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Synthesis of regioisomeric (*S*)-(+)-3,3,4-trimethyl-8-methoxy-3,4-dihydrobenzo[*h*]-isoquinolin-1(2*H*)-one and (*S*)-(+)-1,2,2-trimethyl-8-methoxy-1,2-dihydrobenzo[*f*]-isoquinolin-4(3*H*)-one by the Ritter reaction

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The conservation of chirality at the α-position to the carbocationic centre of (*S*)-(–)-2-methyl-3-(6-methoxynaphth-2-yl)butan-2-ol and the formation of regioisomeric (*S*)-(+)-1,2,2-trimethyl-8-methoxy-1,2-dihydrobenzo[*f*]isoquinolin-4(3*H*)-one were found in the synthesis of (*S*)-(+)-3,3,4-trimethyl-8-methoxy-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one by the Ritter reaction.

The enantioselective synthesis of substituted 3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines and condensed derivatives is of interest.[1,2] In the development of a method for the synthesis of 3,3-dimethyl-3,4-dihydrobenzo[*h*]isoquinoline,[3] we postulated an equilibrium between α- and β-carbocations (**1** and **2**) and showed that only tertiary β-carbocation **2** is able to cyclisation by the Ritter reaction (Scheme 1). In this work, we studied chirality conservation at the α-position to carbocation **2** during the Ritter reaction (Scheme 1). Optically active (*S*)-(–)-2-methyl-3-(6-methoxynaphth-2-yl)butan-2-ol **3** was easily obtained by the Grignard synthesis from ethyl (*S*)-(+)-(6-methoxynaphth-2-yl)-propionate (ethyl naproxenate). Substituted 6-metoxynaphthalenes were chosen inasmuch as a mixture of benzo[*h*]- and benzo[*f*]-isoquinolines was obtained earlier in the Bischler–Napieralsky reaction of *N*-[2-(6-methoxynaphth-2-yl)ethyl]benzamide.[4]

Alcohol **3** reacts with methyl thiocyanate in the presence of concentrated (96%) sulfuric acid, yielding a mixture of thioethers (*S*)-**6** and (*S*)-**7**, isolated as hydrochlorides. The conservation of chirality in carbenium ion (*S*)-**2** leads to a conclusion that (*S*)-**2** is captured by metyl thiocyanate in a fast reaction before its racemization, yielding intermediate nitrilium ion (*S*)-**4**. In our opinion, the reaction passes through spiro-intermediate (*S*)-**5**, and two regioisomeric thioethers (*S*)-**6** and (*S*)-**7** are formed by sigmatropic shift in (*S*)-**5** (Scheme 1).†

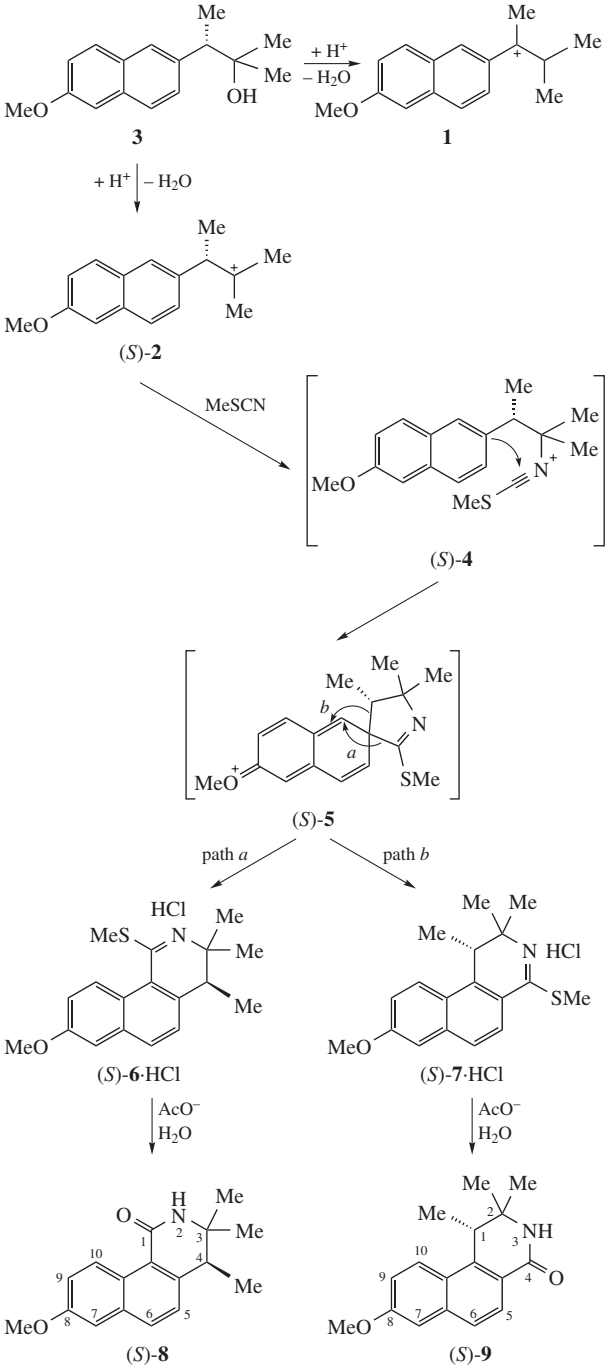
Hydrolysis of this mixture by a known method[5] yields two regioisomers: (*S*)-3,3,4-trimethyl-8-methoxy-3,4-dihydrobenzo-[*h*]isoquinolin-1(2*H*)-one [(*S*)-**8**, 45%] and (*S*)-(+)-1,2,2-trimethyl-8-methoxy-1,2-dihydrobenzo[*f*]isoquinolin-4(3*H*)-one [(*S*)-**9**, 14%], which were separated by column chromatography.

We failed to appreciate the enantiomeric excess of compounds **8** and **9**. This is due to the low basicity of isoquinolin-

† *(S)-(+)-2-(6-Methoxy-2-naphthyl)propionic acid (naproxene)* was obtained from a medicinal form of *Naproxene* by treating with 10% H_2SO_4, filtration, washing with water, drying and crystallization from hexane; mp 157–158 °C, $[\alpha]_D^{20}$ +66±2°.

Ethyl ester of naproxene was obtained by usual esterification. Yield 90%, mp 72–73 °C (hexane), $[\alpha]_D^{17}$ +42.1° (*c* 1, $CHCl_3$). Found, (%): C, 74.51; H, 7.09. Calc. for $C_{16}H_{18}O_3$ (%): C, 74.40; H, 7.02.

(S)-(–)-2-Methyl-3-(6-methoxy-2-naphthyl)butan-2-ol **3**: ethyl ester of naproxene (10.32 g, 0.04 mol) in 50 ml of diethyl ether was added to 0.12 mol of methylmagnesium iodide (from 2.88 g of Mg and 17.04 g of MeI in 200 ml of ether). The reaction mass was refluxed for 2 h, cooled, and 100 ml of saturated NH_4Cl was added. The organic layer was separated; the water layer was extracted with diethyl ether (2×50 ml); the combined organic layer was treated by saturated $NaHCO_3$ and brine, dried by $MgSO_4$; the residue after removing of diethyl ether was crystallised from hexane. Yield 7.13 g (65%), mp 129–130 °C. $[\alpha]_D^{19}$ –17.9° (*c* 1, $CHCl_3$). Found (%): C, 78.59; H, 8.37. Calc. for $C_{16}H_{20}O_2$ (%): C, 78.65; H, 8.25.



Scheme 1

1(2*H*)-ones, which cannot form diastereomeric salts with optically active acids. Our attempts to acylate the model compound 3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline by naproxenyl chloride also failed. Probably, this fact can be explained by serious sterical hindrance of the N atom due to gem-dimethyl groups at C(3).

The structures of compounds (*S*)-**8** and (*S*)-**9** were confirmed by elemental analysis and ^{1}H and ^{13}C NMR data‡ using 2D hetero-nuclear correlation experiments HETCOR. The absolute configuration of compound (*S*)-**9** was determined by X-ray analysis (Figure 1).§

The molecular structure of (*S*)-**9** is given in Figure 1. The naphthalene fragment is plane within ±0.014(2) Å with usual bond lengths. The heterocyclic fragment has a form of a highly distorted bath; the atoms N(3) and C(2) have deviations of 0.285(5) and 0.772(5) Å, respectively, from the C(1)–C(10B)–C(4A)–C(4) plane. The same heterocycle conformation and bond lengths were found in (+)-4-(fluoromethyl)-7-nitro-3,4-dihydroisoquinolin-1(2*H*)-one.[7] In crystal fragments of **9** are dimeric due to H-bonds N(3)–H(3)···O(4) [N–H 0.89(3) Å,

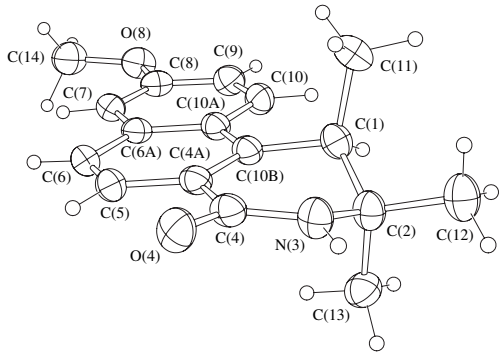


Figure 1 Molecular structure of compound **9**.

A mixture of *1-methylthio-3,3,4-trimethyl-8-methoxy-3,4-dihydrobenzo-[*h*]isoquinoline* [(*S*)-**6**·HCl] and *4-methylthio-1,2,2-trimethyl-8-methoxy-1,2-dihydrobenzo[*f*]isoquinoline* [(*S*)-**7**·HCl] was obtained by the known method.[3] A mixture of compound **3** (1.8 g, 4.8 mmol) and methyl thiocyanate (0.38 ml, 5.5 mmol) in 10 ml of toluene was added dropwise with intense stirring to 98% sulfuric acid (6 ml, 110 mmol) for 0.5 h at room temperature. The reaction mixture was stirred for 0.5 h and poured into 200 ml of cold water. The aqueous layer was separated, made basic (pH ~8) with NH_4OH and extracted with diethyl ether (3×50 ml). The combined organic extracts were washed with brine (50 ml) and dried with anhydrous $MgSO_4$. A flow of dry HCl was passed through the solution. A mixture of hydrochlorides (*S*)-**6**·HCl and (*S*)-**7**·HCl was separated. Recrystallization from ethyl acetate yielded pure (*S*)-**6**·HCl, 51%, mp 159–160 °C. ^{1}H NMR (500 MHz, [^{2}H$_6$]DMSO) δ: 1.21 [d, 3H, C(4)Me, *J* 7 Hz], 1.28 [s, 3H, C(3)Me$_{pseudoax}$], 1.35 [s, 3H, C(3)Me$_{pseudoeq}$], 3.07 (s, 3H, SMe), 3.74 [q, 1H, C(4)H, *J* 7 Hz], 3.92 (s, 3H, OMe), 7.25–8.07 [m, 4H, C(5)H, C(6)H, C(7)H and C(9)H], 8.60 [d, 1H, C(10)H, *J* 9 Hz], 12.74 (br. s, 1H, HCl). Found (%): C, 72.29; H, 7.17; N, 4.73; S, 10.70. Calc. for $C_{18}H_{21}NOS$ (%): C, 72.20; H, 7.07; N, 4.68; S, 10.71.

In a mother liquor, compound (*S*)-**7**·HCl retaines; it was not isolated in a pure form. ^{1}H NMR (500 MHz, [^{2}H$_6$]DMSO) δ: 1.21 [d, 3H, C(1)Me, *J* 7 Hz], 1.34 [s, 3H, C(2)Me$_{pseudoax}$], 1.97 [s, 3H, C(2)Me$_{pseudoeq}$], 3.29 (s, 3H, SMe), 3.69 [q, 1H, C(1)H, *J* 7 Hz], 3.94 (s, 3H, OMe), 7.12 [m, 1H, C(9)H], 7.30 [d, 1H, C(7)H, *J* 3 Hz], 7.61 [d, 1H, C(6)H, *J* 9 Hz], 7.81 [d, 1H, C(5)H, *J* 9 Hz], 8.55 [d, C(10)H, *J* 8 Hz], 12.30 (br. s, 1H, HCl).

‡ *(S)-3,3,4-Trimethyl-8-methoxy-3,4-dihydrobenzo[h]isoquinolin-1(2*H*)-one* [(*S*)-**8**], *(S)-1,2,2-trimethyl-8-methoxy-1,2-dihydrobenzo[f]isoquinolin-4(3*H*)-one* [(S)-**9**] were obtained after the hydrolysis (aqueous AcOH/NaOAc) of a mixture of (*S*)-**6**·HCl and (*S*)-**7**·HCl by the known method.[5] Total yield, 85%. Compounds (*S*)-**8** and (*S*)-**9** were separated by column chromatography (silica gel, hexane–diethyl ether, gradient elution from 9:1 to 1:1).

Compound (*S*)-**8**, R_f 0.50 (silasorb, $CHCl_3$–acetone, 9:1), mp 174–175 °C (from ethanol), yield 45%, $[\alpha]_D^{20}$ +1.9° (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, [^{2}H$_6$]DMSO) δ: 1.13 [s, 3H, C(3)Me$_{pseudoax}$], 1.18 [d, 3H, C(4)Me, *J* 7 Hz], 1.19 [s, 3H, C(3)Me$_{pseudoeq}$], 2.86 [q, 1H, C(4)H, *J* 7 Hz], 3.87 (s, 3H, OMe), 7.20 [m, 1H, C(9)H, $J_{9,10}$ 9 Hz, $J_{7,9}$ 3 Hz], 7.32 [d, 1H, C(7)H, $J_{9,7}$ 3 Hz], 7.39 [d, 1H, C(5)H, $J_{5,6}$ 8 Hz], 7.80 (s, 1H, NH), 7.94 [d, 1H, C(6)H, $J_{5,6}$ 8 Hz], 9.37 [m, 1H, C(10)H, $J_{10,9}$ 9 Hz]. ^{13}C NMR (75 MHz, [^{2}H$_6$]DMSO) δ: 164.7 (C=O), 156.5 [C(8)], 142.2 [C(4a)], 134.1 [C(6a)], 131.6 [C(6)], 127.9 [C(10)], 126.3 [C(5)], 126.2 [C(10a)], 121.5 [C(10b)], 119.3 [C(9)], 106.4 [C(7)], 55.0 (OMe), 52.2 [C(3)], 43.3 [C(4)], 28.7 [C(3)Me$_{pseudoax}$], 24.4 [C(3)Me$_{pseudoeq}$], 16.7 [C(4)Me]. Found (%): C, 75.94; H, 7.20; N, 5.33. Calc. for $C_{17}H_{19}NO_2$ (%): C, 75.81; H, 7.11; N, 5.20.

*(S)-1,2,2-Trimethyl-8-methoxy-1,2-dihydrobenzo[f]isoquinoline-4(3*H*)-one* [(*S*)-**9**], R_f 0.35 (silasorb, $CHCl_3$–acetone, 9:1). Yield 14%, mp 216–218 °C (from propan-2-ol–hexane), $[\alpha]_D^{24}$ +99.7° (*c* 1.75, $CHCl_3$). ^{1}H NMR (500 MHz, [^{2}H$_6$]DMSO), δ: 1.10 [s, 3H, C(2)Me$_{pseudoax}$], 1.13 [d, 3H, C(1)Me, *J* 7 Hz], 1.33 [s, 3H, C(2)Me$_{pseudoeq}$], 3.51 [q, 1H, C(1)H, *J* 7 Hz], 3.91 (s, 3H, OMe), 7.26 [m, 1H, C(9)H, $J_{9,10}$ 9 Hz, $J_{9,7}$ 3 Hz], 7.74 [d, 1H, C(7)H, $J_{7,9}$ 3 Hz], 7.74 [d, 1H, C(6)H, $J_{6,5}$ 8 Hz], 7.74 (s, 1H, NH), 7.90 [d, 1H, C(5)H, $J_{5,6}$ 8 Hz], 8.09 [d, 1H, C(10)H, $J_{10,9}$ 9 Hz]. ^{13}C NMR (75 MHz, [^{2}H$_6$]DMSO) δ: 164.1 (C=O), 158.3 [C(8)], 142.2 [C(10b)], 136.8 [C(7a)], 125.9 [C(10)], 125.2 [C(6)], 124.9 [C(10a)], 124.0 [C(5)], 122.1 [C(4a)], 119.1 [C(9)], 107.2 [C(7)], 55.3 (OMe), 52.8 [C(2)], 37.7 [C(1)], 29.2 [C(2)Me$_{pseudoax}$], 25.3 [C(2)Me$_{pseudoeq}$], 16.7 [C(1)Me]. Found (%): C, 75.86; H, 7.06; N, 5.18. Calc. for $C_{17}H_{19}NO_2$ (%): C, 75.81; H, 7.11; N, 5.20.

H···O 2.04(3) Å, N···O 2.931(4) Å, N–H···O 175(2)°] and are packed according to a centered motif.

Thus, begining from (*S*)-(+)-naproxene, syntheses of optically active (*S*)-3,3,4-trimethyl-8-methoxy-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one [(S)-**8**] and its regioisomer (*S*)-(+)-1,2,2-trimethyl-8-methoxy-1,2-dihydrobenzo[*f*]isoquinolin-4(3*H*)-one [(*S*)-**9**] were carried out. Due to the low basicity, compounds **8** and **9** do not form salts with commonly used optically active acids (tartaric, lactic and mandelic). The corresponding substituted 1,2,3,4-tetrahydroisoquinolines obtained by the reduction of compounds **8** and **9** with $LiAlH_4$ in ether, also elude to form crystalline diastereomeric salts with acids.

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§ *X-ray data for* (*S*)-**9**. $C_{17}H_{19}NO_2$, $M = 269.34$, orthorhombic, $a = 7.866(6)$, $b = 11.480(10)$ and $c = 32.45(3)$ Å, $V = 2931(4)$ Å^3, space group *Pbca*, $Z = 8$, $d_{calc} = 1.221$ g cm^{-3}, $\mu = 0.08$ mm^{-1}, crystal size 0.8×0.36×0.24 mm, 2585 reflections measured [$R = 0.0593$ for 1559 $F_0 > 4\sigma(F)$].

The data were measured on a Bruker P4 diffractometer with graphite-monochromated MoKα radiation using $\theta/2\theta$ scans. The structure was solved by the direct method using the SHELXS-97 program and refined in the full-matrix anisotropic (isotropic for H atoms) approximation by the SHELXS-97 program.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 270419. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2005.

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