Synthesis and Structural Characterization of Novel Camphor-derived Amines

UROŠ GROŠELJ,[1]* ALEN SEVŠEK,[1] SEBASTIJAN RIČKO,[1] AMALIJA GOLOBIČ,[1] JURIJ SVETE,[1,2] AND BRANKO STANOVNIK[1,2]
[1]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia*
[2]*EN-FIST Centre of Excellence, Ljubljana, Slovenia*

ABSTRACT Two novel 4-substituted camphidine derivatives **10a**,**b** have been prepared from (+)-camphor (**1**) in five steps, the *Beckmann* rearrangement being the bottleneck of the synthesis. Isoborneol derivative **5b**, formed as a side product during the hydrogenation of arylidene ketone **3b**, under *Beckmann* rearrangement conditions yielded interesting novel rearrangement products **11** and **12**. (1*S*)-(+)-Camphorquinone (**13**) was transformed into diamines **15** and **16** in two steps, the former being cyclized into an imidazoline salt **17**, an *N*-heterocyclic carbene precursor. The structures of all novel compounds have been meticulously characterized using NMR techniques and/or single crystal X-ray analysis. *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: camphor; enaminone methodology; *Beckmann* rearrangement; camphor-derived amines; NHC ligand precursor

INTRODUCTION

Camphor is one of nature's privileged scaffolds. It is readily available in both enantiomeric forms. It undergoes a wide variety of chemical transformations that, at first glance, functionalize inactivated positions.[1,2] All of the above makes camphor a very desirable starting material for the preparation of a wide variety of products ranging from natural products[1,2] to chiral auxiliaries,[3,4] ligands in asymmetric synthesis,[5–10] organocatalysts,[11–21] NMR shift reagents,[22] and others.

Nevertheless, the literature search (*SciFinder Scholar*) for 4-substituted-1,8,8-trimethyl-3-azabicyclo[3.2.1]octanes of type **A** (4-substituted camphidine derivatives) revealed only two hits,[23–26] whereas for 4-substituted-1,8,8-trimethyl-3-azabicyclo [3.2.1]octan-2-ones of type **B** (4-substituted α-camphidone derivatives) gave 11 hits. The latter could be regarded as precursors of the former transformed *via* a reductive elaboration. The parent α-camphidone[24,27,28] (**B**; R = H) was prepared in useful yields from camphor *via* the *Beckmann* rearrangement[29,30] or from camphoric imide[26] (**B**; R = O). Parent camphidine[27] (**A**; R = H) was prepared in satisfactory yields from camphene[31] and from camphoric imide[32] (**B**; R = O). Similarly, several *N*-substituted camphidine derivatives have been prepared from the corresponding camphor imides *via* reduction with $LiAlH_4$[33] (Fig. 1).

For the isomeric 4-substituted-1,8,8-trimethyl-2-azabicyclo [3.2.1]octanes of type **C** and 4-substituted-1,8,8-trimethyl-2-azabicyclo[3.2.1]octan-3-ones of type **D**, the literature search gave no results except of one for the *N*-substituted derivative of type **D**.[34] The unsubstituted lactam[35] (**D**; R = H) is preparatively accessible[36,37] and can be reductively converted to the corresponding cyclic amine[35,38] (**C**; R = H). The parent lactam (**D**; R = H) can be easily functionalized in position *4*, which is not the case for the isomeric lactam (**B**; R = H). Compounds of types **A** and **C** could potentially be used as catalysts in covalent organocatalysis[39] (Fig. 1).

In this report, the results of a *Beckmann* rearrangement study of 3-arylmethyl substituted camphor derivatives are disclosed, together with the reductive transformation of a camphorquinone-derived diimine. Along the way, several novel cyclic and acyclic camphor-derived amines have been prepared, accompanied by interesting rearrangement products.

EXPERIMENTAL

Materials and Methods

Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100—Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and at 75.5 MHz for ^{13}C nucleus, and Bruker UltraShield 500 plus (Bruker, Billerica, MA, USA) at 500 MHz for ^{1}H and at 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 (Waters, Milford, MA, USA) and Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA), and IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, MA, USA). Microanalyses were performed on a Perkin-Elmer CHN Analyser 2400 II (PerkinElmer, Waltham, MA, USA). Catalytic hydrogenations were performed in a Parr Pressure Reaction Hydrogenation Apparatus (Moline, IL, USA). Column chromatography was performed on silica gel (silica gel 60 (Sigma-Aldrich, St. Louis, MO, USA), particle size: 0.035–0.070 mm). Medium-pressure liquid chromatography (MPLC) was performed with Büchi Flash Chromatography System (BUCHI Labortechnik AG, Flawil, Switzerland) (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 [12–15 μm] (Merck, KGaA, Darmstadt, Germany)); column dimensions (wet filled): 22 × 460 mm, 36 × 460 mm, and 40 × 460 mm; backpressure: 10–20 Bar; detection: UV 254 nm.

Additional Supporting Information may be found in the online version of this article.

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*Correspondence to: Uroš Grošelj, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva cesta 5, PO Box 537, 1000 Ljubljana, Slovenia.
E-mail: uros.groselj@fkkt.uni-lj.si

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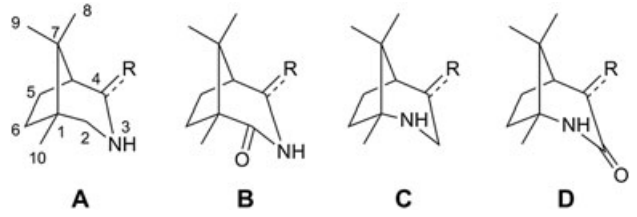


Fig. 1. *SciFinder Scholar* search (Substructure search, R = any atom except H) as of January 2012 for systems **A–D**. Stereoisomers of the some compound are regarded as a single hit.

(+)-Camphor (**1**), (1*S*)-(+)-camphorquinone (**13**), *tert*-butoxy bis (dimethylamino)methane, anhydrous dimethylformamide, *Grignard* reagents, hydroxylamine-*O*-sulfonic acid, and 10% palladium on charcoal are commercially available (Sigma-Aldrich, St. Louis, MO, USA). Compounds **2**,[14] **3a**,[15] **3b**,[15] and **4a**/**4a′**[14] were prepared following the literature procedures.

Source of chirality: (+)-camphor (**1**) (Sigma-Aldrich), product number 21300, purum, natural, 97.0% (GC, sum of enantiomers), $[\alpha]_D^{20} = +42.5 \pm 2.5$ (c = 10, EtOH), mp 176–180 °C, ee not specified, and (1*S*)-(+)-camphorquinone (**13**) (Aldrich), product number 272078, 99%, $[\alpha]_D^{20} = +100$ (c = 1.9, PhMe); mp 197–201 °C, ee not specified.

Syntheses

General procedure for the preparation of arylidene compounds 3c,d. To a solution of enaminone **2** in anhydrous tetrahydrofuran (THF) under argon cooled to 0 °C was added ArlMgBr, and the resulting mixture was stirred at 0 °C for 30 min and 4 h at room temperature. The reaction mixture was quenched with NH_4Cl (aq. sat.), volatile components were evaporated *in vacuo* (the bulk of THF), and the residue was extracted with CH_2Cl_2 (3 × 70 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered, and volatile components were evaporated *in vacuo*. The residue was purified by column chromatography. Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give the arylidene products **3c**,**d**.

(1*R*,4*S*,3*E*)-3-(3,5-Dimethylbenzylidene)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (3c). **2** (4.15 g, 20 mmol); THF (10 ml); (3,5-dimethylphenyl) magnesium bromide (50 ml, 0.5 M, 25 mmol); column chromatography (EtOAc/petroleum ether = 1:20). Yield: 4.63 g (86%) of colorless oil. $[\alpha]_D^{r.t.} = +365.9$ (c = 0.26, $CHCl_3$). ($C_{19}H_{24}O$ requires: C, 85.03; H, 9.01. Found C, 84.38; H, 9.36.); EI-HRMS: *m/z* = 269.1908 (MH^+); $C_{19}H_{25}O$ requires: *m/z* = 269.1905 (MH^+); ν_{max} (NaCl) 2960, 2924, 2871, 1727, 1642, 1600, 1474, 1450, 1389, 1371, 1325, 1268, 1252, 1152, 1106, 1065, 1038, 1014, 934, 866, 844 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80 (s, Me); 1.00 (s, Me); 1.02 (s, Me); 1.46–1.65 (m, 3H); 1.72–1.83 (m, 1H); 2.12–2.24 (m, 1H); 2.34 (s, 6H, 2×Me); 3.10 (d, *J* = 4.2 Hz, H-C(4)); 6.98 (s, CH); 7.08 (s, 2H of Arl); 7.18 (s, 1H of Arl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 9.5, 18.5, 20.7, 21.5, 26.2, 30.9, 46.8, 49.4, 57.2, 127.8, 128.0, 130.7, 135.8, 138.3, 141.9, 208.4.

(1*R*,4*S*,4*E*)-1,7,7-Trimethyl-3-(phenanthren-9-ylmethylene)bicyclo [2.2.1]heptan-2-one (3d). **2** (4.79 g, 23.11 mmol); THF (50 ml); phenanthren-9-ylmagnesium bromide (50 ml, 0.5 M in THF, 25 mmol); column chromatography (EtOAc/petroleum ether = 1:30). Yield: 2.25 g (28%) of yellowish solid; mp 128.3–132.2 °C. $[\alpha]_D^{r.t.} = +211.5$ (c = 0.19, CH_2Cl_2). ($C_{25}H_{24}O$ requires: C, 88.20; H, 7.11. Found C, 88.28; H, 7.06.); EI-HRMS: *m/z* = 341.1894 (MH^+); $C_{25}H_{25}O$ requires: *m/z* = 341.1905 (MH^+); ν_{max} (KBr) 3479, 2958, 2923, 2869, 1720, 1638, 1493, 1449, 1389, 1370, 1322, 1152, 1109, 1069, 914, 765, 743, 724 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (s, Me); 0.98 (s, Me); 1.08 (s, Me); 1.57–1.89 (m, 3H of CH_2); 2.14–2.26 (m, 1H of CH_2); 2.98 (d, *J* = 4.2 Hz, H-C(4)); 7.58–7.73 (m, 5H of Arl); 7.87–7.92 (m, H-C(3′), 1H of Arl); 8.10 (dd, *J* = 1.3; 8.1 Hz, 1H of Arl); 8.66–8.76 (m, 2H of Arl). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 9.5, 18.3, 20.8, 26.7, 30.7, 46.7, 49.3, 58.0, 122.7, 123.2, 125.2, 126.98, 127.01, 127.02, 127.3, 127.7, 129.0, 130.5, 130.6, 131.1, 131.3, 131.7, 144.9, 207.8.

General procedure for the hydrogenation of arylidene compounds 3b–d

To a solution of arylidene compound **3** in anhydrous EtOH (150 ml) under argon was added Pd–C, the reaction vessel was flushed with H_2, and the reaction mixture was hydrogenated in a *Paar* hydrogenator (P = 4 Bar) at room temperature for t_1 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*, and the residue was purified by MPLC. Fractions containing the separated products were combined, and volatile components were evaporated *in vacuo* to give ketones **4**/**4′** and alcohol **5**, respectively.

(1*R*,3*R*,4*R*)-3-(3,5-Bis(trifluoromethyl)benzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4b), (1*R*,3*S*,4*R*)-3-(3,5-bis(trifluoromethyl)benzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4b′), and (1*R*,2*R*,3*R*,4*R*)-3-(3,5-bis(trifluoromethyl)benzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (5b). **3b** (3.78 g, 10.05 mmol); Pd–C (10%, 80 mg); t_1 = 10 min; crude products: **4b**:**4b′**:**5b** = 55:18:27, 100% conversion; MPLC (EtOAc/petroleum ether = 1:30).

4b: Elutes first from the column. Yield: 1.17 g (31%) of yellowish solid; mp 70.2–74.6 °C. $[\alpha]_D^{r.t.} = +69.4$ (c = 0.17, CH_2Cl_2). ($C_{19}H_{20}F_6O$ requires: C, 60.32; H, 5.33. Found C, 60.35; H, 5.27.); EI-HRMS: *m/z* = 379.1499 (MH^+); $C_{19}H_{21}F_6O$ requires: *m/z* = 379.1497 (MH^+); ν_{max} (KBr) 3453, 3050, 2959, 2892, 2877, 2359, 2342, 1735, 1625, 1470, 1449, 1380, 1354, 1326, 1313, 1279, 1173, 1125, 1099, 1019, 925, 896, 845, 727, 710, 682 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.96 (s, Me); 0.97 (s, Me); 0.98 (s, Me); 1.26–1.33 (m, 1H of CH_2); 1.50–1.57 (m, 1H of CH_2); 1.65–1.72 (m, 1H of CH_2); 1.95 (d, *J* = 4.0 Hz, H-C(4)); 1.96–2.04 (m, 1H of CH_2); 2.12 (dd, *J* = 4.2; 9.8 Hz, H-C(3)); 2.68 (dd, *J* = 9.8; 14.5 Hz, Ha-C (3′)); 3.33 (dd, *J* = 4.2; 14.5 Hz, Hb-C(3′)); 7.66 (s, 2H of Arl); 7.74 (s, 1H of Arl). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 9.5, 20.5, 22.0, 29.2, 29.4, 37.3, 47.0, 47.2, 56.2, 57.8, 120.2–120.5 (m), 123.6 (q, *J* = 272.6 Hz), 129.0, 132.0 (q, *J* = 33.1 Hz), 144.2, 219.2.

4b′: Elutes second from the column. Yield: 490 mg (13%) of yellowish solid; mp 97.3–101.2 °C. $[\alpha]_D^{r.t.} = +45.4$ (c = 0.12, CH_2Cl_2). ($C_{19}H_{20}F_6O$ requires: C, 60.32; H, 5.33. Found C, 60.20; H, 5.37.); EI-HRMS: *m/z* = 379.1482 (MH^+); $C_{19}H_{21}F_6O$ requires: *m/z* = 379.1497 (MH^+); ν_{max} (KBr) 3460, 3045, 2966, 2870, 1737, 1624, 1488, 1454, 1381, 1348, 1274, 1169, 1124, 1106, 1047, 1006, 928, 901, 844, 742, 732, 708, 682, 658 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.88 (s, Me); 0.95 (s, Me); 1.01 (s, Me); 1.35–1.42 (m, 1H of CH_2); 1.65–1.72 (m, 1H of CH_2); 1.73–1.80 (m, 1H of CH_2); 1.82–1.91 (m, 1H of CH_2); 1.95 (t, *J* = 3.9 Hz, H-C(4)); 2.63–2.71 (m, Ha-C(3′), H-C(3)); 3.24 (q, *J* = 9.9 Hz, Hb-C(3′)); 7.67 (s, 2H of Arl); 7.73 (s, 1H of Arl). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 9.7, 19.4, 19.8, 20.6, 31.2, 33.0, 46.1, 46.2, 51.5, 59.0, 120.4–120.7 (m), 123.6 (q, *J* = 272.6 Hz), 129.0, 132.0 (q, *J* = 33.1 Hz), 143.2, 219.0.

5b: Elutes third from the column. Yield: 983 mg (26%) of yellowish oil. $[\alpha]_D^{r.t.} = +64.9$ (c = 0.25, CH_2Cl_2). ($C_{19}H_{22}F_6O$ requires: C, 60.00; H, 5.83. Found C, 60.29; H, 6.00.); EI-HRMS: *m/z* = 379.1485 ($M-1)^+$; $C_{19}H_{21}F_6O$ requires: *m/z* = 379.1497 ($M-1)^+$; ν_{max} (NaCl) 3635, 3496, 2955, 2360, 1796, 1736, 1622, 1480, 1464, 1379, 1173, 1134, 1046, 926, 894, 842, 706, 682 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.82 (s, Me); 0.94 (s, Me); 0.96–1.01 (m, 1H of CH_2); 1.02–1.08 (m, 1H of CH_2); 1.23 (s, Me); 1.46–1.53 (m, 1H of CH_2); 1.55 (d, *J* = 3.8 Hz, H-C(4)); 1.62 (d, *J* = 4.2 Hz, OH); 1.66–1.74 (m, 1H of CH_2); 2.06 (q, *J* = 7.9 Hz, H-C (3)); 2.83 (dd, *J* = 7.5; 14.4 Hz, Ha-C(3′)); 3.29 (dd, *J* = 8.1; 14.4 Hz, Hb-C (3′)); 3.76 (dd, *J* = 4.2; 8.1 Hz, H-C(2)); 7.68 (s, 1H of Arl); 7.69 (s, 2H of Arl). ^{1}H-NMR ($CDCl_3$ + D_2O, 300 MHz): δ 0.83 (s, Me); 0.94 (s, Me); 0.97–1.10 (m, 2H of CH_2); 1.23 (s, Me); 1.45–1.54 (m, 1H of CH_2); 1.55 (d, *J* = 4.2 Hz, H-C(4)); 1.64–1.75 (m, 1H of CH_2); 2.06 (deg q, *J* = 7.7 Hz, H-C(3)); 2.83 (dd, *J* = 7.5; 14.4 Hz, Ha-C(3′)); 3.30 (dd, *J* = 8.1; 14.4 Hz, Hb-C(3′)); 3.75 (d, *J* = 8.2 Hz, H-C(2)); 7.69 (s, 3H of Arl). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 11.7, 21.7, 22.2, 30.0, 33.5, 36.3, 47.1, 50.1, 50.5, 52.1, 81.7, 119.6–119.9 (m), 123.9 (q, *J* = 272.5 Hz), 129.3, 131.6 (q, *J* = 32.9 Hz), 146.4.

(1*R*,3*R*,4*R*)-3-(3,5-Dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4c), (1*R*,3*S*,4*R*)-3-(3,5-dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4c′), and (1*R*,2*R*,3*R*,4*R*)-3-(3,5-dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (5c). **3c** (4.39 g, 16.35 mmol); Pd–C (10%, 500 mg); t_1 = 20 min; crude products: **4c**:**4c′**:**5c** = 68:24:8, 100% conversion; MPLC (EtOAc/petroleum ether = 1:30).

4c/4c′: Elute first from the column. **4c/4c′** = 75:25. Yield: 3.46 g (78%) of colorless oil. $[\alpha]_D^{r.t.}$ = +31.8 (c = 0.33, $CHCl_3$). ($C_{19}H_{26}O$ requires: C, 84.39; H, 9.69. Found C, 83.67; H, 9.97.); EI-HRMS: *m/z* = 271.2065 (MH^+); $C_{19}H_{27}O$ requires: *m/z* = 271.2062 (MH^+); ν_{max} (NaCl) 2960, 2873, 1741, 1605, 1447, 1392, 1374, 1323, 1265, 1104, 1040, 1019, 943, 851, 712 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) for **4c**: δ 0.93 (s, Me); 0.94 (s, Me); 0.95 (s, Me); 1.22–1.28 (m, 1H of CH_2); 1.45–1.52 (m, 1H of CH_2); 1.59–1.66 (m, 1H of CH_2); 1.89–1.96 (m, 1H of CH_2); 1.98 (d, *J* = 4.0 Hz, H-C(4)); 2.13 (dd, *J* = 3.7; 10.5 Hz, H-C(3)); 2.29 (s, 2×Me); 2.43 (dd, *J* = 10.5; 14.0 Hz, Ha-C(3′)); 3.16 (dd, *J* = 3.6; 14.1 Hz, Hb-C(3′)); 6.81 (s, 2H of Arl); 6.83 (s, 1H of Arl). ^{1}H-NMR (500 MHz, $CDCl_3$) for **4c′**: δ 0.85 (s, Me); 0.92 (s, Me); 0.96 (s, Me); 1.31–1.38 (m, 1H of CH_2); 1.66–1.73 (m, 1H of CH_2); 1.74–1.80 (m, 2H of CH_2); 2.28 (s, 2×Me); 2.65–2.71 (m, H-C(3)); 3.09 (dd, *J* = 4.3; 14.3 Hz, Hb-C(3′)). ^{13}C-NMR (75 MHz, $CDCl_3$) for **4c**: δ 9.6, 20.6, 21.4, 22.1, 29.4, 29.5, 37.3, 46.7, 46.9, 57.0, 57.7, 126.6, 127.8, 138.0, 141.4, 220.6. ^{13}C-NMR (75 MHz, $CDCl_3$) for **4c′**: δ 9.7, 19.4, 19.7, 20.5, 31.1, 32.7, 45.8, 45.9, 52.0, 58.8, 126.4, 127.8, 137.9, 140.4, 220.4.

5c: Elutes second from the column. Yield: 193 mg (4%) of colorless oil. $[\alpha]_D^{r.t.}$ = +16.7 (c = 0.20, $CHCl_3$). EI-HRMS: *m/z* = 295.2029 (MNa^+); $C_{19}H_{28}ONa$ requires: *m/z* = 295.2038 (MNa^+); ν_{max} (NaCl) 3499, 2950, 1735, 1605, 1477, 1460, 1388, 1370, 1280, 1095, 1048, 848, 698 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.80 (s, Me); 0.92 (s, Me); 0.95–1.08 (m, 2H of CH_2); 1.24 (s, Me); 1.43–1.50 (m, 1H of CH_2); 1.55 (d, *J* = 3.8 Hz, H-C(4)); 1.58 (d, *J* = 3.9 Hz, OH); 1.63–1.70 (m, 1H of CH_2); 2.10 (q, *J* = 8.1 Hz, H-C(3)); 2.29 (s, 2×Me); 2.69 (dd, *J* = 8.1; 14.2 Hz, Ha-C(3′)); 3.02 (dd, *J* = 8.1; 14.2 Hz, Hb-C(3′)); 3.76 (dd, *J* = 3.6; 8.0 Hz, H-C(2)); 6.81 (s, 1H of Arl); 6.86 (s, 2H of Arl). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.9, 21.5, 21.9, 22.3, 30.1, 33.8, 36.1, 47.1, 49.97, 50.03, 52.0, 82.0, 126.8, 127.4, 137.9, 143.2.

(1*R*,3*R*,4*R*)-1,7,7-Trimethyl-3-(phenanthren-9-ylmethyl)bicyclo[2.2.1]heptan-2-one (4d) and (1*R*,3*S*,4*R*)-1,7,7-trimethyl-3-(phenanthren-9-ylmethyl)bicyclo[2.2.1]heptan-2-one (4d′). **3d** (1.69 g, 4.93 mmol); Pd–C (10%, 150 mg); t_1 = 60 min; 100% conversion; MPLC (EtOAc/petrol ether = 1:30). **4d**:**4d′** = 72:28. Yield: 1.48 g (87%) of white solid; mp 49.2–62.0 °C. $[\alpha]_D^{r.t.}$ = +55.8 (c = 0.10, CH_2Cl_2). ($C_{25}H_{26}O$ requires: C, 87.68; H, 7.65. Found C, 87.42; H, 7.84.); EI-HRMS: *m/z* = 343.2061 (MH^+); $C_{25}H_{27}O$ requires: *m/z* = 343.2062 (MH^+); ν_{max} (KBr) 3061, 2957, 2931, 2874, 2365, 2336, 1738, 1607, 1487, 1448, 1265, 1016, 887, 747, 668 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) for **4d**: δ 0.98 (s, Me); 0.99 (s, Me); 1.09 (s, Me); 1.10–1.19 (m, 1H of CH_2); 1.42–1.52 (m, 1H of CH_2); 1.59–1.70 (m, 1H of CH_2); 1.84–1.96 (m, 1H of CH_2); 2.10 (d, *J* = 4.0 Hz, H-C(4)); 2.32 (dd, *J* = 2.9; 9.9 Hz, H-C(3)); 2.90 (dd, *J* = 10.0; 14.6 Hz, Ha-C(3′)); 3.85 (dd, *J* = 2.7; 14.4 Hz, Hb-C(3′)); 7.53–7.71 (m, 5H of Arl); 7.80–7.87 (m, 1H of Arl); 8.23–8.29 (m, 1H of Arl), 8.63–8.79 (m, 2H of Arl). ^{1}H-NMR ($CDCl_3$, 300 MHz) for **4d′**: δ 0.81 (s, Me); 0.97 (s, 2×Me); 1.72–1.82 (m, 1H of CH_2); 1.97–2.01 (m, H-C(4)); 2.93–3.01 (m, H-C(3), Ha-C(3′)); 3.68–3.79 (m, Hb-C(3′)); 8.16–8.23 (m, 1H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$) for **4d**: δ 9.7, 20.6, 22.3, 29.2, 29.4, 35.6, 47.2, 47.3, 55.2, 57.9, 122.6, 123.4, 124.7, 126.3, 126.5, 126.8, 126.9, 127.1, 128.2, 130.1, 130.8, 131.1, 131.8, 135.6, 221.0. ^{13}C-NMR (126 MHz, $CDCl_3$) for **4d′**: δ 9.8, 15.5, 19.5, 19.7, 20.6, 30.2, 31.3, 46.0, 46.3, 50.6, 59.0, 66.0, 122.6, 123.5, 124.4, 126.5, 126.7, 127.0, 129.9, 130.98, 131.01, 131.8, 134.6, 220.8.

(1*R*,3*R*,4*R*,2*E*)-3-(3,5-Dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime (6) and (1*R*,3*S*,4*R*,2*E*)-3-(3,5-dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime (6′). To a solution of **4c** (1.35 g, 5 mmol; d.e. = 50%) in EtOH (30 ml) were added pyridine (4.04 ml, 50 mmol) and NH_2OH–HCl (4.86 g, 70 mmol), and the resulting mixture was heated under reflux for 48 h. Volatile components were evaporated *in vacuo*, and to the residue, H_2O was added. The resulting precipitate was collected by filtration to give the product as a mixture of epimers **6**/**6′**. **6**:**6′** = 71:29. Yield: 1.37 g (96%) of white solid; mp 132–146 °C. $[\alpha]_D^{r.t.}$ = +26.0 (c = 0.23, $CHCl_3$). ($C_{19}H_{27}NO$ requires: C, 79.95; H, 9.53; N, 4.91. Found C, 80.17; H, 9.76; N, 4.88.); EI-HRMS: *m/z* = 286.2180 (MH^+); $C_{19}H_{28}NO$ requires: *m/z* = 286.2171 (MH^+); ν_{max} (KBr) 3443, 3013, 2959, 2928, 1632, 1606, 1474, 1456, 1438, 1391, 1372, 1076, 930, 847, 738, 706, 673 cm^{-1} ^{1}H-NMR (500 MHz, $CDCl_3$) for **6**: δ 0.90 (s, Me); 1.03 (s, Me); 1.06 (s, Me); 1.11–1.17 (m, 1H of CH_2); 1.40–1.47 (m, 1H of CH_2); 1.61–1.70 (m, 1H of CH_2); 1.74–1.79 (m, 1H of CH_2); 1.80 (d, *J* = 3.5 Hz, H-C(4)); 2.30 (s, 2×Me); 2.48 (dd, *J* = 10.0; 13.8 Hz, Ha-C(3′)); 2.67 (dd, *J* = 3.1; 9.9 Hz, H-C(3)); 3.73 (dd, *J* = 2.9; 13.9 Hz, Hb-C(3′)); 6.84 (s, 1H of Arl); 6.89 (s, 2H of Arl); 7.59 (s, OH). ^{1}H-NMR (500 MHz, $CDCl_3$) for **6′**: δ 0.81 (s, Me); 0.89 (s, Me); 0.97 (s, Me); 1.47–1.53 (m, 1H of CH_2); 2.29 (s, 2×Me); 2.42 (dd, *J* = 11.8; 14.3Hz, Ha-C(3′)); 3.17–3.24 (m, H-C(3)); 3.84 (dd, *J* = 4.2; 14.3Hz, Hb-C(3′)); 6.82 (s, 1H of Arl); 6.86 (s, 2H of Arl). ^{13}C-NMR (75 MHz, $CDCl_3$) for **6** and **6′**: δ 11.6, 12.1, 19.1, 19.3, 20.1, 21.0, 21.5, 22.6, 29.2, 32.1, 32.2, 33.5, 36.9, 43.1, 46.5, 47.5, 48.26, 48.33, 50.7, 53.1, 53.4, 126.8, 127.0, 127.57, 127.63, 137.8, 137.9, 141.0, 142.7, 170.1, 172.3.

(1*R*,3*R*,4*R*,2*E*)-3-(3,5-Dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *O*-acetyl oxime (7) and (1*R*,3*S*,4*R*,2*E*)-3-(3,5-dimethylbenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *O*-acetyl oxime (7′). A solution of **6** (57 mg, 0.2 mmol, d.e. = 42%) in Ac_2O (0.5 ml) was heated at 80 °C for 20 h. Volatile components were evaporated *in vacuo*. The residue was dissolved and evaporated four times with PhMe (2 ml) and four times with CH_2Cl_2 (2 ml) to azeotropically remove all traces of Ac_2O. The crude product **7**/**7′** was characterized without further purification. **7**:**7′** = 71:29. Yield: full conversion; colorless oil. EI-HRMS: *m/z* = 328.2286 (MH^+); $C_{21}H_{30}NO_2$ requires: *m/z* = 328.2277 (MH^+); ν_{max} (NaCl) 2962, 2874, 1765, 1651, 1606, 1448, 1391, 1365, 1206, 1042, 1001, 954, 922, 877, 851 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) for **7**: δ 0.93 (s, Me); 1.06 (s, Me); 1.15 (s, Me); 1.15–1.23 (m, 1H of CH_2); 1.46–1.56 (m, 1H of CH_2); 1.65–1.81 (m, 2H of CH_2); 1.84 (d, *J* = 3.6 Hz, H-C(4)); 2.13 (s, OAc); 2.31 (s, 2×Me); 2.59 (dd, *J* = 9.3; 13.9 Hz, Ha-C(3′)); 2.72 (dd, *J* = 3.2; 9.3 Hz, H-C(3)); 3.42 (dd, *J* = 3.1; 13.9 Hz, Hb-C(3′)); 6.82 (s, 1H of Arl); 6.85 (s, 2H of Arl). ^{1}H-NMR (300 MHz, $CDCl_3$) for **7′**: δ 0.84 (s, Me); 1.08 (s, Me); 2.13 (s, OAc); 2.30 (s, 2×Me); 2.49 (dd, *J* = 11.3; 14.3 Hz, Ha-C(3′)); 3.21–3.30 (m, H-C(3)); 3.53 (dd, *J* = 4.6; 14.4 Hz, Hb-C(3′)). ^{13}C-NMR (75 MHz, $CDCl_3$) for **7** and **7′**: δ 11.4, 11.9, 19.0, 19.2, 19.88, 19.94, 20.8, 21.5, 22.6, 28.9, 31.8, 33.0, 33.3, 38.2, 44.1, 46.5, 47.8, 48.5, 48.7, 51.5, 54.3, 54.6, 126.5, 126.6, 127.9, 128.0, 138.06, 138.15, 140.0, 141.8, 168.9, 169.0, 178.0, 180.3.

3-(3,5-Dimethylphenyl)-2-(2,3,3-trimethylcyclopent-1-en-1-yl) propanenitrile (8). To a solution of **6** (57 mg, 0.2 mmol, d.e. = 42%) in a mixture of TFA (120 μl) and toluene (80 μl) was added 2,4,6-trichloro-1,3,5-triazine (2.9 mg), and the resulting mixture was heated at 70 °C for 1 h. Volatile components were evaporated *in vacuo*, and the residue was purified by column chromatography (EtOAc/petroleum ether = 1:100). Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give **8** in approximately 85% purity. Yield: 27 mg (43%, $\omega \approx 0.85$) of colorless oil. EI-HRMS: *m/z* = 268.2065 (MH^+); $C_{19}H_{26}N$ requires: *m/z* = 268.2065 (MH^+); ν_{max} (NaCl) 3015, 2955, 2934, 2863, 2238, 1767, 1660, 1607, 1459, 1379, 1361, 1207, 1163, 851, 704 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.87 (s, Me); 0.96 (s, Me); 1.23 (t, *J* = 2.0 Hz, Me); 1.62–1.71 (m, H_2-C(4)); 2.27 (s, 2×Me); 2.29–2.36 (m, Ha-C(5)); 2.36–2.44 (m, Hb-C(5)); 2.76 (dd, *J* = 8.4; 13.3 Hz, Ha-C(2′)); 3.00 (dd, *J* = 7.0; 13.3 Hz, Hb-C(2′)); 3.61 (dd, *J* = 7.1; 8.2 Hz, H-C(1′)); 6.77 (s, 2H of Arl); 6.87 (s, 1H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 9.6, 21.4, 26.26, 26.32, 30.1, 33.2, 37.9, 38.5, 47.5, 120.8, 125.9, 127.0, 128.8, 137.0, 138.1, 145.1.

General procedure for the Beckmann rearrangement of ketones 4/4′ with hydroxylamine-O-sulfonic acid

A mixture of ketones **4/4′** and NH_2OSO_3H in AcOH was heated under reflux for t_1 h. Volatile components were evaporated *in vacuo*. The residue was dissolved/suspended in CH_2Cl_2 and carefully washed with $NaHCO_3$. Organic phase was dried over anhydrous Na_2SO_4 and filtered, and volatile components were evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:2). Fractions containing the amide product **9/9′** were combined and volatile components evaporated *in vacuo*. The residue was re-purified by MPLC. Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give **9/9′**.

(1*R*,4*S*,5*S*)-4-Benzyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (9a). 4a (2.18 g, 9 mmol, d.e. = 32%); NH_2OSO_3H (2.8 g, 24.76 mmol); AcOH (50 ml); t_1 = 9 h; CH_2Cl_2 (300 ml); $NaHCO_3$ (100 ml, aq. sat.); column chromatography (EtOAc/petroleum ether = 1:2); MPLC (EtOAc/petroleum ether = 1:2). Yield: 189 mg (8%) of dirty white solid; mp 180.1–180.3 °C (CH_2Cl_2/*n*-heptane). $[\alpha]_D^{r.t.} = -88.7$ (c = 0.13, CH_2Cl_2). ($C_{17}H_{23}NO$ requires: C, 79.33; H, 9.01; N, 5.44. Found C, 79.52; H, 9.30; N, 5.44.); EI-HRMS: m/z = 258.1846 (MH^+); $C_{17}H_{24}NO$ requires: m/z = 258.1858 (MH^+); ν_{max} (KBr) 3198, 3080, 2974, 2961, 2943, 2866, 1655, 1602, 1495, 1476, 1454, 1403, 1368, 1345, 1276, 1114, 820, 739, 701 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.96 (s, Me); 1.01 (s, Me); 1.08 (s, Me); 1.70–2.04 (m, 2×CH_2, H-C(5)); 2.71 (d, J = 7.3 Hz, H_2-C(4′)); 3.73 (td, J = 2.7; 7.2 Hz, H-C(4)); 5.22 (br s, NH); 7.14–7.35 (m, Ph). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.5, 19.5, 20.7, 23.4, 37.3, 39.9, 43.7, 48.1, 52.0, 55.3, 127.0, 129.0, 129.3, 137.5, 178.8.

(1*R*,4*S*,5*S*)-4-(3,5-Bis(trifluoromethyl)benzyl)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (9b) and (1*R*,4*R*,5*S*)-4-(3,5-bis (trifluoromethyl)benzyl)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (9b′). **4b** (1.12 g, 2.97 mmol); NH_2OSO_3H (1.01 g, 8.91 mmol); AcOH (50 ml); t_1 = 12 h; CH_2Cl_2 (100 ml); $NaHCO_3$ (50 ml, aq. sat.); column chromatography (EtOAc/petroleum ether = 1:2); MPLC (EtOAc/petroleum ether/Et_3N = 80:160:1). **9a**:**9a′** = 77:23. Yield: 200 mg (17%) of pale yellow solid; mp 104.9–124.7 °C. $[\alpha]_D^{r.t.} = -17.3$ (c = 0.11, CH_2Cl_2). ($C_{19}H_{21}F_6NO$ requires: C, 58.01; H, 5.38; N, 3.56. Found C, 58.15; H, 5.26; N, 3.60.); EI-HRMS: m/z = 394.1623 (MH^+); $C_{19}H_{22}F_6NO$ requires: m/z = 394.1606 (MH^+); ν_{max} (KBr) 2975, 1672, 1466, 1376, 1348, 1285, 1242, 1226, 1178, 1142, 1054, 930, 915, 886, 842, 733, 708, 683 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) for **9b**: δ 0.97 (s, Me); 1.04 (s, Me); 1.08 (s, Me); 1.64–2.05 (m, 2×CH_2, H-C(5)); 2.85–2.99 (m, H_2-C(4′)); 3.81 (td, J = 3.0; 7.3 Hz, H-C(4)); 5.97 (s, NH); 7.65 (s, 2H of Arl); 7.79 (s, 1H of Arl). ^{1}H-NMR ($CDCl_3$, 300 MHz) for **9b′**: δ 0.99 (s, Me); 1.10 (s, Me); 1.28 (s, Me); 1.43–1.54 (m, 1H); 2.11–2.25 (m, 1H); 3.00–3.17 (m, H_2-C(4′)); 3.52 (t, J = 7.7 Hz, H-C(4)); 6.20 (s, NH). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) for **9b**: δ 13.3, 19.5, 20.6, 23.3, 37.2, 39.5, 43.8, 47.3, 52.0, 55.2, 121.0–121.3 (m), 123.4 (q, J = 272.3 Hz), 129.4–129.6 (m), 132.3 (q, J = 33.3 Hz), 140.2, 179.3. ^{13}C-NMR ($CDCl_3$, 75.5 MHz) for **9b′**: δ 13.6, 22.0, 24.3, 31.3, 36.8, 42.3, 42.8, 46.7, 52.3, 61.8, 132.3 (q, J = 33.2 Hz), 141.0, 178.5.

(1*R*,4*S*,5*S*)-4-(3,5-Bis(trifluoromethyl)benzyl)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (9b). **4b′** (300 mg, 0.79 mmol); NH_2O-SO_3H (277 mg, 2.38 mmol); AcOH (15 ml); t_1 = 24 h; CH_2Cl_2 (150 ml); (50 ml, aq. sat.); column chromatography (EtOAc/petroleum ether = 1:2); MPLC (EtOAc/petroleum ether = 1:3). Yield: 51 mg (16%) of white solid; mp 138–143 °C. $[\alpha]_D^{r.t.} = -34.4$ (c = 0.09, CH_2Cl_2). ($C_{19}H_{21}F_6NO$ requires: C, 58.01; H, 5.38; N, 3.56. Found C, 57.97; H, 5.23; N, 3.52.); EI-HRMS: m/z = 392.1458 $(M-H)^-$; $C_{19}H_{20}F_6NO$ requires: m/z = 392.1455 $(M-H)^-$; ν_{max} (KBr) 3228, 3097, 2976, 1675, 1621, 1465, 1375, 1348, 1283, 1242, 1226, 1179, 1128, 1054, 914, 887, 876, 843, 815, 733, 708, 682 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.98 (s, Me); 1.04 (s, Me); 1.09 (s, Me); 1.69–1.72 (m, H-C(5)); 1.77–1.83 (m, 1H of CH_2); 1.86–2.03 (m, 3H of CH_2); 2.89 (d, J = 7.3 Hz, H_2C(4′)); 3.80 (td, J = 2.9; 7.2 Hz, H-C(4)); 5.28 (s, NH); 7.64 (s, 2H of Arl); 7.80 (s, 1H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.5, 19.6, 20.7, 23.4, 37.2, 39.7, 43.9, 47.7, 52.1, 55.2, 121.3–121.4 (m), 123.4 (q, J = 272.7 Hz); 129.4–129.6 (m); 132.4 (q, J = 33.4 Hz); 140.1, 179.1.

(1*R*,4*S*,5*S*)-4-Benzyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octane (10a). A solution of **9a** (212 mg, 0.82 mmol) in $LiAlH_4$ (9 ml, 1 M in THF) under argon was heated at 56 °C for 24 h. The reaction mixture was cooled to room temperature and carefully quenched with NaOH (1 M in H_2O). The resulting mixture was extracted with Et_2O (3 × 30 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered, and volatile components were evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc/Et_3N = 40:1). Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give **10a**. Yield: 80 mg (40%) of colorless oil. $[\alpha]_D^{r.t.} = +41.5$ (c = 0.10, CH_2Cl_2). EI-HRMS: m/z = 244.2065 (MH^+); $C_{17}H_{26}N$ requires: m/z = 244.2065 (MH^+); ν_{max} (NaCl) 3311, 3084, 3062, 3027, 2948, 2358, 1942, 1604, 1495, 1454, 1388, 1372, 1332, 1307, 1268, 1172, 1125, 1098, 1082, 1031, 1010, 935, 861, 818, 748, 700, 648, 618 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.75 (s, Me); 0.84 (s, Me); 0.96 (s, Me); 1.37 (d, J = 3.8 Hz, H-C(5)); 1.49–1.77 (m, 4H of CH_2); 1.91 (br s, NH); 2.20 (d, J = 12.1 Hz, Ha-C(2)); 2.46 (dd, J = 7.0; 13.2 Hz, Ha-C(4′)); 2.61 (dd, J = 7.1; 13.2 Hz, Hb-C(4′)); 2.87 (d, J = 12.1 Hz, Hb-C(2)); 3.36 (t, J = 7.0 Hz, H-C(4)); 7.12–7.31 (m, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.3, 18.2, 20.8, 25.3, 35.0, 41.4, 42.8, 43.1, 49.1, 54.9, 55.6, 126.1, 128.5, 129.4, 139.8.

(1*R*,4*S*,5*S*)-4-Benzyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-3-ium chloride (10a-HCl). **10a** (50 mg, 0.2 mmol) was dissolved in anhydrous Et_2O (20 ml), followed by addition of HCl (2 M in EtOAc, 1 ml). After 5 min of stirring at room temperature, volatile components were evaporated *in vacuo* to give **10a-HCl** as a white solid. Mp 159.9–160.0 °C. $[\alpha]_D^{r.t.} = +53.0$ (c = 0.12, CH_2Cl_2). ($C_{17}H_{26}ClN$ requires: C, 72.96; H, 9.36; N, 5.01. Found C, 72.90; H, 9.47; N, 4.95.); EI-HRMS: m/z = 244.2072 (MH^+); $C_{17}H_{26}N$ requires: m/z = 244.2065 (MH^+); ν_{max} (KBr) 3427, 3028, 2955, 2773, 1595, 1466, 1474, 1456, 1439, 1430, 1401, 1371, 1317, 1259, 740, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.85 (s, 2×Me); 0.95 (s, Me); 1.50 (d, J = 6.2 Hz, H-C(5)); 1.67–1.95 (m, 2H of CH_2); 2.10–2.24 (m, 2H of CH_2); 2.81 (d, J = 12.7 Hz, Ha-C(2)); 3.01 (dd, J = 10.9; 13.2 Hz, Ha-C(4′)); 3.10 (d, J = 12.6 Hz, Hb-C(2)); 3.28 (dd, J = 4.0; 13.3 Hz, Hb-C(4′)); 3.73 (dd, J = 3.7; 10.7 Hz, H-C(4)); 7.15–7.32 (m, Ph); 8.78 (br s, NH_2^+). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 16.8, 17.9, 20.0, 23.9, 33.3, 36.9, 41.8, 42.6, 44.9, 51.2, 56.7, 126.9, 128.7, 129.4, 136.3.

(1*R*,4*S*,5*S*)-4-(3,5-Bis(trifluoromethyl)benzyl)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octane (10b). A solution of **9b** (30 mg, 0.076 mmol) in BH_3 × THF (4 ml, 1 M in THF) under argon was heated under refluxed for 24 h. The reaction mixture was cooled to room temperature and carefully quenched with MeOH (2 ml), followed by addition of KOH (200 mg) and H_2O (1 ml). The resulting mixture was stirred at room temperature for 10 min, then diluted with H_2O (10 ml), and extracted twice with CH_2Cl_2 (50 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered, and volatile components were evaporated *in vacuo*. The oily residue was purified by column chromatography ([1] EtOAc/petroleum ether = 1:1 to remove the nonpolar impurities/starting material; [2] EtOAc/Et_3N = 50:1 to elute the product). Fractions containing the amine product were combined, and volatile components evaporated *in vacuo* to give **10b**. Yield: 10 mg (34%) of colorless oil. $[\alpha]_D^{r.t.} = +35.0$ (c = 0.18, CH_2Cl_2). EI-HRMS: m/z = 380.1799 (MH^+); $C_{19}H_{24}F_6N$ requires: m/z = 380.1807 (MH^+); ν_{max} (NaCl) 2952, 2868, 1468, 1452, 1379, 1278, 1174, 1132, 923, 892, 843, 707, 683 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (s, Me); 0.87 (s, Me); 0.99 (s, Me); 1.35 (d, J = 4.6 Hz, H-C(5));

1.54–1.75 (m, 4H of CH_2, NH); 2.22 (d, J = 12.2 Hz, Ha-C(2)); 2.62 (dd, J = 6.3; 13.5 Hz, Ha-C(4′)); 2.70 (dd, J = 7.7; 13.5 Hz, Hb-C(4′)); 2.88 (d, J = 12.2 Hz, Hb-C(2)); 3.39 (t, J = 6.8 Hz, H-C(4)); 7.62 (s, 2H of Arl); 7.72 (s, 1H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 17.2, 18.3, 21.0, 25.3, 35.0, 41.4, 42.8, 43.3, 49.5, 54.9, 55.6, 120.4–120.6 (m), 123.6 (q, J = 272.7 Hz), 129.4–129.6 (m), 131.7 (q, J = 33.0 Hz), 142.4.

(1*R*,4*S*,5*S*)-4-(3,5-Bis(trifluoromethyl)benzyl)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-3-ium chloride (10b-HCl). To a solution of **10b** (8 mg, 0.021 mmol) in *n*-heptane (3 ml) were added two drops of HCl (2 M in EtOAc). After 2 days in an open flask, the precipitated crystals were collected by filtration to give **10b-HCl**. Yield: 8 mg (91%) of white solid; mp 231–242 °C. $[\alpha]_D^{r.t.}$ = +24.0 (c = 0.1, CH_2Cl_2). ($C_{19}H_{24}ClF_6N$ requires: C, 54.88; H, 5.82; N, 3.37. Found C, 54.83; H, 5.80; N, 3.35.); EI-HRMS: m/z = 380.1805 (M^+); $C_{19}H_{24}F_6N^+$ requires: m/z = 380.1807 (M^+); ν_{max} (KBr) 3471, 2954, 1618, 1582, 1460, 1388, 1376, 1284, 1173, 1151, 1129, 892, 707, 684 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.89 (s, 2×Me); 0.97 (s, Me); 1.39 (d, J = 6.8 Hz, H-C(5)); 1.77–1.86 (m, 1H of CH_2); 1.89–1.97 (m, 1H of CH_2); 2.12–2.22 (m, 2H of CH_2); 2.84 (br d, J = 12.5 Hz, Ha-C(2)); 3.12 (be d, J = 9.6 Hz, Hb-C (2)); 3.22 (br t, J = 12.2 Hz, Ha-C(4′)); 3.51 (br d, J = 11.4 Hz, Hb-C(4′)); 3.75 (br s, H-C(4)); 7.65 (s, 2H of Arl); 7.78 (s, 1H of Arl); 9.13 (br s, 1H of NH_2^+);10.37 (br s, 1H of NH_2^+). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 16.8, 18.1, 20.1, 24.1, 33.4, 36.4, 41.9, 43.0, 45.0, 51.1, 56.4, 121.6, 123.3 (q, J = 272.8 Hz), 129.7, 132.4 (q, J = 33.4 Hz), 138.7.

***rel*-(1*S*,4*R*,2*E*)-2-(3,5-Bis(trifluoromethyl)benzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptane (11) and (3a*R*,4*S*,7*R*,7a*S*)-7-(3,5-bis(trifluoromethyl)benzyl)-3a,7a-dimethylhexahydro-3*H*-4,7-methanobenzo[*d*][1,2]oxathiole 2,2-dioxide (12)**. A mixture of **5b** (380 mg, 1 mmol) and NH_2OSO_3H (1.1 g, 9.73 mmol) in acetic acid (15 ml) was heated under reflux for 24 h. The reaction mixture was cooled to room temperature, and volatile components were evaporated *in vacuo*. The residue was dissolved/suspended in CH_2Cl_2 (200 ml) and carefully washed with $NaHCO_3$ (50 ml, aq. sat.). The separated organic phase was dried over anhydrous Na_2SO_4 and filtered, and volatile components were evaporated *in vacuo*. The residue was purified by column chromatography ([1] EtOAc/petroleum ether = 1:10 to elute **11**; [2] EtOAc/petroleum ether = 1:1 to elute **12**). Fractions containing the corresponding product were combined, and volatile components evaporated *in vacuo* to give crude **11** and **12**. **11** was re-purified by MPLC (EtOAc/petroleum ether = 1:20). Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give **11**. Similarly, **12** was re-purified by MPLC (EtOAc/petroleum ether = 1:5). Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give **12**. **12** was additionally re-crystallized from CH_2Cl_2/*n*-heptane.

11: Elutes first from the column. Yield: 100 mg (27%) of white solid; mp 91.0–95.1 °C. $[\alpha]_D^{r.t.}$ = 0.00 (c = 0.08, CH_2Cl_2). ($C_{19}H_{20}F_6$ requires: C, 62.98; H, 5.56. Found C, 63.12; H, 5.43.); ν_{max} (KBr) 3545, 3416, 2960, 1651, 1615, 1475, 1390, 1374, 1361, 1281, 1169, 1132, 1120, 938, 881, 844, 698, 682 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77 (s, Me); 0.96 (s, Me); 1.06 (s, Me); 1.22–1.29 (m, 1H of CH_2); 1.30–1.37 (m, 1H of CH_2); 1.75 (td, J = 3.8; 11.9 Hz, 1H of CH_2); 1.82–1.90 (m, 1H of CH_2); 1.95 (t, J = 4.3 Hz, H-C(4)); 2.25 (dd, J = 2.1; 16.7 Hz, Ha-C(3)); 2.68–2.75 (m, Hb-C(3)); 6.15 (br s, H-C(2′)); 7.63 (s, 1H of Arl); 7.75 (s, 2H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.3, 19.1, 19.9, 27.9, 34.9, 37.8, 45.2, 48.0, 53.6, 115.1, 118.9–119.1 (m), 123.8 (q, J = 272.6 Hz), 127.6–127.8 (m), 131.6 (q, J = 32.9 Hz), 140.9, 158.6.

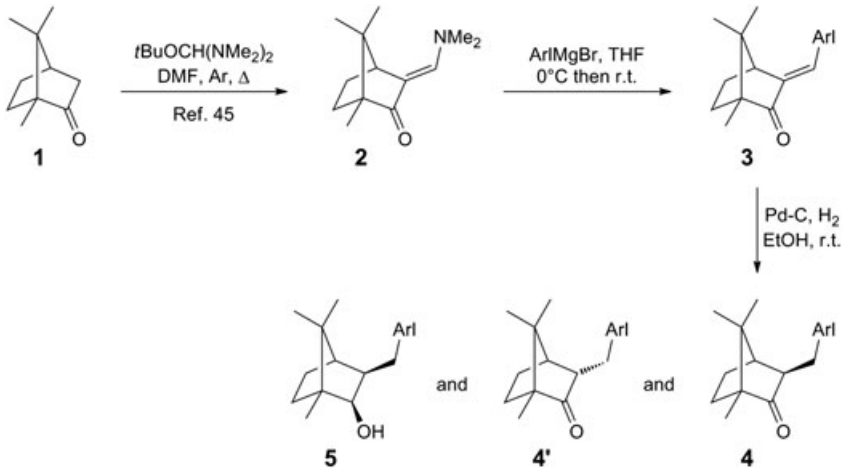
12: Elutes second from the column. Yield: 40 mg (9%) of white solid (CH_2Cl_2/*n*-heptane); mp 160–177 °C. $[\alpha]_D^{r.t.}$ = +12.5 (c = 0.14, CH_2Cl_2). ($C_{19}H_{20}F_6O_3S$ requires: C, 51.58; H, 4.56. Found C, 51.79; H, 4.59.); EI-HRMS: m/z = 460.1378 ($M + NH_4$)$^+$; $C_{19}H_{24}F_6NO_3S$ requires: m/z = 460.1376 ($M + NH_4$)$^+$; ν_{max} (KBr) 3418, 2979, 1624, 1492, 1472, 1442, 1420, 1380, 1340, 1310, 1284, 1193, 1136, 1062, 1046, 933, 898, 885, 846, 786, 714, 683 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.07 (dd, J = 0.9; 10.8 Hz, 1H of CH_2); 1.25–1.39 (m, 3H of CH_2); 1.36 (s, Me); 1.55 (s, Me); 1.57–1.63 (m, 1H of CH_2); 1.99 (br d, J = 10.9 Hz, 1H of CH_2); 2.03 (br s, CH); 2.80 (d, J = 13.6 Hz, 1H of CH_2); 3.17 (d, J = 12.4 Hz, 1H of CH_2); 3.19 (s, CH_2); 7.61 (s, 2H of Arl); 7.77 (s, 1H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 15.3, 21.1, 23.2, 25.8, 35.2, 37.5, 47.4, 51.3, 56.4, 58.5, 98.7, 120.6–120.8 (m), 123.5 (q, J = 272.7 Hz), 130.5–130.6 (m), 131.6 (q, J = 33.2 Hz), 141.0.

(1*S*,2*R*,3*S*,4R)-1,7,7-Trimethyl-N2,N3-diphenylbicyclo[2.2.1]heptane-2,3-diamine (15) and (1*S*,2*S*,3*S*,4*R*)-1,7,7-trimethyl-N2,N3-diphenylbicyclo[2.2.1]heptane-2,3-diamine (16). $NaCNBH_3$ (1.11 g, 17.7 mmol) was added to a solution of **14** (466 mg, 1.47 mmol) in anhydrous MeOH (15 ml) under argon, followed by the addition of glacial acetic acid (0.2 ml), and the reaction mixture was stirred at room temperature for 5 h. Afterwards, water (30 ml) was added, and the reaction mixture was stirred at room temperature for 1 h. MeOH was evaporated *in vacuo* from the reaction mixture, water (70 ml) was added to the residue, and the resulting mixture was extracted with EtOAc (2 × 100 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered, and volatile components evaporated *in vacuo*. The residue (**15**:**16** = 45:55) was purified by column chromatography (EtOAc/hexanes = 1:30). Fractions containing the separated products were combined and evaporated *in vacuo* to give **15** and **16**, respectively.

15: Elutes first from the column. Yield: 192 mg (40%) of colorless oil. $[\alpha]_D^{r.t.}$ = +73.6 (c = 0.33, $CHCl_3$). EI-HRMS: m/z = 321.2330 (MH^+); $C_{22}H_{29}N_2$ requires: m/z = 321.2331 (MH^+); ν_{max} (NaCl) 3386, 3048, 3018, 2953, 2880, 1602, 1503, 1481, 1460, 1422, 1390, 1369, 1303, 1274, 1250, 1193, 1179, 1154, 1142, 1126, 1099, 1069, 1028, 992, 868, 747, 692 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.80 (s, Me); 0.92 (s, Me); 1.10 (s, Me); 1.22–1.44 (m, 2H of CH_2); 1.53–1.64 (m, 1H of CH_2); 1.68–1.80 (m, 1H of CH_2); 1.87 (d, J = 4.3 Hz, H-C(4)); 3.38 (dd, J = 3.4; 8.2 Hz, CH); 3.45 (dd, J = 5.7; 8.1 Hz, CH); 4.77 (d, J = 5.5 Hz, NH); 5.13 (d, J = 3.3 Hz, NH); 6.40–6.45 (m, 2H of Ph); 6.48–6.58 (m, 4H of Ph); 6.94–7.04 (m, 4H of Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.3, 21.2, 21.9, 26.1, 36.3, 47.6, 49.5, 50.3, 62.5, 67.6, 113.2, 113.8, 117.0, 118.0, 129.2, 129.3, 148.3, 149.6.

16: Elutes second from the column. Yield: 256 mg (54%) of dirty white solid; mp 75–86 °C. $[\alpha]_D^{r.t.}$ = −60.7 (c = 0.43, $CHCl_3$). ($C_{22}H_{28}N_2$ requires: C, 82.45; H, 8.81; N, 8.74. Found C, 82.82; H, 9.22; N, 8.80.); EI-HRMS: m/z = 321.2340 (MH^+); $C_{22}H_{29}N_2$ requires: m/z = 321.2331 (MH^+); ν_{max} (NaCl) 3409, 3051, 2952, 2882, 1600, 1503, 1428, 1390, 1371, 1315, 1269, 1195, 1180, 1154, 1098, 1072, 1045, 1029, 992, 868, 747, 692 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.82 (s, Me); 0.83 (s, Me); 1.14 (s, Me); 1.17–1.25 (m, 1H of CH_2); 1.30–1.38 (m, 1H of CH_2); 1.68–1.78 (m, 1H of CH_2, H-C(4)); 1.84–1.93 (m, 1H of CH_2); 2.89 (t, J = 4.8 Hz, H-C (3)); 3.79–3.85 (m, H-C(2)); 5.66 (d, J = 8.7 Hz, H-N(2′)); 5.81 (d, J = 4.9 Hz, H-N(3′)); 6.41–6.50 (m, 4H of Ph); 6.72 (d, J = 7.9 Hz, 2H of Ph); 6.98–7.04 (m, 4H of Ph). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 14.4, 19.1, 21.5, 26.4, 26.9, 47.1, 48.4, 50.5, 65.0, 65.7, 111.8, 112.1, 114.8, 114.9, 128.6, 128.8, 148.4, 149.6.

(3a*S*,4*S*,7*R*,7a*R*)-4,8,8-Trimethyl-1,3-diphenyl-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methanobenzo[*d*]imidazol-3-ium tetrafluoroborate (17). One drop of formic acid was added to a mixture of **15** (171 mg, 0.534 mmol) and NH_4BF_4 (60 mg, 0.57 mmol) in $HC(OEt)_3$ (1 ml) under argon. The reaction mixture was heated at 110 °C for 4 h under microwave irradiation (300 W). Upon cooling to room temperature, Et_2O (20 ml) was added, and the resulting precipitate was collected by filtration and washed with Et_2O (10 ml). The resulting precipitate was dissolved in CH_2Cl_2, filtered through a plug of Celite®, and washed with CH_2Cl_2. Volatile components were evaporated *in vacuo*, and to the residue, Et_2O (20 ml) was given to solidify the product. The



Scheme 1. Preparation of 3-arylmethyl camphor derivatives **4**/**4′** and isoborneol derivatives **5**.

TABLE 1. Synthesis and catalytic hydrogenation of arylidene compounds 3a–d

		3	**4**	**4′**	**5**	**4:4′:5**
	Arl	Yield (%)[a]				
a	Ph	Ref. [46]	Ref. [45]	Ref. [45]	–	66:34:0[45]
b	3,5-CF_3-C_6H_3	Ref. [46]	31	13	26	55:18:27
c	3,5-CH_3-C_6H_3	86	78[b]		4	68:24:8
d	Phenantren-9-yl	28	87[b]		–	72:28:0

[a]Yields after separation.
[b]Ketone epimers **4**/**4′** could chromatographically not be separated.

precipitate was finely crushed, collected by filtration, and washed with Et_2O (20 ml) to give **17**. Yield: 160 mg (71%) of dirty white solid; mp 222–225 °C. $[\alpha]_D^{r.t.} = +40.5$ ($c = 0.15$, $CHCl_3$). ($C_{23}H_{27}BF_4N_2$ requires: C, 66.04; H, 6.51; N, 6.70. Found C, 66.09; H, 6.72; N, 6.73.); EI-HRMS: $m/z = 331.2172$ (M^+); $C_{23}H_{27}N_2^+$ requires: $m/z = 331.2169$ (M^+); ν_{max} (KBr) 3410, 2961, 1619, 1591, 1496, 1444, 1398, 1292, 1266, 1109, 1083, 1069, 1034, 762, 693 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.62 (s, Me); 0.80 (s, Me); 1.03 (s, Me); 1.30–1.37 (m, 1H of CH_2); 1.38–1.44 (m, 1H of CH_2); 1.45–1.52 (m, H of CH_2); 1.76–1.84 (m, 1H of CH_2); 2.21 (d, $J = 4.8$ Hz, H-C(4)); 5.02 (d, $J = 10.9$ Hz, CH); 5.05 (d, $J = 10.9$ Hz, CH); 7.16–7.21 (m, 1H of Ph); 7.23–7.27 (m, 1H of Ph); 7.31–7.39 (m, 6H of Ph); 7.44–7.47 (m, 2H of Ph); 8.18 (s, CH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 12.8, 18.4, 23.2, 24.7, 33.6, 46.1, 49.1, 51.6, 70.0, 73.4, 120.1, 121.8, 128.4, 128.8, 130.2, 130.5, 134.7, 136.0, 154.2.

Single crystal X-ray structure analysis for compounds 4b, 4b′, 9a, 10a-HCl, 10b-HCl, 11, 12, 16, and 17

Single crystal diffraction data for compounds **4b**, **4b′**, **9a**, **10a-HCl**, **10b-HCl**, **11**, **12**, **16**, and **17** have been collected on a Nonius Kappa CCD diffractometer (Bruker, Billerica, MA, USA) at room temperature with MoK_α radiation (0.71073 Å) and graphite monochromator using the Nonius Collect Software.[40] The data were processed using DENZO software.[41] Structures were solved with direct methods, using SIR97.[42] A full-matrix least-squares refinement on F^2 was employed with anisotropic temperature displacement parameters for all non-hydrogen atoms. H atoms bonded to N atoms were located using a difference Fourier map. The remaining H atoms were placed at calculated positions and treated as riding, with C–H = 0.93, 0.98, 0.97, and 0.96 Å for $C_{sp2}H$, $C_{sp3}H$, $C_{sp3}H_2$, and $C_{sp3}H_3$, respectively. *SHELXL97* software[43] was used for structure refinement and interpretation. Drawings of the structures were produced using *ORTEPIII*.[44] Structural and other crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 864587–864595. A copy of the data can be obtained, free of charge, by applying to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

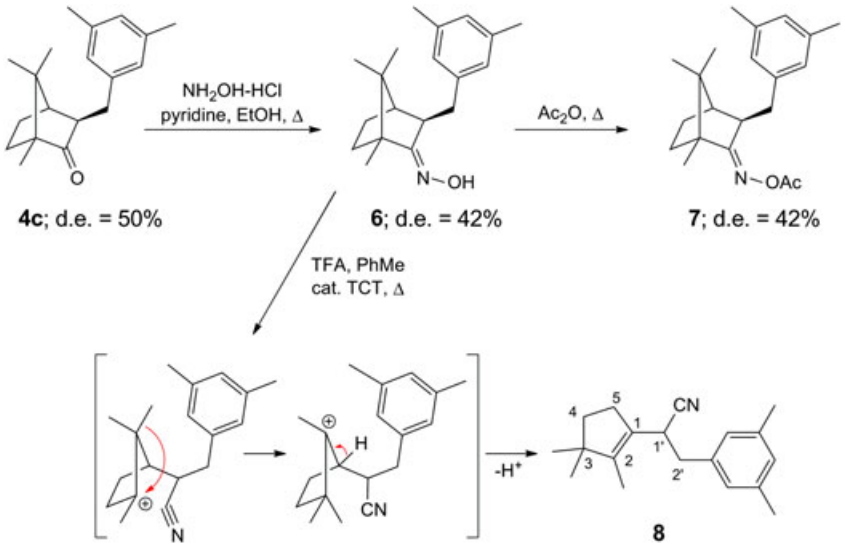
RESULTS AND DISCUSSION

Syntheses

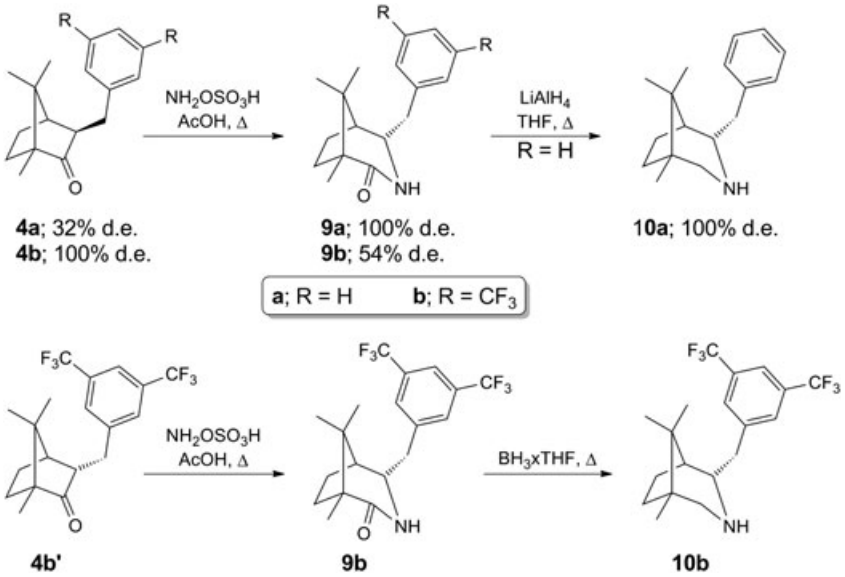
The precursors for the *Beckmann* rearrangement, 3-arylmethyl substituted camphor derivatives **4**/**4′**, were prepared in three steps from (+)-camphor (**1**). Following the literature procedure,[45] **1** was transformed into 3-((dimethylamino) methylene)camphor (**2**). Treatment of enaminone **2** with excess *Grignard* reagent(s) gave arylidene compounds **3a–d** in 28–86% yield, in all cases with the (*E*)-configured exocyclic C=C bond, exclusively. Next, catalytic hydrogenation of arylidene compounds **3a–d** in the presence of 10% Pd–C furnished the expected 3-arylmethyl camphor derivatives as mixtures of the major *exo*-epimers **4a–d** and the minor *endo*-epimers **4a′–d′** in 44–87% yield. Reduction of **3b** and **3c** furnished along the desired ketones (**4b**/**4b′** and **4c**/**4c′**, respectively) also the isoborneol derivatives **5b** and **5c** in 26% and 4% yield, respectively. The ketone products were chromatographically separated from the corresponding isoborneol derivatives, whereas the ketone epimers could only be separated in the case of **4b**/**4b′**. The major *exo*-epimers **4** and **5** are the result of an attack of the reagent from the sterically less hindered *endo* face of the C=C bond[46] (Scheme 1, Table 1).

Next, reaction of ketone **4c** under conditions used by Page *et al.*[47] gave the corresponding oxime **6** in 96% yield and with a slightly decreased diastereoisomer ratio. Various *Beckmann* rearrangement attempts of **6** resulted in complex mixtures of products. Only when **6** was treated with TFA in the presence of catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT) that a *Beckmann* fragmentation product **8** was obtained in 43% yield containing approximately 15% of unidentified co-product. Formation of **8** could be explained *via* the initial *Beckmann* fragmentation of **6**, followed by 1,2-methyl migration and final proton elimination. Heating **6** in Ac_2O yielded *O*-acetylated product **7** in quantitative yields (Scheme 2).

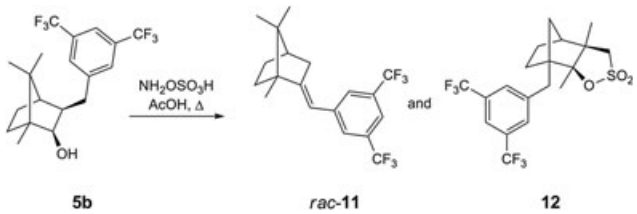
Because of the failure to rearrange oxime **6**, a direct *Beckmann* rearrangement starting from ketones **4**/**4′** was



Scheme 2. *Beckmann* fragmentation of oxime **6**.

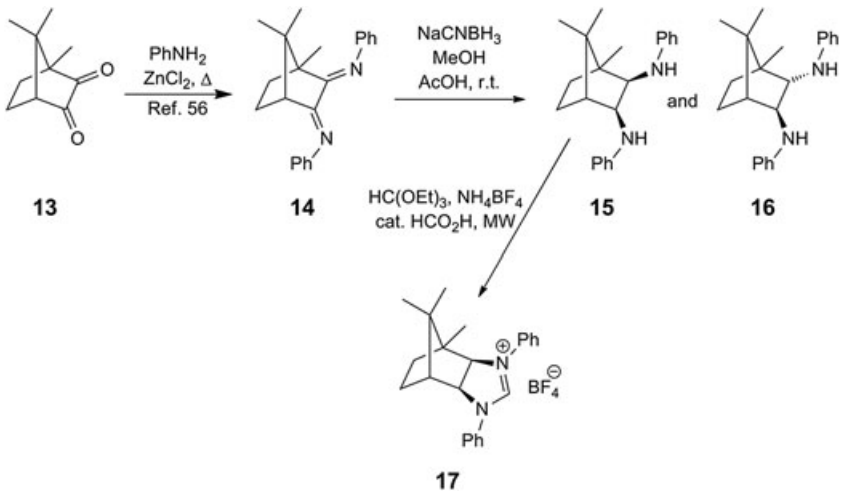


Scheme 3. Synthesis of camphidine derivatives **10**.



Scheme 4. Rearrangement of isoborneol **5b**.

attempted. Thus, upon treatment of **4a**/**4a**′ with hydroxylamine-*O*-sulfonic acid in AcOH at elevated temperature, the *endo*-amide **9a** was isolated in low yield (8%). Similarly, ketone **4b** yielded the corresponding rearrangement products as an inseparable mixture of the major *endo*-epimer **9b** and minor *exo*-epimer **9b**′ in 17% yield (**9**:**9**′ = 77:23), whereas rearrangement of **4b**′ furnished **9b**′ exclusively in 16% yield with retention of configuration. Ketones **4c**/**4c**′ and **4d**/**4d**′ failed to give detectable amounts of the corresponding rearrangement products. Rearrangement of **4b** into a mixture of **9b** and **9b**′ and of **4b**′ exclusively into **9b**′ clearly shows that the applied reaction conditions enable epimerization[48,49] at the chiral center bearing the arylmethyl substituent, thus furnishing the thermodynamically more stable (less sterically hindered) *endo*-product (**9b**; e.g., **9a** when starting from **4a** [d.e. = 32%]). In a complex reaction mixture, no regioisomeric product of type **D** was detected and isolated, although the tertiary carbon center (i.e., C(1)) has a preference for the migration. Migration of C(1) frequently leads to *Beckmann* fragmentation products,[50] which would explain the formation of a complex mixture of products. Finally, reduction of **9a** with $LiAlH_4$ furnished the desired camphidine derivative **10a**, whereas reduction of **9b** with $BH_3 \times THF$ furnished the corresponding amine **10b**. Reduction of **9b** with $LiAlH_4$ leads



Scheme 5. Synthesis of NHC precursor **17**.

to a mixture of amines because of a partial and unselective hydrodefluorination of the CF_3 group[51,52] (Scheme 3).

Cyclic *sec*-amines **10a** and **10b** have been tested as covalent organocatalysts in the *Michael* addition of 1-methylindole to cinnamaldehyde[53] and failed to give the expected product.

Interestingly, treatment of isoborneol **5b** under conditions used for the rearrangement of ketones **4**/**4′** (NH_2OSO_3H, AcOH, elevated temperature) furnished two rearrangement products, compounds **11** and **12** in 27% and 9%, respectively. The letter was formed as a racemate ($[\alpha]_D^{r.t.} = 0$, centrosymmetric space group ($P2_1/a$) of the single crystal used for X-ray analysis). Although mechanistic investigations of the camphene sultone[54,55] have been studied, we could, so far, not explain the formation of the closely related sultone **12** (and of **11**) (Scheme 4).

Finally, starting from (1*S*)-(+)-camphorquinone (**13**), following the literature procedure,[56] camphordiimine **14** was prepared. Reduction of **14** with $NaCNBH_3$ afforded the major *trans*-diamine **16** and the minor *cis*-diamine **15** in 54% and 40% yield, respectively. Cyclization of **15** with $HC(OEt)_3$ in the presence of NH4BF4 and catalytic amounts of formic acid under microwave irradiation yielded the NHC precursor **17** in 71% yield. Attempts to cyclize the *trans*-diamine **16** failed (Scheme 5).

Structure Determination

The structures of novel compounds **3–12** and **15–17** were determined by spectroscopic methods (IR, NMR spectroscopy [^{1}H-NMR 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 **4c**, **4d**, **6**, and **7** were characterized as mixtures of epimers. Compounds **3c**, **4c**/**4c′**, **5c**, **7**/**7′**, **8**, **10a**, **10b**, **15**, and **16** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C-NMR and/or EI-HRMS.

Structures of compounds **4b**, **4b′**, **9a**, **10a-HCl**, **10b-HCl**, **11**, **12**, **16**, and **17** were determined by single crystal X-ray analysis (Figs. 2–10).

The (2*E*)-configuration of oximes **6**/**6′** and **7**/**7′** was ascribed on the basis of the configuration of closely related oximes.[45] The (*E*)-configuration around the exocyclic C=C bond in arylidene compounds **3c** and **3d** was determined

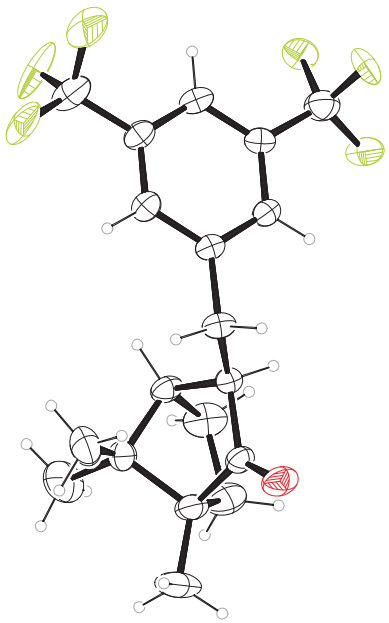


Fig. 2. Ortep drawing of compound **4b**.

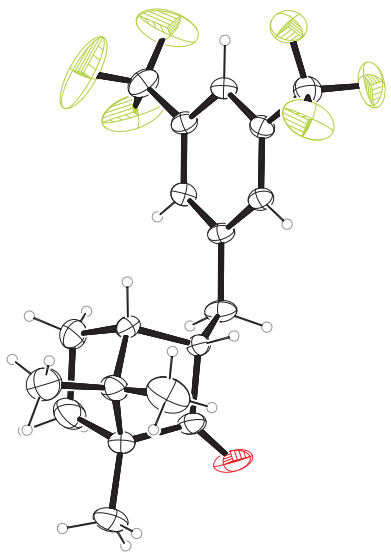


Fig. 3. Ortep drawing of compound **4b′**.

Fig. 4. Ortep drawing of compound **9a**.

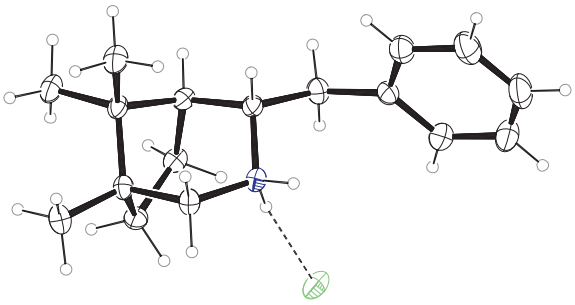


Fig. 5. Ortep drawing of compound **10a-HCl**.

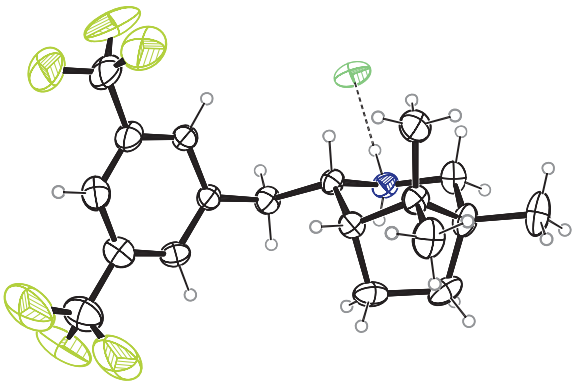


Fig. 6. Ortep drawing of compound **10b-HCl**.

on the basis of NOE between aromatic protons and *H*-C(4) in the NOESY spectra. Similarly, the configuration(s) in position (s) 2 and/or 3 and/or 4 of compounds **4b–d**, **4b–d′**, **5b**,**c**, **9b**, **10a**,**b-HCl**, **11**, **16**, and **17** was/were determined on the basis of NOEs observed in the NOESY spectra between the corresponding key proton signals (Fig. 11).

Alternatively, if NOESY measurements are not available, the configuration at position *3* in camphor derivatives and at position *4* in the corresponding ring expanded camphor derivatives is easily determinable on the basis of the multiplicity

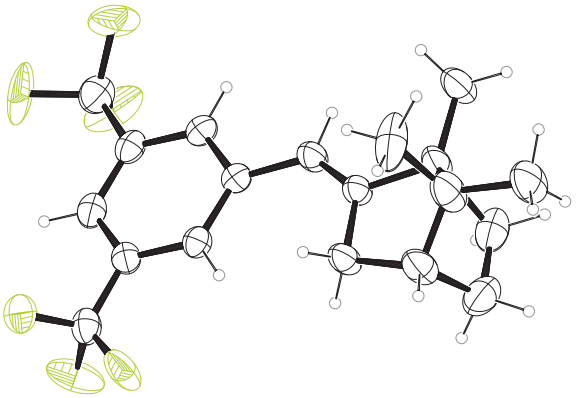


Fig. 7. Ortep drawing of compound **11**.

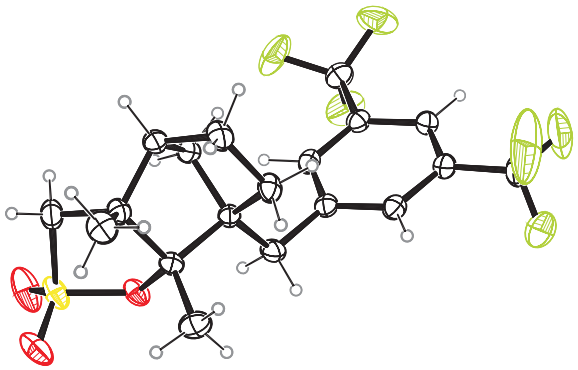


Fig. 8. Ortep drawing of compound **12**.

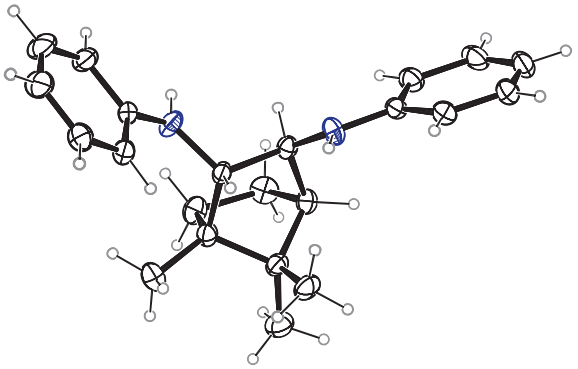


Fig. 9. Ortep drawing of compound **16**.

of the corresponding proton signals (if they do not overlap

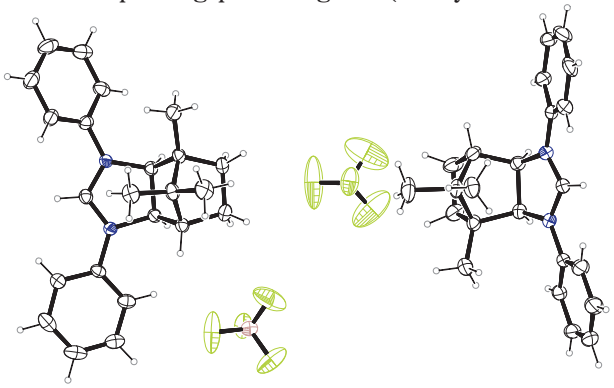


Fig. 10. Ortep drawing of compound **17**.

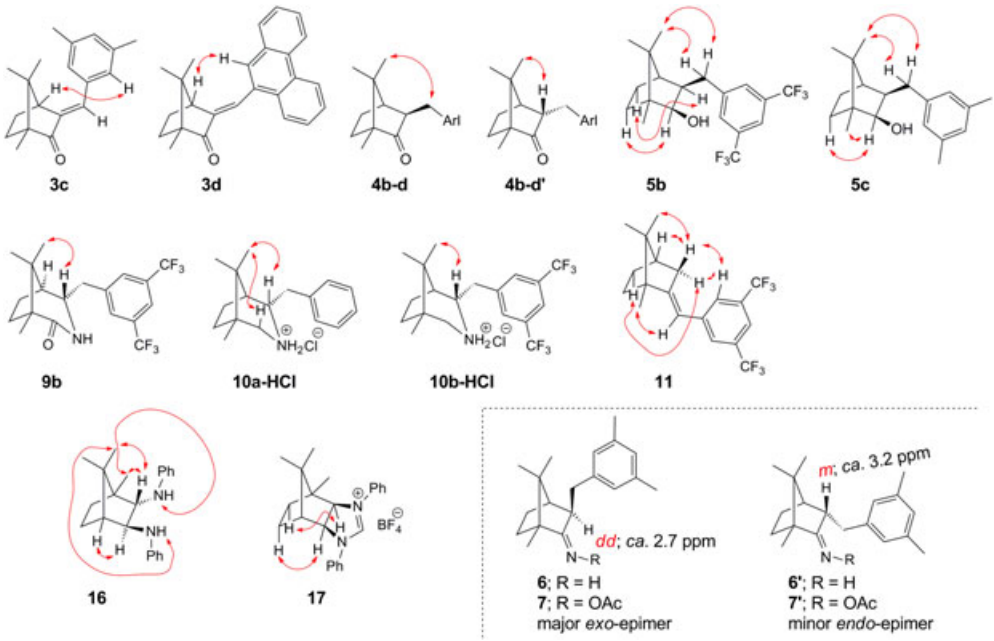


Fig. 11. Key NOEs observed in NOESY spectra of compounds **4b-d**, **4b-d′**, **5b**,**c**, **9b**, **10a**,**b-HCl**, **11**, **16**, and **17** for the determination of configuration in position *3* of camphor derivatives **6**/**6′** and **7**/**7′** based on the multiplicity of the corresponding protons.

with other signals). As has been demonstrated and rationalized previously, the proton signals with higher multiplicity are positioned *exo*, whereas protons with lover multiplicity are positioned *endo*, when comparing a pair of epimers; that is, the *exo*-proton couples also with the adjacent bridgehead proton and the *exo*-proton on the other side of the bridge.[46,57–59] For example, in the major *exo*-oxime **6** and the corresponding OAc derivative **7**, the *endo*-H proton appears as a doublet of doublet at approximately 2.7 ppm, whereas in the corresponding minor *endo*-epimers **6′** and **7′**, the corresponding *exo*-protons appear as multiplet at approximately 3.2 ppm (Fig. 11, bottom right).

CONCLUSIONS

Cyclic *sec*-amines **10a** and **10b** were prepared in five steps starting from (+)-camphor (**1**). The step with the lowest yield turned out to be the direct *Beckmann* rearrangement of ketones **4**/**4′** with hydroxylamine-*O*-sulfonic acid. The *Beckmann* rearrangement of the corresponding oxime failed entirely. Catalytic hydrogenation of arylidene ketone **3b** gave substantial amounts of the unexpected isoborneol derivative **5b**, which was treated with hydroxylamine-*O*-sulfonic acid in acetic acid at elevated temperatures to give two novel rearrangement products **11** and **12**. Their formation, so far, could not be explained. Finally, *cis*-diamine **15** and *trans*-diamine **16** have been prepared from (1*S*)-(+)-camphorquinone (**13**) in two steps. Diamine **15** has been successfully cyclized into the corresponding imidazoline salt **17**, an NHC precursor. **10a** and **10b** were tested as potential organocatalysts in the *Michael* addition of 1-methylindole to cinnamaldehyde and failed to give any conversion. The structures of all novel compounds have been meticulously characterized using NMR techniques and/or single crystal X-ray analysis. The scope and limitations of rearrangement of isoborneol (and borneol) derivatives as well as the formation of exocyclic diamines and the corresponding NHC precursors are the subject of further studies.

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