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HETEROCYCLIZATION OF 3-AMINOCAMPHOR AND 3-AMINOISOBORNEOL DERIVATIVES WITH CYCLIC β-DIKETONES AND FORMALDEHYDE. SYNTHESIS OF OPTICALLY ACTIVE 1,2,3,4-TETRAHYDROQUINOLINE DERIVATIVES WITH TERPENE SUBSTITUENTS

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*Spirocyclic 1,2,3,4-tetrahydroquinoline derivatives were prepared in quantitative yield by three-component condensation of dimedone or Meldrum's acid with formaldehyde and (1*S*,3*R*,4*S*)-1,7,7-trimethyl-3-(arylamino)bicyclo[2.2.1]heptan-2-one or (1*S*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-3-(arylamino)bicyclo[2.2.1]heptan-2-ol.*

Keywords: heterocyclization, reductive amination, camphoroquinone, 1,2,3,4-tetrahydroquinoline, regio- and stereoselectivity.

Heterocyclic compounds of the quinoline series that contain a chiral moiety are widely used in asymmetric synthesis as intermediates, ligands, and catalysts. However, the quinoline core is an active pharmacophore so that quinoline derivatives, as a rule, exhibit various biochemical activities. Many of them are used as pharmaceutical drugs [1, 2].

The natural terpene camphor (2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane) is traditionally one of the most popular chiral moieties owing to its stability, lack of inversion, and available enantiomerically pure starting materials for introducing this fragment [3]. Furthermore, the introduction of a compact lipophilic terpene substituent into the structure of known biologically active compounds in several instances either increased or improved their biological activity [4].

Many synthetic strategies are currently known for producing N-containing heterocycles based on various arylamines [5–7]. In our opinion, cascade heterocyclization (cyclocondensation) involving aromatic aldehydes, amines, and cyclic β-diketones is the most effective method for synthesizing derivatives of benzo[*a*]acridine, 1,7-phenanthroline, benzo[*f*]quinoline, and other condensed azaheterocycles [8–10].

The goal of the present work was to synthesize several 1,2,3,4-tetrahydroquinoline derivatives substituted with the optically active camphor moiety. We showed earlier that treatment of mono-*N*-substituted anilines with cyclic β-diketones in the presence of formaldehyde formed in one step 1,2,3,4-tetrahydroquinoline derivatives [11, 12]. The substituent on the N atom of the starting aniline did not change during the reaction and occupied the 1-position in the tetrahydroquinoline core of the product. We prepared a series of anilines with the optically active camphor substituent on the N atom and used them in three-component condensation with formaldehyde and dimedone (5,5-dimethylcyclohexan-1,3-dione) or Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane).

Anilines substituted by an optically active terpene moiety were synthesized by indirect reductive amination of enantiomerically pure (–)-camphoroquinone (**1**) by a series of aromatic amines [13] (Scheme 1). The mixture of amine and camphoroquinone was refluxed in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ with removal of H_2O. Then the resulting ketimine was reduced without isolation and purification by sodium triacetoxyborohydride both obtained from the bottle and prepared *in situ*.

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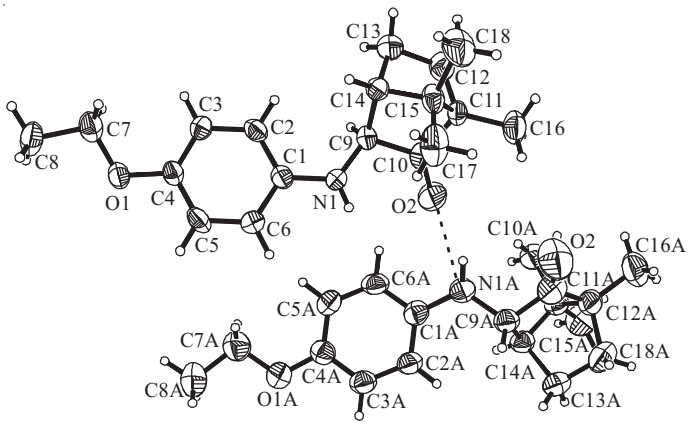
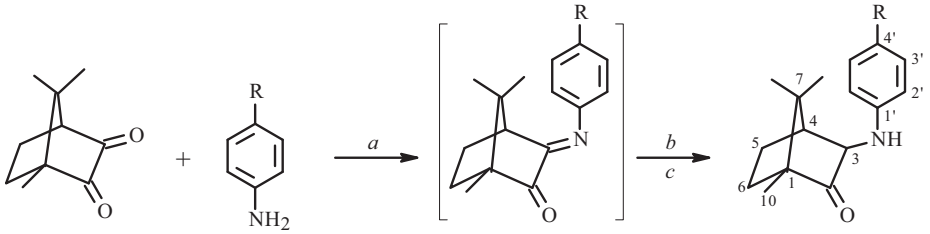


Fig. 1. General view of (1*R*,3*R*,4*S*)-(*p*-ethoxyphenylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**3c**) from an x-ray crystal structure analysis.



1 **2a - d** A **3a - d**

a: R = CH_3, **b:** R = OCH_3, **c:** R = OC_2H_5, **d:** R = C_6H_5

a. PhH, H^+; *b*. $NaBH(OAc)_3$; *c*. $NaBH_4$/AcOH

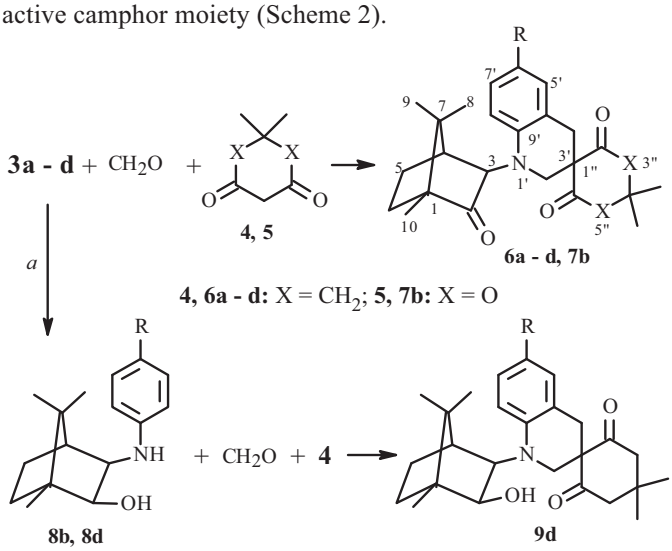
Scheme 1

The reaction occurred regio- and stereoselectively and formed optically active 3-arylamino camphor derivatives (**3a–d**) in yields of 65–85% after crystallization from EtOH. The sterically more accessible carbonyl in the 3-position of the bicyclic core was exclusively aminated whereas the carbonyl in the 2-position was untouched. If $NaBH(OAc)_3$ from the bottle was used, the only reaction product was the aminoketone whereas reduction by $NaBH(OAc)_3$ prepared *in situ* partially reduced the carbonyl in the 2-position to a hydroxyl. Thus, it was found according to NMR spectroscopy that aminoketone **3b** and the aminoalcohol **8b** corresponding to it were formed exclusively with an *exo*-hydroxyl in a 100:12 ratio. Crystallization of this mixture from EtOH isolated the pure aminoketone without the alcohol impurity. This was probably related to the significant difference in their solubilities in EtOH.

IR spectra of **3a–d** showed characteristic narrow strong bands in the range 3363–3387 cm^{-1} that corresponded to stretching vibrations of a secondary amine. Bands at 1742–1749 corresponded to C=O stretching vibrations; at 1514–1616, to C=C stretching vibrations in an aromatic ring. IR spectra of **3b** and **3c** contained bands for C–O–C groups at 1240.

The amine in the products had exclusively the *exo*-orientation. This was consistent with selective attack of the bulky triacetoxyborohydride anion at intermediate ketimine A from the sterically less hindered side. The *exo*-substitution of the C^3 atom in the terpene moiety of all **3a–d** was confirmed unambiguously by PMR spectroscopy. The proton geminal to the amine appeared as a singlet whereas the proton on C^4 was a doublet (splitting only by H^5 *exo*). The lack of spin–spin coupling between the H^3 and H^4 protons was only possible where the dihedral angle H–C^3–C^4–H was almost 90°. A doublet instead of a singlet for the resonance of the C^3 proton and a doublet of doublets instead of a doublet for the resonance of the C^4 proton should have been observed in the spectrum with *endo*-substitution. The structure of **3c** was established unambiguously by an x-ray crystal structure analysis (XSA) (Fig. 1). According to the XSA, two crystallographically independent molecules crystallized in a chiral space group of the monoclinic system. A feature of the crystal packing of this compound was the formation between molecules of an ordinary intermolecular H-bond and not the H-bonded dimers or polymers that are more typical for α-aminocarbonyl compounds. Thus, the NH-donor ability of the second molecule remained unused.

The obtained anilines **3a–d** were used in a three-component heterocyclization reaction with dimedone (**4**) or Meldrum's acid (**5**) and formaldehyde. This formed selectively 1,2,3,4-tetrahydroquinoline derivatives (**6a–d** and **7b**) that were substituted on the N atom by the optically active camphor moiety (Scheme 2).



a: R = CH_3; **b:** R = OCH_3; **c:** R = OC_2H_5; **d:** R = C_6H_5

a. $NaBH_4$/*i*-PrOH

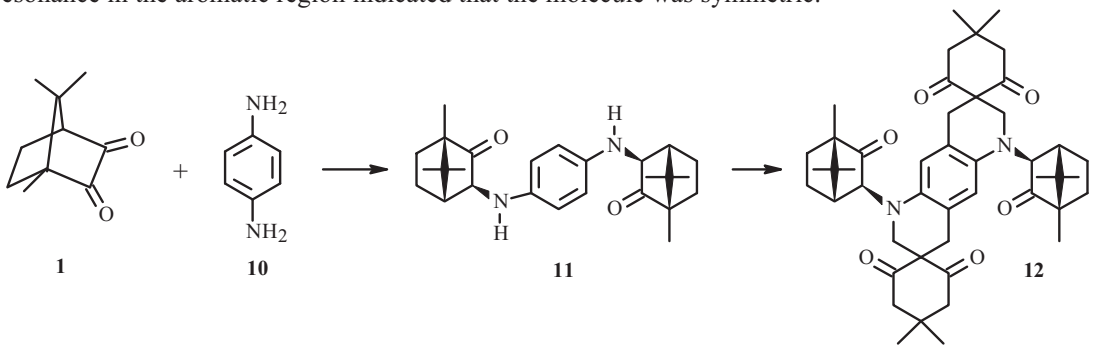
Scheme 2

In all instances the reaction occurred with brief refluxing of the reagent mixture in EtOH without a catalyst. Such synthetic conditions were rather mild and, as a result, did not cause any changes in the terpene part of the molecule. The *exo*-orientation of the C^3 substituent was preserved in the products. The C^3 proton of the camphane moiety appeared as a singlet in PMR spectra of **6a–d** and **7b**. As shown above, this indicated unambiguously that it had the *endo*-orientation. IR spectra of **6a–d** and **7b** showed two strong absorption bands for carbonyls at 1697 and 1740 cm^{-1} and bands at 1502–1610 that were characteristic of C=C bonds of an aromatic ring. Absorption bands of C–O–C groups at 1230–1240 were also characteristic of **6b**, **6c**, and **7b**.

We used anilines **3b** and **3d** as examples to show that the camphor ketone could be reduced stereoselectively. The resulting aminoalcohol (**8d**) was condensed with dimedone (**4**) in the presence of formaldehyde. The product of this reaction was a 1,2,3,4-tetrahydroquinoline (**9d**) substituted at the N atom by an optically active isobornyl moiety.

The aminoketones (**3b** and **3d**) were reduced by $NaBH_4$ in *i*-PrOH at room temperature. The reduction occurred stereoselectively to give 3-*exo*-arylaminoisoborneols (**8b** and **8d**) as the only products. IR spectra of **8b** and **8d** lacked C=O absorption bands and contained a broad absorption band at 3400 cm^{-1} that was characteristic of a hydroxyl. The 2-*exo*-3-*exo*-orientation of the substituents in the compounds was confirmed by the large SSCC ($^3J_{2,3}$ = 7.0 Hz, for 2-*endo*-OH a considerably smaller constant would be observed).

Diamine **11** with two camphor moieties was formed by reductive amination of camphoroquinone and *p*-phenylenediamine (**10**) at a **1**:**10** mole ratio of 2:1. Treatment of **11** with formaldehyde and dimedone caused cyclization into pyrido[2,3-*g*]quinoline **12** (Scheme 3). The relative simplicity of the NMR spectra of **11** and **12** and the presence of only one proton resonance in the aromatic region indicated that the molecule was symmetric.



Scheme 3

Thus, we developed a new two-step synthetic method for optically active 1,2,3,4-tetrahydroquinoline derivatives with terpene substituents. The method was based on reductive amination of enantiomerically pure (–)-camphoroquinone by a series of aromatic amines and heterocyclization of the resulting derivatives of 3-aminocamphor and 3-aminoisoborneol.

EXPERIMENTAL

IR spectra were recorded in KBr pellets or as thin layers on Nicolet Protege-460 and IR-Prestige-21 Fourier spectrophotometers. PMR spectra were taken from solutions in DMSO-d_6 with TMS internal standard on Bruker Avance-II-300 (300.17 MHz for ^{1}H; 75.48 MHz for ^{13}C) and DRX-500 (500.13 MHz for ^{1}H; 125.75 MHz for ^{13}C) spectrometers. Melting points were determined on a TP melter. Optical rotation angles were measured on a Kruss P3002PS automated polarimeter. Elemental analysis was performed on an EA 1110 (CHNSO) elemental analyzer. The XSA was carried out on an Xcalibur-3 x-ray diffractometer with a CCD detector using the standard procedure (λ Mo-Kα, graphite monochromator, ω-scanning). A data set was collected and processed using the CrysAlis software. Absorption corrections were not applied. The structures of all compounds were solved by direct methods using the SHELXS-97 program and refined using the SHELXL-97 program [14] and anisotropic (isotropic for H atoms) parameters. H atoms were partially determined and refined independently, partially including in the refinement a rider model with dependent thermal parameters. According to the XSA the crystal was monoclinic, $P2_1$, a = 14.119(2) Å, b = 7.5590(13) Å, c = 15.486(2) Å, β = 96.213(12)°, Z = 4. A total of 7013 reflections were measured. Of these, 3580 were independent (R_{int} = 0.0493) and 1580 with $I > 2\sigma(I)$. The completeness for θ = 26.37° was 98.6%. The final refinement parameters were R_1 = 0.0349, wR_2 = 0.0292 for reflections with $I > 2\sigma(I)$; R_1 = 0.1149, wR_2 = 0.0334 (over all reflections) for S = 0.864. Silica gel (Lancaster) was used for column chromatography. TLC was performed on Sorbfil plates with detection by I_2. Optically active (–)-camphoroquinone was prepared by the literature method [15] {$[\alpha]_D$ –101.1° (*c* 1.3, toluene), mp 198–199°C}.

General Method for Synthesizing *N*-Aryl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one-3-*exo*-amines (3) by Reductive Amination of (–)-Camphoroquinone (1) by Arylamines (2). Method a): primary arylamine **2** (0.01 mol) and diketone **1** (0.01 mol) were dissolved in benzene (70 mL), treated with $BF_3 \cdot Et_2O$ (5–6 drops), refluxed with a Dean–Stark trap for 4–5 h until the theoretical amount of H_2O was separated, cooled, stirred, treated in portions with $NaBH(OAc)_3$ (0.025 mol), left overnight, and worked up with aqueous NaOH (10%). The benzene layer was separated, washed, and dried over anhydrous $MgSO_4$. The solvent was removed. The resulting oil was crystallized for 30–60 min. The yields of **3a–d** were 65–87% after recrystallization from EtOH.

Method b): primary arylamine (0.02 mol), diketone **1** (0.02 mol), and HOAc (1 mL) were dissolved in benzene (250 mL), refluxed with a Dean–Stark trap for 6–12 h until the theoretical amount of H_2O was separated, cooled, treated in portions with $NaBH_4$ (3.8 g, 0.1 mol), cooled, treated with glacial HOAc (18 g, 0.3 mol), and refluxed for another 24 h. The benzene was distilled off. The residue was worked up with aqueous NaOH (10%). The separated oil was extracted with Et_2O. The Et_2O extract was washed and dried over $MgSO_4$. The Et_2O was removed. The product was crystallized from EtOH.

(1*R*,3*R*,4*S*)-1,7,7-Trimethyl-3-(*p*-tolylamino)bicyclo[2.2.1]heptan-2-one (3a), $C_{17}H_{23}NO$, yield 87%, mp 86–87°C, $[\alpha]_D$ +64.5° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3375 (NH), 2957, 2924, 2878, 1744 (C=O), 1616, 1587, 1522, 1479, 1449, 1393, 1346, 1319, 1300, 1263, 1192, 1117, 1022, 947, 822, 804, 702, 552, 515.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.97 (3H, s, CH_3-9), 0.98 (3H, s, CH_3-8), 1.01 (3H, s, CH_3-10), 1.62–1.78 (3H, m), 2.11 (1H, m), 2.27 (1H, d, J = 4.0, H-4), 2.28 (3H, s, CH_3-Ar), 3.38 (1H, s, H-3), 6.53 (2H, d, J = 7.4, H-2′), 7.03 (2H, d, J = 7.4, H-3′).

^{13}C NMR spectrum ($CDCl_3$, δ, pm): 9.3 (C-9), 20.4 (C-8), 20.5 (C-10), 20.7 (CH_3-Ar), 26.2 (C-5), 28.7 (C-6), 46.9 (C-7), 47.7 (C-4), 56.5 (C-1), 65.3 (C-3), 113.3 (C-2′), 127.2 (C-4′), 129.7 (C-3′), 145.5 (C-1′), 217.8 (C-2, C=O).

(1*R*,3*R*,4*S*)-(*p*-Methoxyphenylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3b), $C_{17}H_{23}NO_2$, yield 85%, mp 75–76°C, $[\alpha]_D$ +58.7° (*c* 0.8, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3377 (NH), 2957, 2874, 2833 (C–H), 1742 (C=O), 1616, 1514, 1460, 1395, 1350, 1317, 1294, 1240 (C–O–C), 1179, 1147, 1113, 1036, 947, 818, 745, 523.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, s, CH_3-9), 0.96 (3H, s, CH_3-8), 0.98 (3H, s, CH_3-10), 1.55–1.80 (3H, m), 2.09 (1H, m), 2.23 (1H, d, J = 4.0, H-4), 3.32 (1H, s, H-3), 3.75 (3H, s, CH_3O-4′), 6.55 (2H, d, J = 9.0, H-2′), 6.80 (2H, d, J = 9.0, H-3′).

^{13}C NMR spectrum ($CDCl_3$, δ, pm): 9.3 (C-9), 20.6 (C-8), 20.8 (C-10), 26.3 (C-6), 28.7 (C-5), 47.1 (C-7), 47.7 (C-3), 55.8 (C-4), 56.7 (C-1), 65.8 (CH_3O), 114.5 (C-2′), 115.0 (C-3′), 142.2 (C-4′), 152.7 (C-1′), 218.0 (C-2, C=O).

(1*R*,3*R*,4*S*)-(*p*-Ethoxyphenylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3c), $C_{18}H_{25}NO_2$, yield 71%, mp 87–88°C, $[\alpha]_D$ +62.7° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3364 (NH), 2974, 2967, 2928, 2872, 2824, 2799 (C–H), 1749 (C=O), 1616, 1589, 1514, 1479, 1449, 1393, 1323, 1292, 1246, 1186, 1150, 1117, 1049, 1024, 950, 922, 818, 758, 600, 523.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.39 (3H, t, J = 7.0, $OCH_3C\underline{H}_3$), 1.60–1.80 (3H, m), 2.09 (1H, m), 2.23 (1H, d, J = 4.0, H-4), 3.32 (1H, s, H-3), 3.97 (2H, q, J = 7.0, $OC\underline{H}_2CH_3$), 6.54 (2H, d, J = 9.0, H-2′), 6.80 (2H, d, J = 9.0, H-3′).

^{13}C NMR spectrum ($CDCl_3$, δ, pm): 9.3 (C-9), 15.1 ($\underline{C}H_3CH_2$), 20.6 (C-8), 20.8 (C-10), 26.3 (C-6), 28.7 (C-5), 47.1 (C-7), 47.7 (C-3), 56.6 (C-4), 64.1 (C-1), 65.8 ($CH_3\underline{C}H_2$), 114.4 (C-2′), 115.9 (C-3′), 142.2 (C-4′), 151.9 (C-1′), 218.1 (C-2, C=O).

(1*R*,3*R*,4*S*)-(1′,1″-Biphenyl-4′-ylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3d), $C_{22}H_{25}NO$, yield 65%, mp 122–123°C, $[\alpha]_D$ +88.1° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3387 (NH), 3028, 2957, 2874, 1746 (C=O), 1611, 1528, 1489, 1449, 1393, 1371, 1323, 1300, 1285, 1196, 1020, 949, 922, 827, 762, 698, 554, 500.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.00 (3H, s, CH_3-8), 1.01 (3H, s, CH_3-10), 1.04 (3H, s, CH_3-9), 1.62–1.83 (3H, m), 2.15 (1H, m), 2.33 (1H, d, J = 4.0, H-4), 3.47 (1H, s, H-3), 6,69 (2H, d, J = 9.0, H-3′), 7.31 (1H, t, J = 7.5), 7.44 (2H, dd, J = 7.5, 8.0), 7.50 (2H, d, J = 9.0, H-2′), 7.59 (2H, d, J = 8.0).

^{13}C NMR spectrum ($CDCl_3$, δ, pm): 9.4 (C-9), 20.7 (C-8), 20.8 (C-10), 26.4 (C-6), 28.7 (C-5), 47.1 (C-7), 47.7 (C-4), 56.8 (C-1), 65.0 (C-3), 113.6 (C-3′), 126.2, 126.4, 128.0, 128.8 (C-2′), 131.2, 141.3, 147.4, 217.8 (C-2, C=O).

Isolation of (1*R*,3*R*,4*S*)-(*p*-Methoxyphenylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3b). The reaction mixture (0.69 g) obtained from reductive amination of camphoroquinone and **2b** in the presence of $NaBH(OAc)_3$ prepared *in situ* was purified by column chromatography (silica gel, hexane:Et_2O, 4:1). The solvent was removed to afford the product as a bright-yellow oil (0.58 g) containing according to TLC (Sorbfil, hexane:Et_2O, 4:1, detection by I_2) two compounds with R_f 0.5 and R_f 0.3. It was found from NMR spectroscopy that these were aminoketone **3b** and aminoalcohol **8b** in a 100:12 ratio. Recrystallization from hot EtOH afforded **3b** with R_f 0.5 as light-yellow fibers. The spectral data agreed with those given above.

General Method for Reduction of 3b and 3d to Aminoalcohols 8b and 8d. A solution of the aminoketone (0.01 mol) in *i*-PrOH (20 mL) was stirred, treated over 10 min with $NaBH_4$ (0.38 g, 0.01 mol) at room temperature and under Ar, stirred for another 19 h, and treated with H_2O (50 mL). The products were separated by extraction (3×) with Et_2O. The organic extract was dried over anhydrous $MgSO_4$. The solvent was removed. The yields of products were 85–86%.

(1*R*,2*S*,3*R*,4*S*)-(*p*-Methoxyphenylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (8b), yield 85%, oil, R_f 0.4 (Sorbfil, hexane:Et_2O, 3:1, detection by I_2). IR spectrum (ν, cm^{-1}): 3402 (OH, NH), 2949, 2883, 2831, 1514, 1462, 1392, 1367, 1238 (C–O), 1143, 1097, 1060, 1037, 819, 779, 520.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.71 (3H, s, CH_3), 1.0 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.51 (1H, m), 1.78 (2H, m), 2.99 (br., OH), 3.3 (1H, d, J = 7.0), 3.70 (1H, d, J = 7.0), 3.77 (3H, s, CH_3O), 6.60 (2H, d, J = 9.0), 6.80 (2H, d, J = 9.0).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.47 (C-8), 21.29 (C-9), 21.89 (C-10), 25.49 (C-5), 33.07 (C-6), 46.82 (C-1), 49.27 (C-7), 51.35 (C-4), 55.83 (C-1), 64.91 (C-3), 79.92 (C-2), 114.89 (C-2), 115.09 (C-3′), 142.64 (C-1′), 152.64 (C-4′).

(1*R*,2*S*,3*R*,4*S*)-3-(1′,1″-Biphenyl-4′-ylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (8d), $C_{22}H_{27}NO$, yield 86%, mp 125–126°C. IR spectrum (ν, cm^{-1}): 3585, 3404 (OH, NH), 2951, 2920, 2880, 1611, 1526, 1485, 1334, 1318, 1185, 1058, 822, 762, 695.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3-9), 1.06 (3H, s, CH_3-8), 1.21 (3H, s, CH_3-10), 1.14–1.26 (2H, m, H-6), 1.60 (1H, m, H-5), 1.83 (1H, m, H-5), 1.90 (1H, d, J = 4.0, H-4), 2.79 (br., OH), 3.47 (1H, d, J = 7.0, H-3), 3.83 (1H, d, J = 7.0, H-2), 4.19 (v.br., NH), 6.76 (2H, d, J = 8.2), 7.33 (1H, t, J = 6.8), 7.46 (2H, dd, J = 6.8, 7.2), 7.52 (2H, d, J = 8.2), 7.60 (2H, d, J = 7.2).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.6 (C-9), 21.3 (C-8), 22.0 (C-10), 26.6 (C-6), 33.2 (C-5), 47.1 (C-7), 49.5 (C-1), 50.7 (C-4), 63.4 (C-3, C–N), 80.1 (C-2, C–O), 113.9, 126.3, 126.4, 128.1, 128.8, 131.1, 141.4, 147.7.

General Method for Multi-component Condensation of *N*-Aryl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-on-3-*exo*-amines (3a-d) or *N*-Aryl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-*exo*-ol-3-*exo*-amine (8d), Dimedone or Meldrum's Acid, and Formaldehyde. The appropriate amine (0.001 mol) and paraformaldehdye (0.12 g, 0.004 mol) in EtOH (25 mL) was refluxed until both components dissolved completely (5 min). The resulting solution was treated with dimedone (Meldrum's acid) (0.14 g, 0.001 mol), refluxed for another 5 min, and cooled. The resulting precipitate was filtered off and washed with EtOH (2 × 5 mL). The mother liquors were left open to air to evaporate most of the solvent. A second crop of product was filtered off. Yields 86–98%.

4″,4″,6′-Trimethyl-1′-{(1*R*,3*R*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-yl}-2′,4′-dihydro-1′*H*-spiro[cyclohexane-1″,3′-quinoline]-2″,6″-dione (6a), $C_{27}H_{35}NO_3$, yield 87%, mp 113–114°C, $[\alpha]_D$ +19.9° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3402, 2957, 2872, 2830, 2733, 1740, 1697, 1611, 1585, 1508, 1458, 1425, 1373, 1319, 1269, 1250, 1211, 1159, 1086, 1047, 1003, 962, 941, 883, 804, 762, 708, 662, 625, 584, 532, 501.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.92 (3H, s, CH_3-9), 0.93 (3H, s, CH_3-8), 0.94 (3H, s, CH_3-10), 1.00 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.62 (2H, m), 1.75 (1H, dd, J = 2.6, 4.0), 2.07 (1H, m), 2.26 (3H, s, CH_3-Ar), 2.29 (1H, d, J = 4.0, H-4), 2.54 (1H, d, J = 14.3), 2.57 (1H, d, J = 14.3), 2.79 (1H, d, J = 14.5), 3.00 (1H, d, J = 15.5), 3.06 (1H, d, J = 14.5), 3.08 (1H, d, J = 15.5), 3.48 (1H, s, H-3), 3.63 (1H, d, J = 12.0), 3.67 (1H, d, J = 12.0), 6.35 (1H, d, J = 8.2, H-8′), 6.94 (1H, d, J = 8.2, H-7′), 6.96 (1H, s, H-5′); eight doublets in the range 2.54–3.67, four methylene groups of the spiro-ring.

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.79 (C-9), 20.45 (C-8), 20.70 (CH_3-Ar), 21.13 (C-10), 26.67 (C-5), 27.75 (CH_3), 29.50 (CH_3), 30.22 (C-6), 30.75 (C-4′), 30.76 (C-4″), 46.19 (C-7), 48.53 (C-4), 49.82 (C-2′), 51.38 (C-4″), 51.62 (C-2′, CH_2–N), 57.98 (C-1), 66.07 (C-spiro), 68.65 (C-3, CH–N), 113.26 (C-8′), 124.47 (C-10′), 127.20 (C-7′), 128.27 (C-6′), 129.45 (C-5′), 142.82 (C-9′), 206.54 (C=O), 206.80 (C=O), 216.88 (C-2, C=O).

4″,4″-Dimethyl-6′-methoxy-1′-{(1*R*,3*R*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-yl}-2′,4′-dihydro-1′*H*-spiro[cyclohexane-1″,3′-quinoline]-2″,6″-dione (6b), $C_{27}H_{35}NO_4$, yield 91%, mp 124–125°C, $[\alpha]_D$ +17.1° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3410, 2953, 2871, 2825, 2732, 1746, 1687, 1623, 1590, 1501, 1455, 1363, 1311, 1253, 1135, 1090, 1013, 969, 801, 764, 589.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, s, CH_3-9), 0.90 (3H, s, CH_3-8), 0.91 (3H, s, CH_3-10), 0.96 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.58 (2H, m, H-5), 1.72 (1H, dd, J = 2.5, 4.0, H-6), 2.04 (1H, m, H-6), 2.25 (1H, d, J = 4.0, H-4), 2.48 (1H, d, J = 14, H-5), 2.52 (1H, d, J = 14, H-5″), 2.77 (1H, d, J = 15, H-3″), 3.03 (1H, d, J = 15, H-4′), 3.08 (1H, d, J = 15, H-4′), 3.10 (1H, d, J = 15, H-3″), 3.36 (1H, s, H-3), 3.54 (1H, d, J = 12, H-2′), 3.68 (1H, d, J = 12, H-2′), 3.73 (3H, s, CH_3O-6′), 6.37 (1H, d, J = 8, H-8′), 6.67 (1H, dd, J = 3.0, 8.0, H-7′), 6.74 (1H, d, J = 3.0, H-5′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 6.58 (C-9), 20.46 (C-8), 20.96 (C-10), 26.40 (C-6), 27.35 (C-5), 29.46 (C-5″), 30.00 (CH_3), 30.01 (CH_3), 30.52 (C-3″), 45.92 (C-7), 48.32 (C-4′), 50.46 (C-3), 51.31 (C-4″), 51.39 (C-2′), 55.36 (C-4), 57.73 (C-1), 66.50 (C-spiro), 68.46 (CH_3–O), 111.40 (C-5′), 114.45 (C-8′), 114.52 (C-7′), 126.58 (C-10′), 139.23 (C-6′), 152.89 (C-9′), 206.09 (C=O), 206.23 (C=O), 216.70 (C-2, C=O).

4″,4″-Dimethyl-6′-ethoxy-1′-{(1*R*,3*R*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-yl}-2′,4′-dihydro-1′*H*-spiro[cyclohexane-1″,3″-quinoline]-2″,6″-dione (6c), $C_{28}H_{37}NO_4$, yield 93%, mp 135–136°C, $[\alpha]_D$ +18.3° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 2963, 2930, 2874, 2783, 1742, 1697, 1614, 1584, 1503, 1472, 1443, 1393, 1372, 1331, 1315, 1240, 1179, 1159, 1115, 1049, 1003, 972, 947, 812, 714, 662, 583, 509.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.39 (3H, t, J = 7.0, $C\underline{H}_3CH_2$). 1.56–1.64 (2H, m, H-5), 1.74 (1H, dd, J = 10.0, 12.0, H-6), 2.06 (1H, m, H-6), 2.26 (1H, d, J = 4.2, H-4), 2.51 (1H, d, J = 14.8), 2.54 (1H, d, J = 14.8), 2.79 (1H, d, J = 14.5), 3.03 (1H, d, J = 15.6), 3.05 (1H, d, J = 14.5), 3.09 (1H, d, J = 15.6), 3.39 (1H, s, H-3), 3.56 (1H, d, J = 11.8), 3.70 (1H, d, J = 11.8), 3.98 (2H, q, CH_2–O) 6.38 (1H, d, J = 8.8, H-8′), 6.68 (1H, dd, J = 2.9, 8.8, H-7′), 6.76 (1H, d, J = 2.9, H-5′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.86 (C-9), 15.16 ($\underline{C}H_3CH_2$), 20.73 (C-8), 21.24 (C-10), 26.70 (C-6), 27.63 (CH_3), 29.78 (CH_3), 30.20 (CH_2), 30.27 (CH_2), 46.22 (C-7), 48.60 (CH_2–N), 50.79 (CH_2), 51.60 (CH_2), 51.70 (CH_2), 58.02 (C-1), 63.86 (CH–N), 66.79 (C-spiro), 68.75 (CH_2–O), 112.41 (C-5′), 114.72 (C-8′), 115.54 (C-7′), 128.84 (C-10′), 139.42 (C-6′), 152.53 (C-9′), 206.44 (C=O), 206.63 (C=O), 217.13 (C-2, C=O).

4″,4″-Dimethyl-6′-phenyl-1′-{(1*R*,3*R*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-yl}-2′,4′-dihydro-1′*H*-spiro[cyclohexane-1″,3″-quinoline]-2″,6″-dione (6d), $C_{32}H_{37}NO_3$, yield 98%, mp 164–165°C, $[\alpha]_D$ +14.0° (*c* 0.1, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3387, 3028, 2959, 2928, 2872, 1746, 1697, 1609, 1520, 1487, 1454, 1389, 1373, 1321, 1283, 1265, 1204, 1161, 1078, 1020, 959, 947, 895, 827, 808, 762, 696, 629, 584, 530, 503.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.96 (3H, s, CH_3), 0.97 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.62–1.83 (3H, m), 2.15 (1H, m), 2.38 (1H, d, J = 4.0, H-4), 2.58 (1H, d, J = 14.5), 2.64 (1H, d, J = 14.5), 2.81 (1H, d, J = 14.7), 3.13 (1H, d, J = 14.6), 3.13 (1H, d, J = 14.7), 3.20 (1H, d, J = 14.6), 3.61 (1H, d, J = 11.7), 3.60 (1H, s, H-3), 3.85 (1H, d, J = 11.7), 6.25 (1H, d, J = 9.1), 7.30 (1H, m), 7.41 (4H, m), 7.58 (2H, m).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.91 (C-9), 20.87 (C-8), 21.27 (C-10), 26.97 (C-6), 27.96 (CH_3), 29.56 (CH_3), 30.30 (C-5), 30.91 (C-4″), 31.48 (CH_2), 46.24 (C-7), 48.78 (C-4), 49.47 (CH_2), 51.46 (CH_3), 51.81 (CH_2), 57.95 (C-1), 65.27 (C-spiro), 68.88 (C-3, CH–N), 113.83, 124.19, 125.51, 126.38, 126.67 (2C), 127.51, 128.80 (2C), 131.59, 141.11, 144.29, 206.23 (C=O), 206.74 (C=O), 216.44 (C-2, C=O).

6′-Methoxy-4″,4″-dimethyl-1′-{(1*R*,3*R*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-yl}-2′,4′-dihydro-1′*H*-spiro{[3″,5″]dioxane-1″,3′-quinoline}-2″,6″-dione (7b), $C_{25}H_{31}NO_6$, yield 87%, mp 137°C. IR spectrum (ν, cm^{-1}): 3407, 2956, 2925, 1740, 1698, 1651, 1619, 1504, 1454, 1383, 1267, 1207, 1161, 1034, 851, 598.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.96 (3H, s, CH_3), 1.55 (1H, ddd, H-5), 1.63 (1H, ddd, H-5), 1.73 (1H, ddd, H-6), 1.76 (3H, s, CH_3–C–O), 1.82 (3H, s, CH_3–C–O), 2.07 (1H, m, H-6), 2.29 (1H, d, J = 4.0, H-4), 3.25 (1H, d, J = 15.8, H-4′), 3.31 (1H, d, J = 15.8, H-4′), 3.40 (1H, s, H-3), 3.57 (1H, d, J = 12.5, H-2′), 3.76 (3H, s, CH_3O-6′), 3.97 (1H, d, J = 12.5, H-2′), 6.57 (1H, d, J = 8.8, H-8′), 6.70 (1H, d, J = 2.9, H-5′), 6.78 (1H, dd, J = 2.9, 8.8, H-7′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.78 (C-9), 20.65 (C-8), 21.10 (C-10), 26.36 (C-6), 28.93 (CH_3), 29.50 (CH_3), 30.14 (C-5), 35.15 (C-4′), 46.49 (C-7), 49.21 (C-4″), 49.58 (C-3), 52.84 (C-2′), 55.68 (C-4), 57.88 (C-1), 69.81 (CH_3O-6′), 105.38 (C-spiro), 112.60 (C-5′), 114.58 (C-8′), 115.01 (C-7′), 124.49 (C-10′), 139.70 (C-6′), 153.23 (C-9′), 167.68 (O–C–O), 168.34 (O–C=O), 216.67 (C-2, C=O).

4″,4″-Dimethyl-6′-phenyl-1′-{(1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2-hydroxybicyclo[2.2.1]heptan-3-yl}-2′,4′-dihydro-1′*H*-spiro[cyclohexane-1″,3″-quinoline]-2″,6″-dione (9d), $C_{32}H_{39}NO_3$, yield 76%, mp 157–159°C. IR spectrum (ν, cm^{-1}): 3380, 2955, 2927, 2872, 1727, 1696, 1613, 1486, 1370, 1199, 1064, 761, 697.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (3H, s, CH_3-9), 0.96 (3H, s, CH_3-8), 1.05 (3H, s, CH_3-10), 1.15 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.55–1.65 (2H, m, H-5), 1.91 (1H, br., OH), 2.42 (1H, d, J = 3.9, H-4), 2.51 (1H, d, J = 13.6), 2.54 (1H, d, J = 13.6), 2.86 (1H, d, J = 14.5), 2.88 (1H, d, J = 14.5), 3.11 (1H, d, J = 15.5), 3.15 (1H, d, J = 3.5, H-2), 3.34 (1H, d, J = 15.5), 3.37 (1H, d, J = 11.9), 3.47 (1H, d, J = 6.5, H-3), 3.81 (1H, d, J = 11.9), 3.88 (1H, br., OH), 6.91 (1H, d, J = 8.4), 7.27 (2H, m), 7.40 (3H, m), 7.52 (2H, d, J = 7.4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.44 (C-9), 22.16 (C-8), 22.58 (C-10), 27.75 (CH_3), 28.99 (C-6), 29.58 (CH_3), 30.93 (C-4″), 32.47 (C-4′), 36.26 (C-5), 46.86 (C-4), 47.51 (C-7), 48.28 (C-2′), 49.49 (C-1), 51.60 (CH_2), 51.94 (CH_2), 62.90 (C-spiro), 70.89 (C-3), 82.73 (C-2), 113.99, 120.47, 126.50, 126.56, 126.89 (2C), 127.01, 128.79 (2C), 131.41, 140.86, 145.48, 206.79 (C=O), 207.05 (C=O).

Bis-*N*,*N*′-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-on-3-*exo*-yl)-*p*-phenylenediamine (11), $C_{26}H_{36}N_2O_2$, yield 90%, mp 206–207°C, $[\alpha]_D$ +131.7° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3360 (NH), 2956, 2879, 2819, 1745 (C=O), 1518 (C=O), 1477, 1448, 1317, 1263, 1026, 817.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.95 (6H, s, H-8,10), 0.97 (3H, s, H-9), 1.55–1.80 (2H, m, H-5), 1.60 and 2.07 (both 1H, m, H-6), 2.21 (1H, d, J = 4.1, H-4), 3.30 (1H, s, H-3), 3.79 (1H, br., NH), 6.51 (2H, s, Ar).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.3 (C-9), 20.5 (C-8), 20.8 (C-10), 26.2 (C-5), 28.7 (C-6), 46.9 (C-7), 47.7 (C-4), 56.5 (C-1), 65.9 (C-3), 114.7 (C-12), 140.6 (C-11), 218.0 (C=O).

1′,6′-Di-(1,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)-4,4,4″,4″-tetramethyl-1′,2′,3′,4′,5′,7′,8′,9′-octahydrobispiro[cyclohexane-1,3′-pyrido[2,3-*g*]quinoline-8′,1″-cyclohexane]-2,2″,6,6″-tetraone (12), $C_{46}H_{60}N_2O_6$, yield 85%, mp 201–202°C, $[\alpha]_D$ –9.4° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 2958. 2872, 1743, 1697 (C=O), 1506 (C=C), 1456, 1423, 1390, 1371, 1325, 1242 (C–O–C), 1010, 954, 860.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, s, H-9), 0.88 (3H, s, H-8), 0.93 (3H, s, H-10), 0.99 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.55–1.78 (3H, m, 2H-5, H-6), 2.07 (1H, m, H-6), 2.32 (1H, d, J = 4.1, H-4), 2.43 (2H, m, J = 14.8), 2.89 (1H, d, J = 14.4), 3.05 (1H, d, J = 15.9), 3.14 (1H, d, J = 15.9), 3.23 (1H, d, J = 14.4), 3.4 (1H, s, H-3), 3.56 (1H, d, J =11.8), 3.71 (1H, d, J = 11.8), 6.28 (1H, s, Ar), eight doublets in the range 2.43-3.71, methylene protons of the spiro-ring.

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.9 (C-9), 20.8 (C-8), 21.3 (C-10), 26.8 (C-5), 27.0 (C-27), 28.4 (C-6), 30.2 (C-18), 30.4 (C-26), 30.9 (C-23), 46.1 (C-7), 48.7 (C-4), 51.6 (C-20), 51.7 and 51.8 (C-22,24), 57.9 (C-1), 66.3 (C-spiro), 68.8 (C-3), 115.0 (C-12), 123.0 (C-17), 138.1 (C-11), 206.5 (C=O), 207.1 (C=O), 217.3 (C-2, C=O).

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