# Synthesis of Scopin Acetate and 6,7-Didehydrohyoscyamin. Intramolecular Phenylsulfenylation of a Nonactivated Methylene Group of Ethyl *N*-Demethyl-3-*O*-(phenylthio)tropine-*N*-carboxylate

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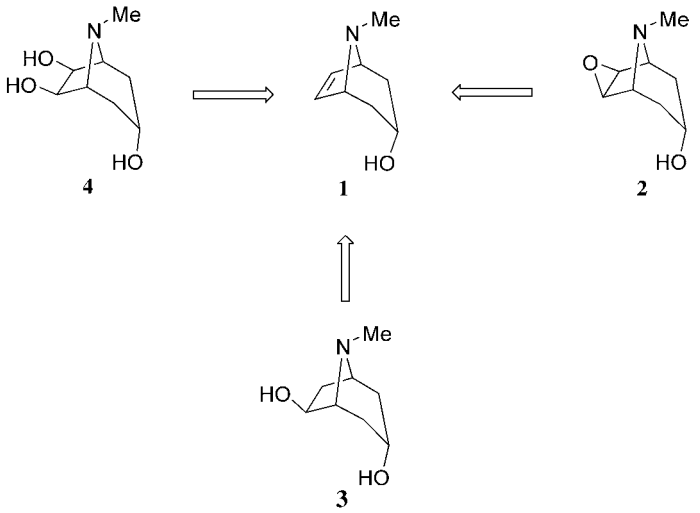
The synthesis of scopin acetate (**6b**) and 6,7-didehydrohyoscyamine (**17**) was achieved by using tropine (**5**) as the starting compound. Formal (phenylthio)-radical transfer to the nonactivated 6-position of ethyl *N*-demethyl-3-*O*-(phenylthio)tropine-*N*-carboxylate (**9**) by irradiation in the presence of hexabutyldistannane is a key step of this synthetic approach, involving ethyl 6,7-didehydro-*N*-demethyltropine-*N*-carboxylate (**15**) as a synthetic intermediate (*Schemes 3* and *5*). The reaction of **9** with tributylstannane in the presence of ethyl acrylate, as a radicophilic olefin, involves *Michael*-type alkylation at C(6) of the tropine skeleton affording ethyl *N*-demethyl-*N*-(ethoxycarbonyl)tropine-6-propanoate (**18**) (*Scheme 6*).

**Introduction.** – The 6,7-didehydrotropine (**1**) is an important compound and common synthetic intermediate in the synthesis of a variety of tropane alkaloids [1]. On oxidation of the olefinic bond by suitable reagents, **1** is generally converted to alkaloids having an O-functional group(s) at C(6) (and/or C(7)). Several naturally occurring tropane alkaloids, including scopin (**2**) [2], valerin (**3**) [2a], teolidine (**4**) [1a,b][3], and others, have been synthetized by using **1** as a key synthetic intermediate (*Scheme 1*). Scopolamine (**6c**), isolated from *Scopola carniolica*, is an important anticholinergic agent that has also been synthetized from **1** [1c][2a][4].

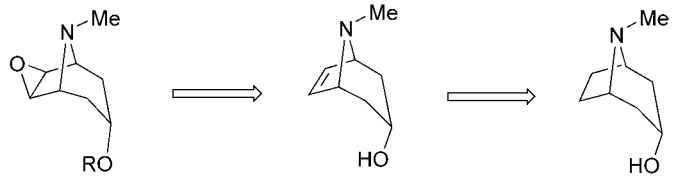
There are several approaches to the synthesis of 6,7-didehydrotropine (**1**) [2a–c] [5–7]. Introduction of an olefinic bond (6,7-position) into the tropine skeleton in our synthetic protocol is based on the elimination of a phenylsulfinyl group from 6(7)-(phenylsulfinyl)tropine. Some years ago, we have discovered that photolytically induced decomposition of alkyl benzenesulfenates in the presence of hexabutyldistannane (to initiate a chain reaction) involves an intramolecular radical reaction at the nonactivated C-atom with introduction of a phenylthio group at the $\delta$-position of the alkyl group [8]. This type of functionalization of the nonactivated methylene group at the 6-position of the tropane skeleton and introduction of a good leaving group at $CH_2$(6) could offer an efficient approach to 6,7-didehydrotropine (**1**) and scopine derivatives **6** by using tropine (**5**) as a starting compound (*Scheme 2*).

The key step in the conversion of tropine (**5**) to 6,7-didehydrotropine (**1**) is the intramolecular 1,5-H transfer from the 6-position to the 3-*endo*-alkoxy radical intermediate [9]. This transposition of the radical center in the tropine molecule is possible because it possesses an appropriate configuration favoring the 1,5-H shift. In the fixed conformation of tropine, the distance between the O-atom and C(6) is *ca.* 2.6 Å, while the O···HC(6) distance of 2.2 Å is almost optimal.

*Scheme 1*




*Scheme 2*




**6a** R = H, scopin
**b** R = Ac, scopin acetate
**c** R = tropoyl, scopolamine

Transposition of the 3-*endo*-alkoxy radical center derived from tropine (**5**) has not been observed previously, although a favorable configuration exists. Thus, $Pb(OAc)_4$ oxidation of **5** and photolysis of tropine nitrite did not lead to functionalization of the nonactivated methylene group in 6-position [9][10][1]). It was necessary to convert the tertiary amino group (N(8)) to an amido group, and only after this structural change, a transposition of the radical center and functionalization at C(6) was possible. There is no explanation so far on how this change of the substituent at N(8) of the tropine skeleton influences 1,5-H migration.

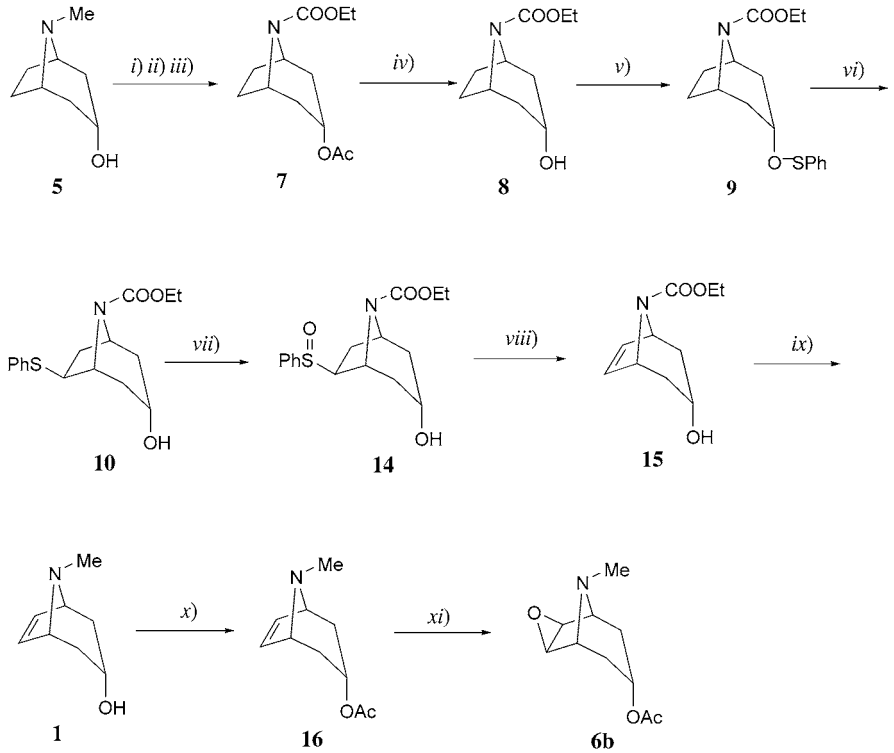
To introduce a latent good leaving group at C(6) of the tropine skeleton, we converted tropine (**5**) to alkyl *N*-demethyltropine-*N*-carboxylate. Thus, the ethyl ester **8** was prepared from **5** by the following reaction sequence: acetylation of the OH group

[1]) Also, intramolecular functionalization of tropine (**5**) by hypoiodite and hypobromite reactions as well as by phenyliodoso diacetate oxidation were unsuccessful [11].

by acetyl chloride gave acetate [2c], which was treated with ethyl carbonochloridate (→ **7**). Subsequent demethylation and selective hydrolysis of the acetyl group afforded ethyl ester **8** (*Scheme 3*) [12]. Then **8** was converted in 78% yield to benzenesulfenate derivative **9** as a good precursor of the alkoxy radical [8][13] by esterification with benzenesulfenyl chloride in $Et_3N$.

Phenylsulfenylation of the nonactivated $CH_2$(6) group of the tropine skeleton was achieved by a sequence of radical reactions involving formal migration of the phenylthio group from an O- to a C-atom [8]. The conversion of ethyl *N*-demethyl-3-*O*-(phenylthio)tropine-*N*-carboxylate (**9**) to the 6-(phenylthio)tropine derivative **10** was achieved in 45% yield by irradiation of **9** with a high-pressure Hg lamp in the presence of hexabutyldistannane (12 mol-%) in benzene solution [7].

*Scheme 3*

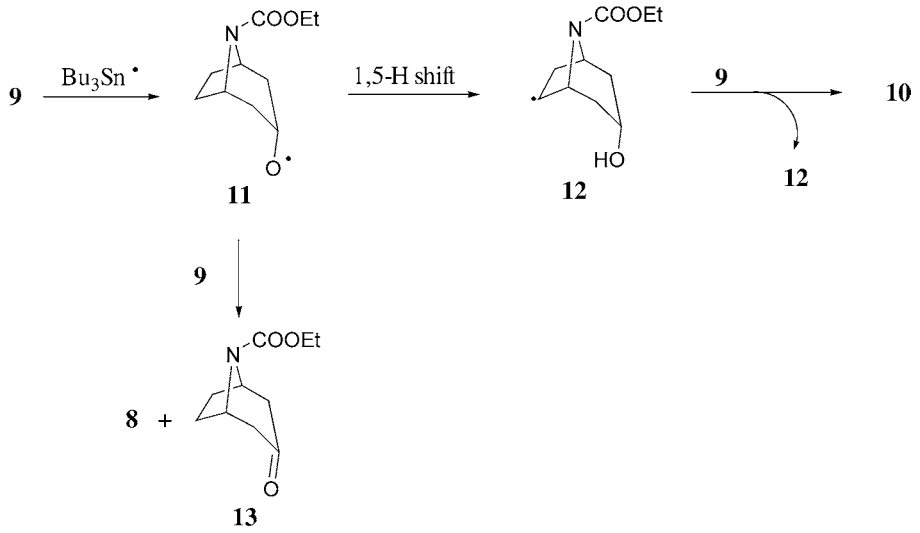



*i*) AcCl, $CHCl_3$, Δ. *ii*) KOH (89%). *iii*) ClCOOEt, PhH, Δ (91%). *iv*) KOH, MeOH, THF, $H_2O$ (100%). *v*) PhSCl, $Et_3N$, $CH_2Cl_2$, −78° (97%). *vi*) $(Bu_3Sn)_2$, PhH, *hv* (45%). *vii*) *m*-CPBA, $CH_2Cl_2$, −78° (91%). *viii*) PhMe, reflux (98%). *ix*) $LiAlH_4$, $Et_2O$, r.t. (85%). *x*) 1. AcCl, $CHCl_3$, Δ; 2. KOH (93%). *xi*) 90% $H_2O_2$ soln., HCOOH, r.t. (40%).

Phenylsulfenylation of the remote nonactivated $CH_2$ group involves an alkoxy radical **11**, which undergoes a 1,5-H shift to give the C-radical **12**. Abstraction of the phenylthio group from the starting benzenesulfenate derivative **9** proceeds preferentially under *exo*-approach of radical **12**, involving an intermediary sulfuranyl radical,

thus affording only the 6-*exo*-(phenylthio) tropine derivative **10** (*Scheme 4*) [14]. In addition to the main reaction product **10**, ethyl *N*-demethyltropine-*N*-carboxylate (**8**; 37% yield) and ethyl *N*-demethyl-3-oxotropine-*N*-carboxylate (**13**) (15% yield) were also obtained as products of disproportionation of alkoxy radical **11**.

*Scheme 4*

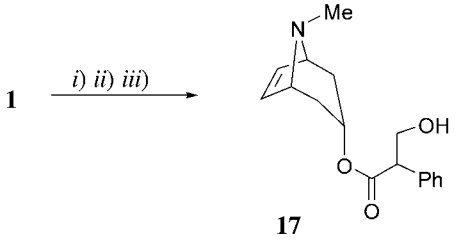



The 6-*exo*-(phenylthio)tropine derivative **10** was oxidized with 3-chloroperbenzoic acid (*m*-CPBA) to the corresponding sulfoxide **14** (*Scheme 3*) [15]. Selective oxidation of the phenylthio group, without attack at the tertiary N-atom, was achieved when the reaction was performed at $-78°$. Elimination of the phenylsulfinyl group from **14** was realized by heating in boiling toluene to give the 6,7-didehydrotropine derivative **15** [15][16]. Reduction of the carbamate moiety of **15** by $LiAlH_4$ gave 6,7-didehydrotropine (**1**) [9a], which was acetylated to the 6,7-didehydrotropine acetate (**16**). Epoxidation of **16** with 90% $H_2O_2$ solution in formic acid afforded scopin acetate (**6b**) [2c]. The $^1$H-NMR spectrum of **6b** shows that epoxidation of the olefinic bond takes place exclusively from the *exo*-side.

Synthesis of 6,7-didehydrohyoscyamin (**17**) was realized by conversion of 6,7-didehydrotropine (**1**) to its ammonium tosylate salt, which was esterified by *O*-acetyltropoyl chloride (*Scheme 5*) [17].

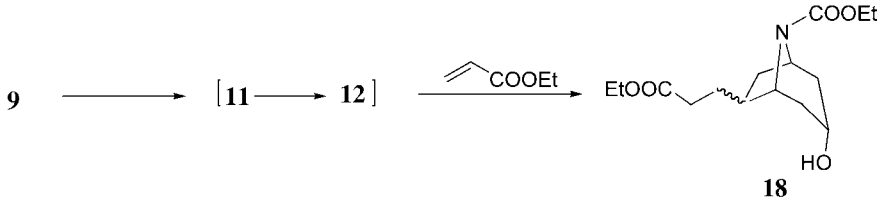
The functionalization of the nonactivated C-atom at the 6-position of the tropine skeleton *via* alkoxy radical **11** and C-radical **12** as the intermediates [9] offers some other synthetically valuable possibilities such as *Michael*-type alkylation of C-radical **12** [9a,b]. Thus, by irradiation of **9** in the presence of excess ethyl acrylate (10 mol-equiv.) and $Bu_3SnH$, alkylation took place and ethyl *N*-demethyl-*N*-(ethoxycarbonyl)tropine-6-propanoate (**18**) was obtained in 31% yield; excess ethyl acrylate was used to favor the intermolecular addition of radical **12** to the olefinic bond (*Scheme 6*).

*Scheme 5*




*i*) TsOH, $Et_2O$. *ii*) $AcOCH_2CH(Ph)COCl$. *iii*) 6M HCl (85%).

*Scheme 6*




The presented methodology offers a convenient route for the introduction of a functionalized alkyl chain at the 6-position of the tropine molecule and for the synthesis of a variety of new tropine derivatives.

## Experimental Part

*General*. Solvents used in all of the experiments were purified by distillation before use (benzene distilled over $CaH_2$ and $CH_2Cl_2$ over $P_2O_5$). Purifications and separations of the reaction products were carried out by distillation and column (CC) or flash chromatography (FC) CC (silica gel 100–200 mesh (60 Å), basic and neutral alumina). FC: dry mode; silica gel (60 Å). Reactions were monitored by TLC (silica gel TLC 60 Å or aluminium oxide $PF_{254+366}$). IR Spectra: $\tilde{\nu}_{max}$ in $cm^{-1}$; *Perkin-Elmer 457* grating instrument. NMR Spectra: $\delta$ in ppm, $J$ in Hz; $CDCl_3$ solns. if not otherwise stated; at 200 ($^1$H) or 50 ($^{13}$C) MHz; *Varian Gemini-200* spectrometer. *Finningan ITDS-700* instrument; in $m/z$ (rel. %).

*Tropine Acetate* (= *(3*-endo*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-ol Acetate*). Tropine (**5**) was acetylated with acetyl chloride in $CHCl_3$: tropine acetate (89%). Colorless oil. B.p. 60°/0.1 Torr. IR (neat): 1734, 1379, 1367, 1265, 1238, 1220, 1065, 1037. $^1$H-NMR: 1.70 (*d*, $J$ = 14.6, 2 H); 1.91–2.17 (*m*, 6 H); 2.04 (*s*, 3 H); 2.27 (*s*, 3 H); 3.10 (*m*, 2 H); 4.96 (*t*, $J$ = 5.4, 1 H). $^{13}$C-NMR: 169.98; 67.11; 59.45; 40.17; 36.31; 25.20; 21.20.

*Ethyl (3*-endo*)-3-(Acetyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate* (**7**). To the soln. of tropine acetate (4.6 g, 0.025 mol) in benzene (150 ml), ethyl carbonochloridate (10.2 g, 0.094 mol) was added. The mixture was stirred and refluxed for 10 h. The cold mixture was diluted with $CH_2Cl_2$ (100 ml) and washed with 2M HCl (50 ml), the aq. phase extracted with $CH_2Cl_2$ (5 × 50 ml), the combined org. phase washed with sat. aq. $NaHCO_3$ soln., dried ($Na_2SO_4$), and evaporated, and the oily residue destilled: **7** (91%). B.p. 117°/0.4 Torr. IR (neat): 1822, 1738, 1703, 1468, 1422, 1384, 1369, 1358, 1316, 1265, 1240, 1213, 1169, 1105, 1080, 1036. $^1$H-NMR: 1.26, 1.37 (2*t*, $J$ = 7, 20, 3 H); 1.76 (*dd*, $J$ = 15.40, 1.20, 2 H); 1.90–2.20 (*m*, 6 H); 2.07 (*s*, 3 H); 4.14, 4.34 (2*q*, $J$ = 7.20, 2 H); 4.20–4.34 (br. *s*, 2 H); 5.08 (*t*, $J$ = 5.00, 1 H). $^{13}$C-NMR: 170.25; 153.70; 67.75; 65.89; 60.85; 52.20; 35.71; 35.00; 28.17; 27.50; 21.49; 14.66; 13.82.

*Ethyl (3*-endo*)-3-Hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate* (**8**). A soln. of **7** (4.9 g, 0.02 mol) in MeOH (3.2 ml) and THF (7.6 ml) was treated with a soln. of KOH (3.9 g, 0.068 mol) in $H_2O$ (6 ml). The mixture was stirred at r.t. for 2 h, and $H_2O$ (100 ml) was added. The mixture was extracted with $CH_2Cl_2$ (5 × 100 ml), and the combined extract was washed with 2M HCl (50 ml) and $H_2O$, dried ($Na_2SO_4$), and evaporated. The oily residue crystallized on standing. **8** (4.0 g, quant.). IR (KBr): 3442, 1674, 1469, 1435, 1384, 1370, 1355, 1345, 1327, 1262, 1221, 1171, 1111, 1088, 1044. $^1$H-NMR: 1.25 (*t*, *J* = 7.2, 3 H); 1.74 (*dd*, *J* = 14.6, 1.4, 2 H); 1.84–2.30 (*m*, 6 H); 3.62 (br. *s*, 1 H); 4.10 (*q*, *J* = 7.2, 2 H); 4.11 (*m*, 1 H); 4.23 (br. *s*, 2 H). $^{13}$C-NMR: 153.81; 64.78; 60.71; 52.57; 38.20; 38.12; 28.27; 27.71; 14.60.

*Ethyl (3*-endo*)-3-(Phenylthiooxy)-8-azabicyclo[3.2.1]octane-8-carboxylate* (**9**). To the soln. of **8** (4.0 g, 0.02 mol) and $Et_3N$ (5.1 g, 0.05 mol) in $CH_2Cl_2$ (150 ml), cooled to −78° under Ar, benzenesulfenyl chloride (3.7 g, 0.025 mol) was added dropwise during 10 min. The mixture was stirred at −78° for 40 min and then allowed to reach r.t. To the mixture was added $CH_2Cl_2$ (400 ml), and the soln. was washed successively with 2M HCl (50 ml), sat. aq. $NaHCO_3$ soln., and $H_2O$. The resulting org. soln. was dried ($Na_2SO_4$) and evaporated and the oily residue purified by FC (silica gel, petroleum ether/acetone 10:0 → 8:2): **9** (6.0 g, 97%). Pale yellow crystals. M.p. 45°. IR (KBr): 2000–1800, 1696, 1583, 1477, 1439, 1383, 1354, 1325, 1314, 1225, 1212, 1169, 1107, 1032. $^1$H-NMR: 1.23 (*t*, *J* = 7.0, 3 H); 1.89–2.13 (*m*, 8 H); 3.78 (*m*, 1 H); 4.11 (*q*, *J* = 7.0, 2 H); 4.24 (*m*, 2 H); 7.11–7.40 (*m*, 5 H). $^{13}$C-NMR: 153.67; 140.05; 128.92; 126.43; 123.74; 80.00; 60.70; 52.15; 36.13; 35.53; 28.24; 27.61; 14.64. CI-MS: 308 (100, $[M+1]^+$). Anal. calc. for $C_{16}H_{21}NO_3S$: C 62.54, H 6.84, N 4.56; found: C 62.68, H 7.05, N 4.42.

*Ethyl (1*RS*,3*RS*,5*SR*,6*RS*)- and (1*RS*,3*RS*,5*SR*,6*SR*)-3-Hydroxy-6-(phenylthio)-8-azabicyclo[3.2.1]octane-8-carboxylate* (**10**). A soln. of **9** (1.5 g, 4.88 mmol) and hexabutyldistannane (0.44 g, 0.76 mmol) in benzene (40 ml) was irradiated with a high-pressure Hg lamp, under Ar during 1.5 h. Benzene was evaporated, and the oily residue was purified by CC (silica gel, benzene and benzene/AcOEt 8:2): **10** (2.7 g, 45%). White crystals. M.p. 119°. IR (KBr): 3413, 2000–1600, 1661, 1483, 1431, 1384, 1330, 1162, 1114, 1097, 1046, 1011. $^1$H-NMR: 1.21–1.30 (*m*, 3 H); 1.69–2.20 (*m*, 6 H); 2.69–2.84 (*m*, 1 H); 4.10–4.40 (*m*, 5 H); 7.18–7.36 (*m*, 5 H). $^{13}$C-NMR: 154.59; 154.25; 136.86; 136.65; 129.92; 129.82; 128.90; 126.24; 64.54; 61.05; 59.55; 59.36; 53.02; 52.76; 47.88; 47.14; 38.29; 37.99; 37.69; 37.63; 36.92; 36.15. CI-MS: 308 (100, $[M+1]$). Anal. calc. for $C_{16}H_{21}NO_3S$: C 62.54, H 6.84, N 4.56; found: C 62.51, H 6.71, N 4.44.

In addition to **10**, *ethyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate* (**13**; 0.15 g, 15%) and **8** (0.36 g, 37%) were obtained as by-products. Spectral data: in agreement with structures **13** and **8**.

*Ethyl (1*RS*,3*RS*,5*SR*,6*RS*)- and (1*RS*,3*RS*,5*SR*,6*SR*)-3-Hydroxy-6-(phenylsulfinyl)-8-azabicyclo[3.2.1]octane-8-carboxylate* (**14**). To the soln. of **10** (2.33 g, 7.58 mmol) in $CH_2Cl_2$ (120 ml), cooled to −78° under Ar, a soln. of *m*-CPBA (1.31 g, 7.58 mmol) in $CH_2Cl_2$ (40 ml) was added during 15 min. The mixture was stirred at −78° for 30 min, then allowed to reach r.t., diluted with $CH_2Cl_2$ (100 ml), and washed with 10% $Na_2SO_3$ soln. (100 ml). The aq. phase was extracted with $CH_2Cl_2$ (3 × 60 ml), the combined org. phase washed with sat. aq. $NaHCO_3$ soln. and $H_2O$, dried ($Na_2SO_4$), and evaporated, and the residual oil purified by dry FC (silica gel, petroleum ether/acetone 10:0 → 6:4): **14** (2.23 g, 91%). White crystals. IR (KBr): 3410, 3058, 1695, 1469, 1443, 1430, 1384, 1354, 1344, 1324, 1224, 1111, 1089, 1045. $^1$H-NMR: 1.21–1.35 (*m*, 3 H); 1.58–2.51 (*m*, 7 H); 3.83–3.96 (*m*, 1 H); 4.00–4.24 (*m*, 2 H); 4.30–4.43 (*m*, 2 H); 4.78–4.88 (*m*, 1 H); 7.45–7.60 (*m*, 3 H); 7.60–7.80 (*m*, 2 H). $^{13}$C-NMR: 153.29; 153.05; 142.22; 141.65; 131.69; 131.26; 129.14; 129.03; 125.72; 125.06; 124.86; 68.28; 66.42; 66.26; 63.65; 61.01; 53.68; 53.15; 52.78; 38.06; 37.66; 37.13; 29.79; 29.50; 28.41; 14.50. CI-MS: 324 ($[M+1]^+$).

*Ethyl (3*-endo*)-3-Hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate* (**15**). A suspension of **14** (2.10 g, 6.5 mmol) and $NaHCO_3$ (5.45 g, 6.5 mmol) in toluene (150 ml) was refluxed during 100 h. The cooled mixture was diluted with $CH_2Cl_2$ (200 ml) and washed with $H_2O$ (100 ml). The aq. phase was extracted with $CH_2Cl_2$ (3 × 60 ml), the combined extract washed with $H_2O$, dried ($Na_2SO_4$), and evaporated, and the residue purified by FC (silica gel, petroleum ether/acetone 10:0 → 7:3): **15** (1.25 g, 98%). Crystals. M.p. 74°. IR (KBr): 3432, 1682, 1601, 1471, 1435, 1385, 1351, 1316, 1262, 1219, 1172, 1107, 1065, 1023. $^1$H-NMR: 1.27 (*t*, *J* = 7.2, 3 H); 1.77 (*d*, *J* = 14.6, 2 H); 2.15–2.40 (*m*, 3 H); 3.95 (*t*, *J* = 5.6, 1 H); 4.17 (*q*, *J* = 7.2, 2 H); 4.60 (br. *s*, 2 H); 6.40 (br. *s*, 2 H). $^{13}$C-NMR: 152.75; 136.00; 135.56; 65.44; 60.86; 56.89; 35.47; 34.83; 14.61. CI-MS: 198 (100, $[M+1]$, 180 (25, $[M+1-H_2O]^+$). Anal. calc. for $C_{10}H_{15}NO_3$: C 60.89, H 7.66, N 7.10; found: C 60.52, H 7.40, N 7.54.

*6,7-Didehydrotropine* (=*(3*-endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-6-en-3-ol*; **11**). To the suspension of $LiAlH_4$ (0.75 g, 19.6 mmol) in $Et_2O$ (25 ml), cooled to 0° under Ar, **15** (0.97 g, 4.92 mmol) was added. The mixture was stirred at 0° for 15 min and left stirring for 5 h to reach r.t. The cooled mixture was carefully treated with $H_2O$ (2 ml) and $Et_2O$ (15 ml), then stirred for 30 min. The suspension was filtered and the precipitate washed successively with $Et_2O$ (150 ml) and $CHCl_3$ (250 ml). The combined extract was dried ($Na_2SO_4$) and

evaporated and the residual oil purified by CC (aluminium oxide (neutral, *Brockmann II*), $CHCl_3$, then $CHCl_3$/MeOH 97:3): 0.58 g (85%) of **1**. Pale yellow oil. IR (neat): 3387, 1657, 1449, 1425, 1321, 1276, 1232, 1120, 1100, 1056, 1023. $^1$H-NMR: 1.82 (*d*, *J* = 14.4, 2 H); 2.17–2.30 (*m*, 2 H); 2.27 (*s*, 3 H); 3.45 (*m*, 2 H); 3.85 (*t*, *J* = 5.6, 1 H); 6.25 (*s*, 2 H). $^{13}$C-NMR: 132.42, 66.02, 65.31 (CH); 41.31 (Me); 37.55 ($CH_2$). CI-MS: 140 (45, $[M+1]^+$), 122 (70, $[M+1]-H_2O]^+$), 113 (100, $[M+1-HCN]^+$).

*6,7-Didehydrotropine Acetate* (**16**). A soln. of **1** (0.12 g, 0.86 mmol) and acetyl chloride (1.10 g, 14.0 mmol) in $CHCl_3$ (3 ml) was refluxed for 5 h. $CHCl_3$ and excess acetyl chloride was evaporated, and the residue was dissolved in $CHCl_3$ (100 ml) and washed with 10% aq. NaOH soln. (8 ml). The aq. phase was extracted with $CHCl_3$ (5 × 10 ml), the combined org. phase dried ($Na_2SO_4$) and evaporated, and the residual oil purified by CC (aluminium oxide (neutral, *Brockmann II*), $CHCl_3$): 0.14 g (93%) of **16**. Pale yellow oil. IR (neat): 3066, 1732, 1650, 1449, 1428, 1378, 1364, 1256, 1225, 1101, 1040, 1028. $^1$H-NMR: 1.69 (*d*, $J_{gem}$ = 14.6, 2 H); 1.97 (*s*, 3 H); 2.23 (*ddd*, $J_{gem}$ = 14.6, $J_{vic}$ = 6.2, 3.4, 2 H); 2.28 (*s*, 3 H); 3.39 (*m*, 2 H); 4.96 (*t*, $J_{vic}$ = 6.2, 1 H); 5.99 (*s*, 2 H). $^{13}$C-NMR: 170.29; 131.66; 66.89; 65.31; 41.42; 33.67; 21.43. CI-MS: 182 (55, $[M+1]^+$), 122 (100, $[M+1-MeCOOH]^+$).

*Acetate Scopin* (= rel-*(1R,2R,4S,5S)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.0$^{2,4}$]nonan-7-ol Acetate*; **6b**). To a soln. of **16** (20 mg, 0.11 mmol) in formic acid (74 µl), 90% $H_2O_2$ soln. (0.62 µl) was added at r.t. The mixture was stirred for two days. Then more 90% $H_2O_2$ soln. (20 µl) was added, and stirring was continued at r.t. for additional 5 days. The mixture was treated with sat. aq. $Na_2SO_3$ soln. (2 ml) and extracted with $CHCl_3$ (20 ml). The extract was washed with 10% aq. NaOH soln. (5 ml), the aq. phase extracted with $CHCl_3$ (6 × 10 ml), the combined extract dried ($Na_2SO_4$) and evaporated, and the oily residue purified by CC (aluminium oxide (neutral, *Brockmann II*), $CHCl_3$, $CHCl_3$/MeOH 100:1): **6b** (9 mg, 45%) and recovered **16** (10 mg, 50%). **6b**: Viscous oil. IR (neat): 1729, 1421, 1381, 1364, 1333, 1264, 1237, 1206, 1063, 1049, 1019. $^1$H-NMR: 1.60 (*d*, $J_{gem}$ = 15.6, 2 H); 2.02 (*s*, 3 H); 2.14 (*ddd*, $J_{gem}$ = 15.6, $J_{vic}$ = 5.5, 4.1, 2 H); 2.54 (*s*, 3 H); 3.19 (*dd*, $J_{vic}$ = 4.1, 1.7, 2 H); 3.63 (*s*, 3 H); 4.98 (*t*, *J* = 5.5, 1 H). $^{13}$C-NMR: 169.98; 66.22; 58.03; 56.57; 42.37; 31.28; 21.56. CI-MS: 198 (100, $[M+1]^+$), 138 (98, $[M+1-MeCOOH]^+$). Anal. calc. for $C_{10}H_{15}NO_3$: C 60.91, H 7.61, N 7.10; found: C 60.69, H 7.51, N 7.18.

*6,7-Didehydrohyosciamin* (= *(αS)-α-(Hydroxymethyl)benzeneacetic Acid (3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-6-en-3-yl Ester*; **17**). To the soln. of **1** (0.11 g, 0.77 mmol) in dry $Et_2O$ (5 ml), a soln. of TsOH (0.13 g, 0.77 mmol) in dry $Et_2O$ (5 ml) was added at r.t. The mixture was stirred for 40 min, and the precipitated salt was filtered off and washed with dry $Et_2O$ (20 ml). The white crystalline TsOH salt of **1** (0.21 g, 88%) was used in the following experiment without further purification.

Acetyltropoyl chloride (= (*αS*)-α-(hydroxymethyl)benzeneacetyl chloride) was prepared by reaction of acetyltropic acid (71.6 mg, 0.34 mmol) with thionyl chloride (0.19 g, 1.6 mmol) in benzene (0.1 ml) under Ar. The mixture was heated at 60° for 2.5 h. Excess thionyl chloride was evaporated, and to the oily acetyltropoyl chloride, the TsOH salt of **1** (92.0 mg, 0.29 mmol), was added. The mixture was heated under Ar at 82° for 2.5 h. Then 6M HCl (0.33 ml) was added at r.t., the mixture stirred during 12 h and then dissolved in $CHCl_3$/MeOH 1:1 (25 ml), the soln. dried ($Na_2SO_4$) and evaporated, and the residual oil dissolved in $CHCl_3$/MeOH 5:1. The precipitate was filtered off and discarded, the clear soln. evaporated, and the oily residue purified by CC (anh. $Na_2SO_4$ 2.7 g) and aluminium oxide (3.3 g; basic, *Brockmann I*), $CHCl_3$/MeOH 100:2). The obtained oil was repurified by CC (aluminium oxide (neutral, *Brockmann II*), $CHCl_3$/MeOH 100:0.25): **19** (72 mg, 85%). Pale yellow oil. IR (neat): 3371, 3065, 3029, 2000–1600, 1724, 1602, 1585, 1495, 1455, 1424, 1375, 1356, 1342, 1325, 1302, 1270, 1222, 1196, 1169, 1116, 1110, 1068, 1035. $^1$H-NMR: 1.51 (*d*, *J* = 15.0, 1 H); 1.68 (*d*, *J* = 15.0, 1 H); 2.13 (*ddd*, $J_{gem}$ = 15.0, $J_{vic}$ = 6.0, 3.6, 1 H); 2.21 (*ddd*, $J_{gem}$ = 15.0, $J_{vic}$ = 6.0, 3.6, 1 H); 2.20 (*s*, 3 H); 2.65 (br. *s*, 1 H); 3.22–3.26 (*m*, 1 H); 3.32–3.36 (*m*, 1 H); 3.69–3.84 (*m*, 2 H); 4.08–4.17 (*m*, 1 H); 5.00 (*t*, *J* = 6.0, 1 H); 5.41 (*dd*, *J* = 5.5, 2.0, 1 H); 5.81 (*dd*, *J* = 5.5, 1.8, 1 H); 7.21–7.38 (*m*, 5 H). $^{13}$C-NMR: 171.93, 135.92 (C); 131.53, 128.69, 128.27, 127.60, 67.73, 65.26, 65.18 (CH); 41.39 (Me); 33.50, 33.32 ($CH_2$). CI-MS: 288 (100, $[M+1]^+$), 123 (70, $[M+1-PhCH(CH_2OH)COO]^+$). Anal. calc. for $C_{17}H_{21}NO_3$: C 71.08, H 7.31; N 4.87; found: C 70.92, H 7.24, N 4.80.

*(1*RS*,3*SR*,5*RS*,6*RS*)- and (1*RS*,3*SR*,5*RS*,6*SR*)-8-(Ethoxycarbonyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-6-propanoic Acid Ethyl Ester* (**18**). A soln. of **9** (0.15 g, 0.5 mmol), ethyl acrylate (0.50 g, 5.0 mmol), and $Bu_3SnH$ (0.14 g, 0.5 mmol) in benzene (40 ml) was irradiated with a 125-W high-pressure Hg lamp at r.t. under Ar during 15 min. Benzene was evaporated and the residue purified by CC (silica gel, petroleum ether/acetone 10:0 → 8:2): **18** (46 mg, 35%), 6-*endo*/6-*exo* 55:45 (by $^{13}$C-NMR). Colorless oil. IR (neat): 3444, 1734, 1699, 1674, 1427, 1259, 1155, 1099, 1048. $^1$H-NMR: 1.25 (*t*, *J* = 7.2, 6 H); 1.40–1.90 (*m*, 6 H); 2.29 (*t*, *J* = 7.6, 2 H); 1.90–2.70 (*m*, 4 H); 3.86–3.92 (br. *m*, 1 H); 4.12 (*q*, *J* = 7.2, 2 H); 4.13 (*q*, *J* = 7.2, 2 H); 4.10–4.40 (br. *m*, 2 H). $^{13}$C-NMR: 173.57, 154.27 (C); 64.97 (CH); 60.81, 60.31 ($CH_2$); 57.94, 57.65, 53.15, 52.99, 41.10, 40.37 (CH); 38.38,

38.22, 37.76, 35.93, 35.14, 32.59, 31.90 ($CH_2$); 14.71, 14.18 (Me). CI-MS: 300 (100, $[M+1]^+$). Anal. calc. for $C_{15}H_{25}NO_5$: C 60.20, H 8.36, N 4.68; found: C 60.47, H 8.42, N 4.40.

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