 1268, 1104, 1074, 1043, 1030, 1018, 757, 730 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) of **9**: δ 0.94 (*s*, 2xMe); 0.97 (*s*, Me); 1.22–1.28 (*m*, 1H of CH_2); 1.46–1.53 (*m*, 1H of CH_2); 1.61–1.67 (*m*, 1H of CH_2); 1.89–1.96 (*m*, 1H of CH_2); 1.97 (*d*, *J* = 4.0 Hz, H—C(4)); 2.16 (*dd*, *J* = 3.8; 10.6 Hz, H—C(3)); 2.48–2.55 (*m*, Ha-C(3′)); 3.25 (*dd*, *J* = 3.8; 14.2 Hz, Hb-C(3′)); 7.18–7.22 (*m*, 3H of Ph); 7.27–7.32 (*m*, 2H of Ph). ^{1}H-NMR (500 MHz, $CDCl_3$) of **9**′: δ 0.85 (*s*, Me); 0.93 (*s*, Me); 1.33–1.39 (*m*, 1H of CH_2); 1.68–1.81 (*m*, 3H of CH_2); 2.68–2.73 (*m*, H—C(3)); 3.18 (*dd*, *J* = 4.3; 14.3 Hz, Hb-C(3′)). ^{13}C-NMR (126 MHz, $CDCl_3$) of **9** and **9**′: δ 9.7, 9.8, 19.5, 19.7, 20.5, 20.7, 22.2, 29.45, 29.48, 31.1, 32.9, 37.3, 45.9, 46.6, 47.0, 52.0, 56.9, 57.9, 58.9, 126.19, 126.23, 128.64, 128.67, 128.69, 128.8, 140.5, 141.5, 220.6, 220.8.

(1*S*,3*R*,4*R*,2*E*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one oxime (10) and (1*S*,3*S*,4*R*,2*E*)-3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime (10′). To a solution of **9**/**9**′ (**9**/**9**′ ≈ 66:34, 1.30 g, 5.36 mmol) in EtOH (100 ml) pyridine (3.27 ml, 40.5 mmol) and NH_2OH·HCl (4.08 g, 58.7 mmol) were added and the resulting mixture was refluxed for 48 h. Volatile components were evaporated in vacuo and to the residue H_2O (50 ml) was added. The resulting precipitate was collected by filtration, dried over NaOH in a desicator for 24 h, and recrystallized from EtOH to give the product as a mixture of epimers **10**/**10**′. Yield: 750 mg (54%, **10**:**10**′ = 66:34) of white solid; mp 141.2–143.0°C. $[\alpha]_D^{20}$ = +28.4 (*c* = 0.08, CH_2Cl_2). ($C_{17}H_{23}NO$ requires: C, 79.33; H, 9.01; N 5.44. found C, 79.47; H, 9.17; N, 5.51); EI-HRMS: m/z = 258.1858 (MH^+); $C_{17}H_{24}NO$ requires: m/z = 258.1855 (MH^+); ν_{max} (KBr) 3264, 3148, 3028, 2966, 2945, 2873, 2366, 2357, 2337, 1601, 1497, 1472, 1454, 1445, 1389, 1375, 1317, 1072, 1021, 934, 834, 740, 699, 513 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) of **10**: δ 0.90 (*s*, Me); 1.03 (*s*, Me); 1.06 (*s*, Me); 1.10–1.17 (*m*, 1H of CH_2); 1.41–1.47 (*m*, 1H of CH_2); 1.61–1.81 (*m*, H—C(4), 2H of CH_2); 2.57 (*dd*, *J* = 10.0; 13.8 Hz, Ha-C(3′)); 2.69 (*dd*, *J* = 3.2; 10.0 Hz, H—C(3)); 3.81 (*dd*, *J* = 3.2; 13.8 Hz, Hb-C(3′)); 7.16–7.22 (*m*, 1H of Ph); 7.23–7.33 (*m*, 4H of Ph); 7.53 (br *s*, OH). ^{1}H-NMR (500 MHz, $CDCl_3$) of **10**′: δ 0.81 (*s*, Me); 0.89 (*s*, Me); 0.97 (*s*, Me); 1.48–1.54 (*m*, 1H of CH_2); 2.50 (*dd*, *J* = 11.9; 14.3 Hz, Ha-C(3′)); 3.21–3.27 (*m*, H—C(3)); 3.92 (*dd*, *J* = 4.3; 14.4 Hz, Hb-C(3′)). ^{13}C-NMR (75 MHz, $CDCl_3$) of **10** and **10**′: δ 11.6, 12.1, 19.1, 19.3, 20.1, 20.9, 22.6, 29.2, 32.26, 32.30, 33.4, 37.0, 43.1, 46.5, 47.5, 48.2, 48.3, 50.6, 53.1, 53.3, 125.9, 126.0, 128.4, 128.5, 129.0, 129.1, 141.1, 142.8, 170.0, 172.1.

Catalytic hydrogenation of (1S,3RS,4R,2E)-3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 10/10′ at 60°C

To a suspension of oxime **10**/**10**′ (**10**/**10**′ ≈ 66:34, 1.36 g, 5.3 mmol) in anhydrous EtOH (30 ml) under Argon Pd–C (10%, 400 mg) was added. The reaction vessel was flushed with H_2 and the reaction mixture was hydrogenated in an autoclave (P = 50–55 Bar) at 60°C for 4 days. The reaction mixture was filtered through a plug of Celite®, washed with CH_2Cl_2 (200 ml), and volatile components were evaporated in vacuo. The residue (ca. 90% conversion according to ^{1}H-NMR; **11**/**12**/**13** ≈ 1:1:0.3) was separated by MPLC (EtOAc/Et_3N = 100:1). Fractions containing the partially separated products were combined and volatile components evaporated in vacuo to give crude amines **11**, **12**, and **13**, respectively.

(1*S*,2*R*,3*R*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (11). **11** elutes first from the column. Yield: 324 mg (25%, ca. 75–85% pure) of yellowish oil. Part of the free amine was transformed into the corresponding hydrochloride salt for NMR characterization. Free amine **11** (70 mg) was dissolved in Et_2O (5 ml) followed by addition of HCl (2 M in EtOAc, 0.2 ml). Volatile components were evaporated in vacuo to give the corresponding **11**-HCl salt for NMR characterization. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.73 (*s*, Me); 0.83–0.90 (*m*, 1H of CH_2); 1.11 (*s*, Me); 1.16–1.23 (*m*, 1H of CH_2); 1.22 (*s*, Me); 1.48–1.62 (*m*, H—C(4), 2H of CH_2); 2.27 (*ddd*, *J* = 4.1; 9.7, 13.5 Hz, H—C(3)); 2.72 (*t*, *J* = 13.2 Hz, Ha-C(3′)); 3.40 (*dd*, *J* = 4.0; 13.2 Hz, Hb-C(3′)); 3.44 (*dd*, *J* = 6.7; 9.2 Hz, H—C(2)); 7.05 (*d*, *J* = 7.1 Hz, 2H of Ph); 7.12–7.21 (*m*, 3H of Ph); 8.45 (s, NH_3^+). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.9, 22.1, 22.6, 29.7, 36.1, 36.5, 46.7, 47.5, 49.2, 49.6, 62.8, 125.9, 128.4, 129.4, 140.9.

(1*S*,2*R*,3*S*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (12). **12** elutes second from the column. Yield: 452 mg (35%, ca. 90–95% pure) of colorless oil. The crude free amine **12** (452 mg, 1.857 mmol) was dissolved in anhydrous Et_2O (25 ml) under argon, cooled to 0°C, followed by addition of HCl (2 M in EtOAc, 1 ml). The resulting precipitate was collected by filtration and washed with anhydrous Et_2O (50 ml) to give analytically pure amine hydrochloride **12**-HCl. Yield: 318 mg (21%, calculated from **10**/**10**′) of white solid; mp 255–262°C. $[\alpha]_D^{20}$ = –41.7 (*c* = 0.06, CH_2Cl_2). ^{1}H-NMR (500 MHz, $CDCl_3$):δ 0.83 (*s*, Me); 1.10 (*s*, Me); 1.13 (*s*, Me); 1.19–1.28 (*m*, 1H of CH_2); 1.51 (br *s*, H—C(4)); 1.58–1.76 (*m*, 3H of CH_2); 2.54 (deg *t*, *J* = 12.5 Hz, Ha-C(3′)); 2.79 (br *s*, H—C(2), H—C(3)); 3.48 (*dd*, *J* = 3.2; 13.0 Hz, Hb-C(3′)); 7.11–7.21 (*m*, 3H of Ph); 7.29 (br *d*, *J* = 7.0 Hz, 2H of Ph); 8.59 (br *s*, NH_3^+). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.5, 20.1, 20.4, 20.8, 36.0, 36.7, 46.4, 47.8, 48.4, 49.1, 64.9, 126.1, 128.5, 129.1, 140.6. (Found C, 72.84; H, 9.60; N, 4.96. $C_{17}H_{26}ClN$ requires: C, 72.96; H, 9.36; N, 5.01.); EI-HRMS: m/z = 244.2071 (M^+); $C_{17}H_{26}ClN$ requires: m/z = 244.2065 (M^+); ν_{max} (KBr) 3473, 3414, 2954, 2894, 1636, 1617, 1605, 1521, 1510, 1496, 1485, 1400, 1388, 1183, 1134, 1053, 1030, 748, 700 cm^{-1}.

12-HCl was dissolved in CH_2Cl_2 (150 ml) and washed with $NaHCO_3$ (aq. sat, 15 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo to give pure free amine **12** for further transformation and NMR characterization. ^{1}H-NMR (500 MHz, $CDCl_3$):δ 0.82 (*s*, Me); 0.82 (*s*, Me); 0.99 (*s*, Me); 1.01–1.06 (*m*, 1H of CH_2); 1.50–1.62 (*m*, H—C(4), 3H of CH_2); 2.10–2.17 (*m*, H—C(3)); 2.30 (*d*, *J* = 5.5 Hz, H—C(2)); 2.62 (*dd*, *J* = 8.8; 13.4 Hz, Ha-C(3′)); 2.84 (*dd*, *J* = 7.0; 13.4 Hz, Hb-C(3′)); 7.15–7.30 (*m*, 5H of Ph). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.2, 20.0, 20.5, 21.4, 37.1, 37.8, 47.9, 48.1, 49.1, 51.9, 67.1, 125.9, 128.5, 129.0, 142.1.

(1*S*,2*S*,3*S*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (13). **13** elutes third from the column. Yield: 133 mg (10%, ca. 75–85% pure) of yellowish oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.80 (*s*, Me); 0.87 (*s*, Me); 0.90 (*s*, Me); 1.16–1.27 (*m*, 1H of CH_2); 1.42 (*t*, *J* = 3.9 Hz, H—C(4)); 1.45–1.55 (*m*, 1H of CH_2); 1.56–1.64 (*m*, 2H of CH_2); 2.50–2.57 (*m*, H—C(3), Ha-C(3′)); 2.81 (*q*, *J* = 11.0 Hz, Hb-C(3′)); 3.12 (*dd*, *J* = 1.7; 10.0 Hz, H—C(2)); 7.13–7.20 (*m*, 3H of Ph); 7.24–7.28 (*m*, 2H of Ph). ^{13}C-NMR (126 MHz, CDCl3): δ 14.5, 18.5, 20.4, 20.4, 26.2, 32.7, 41.2, 46.5, 48.2, 50.4, 57.1, 125.7, 128.4, 128.9, 142.3.

Catalytic Hydrogenation of (1S,3RS,4R,2E)-3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 10/10′ at 90°C

To a suspension of oxime **10/10′** (**10/10′** ≈ 66:34, 2.06 g, 8 mmol) in anhydrous EtOH (40 ml) under Argon Pd–C (10%, 600 mg) was added. The reaction vessel was flushed with H_2 and the reaction mixture was hydrogenated in an autoclave (P = 50–55 Bar) at 90°C for 48 h. The reaction mixture was filtered through a plug of Celite®, washed with CH_2Cl_2 (200 ml), and volatile components were evaporated in vacuo. The residue (100% conversion according to ^{1}H-NMR) was dissolved in Et_2O (200 ml) and washed with HCl (1 M in H_2O, 40 ml). The aqueous phase was extracted with addition Et_2O (100 ml). Combined organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (200 ml) and washed with $NaHCO_3$ (aq. sat., 30 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo to give the crude products, a complex mixture of 3-benzyl-amines **11–13** and corresponding 3-cyclohexylmethyl-amines **11′**-**13′**. Product mixture was used in the following transformation without further purification/separation. Yield: 1.3 g.

Reduction of (1S,3RS,4R,2E)-3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 10/10′ with sodium

To a solution of oxime **10/10′** (**10/10′** ≈ 66:34, 315 mg, 1.223 mmol) in anhydrous *n*PrOH (10 ml) under Argon under reflux sodium (ca. 100 mg) was added. Before all the added sodium reacted, another chunk of sodium (ca. 100 mg) was added, followed by addition of further sodium to ensure a continuous evolution of hydrogen for 1 h. After all the sodium reacted, volatile components were evaporated in vacuo and to the residue H_2O (100 ml) was added followed by extraction with $CHCl_3$ (3x70 ml). Combined organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo to give the crude products, amines **12**, **13**, and **14** in a ratio of about ≈ 0.45:0.45:1, respectively. The product mixture was used in the following transformation without further purification/separation. Yield: 279 mg (100% conversion according to ^{1}H-NMR).

General Procedure for the Formation of 2-thiourea-camphor derivatives 15–20 (GP1)

To a solution of amine or mixture of amines (1 equivalent) in anhydrous Et_2O (V_1) 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**5**) (1 equivalent) was added and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was passed through a plug of Silica gel 60 (length of 5 cm) and washed with Et_2O (100 ml). Volatile components were evaporated in vacuo, and the residue was separated by MPLC (EtOAc/petroleum ether = 1:15). Fractions containing the separated products were combined and volatile components evaporated in vacuo to give the desired product or products. Fractions containing mixtures of products or not fully separated products were discarded.

1-((1*S*,2*R*,3*R*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-(3,5-bis(trifluoro-methyl)phenyl)thiourea (15). Prepared from **11** (223 mg, 0.916 mmol) and **5** (174 μL, 0.916 mmol) in Et_2O (10 ml) following *GP1*. Yield: 177 mg (37%) of white solid; mp 59–70°C. $[\alpha]_D^{20}$ = –17.8 (*c* = 0.17, CH_2Cl_2). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.82 (*s*, Me); 0.90 (*s*, Me); 0.96–1.04 (*m*, 1H of CH_2); 1.16 (*s*, Me); 1.27–1.34 (*m*, 1H of CH_2); 1.54 (*d*, *J* = 3.9 Hz, H—C(4)); 1.55–1.68 (*m*, 2H of CH_2); 2.22 (*td*, *J* = 4.8; 11.0 Hz, H—C(3)); 2.53 (*dd*, J = 11.5; 14.0 Hz, Ha-C(3′)); 2.84 (*dd*, *J* = 4.6, 13.7 Hz, Hb-C(3′)); 4.69 (*t*, *J* = 9.0 Hz, H—C(2)); 7.12–7.21 (*m*, 3H of Ph); 7.23–7.28 (*m*, 2H of Ph); 7.72 (*d*, *J* = 8.8 Hz, H—N(2′)); 7.74 (*s*, 1H of Arl); 8.41 (*s*, 2H of Arl); 10.49 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 12.2, 21.7, 21.9, 29.2, 36.1, 36.1, 47.3, 47.4, 49.1, 51.2, 64.6, 115.9, 121.3, 123.3 (*q*, *J* = 272.7 Hz), 125.5, 128.3, 128.7, 130.1 (*q*, *J* = 32.8 Hz), 141.9, 142.1, 180.9. (Found C, 60.63; H, 5.40; N, 5.39. $C_{26}H_{28}F_6N_2S$ requires: C, 60.69; H, 5.48; N, 5.44.); EI-HRMS: *m/z* = 515.1952 (MH^+); $C_{26}H_{29}F_6N_2S$ requires: *m/z* = 515.1950 (MH^+); ν_{max} (KBr) 3416, 2958, 1622, 1522, 1472, 1381, 1342, 1278, 1182, 1135, 1108, 960, 888, 700, 682 cm^{-1}.

1-((1*S*,2*R*,3*S*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-(3,5-bis(trifluoro-methyl)phenyl)thiourea (16). Prepared from **12** (230 mg, 0.945 mmol) and **5** (179 μL, 0.945 mmol) in Et_2O (10 ml) following *GP1*. Yield: 338 mg (69%) of white solid; mp 167–168°C. $[\alpha]_D^{20}$ = –46.0 (*c* = 0.13, CH_2Cl_2). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.81 (*s*, Me); 0.85 (*s*, Me); 0.93 (*s*, Me); 1.27–1.35 (*m*, 1H of CH_2); 1.45 (br *s*, H—C(4)); 1.51–1.64 (*m*, 2H of CH_2); 1.67–1.74 (*m*, 1H of CH_2); 2.28–2.35 (*m*, H—C(3)); 2.67 (*dd*, *J* = 9.6; 13.5 Hz, Ha-C(3′)); 2.86 (*dd*, *J* = 6.0; 13.6 Hz, Hb-C(3′)); 4.28 (*dd*, *J* = 7.0; 7.9 Hz, H—C(2)); 7.10–7.15 (*m*, 1H of Ph); 7.19–7.26 (*m*, 4H of Ph); 7.72 (*d*, *J* = 8.9 Hz, H—N(2′)); 7.73 (*s*, 1H of Arl); 8.26 (*s*, 2H of Arl); 10.03 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 11.9, 19.7, 20.5, 36.1, 36.5, 46.9, 47.4, 48.7, 50.4, 66.6, 115.8, 121.4, 123.3 (*q*, *J* = 272.7 Hz), 125.6, 128.1, 128.5, 130.1 (*q*, *J* = 32.8 Hz), 141.0, 142.0, 181.0. (Found C, 60.75; H, 5.35; N, 5.42. $C_{26}H_{28}F_6N_2S$ requires: C, 60.69; H, 5.48; N, 5.44.); EI-HRMS: *m/z* = 515.1953 (MH^+); $C_{26}H_{29}F_6N_2S$ requires: *m/z* = 515.1950 (MH^+); ν_{max} (KBr) 3407, 2958, 1618, 1527, 1496, 1471, 1384, 1344, 1279, 1176, 1135, 1108, 962, 889, 700, 682 cm^{-1}.

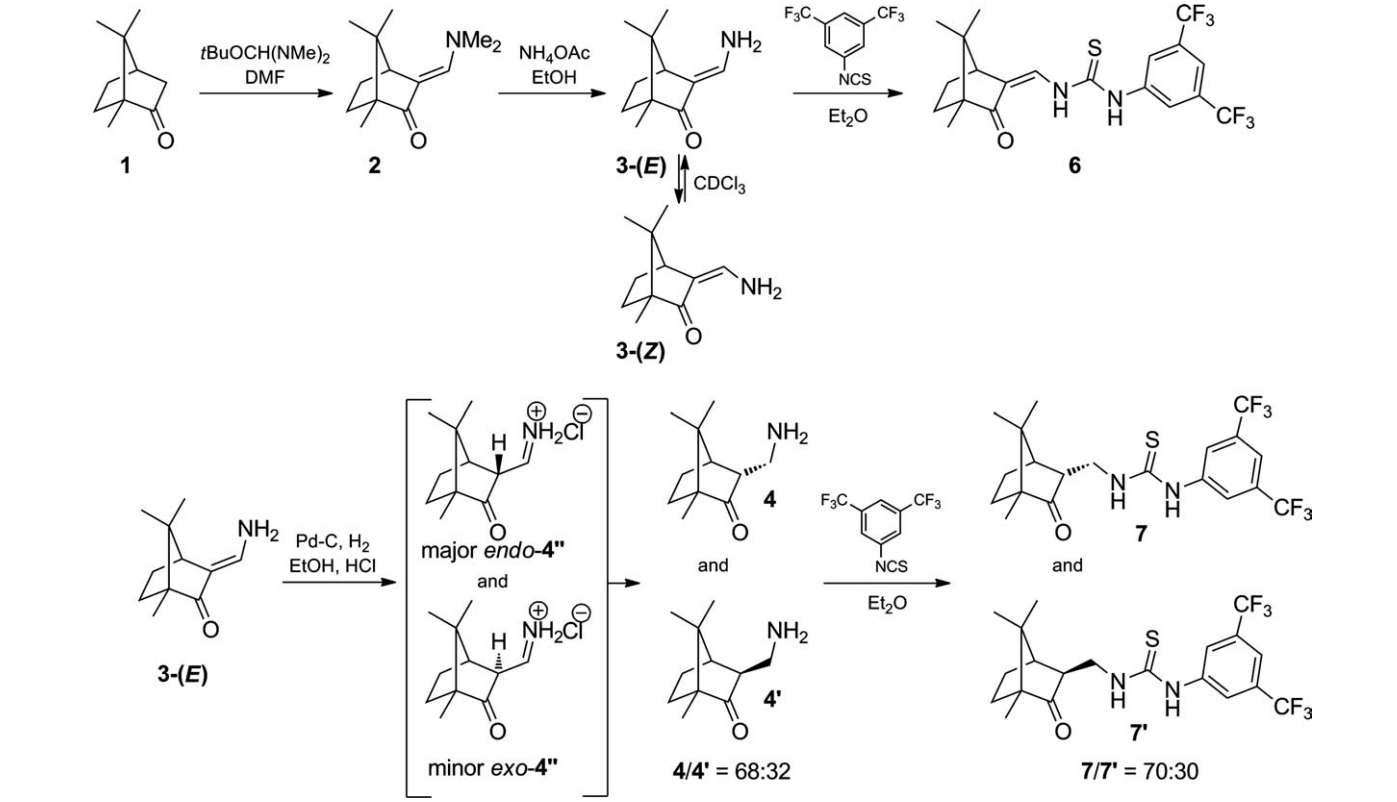
1-((1*S*,2*S*,3*S*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-(3,5-bis(trifluoro-methyl)phenyl)thiourea (17). Prepared from **13** (100 mg, 0.41 mmol) and **5** (78 μL, 0.41 mmol) in Et_2O (5 ml) following *GP1*. Yield: 60 mg (28%) of white solid; mp 151–161°C. $[\alpha]_D^{20}$ = +25.2 (*c* = 0.10, CH_2Cl_2). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.79 (*s*, Me); 0.87 (*s*, Me); 0.97 (*s*, Me); 1.35–1.43 (*m*, H—C(4), 1H of CH_2); 1.48–1.57 (*m*, 1H of CH_2); 1.60–1.70 (*m*, 2H of CH_2); 2.51–2.53 (Ha-C(3′)); 2.62–2.72 (*m*, H—C(3), Hb-C(3′)); 4.82 (*t*, *J* = 9.6 Hz, H—C(2)); 7.10–7.18 (*m*, 3H of Ph); 7.20–7.25 (*m*, 2H of Ph); 7.73 (*s*, 1H of Arl); 8.09 (*d*, *J* = 9.3 Hz, H—N(2′)); 8.34 (*s*, 2H of Arl); 10.14 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 14.2, 18.3, 19.60, 19.65, 27.6, 32.0, 40.0, 46.5, 46.8, 49.7, 59.1, 115.8, 121.4, 123.3 (*q*, *J* = 272.7 Hz), 125.5, 128.2, 128.4, 130.1 (*q*, *J* = 32.8 Hz), 140.9, 142.0, 181.6. (Found C, 60.97; H, 5.74; N, 5.41. $C_{26}H_{28}F_6N_2S$ requires: C, 60.69; H, 5.48; N, 5.44.); EI-HRMS: *m/z* = 515.1960 (MH^+); $C_{26}H_{29}F_6N_2S$ requires: *m/z* = 515.1950 (MH^+); ν_{max} (KBr) 3298, 2958, 1622, 1602, 1538, 1493, 1473, 1384, 1346, 1278, 1223, 1180, 1136, 1108, 976, 961, 888, 720, 700, 682 cm^{-1}.

Reaction of a Mixture of Amines 12, 13, and 14 with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (5)

Prepared from a mixture of **12**, **13**, and **14** in a ratio of about 0.45:0.45:1 (279 mg, 1.146 mmol) and **5** (218 μL, 1.146 mmol) in Et_2O (10 ml) following *GP1*. Fractions containing the separated products were combined and volatile components evaporated in vacuo to give **16**, **18**, and **17**, respectively.

16 elutes first from the column. Yield: 102 mg (17%) of white solid (for exp. details see above).

1-((1*S*,2*S*,3*R*,4*R*)-3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (18). Elutes second from the column. Yield: 216 mg (36%) of white solid; mp 162–167°C.



Scheme 1. Preparation of 3-thiourea functionalized camphor derivatives **6**, **7**/**7**′.

$[\alpha]_D^{20}$ = +30.7 (*c* = 0.11, CH_2Cl_2). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.83 (*s*, Me); 0.84 (*s*, Me); 1.03–1.11 (*m*, 1H of CH_2); 1.16 (*s*, Me); 1.25–1.34 (*m*, 1H of CH_2); 1.51 (*d*, *J* = 3.4 Hz, H—C(4)); 1.56–1.75 (*m*, H—C(3), 2H of CH_2); 2.75 (*dd*, *J* = 10.3; 13.5 Hz, Ha-C(3′)); 2.92 (*dd*, *J* = 5.2; 13.7 Hz, Hb-C(3′)); 4.98 (*t*, *J* = 7.0 Hz, H—C(2)); 7.11–7.27 (*m*, 5H of Ph); 7.73 (*s*, 1H of Arl); 8.22 (*s*, 2H of Arl); 8.25 (*d*, *J* = 9.0 Hz, H—N(2′)); 9.86 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 13.7, 20.0, 21.3, 27.7, 30.2, 40.3, 45.7, 47.5, 50.7, 53.1, 64.6, 115.7, 121.6, 123.3 (*q*, *J* = 272.7 Hz), 125.6, 128.2, 128.6, 130.1 (*q*, *J* = 32.8 Hz), 141.5, 142.0, 181.3. (Found C, 60.95; H, 5.69; N, 5.46. $C_{26}H_{28}F_6N_2S$ requires: C, 60.69; H, 5.48; N, 5.44.); EI-HRMS: *m*/*z* = 515.1944 (MH^+); $C_{26}H_{29}F_6N_2S$ requires: *m*/*z* = 515.1950 (MH^+); ν_{max} (KBr) 3410, 2958, 1617, 1538, 1472, 1384, 1351, 1278, 1176, 1134, 966, 888, 700, 682 cm^{-1}.

17 elutes third from the column. Yield: 73 mg (12%) of white solid (for exp. details see above).

Reaction of a mixture of amines 11–13 and 11′-13′ with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (5)

Prepared from a complex mixture of **11–13** and **11**′-**13**′ (500 mg, ca. 2 mmol) and **5** (373 μL, 2 mmol) in Et_2O (10 ml) following *GP1*. Fractions containing the separated products were combined and volatile components evaporated in vacuo to give **19**, **20**, **16**, **17**, and **15**, respectively.

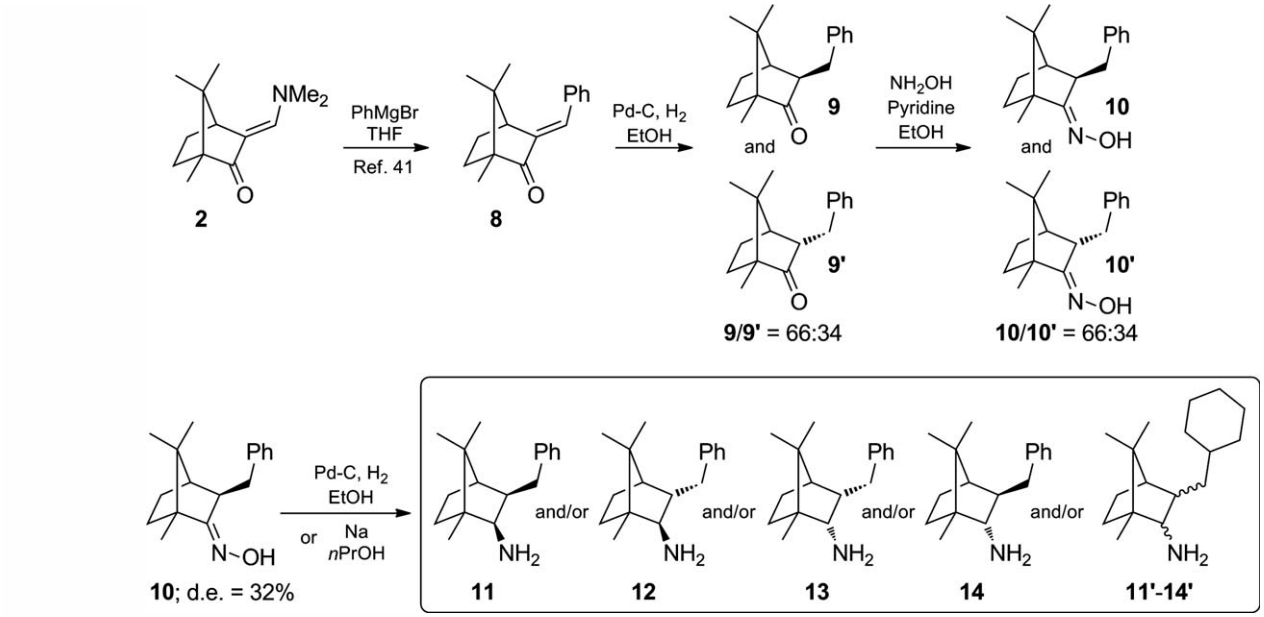
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*R*,3*S*,4*R*)-3-(cyclohexylmethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (19). Elutes first from the column. Yield: 112 mg (10%) of white solid; mp 177–180°C. $[\alpha]_D^{20}$ = –25.4 (*c* = 0.11, CH_2Cl_2). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.82 (*s*, Me); 0.84 (*s*, Me); 0.80–0.89 (*m*, 2H of CH_2); 0.98 (*s*, Me); 1.07–1.30 (*m*, CH, 5H of CH_2); 1.32–1.39 (*m*, 1H of CH_2); 1.41–1.76 (*m*, CH, 8H of CH_2); 2.13 (br *s*, H—C(3)); 4.10 (*dd*, *J* = 6.4; 8.6 Hz, H—C(2)); 7.72 (*s*, 1H of Arl); 7.72 (*d*, *J* = 9.0 Hz, H—N(2′)); 8.31 (*s*, 2H of Arl); 10.12 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 11.9, 19.5, 19.7, 20.6, 25.89, 25.95, 26.2, 32.7, 33.5, 35.4, 36.1, 38.5, 43.1, 47.2, 47.6, 50.1, 67.2, 115.7 (br *s*), 121.2 (br *s*), 123.3 (*q*, *J* = 272.7 Hz), 130.1 (*q*, *J* = 32.8 Hz), 142.1, 180.7. (Found C, 60.19; H, 6.28; N, 5.32. $C_{26}H_{34}F_6N_2S$ requires: C, 59.98; H, 6.58; N, 5.38.); EI-HRMS: *m*/*z* = 521.2438 (MH^+); $C_{26}H_{35}F_6N_2S$ requires: *m*/*z* = 521.2425 (MH^+); ν_{max} (KBr) 3416, 2927, 2852, 1618, 1528, 1472, 1384, 1349, 1278, 1182, 1138, 1108, 962, 888, 710, 682 cm^{-1}.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*,3*S*,4*R*)-3-(cyclohexylmethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (20). Elutes second from the column. Yield: 54 mg (5%) of white solid; mp 155–159°C. $[\alpha]_D^{20}$ = +12.0 (*c* = 0.05, CH_2Cl_2). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.75 (*s*, Me); 0.76–0.88 (*m*, 2H of CH_2); 0.90 (*s*, Me); 0.98 (*s*, Me); 1.05–1.21 (*m*, CH, 5H of CH_2); 1.29–1.43 (*m*, 2H of CH_2); 1.49–1.66 (*m*, CH, 6H of CH_2); 1.70 (*d*, *J* = 12.5, 1H of CH_2); 2.35–2.44 (*m*, H—C(3)); 4.76 (*t*, *J* = 9.8 Hz, H—C(2)); 7.73 (*s*, 1H of Arl); 7.95 (*d*, *J* = 9.6 Hz, H—N(2′)); 8.35 (*s*, 2H of Arl); 10.11 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 14.2, 18.2, 19.5, 19.7, 25.8, 26.0, 26.2, 27.6, 32.1, 33.6, 34.1, 34.5, 35.0, 46.4, 47.4, 49.5, 58.9, 115.8 (br *s*), 121.3 (br *s*), 123.3 (*q*, *J* = 272.8 Hz), 130.1 (*q*, *J* = 32.8 Hz), 142.0, 181.3. (Found C, 60.16; H, 6.65; N, 5.36. $C_{26}H_{34}F_6N_2S$ requires: C, 59.98; H, 6.58; N, 5.38.); EI-HRMS: *m*/*z* = 521.2410 (MH^+); $C_{26}H_{35}F_6N_2S$ requires: *m*/*z* = 521.2425 (MH^+); ν_{max} (KBr) 3412, 2928, 2853, 1618, 1539, 1473, 1447, 1384, 1351, 1278, 1181, 1137, 1108, 974, 959, 888 cm^{-1}.

16 elutes third from the column. Yield: 210 mg (20%) of white solid (for exp. details see above). **17** elutes fourth from the column. Yield: 59 mg (5%) of white solid (for exp. details see above). **15** elutes fifth from the column. Yield: 51 mg (5%) of white solid (for exp. details see above).

Single crystal X-Ray structure analysis for compounds 10/10′, 12-HCl, 16, and 19

Single crystal X-ray diffraction data of compounds **10**/**10**′, **12**-HCl, **16**, and **19** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[45] DENZO and SCALEPACK[46] were used for indexing and scaling of the data and the structures were solved by direct methods using SIR97.[47] Refinement was done by means of Xtal3.4[48] for compound **10** and SHELXL-97[49] for **12**-HCl, **16**, and **19**. Hydrogen atoms positions for all four compounds were placed at ideal positions. Their parameters were not refined. Fig-



Scheme 2. Preparation of 2-amino camphor derivatives **11–14**, **11′–14′**.

ures 4–7 of molecules were prepared with the aid of ORTEP-3[50] program.

Crystallographic data for compounds **10**/**10′**, **12**-HCl, **16** and **19** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 835835–835838. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

RESULTS AND DISCUSSION

Syntheses

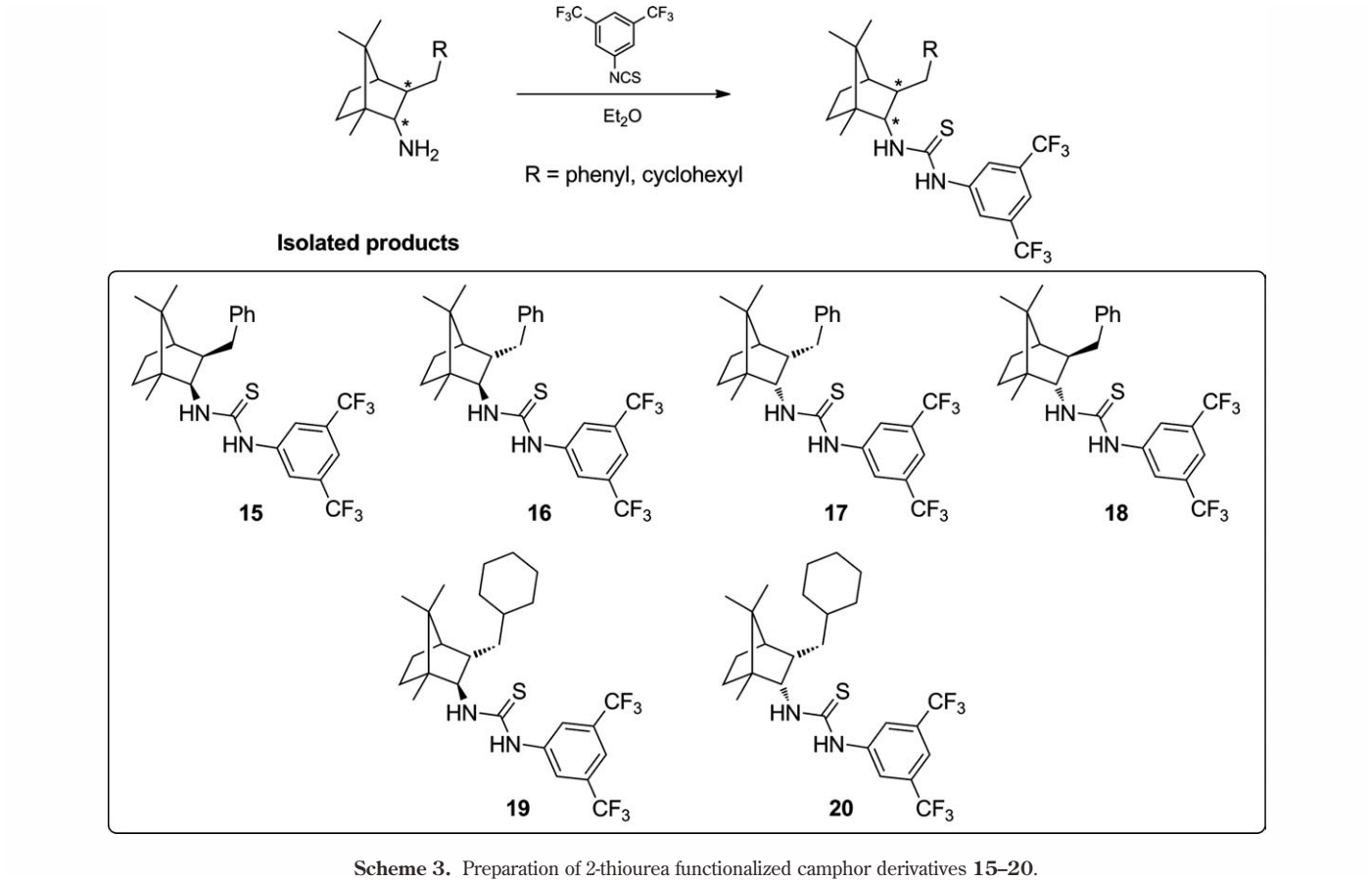
First, 3-methylene- **6** and 3-methyl-thiourea camphor derivatives **7**/**7′** were prepared. Starting from (+)-camphor (**1**), our second common precursor, 3-((dimethylamino)-methylene)-camphor (**2**) was prepared following a modified literature procedure[42] using enaminone methodology.[51] Accordingly, reaction of **1** with *tert*-butoxy bis(dimethylamino)methane under reflux in anhydrous DMF for 24 h gave **2** in 100% conversion and in 77% isolated yield. Treatment of **2** with excess NH_4OAc gave aminomethylene compound **3**[43] in 69% yield. In $CDCl_3$ solution compound **3** exists as (*E*)-isomer, which upon prolonged standing isomerizes[52] into a mixture of (*E*)- and (*Z*)-isomers (ca. 20% of (*Z*)-isomer is formed after 5 days in $CDCl_3$ solution). Next, catalytic hydrogenation of **3** in the presence of 10% Pd–C and a slight excess of HCl gave the corresponding aminomethyl compound as a mixture of the major *endo*- **4**[44] and the minor *exo*-epimer **4′**[44] in about 2:1 ratio and in 87% yield, respectively. Formation of the major *endo*-isomer **4** could be explained by the initial isomerization of enamine **3** in the presence of acid into the thermodynamically more stable *endo*-iminium salt **4″**, which upon reduction yields the corresponding major *endo*-product **4**. Chromatographic separation of **4**/**4′** failed. Finally, reaction of **3** and **4**/**4′** with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**5**) in anhydrous Et_2O gave (*Z*)-3-methylenethiourea **6** and an inseparable 3-methylthiourea mixture **7**/**7′** (*endo*-**7**/*exo*-**7′** = 70:30) in 28 and 65% yield, respectively. Low yield of **6** could be explained by diminished nucleophilicity of the vinylogous amide **3** compared to the amine **4**/**4′**. Base-assisted reactions of **3** with **5** gave complex mixtures of products (Scheme 1).

Next, the 2-thiourea camphor derivatives **15–20** were prepared in five steps from enaminone **2**. Treatment of the crude **2** with PhMgBr following the literature procedure gave (*E*)-3-benzylidene-camphor (**8**).[41] Catalytic hydrogenation of **8** in the presence of 10% Pd–C gave a 2:1 mixture of the major *exo*-3-benzyl-camphor **9**[53,54] and its minor *endo*-isomer **9′**[53,54] in quantitative yields. Major *exo*-epimer **9** is the kinetic product of the reaction due to the approach of the reagent from the sterically less hindered *endo*-face of the double bond in an irreversible transformation—epimerization of **9**/

TABLE 1. Reduction of oxime 10 (d.e. = 32%) under different reaction conditions

Entry	Reduction conditions	Ratio of products and conversion	Separated amines and yield
1	10% Pd–C, H_2 (50–55 Bar), 40°C, 7 days	**11**/**12**/**13** ≈ 1:1:0.3; 60%	No separation attempted
2	10% Pd–C, H_2 (50–55 Bar), 60°C, 4 days	**11**/**12**/**13** ≈ 0.6:1:0.3; 90%	**11**[b] (25%); **12**[c] (35%); **13** (10%)
3	10% Pd–C, H_2 (50–55 Bar), 90°C, 2 days	**11–13**, **11′-13′**[a]; 100%	Separation unsuccessful
4	Na, *n*PrOH, reflux, 1 h	**12**/**13**/**14** ≈ 0.45:0.45:1; 100%	No separation attempted

[a]Unable to determine the product ratio.
[b]For NMR characterization transformed into **11**-HCl salt.
[c]Obtained in analytically pure form as **12**-HCl salt (yield 21%).



Scheme 3. Preparation of 2-thiourea functionalized camphor derivatives **15–20**.

9′ under basic conditions leads to the thermodynamically favored *endo*-product **9′**[41,53,54] Next, treatment of epimers **9/9′** under conditions used by *Page*[55] ($NH_2OH{\cdot}HCl$, pyridine) gave the corresponding oximes **10/10′** with retention of epimer composition in 54% yield. Reduction of epimers **10/10′** with complex hydrides ($LiAlH_4$, $NaBH_4$, $NaCNBH_3$) as well as catalytic hydrogenation in the presence of 10% Pd–C under mild condition (4 Bar, room temperature) failed to give the corresponding amines. On the other hand, catalytic hydrogenation in EtOH under 50–55 Bar of H_2 in an autoclave at 40°C for 7 days gave three out of four amines, compounds **11**, **12**, and **13**, in a ratio of 1:1:0.3, respectively, in about 60% conversion. Hydrogenation under harsher conditions (90°C for 2 days) gave a complex mixture of 3-benzyl amines **11–13** and the corresponding fully saturated 3-cyclohexylmethyl amines **11′–13′**. All attempts to separate this mixture into its constituents failed—therefore the crude reaction mixture was used in the next step. Finally, catalytic hydrogenation at 60°C for 4 days gave amines **11**, **12**, and **13** in a ratio of 2:3.3:1, respectively, in about 90% conversion. Amines **11–13** were partially separated using CC to obtain the corresponding crude amines. Only amine **12** could be prepared in analytically pure form as the corresponding hydrochloride (**12**-HCl salt). Reduction of epimers **10/10′** with Na in *n*PrOH gave a mixture of amines **12**, **13**, and **14** in a ratio of about 0.45:0.45:1, respectively, in full conversion. No separations attempts were undertaken—the crude mixture was used in the following transformation (Scheme 2, Table 1).

Finally, reaction of crude amines **11** and **13**, and free amine **12** (obtained from **12**-HCl salt) with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**5**) in anhydrous Et_2O gave the corresponding 2-thiourea derivatives **15**, **17**, and **16** in 37, 28, and 69% yield, respectively. Reaction of a mixture of

TABLE 2. Reaction of amine/amine mixture with 5—formation of 2-thiourea camphor derivatives[a]

Entry	Amine or amine mixture	Isolated thiourea product(s) and yield	Absolute configuration
1	**11**[b]	**15** (37%)	(1*S*,2*R*,3*R*,4*R*)
2	**12**[c]	**16** (69%)	(1*S*,2*R*,3*S*,4*R*)
3	**13**[b]	**17** (28%)	(1*S*,2*S*,3*S*,4*R*)
4	**12**, **13**, **14**	**16** (17%), **17** (12%), **18** (36%)	**18**-(1*S*,2*R*,3*R*,4*R*)
5	**11–13**, **11′-13′**	**15** (5%), **16** (20%), **17** (5%), **19** (10%), **20** (5%)	**19**-(1*S*,2*R*,3*S*,4*R*); **20**-(1*S*,2*S*,3*S*,4*R*)

[a]Fractions containing mixtures of products after chromatographic separation were discarded.
[b]Crude amine after chromatographic separation used.
[c]Analytically pure amine used.

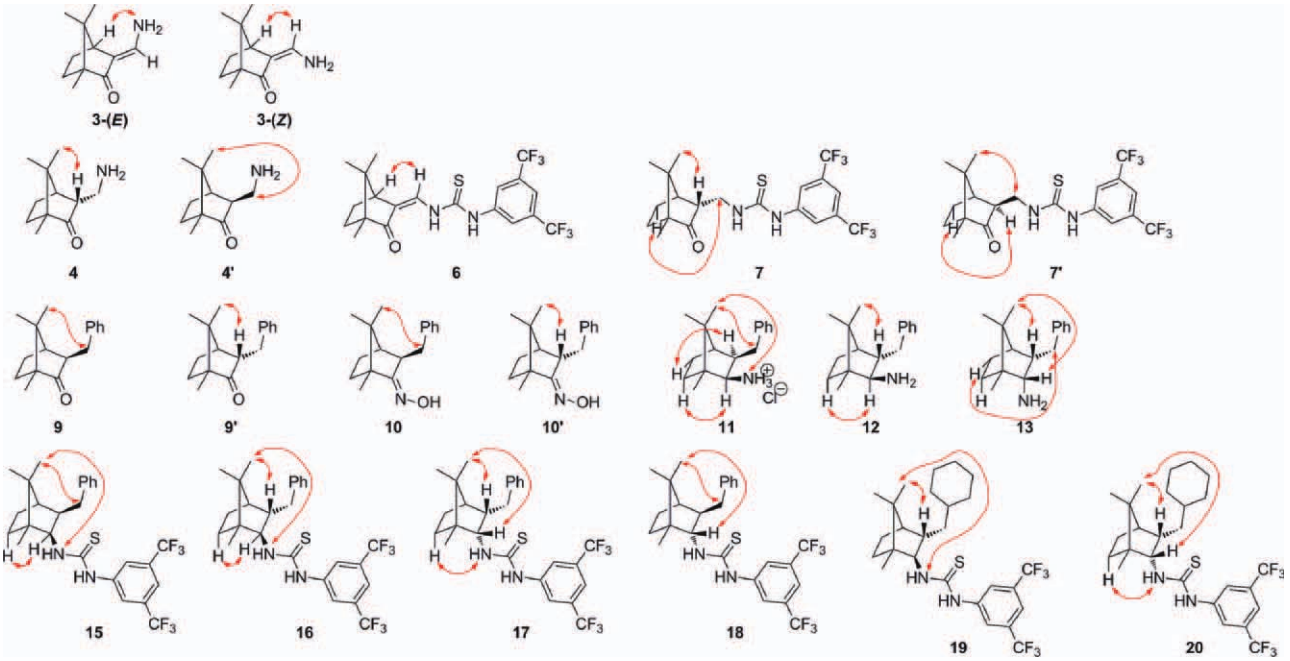


Fig. 3. Key NOEs observed in NOESY spectra of compounds **3**, **4**/**4′**, **6**, **7**/**7′**, **9**/**9′**, **10**/**10′**, **11**-HCl, **12**, **13**, and **15–20** for the determination of configuration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

amines **12**, **13**, and **14** with **5** gave, after chromatographic separation, 2-thiourea derivatives **16**, **17**, and **18** in 17, 12, and 36% yield, respectively. Treatment of the complex mixture of amines **11–13**, **11′–13′** (after the hydrogenation of **10**/**10′** at 90°C) with **5** furnished, after chromatographic separation, 3-benzyl-thiourea derivatives **15**, **16**, and **17** in 5, 20, and 5% yield, respectively, and 3-cyclohexylmethyl-thiourea derivatives **19** and **20** in 10 and 5%, respectively. Thus, all four possible 3-benzyl-thiourea stereoisomers **15–18** have been obtained in analytically pure form (Scheme 3, Table 2).

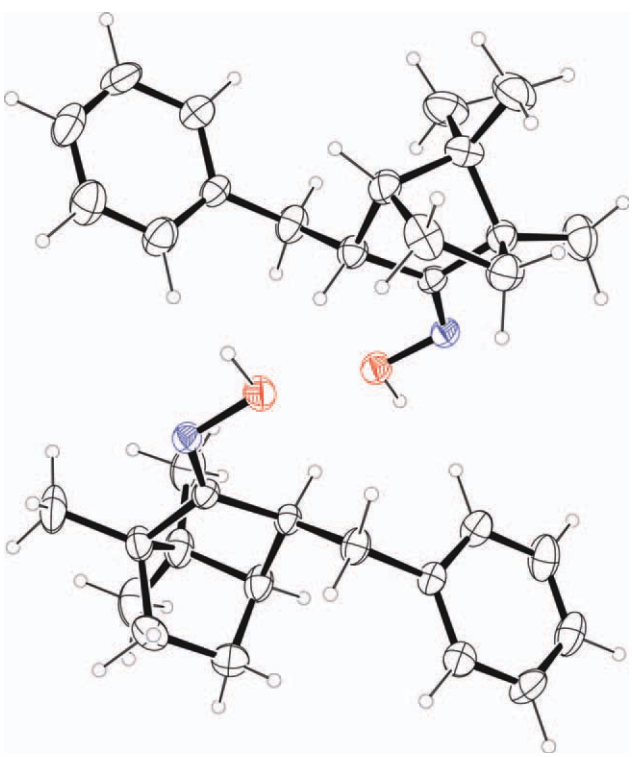


Fig. 4. Ortep drawing of the asymmetric unit consisting of two *C*-3 epimers, compound **10** (top) and **10′** (bottom), respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

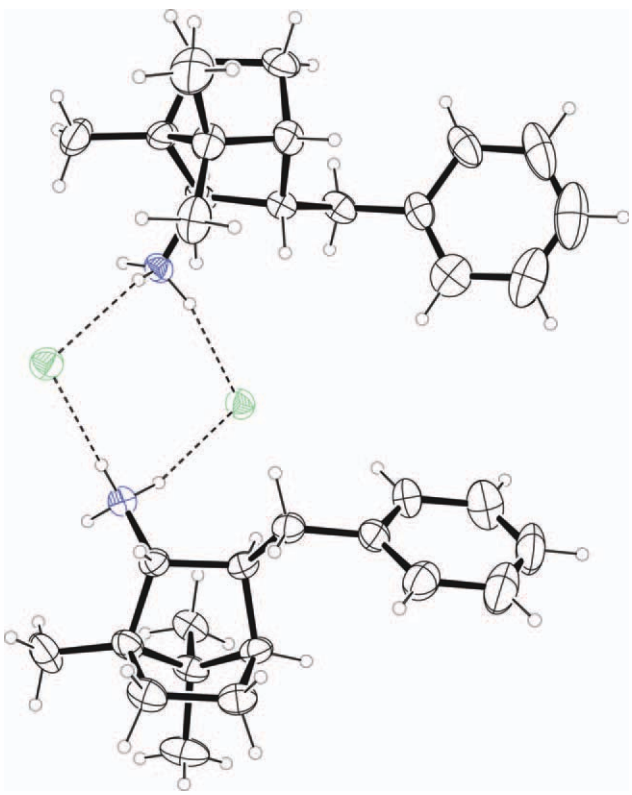


Fig. 5. Ortep drawing of the compound **12**-HCl. The asymmetric unit contains four chloride anions and four protonated molecules of **12** with the same structural formula and absolute configuration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Structure Determination

The structures of compounds **3**[43] and **9/9′**[53,54] and novel compounds **6**, **7/7′**, **11–13** and **15–20** were determined by spectroscopic methods (IR, NMR spectroscopy (^{1}H- and ^{13}C-NMR, DEPT 90 and 135, COSY, HSQC, HMBC, and NOESY experiments), and MS) and by elemental analyses for C, H, and N. Compounds **9/9′**, **11**, **13**, **19**, and **20** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C-NMR and/or EI-HRMS. The structure of amine **14** was established on the basis of the structure of its thiourea derivative **18**. Physical and spectral data for known compounds **2**,[42] **3**,[43] **8**,[41] were in agreement with the literature data.

The (*Z*)-configuration around the C=C bond in the enaminone **3**-(*Z*) and methylene-thiourea **6** was determined on the basis of NOE between H—C(3′) and H—C(4) in the NOESY spectra. Accordingly, the (*E*)-configuration around the C=C bond in the enaminone **3**-(*E*) was determined on the basis of the NOE between NH_2 and H—C(4). Similarly, the configuration(s) in 2- and/or 3-position(s) of compounds **4/4′**, **7/7′**, **9/9′**, **10/10′**, **11**-HCl, **12**, **13**, and **15–20** was/were determined on the basis of NOEs observed in NOESY spectra between the corresponding key proton signals (Fig. 3).

The structures of compounds **10/10′**, **12**-HCl, **16**, and **19** have been confirmed by single crystal X-ray analysis (Figs. 4–7). The configuration of C=N double bond in the solid state in both *exo*- **10** and *endo*-oxime **10′** is (*E*). In the (*E*)-configuration in the solid state, the OH group is accommodated between the two substituents in the *3* position, whereas in the (*Z*)-configuration, the OH group would be near planar with the Me group in position 10 (torsion angle N=C(2)-C(1)-C(10) is ca. 16° in *endo*-isomer **10′** and ca. 25 in *exo*-isomer **10**), which would cause massive 1,5-repulsion[56] (Fig. 4).

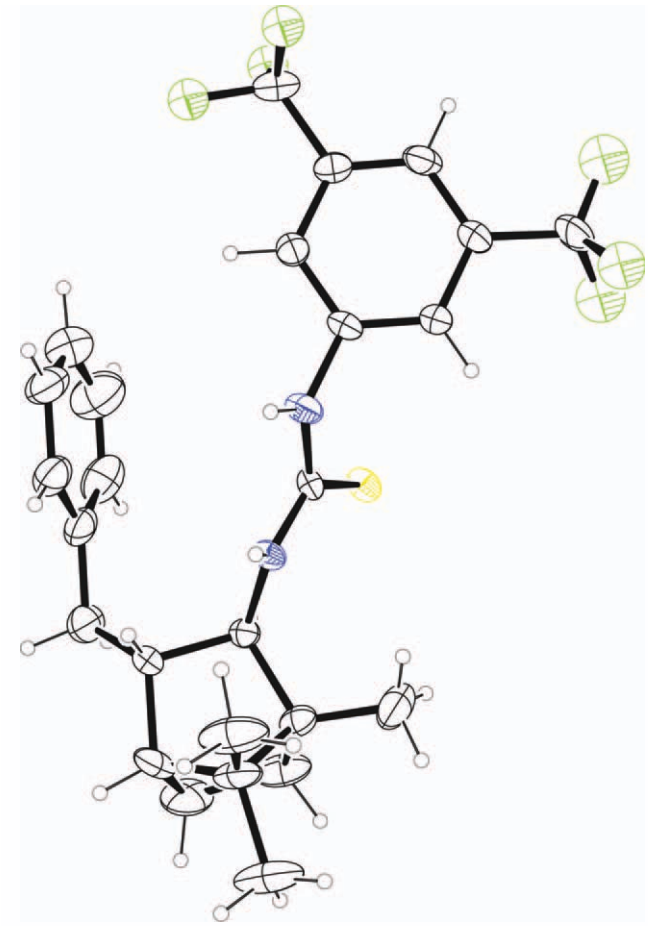


Fig. 6. Ortep drawing of the compound **16**. The asymmetric unit contains two molecules with the same structural formula and absolute configuration. [Color figure can be viewed in the online issue, which is available at wiley onlinelibrary.com.]

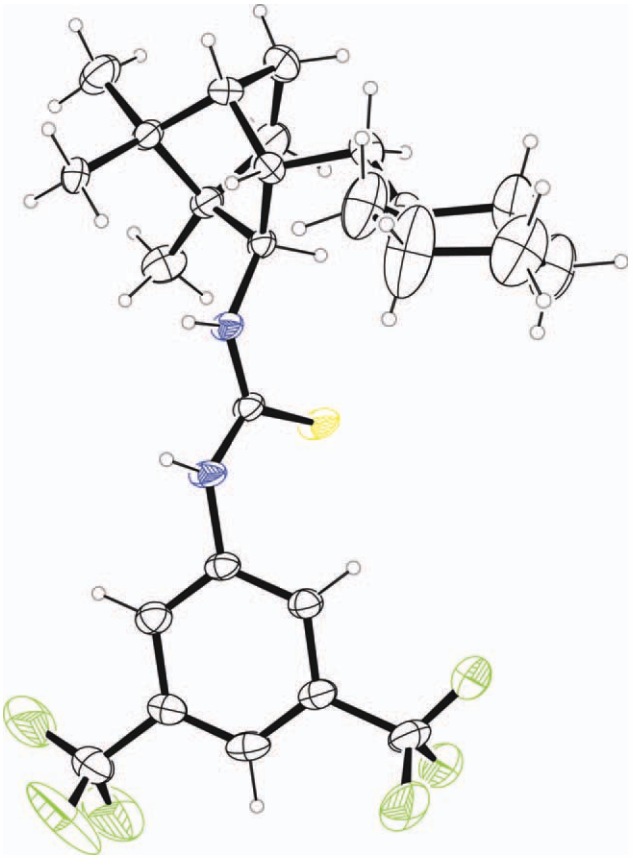


Fig. 7. Ortep drawing of the compound **19**. The asymmetric unit contains three molecules with the same structural formula and absolute configuration. [Color figure can be viewed in the online issue, which is available at wiley onlinelibrary.com.]

CONCLUSIONS

In this preliminary report, new 3-thiourea **6**, **7/7′** and six new 2-thiourea functionalized camphor derivatives **15–20** have been prepared starting from commercially available (+)-camphor (**1**) in three or four and six straightforward steps, respectively, using manipulations at positions 2 and/or 3 of camphor. In a stereo-divergent synthesis all four possible stereoisomers of 3-benzyl-2-thiourea camphor derivatives, compounds **15–18**, have been prepared along with the two corresponding 3-cyclohexylmethyl derivatives **19** and **20**. Structure/configuration of all novel compounds has been carefully characterized using NMR techniques, especially NOESY spectroscopy, and single crystal X-ray crystallography. 3-Thiourea derivatives **6**, **7/7′** are set for further functionalizations. Preparation and testing of these and other potential novel (bi)functional camphor-derived thiourea organocatalysts is an ongoing project results of which will be reported in due time.

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