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Sodium borohydride reduction of 4-aryl-*N*-trifluoroacetyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline ozonide

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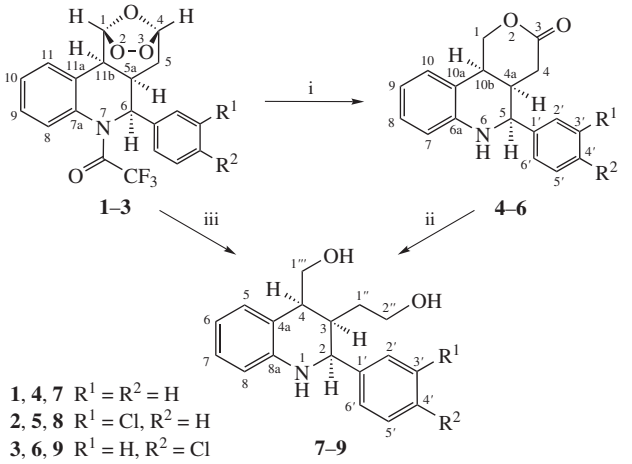
Reduction of the title ozonide with 1 equiv. of sodium borohydride in ethanol leads to the transformation of the ozonide moiety into δ-lactone one, whereas the use of 5 equiv. of the reductant affords the corresponding 1,5-diol, with N-deacylation occurring in all cases.

Reduction of ozonides with complex hydrides leads to alcohols.[1] When a starting compound contains carboxy or hydroxy group lactones can be formed.[2] Herein we discovered that reduction of 7-trifluoroacetyl-6-aryl-4,5,5a,6,7,11b-hexahydro-1*H*-1,4-epoxy-[1,2]dioxepino[5,4-*c*]quinolines **1**–**3** with 1 equiv. of sodium borohydride in ethanol gives δ-lactones **4**–**6** (Scheme 1).† The ozonides **1**–**3** were obtained from the corresponding 4-aryl-*N*-trifluoroacetyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinolines as reported.[3]

The reaction proceeds within 15–30 min (TLC control of the consumption of the starting compound, R_f 0.65). The further aging of the reaction mixture leads to the gradual transformation of the resulting lactone (R_f 0.70) into a mixture of polar compounds (TLC, the extended spot from a starting position to R_f 0.60). The lactone is completely converted into polar compounds in ~10 h (TLC data).



Scheme 1 *Reagents and conditions*: i, 1 equiv. $NaBH_4$/EtOH; ii, 2 equiv. $NaBH_4$/EtOH; iii, 5 equiv. $NaBH_4$/EtOH.

The reduction of ozonides **1**–**3** with approximately fivefold molar excess of the reagent affords the corresponding diols **7**–**9**. Diols **7**–**9** are also formed upon action of twofold molar excess of $NaBH_4$ on lactones **4**–**6** (Scheme 1).‡

The structures of obtained lactones **4**–**6** and diols **7**–**9** were proved by 1D (^{1}H and ^{13}C) and 2D [homo- (COSY, NOESY) and heteronuclear (HSQC, HMBC)] methods of NMR spectroscopy.

† *General procedure*. Sodium borohydride (1 mmol) was added to a solution of ozonide **1**–**3** (1 mmol) in 10 ml of dry ethanol. The reaction mixture was stirred at room temperature until the consumption of the starting ozonide [15–30 min, TLC control, Silufol, eluent: $CHCl_3$/MeOH (20:1), R_f 0.65]. The solvent was evaporated, H_2O was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was concentrated and the residue was purified by column chromatography on silica gel, eluating with $CHCl_3$ to furnish the corresponding lactone **4**–**6**.

*(4a*R*,5*S*,10b*R*)-5-Phenyl-1,4,4a,5,6,10b-hexahydro-3*H*-pyrano-[4,3-c]quinolin-3-one* **4**. Yield 84%, R_f 0.70 ($CHCl_3$/MeOH, 20:1), mp 179–181 °C. IR (ν/cm^{-1}): 3329, 1712, 1607. ^{1}H NMR (400.13 MHz) δ: 2.09 (m, 1H, HC^4), 2.71–2.74 (m, 2H, HC^4 and HC^{4a}), 3.61 (m, 1H, HC^{10b}), 3.97 (br. s, 1H, NH), 4.49 (m, 2H, H_2C^1), 4.65 (br. s, 1H, HC^5), 6.70 (d, 1H, HC^7, *J* 8.0 Hz), 6.83 (t, 1H, HC^9, *J* 8.0 Hz), 7.11 (t, 1H, HC^8, *J* 8.0 Hz), 7.21 (d, 1H, HC^{10}, *J* 8.0 Hz), 7.27–7.43 (m, 5H, Ar′). ^{13}C NMR (100.62 MHz) δ: 27.19 (C^4), 35.11 (C^{10b}), 37.44 (C^{4a}), 59.07 (C^5), 69.93 (C^1), 115.68 (C^7), 118.69 (C^{10a}), 119.44 (C^9), 126.46 (C$^{2'}$, C$^{6'}$), 128.01 (C^{10}), 128.06 (C$^{4'}$), 128.32 (C^8), 128.85 (C$^{3'}$, C$^{5'}$), 139.72 (C$^{1'}$), 145.88 (C^{6a}), 172.38 (C^3). MS (MALDI-TOF), *m*/*z*: 278 [M – H]$^+$ (calc. for $C_{18}H_{16}NO_2$, 278).

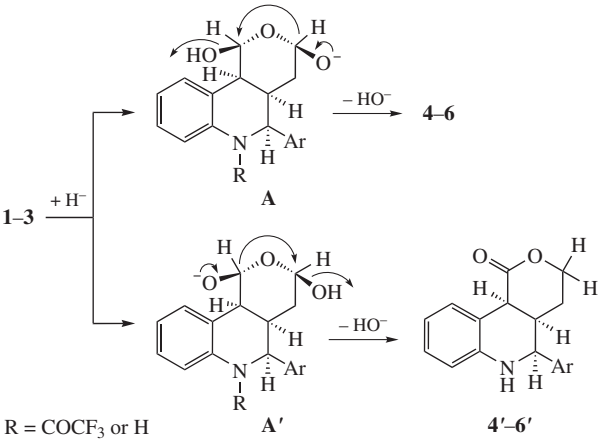
*(4a*R*,5*S*,10b*R*)-5-(3-Chlorophenyl)-1,4,4a,5,6,10b-hexahydro-3*H*-pyrano[4,3-c]quinolin-3-one* **5**. Yield 68%, R_f 0.7 ($CHCl_3$/MeOH, 20:1). mp 65–67 °C. IR (ν/cm^{-1}): 3362, 1725, 1606, 1077. ^{1}H NMR (400.13 MHz) δ: 2.11 (m, 1H, HC^4), 2.70–2.73 (m, 2H, HC^4 and HC^{4a}), 3.62 (m, 1H, HC^{10b}), 3.97 (br. s., 1H, NH), 4.53 (m, 2H, H_2C^1), 4.64 (d, 1H, HC^5, *J* 2.4 Hz), 6.71 (d, 1H, HC^7, *J* 8.0 Hz), 6.84 (t, 1H, HC^9, *J* 8.0 Hz), 7.13 (t, 1H, HC^8, *J* 8.0 Hz), 7.22 (d, 1H, HC^{10}, *J* 8.0 Hz), 7.26–7.35 (m, 3H, Ar′), 7.40 (s, 1H, HC$^{2'}$). ^{13}C NMR (100.62 MHz) δ: 27.06 (C^4), 34.90 (C^{10b}), 37.23 (C^{4a}), 58.50 (C^5), 69.82 (C^1), 115.85 (C^7), 118.42 (C^{10a}), 119.75 (C^9), 124.66 (C$^{6'}$), 126.64 (C^{10}), 127.72 (C$^{5'}$), 128.14 (C^8), 128.30 (C$^{4'}$), 130.17 (C$^{2'}$), 134.93 (C$^{3'}$), 141.86 (C$^{1'}$), 145.36 (C^{6a}), 172.20 (C^3). Found (%): C, 68.98; H, 5.07; N, 4.38. Calc. for $C_{18}H_{16}ClNO_2$ (%): C, 68.90; H, 5.10; N, 4.47.

*(4a*R*,5*S*,10b*R*)-5-(4-Chlorophenyl)-1,4,4a,5,6,10b-hexahydro-3*H*-pyrano[4,3-c]quinolin-3-one* **6**. Yield 62%, R_f 0.7 ($CHCl_3$/MeOH, 20:1). mp 70–72 °C. ^{1}H NMR (400.13 MHz) δ: 2.09 (m, 1H, HC^4), 2.68 (m, 1H, HC^{4a}), 2.72 (m, 1H, HC^4), 3.61 (m, 1H, HC^{10b}), 3.97 (br. s, 1H, NH), 4.53 (m, 2H, H_2C^1), 4.64 (br. s, 1H, HC^5), 6.71 (d, 1H, HC^7, *J* 8.0 Hz), 6.85 (t, 1H, HC^9, *J* 8.0 Hz), 7.13 (t, 1H, HC^8, *J* 8.0 Hz), 7.22 (d, 1H, HC^{10}, *J* 8.0 Hz), 7.34 (d, 2H, HC$^{2'}$, HC$^{6'}$, *J* 8.0 Hz), 7.40 (d, 2H, HC$^{3'}$, HC$^{5'}$, *J* 8.0 Hz). ^{13}C NMR (100.62 MHz) δ: 27.04 (C^4), 34.94 (C^{10b}), 37.27 (C^{4a}), 58.40 (C^5), 69.85 (C^1), 115.82 (C^7), 118.46 (C^{10a}), 119.69 (C^9), 127.73 (C^{10}), 127.84 (C$^{2'}$, C$^{6'}$), 128.11 (C^8), 129.03 (C$^{3'}$, C$^{5'}$), 133.83 (C$^{4'}$), 138.24 (C$^{1'}$), 145.50 (C^{6a}), 172.19 (C^3). Found (%): C, 68.81; H, 5.01; N, 4.32. Calc. for $C_{18}H_{16}ClNO_2$ (%): C, 68.90; H, 5.10; N, 4.47.

‡ *General procedure*. Sodium borohydride (2 mmol) was added to a solution of the corresponding lactone **4**–**6** (1 mmol) in 10 ml of dry ethanol. The reaction mixture was stirred at room temperature until the consumption of the starting lactone [15–30 min, TLC control, Silufol, eluent: $CHCl_3$/MeOH (20:1), R_f 0.70]. The solvent was evaporated, H_2O (3 ml) was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was concentrated and the residue was purified by column chromatography on silica gel, eluating with $CHCl_3$ to furnish the corresponding diol **7**–**9**.

^{13}C NMR spectra of compounds **4–6** contain signals of C^1 (69.82–69.93 ppm) and oxycarbonyl C^3=O (172.19–172.38 ppm) instead of characteristic signals of the ozonides[3,4] at 98.9–101.5 ppm. The relative *cis*-orientation of protons at chiral atoms C^{4a}, C^5 and C^{10b} in compounds **4–6** is confirmed by the NOESY experiment data (there are clear interactions of protons at these atoms). Cross-peak signals of proton at C^{10b} (3.61–3.62 ppm) with protons at C^1 (4.49–4.53 ppm) are observed in the COSY experiment. In the HMBC experiment, there are intense cross-peaks of the proton signals of methylene group H_2C^4 (2.09–2.11 and 2.70–2.74 ppm) with the signal of the carbonyl group C^3=O (172.19–172.38 ppm), which is possible only for the proposed structures of **4–6**. The correlation peaks of proton signals H_2C^1 (4.49–4.53 ppm) in HMBC experiment with the signal C^{10a} (118.42–118.69 ppm) of aromatic ring also confirm the structures of **4–6**. To this, lactones **4–6** have structure of (4a*R**,5*S**,10b*R**)-5-aryl-1,4,4a,5,6,10b-hexahydro-3*H*-pyrano[4,3-*c*]quinolin-3-ones. Relative configuration of the chiral centres of diols **7–9** is 2*S**, 3*R**, 4*R**. Thus, diols **7–9** have structure of (2*S**,3*R**,4*R**)-2-aryl-3-(2-hydroxyethyl)-4-hydroxymethyl-1,2,3,4-tetrahydroquinolines.

It is known[5] that during hydride reduction, an oxygen atom of the peroxide bridge in an ozonide is removed. Probably the migration of hydride ion with elimination of hydroxide ion and the formation of the corresponding δ-lactone **4–6** occurs in the intermediate O-anion **A** (Scheme 2). Alternative formation of isomeric δ-lactones **4′–6′** is less likely due to possible destabilization of OCH-anionic centre of intermediate **A′** by π-electrons of proximate aromatic ring.



Scheme 2

The observed transformation is accompanied by removal of the trifluoroacetyl group, which is consistent with the literature data.[6,7] When the ozonide contained inert to $NaBH_4$[8,9] *N*-acetyl group, attempted reduction with equimolar amount of $NaBH_4$ afforded no lactone.

Thus, reduction of *N*-trifluoroacetyl tetrahydroquinoline ozonides with equimolar amount of $NaBH_4$ in ethanol proceeds regioselectively with formation of the corresponding δ-lactones without *N*-trifluoroacetyl group.

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(2S,3R*,4R*)-2-Phenyl-3-(2-hydroxyethyl)-4-hydroxymethyl-1,2,3,4-tetrahydroquinoline* **7**. Yield 85%, R_f 0.40 ($CHCl_3$/MeOH, 20:1), mp 138–140 °C. ^{1}H NMR (400.13 MHz) δ: 1.28 and 1.67 (m, 2H, $H_2C^{1''}$), 2.52 (m, 2H, HC^3, $HC^{2''}$), 3.34 (m, 1H, $HC^{2''}$), 3.52 (m, 1H, HC^4), 3.78 (dd, 1H, $HC^{1'''}$, *J* 8.0 and 11.0 Hz), 4.10 (br. s, 1H, NH), 4.32 (dd, 1H, $HC^{1'''}$, *J* 6.0 and 11.0 Hz), 4.76 (d, 1H, HC^2, *J* 2.0 Hz), 6.65 (d, 1H, HC^8, *J* 8.0 Hz), 6.70 (t, 1H, HC^6, *J* 8.0 Hz), 6.98 (t, 1H, HC^5, *J* 8.0 Hz), 7.08 (d, 1H, HC^7, *J* 8.0 Hz), 7.27–7.46 (m, 5H, $HC^{2'}$, $HC^{3'}$, $HC^{4'}$, $HC^{5'}$, $HC^{6'}$). ^{13}C NMR (100.62 MHz) δ: 23.36 ($C^{1''}$), 35.69 (C^3), 42.68 (C^4), 59.26 (C^2), 61.60 ($C^{1'''}$), 62.76 ($C^{2''}$), 114.29 (C^8), 117.70 (C^6), 120.63 (C^{4a}), 126.14 (C^5), 126.33 ($C^{2'}$, $C^{6'}$), 127.29 (C^7), 127.41 ($C^{4'}$), 128.52 ($C^{3'}$, $C^{5'}$), 144.46 ($C^{1'}$), 146.17 (C^{8a}). MS (MALDI-TOF), *m*/*z*: 282 $[M-H]^+$ (calc. for $C_{18}H_{20}NO_2$, 282).

(2S,3R*,4R*)-2-(3-Chlorophenyl)-3-(2-hydroxyethyl)-4-hydroxymethyl-1,2,3,4-tetrahydroquinoline* **8**. Yield 79%, R_f 0.40 ($CHCl_3$/MeOH, 20:1), mp 57–59 °C. ^{1}H NMR (400.13 MHz) δ: 1.26 and 1.60 (m, 2H, $H_2C^{1''}$), 2.38 (m, 2H, HC^3), 2.78 and 3.14 (m, 2H, $H_2C^{2''}$), 3.43 (m, 1H, HC^4), 3.74 (m, 1H, $HC^{1'''}$), 3.74 (br. s, 1H, NH), 4.25 (dd, 1H, $HC^{1'''}$, *J* 6.0 and 11.0 Hz), 4.71 (d, 1H, HC^2, *J* 2.0 Hz), 6.60 (t, 1H, HC^6, *J* 8.0 Hz), 6.67 (d, 1H, HC^8, *J* 8.0 Hz), 6.98 (m, 2H, HC^5, HC^7), 7.30 (m, 3H, $HC^{4'}$, $HC^{5'}$, $HC^{6'}$), 7.47 (br. s, 1H, $HC^{2'}$). ^{13}C NMR (100.62 MHz) δ: 23.75 ($C^{1''}$), 35.62 (C^3), 42.88 (C^4), 59.04 (C^2), 61.35 ($C^{1'''}$), 61.88 ($C^{2''}$), 113.46 (C^8), 117.08 (C^6), 121.04 (C^{4a}), 124.77 ($C^{6'}$), 125.77 (C^5), 126.36 ($C^{2'}$), 126.92 (C^7), 126.99 ($C^{4'}$), 129.62 ($C^{5'}$), 133.90 ($C^{3'}$), 144.79 ($C^{1'}$), 145.04 (C^{8a}). Found (%): C, 68.10; H, 6.40; N, 4.49. Calc. for $C_{18}H_{20}ClNO_2$ (%): C, 68.03; H, 6.34; N, 4.41.

(2S,3R*,4R*)-2-(4-Chlorophenyl)-3-(2-hydroxyethyl)-4-hydroxymethyl-1,2,3,4-tetrahydroquinoline* **9**. Yield 82%, R_f 0.40 ($CHCl_3$/MeOH, 20:1), mp 69–71 °C. ^{1}H NMR (400.13 MHz) δ: 1.33 and 1.62 (m, 2H, $H_2C^{1''}$), 2.48 (m, 2H, HC^3), 2.56 and 3.40 (m, 2H, $H_2C^{2''}$), 3.51 (m, 1H, HC^4), 3.78 (t, 1H, $H_2C^{1'''}$, *J* 11.0 Hz), 4.01 (br. s, 1H, NH), 4.32 (dd, 1H, $HC^{1'''}$, *J* 6.0 and 11.0 Hz), 4.74 (m, 1H, HC^2), 6.65 (d, 1H, HC^8, *J* 8.0 Hz), 6.71 (t, 1H, HC^6, *J* 8.0 Hz), 6.97 (d, 1H, HC^5, *J* 8.0 Hz), 7.07 (t, 1H, HC^7, *J* 8.0 Hz), 7.35 (m, 2H, $HC^{2'}$, $HC^{6'}$), 7.39 (m, 2H, $HC^{3'}$, $HC^{5'}$). ^{13}C NMR (100.62 MHz) δ: 23.19 ($C^{1''}$), 35.66 (C^3), 42.69 (C^4), 58.78 (C^2), 61.53 ($C^{1'''}$), 62.83 ($C^{2''}$), 114.47 (C^8), 118.04 (C^6), 120.65 (C^{4a}), 126.11 (C^5), 127.33 (C^7), 127.69 ($C^{2'}$, $C^{6'}$), 128.65 ($C^{3'}$, $C^{5'}$), 133.00 ($C^{4'}$), 140.73 ($C^{1'}$), 144.15 (C^{8a}). Found (%): C, 68.15; H, 6.10; N, 4.32. Calc. for $C_{18}H_{20}ClNO_2$ (%): C, 68.03; H, 6.34; N, 4.41.